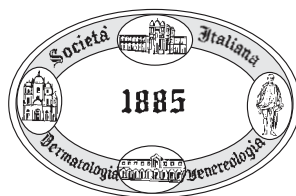


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Epidemiological and clinical characteristics of patients attending STI clinics in Tuscany, Italy: a multicenter report on new infections in 2011

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Aim. The aim of this study was to assess the demographic, behavioral and clinical features associated with newly diagnosed sexually transmitted infections (STIs) among attendees from four STI Clinics during 2011 in Tuscany, Central Italy.

Methods. Electronic and non-electronic medical records of attendees were reviewed to collect socio-demographical and anamnestic characteristics of patients, and to assess the annual incidence and distribution of STIs.

Results. The study included 1293 subjects, for a total number of 1394 newly diagnosed STIs. The male/female ratio was about 2:1, and Italian nationality accounted for 84.1% of the sample. MSM represented the 25.9% of the male population. Condom use was very poor in the large majority of our sample. Genital warts and non-gonococcal cervicitis and urethritis were the most frequent STIs. Anamnestic STIs were recorded in 350 subjects. When stratified for sexual preference, men who have sex with men were found at four to ten fold increased risk for syphilis, gonorrhoea and HIV infection. New diagnoses of syphilis, gonorrhoea, urethritis and molluscum were strictly associated with infections by the same pathogens in the past (re-infections).

Conclusions. Results show that STIs in Tuscany involve a mixed young to adult population, composed by both heterosexual and homosexual subjects who practice unprotected sex and do not seem to be conscious of the associated risks, as demonstrated by the high rates of coinfections and reinfections. These findings reinforce the need for greater education and prevention efforts for HIV and other STIs among the Tuscan population.

KEY WORDS: Sexually transmitted diseases - Epidemiology - Chlamydia trachomatis.

To date, sexually transmitted infections (STIs) remain of major public health importance world-

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wide, due to the ongoing modifications of the pattern of this group of diseases, the awareness of the sequelae of some STIs (infertility, perinatal mortality, cancer and even death), and the recent correlation found between STIs and HIV infection.¹

In 2008, the total number of new cases of the four curable STIs (*Chlamydia trachomatis*, *Neisseria gonorrhoeae*, syphilis and *Trichomonas vaginalis*) in adults aged between 15 and 49 years across the world was estimated to be 498.9 million by the World Health Organization.² Although the highest rates for STIs are recorded in developing regions of Africa and South-West Asia, also industrialized countries show yearly increasing numbers of new STI diagnoses, despite efforts to control STIs by targeted prevention, rapid diagnosis and treatment services.^{3,4}

Indeed, the intrinsic features of STIs greatly limit the feasibility of epidemiological studies. In fact, STIs are often asymptomatic, patients may be ashamed to seek medical advice for genital symptoms, and they possibly spread toward different practitioners (GPs, dermatologists, gynaecologists). Moreover, it is well established that STIs affect primarily poor and

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marginalized groups, immigrants and migrants, sex workers and similar hard-to-reach populations with limited access to health services. Taken together, these aspects lead to considerable under-reporting, suggesting a great deal of uncertainty surrounding the global and regional STI estimates.

In Italy the STI scenario is mainly defined by the Istituto Superiore di Sanità (ISS) that periodically updates the surveillance system based on clinical centers and laboratories scattered throughout the country.^{5, 6} This network was first started in 1991, and accounts today for more than 90,000 new cases of STIs, including HPV, HSV2 and *Chlamydia trachomatis*-related diseases, that are not mandatorily notified. Overall, there seems to be in Italy a great burden of *Condylomata acuminata*, followed by non-gonococcal non-chlamydial cervicitis and latent syphilis.⁷ Taken together these three conditions represent approximately the 50% of all diagnosed STIs reported by the ISS.

Unfortunately, few more studies on the prevalence of STIs in Italy are currently available, due to difficult application of observational methods on large series of subjects. Most of them, in fact, are conducted on small areas and/or peculiar populations (*i.e.*, adolescents, prisons, men who have sex with men [MSM]),⁸⁻¹⁰ therefore rates are not representative of the actual STI situation both for distribution and temporary trends.

Our group has already conducted an analysis about the occurrence of STIs in a random sample of subjects attending a STI Unit in Florence, Italy, focussing on potential associations between socio-demographic and lifestyle factors and risky sexual behaviours.¹¹

On that basis, the Regional Health Agency of Tuscany committed a larger network of STI clinics in Tuscany, aimed to monitor epidemiologic features of STIs in Central Italy.

In this pilot report, we set out to determine the extent of incident STIs and some of their risk factors using data collected in 2011 by four STI clinics in Tuscany.

Materials and methods

The following four STI Units participated into the study: Sexually Transmitted Disease Center, Department of Dermatology, University of Florence; Infec-

tious Diseases Unit, Santa Maria Annunziata Hospital, Florence; Sexually Transmitted Disease Center, Department of Dermatology, University of Siena; Dermatology Unit, Campo di Marte Hospital, Lucca.

Specifically trained clinicians retrospectively reviewed both electronic and non-electronic medical records of patients who had attended the STI Units from January 1 to December 31, 2011. Patients were considered eligible if they had developed 1 or more than one STI in the study period (new diagnoses), whereas they were excluded if attending the STI Units for follow-up and treatment of a previous STI, or for screening blood test. Diagnostic modalities were all considered acceptable methods of detecting the respective STIs according to the most recent CDC and WHO guidelines.^{12, 13}

Selected personal, medical and anamnestic information (Appendix 1) of included subjects were inserted manually in an electronic database (Access file).

Later, a descriptive analysis of newly diagnosed STIs, socio-demographic, epidemiological and anamnestic variables was performed using common methods for proportions; associations between variables were assessed using univariate and multivariate logistic regression. The confidence intervals were computed at the 95% levels. Statistical analyses were performed using STATA software for personal computer (Stata Statistical Software release 12.0; Stata Corporation, College Station, TX, USA).

Results

A total of 1293 patients who suffered from one STI at least were included in the database. Among them 865 (66,8%) were collected from the Sexually Transmitted Disease Center and 123 (9,5%) from the Infectious Diseases Unit in Florence, respectively; 141 (10,9%) came from the Sexually Transmitted Disease Centre of Siena, and 164 (12,6%) from the Dermatology Unit of Lucca.

Study population

In the sample, the mean age was 36,2 years (SD=12,3). A total of 863 (66,5%) subjects were male and 430 (33,5%) were female. The majority of Clinic attendees were Italian (84,1%). A higher percentage of women were found among people

from other countries, rather than among the Italian subgroup (42.4% vs. 30.7%). About 40% of subjects were under the age of 30, while approximately the half of them were between 30 and 50.

A total of 272 females (81.2%) and 539 males (80.4%) described themselves as single. In both sexes similar percentages of attendees were divorced (9.6% of women and 6% of men), widows (0.9% of women and none of men) and married (17% of women and 18.5% of men). However, 465 of subjects (177 [38.1%] of women and 288 [61.9%] of men) had had a stable sexual partner from six months or more.

Overall a good education level was appreciated, since 53.6% of our sample had attended high school or was graduated. According to the young age of our

population, about a half of attendees were students; 70 subjects (21%) were unemployed.

Heterosexual men accounted for 68.6%, bisexual for 5.5% and MSM for 25.9%. The whole of the female group reported themselves as heterosexual. The proportion of MSM engaged in a steady relationship was lower than that of heterosexual people (24.6% vs. 52%).

A previous or current history of injecting drug use was discovered in 3.3% of the sample.

In the medical records, the item about condom use was addressed to "always", "sometimes" or "never". The very large majority of attendees had referred they were using the condom "sometimes". Only 8 subjects had stated "always" and 28 "never". Therefore, condom use resulted inconstant in our study

TABLE I.—Composition of the sample for the characteristics by gender.

Characteristics	Male (N.=863)		Female (N.=430)		Total (N.=1.293)	
	N.	%	N.	%	N.	%
Nationality						
Italian	699	86.4	311	79.3	1.010	84.1
Foreign	110	13.6	81	20.7	191	15.9
ND	54	-	38	-	92	-
Age						
≤20 years	21	2.4	25	5.8	46	3.6
21-30 years	294	34.1	169	39.3	463	35.8
31-40 years	240	27.8	121	28.1	361	27.9
41-50 years	183	21.2	59	13.7	242	18.7
≥51 years	125	14.5	56	13.0	181	14.0
Marital status						
Unmarried	499	74.4	237	70.7	736	73.2
Married	124	18.5	57	17.0	181	18.0
Live-in partner	8	1.2	6	1.8	14	1.4
Divorced/Separated	40	6.0	32	9.6	72	7.2
Widower	0	0.0	3	0.9	3	0.3
ND	192	-	95	-	287	-
Qualification						
No degrees	2	0.3	3	0.9	5	0.5
Lower secondary school	168	25.1	55	16.4	223	22.2
Upper secondary school	260	38.9	165	49.3	425	42.4
University degree (1° or 2° level)	73	10.9	39	11.6	112	11.2
Other	165	24.7	73	21.8	238	23.7
ND	195	-	95	-	290	-
Orientamento sessuale						
Heterosexual	508	68.6	359	98.9	867	78.5
Homosexual	192	25.9	2	0.6	194	17.6
Bisexual	41	5.5	2	0.6	43	3.9
ND	122	-	67	-	189	-
Condom use						
Never	17	2.5	11	3.3	28	2.8
Sometimes	646	96.3	324	96.7	970	96.4
Always	8	1.2	0	0.0	8	0.8
ND	192	-	95	-	287	-

population, independently from age, gender, sexual orientation, presence of a steady partner, history of occasional intercourses and/or previous STIs.

A total of 397 patients (39,6%) had already had their blood screened for HIV infection in the past; 660/1293 (51%) accepted to be screened during consultation in 2011 (Table I).

Prevalence of STIs

In our sample, including subjects attending STI Units in Tuscany in 2011, a total number of 1384 new diagnoses of STIs were made, thus 84 subjects had developed more than one STI during the year, either concomitantly (coinfections) or in subsequent times. A total of 925 diagnoses were posed in the male group and the remaining 459 in the female one.

When looking at the breakdown of STIs (Table II), genital wart was the most common infection (N.=649; 46.9%), followed by non-gonococcal cervicitis and urethritis (219 cases; 15.8%), herpes genitalis (120 cases; 8.6%) and molluscum contagiosum (113 cases; 8.2%). Genital warts and molluscum were also the most common infections disclosed in subjects under the age of 20 (24 and 9 cases, respectively).

In total 53 men and 16 women were diagnosed as having HIV infection: about 10% of these HIV-infected subjects were aged 30 or younger.

Overall, 902 subjects (69.7%) reported being never diagnosed with any other STI apart from the current disease; 267 (20.6%) subjects had already suffered from one STI, 55 (4.2%) from two and 28 (2.1%) from three or more.

Correlates of STI diagnosis

Logistic regression analyses in our sample revealed that female sex was generally associated with a reduced risk of both current and previous STIs, although foreign women were more likely to develop a STI than foreign men (OR: 1.7; 95% CI: 1.2-2.3). Overall, Italian attendees were more likely to report anamnestic STIs (OR: 0.6; 95% CI: 0.4-0.8).

Moreover, in foreigners there was a higher risk for gonococcal urethritis/cervicitis (OR: 2.1; 95% CI: 1-4.3) and non-gonococcal urethritis/cervicitis (OR: 1.2; 95% CI: 1.1-2.7).

Patients who declared they had not had a stable partner in the previous six months were at higher risk for syphilis (OR: 5; 95% CI: 0.2-0.9) and gonorrhoeae (OR: 7.9; 95% CI: 0.1-0.5).

When stratified for sexual preference, MSM and bisexual men were found at four to ten fold increased risk for syphilis, gonorrhoeae and HIV infection (Table III).

Interestingly, subjects with syphilis were those who more likely reported a previous luetic infection (OR: 7.1; CI: 3.9-12.7). A similar observation was also made for new diagnoses of gonorrhoea, urethritis and molluscum, that were strictly associated with infections by the same pathogens in the past (reinfections) (Table IV).

A diagnosis of syphilis was also associated with previous HIV infection, especially in MSM and bisexual men.

On the contrary, genital warts did not seem to occur in patients with a history of syphilis or gonorrhoeae, but they were potentially associated with

TABLE II.—Distribution (N. and %) of the diagnoses of the study population.

STI	Male		Female		Total	
	N.	%	N.	%	N.	%
Syphilis	83	9.0	13	2.8	96	6.9
Gonorrhoea	37	4.0	5	1.1	42	3.0
NG cervicitis and urethritis	120	13.0	99	21.6	219	15.8
Genital herpes	69	7.5	51	11.1	120	8.7
molluscum contagiosum	68	7.4	45	9.8	113	8.2
Genital warts	444	48.0	205	44.7	649	46.9
Hepatitis A	1	0.1	2	0.4	3	0.2
Hepatitis B	10	1.1	5	1.1	15	1.1
Hepatitis C	16	1.7	12	2.6	28	2.0
HIV/AIDS	53	5.7	16	3.5	69	5.0
Other	24	2.6	6	1.3	30	2.2
Total	925	100.0	459	100.0	1384	100.0

TABLE III.—Multivariate logistic regression. Diagnosis associated with sexual orientation (heterosexual vs. homosexual) OR adjusted for age and gender.

STI	OR (IC 95%)	P-value
<i>Syphilis</i>		
Heterosexual	1	
Homo/bisexual	8.62 (5.40-13.74)	0.000
<i>Gonorrhoea</i>		
Heterosexual	1	
Homo/bisexual	4.42 (2.30-8.49)	0.000
<i>HIV/AIDS</i>		
Heterosexual	1	
Homo/bisexual	10.26 (5.55-18.94)	0.000

TABLE IV.—Univariate logistic regression. Patients with re-infection by the same infectious agent (current diagnosis vs. previous) OR adjusted for age and gender.

Previous IST	OR (IC 95%)	P-value
<i>Syphilis</i>		
No	1	
Yes	7.11 (3.96-12.77)	0.000
<i>Gonorrhoea</i>		
No	1	
Yes	4.96 (1.64-15.02)	0.005
<i>NG cervicitis and urethritis</i>		
No	1	
Yes	5.49 (3.07-9.80)	0.000
<i>Genital herpes</i>		
No	1	
Yes	11.57 (5.21-25.65)	0.000
<i>Molluscum contagiosum</i>		
No	1	
Yes	4.46 (1.52-13.06)	0.006
<i>Genital warts</i>		
No	1	
Yes	1.91 (1.35-2.71)	0.000

having had genital warts already (OR: 2; 95% CI: 1.4-2.9).

Discussion

The multicenter revision of 1293 medical records from four STI Clinics revealed a total number of 1384 new infections in year 2011 in Tuscany. To the best of our knowledge, our study represents the first attempt to monitoring STIs and the first available estimate of STIs annual incidence in Central Italy.

It's worth underlining that the results from a study among people who visit STI Clinics should be extrapolated to the wider population with caution. In fact, we are conscious that our results might actually underestimate incident STI cases, since an undeter-

mined part of them could be observed and treated by GPs or private practitioners (*e.g.* gynecologists for the female population); on the other hand STI Clinic attendees are recognized to be a higher risk group, in which Chlamydia infection, gonorrhoeae and syphilis are diagnosed more often (van den Broek IV, unpublished data, 2009). In our opinion and according to many authors^{14, 15} they represent therefore one of the most appropriate sentinel group for monitoring STI trend in a community.

The mean age of the affected population and the composition of our sample closely overlapped Italian data published by the Istituto Superiore di Sanità, regarding the period 1991-2011.⁷ Consistently with what reported, in our study, subjects affected by STIs were mainly young heterosexual men, who did not report to be engaged in stable relationships. Fur-

ther, non-Italian patients and homosexual men also constituted a significant proportion of the sample, thus confirming once more that MSM and migrants should be considered important “core groups” in STI acquisition and transmission. Interestingly, among foreign people, women were more numerous than in the Italian group. This could lead to speculate that foreign females are an extremely vulnerable group, especially those without an adequate access to medical care (*e.g.*, street sex workers), or, on the contrary, that they pay a major attention to their sexual health.

The distribution of STIs was also similar to that reported in the literature,⁷ since condylomas and non-specific urethritis/cervicitis were the most frequent diseases. Herpes genitalis was diagnosed in 8.7% of the sample, but no distinction between primary episode and recurrence was made, therefore we could not draw valuable conclusion about its incidence.

In comparison to the ISS data, molluscum contagiosum seemed to be more frequent (8.2% *vs.* 6.4%).

Limitations of the study

We do not have detailed information about the sexual behavior or sexual partners (*i.e.*, number of partners, type of sexual practice, commercial sex, etc.) of the patients. This is due to the fact that this was a retrospective analysis, and such information is not part of the medical records. Similarly, items concerning condom use were imprecisely worded, because we could only record it as “always” or “never” or “sometimes”. However, we could globally recognize a very poor use of the prophylactic, that was much more alarming in those patients who had already experienced a STI (including HIV infection) and should therefore be aware of risky sexual behaviors.

Previous studies have already reported that substantial numbers of individuals attending the STI clinics continue to practice unsafe sex, despite knowledge of their HIV infection.¹⁶ Moreover, previous papers in the 1990s also showed that HIV-positive patients continued to have new STI diagnoses after HIV diagnosis, and that in 47% of cases where HIV coexisted with newly diagnosed STI, the patients were aware of their HIV status.¹⁷ After two decades, and despite plenty of prevention interventions at an international level, our study still confirms such observations in Tuscany. As mentioned in the results, in fact, in our cohort about one third of STI-affect-

ed subjects had already acquired a STI in the past. Interestingly, a tendency to be reinfected with the same disease emerged for bacterial diseases syphilis and gonorrhea, thus pointing out the existence of disease-specific high risk sexual networks. People belonging to those backgrounds are supposed not to run apart from them after diagnosis and therapy, thus facilitating re-infection and maintaining transmission. These results show that despite tailored prevention measures, more efforts should be made to reach these groups.

Our review could also confirm high rates 84/1293 (6.5%) of concurrent STI infections, including coinfections of chlamydia, gonorrhea, syphilis and HIV, as previously reported.¹⁸ This suggests the need of a complete STI screening in all attendees, even though they refer for symptoms and signs that are diagnostic for one specific STI. In this respect, we also underline the deficient quote of Clinic attendees that agree to be tested for HIV.

Conclusions

In conclusion, results show that STIs in Tuscany involve a mixed young to adult population, composed by both heterosexual and homosexual subjects who practice unprotected sex and do not seem to be conscious of the associated risks, as demonstrated by the high rates of coinfections and reinfections. These findings reinforce the need for greater education and prevention efforts for HIV and other STIs among the Tuscan population.

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APPENDIX 1

STI window for electronic database: incident diagnoses in 2011

Patient Identification Number

Medical Examination Date: dd/mm/yyyy

Name and Surname (Initials)

Age

Gender (male, female, transgender)

Nationality

Place of residence

Marital status (unmarried, married, divorced, widowed, live-in partner)

Schooling (none, primary, secondary, higher, graduate, post-graduate)

Working activity

STI diagnosis in 2011:

- Syphilis
- Gonococcal
- Non-gonococcal urethritis/cervicitis (*Chlamydia trachomatis*, *Mycoplasmas*, *Trichomonas vaginalis*)
- Herpes genitalis (primary)
- *Molluscum contagiosum*
- Hepatitis B
- Hepatitis A
- Hepatitis C
- HIV infection/AIDS

- Others (*Lymphogranuloma venereum*, *Pediculosis pubis*, Scabies, CMV infection)
- Sexual orientation (heterosexual, homosexual, bisexual)
- Injecting drugs use (Yes, No)
- Condom use (never, always, sometimes)
- Stable sexual partner (more than 6 months) (Yes, No)
- Previous STIs (Yes, No)
- If so, specify:
 - syphilis
 - gonococcal
 - non-gonococcal urethritis/cervicitis (*Chlamydia trachomatis*, *Mycoplasmas*, *Trichomonas vaginalis*)
 - Herpes genitalis (primary)
 - Molluscum contagiosum
 - Hepatitis B
 - Hepatitis A
 - Hepatitis C
 - HIV Infection/AIDS
 - Others (*Lymphogranuloma venereum*, *Pediculosis pubis*, scabies, CMV infection)
- Previous HIV testing (Yes, No)
- HIV testing at STI diagnosis in 2011 (Yes, No)

Treatment of mild to moderate acne with a fixed combination of hydroxypinacolone retinoate, retinol glycospheres and papain glycospheres

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Aim. A fixed combination of 0.1% hydroxypinacolone retinoate (synthetic ester of 9-cis-retinoic acid), 1% retinol in glycospheres and 2% papain in glycospheres in aqueous gel has been recently introduced into the Italian market in order to reduce the incidence and severity of irritant contact dermatitis caused by topical retinoids, without compromising their efficacy. Primary objectives of this sponsor-free, pilot, open, multicenter study were to evaluate the efficacy and tolerability of this gel in patients with comedonal-papular, mild to moderate acne of the face.

Methods. Ninety-eight Caucasian patients (28 males and 70 females), with an age ranging from 15 to 40 years, were treated with the gel once daily for 12 weeks. Acne severity and treatment efficacy were evaluated by means of the Global Acne Grading System (GAGS) and lesions count.

Results. Ninety-four patients were considered evaluable. A 41% mean reduction in the GAGS score was observed; a 40.8% mean reduction of total lesions was recorded; 15.3% of patients experienced mild to moderate local side effects (dryness, peeling, erythema, burning). No patients stopped the treatment because of these side effects.

Conclusion. This study, based on a high number of evaluable patients, demonstrates that this fixed combination is an effective and safe option for the treatment of comedonal-papular, mild to moderate acne of the face. A controlled clinical study is necessary to confirm these data.

KEY WORDS: Acne vulgaris - Retinoids - Papain.

The most important mechanism of action of topical retinoids is on the differentiation and proliferation of keratinocytes.^{1, 2} This action facilitates the penetration of other anti-acne drugs: topical retinoids, and in particular tretinoin, isotretinoin

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and adapalene, have been successfully combined ("fixed combinations") with clindamycin, erythromycin and benzoyl peroxide.^{3, 4} Furthermore, the action on differentiation and proliferation of keratinocytes induces the expulsion of mature closed and open comedones and the suppression of microcomedone formation.⁵ Since 2003, topical retinoids are considered of first choice in the treatment of mild to moderate acne, alone or associated with topical antimicrobials and/or oral antibiotics.^{6, 7} The most frequent side effect of topical retinoids is irritant contact dermatitis, also named "retinoid dermatitis" (RD).^{8, 9} RD is characterized clinically by dryness, peeling, erythema, scaling, edema, stinging, burning and itching.^{10, 11} Dryness, peeling, erythema, stinging and burning are the five more frequent side effects, whereas scaling, itching and oedema are rare.^{10, 11} RD is very common, occurring, in our personal clinical experience, in approximately 85% of patients;^{10, 11} the percentage can reach up to 95% in patients treated with tretinoin.^{10, 11} RD usually ap-

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pears after the first applications of the retinoid; very rarely it persists for the entire duration of the treatment.^{10,11} Severity of RD is mainly due to the type of retinoid: tretinoin and tazarotene can be very irritant,¹⁰⁻¹² while retinol and retinaldehyde are not irritant.¹³ RD severity is also concentration-dependent and related to the vehicle used: retinoids in alcoholic gel are more irritant.¹⁰⁻¹² Severity of RD is usually mild to moderate and duration is changeable, from a few days up to 3-4 weeks. However, in our experience, severity of tretinoin-induced RD is moderate to severe in approximately 20% of patients.^{10, 11} Furthermore, always in our experience, 15% of patients stop the treatment with tretinoin because of skin irritation.^{10,11} RD improves after treatment suspension or by application of moisturizers or, in more severe cases, of low- to mid-potency corticosteroids.^{10, 11} Prevention of RD is based on the following items: 1) when possible, to begin the treatment with low concentrations of retinoid; 2) to begin the treatment applying the retinoid every two days; 3) to associate, from the beginning of the treatment, a moisturizer.⁹⁻¹¹ A fixed-combination of 0.1% hydroxypinacolone retinoate, 1% retinol in glycospheres and 2% papain in glycospheres in aqueous gel has been recently introduced into the Italian market with the aim to reduce the incidence and severity of RD, without compromising efficacy. We present the final results of a sponsor-free, pilot, open, multicenter study for the evaluation of the efficacy and tolerability of this gel in the treatment of comedonal-papular, mild to moderate acne of the face.

Materials and methods

Ninety-eight Caucasian patients (28 males [28.6%] and 70 females [71.4%]), with an age ranging from

15 to 40 years (median age: 19.8 years), with comedonal-papular, mild to moderate acne located on the face, were treated with the gel. Mild to moderate acne was defined, on the basis of the Global Acne Grading System (GAGS)¹⁴ score, from 1 to 30. To be included in the study, patients were also required to have 10 to 100 non-inflammatory lesions and 10 to 30 inflammatory lesions. Wash out period was of at least 2 months for topical antiseptics, antibiotics, azelaic acid, salicylic acid, nicotinamide, retinoids and oral antibiotics, and 6 months for oral isotretinoin. The gel was applied once daily, in the evening. The application was preceded by a cleaning. No other topical and/or systemic products or drugs were allowed, except for moisturizers, non-comedogenic make-ups and sunscreens. Abrasive cleansers and chemical peels were not allowed. Treatment duration was 12 weeks. All patients were clinically evaluated every 4 weeks. Acne severity and treatment efficacy were evaluated by means of the GAGS and changes in lesions count. Evaluation of tolerability included assessment of skin irritation (dryness, peeling, scaling, erythema, edema, stinging, burning sensation and itching).

Results

Ninety-four patients (96%) were considered evaluable at the end of the study. Four patients did not complete the trial (Figure 1). The mean GAGS score at baseline was 14.5; 64 patients (65.3%) were considered to have mild acne and 34 patients (34.7%) moderate acne (Figure 2). In the GAGS score assessment of the 94 patients who completed the trial, 78 patients (83%) improved, 15 patients (16%) demonstrated no change, and 1 patient (1%) worsened (Figure 3). The mean GAGS score decreased from

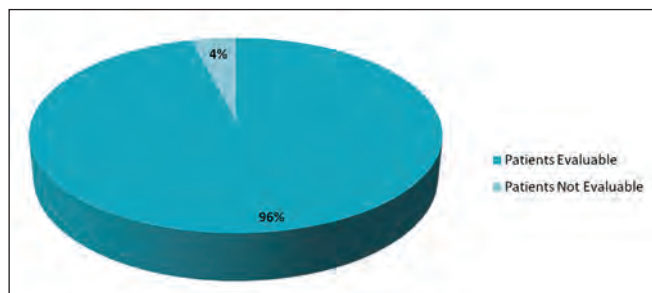


Figure 1.—Number of patients enrolled.

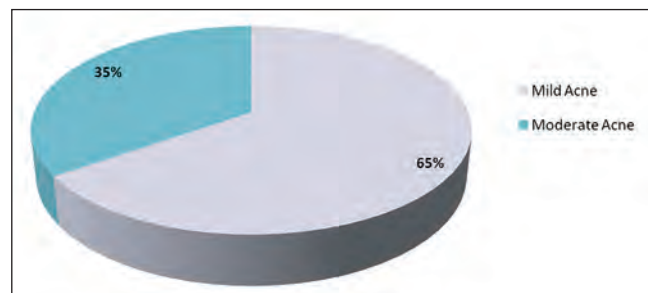


Figure 2.—Clinical varieties of acne.

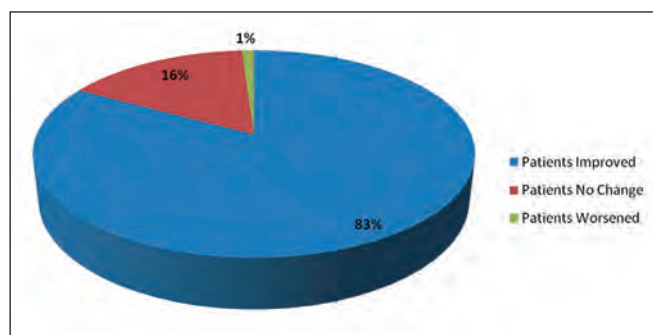


Figure 3.—Results (1): number of patients improved/worsened.

baseline to week 12 from 14.5 to 8.6 (-41%). At baseline, the mean number of non-inflammatory and inflammatory lesions was 42 and 14, respectively. At the end of the study, the mean non-inflammatory lesions count decreased from 42 to 24 (-42.5%); the mean inflammatory lesions count decreased from 14 to 9 (-35.7%); the mean total lesions count decreased from 56 to 33.15 (-40.8%) (Figures 4-6). Fifteen patients (15.3%) reported at least one side effect. All side effects occurred during the first three weeks of treatment, were mild to moderate in severity and transitory. Seven patients (7.4%) reported

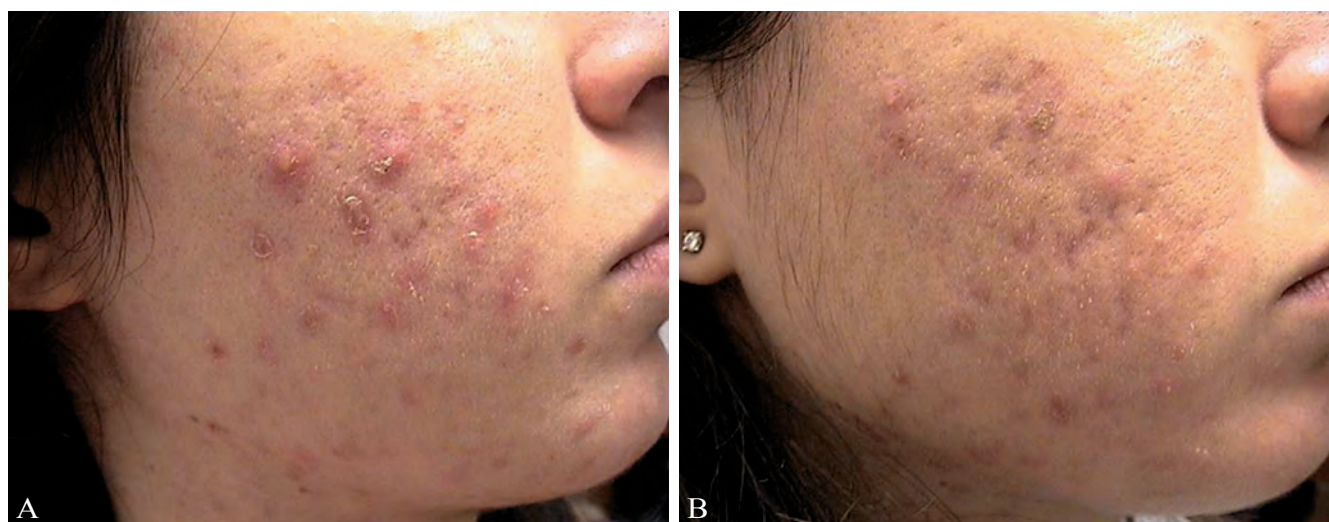


Figure 4.—A) Before the treatment with the gel and B) 12 weeks later.



Figure 5.—A) Before the treatment with the gel and B) 12 weeks later.

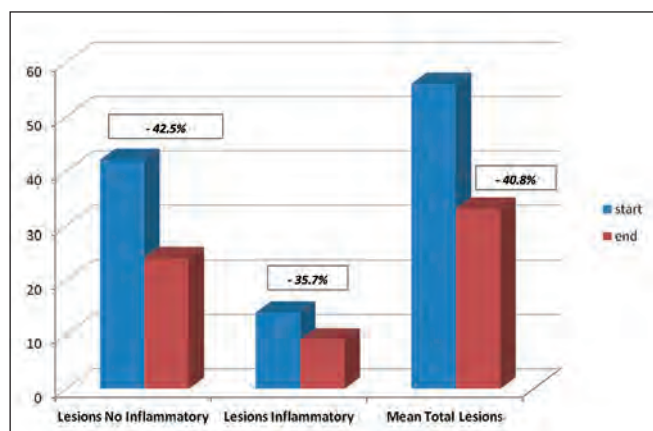


Figure 6.—Results (2): improvement of non inflammatory/inflammatory lesions.

dryness, five (5.3%) peeling, four (4.3%) erythema, three (3.2%) burning sensation and two (2.1%) complained of itching (Figure 7). In all these patients it was unnecessary to stop the treatment.

Discussion

RD due to tretinoin,^{15, 16} tazarotene,¹⁵ isotretinoin^{16, 17} and adapalene⁸ has been extensively studied, both experimentally and clinically. The risk of RD has triggered research for novel and better tolerated topical retinoids: as previously mentioned, tolerability is a critical factor for patient's compliance. Hydroxypinacolone retinoate is a new synthetic ester of 9-cis-retinoic acid. Retinol is one of the best known cosmeceutical forms of vitamin A.¹⁹ Papain is a hydrolase extracted from *Carica papaya* ripe fruit.²⁰ Other ingredients of this gel are Rebuilt Natural Moisturizer Factor (RNMF) that, thanks to its remarkable hygroscopic characteristics, forms a superficial semipermeable film and blocks skin dehydration;²¹ tocopherol, that acts as antioxidant;²² alpha-bisabolol, that possesses anti-inflammatory action;²³ glycerol, that has a moisturizing effect;²⁴ trehalose, a disaccharide with a barrier-like action and *Aloe barbadensis*, that has an antioxidant effect.²⁵ Finally, glycospheres allow a rapid and deep penetration into keratinocytes. Results of our study (open, although sponsor-free, multicenter and based on a high number of evaluable patients) may be summarized as follows: 1) this gel seems to be effective in the treatment of comedonal-papular, mild to mod-

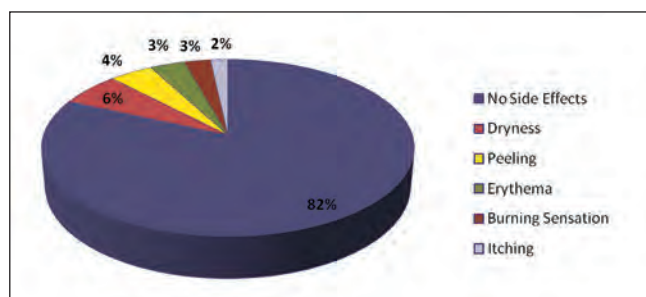


Figure 7.—Side effects.

erate acne of the face, as demonstrated by the results of GAGS and lesions count. However, it is possible that this gel is more effective in non-inflammatory rather than in inflammatory lesions. Furthermore, the improvement is sometimes slow (up to three weeks after the beginning of the treatment) in approximately 15% of patients; 2) tolerability was very good: approximately 15% of patients reported local side effects; however, in all these patients side effects were mild to moderate in severity and transitory; in fact, it was unnecessary to stop the treatment. This very good tolerability allows a high adherence of patients, mainly young patients, to the treatment: this gel markedly improves compliance. A controlled clinical study, in order to confirm these results, is mandatory. An association of this gel with oral antibiotics, in patients with inflammatory acne, should also be considered.²⁶

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Patient perspectives of early detection of melanoma: the experience at the Brescia Melanoma Centre, Italy

A. M. MANGANONI, L. PAVONI, P. CALZAVARA-PINTON

Aim. Skin self-examination is usually recommended for early melanoma diagnosis. Given the current lack of a standardized Skin Self-Examination method, we raised the issue about the suitable approach to explain to patients what can be considered a suspicious lesion. Hereinafter, we report the results of a pilot-study carried out at the Melanoma Centre, University Hospital Spedali Civili Brescia, Italy.

Methods. A consecutive sample of 200 melanoma patients entered into the Melanoma Prevention Project. A detailed survey revealed who had the first suspicion of the melanoma lesion. When melanoma was Self- or Relative-detected, we investigated the signs/symptoms that had alerted patients with reference to the ABCDE rule. The study included also socio-demographic variables, family history of melanoma, skin type, number and type of nevi, and melanoma features.

Results. Eighty-seven melanoma had been Self-Detected and 44 Relative-Detected. Patients report most commonly signs/symptoms such as dark colour (58%) and changing in size (47%). Seventy-nine percent of these patients have less than ten nevi and 92% have small and regular moles.

Conclusion. Sometimes the signs of melanoma seem to be easy to identify. Our patients say that they recognized melanoma on the base of the Colour and the Change in size. Therefore, we propose the short "CC" acronym that could facilitate the melanoma self-diagnosis. The aim is to give a short and effective message that leads patients to have the doubt of a suspicious lesion of melanoma so that they seek medical attention.

KEY WORDS: Self-examination - Melanoma - Moles - Nevus.

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most CM develops with a significant visible preclinical phase when treatment would be likely more of success.^{1, 2} Unfortunately, the basic knowledge and the awareness of sun protection and skin cancer are not optimal yet³ and the international recommendations for the most suitable system of CM screening are disagreeing. However, routine dermatological screenings for skin cancer and Skin Self-Examination (SSE)^{4, 5} are recommended for all individuals beginning at 20 years of age. Previous studies reported that patients most frequently are able to self-detect their own lesions, either incidentally or during a SSE.⁶⁻¹³ For example, the population of CM survivors usually have the second primary melanoma (SPM) thinner than the first CM. This reduction may be the result of a continued medical follow-up, but also of the ability of CM survivors in SSE,⁶ that clearly appear to have higher than average perceptions of their CM risk and seem more likely to SSE.⁷⁻¹⁴

Given the current lack of a standardized SSE method, we raised the issue about the suitable approach to make clearer to patients what can be considered a suspicious lesion. A famous method for the identification of signs and symptoms of CM is the mnemonic "ABCDE" acronym: asymmetrical skin lesion; irregular border; dark or multiple colours; diameter greater than 6 mm; enlarging/evolving/elevation.^{4, 15, 16} In view of the high variance of compre-

Cutaneous melanoma (CM) is the deadliest and fastest growing tumor of the skin, whose mortality rates are not significantly improving, even though

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hension skills in the population, according to the age or level of education, the ABCDE rule may appear ambiguous and therefore an obstacle to SSE.

Hereinafter, we report the results of a pilot-study carried out at the Melanoma Centre, University Hospital Spedali Civili, Brescia, Italy. The aim of this study was to devise a simple and accessible method for SSE that can be done at familiar level for CM recognition in the general population.

Materials and methods

The study subject was drawn from 2500 patients with histologically confirmed CM, including CM *in situ*, followed up by the Melanoma Centre, University Hospital Spedali Civili of Brescia, Italy. A consecutive sample of 200 CM patients entered into the Melanoma Prevention Project between September 1, 2012 and June 1, 2013. All the patients gave an informed consent to be entered into the database. The study protocol was approved by the Research Ethics Committee of the University Hospital Spedali Civili of Brescia, Italy (reference n. 1237).

We gave participants an illustrated brochure explaining the personal risk of developing a CM and the ABCDE rule for SSE. Thereafter, according to the study protocol, a detailed survey was collected by a dermatologist to investigate who had the first perception or suspicion of the CM lesion: the patient by self-skin examination, a relative/friend, the family doctor, or a dermatologist. Among these patients, we gathered patients who fulfilled to the following categories: Self-Detected and Relative-Detected CM. We investigated about perceptions regarding asymmetry, border, colour, diameter, enlarging, evolving, elevation (ABCDE rule) or other changes in the lesion that they had noted before reaching the histological diagnosis of CM. Every patient could report one or more signs and/or symptoms.

The survey included also socio-demographic variables (sex, age, race, education, and state of residence), and family history of CM, assessed via a brief self-report questionnaire.

During the visit, a dermatologist expert in clinical examination of pigmented skin lesions recorded: the patient skin type according to Fitzpatrick (I-IV); the number of nevi classified in pre-established numerical categories (0, <10, 10-50, >50); and the nevi main features: small (<6 mm), big (>6 mm), or atyp-

ical (>6 mm with irregular borders and inhomogeneous colour) naevi.

The CM stage in the American Joint Committee on Cancer (AJCC) staging system 2009¹ and CM histological features were retrieved from the medical charts. CM anatomic site was described according to the following broad areas: head and neck, anterior trunk, abdomen, back, upper extremity, and lower extremity.

Statistical analysis

To assess the differences, we performed the Chi square, Fisher's exact test and Student t-tests as appropriate, and $P < 0.05$ was considered significant. Stata Software (Stata Corp., College Station, TX, USA) was used for statistical analyses. Data are expressed as number of patients, percentage, and mean $\pm$ standard deviation (sd), unless otherwise indicated.

Results

All the 200 patients with CM included in the study were Caucasian (104 male [52%], 96 female [48%]; mean age was 48.81 ± 14.46 years [y] [range 17-82 y]). All patients were resident within 80 km from the hospital where the study had been carrying out.

One hundred and thirty-one patients reported to have noticed CM themselves or by a relative (65.5%), while the remaining were detected by a dermatologist or Primary care Physician (35.5%). The mean age of the 131 Self- Relative-Detected patients was 54 ± 14.25 y; 64 were female (49%) and 67 were male (51%). Eighty-seven CM had been self-detected and 44 relative-detected. Self-detected patients had a lower mean age at CM diagnosis than Relative-Detected patients ($P = 0.0021$). Self-Detected patients were more frequently females (57% vs. 43%) while Relative-Detected patients were males (68% vs. 32%) ($P = 0.0096$). Relatives principally involved in the CM detections were females (84%): 24 were the spouses (54%), 8 daughters (18%), 3 sons (7%), 3 husbands (7%), 2 mothers (5%), 2 sisters (5%), 1 sister in law (2%) and 1 cousin (2%). Fifty percent of patients had less than high school education. Higher education was related to more frequent Self-Detected, but the difference is not statistically significant ($P = 0.28$) (Table I).

TABLE I.—Who first notices melanoma, according to characteristics of the patients and melanoma.

	Total (N.=131)	Self-detected (N.=87)	Relative-detected (N.=44)	P value
Male: N. (%)	67 (51%)	37 (43%)	30 (68%)	0.0096
Female: N. (%)	64 (49%)	50 (57%)	14 (32%)	
Age (years): mean±standard deviation (range)	54±14.25 (21-83)	51.31±13.05 (22-83)	59.31±15.15 (21-82)	0.0021 0.28
Education: N. (%)				
Less than high school	63 (50%)	39 (45%)	26 (59%)	
High school graduate	49 (37%)	35 (40%)	14 (32%)	
College graduate	17 (13%)	13 (15%)	4 (9%)	
Melanoma features:				
Breslow thickness (mm): mean±standard deviation (range)	1.09±1.25 (0-6.2)	1.28±1.42 (0-6.2)	0.73±0.69 (0-2.9)	0.016
Nevus associated melanoma	20 (15%)	12 (14%)	8 (18%)	0.68
Stage (AJCC)				0.25
0	27 (21%)	17 (20%)	10 (23%)	
IA	41 (31%)	22 (25%)	19 (43%)	
IB	28 (22%)	21 (24%)	7 (16%)	
IIA	15 (12%)	10 (11.5%)	5 (11%)	
IIB	11 (8%)	10 (11.5%)	1 (2%)	
III	8 (6%)	6 (7%)	2 (5%)	
IV	1 (1%)	1 (1%)	0 (0%)	
Cutaneous melanoma body location: N. (%)				0.48
Face	2 (1.5%)	1 (1%)	1 (2%)	
Head & neck	4 (3%)	3 (3%)	1 (2%)	
Upper extremities	19 (14.5%)	12 (14%)	7 (16%)	
Lower extremities	49 (37%)	38 (44%)	11 (25%)	
Back	31 (24%)	17 (20%)	14 (32%)	
Anterior trunk	12 (9%)	7 (8%)	5 (11.5%)	
Abdomen	14 (11%)	9 (10%)	5 (11.5%)	
Skin type: N. (%)				0.12
I	3 (2%)	2 (2%)	1 (2%)	
II	93 (71%)	63 (73%)	30 (68%)	
III	28 (22%)	15 (17%)	13 (30%)	
IV	7 (5%)	7 (8%)	0 (0%)	
Family history for melanoma	19 (14.5%)	12 (14%)	7 (16%)	0.95
Nevi count: N. (%)				0.67
0	4 (3%)	2 (2%)	2 (4.5%)	
<10	99 (76%)	64 (74%)	35 (80%)	
>10 and <50	20 (15%)	15 (17%)	5 (11%)	
>50	8 (6%)	6 (7%)	2 (4.5%)	
Major Pattern of nevi				0.31
Small (<6 mm) and regular	120 (92%)	79 (91%)	41 (93%)	
Big (>6 mm) and regular	4 (3%)	4 (4.5%)	0 (0%)	
Atypical	7 (5%)	4 (4.5%)	3 (7%)	

CM features are listed in detail in Table I. Relative-Detected CM were thinner than self-detected (mean thickness 0.73 mm vs. 1.28 mm; $P=0.016$) and correlate with different clinical stage. Self-Detected were more frequently located on the lower limbs (44% vs. 25%) while relative-detected on the back (32% vs. 20%) ($P=0.48$).

The patient skin type according to Fitzpatrick was prevalently II both in Self- and relative-detective groups. Seventy-six percent of self- relative-detected

patients have less than ten nevi ($p=0.67$) and 92% and have small and regular nevi ($P=0.31$) (Table I).

The signs and symptoms of CM most commonly reported by patients were: dark or multiple colour (58%) and change in size (47%). In particular, patients noticed more frequently the change in size, while relatives the dark/multiple colour of the lesion. Ten percent of patients complained of itching and 7% the recent onset of the lesion. None described asymmetry, but 10% of patients reported the irregu-

lar shape of the lesions. Borders, bleeding, amelanotic colour, aspecific evolving, and elevation were reported rarely (<5%). None mentioned the dimension. Ninety-one patients reported only 1 sign/symptom (69%), 30 two (23%), 9 reported 3 (7%) and one patients 4 sign/symptoms (1%).

The most common feature reported by patients diagnosed with thin CM (*in situ* and <1 mm in thickness) was the dark/ multiple colour (P=0.008), while in thickest CM (>1 mm) was the change in size (P≤0.0001). Bleeding was reported only in thickest CM, in particular those with Breslow index greater than 2 mm (P=0.003). Itching was reported in one fifth of very thick CM, however also 8% of thin CM complained it (P=0.14) (Table II).

Discussion

Prevention and public health actions are necessary to reduce the risk of CM. Primary prevention of CM entails decrease of possible risk factors in high-risk

populations by education programs about sun protection, risk factors for skin cancer, and SSE. Secondary prevention of CM is skilled by an early-stage diagnosis and treatment.

Our results agree with previous studies, which have shown that 40-74% of CM is self-detected and relative-detected and that physician-detected CM result to be the minority of cases.^{7, 9, 10} Our data are in agreement with recent literature that reported that partner interventions increase SSE,^{10, 30-34} indeed relative-detected CM were thinner than self-detected. In particular, females have higher shrewdness and therefore give higher contribution in CM detection.^{3, 7, 9, 20, 21} Considering both Self and Relative Detected patients, females have been appeared to be more aware for early CM detection and seem to show more interest in preventive behaviours and are more knowledgeable about the disease.

However, high risk populations should be recognized and evaluated.¹⁰ People with xeroderma pigmentosum, giant congenital nevi,²² immunosuppression, a family history of CM, familial atypi-

TABLE II.—*Influence of the melanoma characteristics on the Self and Relative detection and on the tumour thickness.*

		Total N.=131 (100%)	Self-detected N.=87 (100%)	Relative- detected N.=44 (100%)	P value	<i>In situ</i> N.=27 (100%)	<1 mm N.=50 (100%)	1-2 mm N.=30 (100%)	>2 N.=24 (100%)	P value
A - asymmetry	Y	0 (0%)	0 (0%)	0 (0%)	N/A	0 (0%)	0 (0%)	0 (0%)	0 (0%)	N/A
	N	131 (100%)	87 (100%)	44 (100%)		27 (100%)	50 (100%)	30 (100%)	24 (100%)	
B - borders	Y	3 (2%)	3 (3.5%)	0 (0%)	0.57	0 (0%)	2 (4%)	1 (3%)	0 (0%)	0.57
	N	129 (98%)	84 (97%)	44 (100%)		27 (100%)	48 (96%)	29 (97%)	24 (100%)	
B - bleeding	Y	5 (4%)	5 (5%)	0 (0%)	0.24	0	0 (0%)	1 (3%)	4 (16.5%)	0.003
	N	126 (96%)	82 (95%)	44 (100%)		27 (100%)	50 (100%)	29 (97%)	20 (83.5%)	
C - color: dark or multiple	Y	76 (58%)	42 (48%)	34 (77%)	0.002	15 (55.5%)	37 (74%)	16 (53%)	8 (33%)	0.008
	N	55 (42%)	45 (52%)	10 (23%)		12 (44.5%)	13 (26%)	14 (47%)	16 (67%)	
C - color: amelanotic	Y	2 (1.5%)	2 (2%)	0	0.87	0	1 (2%)	0 (0%)	1 (4%)	0.55
	N	129 (98.5%)	85 (98%)	44 (100%)		27 (100%)	49 (98%)	30 (100%)	23 (96%)	
C - change in size	Y	61 (47%)	49 (56%)	12 (27%)	0.003	8 (29.5%)	12 (24%)	20 (66.5%)	21 (87%)	0.0000001
	N	70 (53%)	38 (44%)	32 (73%)		19 (70.5%)	38 (76%)	10 (33.5%)	3 (13%)	
D - dimension	Y	0	0	0	N/A	0 (0%)	0 (0%)	0 (0%)	0 (0%)	N/A
	N	131 (100%)	87 (100%)	44 (100%)		27 (100%)	50 (100%)	30 (100%)	24 (100%)	
E- evolving	Y	1 (1%)	1 (1%)	0	>0.99	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0.65
	N	130 (99%)	86 (99%)	44 (100%)		27 (100%)	49 (98%)	30 (100%)	24 (100%)	
E- elevation	Y	3 (2%)	3 (3.5%)	0	0.57	0 (0%)	0 (0%)	2 (6.5%)	1 (4%)	0.19
	N	128 (98%)	84 (96.5%)	44 (100%)		27 (100%)	50 (100%)	28 (93.5%)	23 (96%)	
I - itching	Y	12 (9%)	12 (14%)	0	0.01	2 (7.5%)	4 (8%)	1 (3%)	5 (21%)	0.14
	N	119 (91%)	75 (86%)	44 (100%)		25 (92.5%)	46 (92%)	29 (97%)	19 (79%)	
O - onset	Y	9 (7%)	8 (9%)	1 (2%)	0.26	1 (4%)	1 (2%)	4 (13%)	3 (12.5%)	0.14
	N	122 (93%)	79 (91%)	43 (98%)		26 (94%)	49 (98%)	26 (87%)	21 (87.5%)	
S - shape	Y	13 (10%)	7 (8%)	6 (14%)	0.47	4 (15%)	6 (12%)	3 (10%)	0 (0%)	0.3
	N	118 (90%)	80 (92%)	38 (86%)		23 (85%)	44 (88%)	27 (90%)	24 (100%)	

Y: yes; N: no.

cal multiple mole and melanoma (FAMMM) syndrome,²³ unusual-appearing nevi, numerous (>50) nevi, should be educated to be confident in SSE but also be routinely evaluated by a physician.¹⁰ Seventy-nine percent of our self- and relative-detected patients have less than ten nevi and 92% have small and regular nevi. Therefore, we can assume that it is easier to detect a suspicious lesion for patients with few regular moles. On the contrary, patients with multiple moles or atypical nevi are less likely to detect their CM by SSE because it is difficult to recognize a suspicious lesion among multiple benign pigmented lesions showing signs of clinical atypia. For this reason, in this high-risk category of patients an essential role has still to be done by dermatologist through periodic checks. Several studies have demonstrated that dermatologists are better able to diagnose early CM compared with self-detected or relative-detected.²⁴⁻²⁷ The employment of dermoscopy has substantially increased the diagnostic accuracy for CM over clinical examination alone and is extremely useful in those patients with multiple moles.^{27, 29}

The usefulness of the ABCDE rule is still issue of discussion.^{30, 31} Certainly useful for physicians, the traditional dermatologic ABCDE may be of difficult comprehension for patients in recognition of suspicious lesions. Only a few studies examined the effect of ABCDE-based educational interventions on improving people's ability to identify suspicious lesions.³²⁻³⁴ It is clear that change in a lesion is a crucial component in founding an increased clinical suspicion that a pigmented lesion may be a CM.^{12, 15} Although not all changes in moles designate the presence of CM, lesions that have changed warrant dermatological examination. It is important to remind to patients that there are a number of lesions difficult to identify by the ABCDE criteria. For example, nodular CM³⁵ at a curable stage of evolution is typically symmetric in shape, with regular borders and often a single colour; or small CM (<6 mm diameter); or amelanotic CM.³⁶ In addition, sometimes CM lesion may bleed, itch, or ulcerate, but this has been always considered a very late sign.³⁷ Furthermore, many atypical nevi, recurrent melanocytic nevi³⁸ and even seborrheic keratoses³⁹ respond to ABCD criteria.

How to raise awareness of people about early diagnosis? Our results, supported by previous studies,^{16, 17, 40, 41} emphasize the importance of the criteria of dark/multiple colour and the change in size of skin lesion. Even more of the doctor, it is the patient who

is in the position to regularly examine the skin to better perceive changes. In fact, we found that Colour and Change in size of a mole are the criteria that have more alerted patients in the suspicion of atypia.

Conclusions

Sometimes the signs of melanoma seem to be easy to identify. Our patients say that they recognized their CM on the base of the Colour and the Change of the size. Therefore, we propose the short "CC" acronym that could facilitate the CM self-diagnosis. The aim is to give a short and effective message that gets attached in the memory of the patients and that leads patients to have the doubt of suspicious lesion of CM so that they seek medical attention.

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Alitretinoin: a useful agent in the treatment of *hidradenitis suppurativa*, especially in women of child-bearing age

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Aim. Despite a better insight into its pathogenesis, *hidradenitis suppurativa* (HS) remains very frustrating to treat. Acitretin has been described as one of the agents with the highest effective profile. Acitretin however, due to its teratogenicity and prolonged half-life (up to three years) is not an option in young women of fertile age who, unfortunately, are the target of this disease. Alitretinoin has a similar pharmacology action to acitretin, but much shorter half-life (only four weeks), making it a far much more attractive option compared to acitretin for women of child-bearing age. The aim of this paper was to evaluate the use of alitretinoin in treating recalcitrant cases of HS, which have not been responsive to standard treatments.

Methods. Fourteen patients (all female, of child-bearing age), who persistently failed traditional treatments, were treated with alitretinoin 10 mg/day for 24 weeks. The disease trend was evaluated by using both Sartorius and Dermatology Life Quality Index scores at time 0, at week 12 and at week 24.

Results. A significant improvement was recorded in 78.5% of the cases.

Conclusion. Although more studies are necessary, this preliminary study shows that alitretinoin may have a role in the treatment of HS specifically in women of fertile age.

KEY WORDS: Hidradenitis suppurativa - Retinoids - Alitretinoin - Acitretin - Therapeutics.

Prevalence rates for HS of 2% up to 4% have been cited, making this a condition routinely encountered by dermatologists.¹⁻³ HS mostly affects females, with men being a very exiguous proportion.^{4,5}

Its pathogenesis is thought to originate with alteration of the pilosebaceous unit, possibly due to genetic

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factors, leading to occlusion.⁶⁻¹¹ Hormonal influences on gene expression have been suggested which would explain the preponderance of the disease in young, overweight women, with hormonal disturbances.^{4, 12, 13} Following follicular occlusion, inflammation with acute abscesses, fistula formation and scarring ensues.^{7, 10} Recently a reduction in sebaceous tissue global mass in the affected areas, with consequent critical reduction in the homeostatic action exerted by these glands, including antifriction, antibacterial, and anti-inflammatory properties have also been demonstrated, and advocated as a possible co-factor in the initial pathogenesis of the disease.¹⁴ Dysfunctionality of neutrophilic cells, with an exaggerated release of free oxygen radicals has also been found, which can explain the progressive trend typical of the disease.¹⁵ An up-regulation of the innate immune response caused by overexpression of Toll-like receptors 2 demonstrated in macrophages and dendritic cells obtained from HS tissue has also been found as another possible contributory factor to the disease's ability to perpetuate itself and to progress.^{16, 17}

As the disease advances, pain becomes a persistent symptom. The disease has a severe impact on quality of life with depression scores being among the highest within dermatological conditions.^{18, 19}

As yet treatment modalities are not ideal: antibiotics,²⁰⁻²² surgery,²³ carbon dioxide laser,²⁴ antiandrogens,²⁵⁻²⁷ corticosteroids, sulfones, anti-inflammatory

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ries, immunomodulators, metformin,²⁸ dapsone^{29, 30} and biologics³¹⁻³⁵ have all been tried with variable results, but a satisfactory option has not yet been found.

Due to the similarities, in terms of pathogenesis, with acne,^{36, 37} historically a great deal of expectation focused on retinoids, including isotretinoin. Unfortunately, whilst isotretinoin is highly effective in suppressing acne, surprisingly it is almost completely useless when it comes to HS.^{38, 39}

Acitretin has been demonstrated to be significantly more effective than isotretinoin, with a 6-month remission in 75% of the cases after one course.⁴⁰ Considering the very scarce response of the disease to most treatments, a persistent remission in 75% of the patients would be considered a very good result, but this is still very far from being ideal; due to its teratogenicity profile, in fact, women of child-bearing age undergoing treatment with acitretin will have to use contraception for up to 3 years post-treatment, with a significant impact on their capacity to conceive. Given that over three-quarters of those affected with HS are young women, the positive effects of acitretin on the course of the disease are, in fact, in practical terms almost irrelevant for the majority of patients.

Alitretinoin is a first-generation retinoid currently licensed for the treatment of severe chronic hand eczema refractory to potent topical corticosteroids.^{41, 42} Although similar in terms of the mechanism of action, it differs from acitretin in that alitretinoin has a much shorter washout period and women taking it require the use of contraception for only 4 weeks, post-treatment.^{41, 42}

In this study, we investigated the response to alitretinoin in recalcitrant cases of hidradenitis suppurativa, resistant to traditional treatments.

Materials and methods

Over a 4 years period, 14 patients, who had previously been treated with traditional treatments without success including three patients who failed on adalimumab, and one who failed on ustekinumab, were treated with alitretinoin. The patients were all female, all had negative pregnancy tests and normal baseline FBC, renal and liver function tests, glucose and fasting lipid profiles. The off-label use of the medication was extensively explained, importance of pregnancy prevention was stressed and informed consent was obtained. All 14 patients received alitretinoin 10 mg/day for 24 weeks. Based on the presence of side effects, short breaks of up to 3-4 days were allowed. Patients were assessed at time 0, then week 12 and week 24. Assessment was carried out by using Sartorius score⁴³ and Dermatology Life Quality Index (DLQI) (Tables I, II). Data collected was then evaluated for statistical analysis with Bonferroni and student-t tests. In order to stratify patients for statistical analysis, "significant improvement" was defined by a 50% reduction in Sartorius score.

Results

The majority of patients reported the treatment to be beneficial (Figure 1A, B). Six patients (42.8%)

TABLE I.—*Sartorius Score.*

Patient	Age	Sex	Location	Week 0	Week 12	Week 24
1	27	F	Groins, vulva, perianal	32	17	16
2	35	F	Breasts, axillae, groins	28	11	6
3	32	F	Groins, vulva, perianal	26	12	11
4	29	F	Axillae, groins, breasts	23	9	5
5	20	F	Axillae, Groins, Vulva	38	28	22
6	23	F	Groins, Vulva,	29	19	16
7	44	F	Axillae, groins	31	26	19
8	42	F	Breasts, axillae, vulva perianal	51	26	21
9	27	F	Axillae	23	20	21
10	30	F	Axillae, breast, groins	26	23	24
11	31	F	Vulva	16	7	5
12	36	F	Vulva	19	8	10
13	48	F	Axillae	41	40	41
14	31	F	Axillae, breasts	22	15	12

TABLE II.—*Dermatology Quality of Life Index (DQLI) Scores.*

Patient	Age	Sex	Location	Week 0	Week 12	Week 24
1	27	F	Groins, vulva, perianal	21	9	7
2	35	F	Breasts, axillae, groins	19	6	3
3	32	F	Groins, vulva, perianal	22	13	12
4	29	F	Axillae, groins, breasts	17	4	5
5	20	F	Axillae, groins, vulva	19	12	10
6	23	F	Groins, vulva,	15	8	7
7	44	F	Axillae, groins	16	11	8
8	42	F	Breasts, axillae, vulva, perianal	26	15	11
9	27	F	Axillae	13	13	12
10	30	F	Axillae, breast, groins	15	13	15
11	31	F	Vulva	9	4	3
12	36	F	Vulva	11	6	6
13	48	F	Axillae	21	23	24
14	31	F	Axillae, breasts	14	8	6

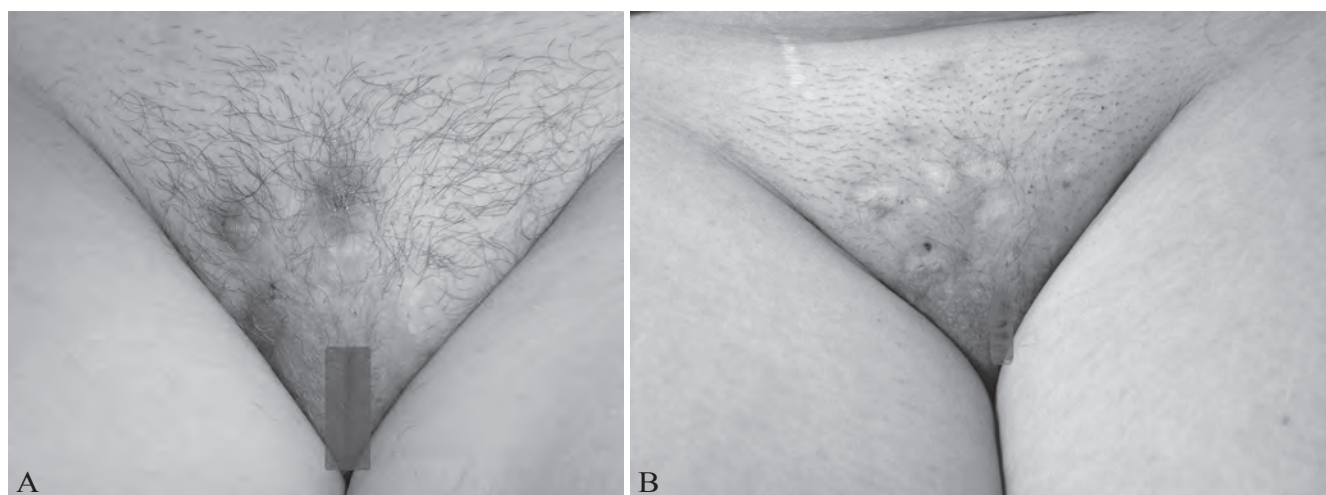


Figure 1.—A, B) Despite the use of a combination of rifampicin, clindamycin, cephalexin and dapsone, this young woman was still significantly affected when the photos were taken (A). Multiple inflamed deep sitting boils were present. After 12 weeks on alitretinoin, a part for pre-existing scars, no acute inflamed spots are seen (B).

significantly improved (Sartorius score reduction 50% or more). Scarring and retraction was still a problem, but any significant inflammation, pus discharge and pain had completely resolved in these patients. Another five patients (35.7%) reported an improvement, although not dramatic (Sartorius score reduction of less than 50%) (Tables III, IV, Figure 2). A similar trend was observed when using the DLQI (Tables V, VI, Figure 3). The improvement was quite long lasting in the majority of the cases (Figure 4A-C), with only 3 patients (21.4%) having suffered a minor rebound of their condition after an average of 4.5 months (19 weeks) from the end of the treatment. More importantly the treatment was very well toler-

ated, with significant headache being the worst symptom reported in 4 patients (28.5%). Mild to moderate dryness of the lips and skin were the most reported side effects in 8 patients (57%). Blood tests were also within the normal range: during this study we only documented a mild increase in cholesterol levels in the majority of the patients, but all other parameters including FBC and renal function were unaffected. Liver function in particular never significantly deteriorated. Cholesterol levels in general returned to complete normality 5-6 months from the end of the treatment. Patients were all quite positive about the treatment, and almost all of them, apart from the three who did not respond, described the treatment as

TABLE III.—Sartorius Score. Student T-test for dependent samples: Marked differences are significant at $P<0.05$. With a $P<0.000062$ the difference induced by Alitretinoin between the beginning and the end of the treatment at week 24 is highly significant.

Variable	Mean	Minimum	Maximum	Standard deviation	Difference	Standard deviation difference	t	P
Time 0	28.9	16	51	9.3270	-	-	-	-
Time 24	16.3	5	41	9.6125	12.5714	8.1118	5.7986	0.000062

TABLE IV.—Sartorius Score. Bonferroni T-test for multiple variables: Marked differences are significant at $P<0.05$. With a $P<0.019$ at 12 weeks, and $P<0.003$ at week 24, the variation induced by Alitretinoin is highly significant.

Variable	Mean	Minimum	Maximum	Standard deviation	Standard Error	Confidence 95%		t	P
						Inferior limit	Superior limit		
Time 0	28.9	16	51	9.32	2.49	23.54	34.31	-	-
Time 12	18.6	7	40	9.33	2.49	13.25	24.03	2.887	0.019
Time 24	16.3	5	41	9.61	2.56	10.80	21.90	3.530	0.003

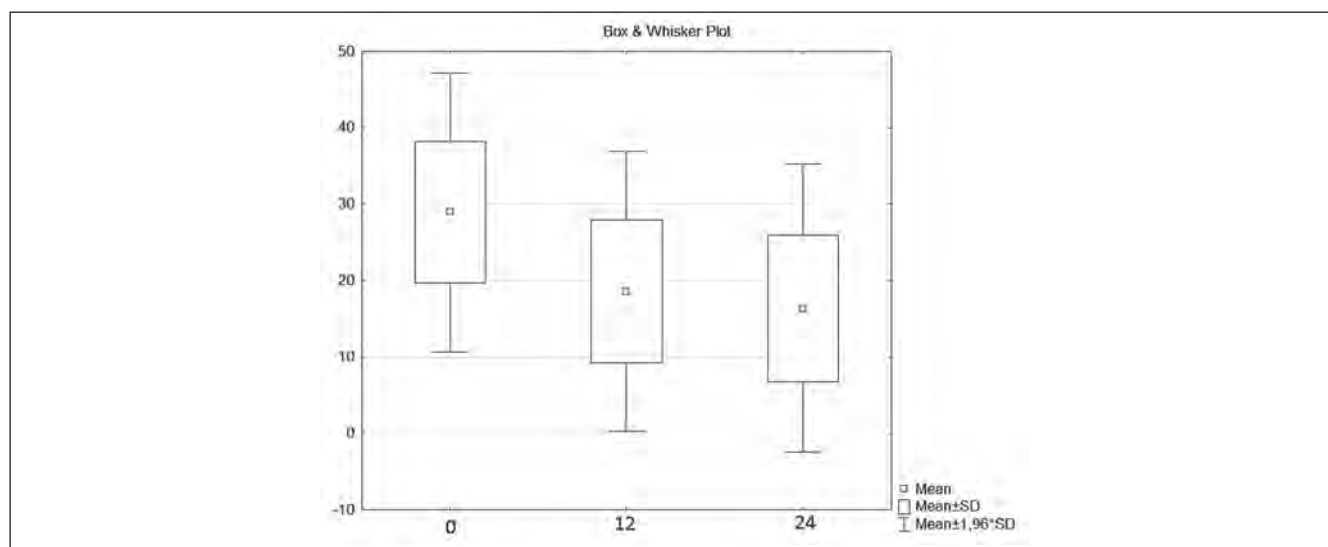


Figure 2.—Sartorius Score trend at time 0, 12 and 24 weeks.

being successful. The most common comment was that the treatment “had dried the lesions from the inside”. Although never proven, retinoids are suspected in some cases to be linked with depression, and HS patients are known to have high depression scores and suicidal ideation. We were rather concerned that alitretinoin, in this cohort of patients, might cause some deterioration, from that point of view but, in fact, the majority were very positive about the treatment and no one had suicidal thoughts or significant deterioration in their moods. The three who showed no improvement, although obviously unhappy about their lack of response to alitretinoin, were quite positive about the fact that they were taking part in the study and strongly encouraged us to persevere with

the study to find a successful treatment for this disease. While one patient said that she did not want to try the treatment again, as she could not see the point, having failed once, the other two patients explained that they would like to try again, should we think that continuing the treatment for an additional 6 months, or increasing the daily dose to 30 mg/day might be beneficial. As such one of these patients is currently undergoing treatment with 30 mg alitretinoin/day with some encouraging results.

Sartorius Score

Although 3 patients (21.4%) did not respond to treatment, six patients (42.8%) significantly im-

proved (drop of Sartorius Score of 50% or more, from an average of 29.3 to 10.6) with 3 of them (21.4%) having almost completely cleared up (drop in Sartorius Score from an average of 22.3 to 5.3) (Figure 1A, B). Another 5 patients (35.7%) had also improved but the condition was still quite active (Sartorius score reduction of less than 50%) although their day to day lives were not disrupted as much as before (Table I). In general Sartorius score dropped by an average of 12.6 points after 24 weeks (from an average of 28.9 to 16.3), which was statistically highly significant (Tables III, IV, Figure 2). Considering that all these patients had previously repeatedly failed on powerful antibiotic combinations, immunosuppressants and isotretinoin, we think that

the results from the alitretinoin, used in our study, are encouraging.

DLQI

DLQI dropped an average of 7.8 points after 24 weeks (from an average of 17.0 to 9.2), which was statistically significant (Tables V, VI, Figure 3). A dramatic drop in DLQI (from an average of 16.5 to 4.5) was seen in 4 patients (28.5%); all were patients who also reported an improvement with significant reduction of their Sartorius Score. DLQI also significantly improved in another 7 patients (50%), with a drop of the DLQI score from an average of 17.5 to 8.5. In a further 3 patients (21.4%) DLQI

TABLE V.—DLQI. Student T-test for dependent samples: Marked differences are significant at $P<0.05$. With a $P<0.00017$ the difference induced by Alitretinoin between the beginning (Time 0) and the end (Time 24) of the treatment is highly significant.

Variable	Mean	Minimum	Maximum	Standard deviation	Difference	Standard deviation difference	t	P
Time 0	17.0	15	26	4.6409	-	-	-	-
Time 24	9.2	3	9	5.5355	7.7857	5.6592	5.1475	0.00017

TABLE VI.—DLQI. Bonferroni T-test: Marked differences are significant at $P<0.05$. With a $P<0.004$ at 12 weeks, and $p<0.001$ at week 24, the difference induced by Alitretinoin is highly significant.

Variable	Mean	Minimum	Maximum	Standard Deviation	Standard Error	Confidence 95%		t	P
						Inferior limit	Superior limit		
Time 0	17.0	9	26	4.64	1.24	14.32	19.67	-	-
Time 12	10.3	4	15	5.09	1.36	7.41	13.29	3.450	0.004
Time 24	9.2	3	15	5.53	1.47	6.01	12.41	4.042	0.001

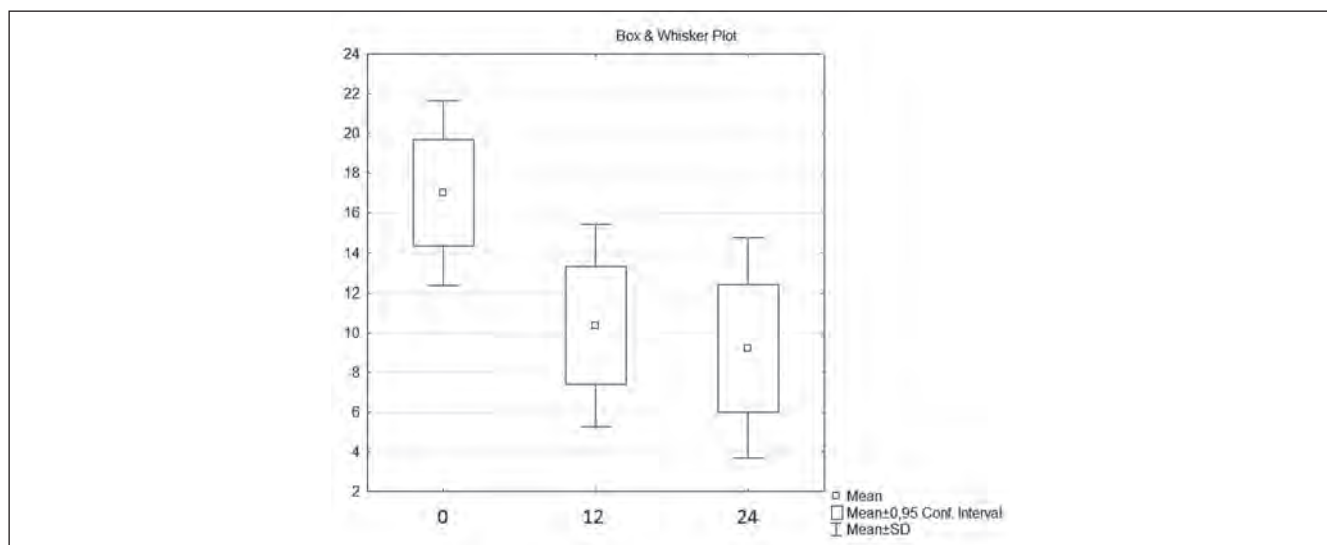


Figure 3.—DLQI trend at time 0, 12, and 24 weeks.

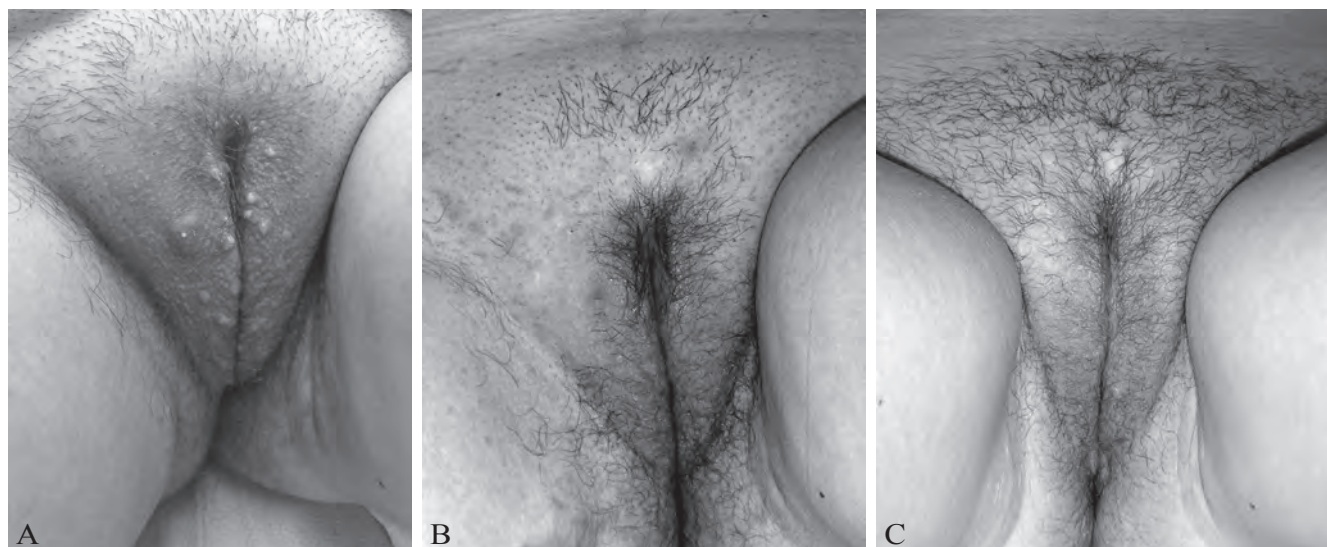


Figure 4.—This young woman was affected with generalised HS, particularly troublesome in her vulva (A). Despite many robust treatments, the condition was quite persistent, with pustules constantly erupting for years (A). Alitretinoin treatment resulted in a complete resolution of the condition (B). After over a year (C), the patient was still remarkably clear.

remained unchanged (Table II). By discussing the outcome of the treatment with patients and their relatives, we suspect that alitretinoin could have been responsible for some mild mood deterioration and a certain degree of irritability in 4 patients (28.5%) and it was independent from the outcome of the treatment, either positive or negative. These transitory mood changes were observed at the end of the treatment, but were described as “mild” and “generic” and mainly by the patients’ partners or other family members. Objectively, however, they could have had a degree of negative impact in the final DLQI evaluation, at week 24. A recent check on these patients however, has not revealed any persistent symptoms, and even the relatives, who had been originally concerned, seem to have forgotten their initial concerns.

Discussion

HS is a frustrating disease to treat. Acitretin remains one of the most effective treatments described in literature⁴⁰ but its impact in routine practice is almost irrelevant: because contraception has to be observed for up to 3 years (thus having a major impact on patients’ lives and family decisions, including the possibility of having children) acitretin cannot be

used in young women of child bearing age who, in fact, represent the target of the disease.

With alitretinoin, however, the recommended timescale is significantly less, given its washout period of only 4 weeks. Used with caution, the impact on a woman’s life is acceptable, and very similar to isotretinoin.^{41, 42}

Alitretinoin (9-*cis* retinoic acid) is a natural analogue of vitamin A which only relatively recently was licensed for the treatment of chronic hand eczema.⁴² As with all the other retinoids, alitretinoin acts by binding specific intranuclear receptors: There are 2 structurally different families of retinoids’ receptors: the first family is the retinoic acid receptors (RAR), subdivided into 3 different subunits (α , β and γ); the second one is the retinoid X receptor (RXR), also containing three distinct subunits (α , β and γ). Whereas the mechanism of action of retinoids in general has not been completely elucidated, it would appear that alitretinoin is the only retinoid capable of acting as a ligand for all the subunits of both the RAR and RXR and, as such, alitretinoin is the only pan agonist of retinoid receptors⁴¹. To its action in inducing cell maturation and differentiation, common to all-retinoids, alitretinoin also adds a marked anti-inflammatory action, most likely minimising the production of molecules with chemokinetic action in the skin, thus blocking the recruitment

of leukocytes. Alitretinoin also seems to exert direct inhibitory action on leukocytes, reducing their proliferation⁴¹. Antigen presenting activity seems also to be significantly reduced, again blocking the cascade of events leading to inflammation.^{41, 42} Inflammation dysregulation is suspected to be one of the factors involved in HS.^{16, 17} Whereas a certain degree of anti-inflammatory action has been described for all the members of the three generations of retinoids, alitretinoin alone is known not to cause reduction in sebaceous gland volume and sebum production,⁴⁴ which instead is one of the main effects of isotretinoin.^{45, 46} If we take into consideration the crucial importance of the sebaceous glands in maintaining skin homeostasis, reported in a recent study,¹⁴ it is arguable that this marked difference on sebum production registered between isotretinoin and alitretinoin treated patients, might explain their difference in terms of effect when treating HS, in particular the scarce response of HS to isotretinoin.

Apart from its short washout period, clinically alitretinoin is very similar to acitretin: its effectiveness in eczema of the hands is well recognized,⁴² but it has been successfully tried also on palmo-plantar pustular psoriasis with good outcome.⁴⁷ Anecdotal evidence of successfully treated cases of *Pityriasis rubra pilaris*^{48, 49} also indicate an analogy of the mechanism of action between alitretinoin and acitretin.

For these reasons we decided to try this medication initially on some cases of recalcitrant HS which had been resistant to all the other traditional treatments. Encouraged by the good response of an initial small cohort of 4 patients,⁵⁰ we extended its use to other young women who failed or were unsuited to other known treatments.

Over the past 4 years we have treated 14 patients. Alitretinoin was administered for 24 weeks, and Sartorius and DLQI scores assessed at time 0, after 12 weeks and finally after 24 weeks.

An improvement was recorded in the majority of the patients. Also, quite importantly, the number of breakouts during the treatment, although not statistically evaluated, was reported to have reduced both in number and intensity by almost all patients. The treatment did not cause any significant side effects and all of the patients were able to complete the treatment. Apart from a transient increase in cholesterol levels, blood tests remained satisfactory in all patients. Six patients, who had previously undergone

treatment with Isotretinoin unsuccessfully, reported a good to excellent response to alitretinoin.

Conclusions

Although small, our case series study provides evidence to support the efficacy of alitretinoin in HS. Because it offers significant reductions in teratogenicity risk compared to acitretin, this would make it the retinoid of choice for this debilitating condition, above all when treating resistant cases in fertile women.

Supplementary studies with a larger cohort of patients are certainly required to provide further evidence in the future, but our preliminary study has shown some encouraging results to support the use of alitretinoin in HS.

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Cutaneous vasculitides and the dermatologist: a fundamental part of clinical practice

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This monograph will focus on the classification, etiology, pathogenesis, diagnosis, and treatment of cutaneous vasculitides (CV).

CV are a major challenge to the clinician, however a simple classification or a nomenclature system (nosology) of CV, functional for daily care, is not available yet. Furthermore, we are still lacking for universally accepted diagnostic criteria for CV with sufficient strength and confidence. Therefore, we will discuss the nomenclature and classifications as well as diagnostic criteria for CV currently available in the Literature. It is well known that consensus-based conferences give the most significant contribution to the formulation of nomenclature system and diagnostic criteria. To this regard, our study group, the SIDeMAST Italian Group of Immunopathology, is actively contributing to the development and validation of diagnostic criteria and classification criteria for cutaneous small vessel vasculitis, by conducting a national prospective observational study on CV.

Given the complexity of the diagnosis of CV, a part of this monograph will focus on a diagnostic cornerstone: histology and direct immunofluorescence. Indeed, few vasculitic syndromes have pathognomonic clinical, radiographic and/or laboratory findings; thus, confident and accurate diagnosis of vasculitis requires histological confirmation. Moreover, direct immunofluorescence of lesional skin might be helpful in some peculiar forms.

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As far as the etiology is concerned, CV can be primary (idiopathic) or secondary to infections, drugs, malignancies or systemic diseases. In our monograph, we will address some of the most relevant CV including: vasculitis induced by infectious agents, drug-induced vasculitis, vasculitis associated with systemic disease, and ANCA-associated vasculitis.

Infections are considered the most common cause of secondary vasculitis. Infectious agents can cause vasculitis by two main mechanisms: directly injury of vessel walls and indirectly by triggering a cross-self reaction of the immune system.

Thirty percent of CV are secondary to drug administration. Several drugs can induce CV, including some medications commonly used in dermatology, such as minocycline and anti-TNF alpha agents.

Up to 10% of patients with connective tissue disease (CTD) present CV. In such cases, the vasculitic process can be primary, identifying a specific idiopathic vasculitis coexisting with the autoimmune disease, or secondary to the underlying pathological process, not fulfilling any definition of primary vasculitis.

Vasculitis can also be a rare cutaneous manifestation of other types of autoimmune diseases, such as inflammatory bowel diseases.

ANCA-associated vasculitides such as granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis commonly present skin involvement, which may also be their presenting sign; therefore, the role of dermatologist is crucial in the early diagnosis of these forms.

We hope to clarify through our monograph some

of most complex aspects of CV and to provide useful tools to deal with cutaneous vasculitides in the daily clinical practice accordingly with other medical specialties (*e.g.* rheumatologists, immunologists) highlighting the importance of dermatological relevance on diagnosis and management of these patients.

A project by the SIDeMaST Immunopathology Group on cutaneous vasculitis

M. PAPINI ¹, P. QUAGLINO ², M. LA PLACA ³, A. V. MARZANO ⁴

Vasculitides are a challenge to the clinician, in terms of both diagnosis and therapy. Multiple classification systems have been implemented and the numerous classification schemes reflect the complexity of establishing a simple classification that could be functional for daily care. Although vasculitis classification has become increasingly elaborated, some areas remain ill defined. Some forms of vasculitis are still difficult to assign to a specific disease entity. Generally accepted operational criteria are available for many vasculitides, but for some entities there are no effective criteria. Moreover, diagnostic criteria for vasculitis with sufficient strength and/or confidence that can be universally accepted are not yet available. The need for diagnostic criteria validated and agreed upon is particularly relevant in the context of cutaneous vasculitis. The project of the SIDeMaST Italian Group of Immunopathology on cutaneous vasculitis is a national prospective observational study designed to develop and validate diagnostic criteria and to improve and validate classification criteria for cutaneous small vessel vasculitis also known as leukocytoclastic vasculitis (CLV). Primary objective of the study will also be that of developing the CUTaneous VASculitis Severity Index (CUVASI). Secondary objectives of the project will be: 1) definition of the etiological agents that are most frequently associated with CLV; 2) search for possible correlations between causative agent and peculiar clinical and/or histopathological aspects; 3) evaluation of immunofluorescence pattern observed in this specific group of primitive cutaneous vasculitis in order to characterize the diagnostic sensitivity and specificity of this technique; 4) identification of a set of clinical investigations and laboratory tests to be performed for a correct CLV assessment. Actually 15 Italian dermatological clinics are contributing to the project and anticipated recruiting >100 patients with CLV. A pilot retrospective study to assess the feasibility of the project is going to be launched and if its results are positive then the pro-

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spective study will be started and it promises to be a unique opportunity to evaluate a large database on CLV in Italian population.

KEY WORDS: Vasculitis, leukocytoclastic, cutaneous - Diagnosis - Severity of illness index.

The term "vasculitis" indicates a group of conditions defined by the presence of inflammation of blood vessel walls and of its consequences, including progressive lumen alteration, stenosis, occlusion, and necrosis, or even aneurysmal dilation. Vasculitides can have many etiologies; some are known, such as infectious invasion of pathogens in the vessel walls, whereas others are due to several immune-mediated mechanisms that are still to be clearly determined. The latter, also known as *primary vasculitides*, are

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classified according to the size of the vessels that are primarily involved, into small-, medium-, and large-vessel vasculitides,¹ whereas those forms for which an etiology is proved or strongly suspected, are called *secondary vasculitides*. Systemic vasculitides involve multiple territories or organs; less frequently the inflammation is restricted to a single organ, where the lesions may be focal or diffuse.²

Vasculitides are a challenge to the clinician, in terms of both diagnosis and therapy. Multiple classification systems have been implemented over the last half century³⁻⁹ and the numerous classification schemes reflect the complexity of establishing a simple classification that could be functional for daily care. Because of heterogeneous nature of vasculitides and the limited knowledge of their causes, identification of natural subgroups is difficult. Furthermore, improved diagnostic techniques and new clinical and immunopathological knowledge led to re-define some forms, thus prompting the need to review outdated classifications and adding further complexity in this field. The publication of the revised 2012 Chapel Hill Consensus Conference (CHCC) for the nomenclature of vasculitis¹ provides an updated view on these entities naming and definitions. The new nomenclature also offers a detailed subcategorization scheme including elements for the classification of vasculitides.

Although vasculitis classification has become increasingly elaborated, some areas remain ill defined.¹⁰ Some forms of vasculitis are still difficult to assign to a specific disease entity. Furthermore, the vessel-size-based nature of vasculitis classification implies that vessel inflammation must be manifest in each vasculitis case. This situation may lead to considering that classification of some cases should be confined to those cases with histologically or clinically obvious vasculitis features and should no longer include cases with incomplete features. Another crucial question is how the current classification schemes can be transposed into clinical practice to guide diagnostic decisions at the bedside. Generally accepted operational criteria are available for the many vasculitides, but for some entities there are no effective criteria. But even more, diagnostic criteria for vasculitis with sufficient strength and/or confidence that can be universally accepted are not available yet.

The need for diagnostic criteria validated and agreed upon is particularly relevant in the context of cutane-

ous vasculitis. The Kawakami algorithm¹¹ to diagnose primary cutaneous vasculitis is still an important tool in clinical practice, but with the new knowledge on the pathophysiology of vasculitis and newer tests in clinical use, it seems to be the right time to revise classification and diagnostic criteria for skin vasculitis.

The SIDEmaST Italian Group of Immunopathology (GIIP) comprises researchers from the Universities of Bologna, Florence, Genoa, Messina, Milan, Padua, Pavia, Rome, Terni, Turin, and Verona, which conducts clinical and experimental research on autoimmune and inflammatory skin diseases. During over 15 years of its activity, the Group published numerous studies regarding clinical aspects, histopathological and immunopathological features, and diagnostic and therapeutic guidelines of herpetiform dermatitis, subacute cutaneous lupus erythematosus, Sjogren syndrome, scleroderma, and several other autoimmune disorders. The GIIP's project on cutaneous vasculitis is a national prospective observational study designed to develop and validate diagnostic criteria and to improve and validate classification criteria for cutaneous small vessel vasculitis also known as leukocytoclastic vasculitis (CLV).¹² Primary objective of the study will also be that of developing the CUTaneous VASculitis Severity Index (CUVASI). This clinical score should allow the evaluation and staging of patients with cutaneous leukocytoclastic vasculitis. CUVASI should also help identify groups of patients with different clinical course as for resistance to treatment, extracutaneous involvement, and special clinical subset.

Secondary objectives of the project will be:

- definition of the etiological agents that are most frequently associated with CLV;
- search for possible correlations between causative agent and peculiar clinical and/or histopathological aspects;
- evaluation of immunofluorescence pattern observed in this specific group of primitive cutaneous vasculitis in order to characterize the diagnostic sensitivity and specificity of this technique;
- identification of a set of clinical investigations and laboratory tests to be performed for a correct CLV assessment.

Patients included in the study will have a CLV diagnosed according to clinical and histopathological aspects. Having started treatment with corticosteroids or other immunosuppressive systemic agents will be considered as an exclusion criteria.

For all patients data from detailed medical history, physical examination, laboratory testing, imaging testing, results of standard biopsy and direct immunofluorescence, treatment, clinical evolution, and quality of life index (DLQI) will be collected.

The following clinical aspects will be evaluated in detail and documented with digital photography:

- anatomical areas involved and percentage of involvement in each area;
- lesion types, *i.e.* purpuric, papules, nodules, wheals, vesicles, ulcers;
- number of lesions present in each area (<10 – 10-50- >50);
- maximum lesion diameter present on each anatomical area;
- subjective symptoms such as itching and pain, quantified by VAS.

These clinical parameters will be used to generate CUVASI according to a methodology similar to that used in psoriatic patients for the calculation of the PASI score. Presence, type and severity of extra cutaneous lesions will be also evaluated. Further assessment will concern then the ascertained, probable or possible aetiology, response to treatment, clinical course and follow-up up to 12 months.

The putative relationships between clinical aspects and laboratory data will then be explored in a multivariate analysis to identify potential novel classification and diagnostic criteria.

Actually 15 Italian dermatological clinics are contributing to the project and anticipated recruiting >100 patients with CLV. A pilot retrospective study to assess the feasibility of the project is going to be

launched and if its results are positive then the prospective study will be started and it promises to be a unique opportunity to evaluate a large database on CLV in Italian population.

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Classification and clinical diagnosis of cutaneous vasculitides

P. FABBRI, D. BONCIANI, E. ANTIGA, M. CAPRONI

The definition, diagnostic criteria and classification of systemic vasculitides, of which cutaneous vasculitides (CV) are a part, have long been discussed by the medical scientific world. The most significant contribution is due to the consensus-based criteria specifically derived by the combination of judgments from groups of experts, after accurate literature reviews and developed using consensus techniques. First of them came from the American College of Rheumatology (ACR) in 1990. In 1994 the Chapel Hill International Consensus Conference (CHCC) produced the Consensus-based Criteria essentially providing proper nomenclature for systemic vasculitis, which has been modified in 2012 by the CHCC2012. Moreover, in 2006 European League against Rheumatism and Pediatric Rheumatology European Society produced consensus criteria for the classification of childhood vasculitis. In CHCC2012 CV, affecting small vessels with a predominant skin involvement, have been included in both small vessel vasculitis and single organ vasculitis. The general characteristics of so-called CV have been described (epidemiology, clinical features, histopathology and etiopathogenesis) and, finally, the major characteristics of each clinical type of CV as well as their diagnostic criteria currently available in the literature have been reported.

KEY WORDS: Vasculitis - Purpura - Classification - Diagnosis.

The currently accepted definition of vasculitis is that proposed by Fauci in 1978, highlighting the importance of vessel wall damage, defined as inflammation directed at vessels which involves or destroys the vessel wall leading to hemorrhagic and/or ischemic events.¹ Otherwise the classification and definition of single form of vasculitis is still debated.

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Moreover the term of cutaneous vasculitides (CV), used exclusively by dermatologist, is not totally proper. CV indicates cases where skin involvement is predominant or, rarely, exclusive; in fact a systemic involvement can be found in a high percentage of cases (*e.g.* involvement of joint, kidney and gastrointestinal tract).²⁻⁶

In this review the classification criteria and the definition of systemic vasculitides (including CV), proposed by various groups of expert, have been explored; then the general characteristics of CV (epidemiology, clinical features, histopathology, etiopathogenesis) have been described and, finally, the major characteristics of each clinical type of CV as well as their diagnostic criteria currently available in the literature have been reported.

Togheter with the small vessel CV, cutaneous polyarteritis nodosa (cPAN), which nosographic autonomy is still under discussion, has been included in the revision. Instead, vasculitides involving both small-size and medium-sized vessels and characterized by the presence of anti-neutrophils cytoplasm antibody (ANCA) as granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) were not included. These forms are not exclusively dermatological skills, despite the cutaneous involvement is frequent.

Classification of vasculitis

Many single authors, through accurate reviews of the literature, tried to classify vasculitis.^{1, 7-10} Moreover the most significant contribution is due to the consensus-based criteria specifically derived by the combination of opinions from a group of experts, after accurate literature reviews and developed using consensus techniques.

First of them came from the American College of Rheumatology (ACR) in 1990.¹¹ ACR consensus-based criteria were implemented with a formal sta-

tistical validation in order to provide accuracy measures (i.e. sensitivity, specificity, positive or negative predictive value). Seven type of systemic vasculitis were proposed (Table I). CV were included in "hypersensitivity vasculitides and IgA vasculitides".

These criteria were not made using as diagnostic tools, but they had a strong impact for clinical practice. The ACR criteria were widely used and accepted and might be considered fundamental for all subsequent developments. However they presented many limitations: 1) they did not include microscopic polyangiitis (MPA) and other primary vasculitides including cryoglobulinemia, central nervous system vasculitis, Cogan's syndrome etc; 2) there was a considerable heterogeneity within clinical varieties; 3) they did not include information about immunopathology, biochemical and radiological investigations; 4) the positive predictive value for diagnosis of vasculitis was low (12-29%).¹²

In 1994, the Chapel Hill International Consensus Conference (CHCC) produced the consensus-based

TABLE I.—*The ACR 1990 Criteria for the classification of vasculitides.*

1. Polyarteritis nodosa
2. Churg-Strauss Syndrome
3. Wegener's granulomatosis
4. Hypersensitivity vasculitis
5. Henoch-Schonlein purpura
6. Giant cell (temporal) arteritis
7. Takayasu arteritis

TABLE II.—*Names for vasculitides adopted by 1994 International Chapel Hill Consensus Conference on the nomenclature of vasculitides.*

<i>Large vessel vasculitis</i>	
Giant cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. Often involves the temporal artery. Usually occurs in patients older than 50 and often is associated with polymyalgia rheumatica.
Takayasu arteritis	Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 50.
<i>Medium sized vessel vasculitis</i>	
Polyarteritis nodosa	Necrotizing inflammation of medium sized, and small arteries without glomerulonephritis or vasculitis in arterioles, capillaries or venules.
Kawasaki disease	Arteritis involving large, medium sized and small arteries, and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children.
<i>Small vessel vasculitis</i>	
Wegener's granulomatosis	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium sized vessels (that is, capillaries, venules, arterioles and arteries). Necrotizing glomerulonephritis is common.
Churg-Strauss Syndrome	Eosinophil rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium vessels, and associated with asthma and eosinophilia.
Microscopic polyangiitis	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (that is, capillaries, venules or arterioles). Necrotizing arteritis involving small and medium sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.
Henoch-Schönlein purpura	Vasculitis with IgA dominant immune deposits, affecting small vessels (that is, capillaries, venules or arterioles). Typically involves skin, gut, and glomeruli and is associated with arthralgia or arthritis.
Essential cryoglobulinaemic vasculitis	Vasculitis, with cryoglobulin immune deposits, affecting small vessels (that is, capillaries, venules or arterioles), and associated with cryoglobulin in serum. Skin and glomeruli are often involved.
Cutaneous leucocytoclastic angiitis	Isolated cutaneous leucocytoclastic angiitis without systemic vasculitis or glomerulonephritis.

criteria, called CHCC1994, essentially providing proper nomenclature for systemic vasculitis (Table II).¹³ These were a set of definitions, rather than classification or diagnostic criteria, but they have been often mistakenly used as such.

Ten vasculitis types were defined using clinical and histological criteria, and these were grouped accordingly to vessel size. For the first time, CHCC included ANCA-testing in their definitions; however, ANCA was only used as distinguish feature of some specific type versus other forms of vasculitis, without clarifying the specific role of these antibodies in terms of etiology, pathogenesis and disease prognosis.

In 2006, European League against Rheumatism (EULAR) and Pediatric Rheumatology European Society (PRES) produced consensus criteria for the classification of childhood vasculitis (Table III).¹⁴ These criteria have been important to underline that there are forms of vasculitis exclusively of children, such as Kawasaki disease, instead the giant cell arteritis (GCA) is exclusively of adults and moreover some forms present different clinical features in children compared to adults, such as panarteritis nodosa (PAN) and granulomatosis with polyangiitis (GPA). These criteria have been validated using retrospective and prospective web-based database in a total of 1398 children first diagnosed before age of 18 years (sensitivity 89.6-100% and specificity 87-99%).^{15, 16}

Despite this classification has been widely accepted,

it has an important limitation: it does not distinguish vasculitis from mimicking conditions. In this classification, granulomatous types (GPA, EGPA), non granulomatous type (MPA, IgA vasculitis), isolated CV and hypocomplementemic urticarial vasculitis (HUV) were included in the group of small vessel vasculitis. cPAN was considered in the group of medium vessel vasculitis and accepted as autonomous nosographic entity.

In 2012, a new international CHCC, called CHCC2012, modified the CHCC1994, nomenclature and definitions.¹⁷ These updated definitions were utilized to improve the understanding of the features of each subtype (Table IV).

TABLE IV.—Names for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides.

Large vessel vasculitis (LVV)
Takayasu arteritis (TAK)
Giant cell arteritis (GCA)
Medium vessel vasculitis (MVV)
Polyarteritis nodosa (PAN)
Kawasaki disease (KD)
Small vessel vasculitis (SVV)
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)
– Microscopic polyangiitis (MPA)
– Granulomatosis with polyangiitis (Wegener's) (GPA)
– Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
Immune complex SVV
– Anti-glomerular basement membrane (anti-GBM) disease
– Cryoglobulinemic vasculitis (CV)
– IgA vasculitis (Henoch-Schonlein Syndrome) (IgAV)
– hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)
Variable vessel vasculitis
Behcet's disease (BD)
Cogan's syndrome (CS)
Single-organ vasculitis (SOV)
Cutaneous leukocytoclastic angiitis
Cutaneous arteritis
Primary central nervous system vasculitis
Isolated aortitis
Others
Vasculitis associated with systemic disease
Lupus vasculitis
Rheumatoid vasculitis
Sarcoid vasculitis
Others
Vasculitis associated with probable etiology
Hepatitis C virus-associated cryoglobulinemic vasculitis
Hepatitis B virus-associated vasculitis
Syphilis-associated aortitis
Drug-associated immune complex vasculitis
Drug-associated ANCA-associated vasculitis
Cancer-associated vasculitis
Others

TABLE III.—EULAR/PRES classification of childhood vasculitis.

Vessel size	Vasculitis subtypes
Large	TAK
Medium	Childhood PAN Cutaneous Polyarteritis Kawasaki disease
Small	Granulomatous – GPA – EGPA Non-granulomatous – MPA – IgA vasculitis – Isolated cutaneous leukocytoclastic vasculitis – Hypocomplementaemic urticarial vasculitis
Other	Behcet's disease Secondary vasculitis Vasculitis associated with connective tissue diseases Isolated vasculitis of the central nervous system Cogan syndrome Unclassified

TAK: Takayasu arteritis; PAN: polyarteritis nodosa; GPA: granulomatosis with polyangiitis (Wegener's); EGPA: eosinophilic granulomatosis with polyangiitis (Churg-Strauss); MPA: microscopic polyangiitis.

Despite the CHCC2012 re-emphasized that the definitions of different form of vasculitides were not diagnostic criteria, in the following years frequently the CHCC2012 nomenclature has also been considered as a classification.

The major interests of this update were: 1) to remove definitively some traditional eponymous terms (*e.g.* Schonlein-Henoch purpura, Churg-Strauss Syndrome, Wegener granulomatosis); 2) to divide into 2 subtypes the group of predominant small vessel vasculitides (SVV): those with paucity of vessel wall immunoglobulin deposits (ANCA-associated vasculitis) and those with predominant vessel-wall immunoglobulin deposits (immune complex [IC] SVV). This last one included types which did not involve the skin (*i.e.* antiglomerular basement membrane disease) and many types with predominant skin involvement (*i.e.* cryoglobulinemia, IgA vasculitis, HUV).

Moreover in CHCC2012 the new group of variable vessel vasculitis (*i.e.* “vasculitis with no predominant type of vessel involved, that can affect any type and size of vessels”), including Behcet’s disease and Cogan’s Syndrome, was identified.

Finally, the distinction between primary and secondary forms was included, introducing for the first time etiologic criteria, with the term “primary” standing for “non infectious vasculitides not caused by direct vessel wall invasion by pathogens”, while “secondary” for vasculitides “caused by direct invasion of vessels wall and subsequent proliferation of pathogens with final inflammation”.

CV were included within 2 subsets: small vessels vasculitides (SVV) and single organ vasculitis (SOV). However, their distinction seems unclear, since SVV are defined as “vasculitides predominantly affecting small vessels, defined as small intra-parenchymal arteries, arterioles, capillaries and venules, despite medium arteries and veins may be affected”, while SOV are defined as “vasculitides in arteries or veins of any size in a single organ that have no features indicating they are a limited expression of a systemic vasculitis”. However, not all the known variants of CV are included either in SVV or SOV.

Among them, leukocytoclastic cutaneous angitis (LCA), a common form of SOV type, was not included in CHCC2012. LCA is described as a vasculitis with prevalent, or exclusive, skin involvement, clinically characterized by purpura, histologically

by leukocytoclastic vasculitis and immunologically by perivascular Ig (IgM, IgG, but not IgA) and complement deposits. Finally, some skin-restricted SVV, erythema elevatum diutinum (EED) and acute hemorrhagic edema of infancy (AHEI) were not included in the CHCC2012 classification.

Despite these attempts, collaborative efforts are still needed to get a shared classification and valid diagnostic criteria, considering recent improved understandings of etiology and pathogenesis, serological tests, newer biomarkers and improved imaging. A multicenter international collaboration is actually in progress, aiming to develop a single classification and diagnostic criteria using data-driven methods.

A total of 75 international centers are aiming to recruit 2000 patients with vasculitis and 1500 with vasculitic mimics. To date over 1600 patients have been recruited; clinical, serological, pathological and radiological features of each patient will be used for a multivariate analysis able to distinguish vasculitis from similar conditions and also among different subtypes.^{12, 18}

General characteristics of so-called CV

Despite difficulties on the definition and classification of the so-called CV, Watts *et al.*¹⁹ reported in adult an estimated overall annual incidence of biopsy-proven CV of 38.6 per million in Norwich. In Spain the reported annual incidence in adults was 55.2 per million.²⁰ The sex prevalence seems controversial in the literature; in fact, while in Malaysia and Kuwait both sex were affected equally,^{2, 3} in UK and Singapore female outnumbered male in a ratio of 2:1,^{4, 19} and in Spain and Australia female were more involved.^{5, 20} Among the different varieties, IgA vasculitis (Schonlein-Henoch) was the most common with a variable incidence between 8.8%³ and 15%.

CV affects all ages. In a review on 303 patients with CV 172 were adults and 131 children (<20-year old). The 10.7% of children had hypersensitivity vasculitis and 88.5% IgA vasculitis.²¹

Cutaneous lesions, observed in CV, are correlated with vessel size (capillaries, postcapillary venules and non muscular arterioles with diameter of <50 µm). More frequent lesions are: maculo-papular rash and palpable purpura (lesions do not disappear when applied pressure on the skin). Other common

skin lesions are urticarial, non-palpable macules and patches, nodules, vesicles, bullous lesions and rarely splinter hemorrhages and ulcerations.²² A combination of different types of lesions is common.²³

Skin lesions are more frequently localized on the legs and buttocks, due to the hydrostatic pressure plus micro trauma.²⁻⁵ They are usually bilateral and symmetrical, preceded or accompanied by systemic symptoms (*i.e.* fever, arthralgia, malaise, gastrointestinal symptoms).

Histopathological features of CV, in biopsies taken from early lesions (24-48 h after appearance), consist of perivascular infiltrate of neutrophils, nuclear dust and vessel wall fibrinoid degeneration with endothelial edema.²⁴ Rarely, eosinophils can be detected in the infiltrate; instead, erythrocytes are very common in the interstice. Lately, neutrophils are replaced by lympho-monocytes, that exceptionally can be the exclusive infiltrating cells.²⁵⁻²⁷

The etiology is not identified in 50% cases (idiopathic CV), while 15-30% of CV are associated with a connective tissue disease.^{2, 3, 20} Infections (Gram positive and negative bacteria) have been implicated in the development of CV with a variable frequency between 14%²⁸ and 25.8%.^{2, 5}

Drugs are implicated in 28.2% of cases reported in Malaysia,² 17% in Australia and Kuwait,^{3, 5} 23% in Spain.²⁰ Jessop and Hodge et al reported 8.7% and 11.1% frequency of drug-induced CV respectively.^{29, 30} Antibiotics and non-steroidal anti-inflammatory drugs are commonly involved. Cancer association with CV is uncommon, with a frequency between 1.7%³¹ and 8%.³² Hematological disorders are the most common neoplasms associated with CV.

Many immunologic pathomechanisms are involved in the development of the cutaneous lesions of CV.

In the majority of patients with CV the cutaneous lesions are caused by deposit in vessel walls of IC, which are formed by the complement activation of the classic cascade with the release of anaphylotoxins (C3a, C5a) and vasoactive factors, as well as the activation of neutrophils and mastcells.^{33, 34}

Rarely, CD4+ T lymphocytes (γ/δ receptor) could induce the cutaneous lesions through the release of cytokines and chemokines.³⁵ Finally, cutaneous lesions may be induced by anti-C1q antibodies (as in UV),³⁶ antiphospholipids, myeloperoxidase (MPO)- and protein 3 (PR3)-ANCA.³⁷

Proposed classification and diagnostic criteria of some specific types of CV

Although some CV have been already defined as unique nosographic entities, defined by clinical features, as well as histopathological and immunopathological findings from the literature, globally accepted diagnostic criteria are still lacking.

The main features of such entities, are reported below.

IgA vasculitis (Henoch-Schoenlein purpura)

In CHCC2012, IgA vasculitis is defined as vasculitis with IgA-1 dominant immune deposits affecting small vessels (predominantly capillaries, venules or arterioles). It often involves skin and gastrointestinal tract and frequently causes arthritis; glomerulonephritis indistinguishable from IgA nephropathy may occur.¹⁷

The cutaneous immunopathologic findings, namely superficial perivascular IgA deposits often associated with alternative complement pathway component and fibrin-like material, are considered paramount to make the diagnosis of IgA vasculitis. Therefore, direct immunofluorescence (DIF) should be performed no more than 48 hours after the occurrence of the lesions; in fact, a biopsy taken from an old lesion could result in a false negative finding.

Recently, it has been demonstrated that the perivascular deposits are composed by IgA1-glicero-glican deficient/anti-IgA1-glicero-glican deficient IgG complexes.³⁸

Cutaneous lesions, consisting in a rash of symmetric erythematous papules, evolving into palpable purpura, are always present and are localized on the lower extremities and buttocks, and are focally elicitable by vasodilatory measures (Figure 1).³⁹

A prodromal phase with fever, anorexia, malaise and headache, followed by abdomen pain (65%) and migratory arthralgia (100%) is often present.^{40, 41}

Histopathological analysis of purpuric lesions shows a small vessel leukocytoclastic vasculitis.⁴²

IgA vasculitis is the most common CV in children (mean age 5-6 years; male prevalence) and is often related to a recent history of upper airway streptococcal infection.⁴² Table V shows diagnostic criteria proposed by the EULAR/PRES in 2006 and then validated by further research, achieving a 100% sensibility and 87% specificity.^{15, 16}

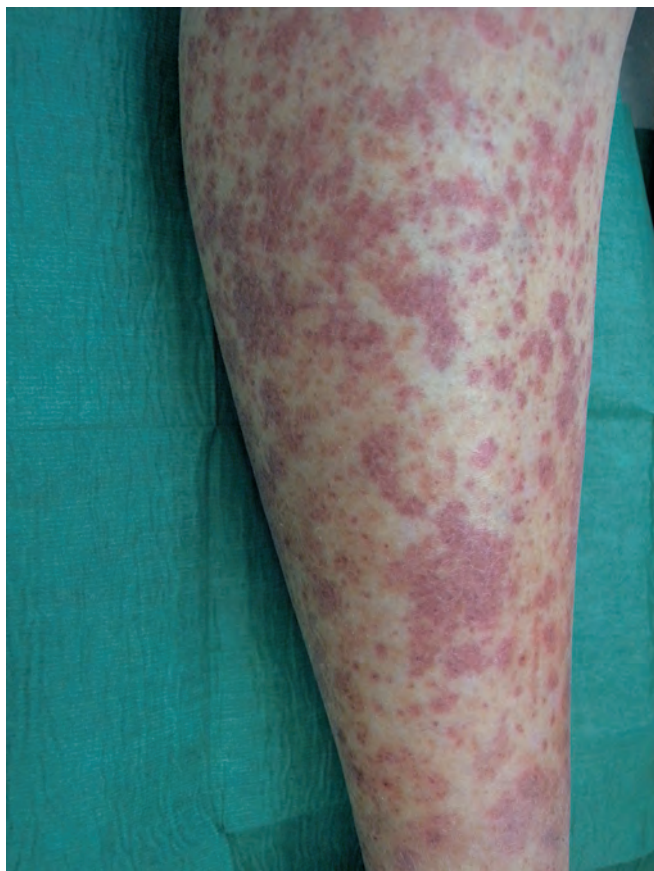


Figure 1.—Typical palpable purpura on the legs of a patient with IgA vasculitis.

TABLE V.—Classification criteria of childhood IgA vasculitis.

Palpable purpura mandatory plus 1 of:
– Diffuse abdominal pain
– Biopsy showing predominant IgA deposition
– Arthritis or arthralgia
– Renal involvement (proteinuria or hematuria)

TABLE VI.—IgAV: Predictive factors of renal involvement and relapse ($\approx 5\%$).

– Age over 30 years
– Persistent high fever
– High increased VES level
– Persisting purpura over 1 month or recurrent (over 1 year), spreading to upper trunk, bullous lesions, necrosis
– IgM+IgA (4 studies: controversial results)

While the pediatric form of the disease is generally considered a benign self-limited condition, in adults IgA vasculitis has a worse prognosis.^{39,43,44} Accordingly, the prognosis is directly associated

with the renal involvement, whose predictive factors are shown in Table VI.⁴⁵⁻⁴⁷

Among them, the presence of perivascular IgM deposits in the skin can be considered one of the most important features leading to glomerulonephritis in patients with IgA vasculitis, although contrasting results are present in the literature. In fact, in a retrospective study of Takenkhi *et al.* (2010) in 25 patients has been revealed a positive correlation between IgM deposition and renal involvement.⁴⁸ Similar results were obtained by Belli and Dervis (2014) in 47 patients ($P=0.003$).⁴⁹ By contrast, Poteruche *et al.* in 47 patients and Tiredo Sanchez *et al.* in 37 children demonstrated no correlation between IgM deposition and systemic involvement (primarily renal).^{50, 51}

Cryoglobulinemia vasculitis

CHCC2012 defined cryoglobulinemia vasculitis (CrV) as a vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules or arterioles) and associated with serum cryoglobulin. Skin, glomeruli and peripheral nerves are often involved.¹⁷

According to the clonality and type of immunoglobulin involved, three basic types of cryoglobulin can be distinguished. In type I cryoglobulinemic vasculopathy and occlusion of cutaneous vessels by gelling cryoglobulin in cold-exposed skin areas is very frequent. In these cases clinical manifestations are represented by cutaneous necrosis sometimes accompanied by livedo in cold-exposed skin. Type II and type III (referred as mixed cryoglobulin because they consist of both IgG and IgM component) are associated with HCV (69-90%), autoimmune diseases (Sjogren Syndrome, systemic lupus erythematosus [SLE]) or neoplasms. Circulating mixed cryoglobulin can develop renal involvement, sensitive-motor peripheral neuropathy or cutaneous lesions, represented by vasculitic lesions.⁵²

The typical presentation of cryoglobulinemic vasculitis is palpable purpura, predominantly localized in the lower extremities, with a necrotic evolution (Figure 2).^{53, 54}

Intermittent episodes of CrV are frequently caused by lower temperature expositions or prolonged orthostatism, often associated with fever, arthralgia and asthenia. A systemic involvement is possible (renal or neurological), but forms with an exclusive skin involvement were reported.⁵³⁻⁵⁶

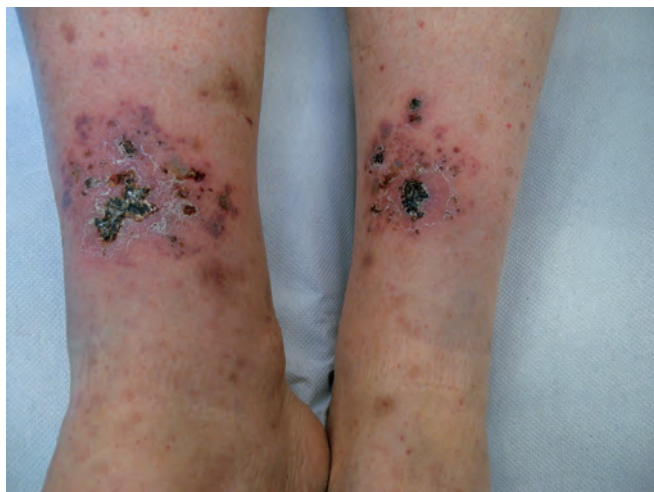


Figure 2.—Necrotic purpuric plaques with ulceration in a patient with cryoglobulinemic vasculitis.

Histopathological cutaneous findings consist in a pan-dermal leukocytoclastic vasculitis; sometimes an involvement of medium-size arteries can be found.

Figure 3 shows the CrV classification criteria proposed by Devita *et al.* in 2011.⁵⁷

Acute hemorrhagic edema of infancy

Acute hemorrhagic edema of infancy (AHEI) is a rare (about 200 cases reported in literature) form of CV that usually affects children from 4 to 24 months of age.⁵⁸⁻⁶²

Skin manifestations consist in large, rosette-shaped, purpuric plaques, often painful, that become edematous and then develop a coin-shape or targetoid appearance.⁶⁰⁻⁶³ Typical localizations are the face or distal extremities.⁵⁸⁻⁶³ Usually, extra cutaneous involvement is absent; the course is benign with spon-

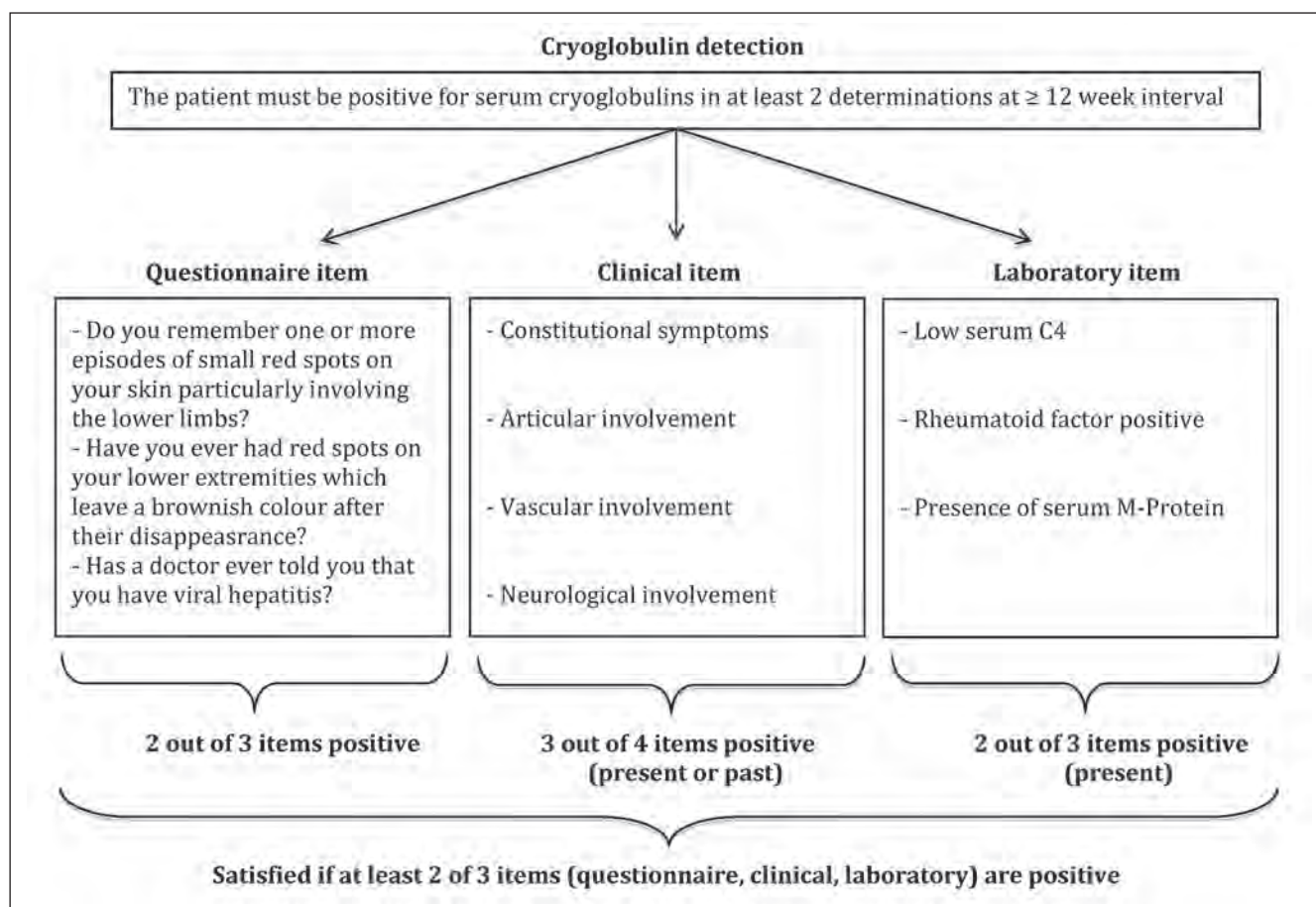


Figure 3.—CrV classification criteria proposed by Devita *et al.* in 2011.

TABLE VII.—*Diagnostic criteria for AHEI.*

1. Age of onset less than 2 years
2. Leukocytoclastic vasculitis of superficial dermis presents as annular, circular or targetoid purpuric plaques, beginning painful edema
3. No extracutaneous involvement
4. Spontaneous resolution with 1 to 3 weeks
5. Usually perivascular deposits of IgA are absent

taneous and complete resolution within 1 to 3 weeks.

Histologically, leukocytoclastic vasculitis involving the capillaries (often also postcapillary venules) of the upper and mid dermis is observed.⁶³⁻⁶⁴ DIF reveals superficial and perivascular IgA deposits in up to one-third of cases. On the basis of these immunologic findings AHEI has been considered a rare form of IgA vasculitis.

Etiology of AHEI is unknown, but 75% of the reported cases occurs in association with a recent infection (staphylococci, streptococci, adenovirus, Coxsackie virus, rotavirus),⁶⁵ drug exposure or immunization.⁵⁸

The pathogenesis is presumably correlated with IC deposition in response to an antigenic trigger.

AHEI, previously considered a form of IgA vasculitis, is now recognized as an autonomous nosology entity. Differential diagnostic criteria of AHEI from IgA vasculitis are age of onset less than two years, diseases even confined to the skin and shorter duration.⁶⁶

Table VII shows the significant classification and diagnostic criteria of AHEI.

Erythema elevatum diutinum

Erythema elevatum diutinum (EED) is a rare disorder (about 100 cases reported to date) characterized clinically by red-brown yellowish papules, plaques or nodules distributed symmetrically at extensor surfaces of the hands and knees.^{67, 68} In the early stage, the lesions are edematous, becoming firm over time due to the fibrosis (Figure 4);⁶⁹ moreover they appear firmer and higher at evening and after a cold temperature exposure. Cutaneous lesions are generally asymptomatic. The disease has a chronic course (years) with periods of waxing and waning.⁶⁷⁻⁶⁹ The majority of cases of EED resolve spontaneously over a 5-year period.^{67, 68}

EED has been described in association with a number of systemic diseases, included infections (staphylococci, HBV, HIV),^{71, 72} autoimmune dis-



Figure 4.—Multiple, dusky red, large nodules and plaques.

eases and both benign and malignant hematologic disorders (IgA monoclonal gammopathy, multiple myeloma, myelodysplasia, myeloproliferative disorders).^{73, 74}

Histological features consist of leukocytoclastic vasculitis of the upper and mid dermis in early lesions, followed by fibrotic replacement of the dermis in older lesions.⁶⁸ Although some authors have included EED among neutrophilic dermatosis, it must be considered an IC vasculitis, due to chronic antigenic exposure or high circulating antibody levels.^{67, 68}

Table VIII shows proposed diagnostic criteria for EED.

Urticarial vasculitis syndrome

Urticarial vasculitis syndrome (UVS) is a cutaneous disorder in which the urticarial lesions persist for more than 24 hours and heal leaving brownish

TABLE VIII.—*Diagnostic criteria for EED.*

1. Symmetric red-violet (or red brown) papules and plaques of extensor surfaces
2. Chronic course with waxing and waning and spontaneous resolution after years
3. Leucocytoclastic vasculitis in early phases followed by fibrotic replacement of the dermis
4. Extracutaneous involvement is extremely rare (sometimes arthralgia may develop in underlining joints)

TABLE IX.—*Special forms of UV.*

- AHA Syndrome
- Arthritis
 - Hives
 - Angioedema
- Cogan's Syndrome
- Interstitial keratinin
 - Hypoacusia
- Muckle-Wells's Syndrome
- Deafness
 - Renal amyloidosis
- Schnitzler's Syndrome
- Hyperostosis
 - Lymphadenopathy
 - Intermittent fever
 - Monoclonal IgM gammopathy

residues and sometimes fine scales. On diascopy, the wheals generally reveal central red spots that represent the clinical expression of vasculitis.^{36, 75-78} The edematous lesions are often figurate and localized mostly at the trunk and extremities. Burning, pain and, rarely, itching can be found (Figure 5).⁷⁵⁻⁷⁸

UV represents a continuum disease whose life-threatening pole is occupied by hypocomplementemic UVS.³⁶ The UVS spectrum embraces the following conditions:

1) the mild form of the disease with slight or absent systemic manifestations and without hypocomplementemia;^{80, 81}

2) UV associated with SLE;⁷⁵

3) various special forms, including arthritis/hives/angioedema (AHA) syndrome, Cogan's Syndrome, Muckle-Wells's syndrome and Schnitzler's syndrome (Table IX);⁸²⁻⁸⁵

4) hypocomplementemic UV (HUV), a systemic form of UV with only mild urticarial skin lesions and numerous organ involvement, frequently associated with C1q antibodies (Table X).⁸⁶

Leukocytoclastic vasculitis of dermal vessels is the commonest histopathological finding of UVS. In biopsies performed in the early phase, perivascular deposits of Ig (IgG, IgM), C and fibrinogen are usually demonstrated.^{79, 80}



Figure 5.—Urticarial vasculitis showing urticarial plaques on the upper extremity.

TABLE X.—*Extracutaneous organ involvement in HUVs.*

Organ	% of total	Symptoms
Joints	70	Arthralgia and arthritis
Kidneys	50	Proteinuria, hematuria, rapid progressive glomerulonephritis, renal insufficiency
Gastrointestinal tract	30	Addominal pain, nausea, vomiting, diarrhea, hepato-, spleno- megalia, ascites
Lung	20	Shortness of breath, coughing, hemoptysis, pleural effusion, chronic obstructive pulmonary disease
Eye	10	Episcleritis, uveitis, conjunctivitis
Heart	Rare	Pericarditis, cardiac valve disease
Nervous system	Rare	Pseudotumor cerebri, aseptic meningitis, central or peripheral nerve palsy

CHCC2012 defined HUV as a vasculitis accompanied by urticaria and hypocomplementemia, affecting small vessels and associated with anti C1q antibodies. Glomerulonephritis, arthritis, destructive pulmonary disease and ocular inflammation are common.¹⁷ IgG to the collagen-like region of C1q are one of the most distinctive findings in HUV.^{36, 85} CHCC2012 recommended the use of the term anti-C1q vasculitis in preference to HUV, but consensus was not reached to recommend it as primary term.¹⁷ Presumably, this is due to the fact that anti-C1q antibodies are not regularly detected in HUV. Moreover, they are not specific, since they are also present in SLE and other musculoskeletal or rheumatic diseases.⁸⁶⁻⁸⁹

Table XI shows laboratory findings of HUVs and tab. XII proposed as diagnostic criteria.

Misdiagnosis of HUV occurs because of similarities to SLE: arthritis and arthralgia is common in both, UV occurs in 5-10% of patients with SLE and 28-47% of patients with SLE have serum IgG antibodies to C1q.⁸⁵⁻⁸⁹

Distinctive, but not absolute, differential criteria are: 1) angioedema and eyes inflammation common in HUV and rare in SLE; 2) obstructive lung disease is more common and severe in HUV, rare (if it even occurs) in SLE.

An overlap of HUV and SLE can rarely be demonstrated in patients with typical findings of SLE associated with severe angioedema, progressive airways obstruction or ocular inflammation.⁷⁵

Cutaneous polyarteritis nodosa

Cutaneous polyarteritis nodosa (cPAN) is a skin-limited form of PAN defined as a vasculitis in arterioles, capillaries or venules, not associated with ANCA.¹⁷

cPAN represents about 10% of PAN cases, it is the most common form in children and it is often associated with streptococcal infections.¹⁴ Other rare associations (above all in adult patients) included HIV and HBV infection and inflammatory bowel diseases.⁹¹

TABLE XI.—*Typical laboratory finding in HUV.*

– ESDR acceleration
– Hypocomplementemia with low C1q, C3, C4
– Anti-C1q antibodies
– ANA at low title without anti dsDNA

Common cutaneous lesions are painful subcutaneous nodules on the lower extremities, cutaneous necrosis, ulcers and a starburst pattern of livedo racemosa.⁹²⁻⁹⁷ A chronic relapsing clinical course is typical and mild systemic symptoms are often present, including fever, myalgia and arthralgia.⁹¹⁻⁹⁵

Histologically, cPAN is characterized by segmental necrotizing vasculitis of small arteries (200-400 µm diameter) in the panniculus and the arterioles at the dermal-subcutaneous junction, fibrinoid deposition in vessel wall and perivascular infiltrate of neutrophils (followed in late phase by lymphomonocytic cells) and erythrocytes. Venous vessels are never involved, while sometimes arterioles of muscles and nerves under the lesional skin can be affected.⁹¹⁻⁹³

Table XIII shows classification criteria of cPAN proposed by EULAR/PRES 2006.

Conclusions

In this review we discussed all the international classifications of systemic vasculitides that used consensus-based criteria specifically derived through the combination of opinions from a group of experts (never including dermatologists) after accurate literature review.

In these classifications, CV were not included or included only partially; moreover, no accepted diagnostic criteria of CV can be found in the literature.

TABLE XII.—*Criteria for HUV diagnosis.*

Major criteria
– Chronic urticarial lesions with special characteristic (see text)
– Mild hypocomplementemia
Minor criteria
– Leukocytoclastic vasculitis
– Arthralgia and arthritis
– Uveitis or episcleritis
– Glomerulonephritis
– Abdominal pain
– Positive anti C1q antibodies

TABLE XIII.—*Classification criteria for cutaneous polyarteritis (EULAR/PRES 2006 childhood vasculitis).*

– Skin involvement (livedo reticularis, tender subcutaneous nodules, other vasculitic lesions)
– No systemic involvement (except myalgia, arthralgia and non erosive arthritis)
– Skin biopsy showing non granulomatous vasculitis
– Negative ANCA
– Evidence of streptococcal infection

Finally, rare forms of CV, such as EED, are not reported in the current nomenclature.

Several unsolved problems are still present about the nosography of CV, including:

1) the nosographic autonomy of so-called child and adult cPAN;

2) the definition of the various forms of UVS and the relationship between HUV and SLE with cutaneous manifestation of UV;

3) the prognostic value of perivascular deposition of IgM in the lesional skin of patients with IgA vasculitis;

4) the definition of the epitopes targeted by anti-C1q antibodies, found in HUV and many autoimmune rheumatic diseases, in order to obtain serological elements for the differential diagnosis between the different entities.

Further research should address such points and should provide consensus about the nomenclature, the classification and the diagnostic criteria of CV, with the final aim of a better management of these patients.

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Cutaneous vasculitidis: histology and immunofluorescence

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Cutaneous vasculitis comprises a wide spectrum of diseases that involve predominantly the blood vessels and surrounding tissues of the skin. Few vasculitic syndromes have pathognomonic clinical, radiographic and/or laboratory findings; thus, confident and accurate diagnosis of vasculitis requires histological confirmation. Skin biopsy should be done, optimally within 24 to 48 hours after vasculitic lesions appear. Deep excision biopsy must be preferred. Direct immunofluorescence of lesional skin is helpful in the diagnosis of vasculitides in the light of a proper clinico-pathological setting and diagnostic in some peculiar forms.

Cutaneous histological patterns can be used to generate relevant clinical differential diagnoses, and, when coupled with patient's history, clinical and laboratory data, allow more precise and accurate diagnosis of vasculitic syndromes. This review will focus on histopathological and immunologic pattern of the more common cutaneous vasculitis syndromes, based on the 2012 Revised International CHCC.

KEY WORDS: Vasculitis - Fluorescent antibody technique, direct - Immunoglobulin A - Immunoglobulin G - Immunoglobulin M.

Vasculitis is an inflammatory process that affects the small, medium or large-sized vessels. Cutaneous vasculitis (CV) affects the small or medium-sized vessels of the skin and subcutaneous tissue and clinically comprise a wide spectrum of diseases.¹ All of them share the presence of vascular inflammation and blood vessel damage with inflammation of the small blood vessels including arterioles, capillaries and post-capillary venules.² Histologic examination of CV usually detects infiltration of the vessel

wall by inflammatory cells, resulting in disruption and destruction of the vessel wall, intramural and intraluminal fibrin deposition (fibrinoid necrosis), extravasation of red blood cells (RBCs) and/or nuclear debris (leukocytoclasia) (Figure 1A, B).³

Classifying primary CV has proven controversial. There has yet to emerge a single, unified system that can be applied to clinical diagnosis. Given the current lack of knowledge regarding the pathogenesis, vessel size has been used since now to diagnose this condition because size can be ascertained relatively easily by clinical and histopathological examination. As a result, currently, the most widely adopted vasculitis classification system (nosology) is that of 2012 Revised Chapel Hill Consensus Conference (CHCC) (Table I),^{4,5} which represent not such a classification but a nomenclature system that names vasculitis on the basis of the size of the vessel affected. The other widely used system is that of the American College of Rheumatology (ACR), predominately based on clinical findings.^{6,7} Both schemes were developed to compare groups of vasculitis patients, not as diagnostic criteria for individual patients.

In this review we will approach CV focusing on the histopathological pattern of the vasculitis com-

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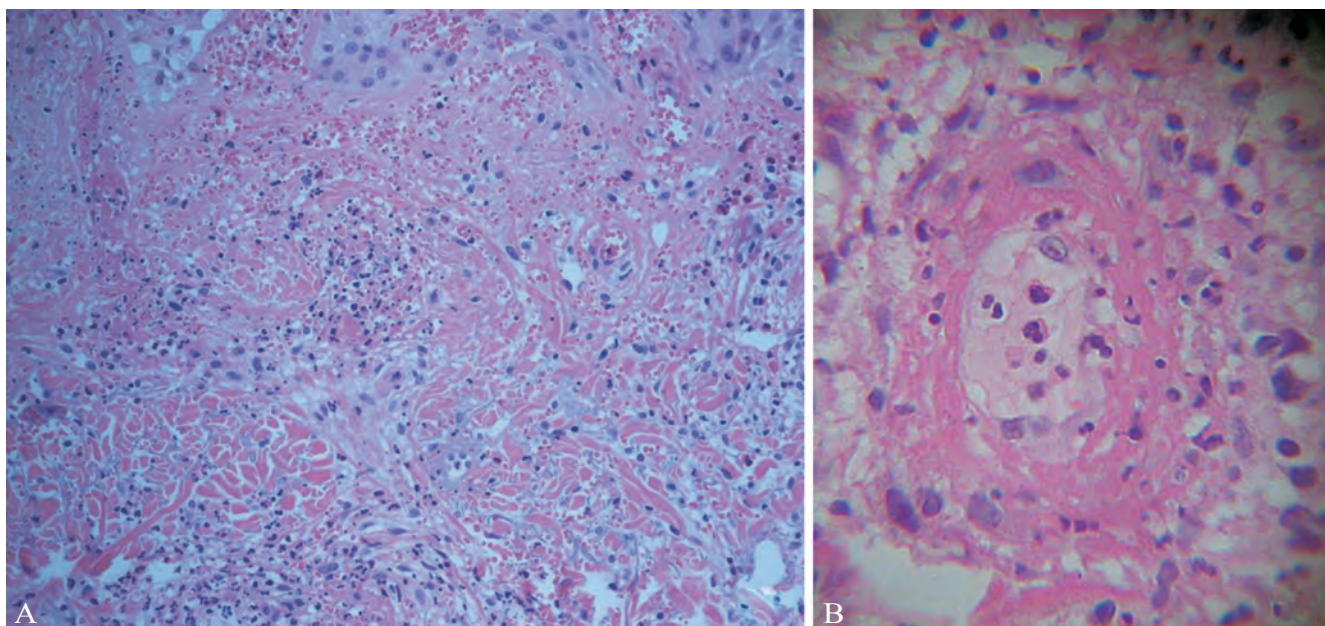


Figure 1.—A) Leukocytoclastic vasculitis: erythrocytes extravasation and nuclear dust (hematoxylin and eosin stain; 100 X); B) leukocytoclastic vasculitis: fibrinoid necrosis (Hematoxylin and eosin stain; 400X).

monly affecting the skin, describing also their immunofluorescence specific characteristics.

Histopathological examination

Few vasculitic syndromes have pathognomonic clinical, radiographic and/or laboratory findings; thus, confident and accurate diagnosis of vasculitis requires histological confirmation.⁸ Skin biopsy should be done, optimally within 24 to 48 hours after vasculitic lesions appear.⁹ If the biopsy is poorly timed, the pathological features of vasculitis may be absent, a fact that must be considered when interpreting a negative biopsy from a patient whose clinical findings suggest vasculitis. Diagnostic yield depends on the depth of the biopsy. Generally, deep punch biopsy or excision biopsy into the subcutis is preferred; these biopsies can sample small- and medium-sized vessels. Shave biopsy is usually inadequate.³ Infiltrate content will depend on the timing of the skin biopsy because polymorphonuclear leukocytes may be replaced by lymphocytes and monocytes as the lesions develop. Edema and inflammatory infiltration of the vessel wall lead to progressive thickening of the wall, and very slight fibrinoid necrosis of the vessel walls will sometimes be observed. Endothe-

lial cells are frequently swollen and intravascular thrombi or extravasation of RBCs into the dermis may occasionally be observed. Marked subepidermal edema sometimes gives rise to vesiculobullous skin lesions. Extravasation of RBCs (purpura) and necrosis are supportive, but not diagnostic of vasculitis as they are also seen in haemorrhagic and/or vaso-occlusive disorders (pseudovasculitis). Vasculitic foci associated with extravascular granulomas (palisaded neutrophilic and granulomatous dermatitis), tissue eosinophilia, or tissue neutrophilia signal the risk for, or co-existence of systemic disease.¹⁰ Biopsy specimens should also be obtained from non-ulcerated sites due to frequent finding of incidental vasculitis seen underlying an ulcer bed.

Direct immunofluorescence examination

Direct immunofluorescence (DIF) of lesional skin may be helpful in the diagnosis of vasculitis in the light of a proper clinico-pathological setting. DIF testing uses fluorescein-conjugated antibodies monospecific for immunoglobulin (Ig) G, IgM, and IgA and complement (C) fractions including C3, C3d, C4d, and C1q directly overlaid on frozen sections of patient tissue.¹¹ Similar to haematoxylin and eosin

TABLE I.—*Chapel Hill Consensus Conference nomenclature of vasculitides 2012.*

SMALL VESSEL VASCULITIS (SVV)
Immune complex SVV
– IgA vasculitis (Henoch-Schönlein) (IgAV)
– Cryoglobulinemic vasculitis
– Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)
– Anti-glomerular basement membrane (anti-GBM) disease
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)
– Microscopic polyangiitis (MPA)
– Granulomatosis with polyangiitis (Wegener's) (GPA)
– Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
MEDIUM VESSEL VASCULITIS (MVV)
– Polyarteritis nodosa (PAN)
– Kawasaki disease (KD)
LARGE VESSEL VASCULITIS (LVV)
– Takayasu arteritis (TAK)
– Giant cell arteritis (GCA)
SINGLE-ORGAN VASCULITIS (SOV)
– Cutaneous leukocytoclastic angiitis (CLA)
– Cutaneous arteritis
– Primary central nervous system vasculitis Isolated aortitis
– Others
VASCULITIS ASSOCIATED WITH SYSTEMIC DISEASE
– Lupus vasculitis
– Rheumatoid vasculitis
– Sarcoid vasculitis
– Others
VARIABLE VESSEL VASCULITIS (VVV)
– Behcet's disease (BD)
– Cogan's syndrome (CS)
VASCULITIS ASSOCIATED WITH PROBABLE ETIOLOGY
– Drug-associated immune complex vasculitis
– Drug-associated ANCA-associated vasculitis
– Hepatitis C virus-associated cryoglobulinemic vasculitis
– Hepatitis B virus-associated vasculitis
– Syphilis-associated aortitis
– Cancer-associated vasculitis
– Others

evaluation, the sensitivity of the test is influenced by the timing of the biopsy. Lesions less than 48 hours old yield the most frequently positive results while older lesions may have negative DIF because of the rapid degradation of immune deposits.¹² A diagnosis of vasculitis should not be made solely on the presence of positive DIF findings, nor should the diagnosis be excluded with a negative DIF test. The findings of DIF should be interpreted along with clinical, histologic, and other laboratory findings.¹³

CHCC 2012

On the basis of the 2012 Revised International CHCC the CV described by the authors are divided

into: 1) small vessel vasculitis (SSV); 2) medium vessel vasculitis (MMV); 3) large vessel vasculitis (LVV); 4) single-organ vasculitis (SOV); 5) vasculitis associated with systemic disease; 6) variable vessel vasculitis (VVV), 7) vasculitis associated with probable etiology. For each group we describe only the entities that have skin lesions as a substantial manifestation of the disease.

SVV

IMMUNE COMPLEX SVV

Immune complex SVV is vasculitis with moderate to marked vessel wall deposits of Ig and C components predominantly affecting small vessels.⁴ This category includes spectrum of disease variably affecting the skin.

IgA vasculitis (Henoch-Schönlein) (IgAV) represents about 10% of all cases of CV and is the most common vasculitis in children. The appearances are usually indistinguishable from those seen in leukocytoclastic vasculitis (LCV).¹⁴ On biopsy, most patients will show a small-vessel neutrophilic vasculitis restricted to the superficial dermis, with whole dermis involved only occasionally. It is characterised by IgA deposits (75-100%), predominately the IgA₁ subclass, with a granular pattern in the vessel walls of the superficial dermis (Figure 2A).¹⁵ In IgAV, deposition of IgM, IgG, C3, properdin and fibrinogen accompanying the IgA may also be encountered. The demonstration of IgA deposits affecting small vessels is sensitive for IgAV but not specific, since IgA vascular deposits are also seen in vasculitis associated to systemic diseases, cryoglobulinemia, paraproteinemia/gammopathy, erythema nodosum, venous stasis, coagulopathic vasculopathies, and livedoid vasculitis.¹⁶ Therefore, the diagnosis is made by isolated or predominant IgA vascular

deposits, associated to two or more of these clinical features: age 20 years, gastrointestinal involvement (colicky pain or hematochezia), upper respiratory tract infection prodrome, and/or haematuria or renal biopsy showing mesangioproliferative glomerulonephritis with or without IgA deposits.¹⁷ In recent studies, a relationship among the IgM deposition, along with IgA, in skin lesions and systemic involvement was investigated and a significant correlation was found between skin deposition of IgM and renal involvement.^{18, 19} In this view, IgM may be a use-

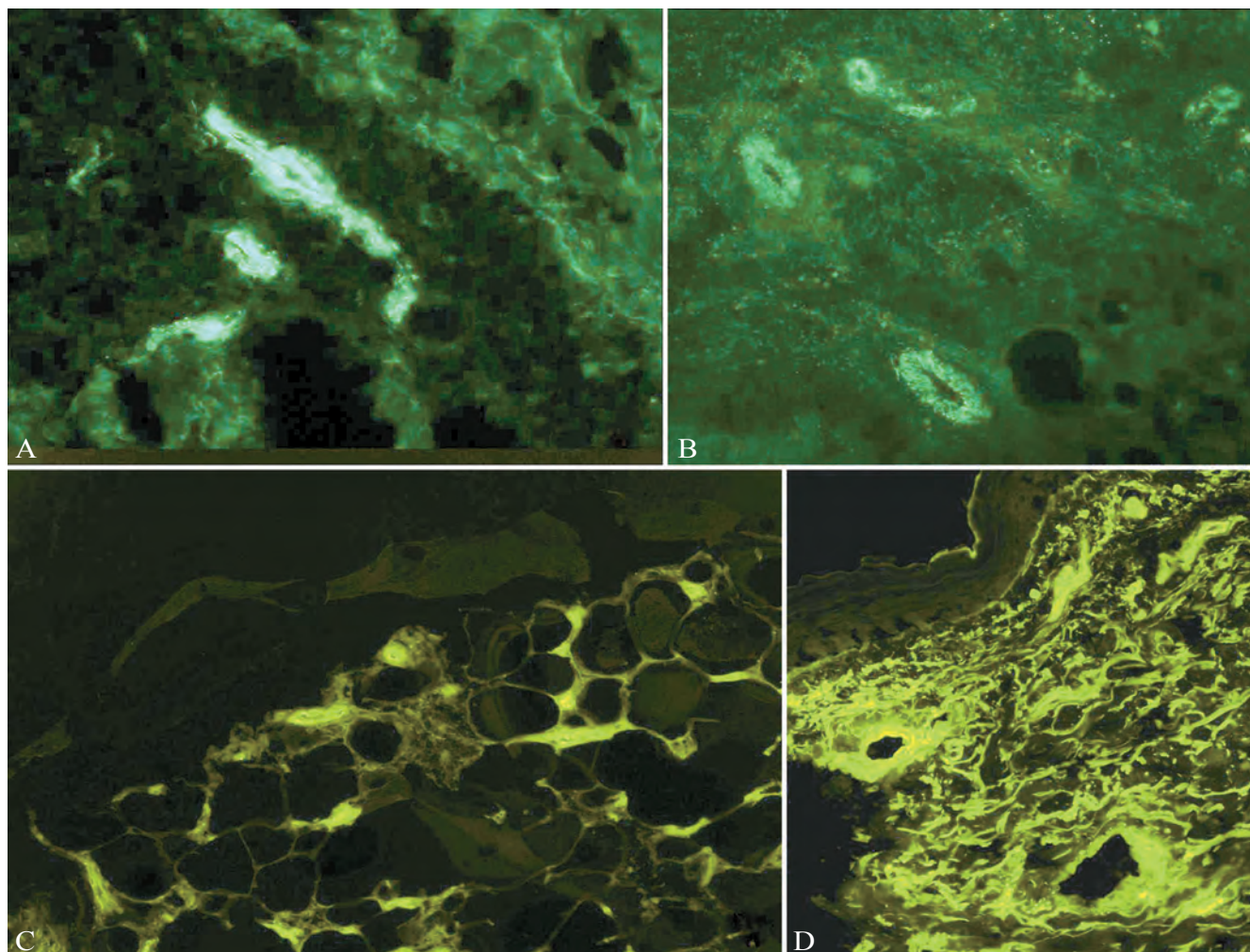


Figure 2.—A) IgAV: superficial, perivascular IgA deposits (DIF; 250 X); B) cryoglobulinaemic vasculitis: superficial, perivascular IgM deposits (DIF; 250 X); C) GPA: vascular deposits of IgG among interlobular septa of the adipose tissue (DIF; 250 X); D) Neutrophilic vasculitis of small vessels in lupus erythematosus systemic. Immunodeposits at the dermo-epidermal junction (DIF: 200X).

ful marker of renal involvement but more studies are needed since not all of them confirmed the same relationship.²⁰

Cryoglobulinaemic vasculitis is vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) (Figure 3) and associated with cryoglobulins in serum, either in association with hepatitis C infection or less frequently connective tissue disease (CTD).¹⁻³ Skin, glomeruli and peripheral nerves are often involved. In most cases, skin biopsy will show a small vessel neutrophilic vasculitis equally affecting superficial dermal and subcutis vessels, and in a

minority of cases neutrophilic muscular vessel vasculitis (polyarteritis nodosa [PAN]-like). There are usually some extravasated RBCs; in cases of long standing lesions, hemosiderin may be present. Intravascular hyaline deposits are the exception, but they may be found beneath areas of ulceration. DIF frequently reveals the presence of granular deposits, typically IgM and/or C3, in a vascular pattern in the papillary dermis vessels (Figure 2B). Deposition of immunoreactants along the basement membrane zone is not commonly seen.²¹

Urticarial vasculitis (UV) patients have painful, tender, burning or pruritic papules and plaques affect-

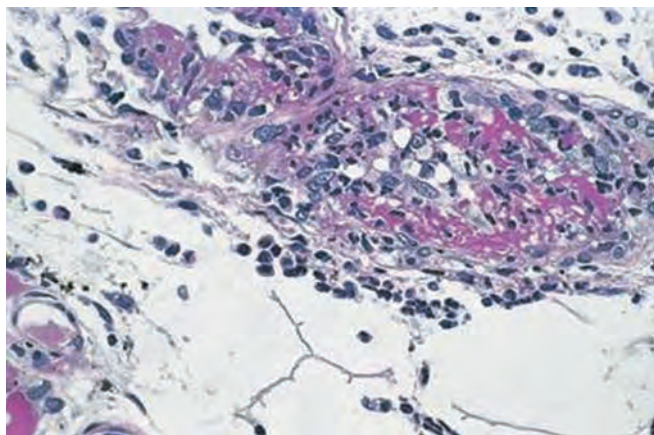


Figure 3.—Cryoglobulinaemic vasculitis: partial obstruction of lumen vessel by cryoglobulinic deposits (hematoxylin and eosin stain; 400X).

ing any cutaneous surface, and which persist more than 24 hours and less than 72 hours, and in some cases leave residual purpura or hyperpigmentation.^{1,2} UV patients do not have fully developed lesions of LCV; either focal nuclear debris or vascular fibrin deposits, with or without extravasated RBCs, will be evident (Figure 4). Histopathology findings are similar to those seen in LCV, although there is usually prominent edema of the upper dermis. Infection-triggered LCV is suspected to show a greater frequency of subcorneal, intraepidermal and subepidermal neutrophilic pustules, tissue neutrophilia, predominant IgA vascular deposits, and have relatively less eosinophils and lymphocytes compared with idiopathic LCV and drug-related cutaneous LCV.²² UV may be divided into three forms: normocomplementemic UV, hypocomplementemic UV associated with anti-C1q antibodies and hypocomplementemic UV not associated with anti-C1q antibodies. As regards hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis), vascular deposition of C3 and IgM has been found in more than 50% of patients and in 18-34 % of patients there is a deposit of Ig and C3 at the basement membrane. About 70% of patients with basement membrane deposition of immunoreactants will also have glomerulonephritis.⁹

ANTINEUTROPHIL CYTOPLASMIC ANTIBODY-ASSOCIATED VASCULITIS

AAV is necrotizing vasculitis predominantly affecting small vessels, associated with MPO-ANCA

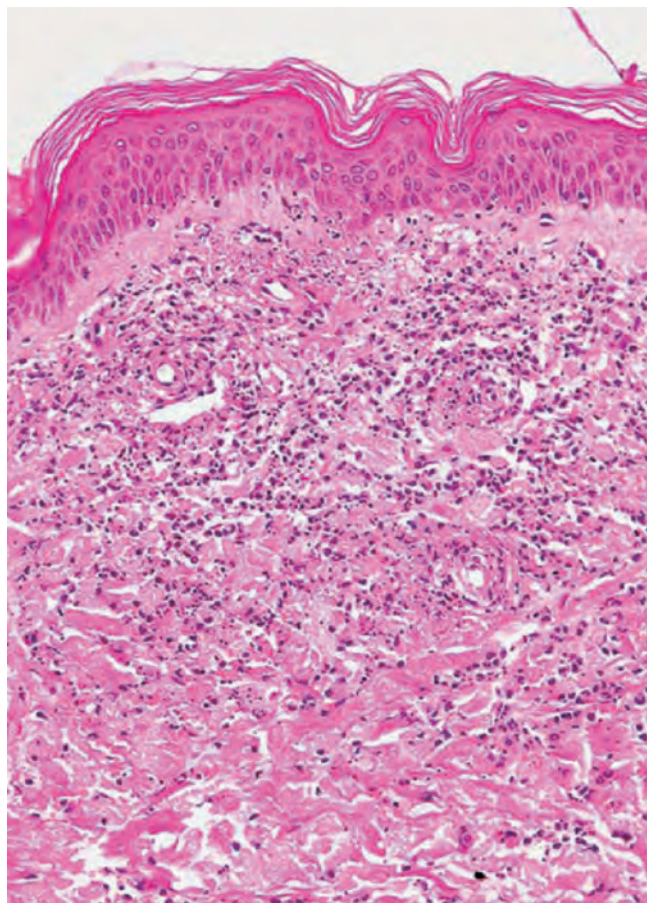


Figure 4.—Urticarial vasculitis: superficial dermal edema, vasculitis and eosinophils infiltration (hematoxylin and eosin stain; 100X).

or PR3-ANCA. It is generally considered a “pauci-immune” systemic vasculitis indicating the low incidence of overt Ig and C vessel deposits. The categories of AAV that were included in CHCC 2012 are microscopic polyangiitis (MPA), granulomatosis with polyangiitis (Wegener’s) (GPA), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA).⁴

Less than 20% of granulomatosis with polyangiitis (Wegener’s) (GPA) patients will present with cutaneous disease, which could be divided into three categories: 1) palpable or non-palpable lesions due to LCV; 2) subcutaneous nodules, ulcers and digital infarcts (gangrene) secondary to medium vessel vasculitis; 3) polymorphic lesions, produced by neutrophilic and/or granulomatous infiltrates. Therefore,

cutaneous lesions may have a quite non-specific histological pattern, with only a chronic inflammatory cell infiltrate in the dermis. The infiltrate is sometimes perifollicular and acneiform.² Proposed criteria for the diagnosis of GPA include biopsy or granulomatous inflammation of the respiratory tract, biopsy-verified necrotizing vasculitis in small to medium-sized vessels or biopsy for glomerulonephritis confirmation. While DIF typically fails to demonstrate Ig or C deposition on renal biopsies, skin biopsies frequently show perivascular deposits of IgM, IgG, IgA, and C3 in subepidermal (Figure 2C) and dermal vessels. In patients who have had a relapse of GPA, Ig deposits can be seen along the basement membrane and within the dermis.²³

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) is characterized by the presence of asthma, usually of adult onset, and other allergic symptoms (allergic rhinitis), peripheral and tissue eosinophilia, and systemic vasculitis.¹⁻³ Cutaneous biopsy reveals three broad categories of changes, which can frequently be identified together: 1) palpable purpura, petechiae, ecchymoses, livedo racemosa and/or haemorrhagic bullae vasculitis due to small-vessel eosinophil rich neutrophilic vasculitis affecting both dermal venules and arterioles and, less commonly, muscular vessel eosinophil-rich arteritis or histiocyte-rich granulomatous arteritis in dermo-subcutaneous junction or subcutis; 2) urticarial plaques due to dermal eosinophilia; 3) dermal and subcutaneous papules and nodules often located on the scalp or symmetrically distributed over the extremities produced by palisading neutrophilic and granulomatous dermatitis with either neutrophilic debris among basophilic degenerated collagen bundles, or abundant eosinophils and eosinophilic granules and debris coating degenerated collagen bundles ("red" granulomas).²⁴ It is usually characterized by no immune deposits at DIF.

Microscopic polyangiitis (MPA) is defined as systemic neutrophilic small-vessel vasculitis without extravascular granulomas or asthma. The skin lesions found in MPA include palpable purpura and petechiae in more than three-quarters of patients, and in the remainder splinter haemorrhages, nodules, palmar erythema and/or livedo. There is a neutrophilic vasculitis with variable leukocytoclasia, accompanied by extravasation of RBCs and patchy fibrinoid degeneration of vessels. Usually the process involves arterioles but capillaries and postcapillary venules

may also be involved while medium-sized muscular arteries are spared.²⁵ Immunofluorescence studies in MPA are generally negative or show few deposits of Ig and C in the skin while minimal deposition of Ig or C can be found in the glomeruli and renal vessels. The criteria for diagnosis of MPA are biopsy confirmation of neutrophilic small-vessel vasculitis and/or glomerulonephritis with few or no immune deposits, and involvement of more than one organ system documented by biopsy or surrogate marker such as proteinuria and haematuria for glomerulonephritis.²⁶

Medium vessel vasculitis

Cutaneous polyarteritis nodosa (CPAN) should be suspected in patients presenting with tender nodules, livedo vasculopathy, livedo racemosa, ulcers, acral gangrene and/or neuropathy.^{2,3} Deep punch or incisional biopsy to fascia is mandatory. Small and medium-sized arteries and/or arterioles in the subcutis and occasionally the deep dermis are involved. The inflammation is localized to the vessel and its immediate vicinity, allowing a distinction to be made from the various panniculitides. There may be a mild perivascular lymphocytic infiltrate in the overlying dermis. In the early stages there is marked thickening of the wall of the vessel, particularly the intima, as a result of edema and a fibrinous and cellular exudate. The infiltrate is composed of neutrophils, with some eosinophils and lymphocytes. Leukocytoclasia is sometimes present. In older lesions there is a greater proportion of mononuclear cells, particularly lymphocytes. Luminal thrombi and aneurysms may form.^{27, 28}

Nodular vasculitis (erythema induratum of Bazin) and thrombophlebitis can be clinically or pathologically mistaken for CPAN.² Nodular vasculitis is a lobular panniculitis and vasculitis affecting mostly venules or septal veins and less commonly arteries.²⁹ In contrast, CPAN is an arterial vasculitis with minimal extension of its inflammation into the adjacent subcutis. To differentiate between venous and arterial vasculitis, the pattern of elastic tissue distribution and vessel silhouette is a diagnostic aid. DIF frequently reveals IgM and C3 deposition in and around deep dermal vessels, however, interestingly, IgG and IgA are almost universally negative in all cases of CPAN.²⁷

Kawasaki's disease is an acute, multisystem, febrile illness of unknown cause that occurs predomi-

nantly in infancy and early childhood. Biopsies of the skin lesions are infrequently performed. They have shown non-specific features which include edema of the papillary dermis and a mild perivascular infiltrate of lymphocytes and mononuclear cells.³⁰

Large vessel vasculitis

Takayasu's arteritis (TA) is a chronic inflammatory and fibrosing arteriopathy that can also involve cutaneous vessels. Lesions considered to be "specifically" associated with TA have been described most frequently simulating erythema nodosum, erythema induratum and pyoderma gangrenosum with a specific and limited extension into subcutaneous fat.³¹ Cutaneous involvement in giant cell arteritis is uncommon. Reported dermatological abnormalities are limited to either tendon nodules overlying inflamed superficial arteries or to presumed ischaemic sequelae-such as purpura, necrotic ulcers, or gangrene. The histological examination of the skin specimen usually shows foci of large sized blood vessels with obliterated lumina and thickened walls within the subcutaneous fat. These vessel walls were infiltrated with lymphocytes, histiocytes, polymorphonuclear leucocytes, and a few eosinophilic leucocytes, as well as multinucleated giant cells. In addition to arteritis and disruption of the elastic tissues, areas of calcification could be noted within the vessel walls. The involvement is generally limited to vessels in the subcutaneous fat and septae, the overlying epidermis and dermis appearing histologically normal.³²

Single-organ vasculitis

Single-organ vasculitis (SOV) is vasculitis in arteries or veins of any size in a single organ, with no features that indicate that it is a limited expression of a systemic vasculitis. Some patients originally diagnosed as having SOV will develop additional disease manifestations that warrant reclassifying the vasculitis as one of the systemic vasculitides (*e.g.*, cutaneous arteritis later becoming systemic PAN).⁴

The diagnosis of cutaneous leukocytoclastic angitis (CLA) is based on the exclusion of predominant IgA vascular deposits, visceral disease, co-existing systemic disease, and antecedent infection or drug ingestion. On biopsy, a small vessel neutrophilic vasculitis affecting the superficial dermal plexus will be found, and DIF examination will show both C and

IgG in vessel walls.¹⁻³ There is infiltration of small venules walls with neutrophils which also extend into the perivascular zone and beyond. These neutrophils undergo degeneration with the formation of nuclear dust. The vessel walls are thickened by the exudate of inflammatory cells and edema fluid. There is also fibrinoid necrosis which often extends into the adjacent perivascular connective tissue. Endothelial cells are usually swollen and some are degenerate. Thrombosis of vessels is sometimes present. The dermis shows variable edema and extravasation of RBCs. In some lesions, particularly those of longer duration, eosinophils and lymphocytes are also present, particularly in a perivascular location. Macrophages, which are scattered in the interstitium even in the early stages, show a time-dependent increase. The most frequent deposit is C3, followed by IgG, IgM, and fibrinogen. The site of immune deposits is within the walls of postcapillary venules in the superficial dermis. The deposition is usually granular or fibrillar and is seen in blood vessel walls extending into both the extravascular and the intravascular space. Deposition of fibrinogen is frequently diffuse throughout the dermis.²⁸

Vasculitis associated with systemic disease

Secondary vasculitis due to connective tissue disease (CTD) should be considered in patients presenting with biopsy-proven CV who have signs and symptoms of dry eyes or mouth, arthritis, sclerosis, photosensitivity, or serological evidence of anti-nuclear antibodies (ANA), RF, antiphospholipid antibodies, or anti-DNA, -Ro or -La antibodies;¹⁻³ CTD vasculitis occurs frequently in lupus erythematosus systemic (SLE), rheumatoid arthritis (RA) and Sjögren's syndrome, and less commonly in dermatomyositis (DM), scleroderma (SS), and polychondritis.³³ In general, CTD vasculitis shows small and muscular vessel involvement. Arterioles and postcapillary venules are the most commonly affected by vasculitis, and manifests with purpura, vesiculobullous lesions, urticaria, and splinter hemorrhages. One should suspect arterial involvement if cutaneous ulcers, nodules, digital gangrene, (necrotizing) *livedo racemosa*, punctuate acral scars, or pyoderma gangrenosum-like lesions are present; these patients have a higher probability of visceral vasculitis.

Skin biopsy shows a mixed, mostly small and, less commonly, muscular vessel neutrophilic vas-

culitis with lesions that can resemble either typical CLA or PAN; the coexistence of small and muscular vessel vasculitis in the same biopsy specimen or different lesional skin is a characteristic feature of CTD vasculitis. Extravascular histologies can provide a clue to diagnosis of CTD vasculitis, such as the presence of interface dermatitis, dermal and/or subcutaneous sclerosis in SS, palisaded neutrophilic and granulomatous dermatitis in RV, and tissue neutrophilia (neutrophilic urticaria) in SLE and Sjögren syndrome. In lupus vasculitis DIF (Figure 2D) reveals vascular deposition of IgG, IgM, or C in approximately 55% of cases and co-existing basement membrane zone deposition of Ig (mostly IgM but rarely IgG) and C in 60% of cases.¹² In rheumatoid vasculitis a vascular deposition of Ig, typically IgM, can frequently be seen on DIF and is associated with the presence of extra-articular manifestations.³³

Variable vessel vasculitis

Behçet's disease (BD) is a multisystemic, relapsing inflammatory disorder with an obscure etiology and pathogenesis. Diagnosis depends on the clinician's ability to identify a group of nonspecific mucocutaneous lesions, which also manifest in a number of other diseases. In recent years, there has been an increase in the studies focusing on the histopathological aspects of Behçet's disease diagnostic mucocutaneous lesions. Their results emphasize the value of histopathology and DIF in the differential diagnosis of Behçet's disease. Whether this vasculitis is a result of autoimmunity is controversial. Knowledge of histopathological features of BD mucocutaneous lesions may be beneficial for differential and early diagnosis. Lymphocytes, macrophages, neutrophils at the base of the ulcer, sometimes penetrating epidermis at the periphery are characteristic in aphtous and genital ulcers with a similar infiltrate at the perivascular regions in dermis and rarely fibrinoid necrosis of vessel walls. In cutaneous papulopustular lesion we can observe intraepidermal pustules, spongiosis, neutrophil/lymphocyte exocytosis, and basal keratinocyte vacuolization, associated with dermal edema, lymphohistiocytic/neutrophilic inflammatory infiltration between collagen fibers, and perivascular areas. A significant deposition of immunoreactants in BD, especially in the negative pathergy and the normal skin sites, were observed, consisting mostly of IgM, IgA, and/or C3 or C1q.³⁴

Cogan's Syndrome is a rare autoimmune vasculitis, and its pathogenesis is unknown. Infection, but primarily autoimmunity, may play contributing roles in the pathogenesis of this disease. It is characterised by ocular and audiovestibular symptoms similar to those of Meniere's syndrome. Approximately 70% of patients have underlying systemic disease with mucocutaneous manifestations, for which vasculitis is considered the pathological mechanism. However, there are relatively few reports with a histological confirmation. Although there is usually large and/or medium vessel vasculitis, any size vessel may be affected.³⁵

Vasculitis associated with probable etiology

About a fifth of all cases of cutaneous vasculitis represent an adverse drug eruption which on biopsy will show a superficial dermal small-vessel neutrophilic or lymphocytic vasculitis. Concurrent tissue eosinophilia is a clue to a drug etiology.³⁶

Septic vasculitis is a variant of small-vessel neutrophilic vasculitis. On biopsy, mixed neutrophilic small and muscular vessel vasculitis with deep dermal and subcutaneous vessel involvement is found and associated with scant perivascular fibrin or fibrin thrombi, and no or little nuclear debris; these features help differentiate between septic vasculitis and conventional CLA (Figure 3C).¹⁻³

Conclusions

The new naming system (CHCC) recognizes advances in our understanding of vasculitis. It separates forms of vasculitis due to known causes such as infections from those without known causes, and is more specific for the disease process resulting in blood vessel inflammation. Histological verification and accurate histological classification are the first steps in arriving at a reproducible diagnosis of specific vasculitis syndrome in the evaluation of a patient presenting with CV. Choice of clinical lesions and type of pathological assessment has great impact on the diagnostic yield of cutaneous biopsies. Choice of a shave biopsy, punch biopsy or excisional biopsy will affect which vessels are examined, as the type of vessel is dependent on location within the skin and subcutis, i.e. the deeper the location, the larger the vessel. A biopsy extending to subcutis taken from

the most tender, reddish or purpuric, lesional skin is the tool to obtain a significant diagnostic result. The optimal time for skin biopsy is less than 48 hours after the appearance of a vasculitic lesion. DIF and indirect IF serological evaluation to detect and identify vascular Igs and/or ANCA, respectively, are the next steps. The final steps are to correlate these data with clinical evaluation for systemic disease and pertinent laboratory studies in order to classify accurately the type of cutaneous vasculitis. Accurate and reproducible diagnosis will result in a complete and effective management of CV patients.

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Granulomatous vasculitis

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Granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Wegener's granulomatosis and Churg-Strauss Syndrome respectively, are systemic granulomatous vasculitides affecting small- and medium-sized blood vessels. Both GPA and EGPA are included within the group of antineutrophilic cytoplasmic antibodies (ANCA)-associated vasculitides, on the basis of the detection of such autoantibodies in a significant proportion of affected patients. Two main settings of GPA, possibly overlapping each other, are recognized: a localized form, which is limited to the upper airways but is highly relapsing and refractory, and a diffuse form, which is initially more severe but then less commonly recurrent. In EGPA, a prodromic phase characterized by asthma and rhino-sinusitis is followed by an eosinophilic phase, marked by peripheral eosinophilia, and then by a vasculitic phase, in which skin lesions are a prominent feature together with peripheral neuropathy and renal involvement. Polymorphic cutaneous manifestations can occur during the course of both GPA and EGPA, and include palpable purpura, *livedo reticularis*, papules, nodules, vesiculo-bullae and necrotic-ulcerative lesions most commonly involving the lower extremities; pyoderma gangrenosum-like ulcers and lesions resembling erythema multiforme have been described in GPA and EGPA, respectively. Oral involvement is not uncommon in GPA and may manifest as nonspecific erosive lesions or as a hyperplastic gingivitis named strawberry gingivitis. Considering that skin involvement is common in ANCA-associated vasculitides and may also be their presenting sign, the role of dermatologist is crucial in the early diagnosis of these forms as well as of vasculitis in general.

KEY WORDS: Antibodies, antineutrophil cytoplasmic - Vasculitis - Granulomatosis with polyangiitis - Churg-Strauss Syndrome.

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Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, and eosinophilic granulomatosis with polyangiitis (EGPA), called Churg-Strauss Syndrome (CSS) for many years, are systemic, necrotising and granulomatous vasculitides which affect small- and medium-sized blood vessels;¹ based on that antineutrophil cytoplasmic antibodies (ANCA) are detectable in a significant proportion of GPA and EGPA patients, both forms have been included in the spectrum of ANCA-associated vasculitides, together with microscopic polyangiitis (Table I).² Two main subsets of GPA have been recognized: localized forms, which are limited to the upper respiratory tract but are recurrent and may show a locally aggressive behavior, and diffuse forms, which manifest mainly through renal and pulmonary involvements and are usually more serious initially but less commonly relapsing.^{3, 4} The transition from a localized form to a diffuse form and *vice-versa* is possible during the course of the disease.⁴ In EGPA, the disease's course may be subdi-

TABLE I.—*Clinical manifestations and laboratory findings in GPA and EGPA.*

	Skin	Mucosae	Upper respiratory airways	Lung	Kidney
GPA	(10-50%) Palpable purpura, tender subcutaneous nodules, papules, vesicles, blisters, necrotic-ulcerative lesions, livedo reticularis; ulceration/ gangrene of the digits or penis, PG- like ulcers.	(10-50%) Nonspecific erosive/ ulcerative oral lesions; strawberry gingivitis.	(70-100%) Sinusitis with purulent or hematic discharge; ulceration of the nasal mucosa and palate; nasal deformity with a saddle nose appearance, perforation of the septum.	(50-90%) Cough, dyspnea, hemoptysis.	(40-100%) Hematuria, proteinuria, cellular casts on urine cytology, acute kidney injury, chronic kidney disease, end-stage renal failure.
EGPA	(40-52%) Subcutaneous nodules, purpura, livedo reticularis, vesicles, aseptic pustules, urticarial, necrotic-ulcerative and EM-like lesions	—	Asthma (91-100%), nasal poliposis, allergic rhinosinusitis, epistaxis; neurosensory hearing loss (48%- 75%)	(65-91%) Pulmonary eosinophilic infiltrates	(27%) Pauci-immune crescentic glomerulonephritis or rapidly progressive glomerulonephritis

GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; CNS: central nervous system; PNS: peripheral nervous system; c (cytoplasmic); ANCA: antineutrophil cytoplasmic antibodies; p (perinuclear); PG: pyoderma gangrenosum; EM: erythema multiforme.

vided into a prodromic phase characterized by asthma and rhino-sinusitis, an eosinophilic phase marked by peripheral eosinophilia and organ involvement, and a vasculitic phase with clinical manifestations related to small/medium vessel vasculitis, most notably peripheral neuropathy and renal changes; in this phase also skin lesions are a prominent feature.^{5, 6} In this review, we will describe the clinical, histopathological and physiopathological features of GPA and EGPA, focusing particularly on the wide variety of cutaneous manifestations that can occur at presentation or in different stages of these diseases.⁷

Granulomatosis with polyangiitis (Wegener's granulomatosis)

Definition

Wegener's granulomatosis is a rare immune-mediated multisystem disease of unknown etiology which is characterized by a pathological triad consisting of granulomatous inflammation of the upper and/or lower respiratory tract, glomerulonephritis and systemic necrotising vasculitis of small and medium vessels.^{8, 9} It was first described in the medical literature in a clinical case report in the late 19th century and was formerly known by the eponymous name, Wegener's Granulomatosis, after Friedrich Wegener who described the clinical triad associated with this

disease in 1936. The use of a histopathology-based nomenclature is now recommended to avoid the use of eponymous names; therefore, since 2011 Wegener's granulomatosis has been renamed as granulomatosis with polyangiitis (GPA).¹⁰ GPA is a rare disease, its annual incidence being 5-10 cases per million population with equal frequency in males and females. The published point prevalence of GPA ranges between 24 and 157 cases per million with a distinctly higher prevalence of GPA amongst Caucasians, especially those from Northern Europe, compared to Asian, African, Afro-Caribbean and African-American populations. The age at diagnosis is between 45 and 60 years and the disease occurs very rarely in children. The survival rate of GPA ranges from 86% to 100% at 5 years.

Etiology and pathogenesis

The aetiology of GPA may originate from infectious (most notably infections of the upper respiratory tract usually caused by *Staphylococcus aureus* and more rarely due to mycobacteria, fungi or viruses), environmental (pollution, smoking, inhaled toxins, inhaled chemicals and exposure to metals), chemical, toxic or pharmacological triggers in subjects who are genetically predisposed to this autoimmune disorder (HLA-DP1*0401, HLA-DRB1*15, HLA-DRB1*1501, polymorphisms). The pathogenesis of the disease is mediated by a T cell

CNS	PNS	Heart	Eyes	Laboratory investigations
(6-13%) Headache, meningitis, cerebro-vascular events.	(33%) Peripheral neuropathy, sensory-motor and cranial nerve palsies.	(<10%) Pericarditis, valvular abnormalities, cardiomyopathy.	(14-60%) Conjunctivitis keratitis, uveitis, retinal vasculitis or thrombosis, orbital granulomatous masses possibly leading to blindness.	Localized form: c-ANCA positivity in 50-80% of cases. Systemic form: c-ANCA positivity in >90% of cases.
(5-9%) Subarachnoid hemorrhage, intracerebral hemorrhage, cerebral/cerebellar infarct or gliosis and spinal cord lesion	(55-72%) Peripheral (sensory-motor) neuropathy, mononeuritis multiplex with axonal damage	(27-35%) Myocardial infarction, pericarditis, congestive heart failure	—	Peripheral eosinophilia (>1500 μ L); ANCA (especially p-ANCA) positivity in 30-40% of cases

immune response, with a predominant Th1 profile, responsible for the production and release of pro-inflammatory cytokines, particularly tumor necrosis factor (TNF)- α and interferon (IFN)- γ , which stimulate the expression of surface antigens on activated neutrophils. The most important of these antigens is proteinase 3 (PR3), which is the target of cytoplasmic (c)-ANCA, present in 80% of cases; in 10% of cases the target is represented by myeloperoxidase (MPO), which induces the production of perinuclear (p)-ANCA autoantibodies. The interaction between c-ANCA and their antigen causes neutrophil's degranulation, with release of proteases and reactive oxygen species and production of pro-inflammatory cytokines and other effector molecules responsible for the tissue damage.¹¹ The activation of the complement cascade, with formation of the membrane attack complex (MAC [molecular complex attack]C5b6789), further promotes the ANCA-associated activation of neutrophils amplifying the inflammation and tissue damage. These pro-inflammatory pathways determine the development of systemic necrotizing vasculitis, glomerulonephritis and necrotizing granulomatous inflammation with predominant involvement of the upper airways.¹² On the other hand, a Th2-mediated immune response seems to play a pivotal role in more severe forms of GPA.^{13, 14} Recent studies have also pointed at a Th17 immune response in the disease.^{15, 16} Finally, an impaired function of

regulatory T cells (Tregs) has been demonstrated in GPA, leading to an imbalance between Tregs and Th17.¹⁶⁻¹⁸

Cutaneous features

Skin involvement is seen in around 50% of patients suffering from GPA.^{7, 19} The most common skin lesion is palpable purpura; tender subcutaneous nodules, papules, vesicles and blisters as well as necrotic-ulcerative lesions and livedo reticularis complete the wide clinical spectrum. This cutaneous picture is similar to that of the so-called cutaneous small vessel vasculitis, which is the most common type of vasculitis with predominant skin involvement. These cutaneous manifestations most commonly occur on the lower extremities but may also appear on the face and scalp.^{7, 19} Ulceration and gangrene of the digits or penis can rarely develop (Figure 1A).^{4, 7} Few cases of GPA presenting with skin ulcers clinically mimicking pyoderma gangrenosum have also been reported (Figure 1B).^{4, 7, 20-23} A rare distinctive subset of GPA limited to the facial region and upper airway mucosa, lacking systemic involvement but showing a locally aggressive behavior with cartilage and bony destruction, has recently been described;^{3, 24} these cases have to be included in the setting of localized GPA mentioned above. Oral lesions have been reported in 10-62% of patients and may be the presenting sign in 5-6% of cases. Oral involvement most



Figure 1.—A) Gangrene of penis in a patient with granulomatosis with polyangiitis (GPA); B) pyoderma gangrenosum-like presentation of GPA; C) nasal deformity with a saddle nose appearance in GPA.

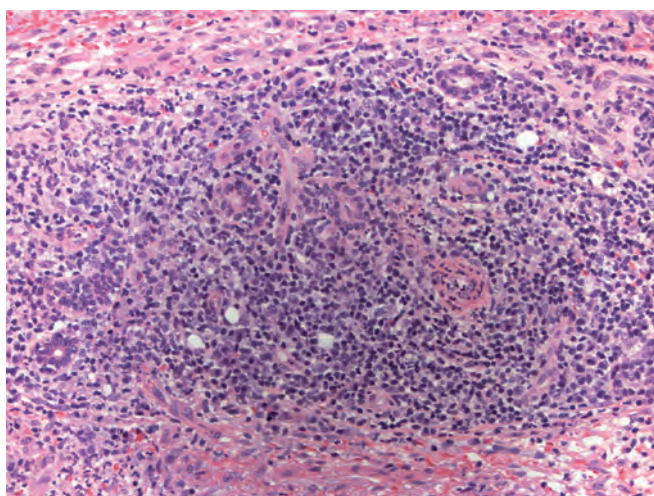


Figure 2.—Skin biopsy specimens showing granulomatous inflammation around dermal small vessels in granulomatosis with polyangiitis (hematoxylin-eosin stain; original magnification, X 200).

commonly manifests as nonspecific erosive/ulcerative lesions or can rarely presents with the so-called strawberry gingivitis, which is a hyperplastic granular gingivitis nearly pathognomonic for GPA.²⁵⁻²⁷ The extracutaneous manifestations involve different organs and systems; particularly common is the involvement of the upper airways, which is found in 95% of patients and is characterized by sinusitis with purulent or hematic discharge and may cause ulceration of the nasal mucosa and palate. Nasal deformity with a saddle nose appearance is not uncommon (Figure 1C), while less frequent is the perforation of the septum. Pulmonary involvement (85-95% of cases) clinically presents with cough, dyspnea, and, sometimes, hemoptysis. The most common ocular

manifestations of active GPA include conjunctivitis, keratitis and uveitis; retinal vasculitis or thrombosis and orbital granulomatous masses can also develop, possibly leading to blindness. Cardiovascular (pericarditis, valvular abnormalities and cardiomyopathy) and central and peripheral nervous system involvement (headache, meningitis, cerebrovascular events, peripheral neuropathy, sensory-motor and cranial nerve palsies) are rare. Renal involvement (75%) usually dominates the clinical picture and, if untreated, is directly or indirectly an important cause of death. The criteria for the diagnosis of GPA, recently revised, are based on a combination of clinical manifestations of vasculitis affecting the upper and lower airways as well as renal district with positive serology for c-ANCA antibodies.¹¹

Histopathological aspects

The histopathological pattern of leukocytoclastic vasculitis is present in up to 50% of skin biopsy specimens, sometimes with associated granulomatous inflammation. Leukocytoclastic vasculitis is characterized by a perivascular inflammatory infiltrate mainly consisting of neutrophils, with variable numbers of lymphocytes and eosinophils, and fibrinoid necrosis of the wall of dermal small vessels; endothelial cell swelling, neutrophil fragmentation, nuclear dust and red blood cell extravasation are also seen. Granulomatous inflammation around vessels or palisading necrotising granulomas as seen in the internal organ infiltrates are uncommonly demonstrated in GPA lesional skin (Figure 2). In the remaining cases, histology shows nonspecific perivascular lymphocytic infiltrates.^{7, 24}

Direct immunofluorescence studies

Direct immunofluorescence on lesional skin usually shows immunoglobulin (Ig), particularly IgM, and complement (C)3 deposits around the wall of dermal small vessels.^{7, 28}

Laboratory findings

The presence of c-ANCA (PR3-ANCA) has been reported in 90% of cases of the systemic form,⁴ suggesting to consider these autoantibodies an useful marker for multisystem GPA. On the other hand, c-ANCAs are absent in up to 40% of patients with localized GPA.^{3, 24, 29}

Differential diagnosis

From a dermatological point of view, cutaneous small vessel vasculitis is the first condition which has to be ruled out; the latter may be excluded based on the absence of visceral involvement showing histopathological aspects typical of GPA. Differential diagnosis to consider with the presentation of GPA limited to the face and upper respiratory tract includes a heterogeneous group of disorders. The main differential diagnosis is an aggressive form of pyoderma gangrenosum (PG) involving predominantly the face, neck and upper truncal region, originally mentioned as malignant pyoderma. Indeed, patients initially diagnosed as malignant PG upon follow-up can be reclassified as GPA due to evidence of systemic involvement. However, in PG, the ulcer presents with an undermined raised erythematous-violaceous border, is often associated with papulo-pustules and its histology shows a mainly neutrophilic infiltrate, usually without frank leukocytoclastic vasculitis. Extranodal natural killer / T-cell lymphoma should also be considered; however, the histopathological findings combined with lacking of clonality on molecular biology allow one to rule out lymphoma.²⁴ Cocaine-induced destructive lesions of the midline may mimic ear, nose and throat-limited GPA; however, inconsistent ANCA pattern and particularly histological findings not suggesting GPA should be recognized as features of cocaine-induced midline destructive lesions.³⁰ Finally, infectious disorders, particularly deep mycoses such as blastomycosis, may be excluded on the basis of microbiological grounds.²⁴ When ulceration or gangrene of the dig-

its or penis develops, polyarteritis nodosa should be ruled out. Strawberry gingivitis may resemble other forms of hyperplastic gingivitis, such as that triggered by cyclosporine treatment or Langerhans cell histiocytosis involving oral mucosa.³¹

Prognosis

After the introduction of corticosteroid and immunosuppressive therapy, GPA prognosis is generally good, with a reported survival between 85% and 97% at 1 year, 69% and 91% at 5 years, and 75% and 88% at 10 years.³² Renal involvement is the major prognostic factor in GPA patients, and infections and renal failure are the main causes of mortality in the first 5 years following the diagnosis. Moreover, age affects survival since patients over the age of 50 years have a poorer survival.^{4, 5, 32} The localized forms with an ear, nose and throat presentation are less severe than the systemic forms with renal involvement but are locally aggressive and show a more chronic-relapsing clinical course.^{4, 7, 24}

Treatment

“Pulsed” glucocorticoids, namely methylprednisolone 500 or 1000 mg intravenously daily for 3 days followed by oral prednisolone 0.5-1 mg/kg/daily for at least 4 weeks, are commonly used to induce clinical remission in GPA. Oral and “pulsed” intravenous cyclophosphamide is considered equally effective in inducing clinical remission.^{33, 34} Methotrexate is used in limited or mild non-organ, non-life threatening GPA for remission induction.³⁵ However, methotrexate induction has been reported to be associated with a higher relapse rate in comparison to patients treated with a cyclophosphamide-containing induction regimen.³⁶ Recently, rituximab, the anti-CD20 monoclonal antibody, has been approved by the United States Food and Drug Administration (FDA) for the management of GPA. The attack schedule consists of a dose of 375 mg/m² weekly for 4 weeks. Rituximab proved to be effective both in achieving clinical remission in active GPA and in preventing relapses.³⁷ Cutaneous manifestations of GPA are usually responsive to immunosuppressive agents given to control systemic disease. For the recently described subset of GPA limited to the face and upper airways mucosa, the combination of prednisone and cyclophosphamide represents the main-

stay of treatment as for systemic disease, due to its locally aggressive behavior.²⁴

Eosinophilic granulomatosis with polyangiitis (CSS)

Definition

CSS, actually known as eosinophilic granulomatosis with polyangiitis (EGPA), is a rare systemic vasculitis involving small and medium vessels and affecting several organs and systems.²⁸ The estimate incidence is approximately 0,11 to 2,66 new cases per 1 million people per year, with an overall prevalence of 10,7 to 14 per 1 million adults.^{38, 39} No gender predominance or ethnic predisposition has clearly been demonstrated in EGPA.^{40, 41} The disease usually manifests between 7 and 74 years of age, with a mean age at onset of 38 to 54 years. EGPA usually starts with asthma, often accompanied by allergic rhinitis and sinusitis (first step of the disease). The second step of the disease is characterized by peripheral eosinophilia and extravascular granulomas in different organs. In the third step, clinical manifestations due to systemic vasculitis are evident.⁴² Two EGPA subsets have been recognized, depending on the presence or absence of ANCA: ANCA-positive patients suffer more from vasculitis symptoms, such as glomerulonephritis, peripheral neuropathy and lung disease, whereas ANCA-negative patients more frequently develop heart involvement.⁴³⁻⁴⁵ The survival rate of EGPA ranges from 68% to 100% at 5 years.⁴⁶

ETIOLOGY AND PATHOGENESIS

Genetic studies have shown an association with HLA-DRB1 * 04 and HLA-DRB1 * 07. The potential triggering agents in EGPA are drugs (anti-asthmatic drugs, leukotriene receptor antagonists, macrolides, anticonvulsants), vaccines and environmental factors, particularly infections.

The pathogenesis of the disease is mediated by a T cell immune response with a predominant Th2 profile but with an important cooperating role of Th1 and Th17 lymphocytes.⁴⁷ There have been several reports of an association between EGPA and thrombosis, as documented for hypereosinophilic syndromes.⁴⁸⁻⁵⁰ A prothrombotic state in EGPA has

recently been demonstrated; with this background, it has been suggested that eosinophil-derived tissue factor, activating the coagulation cascade, may play a role in the mechanism leading to thrombosis in patients with EGPA or hypereosinophilic syndromes as well as in patients with bullous pemphigoid, an eosinophil-mediated autoimmune bullous disease.⁵⁰⁻⁵³

CUTANEOUS FEATURES

Cutaneous involvement occurs in 40-50% of EGPA patients.^{43, 44} Palpable purpura and nodules, typically located on the limbs and scalp, are the most common skin manifestations, but livedo reticularis, vesicles, aseptic pustules and urticarial lesions can also appear at the same time or in different stages of the disease; papular and nodular lesions may undergo a necrotic–ulcerative evolution (Figure 3).²⁸ A maculopapular erythematous eruption resembling erythema multiforme has also been described.^{5, 7}

HISTOPATHOLOGICAL ASPECTS

The skin biopsy shows a leukocytoclastic vasculitis mostly involving venules; in some lesions, the vessel wall reveals fibrinoid changes surrounded by a granulomatous inflammatory process. Peculiar to this form of vasculitis is the finding of numerous eosinophils in the inflammatory infiltrate, in addition to neutrophils, lymphocytes and macrophages: this represents an important diagnostic clue. A relevant number of eosinophils are detectable also in EGPA granulomas, where they are associated with macrophages and multinucleated giant cells.^{7, 28}

DIRECT IMMUNOFLUORESCENCE STUDIES

Direct immunofluorescence on lesional skin usually shows the presence of IgM and C3 around the wall of dermal small blood vessels.^{7, 28}

LABORATORY FINDINGS

Classical laboratory findings of EGPA are peripheral blood eosinophilia (defined as a persisting eosinophil count >1500/μL), which is the most striking laboratory finding in EGPA,¹ and circulating ANCA autoantibodies, especially p-ANCA (MPO-ANCA), which are present in 30-40% of patients.^{43-45, 54}



Figure 3.-Necrotic-ulcerative lesions (A), livedo reticularis (b) and palpable purpura (C), and in eosinophilic granulomatosis with polyangiitis.

Differential diagnosis

When the disease presents with palpable purpura in combination with papules and nodules possibly evolving into necrotic-ulcerative lesions, cutaneous small vessel vasculitis should be considered; presentation with only livedo reticularis may suggest polyarteritis nodosa, while urticarial lesions can lead to misdiagnosing urticarial vasculitis. However, asthma, rhinitis and sinusitis as well as typical granulomas in different organs associated with peripheral eosinophilia support the diagnosis of EGPA.⁷

Prognosis

As for GPA, corticosteroids and immunosuppressants have dramatically improved the survival in patients affected by EGPA and, today, the overall 5-year survival of EGPA may reach 97%.⁶ The French Vasculitis Study Group has identified five prognostic factors, including elevated serum creatinine levels (>1.58 mg/dL), proteinuria (>1 g per day), gastrointestinal tract involvement, cardiomyopathy and central nervous system involvement.⁵ Moreover, disease-related organ damage, particularly heart and

kidney failure as well as chronic neuropathy, may severely impair the quality of life of EGPA patients.

TREATMENT

The first-line therapy are glucocorticoids alone or in association with immunosuppressants,⁵⁴ particularly methotrexate, which is also used as maintenance drug.⁵⁵ "Pulsed" intravenous cyclophosphamide represents also a first choice treatment for remission induction has been successfully used for remission induction.⁵⁴ High-dose intravenous immunoglobulins may be used in combination with immunosuppressants or in monotherapy for refractory cases or for those complicated by severe infections, respectively.⁵⁶

Recent trials have demonstrated that targeting IL-5, the major survival factor for eosinophils, significantly reduces exacerbations in asthmatic patients with sputum eosinophilia and allows glucocorticoid tapering in patients with hypereosinophilic syndrome.⁵⁷ These results prompted the use of the anti-IL5 antibody mepolizumab in EGPA.⁵⁸ Rituxumab has also been successfully given in refractory cases^{59, 60} and in patients with predominant renal involvement.⁵⁸ Cutaneous manifestations of EGPA are usually responsive to the drugs administered for controlling systemic disease.⁷

Conclusions

GPA is a multifocal vasculitis characterized by frequent involvement of the upper and lower respiratory tract and kidneys. The presence of c-ANCA with anti-PR3 specificity is observed in more than 90% of patients with GPA. Two phenotypes of the disease are recognized: systemic forms, with potentially life-threatening manifestations, and other ones that are more limited forms.

EGPA is a disseminated necrotizing vasculitis with extravascular granulomas occurring exclusively among patients with asthma and tissue eosinophilia. Circulating ANCA autoantibodies, especially p-ANCA with anti-MPO specificity are present in 30-40% of EGPA patients. After the introduction of corticosteroid and immunosuppressive therapy, the prognosis of these two ANCA-associated vasculitides is generally good, with a survival at 5 years varying from 69% to 97%. Polymorphic cutaneous manifesta-

tations can occur during the course of both disorders, including palpable purpura, livedo reticularis, papules, nodules, bullae and necrotic-ulcerative lesions; PG-like ulcers and lesions resembling erythema multiforme have been described in GPA and EGPA, respectively. Oral involvement is not uncommon in GPA and may manifest as nonspecific erosive lesions or as the so-called strawberry gingivitis. Considering that skin involvement is common in ANCA-associated vasculitides and may also be their presenting sign, the role of dermatologist is crucial in the early diagnosis and management of these forms.

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Drug-induced cutaneous vasculitides

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Cutaneous vasculitides (CV) can be idiopathic or secondary to several triggers, including drugs, which account for up to 30% of all the cases of CV. Several drugs can induce CV, including some medications commonly used in dermatology, including minocycline, and several new drugs, such as anti-TNF agents. Different pathomechanisms are involved in the development of drug-induced CV, including the formation and deposition of immune complexes, the induction of neutrophil apoptosis, the formation of neoantigens between the drugs and proteins from the host, the shift of the immune response, and others. Although the diagnosis is difficult, because the clinical picture of drug-induced CV is in general indistinguishable from that of other forms of CV, it is important to recognize such entities in order to correctly manage the patient. Anamnesis, diagnostic algorithms to assess the likelihood of the association between a drug and a cutaneous reaction, skin biopsy and laboratory testing (including the search for antineutrophil cytoplasmic antibodies) are useful tools to make a diagnosis of drug-induced CV. About the therapy, while in idiopathic vasculitides the treatment is usually more aggressive and long-lasting, very often requiring a maintenance therapy with immunosuppressive drugs, in drug-induced CV the discontinuation of the suspected drug alone is usually enough to achieve complete remission, making the prognosis usually very good.

KEY WORDS: Vasculitis - Drug-related side effects and adverse reactions - Antibodies, Antineutrophil Cytoplasmic

Vasculitides are a heterogeneous group of diseases characterized by inflammation and necrosis of blood vessels. Vasculitides presenting with skin involvement, namely cutaneous vasculitides (CV), may be: 1) skin-limited vasculitis; 2) skin-dominant

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variant of a systemic vasculitis; or 3) cutaneous manifestation of a systemic vasculitis.

CV may be primary or secondary. Secondary CV recognize a wide range of causative agents, including drugs and medications, that account from 10 to 30% of all the forms of CV,¹⁻⁶ although the estimated incidence of drug-induced CV is very low, probably less than 1/100 000 people per year, and vasculitis is one of the rarer patterns that occur as a drug reaction (accounting for about 1-3% of reactions to any individual drug).^{7, 8}

In the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC2012),⁹ drug-induced vasculitides were included for the first time within the group of vasculitis, while, for example, they were not included in the previous CHCC1994.¹⁰

In fact, in CHCC2012, they are reported within the group of vasculitis associated with probable etiology, and are reported as drug-associated immune complex vasculitis and drug-associated anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis.⁹ However, the cutaneous forms of drug-induced vasculitides do not have a proper category in such a nomenclature system.

Theoretically, all the forms of CV, including polyarteritis nodosa (PAN), immune complex vasculitis, ANCA-associated vasculitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis

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(Churg-Strauss), urticarial vasculitis and others, can be triggered by drugs.

In this review, the causative drugs, the pathogenesis, the clinical features as well as the diagnosis and treatment of drug-induced CV will be described and discussed, in order to improve the knowledge of this often unrecognised clinical entity with the aim of a better care of the patients.

Causative drugs

Many drugs may cause CV, as reported in several papers.¹¹⁻¹³ The importance of various drugs as a trigger is questionable, since in most of the reported cases in the Literature the diagnosis was not confirmed neither by histopathological examination nor by re-challenge with the offending drug. However, among the medications that can cause vasculitis (Table I), some of them seem to be more frequently implicated, including penicillins, cephalosporins, clindamycin, erythromycin, quinolones, propylthiouracil, hydralazine, thiazides, phenytoin, allopurinol, and non steroideal anti-inflammatory drugs. Although less frequently than the medications reported above, some of very commonly used drugs in dermatology, such as minocycline,¹⁴ tumor necrosis factor (TNF)-inhibitors,¹⁵ retinoids,¹⁶ methotrexate,¹⁷ and rituximab¹⁸ can cause CV.

Minocycline

Minocycline is a tetracycline antibiotic widely used for the treatment of acne vulgaris and has been

implicated in the development of drug-induced lupus erythematosus. Several cases of minocycline-induced CV have been reported in the Literature.¹⁴ Most of the patients had lesions resembling PAN (either the systemic or the cutaneous variants), showing subcutaneous nodules associated with livedo reticularis. Histopathological examination showed involvement of small vessels, medium vessels or both. Systemic involvement was not uncommon, including fever, weight loss, malaise, arthritis, myalgias and neuritis; moreover, anti-nuclear antibodies (ANA) and ANCA were often detected. Most cases of vasculitis due to minocycline have been reported after long-term use (>2 years), mainly in patients treated for acne. Therefore, in CV affecting young people exhibiting autoimmune clinical manifestations, a potential role for minocycline should be ruled out.¹⁹

TNF- α inhibitors

The group of TNF-inhibitors encompasses different types of drugs that are able to block the TNF- α pathway. In dermatology, they are mainly used for the treatment of psoriasis and psoriatic arthritis, although they are effective even in other inflammatory skin diseases. Along with increasing use of these agents in clinical practice, secondary autoimmune conditions paradoxically induced by anti-TNF- α therapy have developed,^{20, 21} including vasculitis, that is the most common autoimmune disease associated with TNF-inhibitors.²² According to a recently published paper by Sokumbi *et al.*,¹⁵ more than 200 cases of anti-TNF-induced vasculitis have been reported in the literature. Among the anti-TNF agents involved,

TABLE I.—Drugs associated to the development of cutaneous vasculitis (modified from Kim MJ *et al.*).¹⁸

Common	Uncommon	Rare
Penicillins	ACE inhibitors	Amiodarone
Cephalosporins	Beta-blockers	Aspirin
Minocycline	Clindamycin	Antipsychotics
Quinolones	Cocaine+levamisole	Gabapentin
D-penicillamine	COX-2 inhibitors	Insulin
Propylthiouracil	Furosemide	Leflunomide
TNF- α inhibitors	Interferons	Metformin
Hydralazine	Isoniazide	Mefloquine
Methotrexate	Leukotriene inhibitors	Methamphetamine
NSAIDs	Macrolides	Phenothiazines
Allopurinol	Retinoids	Contrast media
Thiazides	Sulfonylureas	Rituximab
Phenytoin	Vancomycin	Antidepressants
Cimetidine	Warfarin	Bortezomib

etanercept, infliximab and adalimumab were the most frequently implicated, but also golimumab was reported to be the trigger in some cases.^{23, 24}

Cutaneous involvement has been described in about 60-80% of the patients, and includes palpable purpura, ulcerated lesions, blisters, erythematous macules and other manifestations. About half of the cases show systemic disease, including neuropathy as well as renal and lung involvement. Histopathological examination showed the presence of leukocytoclastic vasculitis of the small vessels in the majority of the patients with skin involvement; direct immunofluorescence of the skin revealed immunoglobulin A (IgA) deposits in the skin and/or in the kidneys in some cases, supporting a diagnosis of IgA vasculitis.¹⁵

The discontinuation of the drug alone causes an improvement of the manifestations in the majority of the cases; moreover, although the subsequent use of alternative anti-TNF- α agents may be possible, this decision should be approached with caution.¹⁵

Retinoids

Retinoids are synthetic derivatives of vitamin A that are able to modulate cell proliferation and differentiation, as well as humoral and cellular immune response. Retinoids are used for several skin conditions, including acne and psoriasis. Some cases of drug-induced CV due to isotretinoin and etretinate have been reported in the Literature, together with the so called "retinoic acid syndrome", that is associated with the use of all trans retinoic acid in patients acute promyelocytic leukemia and is characterized by systemic involvement generally without skin lesions.¹⁶ By contrast, both isotretinoin and etretinate have been implicated in cases of ANCA-positive CV, granulomatosis with polyangiitis (Wegener's), PAN, and others.^{16, 25-27}

Methotrexate

Methotrexate is one of the more commonly immunosuppressant drugs used for numerous immune-mediated skin diseases, including psoriasis. Moreover, it is widely used in rheumatology, gastroenterology and in oncology. In the Literature, some cases of methotrexate-induced CV have been reported, including cases of skin-restricted vasculitis with a histopathological pattern of leukocytoclastic

vasculitis,^{17,28,29} a case of a patient with exacerbation of a pre-existing urticarial vasculitis,³⁰ and a case of systemic vasculitis with diffuse skin involvement.³¹

Rituximab

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody against the CD20 antigen expressed on the surface of normal and malignant B lymphocytes. In dermatology, it is mainly used for the treatment of patients with autoimmune bullous diseases, connective tissue diseases and vasculitis. According to a review by Kim *et al.*,¹⁸ three cases have been reported yet of biopsy-proven rituximab-induced vasculitis involving the skin. Two of them developed purpuric lesions on the lower limbs and the abdomen,³² while the third patient presented with generalized hemorrhagic vesicles and blisters.³³

Interestingly, the pathophysiology of vasculitis in patients treated with rituximab, although controversial, could be related with the deposition of rituximab-antirrituximab antibody immune complexes in the vessel walls. Another possible explanation, as for anti-TNF- α agents, is linked to the immunomodulatory effect of the drug with a shift of the immune response.

Some increasingly used drugs, including leukotriene inhibitors, interferons, and several monoclonal antibodies can cause CV. In these cases, it may be difficult to distinguish drug-induced CV from CV due to the underlying disease.³⁴

Finally, illicit drugs, excipients, drug and food additives, nicotine patches, pigment used in tattoos, intravenous drugs and vaccines can cause CV. Among them, cases of CV induced by the intake of cocaine adulterated with levamisole are increasingly reported. Levamisole is a drug used both for human and animals for its anti-helminthic and immunomodulatory effects. Levamisole is also able to potentiate the pharmacologic effects of cocaine, so its addition allows for the adulteration of cocaine with minimal impact on its perceived potency.³⁵ Levamisole-induced CV is characterized by the occurrence of purpuric lesions on the face and the extremities; ANCA specific for human neutrophil elastase (HNE) are frequently detected.³⁶ The differential diagnosis includes Wegener granulomatosis and cocaine-induced midline destructive lesions, due to the localization and the association with cocaine intake. Since levamisole is

found as an adulterant in about 80% of cocaine,³⁷ clinicians need to be aware of this entity.

Pathogenesis

The pathogenesis of drug-induced CV is not fully understood. In some cases, different drugs may produce a similar clinical picture together with a similar autoimmune profile, suggesting a common mechanism. In other situations, the inflammatory response leading to the vascular damage directly depends on the nature of the causative agent. Therefore, the pathogenesis of drug-induced CV can be considered multifactorial.³⁴

Among the potential mechanisms underlying the development of drug-induced CV, the most commonly implicated are the formation and deposition of immune complexes (IC), the direct activation of the complement by the culprit drug, the direct damage to the neutrophils with consequent liberation of autoantigens, the induction of neutrophil apoptosis, the formation of neoantigens between the drugs and proteins from the host, the shift of the immune response, and others.¹² Some of the main mechanisms responsible for the development of drug-induced CV are described in detail below.

IC deposition

Most of the drug-induced CV are caused by the formation of IC that form in the presence of antigen excess. Accordingly, after drug intake, antidrug antibodies develop and bind the culprit drug that acts as autoantigen with the eventual formation of IC. IC deposition in postcapillary venules activates the complement which, in turn, induces mast cell degranulation and neutrophil chemotaxis. Neutrophils release proteolytic enzymes and free oxygen radicals, leading to damage of the vessel wall.³⁸ This mechanism probably accounts for 10-20% of small vessel CV³⁹ and is associated with several drugs including antibiotics, diuretics, anticonvulsivants and also by TNF-inhibitors.⁴⁰

Neutrophil apoptosis

Some drugs, including sulfasalazine, can induce neutrophil apoptosis that is associated with translocation of ANCA antigens to the cell surface, which

then induce the production of ANCA. ANCA, in turn, are able to bind the membrane-bound antigens, causing a self-perpetuating constitutive activation by cross-linking proteinase-3 (PR3), myeloperoxidase (MPO) or other antigens and Fcγ receptors.⁴¹

Shift of the immune response

Some of the culprit drugs may act as modulators of the immune system, facilitating the development of an autoimmune response. As an example, anti-TNF-α agents, via the inhibition of TNF-α, can promote the expression of type 1 interferon by altering the balance between Th1 and Th2, leading to the upregulation of antibody production and thus to the development of vasculitis. Similar mechanism affecting the immune response can be caused by the therapeutic use of cytokines, such as interferon, that is reported to cause drug-induced CV.⁴²⁻⁴⁴

Clinical features

The clinical manifestations of drug-induced CV are similar to those of primary CV, and may include both cutaneous signs and systemic involvement.

Skin involvement encompasses a wide range of manifestations, from palpable purpura to livedo reticularis, petechiae, urticarial lesions, papules, nodules, necrotizing vasculitis, ulcerations, or polyarteritis-like appearance (Figure 1).



Figure 1.—Allopurinol-induced cutaneous vasculitis presenting as purpuric and necrotic lesions of the legs.

Systemic involvement is usually mild and non specific and can occur with fever, malaise, arthralgia, myalgia and weight loss. By contrast, renal or pulmonary involvement, that can complicate systemic vasculitis and are associated with a worse prognosis, are usually absent.⁴⁵

Due to the fact that clinical manifestations, and in particular the skin signs, are quite unspecific, the differential diagnosis between drug-induced CV and primary vasculitis or CV secondary to causes different from drugs based only on clinical appearance is not possible, and other diagnostic tests should be performed.

Pathology

As in other forms of CV, skin biopsy for histopathological examination and direct immunofluorescence is mandatory to achieve the diagnosis and should be performed in the right site and at the right time, in order to avoid unspecific or false negative results (see the paper by Filosa *et al.* in this issue).

In general, findings from histopathological examination usually do not differ between idiopathic and drug-induced CV, being leukocytoclastic vasculitis of the small vessels the most common finding in case of CV. However, in some cases, histopathological examination can also suggest a potential drug etiology. In fact, as demonstrated by Barhami *et al.*,¹¹ a high tissue eosinophilia ratio in biopsy samples is a quite specific finding related to drug-induced CV.

Direct immunofluorescence of the skin can show immune deposits around blood vessels. This may be important for the diagnosis of IgA vasculitis (formerly Henoch-Schoenlein purpura), where IgA deposits can be found both in the skin and in the mesangial areas.

Diagnosis

As reported above, in general drug-induced CV are clinically indistinguishable from primary CV or CV due to other causes. Therefore, the differential diagnosis from other forms of CV is difficult and several issues should be considered.

The first step is a correct diagnosis of CV, that should be made combining data from the clinical observation, from the histopathological examina-

tion, from the direct immunofluorescence of the skin, and from the laboratory; moreover, all the tests that are useful to exclude CV secondary to infections, neoplasms or other known causes should be performed (the detailed discussion of these points do not fall within the scopes of the present review and is reported in other papers in this issue).

After the confirmation of the diagnosis of CV, the main tool to be used to suspect a drug as a causative agent is the anamnesis, that should investigate the timing of the eruption in relation to the introduction of new drugs (although sometimes the onset may be delayed for several months or even years from drug administration) and may be helpful to exclude other potential causes of vasculitis. Together with the anamnesis, several questionnaires have been designed for determining the likelihood of whether an adverse drug reaction is actually due to the drug rather than the result of other factors and can be helpful as additional tools for the diagnosis of drug-induced CV. Among them, the most commonly used are probably the Naranjo algorithm⁴⁶ and the Korean algorithm score.⁴⁷

One of the main points of these algorithms is the implementation of a challenge-dechallenge-rechallenge test, that is one of the standard means of assessing adverse drug reaction, but is not always easy to be performed. Positive dechallenge reactions with the resolution of CV on withdrawal of the medication associated with the recurrence of the manifestations after the reintroduction of the drug can be considered diagnostic of a drug-induced CV.

As reported above, histopathological examination it is not only crucial for the diagnosis of CV, but can also suggest a potential drug etiology in case of a high tissue eosinophilia ratio.¹¹

Together with the anamnesis, the challenge-dechallenge-rechallenge test, histopathology and laboratory data, although not very specific, can be helpful in diagnosing a drug-induced form of CV. In particular, about 20% of patients with drug-induced CV (and up to 80% of patients with drug-induced systemic vasculitis) have blood eosinophilia.^{11, 48} Moreover, ANCA testing is another laboratory test that should always be performed in the suspect of drug-induced vasculitis. In particular, ANCA assays using combined indirect immunofluorescence (IIF) and antigen-specific enzyme-linked immunosorbent assays (ELISA) rather than relying on either test alone are recommended.^{12, 48} In fact, IIF can be false

negative in some cases and cannot detect ANCA specificities, that can be important for the diagnosis since drug-induced CV have usually multispecific ANCA, while the other forms of ANCA-associated vasculitis usually show single ANCA specificity. More in detail, the majority of ANCA-positive drug-induced CV have been associated with P-ANCA pattern, MPO being the most frequently related antigen, although cases associated with PR3 C-ANCA have also been described.¹⁹ Other antibodies that can be found in drug-induced CV, often in combination with anti-MPO and/or anti-PR3, are directed against lactoferrin, cathepsin G, HNE, bactericidal permeability increasing protein (BPI), and azurocidin.⁴⁹ Regarding the most frequent implicated drugs, patients with hydralazine-induced CV are almost always positive for high-titer MPO-ANCA, that can be accompanied by HNE-ANCA and lactoferrin-ANCA. Patients with minocycline-induced CV are usually positive for MPO-ANCA, with some cases positive also for HNE, cathepsin G, BPI. Propylthiouracil is often associated to MPO-ANCA and, in a minority of cases, to HNE, lactoferrin, BPI, azurocidin,

cathepsin G. The positivity for both MPO- and PR3-ANCA is considered quite specific for patients with CV induced by levamisole-adulterated cocaine; in such patients, ANCA directed against HNE, cathepsin G, lactoferrin may also be found.

Other markers that are often positive in patients with drug-induced CV are ANA (that are almost always positive in patients with hydralazine-induced CV), anti-double strand DNA, and anti-histone antibodies, with few patients positive also for antiphospholipid antibodies.

Finally, although systemic involvement is usually less frequent than in CV not induced by drugs, several laboratory tests should be performed in order to assess the involvement of different systems basing on the clinical features (Table II). When necessary, medical imaging and/or biopsies in potential involved organs, including kidneys and lungs, should be performed.

Treatment

Since the pathogenesis of a confirmed drug-induced CV is directly linked to the culprit drug, the first step for the treatment of the disease is the discontinuation of any suspect medication, that may be all that is required to achieve the complete remission of the clinical manifestations. This is particularly important because the treatment for primary CV includes more aggressive procedures and might not be suitable for patients with drug-induced CV, who in general have a less severe course and usually do not require maintenance therapy.⁵⁰

Therefore, treatment should be based on individualised assessment and, in patients with organ involvement, it should depend on the severity of the clinical manifestations. Accordingly,

in patients with exclusive skin involvement, a short course of systemic or even topical corticosteroids, in association with supportive therapy (including compression and wound care in case of ulcerations) may be enough to control the disease.³⁴

By contrast, in cases with systemic disease, corticosteroids and other immunosuppressive agents (such as mycophenolate, azathioprine or, in severe cases, cyclophosphamide) may be necessary in order to improve organ function and prevent progression to severe, irreversible disease.

As general measures, it is important to avoid rechallenge and to carefully consider the use of drugs of the same class of the culprit one. Finally, the patient should be also followed-up (including ANCA testing) in order to monitor the occurrence of a chronic vasculitis even after the discontinuation of the drug.¹²

Conclusions

CV can be secondary to drug intake in up to 30% of all the cases of CV. Several drugs can induce CV, including some medications commonly used in dermatology and several new drugs, such as anti-TNF

TABLE II.—*Suggested laboratory investigations in patients with drug-induced cutaneous vasculitis.*

Complete blood count, ESR, C-reactive protein, electrolytes, protein electrophoresis
Liver function tests
Blood urea nitrogen, creatinin, urinalysis, urine cocaine and levamisole
C3, C4, ANCA, ANA, ENA, anti-dsDNA, anti-phospholipides

agents. Although the diagnosis is difficult, because the clinical picture of drug-induced CV is in general indistinguishable from that of other forms of CV, it is important to recognize such entities in order to correctly manage the patient. In fact, while in primary vasculitis the treatment is usually more aggressive and long-lasting, very often requiring a maintenance therapy with immunosuppressive drugs, in drug-induced CV the discontinuation of the suspected drug alone is usually enough to achieve complete remission, making the prognosis usually very good.

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Vasculitis and infectious diseases

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Vasculitis usually presents without a well-known underline cause (idiopathic vasculitis), nevertheless, it is sometimes possible to find out one or more causative agents (secondary vasculitis). Nowadays, thanks to the increasing amount of precise diagnostic tools, a piece of idiopathic vasculitis is reclassified as associated with probable etiology, which can be set off by several factors, such as infections. Infections are considered to be the most common cause of secondary vasculitis. Virtually, every infectious agent can trigger a vasculitis by different mechanisms which can be divided in two main categories: direct and indirect. In the former, infectious agents destroy directly the vascular wall leading, eventually, to a subsequent inflammatory response. In the latter, indirect form, they stimulate an immune response against blood vessels. Different infectious agents are able to directly damage the vascular wall. Among these, it is possible to recognize *Staphylococcus spp*, *Streptococcus spp*, *Salmonella spp*, *Treponema spp*, *Rickettsia spp*, *Cytomegalovirus*, *Herpes Simplex Virus 1* and *2*, and many others which have a peculiar tropism for endothelial cells. Conversely, another group of microbial agents, such as *Mycobacterium tuberculosis*, *Mycobacterium leprae*, Hepatitis B Virus, Human Immunodeficiency Virus and others, trigger vasculitis in the indirect way. This is due to the fact that they can share epitopes with the host or modify self-antigens, thus leading to a cross-self reaction of the immune system. These mechanism, in turn, leads to immunological responses classified as type I-IV by Gell-Coombs. Nevertheless, it is difficult to strictly separate the direct and indirect forms, because most infectious agents can cause vasculitis in both ways (mixed forms). This paper will analyze the link between infectious agents and vasculitis, focusing on direct and indirect secondary vasculitis, and on a group of probable infection-related idiopathic vasculitis, and finally on a group of idiopathic vasculitis with microbiological trig-

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gers. Furthermore, a diagnostic and therapeutic approach to vasculitis when an underline infection has been suspected is suggested.

KEY WORDS: Vasculitis - Etiology - Infection.

Vasculitis are a heterogeneous group of disorders characterized by a specific pattern of inflammation that affects the vessel wall resulting in necrosis, occlusion and aneurysm formation. Vasculitis can be divided in many different types according to the caliber of vessels affected and the involvement of one or more organs or systems. The skin may be organ seat of vasculitis in isolation or in combination with other organs.¹ Several classifications of vasculitis have been proposed in the literature,² among these, one referring to the caliber of vessels is commonly used.³ Chapel Hill Consensus Conference (CHCC2012) is a new vasculitis nomenclature system that specifies what findings must be observed in a specific patient to classify that patient for clinical research. This classification adds important categories to traditionally vasculitis. Features that vary among different forms of vasculitis include etiology, pathogenesis, type of vessels affected, clinical manifestations.

Vasculitis can be dichotomized in infectious vasculitis, known to be caused by invasion of pathogens in vessels, *versus* non-infectious vasculitis, not known to be caused by vessel wall invasion by pathogens.

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TABLE I.—*Antigens of secondary vasculitis.*

Infectious antigens	Non microbial antigens
Bacterial	Autoantibodies (ANA, IgG)
Viral	Allergens
Fungal	Drugs
Parassites	Tumoral antigens
	Others

CHCC addresses only vasculitis that are not known to be caused by direct invasion by pathogens; however, many infections are indirectly involved in the pathogenesis of some of the vasculitis addressed in CHCC. One example is the cryoglobulinemic vasculitis in HCV-patients. If a idiopathic-primary vasculitis is strongly associated with a specific etiology, the name (diagnosis) should have a prefix specifying the association (*i.e.*, HCV-cryoglobulinemic vasculitis: cryoglobulinemic vasculitis caused by an autoimmune response initiated by hepatitis C virus infection).⁴

Pathogenesis and causative agents of secondary vasculitis

The first descriptions of syphilitic aortitis date back to the last century. Vasculitis can be divided into primary (or idiopathic) and secondary vasculitis (caused by drugs, infections, neoplasms or systemic inflammatory diseases) (Table I). Among the secondary forms, infectious agents represent the most frequent responsible cause.⁵⁻⁷ The increasing devel-

opment of diagnostic tools has allowed to reclassify some forms of vasculitis, previously considered as idiopathic, such as probable infection related vasculitis.

In the literature infectious secondary vasculitis are related to different microbial agents such as bacteria, fungi, viruses, protozoa.⁸ The numerous infectious agents that can cause secondary vasculitis are listed in Table II.

Infectious agents can cause secondary vasculitis in two different ways: direct and indirect. In the former they destroy directly the vascular wall, in the latter they trigger immunological phenomena. Secondary indirect vasculitis can be classified by different immunological mechanisms, variously implicated in their pathogenesis, described by Gell-Coombs.^{6,9}

Secondary direct vasculitis

The damage of the vascular wall is directly caused by microbial agents in the direct secondary vasculitis, in which different pathogenic mechanisms can contribute to the inflammation of the vascular wall, such as vascular invasion by microbial agents from a contiguous infectious focus or by septic emboli departing from an infectious site faraway.^{10, 11}

Several bacterial agents, Gram positive and Gram negative such as *Staphylococcus spp*, *Streptococcus spp*, *Rickettsia spp*, *Salmonella spp*, *Treponema spp*, *Neisserie spp* usually show tissue tropism to vascular endothelium. In particular, *Staphylococcus*

TABLE II.—*Infectious underlying causes of secondary vasculitis.*

Mycoplasma spp	HBV	Aspergillus	Toxocara C.
Streptococcus spp	HCV	Mucor	Cystiercus
Staphylococcus spp	HSV 1-2	Coccidioides I.	Angiostrongylus
Salmonella	CMV	Niocardia	Loa loa
Rickettsiae	EBV	Curvularia	
Pseudomonas	Herpes hominis	Pseudallescheria	
Legionella	Human T cell V.	Fusarium	
Mycobacterium T.	Parvovirus B19	Metarrizium	
Neisseria spp	Rubella virus	Candida	
Klebsiella	Adenovirus		
Escherichia coli	Echovirus		
Aeromonas	Cosackie		
Treponema P.	Parainfluenza V.		
Borrelia B.	HAV		
Spirochete	HIV		
Morganella			



Figure 1.—Petechie spread centrifugally in Rickettsial infection.

aureus binds to endothelial cells leading to activation and subsequent enhanced expression of adhesion molecules, in particular P-selectin. As a result, there is an increased production of cytokines and chemotactic factors that activate the inflammatory cascade which in turn produces a vascular injury.^{6,9} *Rickettsia spp* is an obligate intracellular agent that damages directly the vessels by provoking endothelial cell lysis and consequent microleaks (Figure 1). Then these activate vascular cells that subsequently lead to phenomena of thrombosis.⁷ Conversely, *Neisseria gonorrhea*, a Gram negative bacteria, releases an endotoxin lipopolisaccharide which activates the complement with the subsequent destruction of the vascular wall.¹² *Neisseria meningitidis*, a Gram negative bacteria, causes meningococemia, a disease characterized primarily by fever and a petechial rash vasculitis. At least 13 strains of *N. meningitidis* are known, among these A, B, C, Y and W135 strains are mostly implicated in human disease. *N. meningitidis* owes its virulence to its polysaccharide capsule. In addition, these bacteria elaborate an endotoxin that is the primary trigger of the inflammation processes which in turn lead to vasculitis with multiorgan failure. In the early phase, *N. meningitidis* invades directly the vascular wall causing massive vascular necrosis and endothelial destruction (Figure 2). While the vasculitic process is mainly direct during acute meningococemia, it is predominantly indirect under chronic meningococemia. In fact, in this case, bacteria might not be detectable in skin lesions. This is because, in this phase, the vasculitis is caused by a deposit of circulating immune complex in the vascular wall.¹³

Treponema pallidum is a known cause of aortitis.



Figure 2.—Skin ulcers in a child with meningococemia.

Luetic aortitis, that typically occurs during tertiary syphilis, is characterized by an inflammatory infiltrate composed by lymphocytes and plasma cells around the vasa-vessel of the adventitia, and *T. pallidum* is rarely detected in arterial wall lesions. In addition syphilis can lead to retinal and cerebral vasculitis.¹⁴ Also *Borrelia* determines direct vasculitis with lymphocytic infiltration of the endothelial wall.^{15, 16} *Bartonella henselae*, a Gram positive bacterium is transmitted by cat scratches and bites and it causes cat-scratch disease. Cutaneous vasculitis may be associated with *Bartonella* infection, that has a well known tropism for endothelial cells.¹⁶ In *Pseudomonas aeruginosa* or Gram negative bacteremia, observed in neutropenic patients, smaller vessels may also be affected directly, with peripheral septic embolizations.

Some fungal agents as *Aspergillus* and *Candida* can invade directly the vascular wall by forming hyphal thrombus which in turn causes necrosis of the vessel involved. Zygomycosis (mucormycosis) is an increased important pathogen because of its high morbidity and the rising prevalence of immunosuppressive therapies (Figure 3). The organism is vasculotropic and vasculodestructive and is visible in histological sections as wide, brightly eosinophilic ribbons with hollow centers. *Fusarium* has



Figure 3.—Mucormycosis.



Figure 4.—Leucocytoclastic vasculitis in HBV patient.

been replacing *Candida* and *Aspergillus* as fungal pathogens in immunocompromised hosts because of better prophylaxis that has decreased the incidence of the other two pathogens. Skin lesions typically present as leathery, black eschars with edematous borders. The organism may be recovered in the vessels from a skin biopsy with specific stains or from blood cultures.

Several viral agents such as CMV, HSV1,2, HZV cause direct invasion of the endothelial wall, with cytopathic oedema and subsequent necrosis of the endothelium.¹⁷ Viral HSV particles and antigens were visualized in the media of affected blood vessels. In these patients, pathological studies performed on skin biopsy showed necrotizing arthritis and thrombosis of large and small vessels. During CMV infection, characteristic cytological features of small vessels, and viral particles and antigens, in medium vessels, are detectable in endothelial cells, arguing for a potential direct vasculitis-inducing effect of the virus. Prions may be correlated with endothelial damage.¹⁸

Secondary indirect vasculitis

Many microbiological pathogens can also induce secondary vasculitis by several different indirect mechanisms and in these cases vasculitis is the result of the immune response triggered by the infectious agent.

In particular *Mycobacterium tuberculosis*, *Myco-*

bacterium leprae, Hepatitis B Virus (HBV), Human Immunodeficiency Virus (HIV) and many others pathogens cause vasculitis by the indirect way.¹⁸ This is due to the fact that they can share epitopes with the host or modify self-antigens thus leading to a cross-self reaction of the immune system. In addition, they can lead to epitope spreading by injuring barrier zones such as blood-testis barrier or blood-brain barrier. These mechanisms in turn trigger immunological responses classified as type I-IV by Gell-Coombs.

More frequently infectious agents can trigger immune complex reactions, classified as type III by Gell-Coombs, in which antigens, that can be represented by entire organisms or antigenic portions of them, and immunoglobulins, IgM or IgG, form immune complexes. These, once they have reached the zone of equivalence, precipitate and are trapped within the vessel walls thus stimulating immune response which in turn leads to vascular injury that appears as vasculitis.¹⁴

HBV infection provides the typical example of viral mediated immune complex disease that causes indirect vasculitis (Figure 4). Immune complexes of HBV early-antigen and its antibodies are found in vessels, in association with complement, during vasculitis.¹⁶

With the advent of the AIDS epidemic, various types of vasculopathies have increasingly been described in HIV infected patients. The prevalence of vasculitis among HIV patients seems to be around 1-2%, but it highly increases to 23% in studies per-

formed on patients with symptoms and/or signs of vasculitis.

Vasculitis can be triggered by HIV through several pathogenic mechanism.¹⁴ In fact, it can either invade directly the vascular wall or set off a series of immunological reactions directed against vessels, such as immune complex formation and inflammatory cytokines production.

Vessels of every sizes, and any organ or system can be affected, nevertheless skin, peripheral and central nervous tissue are most commonly involved.

HIV infection can also lead to a hypersensitivity vasculitis which usually involve the skin and clinically appears as a palpable purpura. Types 2 and 3 cryoglobulinemia are detected in HIV-patients, nevertheless HCV-negative/HIV-positive patients are usually asymptomatic. Other types of vasculitis have been reported in association with HIV infection such as granulomatosis with polyangiitis-like, Churg-Strauss-like granulomatosis, Kawasaki-like disease, primary central nervous system angiitis, Behcet's syndrome and giant cell arthritis-like.¹⁹

Secondary mixed (direct and indirect) vasculitis

There are microbiological agents capable of activating mixed forms, characterized not only by a direct invasion of the wall but also by the activation of indirect immune mechanisms. For example, mycobacteria tuberculosis are able both to infiltrate the aortic wall by contiguity, departing from the mediastinal lymph nodes, and to induce indirectly leukocytoclastic vasculitis, by the formation of immune complex composed by bacterial antigenic fractions (Figure 5). Moreover, they can typically induce a type IV immunological response that lead to vasculitis, as observed in erythema induratum of Bazin. In this case, although the research culture give negative results, PCR could highlight antigenic fractions.¹⁴

Mycobacterium leprae, that has endothelial tropism, can cause direct and indirect vascular damage. It also cause vasculitis by immunological mechanisms triggering type IV reaction that produces a nodular vasculitis called erythema nodosum leprosum with typical macrophagic granulomas. In addition, immune complexes can determine Lucio's phenomenon with widespread lepromatous reactions during *Mycobacterium leprae* infection.²⁰

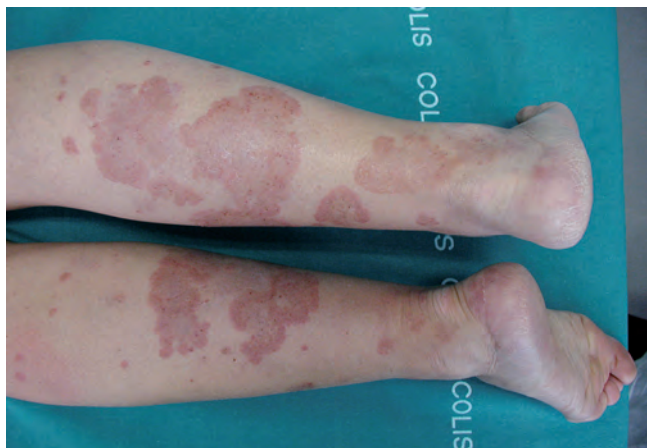


Figure 5.—Leucocytoclastic vasculitis in patient with tuberculosis.

Idiopathic vasculitis associated with probable infectious etiology⁴

These vasculitis have a strong association with a specific infectious agent, and the link is proved by clinical, laboratory and epidemiological data. In addition, clinical and prognostic features might be slightly different compared with the idiopathic non-infectious form. Moreover, these vasculitis use to regress or even resolve after specific antimicrobial therapy.

Polyarteritis Nodosa (PAN) is necrotizing arteritis of medium arteries not associated with ANCA. In the past the association between HBV and a PAN-like vasculitis was frequently reported (30-70%),²¹ but nowadays after the vaccination campaign, the prevalence of HBV infection in patients with PAN has dramatically decreased, in fact only 5-8% of cases of PAN are HBV related.^{1, 2} A possible link between HBV vaccination and PAN has also been hypothesized.^{4, 14} When an idiopathic-primary vasculitis is associated with a probable specific etiology, the name (diagnosis) should have a prefix specifying the association.

HBV-PAN is a classic example of type III or immune complex reaction in which early antigen (HBeAg) and its antibodies, after reaching the zone of equivalence, precipitate in blood vessels leading to an immune-mediated vascular injury.⁷

Histology shows a leukocytoclastic vasculitis with the deposition of immune complexes formed by viral antigens and antibodies.



Figure 6.—Petechiae and multiple purpuric papules with central necrosis on the plantar surface due to mixed cryoglobulinemia in HCV patient.



Figure 7.—Vasculitis in infection with hepatitis C virus.

HBV-PAN is seen predominantly within 6 months after the infection (average onset in 4 months) and may precede or follow overt liver disease.^{1, 3} HBV-PAN is virtually indistinguishable from idiopathic PAN, however minor clinical and prognostic differences have been reported. In fact in HBV-PAN the onset is acute, sero-conversion is followed by complete healing and relapses are very rare (10%). Some authors report a positive outcome,³ others a higher mortality rate compared with the idiopathic form (30% vs. 10%).¹ Moreover, in HBV-PAN it is eventually recognizable an early phase with acute serum sickness-like illness, a mild phase showing arthritis and/or cutaneous vasculitis and a severe stage consisting with multi-system PAN disease.⁴

The differential diagnosis between HBV-PAN and PAN is significant as the differences in the pathogenesis subtend a distinct therapeutic approach (see later). A HIV-PAN-like seems to be most frequently associated with HIV infection, arising in HBV-negative patient. This HIV-PAN is less aggressive and chronic than idiopathic-PAN, involving mainly muscles and peripheral nerves.¹⁹

After 1989, when HCV have been discovered, a strong association between HCV and CV was noted and since then, several cases of CV in HCV-patients have been reported reaching the amount of 80-90% of CV arising in chronic HCV-patients. HCV-Cryoglobulinemic vasculitis is an idiopathic form that in most of the cases can be caused by an autoimmune

response initiated by hepatitis C virus infection. HCV stimulates an immune response that results in producing monoclonal IgM against the Fc of IgG, these immune complexes associated with viral antigens tend to precipitate at low temperature (4 °C), thus being named cryoglobulins. These cryoglobulins once trapped in blood vessels activate the classic complement pathway thus attracting neutrophils and causing the vasculitic process.²¹

The prevalence of cryoglobulins in HCV-patients is 40-60 % and it is usually type II; it has been seen that type III cryoglobulinemia in HCV-patients converts in type II suggesting that this may represent the final evolutionary form. 80-90% of patients with cryoglobulinemia are HCV-infected, with presence of circulating HCV-RNA, HCV in lesions and HCV-RNA in cryoprecipitate. Although there is a high prevalence of cryoglobulinemia in HCV-patients fortunately overt CV arises in only 5-10% of cases.²²

The most frequent clinical presentation is palpable purpura (70-90% of CV), being the main sign. It involves the lower limbs and may extend to the abdominal area and rarely affects the upper limbs ^{21, 22} (Figures 6, 7).

Extracutaneous involvement consists with arthralgia (40-80%), arthritis (10%), neuropathy (8-55%) and renal manifestations (20-35%).²³

HBV has also been associated with CV (predominantly type III). Cryoglobulinemia and vasculitis have also been reported in HIV infected patients.¹⁹

Idiopathic vasculitis with possible infectious trigger

The link between these vasculitis and infections is weak and there isn't an association with a specific infectious agent. Different types of infections can anticipate, follow or onset with the same idiopathic vasculitis. Clinical, prognostic and laboratory features are typical of the idiopathic form and it is not possible to distinguish these forms from those not triggered by infections. Moreover the antimicrobial therapy don't affect the outcome at all, or might modify it slightly.

Several epidemiological and clinical data suggest that granulomatosis with polyangiitis or Wegener's Granulomatosis (WG) can be triggered by infectious agents; among these a peculiar role is probably played by *Staphylococcus Aureus* (SA). In WG relapses are usually associated with respiratory tract infections and circulating immune complexes leading to the formation of granulomatous inflammation of the respiratory tract. Chronic nasal carriage with SA has been associated with relapses of WG, and it has been seen that treatment with cotrimoxazole reduces the incidence of relapses.²⁴ Antineutrophilic cytoplasmic antibodies (ANCA) directed against proteinase and myeloperoxidase are closely associated with Wegener's granulomatosis (ANCA associated vasculitis).

It has been speculated that SA superantigens could stimulate autoreactive B-cells to produce PR3-ANCA. Wegener's granulomatosis-granulomas are rich in neutrophils and display features of tertiary lymphoid tissue neof ormation, including presence of B cells and plasma cells.²⁵ SA (as other infectious agents) can stimulate the production of TNF- α . Furthermore SA can both activate LcT and LcB. T lymphocytes respond to some SA antigens, which can act as superantigens, determining the proliferation of T cells. Instead, LcB are stimulated to produce ANCA by some cell-wall component of SA.³ Moreover, SA can stimulate directly the neutrophils leading to surface expression of proteinase 3, the target antigen in WG. Finally peptides from SA may induce, by molecular mimicry, antibodies to PR3.^{26, 27}

Also Parvovirus b19 and *Nocardia* are related to WG, but this association is weak and due predominantly to case reports.²⁸

Among idiopathic small vessel vasculitis forms, Henoch Schonlein purpura (HSP) frequently onsets

2 weeks after an upper respiratory tract infection. Several studies have reported that positive ASLO are detectable in a minority of patients, but no causal role has been demonstrated. Immune complexes are said to play a role in HSP pathogenesis in response to an antigenic trigger, as in other idiopathic cutaneous small vessel vasculitis (acute hemorrhagic edema (AHE) of infancy and erythema elevatum diutinum (EED)). Although the etiology of these vasculitis, AHE and EED, is unknown, 75% of reported cases have occurred in association with a recent infection. The most commonly associated infectious agents are *Staphylococci*, *Streptococci* and *Adenovirus* but other bacteria and viruses have been reported. The pathogenesis is thought to involve immune complex deposition in response to an antigenic trigger.²⁹

Kawasaki disease (KD) has also been associated with infections. Although several pathogens have been studied there is no evidence for their contribution to pathogenesis. Nevertheless, KD has got the typical clinical and epidemiological feature of infectious related disease. In fact, it always arises in childhood, is more common in boy and presents seasonal variation, furthermore its clinical presentation is characteristic of an acute childhood infection.²⁹

In animal experimental model it has been established a pathogenetic role for *Candida* and *Lactobacillus*. It is possible that super antigens can stimulate LcT. Probably, KD's pathogenesis is multifactorial being present environmental, genetic and immunological factors.³ Among idiopathic large vessels vasculitis, Takayasu arteritis (TAK) and giant cell arteritis (GCA) show a possible link with microbiological agents. T cells are probably implicated in the initiation of the disease; their involvement together with various infections preceding the onset of TA so far described suggest that infections can be a trigger for TAK.^{2, 3} *Mycobacterium tuberculosis* has been suggested, as high immunoglobulin levels against an extract of *M. tuberculosis* and its 65KDa heat-shock protein have been demonstrated in TAK patients but not in controls.¹¹ Nevertheless, a sure link between infections and TAK has never been proven so far. Other possible triggering agents for TAK could be *Chlamydia pneumoniae*, RNA virus, Herpes virus and CMV.³⁰

GCA is a T cell mediated vasculitis probably triggered by infective antigens. Various infectious agents (HVZ, Parvovirus B19, EBV, MCV, *Chlamydia pneumoniae*)^{2, 3, 10} have been reported as putative

agents of the onset of this process. It is possible that they can operate on a genetic predisposition together with environmental factors. This hypothesis is supported both by epidemiologic (seasonal and geographical variation in presentation)¹⁰ and laboratory (C. pneumonia, Parvovirus B19 and Parainfluenza virus have been identified by PCR and/or serological tests in GCA patients) data.³¹

Diagnosis

Once the clinic-pathologic diagnosis of vasculitis has been established, infections as secondary cause must be excluded. A detailed history, to deduce potential causative factors, and a clinical examination are important to guide investigations. The clinician should assess the duration and acuity of symptoms and inquire about antecedent illness. The presence of systemic involvement should be verified through a review of symptoms and signs. The physical examination may be helpful in identifying the predominant vessel size affected, determining the extent of systemic involvement and formulating the differential diagnosis. Constitutional signs such as fever suggest systemic involvement. A complete head and neck, cardio-pulmonary, abdominal, musculoskeletal and neurologic examination should be performed. If it is indicated, laboratory tests should always include blood cultures to exclude an infectious aetiology, VDRL title, hepatitis panel, HIV antibodies, and Lyme enzyme-linked immunosorbent assay, Quantiferon and complete blood count, C reactive protein, cryoglobulins and urinalysis. Stains of the biopsy should include hematoxylin and eosin, Gram stain, fungal and Mycobacterium stains.³² In the direct secondary forms the microbiological agents invade directly the blood vessels and it is possible to detect them in skin lesions by different diagnostic investigations such as culture or PCR performed on skin samples. On the contrary, other infectious agents, such as *Neisseria gonorrhea* and *Neisseria meningitidis*, although they act directly releasing toxins that injury the vascular wall, are not usually detected in skin lesions.³³

Therapy

The first step, in the treatment of patients with cutaneous vasculitis, consists in determining whether

the disease is primary or secondary to an underlying condition, such as infections that must be treated.

Early treatment with antimicrobial therapy against the causative organism is imperative in order to avoid the potential catastrophe of immunosuppressive treatment in the secondary vasculitis.

Therapeutic approach in infectious related vasculitis can be quite complex for several reasons. First of all the severity of the inflammatory process may require high doses of immunosuppressive drugs, which in turn can aggravate the underlying infectious disease that is the cause of the vasculitis. For this reason it is necessary to find the appropriate balance between reducing the inflammation, in order to decrease the damage that the vasculitis is causing to vital organs, and worsening the infection. Therefore the severity and extension of the vasculitic process define the appropriate therapeutic approach.^{34, 35}

Secondly, even if clinical presentation and laboratory tests suggest an underlying infectious disease, it might not always be possible to define the specific microbial agent, therefore it will not be possible to start a target antimicrobial therapy. In these cases a broad-spectrum antibiotic therapy needs to be started along with immunosuppressive therapy. However, most infectious related vasculitis respond only to specific antimicrobial treatment such as HAART in HIV-vasculitis, Peg-IFN and ribavirin in HCV-vasculitis or anti mycobacterium therapy in M.T-vasculitis; thus define the infectious agent might be crucial to establish the proper treatment.³⁶

Furthermore, some infectious agents can trigger different types of vasculitis which in turn might require different immunosuppressive treatment, for example most of HIV-vasculitis respond to corticosteroids associated with HAART, however the appropriate treatment for HIV-related Kawasaki-like disease is high dose of aspirin, intravenous immunoglobulin and HAART. Therefore, it is precious not only find out which infectious disease is triggering the vasculitic process, but also understand which type of vasculitis has been set off.

Keeping in mind the difficulties in the therapeutic management of infectious related vasculitis, a specific, when it is possible, or a broad-spectrum antimicrobial therapy has to be started in order to avoid the spreading of the infectious disease due to the necessary immunosuppressive therapy. At

least 6 weeks of intravenous therapy is usually necessary for bacterial, treponemal and fungal infections. Mycobacterial infections usually require longer courses of anti-tuberculous therapy, extending for up to 1 year. Severity, extension and, when it is known, type of vasculitis define which is the dose and the most appropriate immunosuppressive treatment that needs to be started. Among these different drugs have been suggested in literature such as corticosteroids, azathioprine, cyclophosphamide, plasmapheresis.³⁷

The management of HCV-CV depends on the severity of the vasculitic process and the underlying liver disease. We can consider two classes of therapeutic drugs: immunosuppressive and antiviral. The former can control the inflammation process, but lead to the spreading of the infection which is the cause of the vasculitis, and furthermore worsens the liver function already compromised. Conversely, antiviral agents can control mild form of CV but if administer in severe disease can paradoxically exacerbate the inflammatory-disease state.

In mild-moderate phase is suggested antiviral therapy with Peg-IFN and ribavirin. In patients with severe disease (renal involvement, progressive neuropathy and extensive skin disease) a short course of high-dose glucocorticoids is often necessary, and for more severe cases combined therapy with cyclophosphamide until a clinical remission is achieved; at this point antiviral therapy should be started. Apheresis combined with immunosuppression is used in the most fulminant forms. Nowadays, some new therapies with anti-CD20 monoclonal antibody (Rituximab) are discussed but still many questions exist about the appropriate position of this treatment in HCV-CV.^{22, 35-37}

In HBV-PAN, therapy with corticosteroids and other immunosuppressive agents can control HBV-PAN but, on the other hand, they enhance viral replication and, in prolonged use, accelerate the progression to cirrhosis in chronic hepatitis B. It has been suggested a combination of antiviral agents (such as IFN- α , vidarabine, lamivudine) and glucocorticoids. Plasma exchange has also been reported as being useful in severe.³⁴

The little data available in literature suggest to use glucocorticoids to treat HIV-vasculitis, however, in resistant cases other immunosuppressant agents and plasmapheresis have been proposed. All patients require concomitant antiretroviral therapy.³⁸

Conclusions

The association between infectious agents and vasculitis has long recognized. Microorganisms directly and /or indirectly through immunological mechanisms can trigger the development of vasculitis. Microbiological agents constitute the most common cause of secondary vasculitis. Recent evidence support a probable role of microbes in the pathophysiology of some primary or idiopathic forms of vasculitis. For instance, CV is now known to be related to HCV infection in the majority of cases. In addition, circumstantial evidence suggests that even vasculitis still classified as idiopathic might be triggered, at least in some cases, by environmental agents.

Furthermore vasculitis can be triggered by the drugs used to treat an underline infectious disease thus leading to drug-induced vasculitis type. Finally, immunosuppressive treatments for vasculitis can create a favorable field for the onset of an infectious disease.³⁹

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Vasculitis associated with connective tissue diseases

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Vasculitis in connective tissue disease (CTD) is quite rare, it is reported in approximately 10% of patients with CTD; systemic lupus erythematosus (SLE) shows the highest association rate. Vessels of any size may be involved, but mainly small vessels vasculitis is reported. At present the classification of these vasculitis is unsatisfactory. According to the 2012 revised International Chapel Hill Consensus Conference, vasculitides secondary to CTD are a well identified entity and are classified under the category of "vasculitis associated with systemic disease". However only lupus vasculitis and rheumatoid vasculitis are explicitly listed, while the remaining are generically included under the heading "others". Petechiae, purpura, gangrene and ulcers are the most frequent cutaneous manifestations that should be investigated in order to rule out potentially dangerous systemic involvement, especially if cryoglobulinemic or necrotizing vasculitis are suspected. This review will focus on the cutaneous involvement in CTD associated vasculitis.

KEY WORKS: Vasculitis - Connective tissue diseases - Antibodies.

In patients affected by connective tissue disease (CTD) the vasculitic process can be primary, identifying a specific idiopathic vasculitis coexisting with the autoimmune disease, or secondary to the underlying pathological process, not fulfilling any definition of primary vasculitis.¹

The generally accepted members of the group of CTD are rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's Syndrome (SS), systemic sclerosis (SSc), dermatomyositis/polymy-

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ositis (DM/PM), and mixed connective tissue disease (MCTD).

The original Chapel Hill Consensus Conference in 1994 classification of vasculitis considered only primary vasculitis, but didn't address vasculitis in patients with well-defined systemic autoimmune disease. Instead, according to the 2012 revised International Chapel Hill Consensus Conference (CHCC) Nomenclature of Vasculitides, vasculitides secondary to CTD are a well identified entity and are classified under the category of "vasculitis associated with systemic disease". Only lupus vasculitis and rheumatoid vasculitis are explicitly listed, while the remaining are generically included under the heading "others".¹ Indeed, vasculitis is most commonly seen in SLE and RA and these two kind of CTD-associated vasculitis are the best defined and known. However, cases may also occur in patients affected by Sjögren's syndrome, systemic sclerosis, dermatomyositis, scleroderma, and mixed connective tissue disease.

In Carlson's classification of cutaneous vasculitides, CTD-associated vasculitides are inserted into multiple categories depending on the size of vessel involved and the type of pathogenic mechanism.² However, it is not indicated which connective tissue

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disorder is associated to each specific type of vasculitis. Hence, both classifications are not properly exhaustive as far as connective tissue disease vasculitides are concerned.

Vasculitides associated with CTD represent a heterogeneous group of conditions. Vessel of any size may be involved, but mainly small vessel vasculitis (SVV) is reported. Approximately 10% of patients affected by CTD develop small vessel vasculitis.³

The affected organs and severity of the clinical condition may vary; ranging from mild isolated cutaneous involvement to life-threatening organ involvement.⁴ Generally patients affected by CTD who develop vasculitis have a poorer prognosis.

Vasculopathy is an integral part of most CTD and in certain cases is the actual hallmark of the disease as in SSc. However, vasculopathy and vasculitis are no synonyms. Vasculitis is by definition the inflammation of the vessel wall, demonstrable by histopathology, showing an inflammatory infiltrate. Vascular damage caused by different mechanisms other than blood vessel wall inflammation, such as coagulation abnormalities in antiphospholipid syndrome, or vasospasm in Raynaud's phenomenon, differ from vasculitides and will not be covered in this paper.

Vasculitis can result in a vast variety of skin lesions depending on the location and size of the vessels and on the mechanism determining vascular damage. The formation of thrombi on damaged endothelium resulting in ischemia in the territory served by the occluded vessels, it may manifest as infarcts (*e.g.*, in fingertips), gangrene (distal portion of limbs, typically fingers and toes), or ulcers. Petechiae and purpura instead, may be the clinical expression of increased capillary and venule permeability induced by inflammation or of rupture of the vessels, due to rapid vessel wall necrosis. Cutaneous lesions may be an early warning signs for systemic involvement. This review will focus on the cutaneous involvement in CTD associated vasculitis.

Vasculitis in SLE

SLE is the CTD with the greatest number of associated cases of vasculitis. The prevalence of vasculitis in SLE patients is approximately 10-20%.⁵⁻⁹ Most studies report that SLE patients with vasculitis are mostly females (89-97%).^{5, 10} Female gender doesn't imply a higher risk of developing vasculitis

in SLE patients, as demonstrated by Shinjo *et al.*;¹⁰ simply females are consistently more affected by SLE than men. Yet, a fewer number of authors report a higher frequency SLE with vasculitis in men.^{6, 11, 12} SLE patients with vasculitis are generally younger than those without vasculitic damage. According to a comparative study between juvenile and adult onset of SLE, vasculitis appears to be more common in children.¹³

Cutaneous vasculitis is found in approximately 19% of patients with SLE.^{8, 14, 15} Indeed, almost all SLE patients with vasculitis present cutaneous lesions (89% up to 94%).^{5, 12} In the modified Gilliam classification of skin lesions associated to SLE, vasculitis is considered as non-specific cutaneous lesions for SLE.¹⁶ To a lesser extent visceral vasculitis is reported in 11-18% of cases.^{5, 12} The latter is more rare but definitely more severe, since it may result in ischemic injury of the involved vascular districts.^{5, 6, 7, 12} The most frequently affected organs are kidneys, lungs (necrotic alveolar capillaritis), brain, peripheral nervous system and gastrointestinal tract (intestinal vasculitis, mainly located in the ileum and colon).⁵

Small vessel are involved in most cases (80-90%), especially post capillary venules, rarely medium size vessels (19-15%) and sporadically large vessels. Of all vasculitides in SLE leukocytoclastic vasculitis (60%) predominates, followed by cryoglobulinemic vasculitis (25-30%) and only in a few cases other types of medium vessel vasculitis such as polyarteritis nodosa (PAN) 6%.^{5, 6, 8}

Small vessel vasculitis in SLE

Small vessel vasculitis (SVV) in SLE comprise: leukocytoclastic vasculitis secondary to SLE, and coexisting urticarial vasculitis and cryoglobulinemic vasculitis.⁵ Anecdotal reports include associated primary granulomatosis with polyangiitis (Wegener's) and eosinophilic granulomatosis with polyangiitis (Churg-Strauss).¹⁷

The most frequent cutaneous manifestations of leukocytoclastic vasculitis are erythematous or violaceous punctate lesions on fingertips and/or palms of the hands not disappearing on pressure. Such lesions are the most suggestive and characteristic elements of vasculitis in SLE patients⁵⁻⁷ and leukocytoclastic vasculitis can be considered the expression of lupus vasculitis.

Leukocytoclastic vasculitis may also frequently present with palpable purpura generally of the lower limbs, if the pathological process takes place in the upper dermis and to a lesser extent ischemic and/or ulcerated lesions, erythematous macules and papules. Rarely, if leukocytoclastic vasculitis affects instead the deeper septal venules of subcutaneous fat, it will result in cutaneous panniculitis with palpable nodules evolving into contusiform discoloration upon healing (due to the metabolism of extravasated hemoglobin).⁷

A rare presentation of leukocytoclastic vasculitis in SLE is erythema gyratum repens-like eruption.^{18,19}

Cryoglobulinemia is the second most common form of vasculitis in SLE patients. In this case, as in leukocytoclastic vasculitis the most frequent manifestations are cutaneous; in order of frequency: palpable purpura in the legs (detectable in 2/3 of patients), erythematous punctuate lesions on the fingertips, erythematous macules and/or papules, urticarial lesions, nodular lesions.^{5,20} Visceral involvement is also reported, including mononeuritis multiplex, glomerulonephritis and pulmonary alveolitis. In 1/4 of patients hepatitis C virus (HCV) infection is detectable.^{5,14} The immunoglobulins responsible for vascular damage in patients with CDT are mixed cryoglobulins: type II, monoclonal Igs (immunoglobulins) that coprecipitate with polyclonal IgG or type III, polyclonal Igs. Mixed cryoglobulinemia induces vasculitis by the precipitation induced by cold temperature in the vessels of circulating Igs, which determines the activation of the complement system and consequent inflammation. A secondary hypocomplementemia can be observed as a consequence of complement consumption.²⁰

Urticarial vasculitis (UV) is the third most described vasculitis in SLE. It is unclear whether it should be considered a clinical variant of lupus leukocytoclastic vasculitis or separate type of vasculitis.

Patients affected by UV can be divided in three groups: patients with normal complementemia, patients with hypocomplementemia associated with anti-C1Q antibodies and patients with hypocomplementemia without anti-C1Q antibodies. Hypocomplementemic urticarial vasculitis (HUV) without anti-C1Q antibodies is the most frequently associated to SLE (54%), while normocomplementemic UV in SLE patients occurs only in 2% of cases.²¹

It is debated whether HUV represents an early

stage of SLE or if it is actually a subtype of SLE.²¹ UV is characterized by small asymptomatic or painful rarely pruritic wheals, persisting for more than 24 hours, unlike classic urticarial lesions which are transient by definition. Lesions evolve in petechiae or purpura, to then disappear leaving post-inflammatory hyperpigmentation.^{5, 7, 21, 22} Patients with HUV may present Raynaud's phenomenon, constitutional symptoms (such as fever, malaise, fatigue), arthralgia, arthritis, serositis, glomerulonephritis, interstitial nephritis, conjunctivitis and episcleritis.²¹ Angioedema-like lesions are present in 40% of patients, mostly involving lips, tongue, periorbital tissue, and hands.²³

Medium vessel vasculitis in SLE

Medium vessel vasculitis (MVV) have a different pattern of clinical manifestations compared to SVV, with mostly visceral involvement and less frequently cutaneous lesions (40%), which tend to be severe (ulcers and ischemic lesions).

SLE patients with MVV most frequently present coexisting PAN or MVV secondary to lupus. However, isolated cases of associated Kawasaki disease²⁴ and Buerger disease⁵ have also been described.

In MVV secondary to SLE mononeuritis multiplex is the most common manifestation of MVV and is the main clinical marker for suspecting MVV in SLE, followed by abdominal vasculitis.^{5, 6} Less frequently involved sites include: coronary arteries,^{6, 25} pancreas,²⁶ gallbladder,²⁷ urinary bladder,²⁸ liver²⁹ and uterus.³⁰

Clinically PAN presents in lupus with mononeuritis multiplex of the lower limbs, demonstrable by sural nerve biopsy. Cutaneous manifestations such as subcutaneous nodules and bleeding, ulcers, gangrene and livedo racemosa characterize PAN. Livedo reticularis is also frequently associated with PAN. Other manifestations include nephropathy, abdominal pain and bleeding due to the involvement of visceral arteries.^{5, 31}

Large vessel vasculitis in SLE

Large vessel vasculitis (LVV) in SLE is uncommon, however sporadic cases of primary coexisting vasculitis such as Takayasu arteritis (TAK)³² and giant cell arteritis (GCA)³³ have been reported. LVV secondary to SLE, not fulfilling any CHCC defini-

tion of idiopathic vasculitis, involving large arteries of the limbs has also been reported.⁶

Vasculitis as predictive and prognostic factor in SLE

Generally, vasculitis develops in patients already diagnosed with SLE. However, in 21% of patients vasculitis actually precedes, in average of three years, full-blown SLE.¹² Therefore, vasculitis may be an early marker of the underlying disease, allowing an earlier diagnosis of SLE.⁵

From a prognostic point of view, a close correlation between vasculitis and lupus disease activity is reported by many studies. Patients with vasculitis have a longer disease duration, younger age of SLE onset and a higher European Consensus Lupus Activity Measurement (ECLAM) score.^{5, 6, 11} Lupus flares may go hand in hand with acute episodes of vasculitis, together with erythrocyte sedimentation rate (ERS) and C reactive protein elevation, anaemia and hypocomplementemia.^{4, 5}

However, as pointed out by Shinjo *et al.* most studies reporting such associations analyse simultaneously cutaneous and visceral vasculitis, in spite of their substantial differences. In fact, cutaneous vasculitis is definitely more frequent in SLE patient but less severe; while visceral vasculitis instead is reported in fewer patients but constitutes a major morbidity and mortality.^{5, 8} Probably the correlation between each specific subtype of vasculitis and the risk of more severe lupus should be further investigated.

From a dermatological point of view depending on the skin lesions you can roughly guess the severity of the patient. For example, the isolated digital vasculitis is often associated with SVV and moderate manifestations of lupus,¹⁰ while the detection of ischemic lesions and necrotizing are more suggestive of MVV and therefore potentially a greater severity of the clinical situation. However, since severe skin lesions may be actually present in different types of vasculitis a skin biopsy and further investigation are always required.⁵

Furthermore, patients with vasculitis show more frequently anti-phospholipid syndrome (APS) features such as livedo reticularis and antiphospholipid antibodies (aPL).⁴⁻⁶ APS and vasculitis often coexist in patients with lupus, and differential diagnosis can be challenging, especially in case of ischemic lesions; in such cases a skin biopsy is mandatory since differentiating between the two lesions has im-

portant therapeutic implications (anticoagulation vs. immunosuppression).⁵

Patients with SLE who develop vasculitis also have a peculiar antibody profile. Different studies report a higher prevalence of anti-dsDNA,³⁴ anti-Sm,³⁵ anti-ribosomal P protein,¹⁰ anti-Ro/SSA,³⁴ and anti-La/SSB⁵ antibodies in SLE patients with vasculitis compared to SLE patients without vasculitic damage.

Besides, patients with anti-Ro/SSA or La/SSB antibodies have a risk 1.65 times higher to eventually develop cutaneous vasculitis and such antibodies are an independent serological marker for vasculitis.³⁴

Vasculitis in Sjögren's Syndrome

Vasculitis is one of the most characteristic extraglandular manifestations of Sjögren's Syndrome (SS). The prevalence of vasculitis in SS ranges from 5-10% (in a few case series even reaches 32% of patients).³⁶⁻³⁹ However, all case series considered a relatively limited number of patients.

The most affected organs in SS patients with vasculitis are the skin (58%)⁴ and peripheral nerves.^{36, 40} Vasculitis in SS may be both secondary to the CTD or a coexisting primary vasculitis. SS vasculitis mainly affects small vessels (95%) and less frequently medium vessels (5%).^{4, 37}

Small vessel vasculitis in SS

Three main types of SVV are described in SS patients, resembling the scenario seen in SLE patients. The most frequently reported vasculitis is leukocytoclastic vasculitis, followed by cryoglobulinemic vasculitis and urticarial vasculitis. About the latter, it is debated whether it should be considered a proper nosological entity or a clinical variant of SS-associated leukocytoclastic vasculitis.³⁶ Patients affected by SS present as clinical signs of vasculitis palpable purpura (73% of patients), erythematous macules (33%), erythematous papules (33%) and/or ulcers (4%). The most frequently affected areas are: lower limbs (92%), upper limbs (24%), trunk (10%) and head (6%).³⁶⁻³⁸

Leukocytoclastic vasculitis (non-purpuric and non urticarial) is the most common SVV in SS, mostly presenting with palpable purpura in the lower limbs. Cryoglobulinemia is the cause of SVV in 16-30% of

patients with SS.^{37, 41} Clinical manifestations include mostly palpable purpura in the lower extremities, ulcers and digital ischemia.

Twenty percent of patients present urticarial vasculitis with erythematous urticarial papules and macules, predominant on the upper extremities, face and trunk. Unlike classical urticaria, the hives in urticarial vasculitis persist longer and evolve into purpuric lesions.

MVV in SS

MVV is less common than SVV, affecting only 5% of patients with SS. MVV in SS patients is characterized by acute necrotizing arteritis of medium-sized vessels, clinically resembling PAN, but lacking of the typical aneurismal formation.⁴⁰ Thus, it may be considered that necrotizing MVV is a very uncommon vasculitis secondary to SS; while PAN, as a true primary vasculitis may only exceptionally coexists with SS. SS-associated MVV may sometimes coexist with cryoglobulinemic vasculitis in the same patient.^{36,37,40} SS-associated MVV determines papulonecrotic cutaneous skin lesions.³⁷ Necrotizing vasculitis can affect many organs, including: muscles, gastrointestinal tract, peripheral nerves, kidney, central nervous system, pancreas, gallbladder, spleen, parotid gland, and spinal cord.

LVV in SS

LVV is definitely exceptional in SS. Only two cases of coexisting GCA have been reported in the literature.^{37, 42, 43}

Vasculitis as predictive and prognostic factor in SS

Generally speaking vasculitis in SS implies a worse prognosis, higher morbidity and mortality.^{37,44} SS patients with vasculitis have a peculiar analytical and immunological profile, presenting more frequently than those without vasculitic damage, anemia, high ESR levels, hypergammaglobulinemia, C4 reduction, anti-nuclear antibodies (ANA), rheumatoid factor (FR), anti-Ro/SSB and anti La/SSA. This profile identifies a subgroup of patients with increased inflammation and immune dysregulation.^{5,37,38,40} However, in the case of SS, the same prognostic considerations made for lupus should be taken in account. Hence one must distinguish the

different subtypes of SS-associated vasculitis and the consequently related prognostic implication for each.

Tsokos *et al.* pointed out that the histological type (necrotizing is more severe than leukocytoclastic) and the site (internal is more severe than external) of the vasculitis should be considered in defining the disease severity and prognosis. Therefore, the benign and limited forms of vasculitis such as cutaneous leukocytoclastic angiitis have a better prognosis than the more severe forms of internal necrotizing MVV.⁴⁰

Cryoglobulinemic vasculitis is also strongly associated to life-threatening vasculitis involving internal organs.⁴ Furthermore, the development of lymphoproliferative disorders in SS has been associated to palpable purpura, low C4, and mixed cryoglobulinemia.⁴⁵ Therefore, in patients with SS showing such findings, lymphoproliferative disorders must be ruled out.³⁶⁻³⁸

Patients with cutaneous leukocytoclastic vasculitis or cryoglobulinemic vasculitis have a higher prevalence of extraglandular manifestations, including fever, arthritis, glomerulonephritis, peripheral neuropathy, and Raynaud's phenomenon.^{4, 36, 37, 41} Cutaneous vasculitis also is a criterion for the evaluation of the disease activity in European League Against Rheumatism (EULAR) and in Sjögren Syndrome Disease Activity Index (ESSDAI).⁴⁶

Neurological problems are frequent in patients with SS-associated vasculitis and may include peripheral neuropathy, mononeuritis multiplex, and cranial nerve involvement. The first is associated mainly with SVV and the other two with MVV.⁴

Vasculitis in systemic sclerosis

Vasculopathy of small vessels is one of the first, more severe and characteristic manifestations of SSc; while vasculitis instead is very rare 1-2% of sclerodermic patients.^{47, 48} These two processes differ in their pathogenesis and histology. In vasculopathy endothelial cells apoptosis, myofibroblast proliferation and matrix deposit lead to obliterative thickening of the vessel walls; while in vasculitis histopathological an inflammatory infiltrate is always detectable.⁴⁹

Vasculitis is associated to both limited and diffuse SSc (disease ratio 3.5:1)⁵⁰ and it is generally diagnosed after SSc diagnosis.⁴⁷

Mainly SVV is observed, in particular ANCA-associated vasculitis (AAV) and mixed cryoglobulinemic vasculitis (MCV).^{47, 48}

AAV occurs rarely in SSc, mostly in cutaneous type SSc; the prevalence reported in the literature ranges from 0-1.3% of SSc patients. Necrotizing ANCA associated vasculitis are often severe, since aside from the skin also internal organs are involved. Skin lesion may be an alarming sign for potential systemic involvement.

From Quéméneur's⁴⁷ review of the literature it emerges that the AAV in SSc mainly affects the kidney (77%), lungs (30%), the nervous system (16%) and the skin (24%). ANCA-associated glomerulonephritis can lead to "renal crisis" in 10% of cases;^{49, 50} pulmonary involvement instead leads to pulmonary fibrosis.⁵¹ Skin manifestations include palpable purpura, cutaneous nodules, ulcers. In almost all patients immunofluorescence reveals p-ANCA pattern and ELISA reveals anti-Myeloperoxidase (MPO) antibodies⁴⁷ and less frequently c-ANCA and anti-proteinase 3 (PR3) antibodies.⁵⁰

Cryoglobulins are detectable in 2.8% of patients but overt MCV in SSc is reported only in 0.3-2% of cases. Probably the association between SSc and MCV has been poorly investigated and its prevalence might be underestimated.⁴⁸ It was hypothesized that MCV in such patients was the expression of SS linked to SSc.^{47, 48, 52} Almost all patients with MCV reported by Giuggioli *et al.* presented HCV infection. In almost all cases the diagnosis of SSc precedes of 3-17 years the onset of MCV.⁴⁸ Most patients had limited cutaneous SSc complicated non-healing ulcers, pulmonary hypertension, serum anti-centromere antibodies together with the typical MCV syndrome, i.e. clinical triad of purpura, weakness, and arthralgias, plus peripheral neuropathy, serum mixed cryoglobulins with rheumatoid activity and low C4. The clinical manifestations mostly include skin involvement, mononeuropathy multiplex, pulmonary hypertension.⁴⁷ The skin lesions range from palpable purpura to digital ischemia, ulcers and gangrene.⁴⁷ Ulcers and gangrene are the expression of a severe vascular damage and together with pulmonary hypertension are responsible for very poor prognosis. The markedly severe vascular manifestations, which peculiarly characterize the patients with SSc-CV overlap syndrome are probably attributable to the synergic activity of both typical scleroderma microangiopathy

and the immuno-complex-related cryoglobulinemic vasculitis.

Anecdotal reports of other types of associated vasculitis include: LVV (six cases of GCA)⁵³⁻⁵⁵ and four cases TAK⁵⁶⁻⁵⁸ and MVV (only one case of PAN)⁵⁹ and two cases Behçet syndrome.^{49, 60, 61}

Vasculitis in dermatomyositis

Vasculitis in dermatomyositis/polymyositis is very rare; a small number of case reports can be found in the literature. The two biggest studies conducted report a variable prevalence approximately 9.2-30.4%.^{62, 63} However, the number of patients included in these studies was very limited and the prevalence of vasculitis in patients with DM/PM is probably overestimated.

It should be noted that dermatomyositis commonly present with various vasculopathies, that however differ from vasculitis.

SVV is associated to DM/PM. The clinical manifestations include tender dermal/subcutaneous nodules, periungueal haemorrhages, ulcers.^{62, 64} Histopathological examinations generally reveal leukocytoclastic vasculitis, with neutrophilic and/or lymphocytic infiltrate of arterioles, capillaries and venules of the dermis and/or subcutis.^{3, 62} One case was reported of necrotizing vasculitis with fibrinoid necrosis of the vessels, clinically presenting with haemorrhagic bullae and ulcers in the lower limbs.⁶⁴

In the past an association between vasculitis and paraneoplastic dermatomyositis was observed;^{62, 63} however later studies didn't confirm these findings.^{3, 64-68}

The detection of dermatomyositis specific anti-PL7 antibodies is associated to necrotizing vasculitis.⁶⁴

Vasculitis in rheumatoid arthritis

Vasculitis associated with RA is generally a secondary process to RA itself. In practice, RV is considered when clinical manifestations of vasculitis unexplained by other pathological conditions.⁶⁹ Rheumatoid vasculitis (RV) is probably the most widely recognised form of secondary vasculitis. As in other CTD, vasculopathy is an integral part of the pathogenesis of RA^{69, 70} and it involves post capillary venules in the inflamed rheumatoid synovium.⁷¹

Vasculitis instead is a widespread inflammation of blood vessels.

The prevalence of RV in patients with established RA is 1-5%.^{69, 72, 73} Some recent data suggest that the incidence of RV may be decreasing.⁷⁴ The incidence of RV is higher in males than females, with a lifetime risk of 1 in 9 for males and 1 in 38 for females with RA.^{65, 75} Vasculitis develops on average 10.8 years after the onset of rheumatoid arthritis.⁷⁶

RV mainly involves small vessels, more than medium-sized.⁷⁷

RV is histologically necrotizing or leukocytoclastic vasculitis. Systemic RV is a heterogeneous condition with a wide range of clinical manifestations.⁶⁹ The vessels most commonly involved are those of the skin (90% of patients) and the vasa nervorum of peripheral nerves (40%). Less frequently vasculitis affects the central nervous system, the eyes, the heart, the lungs, the kidneys, and the gastrointestinal system.^{69, 78}

Studies have shown a 0.7% to 5.4% incidence of cutaneous RV in RA patients. Focal digital lesions (up to 41%), petechiae and purpura (up to 56%), ulcers (up to 62.5%), and gangrene (up to 37.5%) are the most common dermatologic manifestations.⁷⁶ Isolated ischemic focal digital lesions are relatively common in RA patients and can represent the only manifestation of RV; in such scenario they follow a benign course and don't require a specific treatment.^{79, 80} Petechiae and purpura occur mostly in the lower extremities and cannot be distinguished from those occurring in other clinical contexts. Ulcers are usually deep and tend to be found in the lower extremities in unusual locations, such as the dorsum of the foot or the upper calf.⁶⁹ Other possible cutaneous lesions are nonspecific maculopapular or nodular erythema, hemorrhagic blisters, livedo reticularis, erythema elevatum diutinum, and "atrophie blanche".^{76, 81} Such patients also often present with a greater number of rheumatoid nodules.⁷⁶ Most patients with RV have anaemia, elevated ESR rate and C-reactive protein, thrombocytosis, leukopenia, leukocytosis, eosinophilia, and hypoalbuminemia.^{69, 76} An increased concentration of RF is the strongest association with the development of RV (38% with titers 1:2,560).^{82, 83} RV, like other major extra-articular manifestations, increases the mortality rate in RA.⁸⁴ Five-year mortality rates were high, 33 to 43%, depending on the study considered, with marked morbidity.^{79, 85, 86}

Vasculitis in mixed connective tissue

A few cases of vasculitis associated to mixed connective disease have been described in the literature. Mainly cutaneous and neurologic involvement was reported and only one case of gastrointestinal involvement.⁴ Case reported in the literature include: urticarial vasculitis,^{87, 89} leukocytoclastic vasculitis with duodenal bleeding and recurrent skin eruptions⁹⁰ ANCA-associate vasculitis (anti-PR3 or anti-MPO positive)⁹¹⁻⁹³ and microscopic polyangitis (but p-ANCA positive).⁹⁴

Conclusions

Vasculitis in CTD is quite rare, it is reported in approximately 10% of patients with CTD; SLE shows the highest association rate. Both coexisting primary vasculitis and secondary vasculitis to the CTD are described. The primary vasculitides associated to CTD are mostly cryoglobulinemic vasculitis and PAN. Urticarial vasculitis is debated whether it should be considered a separate entity or a variant of leukocytoclastic vasculitis secondary to CTD. The secondary forms of vasculitis are often leukocytoclastic involving small-vessel or necrotizing involving the medium-vessels. Lupus vasculitis and rheumatoid vasculitis are the best known CTD-vasculitis.

Often vasculitis is a predictive and prognostic factor in CTD. In SLE, especially leukocytoclastic vasculitis is associated to poor prognosis, a higher ECLAM score, and younger age of onset and longer duration of the disease. In SS disease, leukocytoclastic vasculitis is often associated with higher prevalence of other extraglandular manifestations (such as peripheral neuropathies) and cryoglobulinemic vasculitis lymphoproliferative disorders. In SSc even if very rare vasculitis is very severe, especially affecting the renal, pulmonary and cutaneous vascular districts (Table I).

Interestingly anti-Ro/SSA antibodies have been associated to vasculitic manifestations in SLE,³⁴ SS^{95, 96} and RA;^{97, 98} even patients with SSc tend to present SS traits, including anti-Ro/SSA,⁴⁷ if a MCV is reported. The similar antibody profile, might be one of the characteristics defining this particular subset of patients with CTD and vasculitis. Perhaps other common aspects will be found in the future.

The correlation between cutaneous lesions and

TABLE I.—*Prevalence of primary and secondary vasculitis associated with connective tissue diseases: review of the literature.*

Connective tissue disease	Prevalence of vasculitis	Vasculitic cutaneous involvement	Associated vaculitis
Systemic lupus erythematosus	10-20%	89-94%	Small-vessel vasculitis Primary Cryoglobulinemic vasculitis Urticarial vasculitis Granulomatosis with polyangiitis* Eosinophilic granulomatosis with polyangiitis* Secondary to SLE Leukocytoclastic vasculitis Medium-vessel vasculitis Primary Polyarterteritis nodosa Kawasaki disease* Secondary to SLE Necrotizing vasculitis Large-vessel vasculitis Primary Takayasu arteritis* Giant cell arteritis* Secondary to SLE Involvement of large arteries
Sjögren syndrome (SS)	5-10%	58%	Small-vessel vasculitis Primary Cryoglobulinemic vasculitis Urticarial vasculitis Secondary to SS Leukocytoclastic vasculitis Medium-vessel vasculitis Secondary to SS Necrotizing vasculitis Large-vessel vasculitis Giant cell arteritis*
Systemic sclerosis	1-2%	90%	Small-vessel vasculitis ANCA-associated vasculitis Mixed cryoglobulinemic vasculitis Medium-vessel vasculitis Polyarteritis nodosa* Large-vessel vasculitis Giant cell arteritis* Takayasu arteritis* Variable vessel vasculitis Behçet disease*
Dermatomyositis/Polymyositis	9,2%	100%	Small-vessel vasculitis Luekocytoclastic vasculitis
Rheumatoid Arthritis	1-5%	90%	Small and medium vessel vasculitis secondary to RA
Mixed connective tissue disease	Anecdotal reports	100%	Small-vessel vasculitis Leukocytoclastic Urticarial vasculitis ANCA-associated

*Anecdotal reports.

Cutaneous lesions	Peculiar features	Reference
Palpable purpura; erythematous punctuate lesions on fingertips; erythematous macules/papules; nodules; urticarial lesions	¼ of patients present HCV infection	(5)(14)(20)
Small, asymptomatic wheals persisting >24h with petechiae or purpura; angioedema-like lesions in 40%	Hypocomplementemic in 54%	(5)(7)(21)(22)
		(17)
		(17)
Erythematous-violaceous punctuate lesions on fingertips; palpable purpura; ischemic/ulcerated lesions; erythematous macules/papules; nodules; erythema giratum repens		(5)(6)(7)(18)(19)
Subcutaneous nodules; ulcers and gangrene	Important and severe visceral involvement;	(5)(6)(17)(24)
Severe ischemic lesions; ulcers	Important and severe visceral involvement; especially mononeuritis multiplex	(5)(6)
		(32)
		(33)
		(6)
Palpable purpura in the lower extremities, ulcers and digital ischemia	Associated with lymphoproliferative disorders	(36) (37)(41)
Erythematous urticarial papules and macules predominant in upper extremities, face and trunk, that evolve into purpuric lesions		(36)
Palpable purpura in the lower limbs	Associated with a higher incidence of extraglandular manifestations	(36)
Papulonecrotic cutaneous skin lesions		(40)
		(42)(43)(37)
Palpable purpura, cutaneous nodules, ulcers		(47)(48)(49)(50)
Purpura	HCV infections in almost all patients	(47)(48)
		(59)
		(54)(55)(56)
		(57)(58)
		(60)(61)
Tender dermal/subcutaneous nodules, periungueal haemorrhages, ulcers		(3)(62)(63)(64)
Focal digital lesions, petechiae, purpura, ulcers, gangrene		(69)(70)(71)(76)
		(87)(90)(91)(93)
		(87)(89)(88)
		(92)(94)

the type of vasculitis is not always clear; a skin biopsy is generally necessary to formulate the correct diagnosis. Some lesions such as purpura or maculopapules can be associated with SVV, especially leukocytoclastic vasculitis; while ischemic lesions and/or ulcers generally correspond to cryoglobulinemic vasculitis or MVV. According to the type of skin lesion the underlying vasculitis is hypothesizable: erythematous-violaceous punctuate lesions of the fingertips are generally a mild expression and often the only manifestation of SVV vasculitis. On the other hand ischemic lesions, ulcers and gangrene are more often associated to MVV.

Cutaneous lesions may be an early warning signs for systemic involvement. If a patients affected by CTD presents vasculitic cutaneous involvement further investigation is suggested, in order to rule out potentially dangerous systemic involvement, especially if cryoglobulinemic or necrotizing vasculitis are suspected.

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Cutaneous vasculitis and inflammatory bowel diseases

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Extraintestinal manifestations occur in up to 40% of patients living with inflammatory bowel disease (IBD) and may precede the onset of gastrointestinal symptoms by many years. Vasculitides are considered rare cutaneous manifestations, but they often represent an important cause of morbidity and a relevant diagnostic issue in IBD. In addition, the increasing use of biological therapies for IBD may also play a pivotal role in the development of vascular disorders of different type. Hence, we provide a complete and in-depth review of the main features of cutaneous vasculitides observed in IBD, with a specific focus on their clinical presentation and possible pathophysiological mechanisms.

KEY WORDS: Vasculitis - Crohn disease - Colitis, ulcerative.

Our body is an integrated system where gastrointestinal tract (GI) and cutis represent a good example of communication.

Inflammatory bowel diseases (IBDs) are common causes of gastrointestinal morbidity in developed countries and the incidence of IBD has dramatically increased over the past 50 years and has been linked with modernization and western lifestyles. Recent data suggest that children and adolescents show the highest incidence of IBD.^{1, 2}

The two most common forms of the condition include Crohn's disease (CD) and ulcerative colitis (UC), marked by episodes of relapse and remission. UC affects only the colon and is primarily confined to the mucosal and to a lesser degree, the submucosal compartments. In contrast, CD can involve any component of the gastrointestinal tract from the

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oral cavity to the anus and may involve all layers of the gut.³ CD and UC are diagnosed on the basis of a clinical suspicion and laboratory, radiological, endoscopic, and histological findings.⁴ These diseases are associated with considerable morbidity, and place a significant burden on individuals, families, and society.

The cause of IBD remains unknown; however, it is thought to occur in genetically-predisposed individuals who are exposed to microbial, dietary, and environmental triggers. In particular both the innate and adaptive arms of the immune system have been shown to play a role in IBD, with altered adaptive immune function being the primary contributor to disease pathogenesis.⁵ In general, this occurs mainly through increased pro-inflammatory cytokines driven by the T-helper subsets or by lack of effective anti-inflammatory regulatory T-cells.⁵

Extraintestinal manifestations (EIMs) are frequent in the course of IBD and, in some cases, may be the first manifestation of IBD, sometimes preceding the onset of gastrointestinal symptoms by many years.⁶

EIMs may occur in up to 40% of IBD patients. In some series, but not in all, these are more common in CD than in UC. Vavricka *et al.*⁷ have found EIMs in 43% of 580 CD and 31% of 370 UC patients. In other large series of studies, EIMs were found in 329

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cases (40.6%) (119 CD, 210 UC) with a prevalence of 35.3% and 55.1% respectively.⁸ The clinical spectrum varies from mild transitory to very severe manifestations, sometimes more debilitating than the underlying intestinal disease itself.

EIMs can involve any organ or system, even if the musculoskeletal and the cutaneous are the most common ones. In fact the frequency of mucocutaneous manifestations is reported in 22% to 75% of patients with CD⁹ and in 5% to 11% in UC.¹⁰

The skin manifestations of IBD have been classified into four categories according to their pathophysiology: 1) specific: these lesions have identical pathologic mechanisms to lesions of the gastrointestinal tract; 2) reactive: these lesions do not have the same pathologic features as lesions of the gastrointestinal tract; 3) associated: these likely relate to human leukocyte antigen linkage and a chronic inflammatory state; and 4) induced by IBD treatment.¹¹ Between skin diseases that can be associated to IBD, vasculitis are very uncommon. There is very limited number of cases and most of them are anecdotal. In this review we focused on cutaneous small vessels vasculitis (CSVV), cutaneous polyarteritis nodosa (C-PAN) and vasculitis induced by biologics.

CSVV

CSVV, also known with the histologic term of leukocytoclastic vasculitis, is the most common type of vasculitis and it is characterized by neutrophilic invasion and fibrinoid necrosis along with endothelial enlargement in postcapillary venules.¹² It affects both children and adults, usually more common in females.^{13, 14}

The major cutaneous aspect of CSVV is palpable purpura commonly in the lower limbs and ankles. Lesions range from 1 mm to several centimetres, usually appearing as purpura but may also appear as urticarial papules, nodules, vesicles, plaques, haemorrhagic bullae and necrotic ulcers. The skin lesions typically arise as a simultaneous "crop" and usually resolve within several weeks or a few months. Approximately 10% of patients follow a chronic-relapsing course over a period ranging from few to several years.¹⁵ Fever, arthralgia, myalgia and ankle swelling may be present, but renal involvement is uncommon.¹⁶ Patients with leukocytoclastic vasculitis

usually are asymptomatic, but sometimes they can experience burning, pain or more rarely pruritus.¹⁷

It is believed to be an immune-complex disorder triggered by various drugs, infections, malignancies, and systemic and autoimmune disorders.¹⁸⁻²⁰

Although it has to be present that at least 50% of cases of CSVV are "idiopathic",^{16, 21} it is also important to be aware that CSVV can occur as part of systemic vasculitides.¹⁶

CSVV as a cutaneous manifestation of CD is rare, in fact less than ten cases were described as associated to the gastrointestinal disease. Nevertheless Limbdi suggests that CSVV, although considered the least common cutaneous manifestation of CD, is probably more prevalent than recognized, often mistaken as bacterial cellulitis, a viral or allergic phenomenon. So the author proposes to biopsy new skin lesions in order to establish the diagnosis.²²

CSVV is rarely seen in patients with UC as compared to other skin manifestations. Clinically, it is generally synchronous with ulcerative colitis.²³ Nevertheless, four ulcerative colitis cases who presented leukocytoclastic vasculitis before the onset of the intestinal disease have been reported. Vasculitic symptoms appear 1 month to 2 years before the onset of intestinal symptoms.²⁴⁻²⁶

In these cases, the cutaneous lesions always precede the intestinal symptoms with different lag periods, in contrast to CD, where the extraintestinal cutaneous manifestations appear not only as onset symptoms but also during exacerbation periods of the disease.²⁶

Treatment varies and depends on different factors. In a relevant number of patients, treatment is not necessary as the disease is left-limiting. An isolated episode of CSVV associated with a known inciting factor may be managed by removal or treatment of the trigger, along with symptomatic measures.²⁷ In patients with mild disease the therapeutic approach consists of topical corticosteroids, in combination with oral antihistamines to reduce burning and itching; whereas systemic corticosteroids are considered the first line agents for patients with painful ulcerative necrotic skin lesions, namely methylprednisolone at the initial dose of 0.8 to 1 mg/kg daily.¹¹ Chronic, idiopathic CSVV may be treated with colchicine or dapsone. Patients not responsive to the aforementioned therapies may require initiation of an immunosuppressive agent such as azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, or rituximab.²⁷

Cutaneous polyarteritis nodosa

Cutaneous polyarteritis nodosa (C-PAN) is a rare, severe necrotizing vasculitis of small and medium-sized arteries in the reticular dermis and subcutaneous tissues.²⁸

C-PAN is characterized by a chronic relapsing, benign course and, conventionally, does not progress to systemic PAN. If present, extracutaneous manifestations (arthralgias, myalgias, neuropathy) should remain localized to the region of affected skin.^{29, 30}

This cutaneous vasculitis affects all ages, ranging from neonatal up to 81 years.^{30, 31} Women are commonly affected with a peak incidence in middle age.^{30, 32} The average age at the time of diagnosis was 43.5 years (range, 6-72) for patients without skin ulceration, and 47 years (range 16-81) for those with ulcers.³⁰

Clinically it presents as tender subcutaneous nodules (0.5-2 cm), with or without livedo reticularis, and are the predecessor to ulceration in 50% of the cases. A typical "burst" pattern of irregularly shaped *livedo reticularis* around an ulcer is highly suggestive of C-PAN. Other findings include petechiae, purpura, cutaneous necrosis, autoamputations. These most commonly occur on the legs (97% of the cases), followed by the arms and the trunk.^{16, 29, 33}

The etiology of C-PAN is unknown. Cutaneous polyarteritis nodosa is probably best viewed as an immune complex-mediated disease. Direct immunofluorescence (DIF) often shows IgM and C3 deposits within affected arterial walls.^{32, 34, 35}

Recently, recessive mutations in CECR1, the gene encoding adenosine deaminase 2 (ADA2) were found to be related to a familial vasculopathy syndrome.³⁶

In the early course of C-PAN, lesions show the typical pattern of leukocytoclastic vasculitis whereas, later, the infiltrate is predominantly composed of lymphocytes and histiocytes.²⁹

Inflammatory bowel disease has been reported in 6-10% of C-PAN cases, generally precedes the C-PAN diagnosis.^{29, 30} More likely associated with CD than UC, since the initial report in 1970, fewer than 25 cases of C-PAN associated with CD have been reported.^{29, 37}

Interestingly it has been observed that, when associated with IBD, the biopsy specimen of C-PAN may also have granulomatous features reminiscent of classic CD pathology.³⁸

Systemic corticosteroids, namely methylpred-

nisolone at the initial dose of 0.8 to 1 mg/kg daily, and nonsteroidal antiinflammatory drugs, usually control C-PAN.^{11, 29} Low-dose weekly methotrexate (7.5-20 mg/week) may be considered for patients unresponsive to corticosteroids.¹¹ Anecdotal reports documented the use of warfarin and infliximab.¹⁶

Vasculitis induced by biologics

The monoclonal antibody against the tumor necrosis factor alpha (TNF- α), otherwise known as "biologics," have become a mainstay of therapy for IBD.³⁹

With this use and longer follow-up periods of treatment, there are a growing number of reports of the development of autoimmune processes related to anti-TNF agents.

Vasculitis is the most common autoimmune disease that results from anti-TNF- α therapy reported in the medical literature.^{40, 41}

Although the spectrum of vasculitis was broad, there was a notable predominance of cutaneous involvement (5/8; 63%), with palpable purpura being the most common cutaneous lesion.⁴² Other cutaneous less common features include ulcerations, blisters, and erythematous macules. The main histologic finding was leukocytoclastic vasculitis.⁴² Nearly all cases disappeared when anti-TNF therapy was suspended.

UC and CD may be considered systemic disorders that involve other organs (hepatobiliary, musculoskeletal, dermatologic etc.) in different steps of the disease, predominantly affecting the gastrointestinal tract.

In conclusion, vasculitides are reactive lesions, seen in both UC and CD. These lesions are induced by the underlying IBD without exhibiting the exact pathologic features of the gastrointestinal tract lesions. One possible hypothesis for the association between vasculitis and IBD is that the pathogenesis of both is based on immune mechanism and the position of immune complexes in the vascular structure and intestinal mucosa for vasculitis and IBD, respectively.⁴³

Vasculitides associated with IBD are actually in greater number than those reported in the literature. Thus, it is obvious that a physician treating IBD/patients should be able to recognize dermatological events, consider their association with IBD, and address a proper diagnostic and therapeutic work-up, possibly with the collaboration of a consultant dermatologist.

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Management of chronic spontaneous urticaria: practical parameters

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Chronic urticaria (CU) is a skin disorder characterized by transient, pruritic wheals persisting for longer than 6 weeks. According to the European Academy of Allergy and Clinical Immunology (EAACI) guidelines, CU can be categorized into two main types: chronic spontaneous urticaria (CSU), in which the wheals appear spontaneously, and inducible urticaria, that is triggered by physical agents. CSU may be due to triggering factors such as food allergens or infections, but in at least 40% of cases it is autoimmune in origin, caused by circulating autoantibodies anti-FcεR1 or anti-IgE, or autoreactive. In the present paper, re-evaluating the EAACI guidelines, we have developed a document containing some practical indications which are useful for diagnosis and management of CSU in the context of the Italian situation. Concerning CSU treatment, second generation antihistamines are the first-line treatment; these drugs can be used, as second-line treatment, at a higher than licensed dose in patients who do not respond adequately at licensed doses. The third-line treatment includes leukotriene receptor antagonists which, however, do not have a specific indication for the treatment of CSU, cyclosporine, whose use in this disease is still off-label, and omalizumab. The latter is a recombinant monoclonal IgG antibody that binds free IgE, down regulates mast cell function and induces eosinophil apoptosis. Recently, it has emerged as an effective and safe treatment for antihistamine-unresponsive CSU of both autoimmune/autoreactive and non-autoimmune/non-autoreactive, and has been officially approved for use against this disease.

KEY WORDS: Urticaria - Histamine antagonists - Omalizumab.

Urticaria has been described as a distinct entity by Hippocrates, but the different subtypes have been recognized only recently. This disease is

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characterised by transient, more or less diffuse and intense pruritic wheals that disappear within a few hours. The wheals tend to have a relapsing-remitting course resulting in transitory worsening for an average duration of 1 to 24 hours. In a portion of patients with urticaria, this skin disorder is associated with angioedema, involving lower dermis and mucous membranes, not associated with pruritus, and resolving up to 72 hours.

Urticaria without angioedema accounts for nearly 50% of cases, urticaria with angioedema 40%, angioedema without urticaria 10%.¹ The lifetime prevalence of urticaria is 15-20%¹⁻³ and the age peak is between 20 to 40 years. It is more prevalent in women than men.¹ Acute urticaria defined as the

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occurrence of spontaneous wheals, angioedema, or both for less than 6 weeks, is present in two thirds of patients, whereas chronic urticaria (CU), defined as urticaria persisting longer than 6 weeks, has a lifetime prevalence of 0.5-1% and affects one third of urticaria patients.^{2, 4}

Patients with CU have a poor quality of life (QoL) in comparison with other dermatological and medical conditions.⁵ The major concern is uncertainty, which compromises their QoL. Other factors contribute to patients' frustration. A new tool of evidence-based medicine, the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL), has been assessed and then validated for determining health status, and used worldwide by both dermatologist and patients for further research in this field.

CU can be categorized according to European Academy of Allergy and Clinical Immunology (EAACI) guidelines⁶ into two main types: chronic spontaneous urticaria (CSU) (spontaneous appearance of wheals, angioedema or both for ≥ 6 weeks due to known or unknown causes) and physical or inducible urticaria (Symptomatic dermatographism, Cold urticaria, Delayed pressure urticaria, Solar urticaria, Heat urticaria, Vibratory angioedema, Cholinergic urticaria, Contact urticaria, Aquagenic urticaria). A combination of various subtypes is possible. CSU and inducible urticaria variants have a highly protracted course potentially spanning over many years. These guidelines, validated by the approval of many experts of the field, represent a publication with an international character that cannot meet the needs of every single national reality with its local issues of management and specific procedures.

Therefore, it was decided to re-evaluate this guidelines and develop a shared document (focused on CSU) that may be useful to the Italian reality as well as clinical activity.

Diagnosis of chronic spontaneous urticaria

The first step in the diagnosis of chronic spontaneous urticaria (CSU) is to obtain thorough patient's history, including all potential triggering factors and other relevant aspects aimed at characterizing the nature of urticaria.⁶ Questions should be asked regarding most notably items such as time of disease onset, frequency and duration of wheals, associated symptoms such as itch and pain, associated angioedema, underlying internal diseases, preceding infections, and use of drugs. Other significant aspects that need to be considered include occurrence of wheals in relation to foreign travels, work and hobbies, induction of wheals by physical agents, exercise, their relation to foods or previous therapy, if any, and response to it. The second step is the physical examination of the patient, which should also include a test for dermatographism. The third step is the identification of possible causes of urticaria, particularly associated systemic disorders, by means of basic laboratory tests. Nowadays, wide and costly screening programs for identifying causes of CSU are advised against; on the contrary, a reduced panel of routine laboratory examinations is recommended.⁶ Considering that autoimmune thyroiditis is frequently associated with CSU, we suggest adding to the list thyroid stimulating hormone and anti-thyroid autoantibodies⁷⁻¹⁰ (Table I). More extensive diagnostic measures are indicated only in CSU patients with severe and long lasting disease or providing clues for coexisting conditions from their history,⁶ giving rise to suggesting a second-step examination panel (Table II). In particular, gastric pain may point to helicobacter pylori as eliciting agent, whereas systemic symptoms and signs like arthralgia/arthritis and Raynaud's phenomenon may suggest autoimmune disease. Based on the findings of recent studies published by some

TABLE I.—Basic laboratory and in-vitro examinations for the diagnosis of chronic spontaneous urticaria.

Full differential blood count
Blood glucose level
Blood creatinine level
Aspartate aminotransferase, alanine aminotransferase
Protein electrophoresis
ESR, CRP
TSH
Antithyroperoxidase/antithyroglobulin antibodies

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TSH: thyroid stimulating hormone.

TABLE II.—Second- and third-step investigations in chronic spontaneous urticaria.

Second-step diagnostic panel
HP stool test
ANA
C3, C4
D-dimer plasma level
Third-step diagnostic panel
ASST
Autologous plasma skin test

HP: helicobacter pylori; ANA: antinuclear antibodies; C: complement fraction; ASST: autologous serum skin test.

of us¹¹⁻¹⁴ demonstrating that the activation of blood coagulation plays a role in the CSU pathogenesis, we suggest to introduce the coagulation/fibrinolysis marker D-dimer in the list of laboratory investigations that may be indicated in CSU (Table II). In fact, increased plasma levels of this coagulation factor have been found in the patients with active CSU, with a direct correlation between D-dimer levels and disease's severity.¹¹⁻¹⁴ Regarding the Autologous Serum Skin Test (ASST)¹⁵ or the Autologous Plasma Skin Test,¹⁶ which are nonspecific screening tests evaluating the presence of circulating histamine-releasing factors, their diagnostic usefulness remains controversial. In fact, a relatively high prevalence of ASST positivity has been reported in patients with allergic or non-allergic asthma as well as in healthy subjects.¹⁷⁻²¹ However, considering that ASST/Autologous Plasma Skin Test are the only tests available for suspecting an autoimmune/autoreactive origin in a certain case of CSU, we propose to include them in a third-step diagnostic panel for CSU (Table II).

Differential diagnosis of chronic spontaneous urticaria

There are a number of conditions that may present with urticaria-like skin lesions, the heterogeneous group of the so-called urticarial syndromes, which have to be differentiated from CSU.^{22, 23} Some of these urticarial syndromes are purely cutaneous dis-

eases, such as bullous pemphigoid (BP) and exanthematous drug eruption, whereas others are forms with predominant skin involvement but potentially affecting also internal organs, like urticaria pigmentosa and urticarial vasculitis (UV); finally, there are conditions in which the cutaneous manifestations occur in the context of a multisystem disorder, as in the cryopyrin-associated periodic syndromes (CAPS), which are classic autoinflammatory diseases (Table III). In exanthematous drug eruption, lesions, which usually develop 4 to 14 days after drug intake, closely resemble wheals, but they have a bilateral and symmetrical distribution and are persistent (>24 hours).²⁴ In arthropod bite reactions wheals more often appear during summer, mainly on exposed areas, and then evolve into papules, sometimes capped by a vesicle and usually distributed in clusters. In atopic dermatitis as well as in contact dermatitis, urticarial lesions may occur, but the clinical picture is dominated by the eczematous lesions.²² Pruritic urticarial papules and plaques of pregnancy (PUPPP) is a form of unknown etiology usually affecting women during the third trimester of their first pregnancy and presenting with erythematous papules that subsequently coalesce into urticarial plaques; however, this eruption is typically polymorphic, with additional features including eczematous, vesicular or targetoid lesions, and has a symmetrical distribution.^{25, 26} BP is a rare autoimmune blistering disease occurring typically in the elderly, which may present solely with urticarial lesions in its early phases, often having a symmetrical distribution and being persistent; histology, direct immunofluorescence examination of perilesion skin and enzyme-linked immunosorbent assay detecting serum autoantibodies against the two hemidesmosomal antigens BP180 and BP230 are needed to confirm the diagnosis.²⁷⁻³⁰ Eosinophilic cellulitis (Wells syndrome) is a rare eosinophil-driven entity clinically characterized by single or multiple erythematous plaques, most commonly localized on the lower extremities; an atypical urticaria-like presentation is also well-recognized, but lesions are persistent, their histology shows a marked eosinophilic infiltrate and they are usually associated with a peripheral eosinophilia.³¹ Mastocytosis is a heterogeneous disease characterized by accumulation of mast cells in one or more organs, most frequently the skin.³² Urticaria pigmentosa is the most common cutaneous manifestation of mastocytosis, which manifests with brownish macules and papules, accompanied by urticarial

TABLE III.—*Main diseases that can manifest with urticarial lesions (cutaneous, mainly cutaneous and multisystem).*

Cutaneous:
– Exanthematous drug eruption
– Arthropod bite reactions
– Atopic dermatitis
– Contact dermatitis (irritant or allergic)
– Pruritic urticarial papules and plaques of pregnancy (PUPPP)
– Bullous pemphigoid (and other rarer autoimmune bullous diseases)
– Eosinophilic cellulitis (Wells syndrome)
Mainly cutaneous:
– Urticaria pigmentosa (mastocytosis)
– Urticarial vasculitis
– Cutaneous small-vessel vasculitis
Multisystem:
– Cryopyrin-associated periodic syndromes (CAPS)
– Schnitzler syndrome
– Urticarial lesions associated with:
– Connective tissue diseases
– Systemic vasculitis
– Hematologic disorders

lesions; a positive Darier sign following skin rubbing as well as histologic and immunohistochemical examinations are important diagnostic clues. Systemic involvement has to be excluded in adults and serum tryptase is an useful marker in the screening of patients for systemic disease.³² UV is a small vessel-vasculitis with predominant skin involvement, which represents the principal differential diagnosis from CSU. It manifests with urticarial lesions, persisting for more than 24 hours, burning rather than itching and resolving with hyperpigmentation; a number of skin lesions including purpura, vesicles, bullae, papules, nodules and necrotic ulcerations may coexist.^{33, 34} All the other manifestations, including urticarial lesions, are the typical cutaneous features of the so-called cutaneous small-vessel vasculitis (CSVV), which is the most common vasculitis with predominant skin involvement, affecting the post-capillary venules.³³ Both UV and CSVV may be associated with multisystem diseases, particularly connective tissue diseases, or part of the complex clinical picture of systemic vasculitis, most notably Wegener's granulomatosis (now called granulomatosis with polyangiitis) and Churg-Strauss syndrome (now called eosinophilic granulomatosis with poly-

angiitis). Histology and direct immunofluorescence are needed to establish the diagnosis.³³ A characteristic urticarial rash associated with a number of other clinical manifestations is typical of familial cold autoinflammatory syndrome, Muckle-Wells syndrome and chronic infantile neurologic cutaneous and articular syndrome (CINCA). These diseases represent the clinical spectrum of different mutations of a gene named cold-induced autoinflammatory syndrome I (CIAS-1 or NLRP3), coding for a protein called cryopyrin, which led to coining the term cryopyrin-associated periodic syndromes to define them.³⁵⁻³⁷ CAPS as well as Schnitzler's syndrome, the latter presenting as urticarial lesions, immunoglobulin M gammopathy, fever and arthralgia, are included in the group of autoinflammatory diseases, genetically determined forms due to mutations of genes regulating the innate immunity.³⁵⁻³⁸ Urticarial lesions occurring in the context of autoinflammatory diseases are usually more persistent than typical CSU hives and symmetrically distributed; they are accompanied by burning or pain as well as systemic symptoms, such as recurrent fever, fatigue and arthralgia; histologically, they are usually characterized by a neutrophil-rich inflammatory infiltrate.³⁹ Finally, ur-

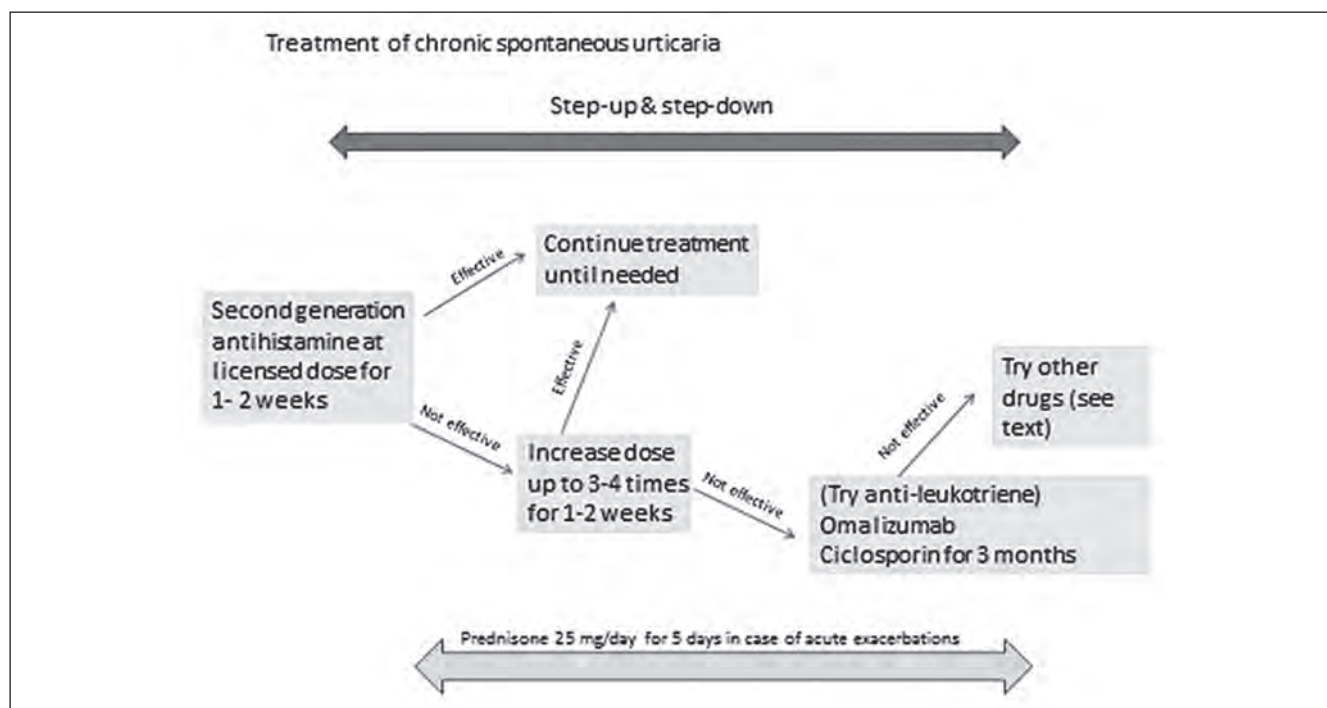


Figure 1.—Treatment of chronic spontaneous urticaria.

ticarial lesions may be the manifestations of a variety of hematological disorders, most notably Waldenström macroglobulinemia and hypereosinophilic syndromes.²³

Treatment of chronic urticaria

A flow chart for the treatment of CSU is proposed in Figure 1.

Antihistamines

Second generation antihistamines are unquestionably the first line treatment of chronic urticaria.⁶ Their efficacy may slightly differ from one compound to another with cetirizine, levocetirizine and, possibly, bilastine appearing as the most effective ones.⁴⁰⁻⁴² Sedation and psychomotor function studies have produced variable results with no relevant differences between levocetirizine, cetirizine, and loratadine in some cases,⁴³ and a greater sedative effect of cetirizine over fexofenadine, or loratadine in other cases.⁴⁴

First generation antihistamines are effective also but their efficacy does not seem superior to second generation antihistamines,⁴⁵⁻⁴⁷ while they bear a higher degree of sedation and cognitive impairment.⁴⁸ Altogether, there is no reason to use these drugs as first line treatment or as an add-on treatment for CU patients who don't respond to second generation antihistamines.⁶

Second generation antihistamines can be used at higher than licensed doses in patients who do not respond adequately at licensed doses,^{6, 49, 50} in some cases getting a better therapeutic effect without an increase in side effects. However, the safety of this approach in the long term has not been studied, and increasing the dosage is not always effective.⁵¹

H2-antagonists are not recommended as an add-on treatment of difficult CU because of lack of evidence supporting such approach.

Corticosteroids

Oral corticosteroids are able to control the disease in most CU patients who do not respond to antihistamines,⁵² but long-term treatments are associated with potentially severe side effects (diabetes, hypertension, osteoporosis, gastrointestinal bleeding, and

weight gain). Thus, these drugs are recommended for short periods and at the minimal effective dose to treat CU exacerbations.⁶ The strategy of giving 25 mg of prednisone for 3-5 days along with gastrointestinal protection and then to taper it down seems a reasonable compromise between efficacy and avoidance of most side effects.⁵²

LEUKOTRIENE RECEPTOR ANTAGONISTS

Both anecdotal reports and placebo-controlled studies have suggested the effectiveness of cysteinyl-leukotriene receptor antagonists (Montelukast and Zafirlukast) in antihistamine-resistant CU,⁵³⁻⁵⁶ but this has not been confirmed by other studies.⁵⁷ Altogether, there is limited evidence of effectiveness of these drugs, and although they do not have a specific indication for the treatment of this disease, in view of their excellent safety profile, they might be tried as an add-on treatment before considering other, more engaging, drug options.

Biologicals

OMALIZUMAB

The recombinant humanized monoclonal IgG antibody omalizumab binds free IgE, down regulates mast cell function and induces eosinophil apoptosis.⁵⁸⁻⁶⁰ Recently, it has emerged as an effective treatment for different subsets of antihistamine-unresponsive CU/angioedema of both autoimmune/autoreactive and non-autoimmune/non-autoreactive.⁶¹⁻⁷¹ Overall, across the phase III development program, 975 patients with moderate-severe chronic spontaneous urticaria and persistent symptoms despite background treatment with antihistamines were enrolled in three studies. Compared to placebo, add-on therapy with subcutaneous omalizumab 300 mg every 4 weeks for 12⁶⁸ or 24 weeks^{69, 71} significantly reduced the severity of itching and the number and size of hives and the proportion of angioedema-free days. Consistently, a significant increase in patients' health-related quality of life was observed. Omalizumab was well tolerated and reduced the signs and symptoms of CU, although symptoms gradually recurred over a period of about 10 weeks after discontinuation.⁷¹ Omalizumab has been included as a second choice treatment in the recent EAACI guidelines⁶ and has subsequently been officially approved

by the European Regulatory Agency for the use in this disease.

INTRAVENOUS IMMUNOGLOBULIN (IVIG)

IVIG has been suggested as a possible therapeutic option in patients with chronic, unremitting urticaria with positive ASST and basophil histamine release assay who don't respond to other therapies,⁷²⁻⁷⁵ although other studies did not confirm its efficacy.⁷⁶ IVIG is relatively safe, but the high cost limits its use.

Anti-inflammatory drugs

These drugs include different compounds that, although reportedly effective by some studies, show a limited evidence of efficacy and are not recommended by all the current guidelines on the treatment of CU.

Dapsone has produced variable results in CU.^{77, 78} It is not available in Italy and its use is limited by dose-related, though rare, side effects, including anemia, peripheral neuropathy, skin rash, gastrointestinal complaints, hepatotoxicity, methemoglobinemia, blood dyscrasias, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, and its contraindication in G6PD-deficient.

Sulfasalazine use is supported by some case reports and one single retrospective observational study.⁷⁹

Hydroxychloroquine use is suggested by a randomized, double-blind, placebo-controlled study showing a significant improvement in quality of life score in CU treated with hydroxychloroquine but with no change in urticaria activity scores.⁸⁰

Immunosuppressive drugs

CYCLOSPORINE

The effectiveness of cyclosporine in severe, antihistamine-resistant chronic urticaria is supported for more than 20 years by case reports, case series, and controlled trials.⁸¹⁻⁸⁸ Nonetheless, its use in CU is still off-label. The effective dose ranges between 3 and 5 mg/kg/day, and the treatment should last for approximately 3-6 months. During the treatment period, blood pressure, kidney function, and liver function should be assessed regularly.

Other immunosuppressive agents

A number of other immunosuppressive agents, including methotrexate, cyclophosphamide, azathioprine, and some purine biosynthesis inhibitors such as mycophenolate mofetil and mizoribine have been used to treat severe, unremitting, antihistamine-resistant CU.⁸⁹⁻⁹⁶ However, the quality of supporting evidence on the use of these drugs is low since only case reports and open uncontrolled studies are available.

RITUXIMAB

Rituximab, a chimeric monoclonal antibody specific for the protein CD20, which is primarily present on the surface of B cells, was effective in two chronic urticaria patients resistant to H₁ antihistamines,^{97, 98} but was ineffective in a third case.⁹⁹

Anticoagulants

Recent studies showing that CU is frequently characterized by the activation of coagulation and fibrinolysis during severe exacerbations of the disease possibly as a consequence of tissue factor expression by activated eosinophils,^{11-14, 100} which decreases to complete normalization during remission,¹⁰¹ have provided the rationale for an anticoagulant and antifibrinolytic therapy in patients with severe CU. Indeed, the effectiveness of anticoagulant therapy in some patients with refractory CU was observed several years ago by the use of both oral anticoagulants¹⁰² and heparin.^{103, 104} Recently, the efficacy of serine protease inhibitors nafamostat mesilate and camostat mesilate in refractory CU was shown.¹⁰⁵ Such drugs inhibit different proteases, including tryptase, kallikrein, complement, factor XII and plasmin, and show an anticoagulant effect similar to that of heparin.¹⁰⁶

Other treatments

Plasmapheresis has been suggested in patients with severe, unremitting and refractory chronic urticaria;¹⁰⁷ however, such approach is not easily available and cannot be recommended for routine use.

Miltefosine, a lipid raft modulator, was effective in a randomized controlled multicentre study in CU patients who do not respond to standard-dosed H₁ antihistamines.¹⁰⁸

Conclusions

Chronic urticaria is a highly frequent clinical event that occurs as either an isolated manifestation or associated with other signs or symptoms of systemic diseases (urticarial syndromes). It is often accompanied by angioedema that shares with urticaria several pathophysiological and etiopathogenetic features. While the clinical diagnosis of urticaria is relatively easy given the classical appearance of wheals, understanding its cause is often very difficult. In some cases chronic urticaria is associated with a type I hypersensitivity reaction induced, for example, by food allergens or latex. In other cases urticaria is an autoimmune disorder associated with the presence of circulating autoantibodies anti-FcεRI or anti-IgE. It is always important to consider the possibility that chronic urticaria may be the presenting symptom of an underlying condition such as chronic inflammatory and autoimmune disorders, infections (either viral, bacterial or parasitic) and, rarely, neoplastic diseases.

A careful history and a complete clinical evaluation are usually sufficient to lead to selected diagnostic tests that allow classification of the type of urticaria. In most cases, however, the eliciting factors of chronic spontaneous urticaria remain elusive.

Second generation antihistamines are the first line treatment of chronic spontaneous urticaria. While most patients respond to the usual dosage of antihistamines, some of them require higher dosages or the addition of other drugs to control urticaria. The use of leukotriene receptor antagonist or anti-H₂ has little supportive evidence of effectiveness in chronic spontaneous urticaria. However, given the lack of important side effects, they are often used as second line treatments, usually as an add-on to antihistamines. The monoclonal anti-IgE antibody omalizumab has been recently approved for treatment of chronic urticaria unresponsive to antihistamines. Omalizumab represents an effective and safe therapeutic option for patients that were previously considered very difficult to treat. Several unmet needs still remain in the diagnosis and treatment of chronic urticaria even though this condition has been the target of extensive clinical research in the last decades. Pathogenetic mechanisms underlying CU are still largely undefined and this lack of knowledge makes it difficult to develop targeted therapies. Assessment of response to treatments is hampered by the lack of validated

tools to evaluate clinical activity. A larger implementation of questionnaires, such as UAS and CU-QoL, assessing patient reported outcomes (PROs) would be desirable. There is still not a general consensus on the duration of antihistamine treatment to assess its efficacy or not in CU, although 1 week is usually sufficient in most patients to get a clear answer. In addition, further studies are needed to better define those patients who will benefit by increasing antihistamine dosage to four-fold those recommended. A careful balance between expected gain of efficacy of high antihistamine dosages vs. their potential side effects should always be considered. Omalizumab is entering the scenario with strong evidence of efficacy even in the most severe and refractory cases of CU. The criteria to select omalizumab among other second line treatments, *e.g.*, ciclosporin, should be clearly defined and should take into account safety and patients' preference issues. Answering these question together with a better understanding of its complex pathogenetic mechanisms of CU will lead to more successful diagnostic and therapeutic strategies that will definitely improve the quality of life of CU patients.

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Acne: a new model of immune-mediated chronic inflammatory skin disease

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Acne is a chronic inflammatory disease of the sebaceous-pilosebaceous unit. Interestingly, inflammation can be detected by histopathological examination and immuohistochemical analysis even in the apparently non-inflammatory acneic lesions, such as comedones. In the last years, it has been clearly demonstrated that acne development is linked to the combination of predisposing genetic factors and environmental triggers, among which a prominent role is played by the follicular colonization by *Propionibacterium acnes* (*P. acnes*). *P. acnes* displays several activities able to promote the development of acne skin lesions, including the promotion of follicular hyperkeratinisation, the induction of sebogenesis, and the stimulation of an inflammatory response by the secretion of proinflammatory molecules and by the activation of innate immunity, that is followed by a *P. acnes*-specific adaptive immune response. In addition, *P. acnes*-independent inflammation mediated by androgens or by a neurogenic activation, followed by the secretion in the skin of pro-inflammatory neuropeptides, can occur in acne lesions. In conclusion, acne can be considered as a model of immune-mediated chronic inflammatory skin disease, characterized by an innate immune response that is not able to control *P. acnes* followed by a Th1-mediated adaptive immune response, that becomes self-maintaining independently from *P. acnes* itself.

KEY WORDS: Acne vulgaris - *Propionibacterium acnes* - Acne vulgaris, genetics.

Acne is a chronic inflammatory disease of the sebaceous-pilosebaceous unit. Interestingly, inflammation can be detected by histopathological examination and immuohistochemical analysis even in the apparently non-inflammatory acneic lesions,

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such as comedones. Acne primarily affects the pilosebaceous follicles (PSF) of the sebaceous regions, due to: 1) the presence of androgen receptors on the PSF cells (*i.e.* keratinocytes and sebocytes);¹ 2) the specific activity of the 5 α -reductase on such cells;² 3) gain-of-function genetic polymorphisms of such receptors in patients with acne.³

The inflammatory reaction of acne usually involves only a small number of PSF, because of their different level of maturation and, consequently, of sebum production, that is directly related to the colonization of *Propionibacterium acnes* (*P. acnes*) from nasal mucosa.⁴

In the last years, it has been clearly demonstrated that acne development is linked to the combination of predisposing genetic factors and environmental triggers, including *P. acnes*. In this paper, the role of the latter in the induction of acne lesions will be reviewed, focusing the attention on the activation of both innate and adaptive immunity as well as on the neuroendocrine modulation that leads to its promotion and maintenance.

Genetic factors

Classic twin-⁵ and population-based⁶ studies provided clear evidence concerning the role of inherited

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factors in the pathogenesis of acne. Systematic twin studies suggest a strong concordance in the occurrence and severity of acne symptoms in identical twins and the accumulation of affected individuals in certain families.⁵

Cross-sectional studies in developed countries involving adolescent schoolchildren have revealed that the prevalence of acne progressively increases during the teen-age years and, in cases in whom acne persists even in the adult years, a strong familial predisposition can be detected.⁷

Systematic molecular genetic analyses on acne population where performed only in recent years. The genes studied so far are either key players of innate and adaptive immunity or have a function in steroid hormone metabolism and in some metabolic processes (insulin growth factor-1 and fibroblast growth factor receptor genes) related to acne pathogenesis. Although the latter play an important role in the pathogenesis of the disease, in this paper only the genetic alterations involving the immune systems and potentially involved in acne will be reviewed.

The pathogen recognition receptors TLR2 and TLR4 are important in the recognition of *P. acnes* in epidermal keratinocytes and sebocytes, and regulate downstream innate immune events. However, although direct sequencing has revealed that the rare A allele of the Arg753Gln polymorphism of TLR2 gene is missing and that the Asp299Gly and Thr399Ile changes of TLR4 occur simultaneously with significant low frequency in Central Eastern European study population, no association was demonstrated between the carriers of the polymorphisms and acne.⁸

Mucins are high-molecular-weight glycoproteins expressed by different cell types of epithelial origin. MUC1, a cell surface mucin, has been demonstrated to be involved in various processes during pathogen infection, including the binding of the attacking pathogens.⁹

One study investigating variable number of tandem repeat polymorphisms (VNTP) in a Japanese population with acne vulgaris, revealed a significant difference between patients with severe acne and controls, concerning the heavily glycosylated extracellular domain of long-length MUC1.¹⁰ Such genetic polymorphisms in Japanese patients with severe acne would increase MUC1 pathogen-binding ability, enhancing bacterial colonization and susceptibility.¹¹

Regarding the gene encoding the TNF- α cytokine, there have been some reports of the role of TNFA promoter SNPs in the pathogenesis of acne vulgaris.¹² The TNFA -308G>A polymorphism was common in all of them, and their pathogenetic role could be related to an augmented release of TNF- α by both keratinocytes and sebocytes in carriers of the TNF- α -308 SNP.

Even genetic modifications to IL-1 pathway can be relevant for the pathogenesis of acne. A case-control study revealed a positive association between the rare T allele of the +4845(G>T) SNP and acne.¹³ Patients carrying this SNP result in enhanced cleavage of pre-IL-1 α , with an increased production of the mature isoform.

Finally, a recent case-control study from Saudi Arabia demonstrated a significant association of IL-4R (Q551R A/G) genetic polymorphisms with the susceptibility rather than severity of acne vulgaris.¹⁴

***P. acnes* as a trigger for the development of acne lesions**

As discussed above, the individual genetic background of patients with acne has long been suggested to play an important role in the disease pathogenesis but, because of the polygenic character, all these factors cannot thoroughly explain the extremely high prevalence rate of acne that can be observed in Western countries. Thus, the role of environmental and lifestyle factors is becoming more and more considered in recent researches.

Among the environmental triggers, there is an increasing evidence of a strong association between acne and the consumption of high glycaemic-load foods, of cows milk and dairy products, and with an augmented body mass index.¹⁵ Limited evidence was also shown about the excess of salt and saturated and hydrogenated fatty acid intake.¹⁶ Although earlier observational studies suggested an inverse association between smoking and acne, following studies have shown that severe acne increases with smoking.¹⁷

However, among the other triggering factors, a prominent role is played by the follicular colonization by *P. acnes*. *P. acnes* is a Gram + anaerobic, aerotolerant, microaerophilic bacterium belonging to the normal resident microbiota of the skin, oral cavity, gastrointestinal and genitor-urinary tracts.

The analysis of ribosomal RNA gene sequences of the microbial profile (microbioma) of the sebaceous areas obtained by Grice *et al.*, completely changed our previous knowledge about the skin resident microorganisms, based on classical culture-based methods.¹⁸

In fact, this new topographical and temporal survey has provided a specific characterization of microbioma in the healthy human skin. In the sebaceous sites, *Propionibacteria* species were the most predominant followed by *Staphylococci* species (in particular *Staphylococcus epidermidis*). In the moist sites, *Corynebacteria* and *Staphylococci* species predominated, though β -*Proteobacteria* also were represented. In the dry sites, a mixed population of bacteria resided with a greater prevalence of β -*Proteobacteria* and *Flavobacteriales* species.¹⁸

To date, many lines of evidence associate pathogenicity of *P. acnes* with imbalance of microorganisms, known as “dysbiosis”. In acneic skin, the relationship between bacterial communities granted by microbial interdependence is imbalanced, with consequent overgrowth of *P. acnes* and reduction (up to disappearance) of *S. epidermidis*.¹⁹ Such alterations are also favoured by the microaerophilic environment found in the PSF. Moreover, the production of antimicrobial peptides (PAMs) such as batteriocide, epidermine, epilancine k7, phenol soluble moduline γ and δ by *S. epidermidis* is reduced, and the growth of *P. acnes* increases accordingly. In fact, PAMs produced by *S. epidermidis* are able to inhibit *P. acnes* proliferation, to control the secretion of keratinocytes-derived PAMs, as well as to modulate the formation of biofilm by *P. acnes*, that is considered an important factor for the survival and the proliferation of *P. acnes* in the PSF. Biofilms are complex sessile microbic communities that consist of one or more bacterial species surrounded by extracellular polymorphic substances. Recently, Jahns *et al.* demonstrated that *P. acnes* is able to form macrocolonies/biofilms not only *in vitro*, but also *in vivo* in PFS of acne patients.²⁰

Genetic analysis with multilocus sequence typing (MLST) have demonstrated that among 203 *P. acnes* isolates from the facial skin of 64 volunteers, type IA and IB organisms are the dominant lineages present. The absence of type IB strains among acne isolates despite their presence on facial skin provides evidence that type IA specific factors are responsible for the association with acne. Three

genotypes of *P. acnes* can be identified with a high homology (99.8-99.9%). Moreover, it has been demonstrated that the IA genotype is associated to moderate to severe acne.²¹ More in detail, some *P. acnes* IA subtypes, including the ST6 clone, are more frequently detected, show a geographically and temporal widespread dissemination, are able to produce several disease-associated virulence factors (*i.e.*, lipases, proteases, neuroaminases, dermatan sulphate adhesion 1 and 2) as well as highly immunogenic proteins.²¹ Such clones, in a microaerophilic environment, modify their protein synthesis profile (“ecologic flexibility”), increasing the synthesis of several enzymes that are crucial for *P. acnes* growth, virulence and immunogenicity (transcriptome analysis).²²

P. acnes displays several activities that are able to promote the development of acne skin lesions, including the following: 1) to promote follicular hyperkeratinisation; 2) to induce sebogenesis; 3) to trigger an inflammatory response by the secretion of pro-inflammatory molecules and by the activation of innate immunity, that is followed by a *P. acnes*-specific adaptive immune response.

***P. acnes* triggers the release of proinflammatory factors**

Several studies demonstrated that *P. acnes* is able to produce lipases that, using triglycerides as a substrate, allow the release of free fatty acids as well as β -defensins (h β D₂).²³ Free fatty acids favor the adherence between *P. acnes* and keratinocytes, have a proinflammatory activity, are potent chemoattractant for the neutrophils and induce follicular hyperkeratinization.²³ h β D₂, whose synthesis is triggered by free fatty acids, have a dual role in the pathogenesis of acne: 1) a protective role against *P. acnes* colonization when its local concentration rises above the bactericidal level; 2) role in the regulation of adaptive immunity (chemoattractive for immature dendritic cells and memory T cells).²⁴

The production of proteases is another eliciting factor for PSF inflammation.²⁵ In fact, linking with protein activated receptors 2 (PAR2) on keratinocytes, *P. acnes*-derived proteases induce the release of proinflammatory cytokines, h β D₂, LL37, as well as several metalloproteases (MMP), including MMP1, 2, 3, 9, and 13.²⁵ In particular, the aug-

mented concentration of MMP, associated to the reduction of tissue MMP inhibitors (TIMP 1 and 2), is responsible for an accelerated collagen degradation with disruption of the PSF and consequent scar formation.²⁵

P. acnes also synthesizes coproporphirin III that, acting on keratinocytes, promotes the production of IL-8, of reactive oxygen species (ROS) and of catalytic agents that induce the peroxidation of sebum-derived squalene.²⁶ The augmented production of superoxid anions, together with the reduced keratinocyte synthesis of antioxidants such as glutathione and vitamin E, are able to trigger PSF hyperkeratinization and the development of a microaerophilic environment.²⁷ The latter favors *P. acnes* proliferation, the secretion of proinflammatory cytokines by keratinocytes,²⁷ and PPAR α and γ stimulation, followed by 5-lipoxygenase and B₃-leukotriene.²⁸ Finally, PPAR γ receptors trigger sebocytes to produce COX₂ and PGE₂.²⁹

***P. acnes* activates innate immunity**

It is well known that *P. acnes* is able to activate the complement cascade by both the classic and the alternative pathways, leading, in perifollicular area, to an accumulation of C5a, a potent chemotactic agent for neutrophils. Moreover, *P. acnes* stimulates TLR2 and 4 that are hyperexpressed on follicular keratinocytes in acne patients³⁰ and promote the production of proinflammatory cytokines and the maturation of dendritic cells.

TLR2 and 4 stimulation by *P. acnes* leads to an augmented synthesis of IL-1 α , IL-1 β , TNF- α and GM-CSF.³¹ All these cytokines show potent proinflammatory and chemotactic activity for several cell types (including neutrophils, lymphocytes and macrophages). Moreover, keratinocytes increased their production of h β D1 and 2³¹ that, together with a microbicidal activity, are able to stimulate the production of IL-8 by perifollicular macrophages and the expression of IL-8 receptor by keratinocytes which, in turn, increase their proliferation and differentiation.

Moreover, *P. acnes* lipoproteins stimulate TLR2 expressed on sebocytes, inducing h β D₂ production. Accordingly, TLR2 expressed on perifollicular macrophages induce an augmented secretion of h β D₂, IL-8 and, mainly, IL-12, a cytokine that play

a crucial role in switching the T cell-mediated adaptive response towards a Th1 pattern.³²

P. acnes is also able to activate CD1a, a transmembrane glycoprotein expressed on both keratinocytes and sebocytes. CD1a shows a high homology with I class MHC molecules and presents *P. acnes*-derived both lipidic and glycolipidic antigens to T NK cells, which are involved in dendritic cell maturation and in the switching of the immune response toward a Th1 pattern.³³

Finally, *P. acnes* stimulates CD36, a scavenger receptor expressed on both keratinocytes and sebocytes whose activation induces an augmented production of superoxide anions that form peroxynitrites from the combination with nitric oxide.³⁴ Moreover, CD36 stimulation allows the release of free fatty saturated acids (FFSA) from the cell membrane of sebocytes, with consequent hyperproduction of h β D₂.³⁵ *In situ* studies performed on acne lesions show that genes coding for IL-8, β_2 -defensin 4, MMP-1, MMP-2, TLR2, and TLR4 are up-regulated in epidermis in association with the activation of the transcription factors NF- κ B and AP-1.³⁶ These results confirm a prominent role for innate immunity that, via the production of antimicrobial peptides, inflammatory cytokines and MMPs, is able to trigger the inflammatory response seen in acne lesions.

***P. acnes* stimulates a specific adaptive immune response**

As previously observed, the activation of innate immunity is the premise of the development of an adaptive immune response against antigens of *P. acnes*. Probably, the most important step is represented by the maturation of dendritic cells, that are considered a sensor that links innate to adaptive immunity.³⁷ The differentiation of immature dendritic cells into mature ones is associated with the upregulation of costimulatory, adhesion and MHC molecules on the cell membrane, as well as with the secretion of several cytokines and chemokines, and allows dendritic cells to acquire antigen-presentation function and to migrate into the lymph nodes.³⁸ Such a process is driven by the augmented production of TNF- α that followed the interaction between *P. acnes* and TLR2 expressed by immature dendritic cells.³⁹ In addition, *P. acnes* is able to

stimulate both keratinocytes and sebocytes that, in turn, trigger the production by NK T cells of IL-15 and GM-CSF, two cytokines that induce dendritic cell maturation.³⁹

Mature dendritic cells express CD1b, process and expose *P. acnes* antigens on class I and II MHC molecules and drive the activation of B and T cells in the draining lymphnode, resulting in antibody production and Th1 immune response polarization, respectively. *P. acnes* antigens that are recognized by dendritic cells are represented by peptoglycans, lipoteichoic acid, lipo-arabinomannans, lipoglycans (DNAK) and different types of heat shock proteins, including GroEL, which has a high homology with human heat shock protein 60.⁴⁰

The B-cell specific adaptive response against *P. acnes* results in the production of IgG and IgM antibodies. Their titer is very low in healthy controls while it is elevated in acne patients, where such autoantibodies are of the IgG1 and IgG3 subclasses and do not correlate with the severity of the disease.⁴¹ Anti-*P. acnes* antibodies target about 25 different antigens which have a molecular weight between 30 and 300 kD; however, most of them are directed against a 96 kD antigen.⁴²

While the antibody response does not seem to play a prominent pathogenetic role and can be considered only an epiphenomenon related to the *P. acnes* colonization of the PSF, the T cell-mediated immune response is paramount for the development of acne lesions. The latter is polarized toward a Th1 pattern due to the presence of IL-12 and IL-18, produced by keratinocytes and perifollicular macrophages, and of IL-8 and GM-CSF, produced by circulating mononuclear cells.

Th1 immune response against *P. acnes* is very early and precedes not only microcomedone formation,^{31, 32} but also all the keratinocyte changes responsible for the beginning of the follicular hyperkeratinization, such as the expression of the proliferation marker Ki-67 and of the differentiation marker K16.⁴³

The effects of the immune activation in acne lesions are represented by a perifollicular CD3+ CD4+ T cell infiltrate; most of T cells are CD4RO+ (memory/effector cells) and express $\alpha\beta$ TCR as well as CLA.⁴⁴ Moreover, T cells extracted from acne lesions and cultured *in vitro* are able to produce high amounts of IFN- γ , but not of IL-4, after challenge with *P. acnes* antigens.⁴⁴

Interestingly, together with a hyperactivation of Th1-mediated immune response, acne patients show a reduced production of the regulatory cytokine IL-10. In fact, it has been demonstrated that PBMC from acne patients produced significantly lower amounts of IL-10 than those from healthy subjects, when stimulated with *P. acnes* antigens.⁴⁵ Moreover, CD14+ monocytes from acne patients show a reduced fagocytic activity against *P. acnes* that is restored by the administration of IL-10.⁴⁵ The reduced fagocytic activity is probably responsible for the prolonged survival *in vivo* of *P. acnes*.⁴⁵

Very recently, it has been shown that *P. acnes* can induce a Th17-mediated immune response and therefore that Th17 cells may be involved in the pathogenesis of acne. Agak *et al.*⁴⁶ showed that the secretion of IL-17 by native CD4+ cells can be induced by *P. acnes*, thus suggesting that both Th1 and Th17 responses may be involved against this microorganism.

Kistowska *et al.*⁴⁷ showed that, besides Th17, *P. acnes* promotes mixed Th17/Th1 response by inducing the concomitant secretion of IL-17A and IFN- γ from specific CD4+ T cells *in vitro*. Th17/Th1 *P. acnes* reactive cells can be found in the peripheral blood of patients with acne, and at a lower frequency in healthy individuals. Finally, in the same study, IL-17A was shown to be secreted by two distinct subsets of T cells, producing either IL-17A alone or in conjunction with IFN- γ . In particular, Th1 cells could be induced in only 40% of the tested donors, whereas Th17 or Th17/Th1 cells could be induced by *P. acnes* in 100% of them.

***P. acnes*-independent inflammation in acne lesions**

It has been recently demonstrated that a *P. acnes*-independent inflammation can occur in acne lesions. Such inflammatory response is mediated by androgens or by a neurogenic activation of the CRH-POMC (Pro-opio-melanocortin)-CS system, followed by the secretion in the skin of pro-inflammatory neuropeptides.⁴⁸ Androgens have been demonstrated to trigger the development of an inflammatory response *via* the stimulation of specific androgenic receptors in the cytoplasm of the fibroblasts. Such stimulation induces the production of FGF7 and 10, that interact with FGFR2 on kerat-

inocytes and drive the secretion of IL-1 α .⁴⁹ The latter is able to lead to inflammation both directly and in an indirect way, *via* the induction of substance P release from the terminal nervous fibers.⁵⁰ Moreover, androgens interact with the specific androgenic receptors on sebocytes, leading to the production of IL-6, TNF α and h β D₂, which in turn has a chemotactic and activating effect on monocytes, immature dendritic cells and T cells.⁵¹

Finally, both sebocytes and follicular keratinocytes are able to release CRH, CRH-binding protein, CRH receptors 1 and 2 (CRHR1 and 2), as well as some melanocortins, such as ACTH, MSH and its receptor MCR5.^{6, 19} All these data suggest that PSF can be considered as a neuroendocrin organ and that CRHR1 and 2, as well as MCR5 stimulation favors not only comedon formation and sebogenesis,⁵¹ but also mast cell-mediated perifollicular inflammation.⁵²

The activation of this neuroendocrin pathway is also able to explain stress-induced exacerbation of acne.⁵²

Conclusions

In the last years, several studies investigated the pathogenesis of acne allowing to explain the main mechanisms involved in the disease and to highlight key areas of research that need to be addressed in the future.

First of all, recent papers confirmed the role of *P. acnes* as the most important environmental trigger of the disease. The microbial profile (microbiome) of the sebaceous areas obtained by Grice³² with ribosome RNA gene sequences analysis completely changes our previous knowledge about the skin resident microorganisms based on classical culture-based methods. Microbiome of the sebaceous sites of healthy human skin demonstrates that Propionibacteria species were predominant, followed by Staphylococci species. In acneic skin, the relationship between bacterial communities granted by microbial interdependence is imbalanced (dysbiosis), with consequent overgrowth of *P. acnes* and significant reduction, up to disappearance, of Staphylococci species. Such an imbalance leads to an impaired production of staphylococcal antimicrobial peptides, which are no more able to inhibit *P. acnes* proliferation and to modulate the *P. acnes* biofilm

that has been demonstrated in vivo in PSF of acne patients.

IA genotype of *P. acnes* is associated to moderate to severe acne and, in particular, the ST6 clone is not only the more frequently detected, but also shows a geographical and temporal widespread dissemination. This clone is also able to produce several disease-associated virulence factors and high immunogenic proteins. Accordingly, the release of proinflammatory factors and the following activation of both innate and adaptive immunity lead to follicular hyperkeratinization, sebogenesis and inflammatory response.

Interestingly, the pivotal role of *P. acnes* in the triggering of the immune response has been demonstrated even in the first phases of the disease, changing the classical view of the pathogenesis of acne that suggested a progression from the hyperkeratinization of the PSF to the development of inflammation. Accordingly, it is now clear that the immune response is present from the beginning of the disease, even in the absence of acne inflammatory lesions.

Moreover, recent studies suggested also that triggering factors other than *P. acnes* are involved in the induction of acne inflammation, including androgens and the neurogenic activation of CRH-POMC, that are able to explain stress-induced exacerbation of acne.

Although the recent advances in the pathogenesis of acne, including the knowledge of the several immune pathways involved in the development of the lesions, several points should be further addressed by future acne research, including the following:

1. the role of genetic factors in the clinical manifestations of the disease, including not only the role of immune-related genes, but also of those involved in steroid hormone metabolism and in other metabolic pathways, such as cytochrome P450 family, insulin growth factor 1, and FGFR2 gene polymorphisms;
2. the immunophenotype of dendritic cells involved in the development of acne lesions;
3. the antigens of *P. acnes* toward the Th1 immune-response is directed against;
4. the role of other T cell populations potentially involved in the enhancement of the immune response, such as Th17 cells;
5. the role of regulatory T cells and of the immunomodulatory cytokines such as IL-10 and TGF- β in the modulation of acne immune response.

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Toll-like receptors pathways implication in common autoimmune diseases and therapeutic perspectives

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Toll-like receptors (TLRs) are a category of receptors that recognize and activate their signaling pathways to defend against the pathogen factors. However, an alteration in the proper activation might occur, resulting in the production of proinflammatory cytokines. This improper activation is the beginning of an autoimmune disease. The inhibition of the implicated receptors or their pathways may prevent the induction of autoimmunity. This paper describes in detail new therapeutic opportunities based on the alteration of the TLR activation for rheumatoid arthritis and systemic lupus erythematosus.

KEY WORDS: Toll-like receptors - Autoimmunity - Rheumatoid arthritis - Lupus erythematosus, systemic - Psoriasis.

It has always been believed that autoimmune diseases were the result of a genetic predisposition, based on the HLA system. However, the correlation between a great variety of diseases and infectious agents support the hypothesis of infectious trigger for pathogenesis of immunity. Skin is the first component of human body that comes in contact with pathogenic and non-pathogenic agents. The role of skin is multifunctional, because it stops mechanically the invasion of the above agents and promotes the immunologic defence by activating the immune system.

Once the pathogens come over the physical barrier of epidermis, they are recognized by specific cells that express specific receptors. These receptors are called toll like receptors (TLRs) and represent a member of the family of pattern recognition recep-

tors (PRPs). Their roles were settled in the maintenance of the innate and acquired immunity and were first recognised in *Drosophila*. In humans, TLRs are located in macrophages, dendritic cells and epithelial cells. Keratinocytes, as the first to come in contact, are not the only category of cells that contribute to the immune response. There are also two major cell populations that interfere, and these are the Langerhans cells and the Melanocytes. Keratinocytes express TLRs 1, 2, 3, 5 and there are doubts about the expression of TLRs 4 and 9. Langerhans express mostly TLR 2 and to a lesser degree TLR 3, 4, 8, 10. Melanocytes, lastly, express TLR 2, 3, 4, 5, 7, 9.¹ TLRs are also seen on cell surface of T cells subtypes, such as conventional α BT cells, $\gamma\delta$ T cells and natural killers T cells.^{2,3}

In humans, there are recognised 11 types of TLRs. TLRs are intracellular and extracellular. The extracellular ones include TLR 1, 2, 4, 5, 6 and have the ability to recognize components of bacteria (Gram (+) and (-)), mycobacteria, fungi, virally encoded proteins and heat shock proteins. The intracellular category consists of TLR 3, 7, 8, 9 and recognizes double and single stranded RNA, which means components of viruses. The pathogenic components of the infectious agents are characterised as pathogen associated molecular patterns (PAMPs) and the cell

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products from tissue injury are called DAMPs (damage associated molecular pattern molecules).

TLRs have five adaptor components that initiate the cascade for the immune response, including MyD88, TRIF, TRAM. The major one is the myeloid differentiation factor 88 (MyD88) that interacts with the TIR domain of TLRs. This domain is identical to the intracellular part of the IL1 receptor. The role of MyD88 is essential, because in case of MyD88 deficiency the activation of only TLR 2, 4, 9 do not promote an immunologic response. On the contrary, activation of IL1r may result in an immunologic phenomenon and this means that IL1r pathway is a MyD88 independent signaling pathway. IL1R and all TLRs, except from TLR3, use MyD88 as a signaling pathway. The TRIF pathway is used by TLR3, 4. TLR4 may use as well the TRAM pathway.⁴ TLR7, 9 may produce inflammatory cytokines, such as TNF α , IL-6 and 12, by activating the MyD88 pathway and alternatively use the IRAF6 pathway to produce IFN α .⁵

My88 is used by TLR 1,2,4,5,6,7,8,9 and leads to the activation of interferon regulatory factor 3 (IRF 3) and central transcription factor- kappa B (NF- κ B). The last one acts as a trigger for cytokine production, such as TNF α and IL 6, 12, so as to move the phagocytes, such as macrophages and dendritic cells (DCs), to ingest the pathogens. The presence of the receptors in the phagosomes (phagocytic receptors and PRPs) is essential to distinguish the host components from the real pathogens, so as to load onto the MHC system the right antigen and begin the antigen presentation to T cells. In case of MyD88 deficiency the Th1 immune response is impaired and there is a tendency of Th2 predominance, which promotes the equivalent production of cytokines.^{2, 6, 7-9}

Mechanisms of autoimmunity induction

The effectiveness of the immune system is quantitative and qualitative characterized by the proper and well organized defense against truly invaders. In case of any disturbance in the activation of the immune response, then inappropriate immune responses may appear, possibly against self components. The last reaction figures out the nature of autoimmunity. The ways by which pathogens can promote autoimmunity are divided in the antigen-specific and non antigen specific mechanisms. Molecular mimicry, the

cryptic antigens and superantigens compose the first category. In molecular mimicry, the components of the pathogens are similar to elements of the host, and so an immune response can begin against self molecules via cross reactivity. The cryptic antigens are host proteins that have been produced during tissue injury and are recognized as non-self. Lastly, superantigens are proteins with bacterial or viral origin that bind nonspecifically to TCR (T cell receptor), elicit an immune response of lymphocytes without the same antigenic specificity and do not need fully co activation molecules interaction. The Bystander activation, or epitope spreading, belongs to the second category of mechanisms. It stimulates the immune response without enhancing a specific TCR stimulation and may occur during the infective stage of an infectious disease or even on late onset. Bystander activation demonstrates an immune response to epitopes that do not concern the disease causing epitope.^{7, 10, 11}

The way that human organism responds, depends on the kind of the pathogen. For example, viruses activate the MyD88 pathway and results in the IFN α production, which is essential for the defense against viruses. But, the effect of IFN α in immature DCs (pDCs) up regulates TLR 7 in B cells and force DCs to react more efficiently to the complexes composed of self RNA, derived from virus induced cell death, and auto-Ab.⁵ Recent data from experiments in mice have shown that the survival of autoreactive B cells in the periphery depends on the presence of the BAFF (B cell activating factor), IRAK4, MyD88 and UNC93B pathways. More specific the up regulation of BAFF supports the survival of autoreactive B cells in the periphery, in contrast to the regulation of the above pathways, which are activated by TLR.^{7-9, 12}

Bacterials and parasites trigger different receptors and as a result activate another immunological pathway, by signaling different TLRs. As it is mentioned above, TLR3 is mostly used by viruses, while TLR4 by bacterials. The engagement of bacterial lipopolysaccharide (LPS) to TLR 4 prompts the maturation of DCs. As a result, IL 12 is produced and modulates Th1 response and maturation of CD8 cytotoxic T cells. This cytokine seems to be necessary in induction of autoimmunity when self antigens are used to mature DCs via TLR4, but is not required when TLR3 is activated. In the last case, IFN α may be used as an autoimmunity sensitizer instead of IL12 or in combination so as to modulate CD 8 T cells.¹³

It is also essential to determine the importance of the roles of TLRs and TLR pathways. There has already been mentioned that in MyD88 deficient pathway a Th2 polarized cytokine production is mentioned, irrespectively of the activated TLRs. Experimental data on animals have shown that TLR 2, 4, 9 are not necessary to induce autoimmunity, such as experimental autoimmune uveitis, when MyD88 pathway is efficient. Moreover, IL1r signaling is necessary for autoimmunity induction, in contrast to IL18r, with which share molecular similarity to MyD88. IL1 seems as well to have an non-MyD88 dependent pathway in promoting autoimmune diseases.^{9, 14}

Based on the above data, a possible negative interaction among an inhibitor and TLRs or their recruitment might impair the whole process. The transmembrane inhibitors have the ability to isolate the TLR adaptors or to attach to the TLR and thus make impossible the connection between TLR and TLR ligand. Some examples of this category include ST2, SIGIRR and TRAILR. ST2 is a suppressor of tumorigenity and SIGIRR is the single immunoglobulin IL1 related protein, which is also known as TIR-8. The last one is mostly observed in epithelial cells (kidney, gut, liver) and dendritic cells (DCs). Lastly, TRAILR is the receptor of TNF related apoptosis inducing ligand and is a member of the TNF superfamily. It is interesting to mention that in TRAIL and TRAILR deficient mice there was superiority in clearance of CMV infection.¹⁵

Possible therapeutic options for autoimmune diseases

Autoimmune diseases may affect multiple organs and lead to life threatening conditions, according to the affected system. Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) consist two of the great importance autoimmune diseases. Therapeutic opportunities for them include the use of immunosuppressive and immunomodulating agents such as corticosteroids, cyclosporine, anti-TNF α . However, the role of TLRs and their molecular pathways may allow the development of new therapeutic factors that could alter or inhibit the autoimmune process.

Rheumatoid arthritis (RA) is an autoimmune disease that mostly threads the musculoskeletal system,

causing skeletal deformities. The causative factor of the disease was unable to be identified. However, the reproduction of arthritis similar to that of RA after infectious involvement suggest an immune response based on the TLR activity and especially the interference of TLR1 to 6. New experimental data have also shown that there is a TLR2, 3, 4 predominance in synovial fibroblasts of the affected joints in chronic cases, whereas TLR3,4 are mentioned in cases of early disease. The negative regulation of TLR and their recruitment may lead to the inhibition of the inflammatory process.^{16, 17}

Before the extensive report of the new therapeutic agents, there must be mentioned that the wide range of the clinical response of RA patients in anti-TNF α probably depends on the gene polymorphism of TLRs and NF κ B. NF κ B activates and is activated by TNF. The single nucleotide polymorphism (SNP) of TLR2,4 and NF κ B results in reduced anti-TNF α response. Eight SNPs are found to be involved and six of them are specified to Etanercept.¹⁶

As it was mentioned above, one of the possible therapeutic options for RA is the negative regulation of TLRs. The negative regulators might be categorized in soluble extracellular, transmembrane, intracytosolic and intraendosomal regulators. Of great importance are the soluble TLR2 and 4 (sTLR2 and 4), which affect TLR2 and 4, resulting in blocking the equivalent receptors. The inhibition can take place in three portions according to the molecular structure of TLR. The extra cellular inhibition is made by the soluble Decoy TLRs, which contend with TLR agonists. Despite the number of isoforms for every TLR, currently there are extracellular inhibitors for TLR2 and 4. Interestingly, there has been found a natural sTLR2 in human milk and plasma.

IRAKM is also an important intracytosolic regulator that inhibits IRAK1 phosphorylation and thus negative regulates the activation of TLR4 and 9, *via* the inhibition of the formation of the complex IRAK/TRAF6. A20 as well inhibits the NK κ B activation. There will be a more extended report for these regulators below in the text. However, it is interesting to mention that the final activation of the receptors is determined by the type and the amount of the factor that affects him. This regulator may be used in either RA or SLE.¹⁷⁻¹⁹

Systemic lupus erythematosus (SLE) is the other major autoimmune disease that is characterized by the hyperactivity of B cells leading to the produc-

tion of antibodies against self-components. New experimental data on mice have proven that nucleic acid sensing TLRs (NA-TLRs) mediate the production of antinuclear Abs in SLE.²⁰ The composition of immune complexes of anti-ds-DNA and nucleic acids promote the production of IFN α , which is essential in the induction and reflects the severity of SLE. TLRs have also been incriminated for the etiopathogenesis of the disease and more specific the nucleic binding TLR7 and 9. Experimental studies in human patients suffering from Lupus have shown that single nucleotide polymorphism (SNP) in the 3' untranslated region of TLR7 human gene increase its transcription levels. On the contrary, SNP in TLR9 gene is not associated with lupus activity, but with the autoantibody production. The regulation of the above receptors is also a new therapeutic option, as it was mentioned in RA. Here must be mentioned that the activation of TLR8 may inhibit TLR7 activation.^{18, 21}

There are also other factors, such as synthetic oligonucleotides that inhibit TLR7 and 9. Synthetic oligonucleotides with immunomodulating sequences (IRS) interfere the TLR7 and TLR9 signaling and IFN α production. Most of them are adenosine or guanine analogues. IRS targeting TLR7, but not TLR9, are IRS661, IRS967, IRS957, IRS986, IRS987, IRS988. Responsible for TLR9 inhibition seems to be IRS869. IRS954 may target both TLR7 and 9.^{5, 18, 22}

Belimumab is a human monoclonal antibody that is now approved by FDA especially for SLE treatment, as it targets B cell stimulator. IFN α is the result of probably TLR7 activation and also another specialised therapeutic target for SLE. It is known that lupus patients present high levels of IFN α , representing the disease severity and activity. Sifalimumab is a fully human IgG1 κ monoclonal antibody that inhibits IFN α acting on the receptor IFNAR. The efficacy of the drug is dose-dependent. It is not yet approved by FDA.^{18, 21, 23, 24}

Glucocorticoids are the mainstay therapy for a great variety of autoimmune diseases. They may reduce NF κ B activity and cause apoptosis in plasmacytoid dendritic cells (PDCs), which produce IFN α . Corticosteroids are also responsible for the reduction of TLR2 and 4 protein expression.²⁵ In SLE, the increased IFN α levels are not influenced by oral glucocorticoid treatment, but only by the intravenous pulse therapy, which cause a transient reduction of PDCs.

This persistence of IFN α levels is explained by the constant trigger of TLR 7, 9 and immune complexes on PDCs. So, a possible inhibition of TLR7,9 might lead to a proper response to glucocorticoid therapy. IRS954 has been used to inhibit in vivo TLR7,9.²⁶

Other therapeutic options for SLE treatment include the inhibition of TLRs and their pathways. One of this is ST2825, which is a MyD88 inhibitor. More specific, ST2825 inhibits the homodimerization of the TIR domain (Toll/IL1R translation initiation region) of MyD88 and subsequently inactivates the IRAK1, 4 signaling. The latest results in the inhibition of IL1 β -NF κ B activation and a dose dependent decrease in IL6 production. In addition, ST2825 may interfere with TLR9 signaling and thus restrain the B cell proliferation and differentiation into plasma cells.^{4, 5, 18}

Inhibition of the IRAK1, 4 pathways might have a therapeutic result as well. IL1 modulates the IRAK1 pathway, while IRAK4 is activated after TNF signal. The inactivation of both of them with RO0884 leads to IL1, TNF and IL6 inhibition.

Another group of negative TLR regulators include MyD88 short (MyD88s) which does not present the full molecular sequence of MyD88 and acts by inhibiting the activation of IRAK 4. This leads to IRAK 1 phosphorylation and altered activation of NF- κ B. The MyD88-independent pathway is negatively regulated by SARM. SARM acts on the TRIF pathway, related to TLR 3 and 4. Except from the above, there is a great variety of factors that may act intracellular as negative regulators and some of them are IRAK-M, TRAF-4, Toll-interacting protein (Tollip), A20, Suppressor of cytokine signalling-1 (SOCS-1), Transforming growth factor- β (TGF- β) and IL-10. These factors have a unique way of action and their role is essential in the use for treatment of both RA and SLE.^{15, 17, 18}

In the category of autoimmune diseases psoriasis may be involved. The etiopathogenesis of this disease is not completely understood, however it is known that it is a Th1 and Th17 induced inflammatory procedure. Yet, recent experimental reports mention the importance of the TLR role in the clinical expression of the disease. In psoriatic lesions a predominance of TLR 1, 2, 4, 5 and 9 exists in comparison to normal skin. Interestingly, TLR2 is overexpressed in upper epidermis and a TLR 5 reduction in basal cells, in contrast to normal skin, where TLR 2 and 5 are mostly expressed in basal cells. These findings

may easily be explained by the hyperproliferation of keratinocytes. The result is that immature cells reach the higher levels of epidermis and this is reflected by the TLR expression. A new antagonist against TLR 7, 8 and 9 seems to reduce the Th1 and Th17 activity. This may be a new alternative psoriasis treatment and possible to multiple inflammatory process.²⁷⁻³⁰ Adalimumab which is one of the new well known treatments for psoriasis affects TLR1 and TLR2 expression in psoriasis.³¹

However, new experimental data on psoriasis show that LL-37 increase TLR9 expression on keratinocytes. LL-37 is an antimicrobial peptide of human cathelicidin. TLR9 response to LL-37 is the overproduction of IFNs type I. Still, there is no therapeutic molecule that inhibits the LL-37 action on psoriatic skin.^{30, 32}

Conclusions

TLRs are essential for the immune defense and their activation depends on the invading factor. There are five signaling pathways, e.g. MyD88, TRIF, that are activated by TLRs and produce proinflammatory cytokines. However, the same factors are involved in autoimmunity and elicit a reaction like that either by an antigen specific nor a non-antigen specific mechanism. The inhibition of the activation of TLRs or their pathways may interfere in the induction of autoimmunity. Systemic lupus erythematosus and Rheumatoid arthritis confirm this theory about TLR interference. It is interesting that the alteration or inhibition of their action may have a positive clinical response and provide opportunities for different therapeutic interventions in the area of autoimmune diseases.

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Minocycline: a new molecule inducing subacute cutaneous lupus erythematosus?

TO THE EDITOR: A 20-year-old Caucasian girl presented to our department with multiple annular infiltrated lesions involving mostly the face but also the neck and the upper part of the back. In the month of November she had started a therapy with minocycline at the dosage of 100 mg once per day for the treatment of acne, discontinued after two weeks due to the appearance of intense diffuse pruritus on the body. Accordingly, she started a topical treatment with a retinoid that she had to stop after few days for the eruption of a diffuse erythema on the face.

When the patient arrived at our observation she showed multiple erythematous papules and annular/polycyclic plaques with central blanching on the face (Figure 1) while

residual lesions were present on the neck and the upper part of the back. No symptoms were reported except general fatigue. The patient had a personal history of mild thyroiditis of Hashimoto, no documented drug allergies, no history of photosensitivity and denied family history for autoimmune diseases. She referred judicious solar exposure.

Routine laboratory data were normal or negative. A non-significant positivity to ANA (1:40, speckled pattern) was found, while anti-ds DNA, anti-Ro/SS-A, anti-La/SS-B antibodies were negative. Biopsy was not carried out due to the patient's refusal. The patient started a therapy with hydroxychloroquine with complete resolution after a month (Figure 2). At the follow-up, two months later,

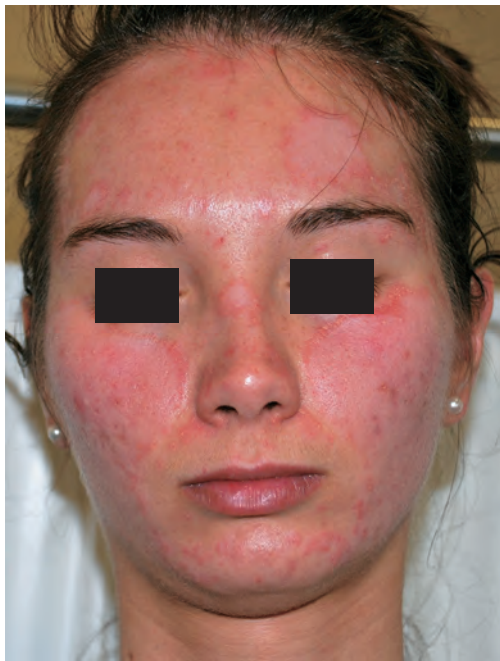


Figure 1.—Multiple erythematous papules and annular/polycyclic plaques with central blanching on the face.



Figure 2.—Complete resolution after a month of treatment with hydroxychloroquine. Only acne scars and hypopigmented residual lesions are visible.

TABLE I.—*Updated list of SCLÉ-inducing drugs in literature.*

SCLE-inducing drugs	Cases in literature	References
Antihypertensives		
Calcium channel blockers		
Diltiazem	6	Crowson AN <i>et al.</i> 1997, Srivastava M <i>et al.</i> 2003
Verapamil	5	Crowson AN <i>et al.</i> 1997, Kurtis B <i>et al.</i> 2005
Nifedipine	3	Crowson AN <i>et al.</i> 1997, Srivastava M 2003 <i>et al.</i> , Gubinelli E <i>et al.</i> 2003
Nitrendipine	1	Marzano AV <i>et al.</i> 2003
Diuretics		
Hydrochlorothiazide	10	Sontheimer RD <i>et al.</i> 2005, Srivastava M <i>et al.</i> 2003, Goodrich AL <i>et al.</i> 1993
Hydrochlorothiazide + triamterene	3	Darken M <i>et al.</i> 1988
Chlorthiazide	2	Brown CW <i>et al.</i> 1995
Beta blockers		
Oxprenolol	4	Gange RW <i>et al.</i> 1979
Acebutolol	1	Fenniche S <i>et al.</i> 2005
Angiotensin-converting enzyme inhibitors		
Enalapril	2	Srivastava M 2003 <i>et al.</i> , Marzano AV <i>et al.</i> 2011
Lisinopril	1	Srivastava M <i>et al.</i> 2003
Captopril	1	Fernandez Diaz ML <i>et al.</i> 1995
Cilazapril	1	Fernandez Diaz ML <i>et al.</i> 1995
Ramipril	1	Marzano AV <i>et al.</i> 2011
Antifungals		
Terbinafine	31	Kasperkiewicz M <i>et al.</i> 2009, Lorents K <i>et al.</i> 2008, Hivnor CM <i>et al.</i> 2008
Griseofulvin	1	Miyagawa S <i>et al.</i> 1989
Chemotherapeutics		
Docetaxel	4	Chen M <i>et al.</i> 2004
Paclitaxel	3	Adachi A <i>et al.</i> 2007
Tamoxifen	2	Fumal I <i>et al.</i> 2005
Capecitabine	4	Weger W <i>et al.</i> 2008, Fernandes NF <i>et al.</i> 2009, Floristan U <i>et al.</i> 2009, Kindem S <i>et al.</i> 2012
Doxorubicin	4	Guhl G <i>et al.</i> 2009, Funke AA <i>et al.</i> 2010, Chen JK <i>et al.</i> 2012
Methotrexate	1	
fluorouracil	1	Almagro BM <i>et al.</i> 2011
Antihistamines		
Ranitidine	4	Crowson AN <i>et al.</i> 1999
Brompheniramine	1	Crowson AN <i>et al.</i> 1999
Cinnarizine + thiethylperazine	1	Toll A <i>et al.</i> 1998
Immunomodulators		
Leflunomide	7	Marzano AV <i>et al.</i> 2008, Chan SK <i>et al.</i> 2005, Kerr OA <i>et al.</i> 2004, Gensburger D <i>et al.</i> 2005, Goeb V <i>et al.</i> 2005, Elias AR <i>et al.</i> 2005
Interferon α and β	4	Srivastava M <i>et al.</i> 2003, Nousari HC <i>et al.</i> 1998, Lee HY <i>et al.</i> 2010
Antiepileptics		
Carbamazepine	3	Capponi A <i>et al.</i> 2005, Amerio P <i>et al.</i> 2006, Marzano AV <i>et al.</i> 2011
Phenytoin	1	Ross S <i>et al.</i> 2002
Lamotrigine	1	Cabanillas M <i>et al.</i> 2012
Statins		
Simvastatin	4	Noel B <i>et al.</i> 2004, Suchak R <i>et al.</i> 2007, Srivastava M <i>et al.</i> 2003, Rüger RD <i>et al.</i> 2011
Pravastatin	1	Srivastava M <i>et al.</i> 2003
Biologics		
Etanercept	3	Marzano AV <i>et al.</i> 2011, Bleumink GS <i>et al.</i> 2001, Williams VL <i>et al.</i> 2011
Efalizumab	3	Sánchez-Cano D <i>et al.</i> 2009, Bentley DD <i>et al.</i> 2006
Adalimumab	1	Sheth N <i>et al.</i> 2007
Golimumab	1	Wilkerson E <i>et al.</i> 2012

TABLE I.—Continues from previous page.

SCLE-inducing drugs	Cases in literature	References
Proton pump inhibitors		
Lansoprazole/Pantoprazole/ Omeprazole/Esomeprazole	14	Panting KJ <i>et al.</i> 2009, Bracke A <i>et al.</i> 2005, Dam C <i>et al.</i> 2008, Toms-Whittle LM <i>et al.</i> 2011, Mankia SK <i>et al.</i> 2010, Popovic K <i>et al.</i> 2008, Wee JS <i>et al.</i> 2012, Reich A <i>et al.</i> 2012, Alcántara-González J <i>et al.</i> 2011
Nonsteroidal anti-inflammatory drugs		
Naproxen	1	Parodi A <i>et al.</i> 1992
Piroxicam	2	Marzano AV <i>et al.</i> 2011, Roura M <i>et al.</i> 1991
Hormone-altering drugs		
Leuprorelin	1	Wiechert A <i>et al.</i> 2008
Anastrozole	1	Trancart M <i>et al.</i> 2008
Antithrombotics		
Ticlopidine	1	Reich A <i>et al.</i> 2006
Antidepressants		
Bupropion	1	Cassis TB <i>et al.</i> 2005
Citalopram	1	Röhrs S <i>et al.</i> 2012
Sertraline	1	Hussain HM <i>et al.</i> 2008
Antibiotics		
Doxycycline	1	Miller KK <i>et al.</i> 2011
Minocycline	1	Our case
Amoxicillina plus clavulanic acid	1	Marzano AV <i>et al.</i> 2011
Other drugs		
Hydroxychloroquine	2	Marzano AV <i>et al.</i> 2011
Allopurinol	1	Marzano AV <i>et al.</i> 2011
Tiotropium	1	Pham HC <i>et al.</i> 2005
Imiquimod	1	Burnett TJ <i>et al.</i> 2010
Radioiodine	1	Abbott RA <i>et al.</i> 2012
Psoralen	2	Dowdy MJ <i>et al.</i> 1989, Mc Grath <i>et al.</i> 1990

a solitary vitiligo macule on the groin was detected. The diagnosis of drug-induced subacute lupus erythematosus (DI-SCLE) by minocycline was suspected in consideration of the typical clinical features, the close association with the minocycline treatment in absence of other SCLE-inducing drugs and the dramatic resolution after the discontinuation of minocycline and the treatment with hydroxychloroquine.

Drug-induced subacute cutaneous lupus erythematosus (DI-SCLE) is a lupus variant with predominant skin involvement related drug exposure and solves after drug discontinuation¹. Various drugs in unrelated pharmacological classes have been related to DI-SCLE however terbinafine, hydrochlorothiazide and the proton pump inhibitors have been the most frequently implicated (Table I).

Since the first case due to hydrochlorothiazide was described,¹ 160 cases have been reported (Table I). Nevertheless, no antibiotic has shown to be related to DI-SCLE except two recent cases due to doxycycline²⁻⁶⁹ and amoxicillin plus clavulanic acid.¹³ The onset of SCLE can occur after few days as well as after years of treatment with the same drug.¹ Specifically, the two cases induced by antibiotics had a very rapid onset respectively 3 days of incubation for doxycycline² and 2 weeks for amoxicillin plus clavulanic acid³ in accordance with the brief incubation time of our case (2 weeks).

We think that our case is the first DI-SCLE induced by

minocycline, a drug already known to induce autoimmunity such as for systemic lupus erythematosus and autoimmune hepatitis.⁶⁹⁻⁷⁴ The exposure to minocycline probably triggered the manifestation of an underlying autoimmunity predisposition. In fact the patient suffered from thyroiditis of Hashimoto and a vitiligo macule was detected during the second follow-up.

Clinically DI-SCLE presents as a break out of erythematous, annular and/or papulosquamous lesions in a characteristic distribution with and without scales, occurring mainly in sun-exposed areas.¹ Our case is in accordance with Lowe *et al.*'s statement: "the clinical descriptions of SCLE lesions in the reviewed reports of drug-induced SCLE cannot be distinguished from those of idiopathic SCLE".¹ Nevertheless, recently, Marzano *et al.* have suggested that DI-SCLE in comparison to the idiopathic form presents more often as widespread and it can be associated to malar rash, bullous and erythema multiform-like and vasculitic.¹³

DI-SCLE usually shows serum anti-Ro/SSA antibodies but sometimes they cannot be detected, as in our case. In fact, Lowe *et al.*, report that 19% of his cases were negative for anti-Ro/SSA and 18% for ANA.¹

As regard the pathogenesis in our case, the induction of DI-SCLE could have been secondary to: 1) an enhanced Ro/SS-A antigen expression or Ro/SS-A antibody production in a patient with an autoimmunity predisposition

with serological negativity due to discontinuation of minocycline several weeks before serological screening; 2) an epidermal cytotoxicity of topic retinoids that could have triggered the minocycline-induced SCLE.

We are aware that the diagnosis of SCLE should have been confirmed histopathologically⁷⁵ but still the typical clinical presentation, the resolution of the skin lesions after discontinuing the drug and after therapy with hydroxychloroquine, the brief incubation time in accordance with the other two cases induced by antibiotics and the predisposition to autoimmunity of our patient validate the diagnosis. We therefore think that our case should increase dermatologists' awareness of the possible risk of inducing DISCLE with minocycline therapies.⁷⁶

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A case of allergic contact dermatitis due to tetracaine with unusual presentation

TO THE EDITOR: Hypersensitivity reactions to local anesthetics are not so rare, and allergic contact dermatitis represents one of the most frequently reported side effect in the clinical practice.¹⁻⁵ A 51-year-old nonatopic maid was referred to our Department from Emergency Unit with a dermatitis localized in the interbuttocks groove. At the physical examination she presented an erythematous-bullous eruption with itching and stinging (Figures 1, 2). She reported that the dermatitis appeared for the first time 6-8 hours after having worn new blue colored panties. She described a similar dermatitis with vesicles and blisters occupying the perineal area and the pubes 5 years ago, after wearing black tights. Her medical and drug history revealed that she was undergoing a therapy for the blood pressure control based on Angiotensin I-Converting Enzyme (ACE) inhibitors. The blisters were handled with a topical treatment, a 0.025% potassium permanganate solution, moreover oral corticosteroids (methylprednisolone) therapy was started up to the complete resolution, approximately 3 weeks later. One month after the patch tests were performed with enlarged Società Italiana di Dermatologia Allergologica Professionale ed Ambientale (SIDAPA) standard series, and with a fragment of her blue panties. The test, carried out according to the International Contact Dermatitis Research Group Guidelines, showed positive reactions

to Caine Mix 10% (lidocaine, tetracaine hydrochloride, dibucaine hydrochloride) (Figure 3A) and Nickel at D2 and D4. After a more detailed medical history the patient revealed the employment of an anaesthetic ointment with tetracaine and ruscogenin, Ruscoroid® 1% (Sanofi-aventis, Amilly, France), and a similar soothing ointment, Fitoroid® (Aboca, Sansepolcro, Italy) containing ruscogenin, applied in the interbuttocks groove for reducing the discomfort of sexual practices. Therefore we decided to perform additional patch tests with both Fitoroid® and Ruscoroid® ointments, the sensitizing components (cetyl alcohol, polyethylene glycol 400, rosemary oil) and the single components of Caine Mix. We observed positive reactions exclusively to Ruscoroid® (Figure 3B) and tetracaine hydrochloride on D2 and D4 (Figure 3C). Tetracaine hydrochloride is an ester derived from the organic *p*-aminobenzoic acid (PABA) and ethanol. Ester-type local anaesthetics, like this one and others (benzocaine, procaine) are more commonly responsible for allergic contact dermatitis in comparison with the amide-type anaesthetics (lidocaine, prilocaine, mepivacaine, bupivacaine). The cross-reactivity between tetracaine and other ester-type caines like benzocaine, procaine did not occur commonly. While systemic side effects are rare, thanks to the low quantity and the slow absorption of topical tetracaine, the localized allergic contact dermati-



Figure 1.—The erythematous-bullous dermatitis, characterized by the presence of itching and stinging.



Figure 2.—The involvement of the interbuttocks groove.



Figure 3.—A) The first patch tests showed positive reactions to Caine Mix 10% (lidocaine, tetracaine hydrochloride, dibucaine hydrochloride) at D2 and D4. B) Additional patch test with Ruscoroid® ointment showed a positive reaction at D4. C) The positive reaction due to tetracaine hydrochloride at D4.

tis is quite common. Tetracaine hydrochloride is a known cause of occupational contact dermatitis in dentists, chiropodists, oculists, otorhinolaryngologists, laser practitioners, nurses.^{3, 4} Moreover several non-occupational cases have been described, mainly in patients using it as antihemorrhoidal ointment, an “over the counter” product.⁵ The presented case allows us to emphasize some particular features of allergic contact dermatitis to local anesthetics. First of all the unusual bullous presentation of such dermatitis instead of a typical eczematous reaction, where the appearance of blisters could be explained for the particular conditions of the interbuttocks groove, characterized by a repeated rubbing, a considerable sweating and a thinner cutaneous layer. The second significative element is represented by the “off label” use of tetracaine hydrochloride ointment. Furthermore this case highlights the importance of medical history and patch testing. Although benzocaine represents the most frequent anesthetic involved in contact dermatitis, it is the only local anesthetic present in the SIDAPA and European baseline series; since the cross-reactivity between benzocaine and other ester-type caines does not occur commonly, it is not a reliable marker of sensitization to the other ester-type anaesthetics. For this reason we and many other authors suggest to include other local anesthetics (e.g. Caine Mix) in standard series.

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Localized aquagenic acrokeratoderma on the right hand

TO THE EDITOR: Aquagenic acrokeratoderma (AA) is a rare acquired condition with females and adolescents predilection.¹⁻³ The "hand-in-the-bucket" sign, an indication to demonstrate the lesions, is characterized by translucent or whitish papules and plaques after submerging the hands or soles in water transiently, and resolving soon after drying.^{1,2} Herein, we report an unusual case with involvement of the right hand alone.

A 38-year-old man presented with 1-year history of asymptomatic erythema on the right hand including the dorsal aspect, which became white and edematous after minutes of water exposure, and disappeared soon after drying. Warmer water exacerbated the lesions more rapidly than did cold water. The patient had no history of other skin and systemic diseases including hyperhidrosis, and was on no medications. He had been absent from the features of cystic fibrosis since his birth, including allergic bronchopulmonary aspergillosis, chronic pansinusitis or nasal polyposis, bronchiectasis, cutaneous vasculitis, nutrient deficiency dermatitis and atopy. No other family members had either similar features or cystic fibrosis.

Cutaneous examination before water exposure showed erythema with clear margins on all the distal fingers of the right hand including their distal dorsal aspects, and the dorsum of the second finger-web. After immersing the right hand in water at 40°C for 1 minute, small white papules appeared over the erythema including both palmar and dorsal aspect of the distal fingers, and some of the papules coalesced into edematous (Figure 1). The lesions started decreasing within 10 minutes and disappeared within 30 minutes after drying. A biopsy specimen from the interdigital web after water immersion for 5 minutes showed evident sponge-like thickness of horny layer, hypergranulosis and acanthosis, and dilation of sweat duct ostia, mild increase of capillaries as well as mild perivascular lymphocytic infiltration in the upper dermis (Figure 2A, B), the eccrine glands were normal. The patient gave up any therapies and refused to test cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Aquagenic acrokeratoderma was first reported in 1996 by English and McCollough. To date, fifty-five cases have been previously described.² The lesions usually present on the palms and occasionally on the soles in symmetry, and in rare instance, unilateral cases, localized forms and even involvement of the dorsum of the hands have also been described.¹⁻³ The present patient had involvement of right hand only and the dorsal aspect as well, which is rather unusual. The associations of AA may include pain, tingling, tightness, burning sensation and hyperhidrosis, even cystic

fibrosis, allergic rhinitis, palmar erythema, asthma and malignant melanoma;¹ but most of the patients are asymptomatic¹ as did the present patient. Histopathology may be nonspecific or reveal hyperkeratosis and dilated eccrine ducts,¹⁻³ other findings include abnormal staining of the stratum corneum, hyperplasia of eccrine glands with clear cell change and vacuolation.² Conde-Salazar *et al.*⁴ even reported a case with perivascular lymphocytic infiltrate in the dermis as the present case did. As the thickness of the horny layer is related to imbibitions of increased water content, Rongioletti *et al.*² suggested that the thickness should no longer be considered a real keratoderma but a "pseudokeratoderma". Because the drying skin reveals no abnormalities, only biopsy taken after water exposure is suggested.²

The pathogenesis is not fully understood. In rare instance, it would be caused by cyclooxygenase-2 enzyme inhibitors such as celecoxib and rofecoxib.^{1,2} But it has also been confirmed that some cases link to cystic fibrosis caused by the mutation of CFTR gene, especially the mutation of $\Delta F508$.^{2,5} The loss of functional CFTR may result in increased keratin binding to water by reduced electrolyte reabsorption in the eccrine ducts and hypertonic sweat, or the altered regulation of water membrane channels.^{1,2,5} A recent study demonstrated that sometimes, AA is a sign of CF or carrier state.⁵ Although CFTR gene was not tested, the present patient was absent for any clinical features of CF and presented



Figure 1.—After submerging the right hand in water for 1 minute, small white papules appear over the erythema, some of the papules coalesce into edematous.

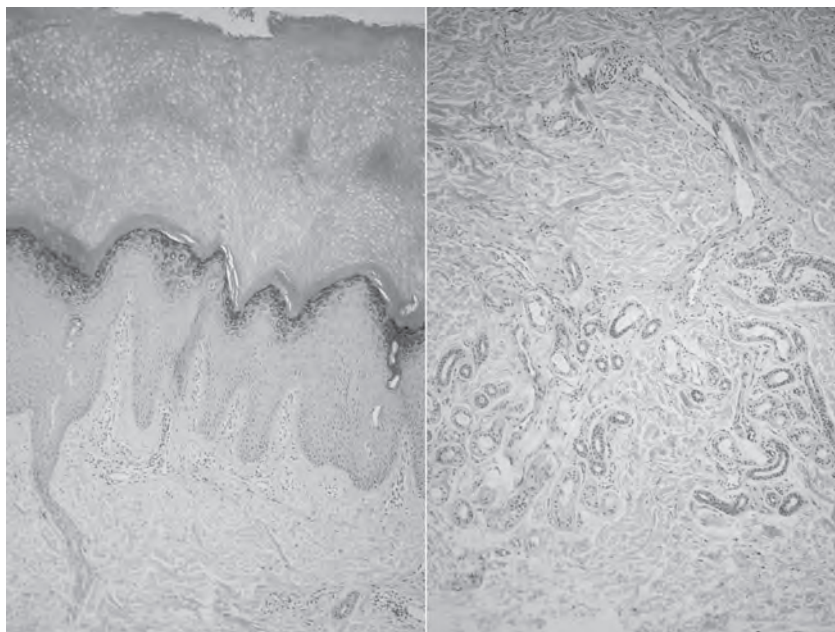


Figure 2.—A, B) Histopathology after water immersion reveals evident spongy thickness of horny layer, hypergranulosis and acanthosis, and dilation of sweat duct ostia, mild increase of capillaries as well as mild perivascular lymphocytic infiltration in the upper dermis. (Hematoxylin-eosin staining, original magnification: a, $\times 100$; b, $\times 250$).

his lesions on adult stage, we considered CF-induced AA can be excluded.

Aluminum salts, salicylic acid, urea ointment, tazarotene gel, formalin, oral antihistamines, etc, have been described for the treatment with variant results^{1, 2} but no optimal therapeutics for AA has been suggested to date. Fortunately, most of the cases have a tendency of spontaneous remission or self-limited.^{1, 2}

The present case is notable because the lesion was unilateral, localized, involving the dorsum of hand, and showing perivascular lymphocytic infiltrate in the upper dermis.

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Genital melanosis in two brothers

TO THE EDITOR: Melanosis of genital mucosa is characterized by one or often more light brown to almost black spots. They are usually asymptomatic, sometimes have an irregular shape, and tend to be confluent. Such findings are of benign nature, and sometime represent a differential-diagnostic challenge, especially in consideration of mucocutaneous melanoma.¹⁻⁵

They typically present in adults males, with predilection for glans and balano-preputial sulcus.

Hereby we report the case of two brothers, 22 (Figure 1A) and 24 years old, respectively. The anamnesis, beside this dermatological affection by the brother, was unremarkable.

The older complained of a brown spot on the glans, close to urethral meatus (Figure 1B). He also suffered from genital lichen annularis. The younger, by the same circumstance, reported several spots on glans and balano preputial sulcus (Figure 1A). Both brothers referred us to have the spots since first years of life. In the last months the

younger reported the development of white areas within the pigmented spots. At the dermoscopic image (Figure 1C) showed linear pattern, with globular pigmented reinforcement and acromic area. In order to exclude the diagnosis of melanoma in the younger brother, skin biopsy was performed. Histopathological examination reported hyperpigmentation of basal layer (Figure 1D), and slightly increased melanocytes. Hence, the diagnosis of penis melanosis had been established for both brothers. The melanosis were not secondary to an inflammatory skin disease. In fact, the biopsy did not show any sign of lichen sclerosus and also the clinical history allowed us to exclude it. Moreover, the melanosis secondary to lichen sclerosus is characterized mainly by an increase of melanophages, while our case was characterized by hyperpigmentation of basal layer and slightly increased melanocytes.

In the older brother, the lesions of anular lichen were far from melanosis and also the clinical history did not support the development of melanosis, as result of lichen anularis.

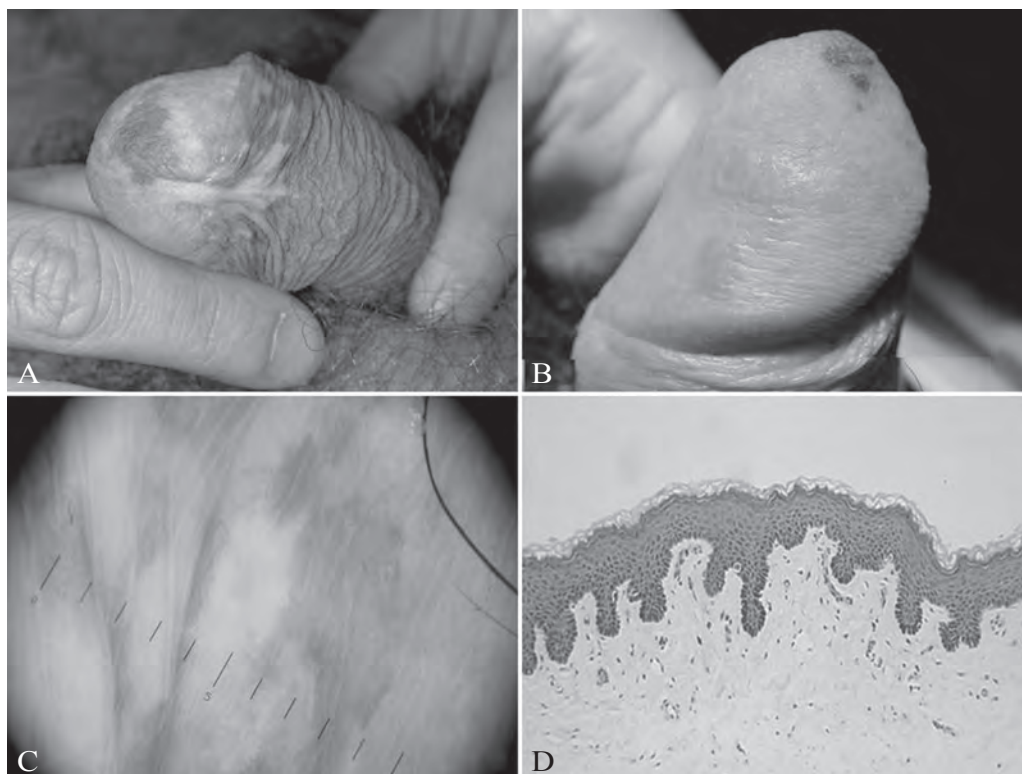


Figure 1.—A, B) Clinical image of the patients; C) a parallel pattern is clearly visible; D) histological image: hyperpigmentation of the basal layer.

This case was peculiar for presence of the same manifestation in two brothers, suggesting a role for genetic factors in the pathogenesis of these conditions that, even though benignant, must be well defined.

The absence of comorbidities allowed to exclude other syndromes with spots of the penis as, for example, Bannayan-Riley-Ruvalcaba syndrome.⁶

Genital melanosis – whose spots are sometimes erroneously termed lentigines – are rare, idiopathic, benignant lesions whose diagnosis could be challenging, as in our case.¹

Genital dermatoscopy can support the clinical observation, identifying the most suitable biopsy site. Recently it has been noted that in these lesions a parallel pattern and a ring-like pattern (including its variants: fish scale-like pattern and hyphal pattern) are as frequent as the dotted-globular pattern and the homogeneous pattern.^{2, 3}

Unlike melanoma, melanotic maculae tend to present in adulthood, instead of elderly, usually remaining stable for decades. In a melanoma it is possible to observe dishomogeneity in the pigmentation and in the rete ridge pattern, blots, pigmented dots, dark globules, and vascular pattern whose observation is uncommon in melanoses.

The role of environmental or individual risk factor is unknown. In spite of not being considered melanoma precursors, a small number of publications describe a possible malignant transformation.^{1, 4, 7}

While individual risk factors for melanoma have been well investigated, at present very little is known about melanosis.^{1, 4} This case shows that individual risk factors may play a role in such manifestations, as it has been reported already for cases of congenital oral melanosis.^{5, 8}

In agreement with the literature, periodic follow-up is advisable: given the stability of the lesions, in most cases repeated biopsies would not be necessary, limiting invasive procedures to cases with suspicious clinical presentation.

Both brothers were set on a follow-up program and, until now, no changes have been observed. Further studies are needed to add more data in the management of this condition by dermatologists and general practitioners.

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Tinea Capitis caused by *Microsporum Canis* infection in a 75-year-old woman

TO THE EDITOR: *Tinea capitis* is an infection of the scalp most commonly caused by *Microsporum canis*, a zoophilic dermatophyte whose natural endemic reservoirs are cats and dogs, which often behave as healthy carriers. Infection can spread from human to human, but it appears to decrease virulence in each passage. Pre-puberal children are the most affected, due to the absence of fungistatic activity of the sebum. Events in adults are very rare and thus often misdiagnosed.¹

We report the case of a 75-year-old Italian woman presented with a recent history of tension, burning pain and itch diffuse to the whole scalp, associated with focal hair loss (Figure 1). She was otherwise well. No previous history of eczema, psoriasis, contacts with children or animals were known.

The patient wasn't undertaken any drug or treatment in the past which could favour a fungal infection (*i.e.* corticosteroids or immunosuppressive drugs).

Clinical findings were initially misinterpreted as psoriasis and the patient was treated with topical betametasone propionate foam. She hadn't clinical improvement and symptoms dramatically worsened with the occurrence of erosive lesions, serum-leaking brown crusts and alopecia. Due to its extension and atypical appearance, several diagnosis could be put forward, including an autoimmune disease, such as discoid erythematous lupus, or a skin neoplasm like an inflammatory squamous cell carcinoma.

In order to better define the case, scalp biopsies were performed and either formalin fixed for routine histology or imbibed in saline solution for direct immunofluorescence (DIF). Scalp scrapings were also sent to microbiology lab for bacterial and fungal cultures.

Haematoxylin-eosin (H&E) stained sections of the skin showed a dense perifollicular acute inflammatory infiltrate, mainly composed by neutrophils and by a less amount of lympho-monocytes. (Figure 2A) Periodic acid Schiff (PAS) staining showed fungal spores filling the infundibula of the hair follicles, in the typical ectothrix pattern (Figure 2B) DIF on frozen tissue was negative for the whole antibody panel (IgA, IgM, IgG and C3). Altogether, these findings were suggestive for a suppurative fungal folliculitis.

The other part of the material was meanwhile cultured on Sabouraud dextrose agar (SDA) at 30 °C. The growth was rapid (5-8 days) and the colonies were flat, granular and fluffy. The colour was cream-white, with a bright, lemon yellow peripheral margin. The reverse was deep yellow, becoming yellowish-brown with age. Microscopic examination of culture evidenced septate hyphae and thick-walled, multi-celled and echinulate macroconidia (30-120x10-25 µm) with a distinct, curved beak on the tip. (Figure 3) Microconidia was rare, smooth and pear-shaped. The fungus

isolated from the lesion was identified as *Microsporum canis* on the basis of its morphological characteristics and the species identification was confirmed by matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI TOF MS, Bruker Daltonics, MA, USA).

The patient was consequently treated with oral itraconazole 200 mg/die and topic terbinafine cloridrate spray and progressively improved.² She is now doing well, with a *restitutio ad integrum* of the scalp skin and a slow but constant re-growth of the hair.

Tinea capitis is a dermatophytosis estimated to account for 1% of superficial fungal infections in northern and western Europe. Prepuberal children are the most affected, followed by adults with low socio-economical status and



Figure 1.—The scalp of the patient showed epidermal esulceration, serum-leaking brown crusts and alopecia.

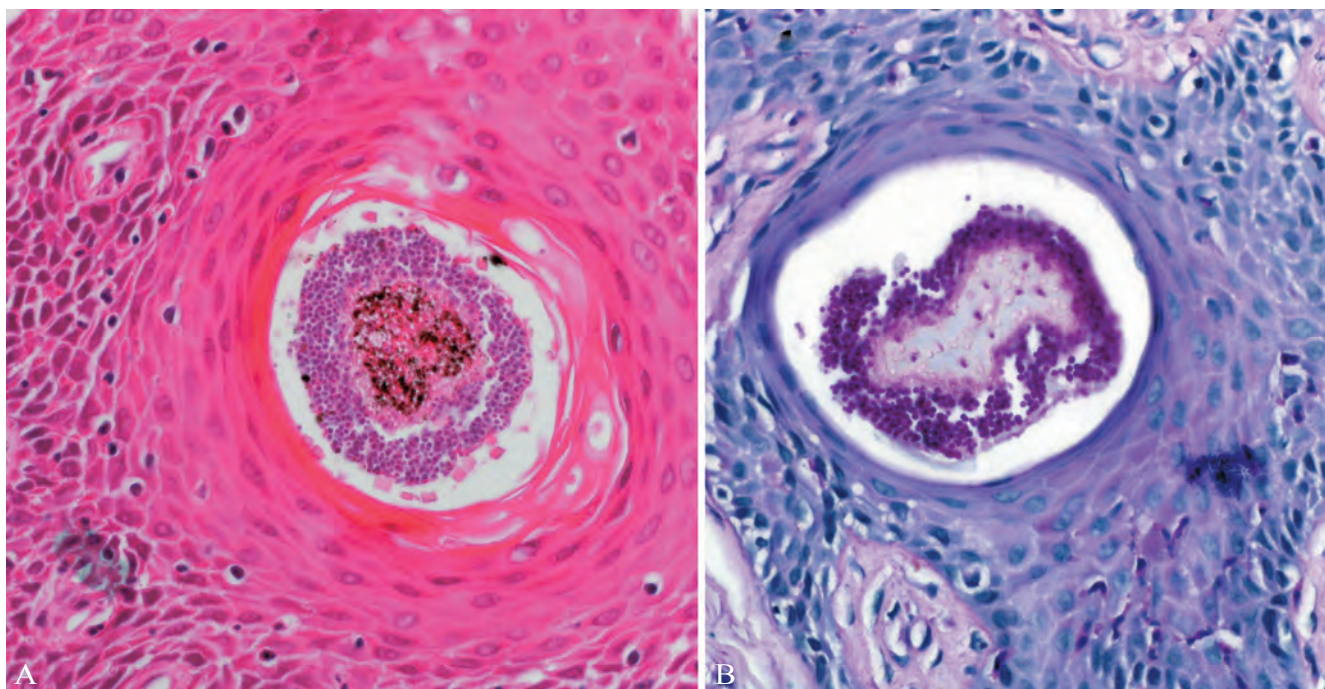


Figure 2.—Histology sections of the skin: A) fungal spores filling the infundibulum of an hair follicle (H&E, 40x Original Magnification); B) better seen with PAS staining (PAS, 40x Original Magnification).

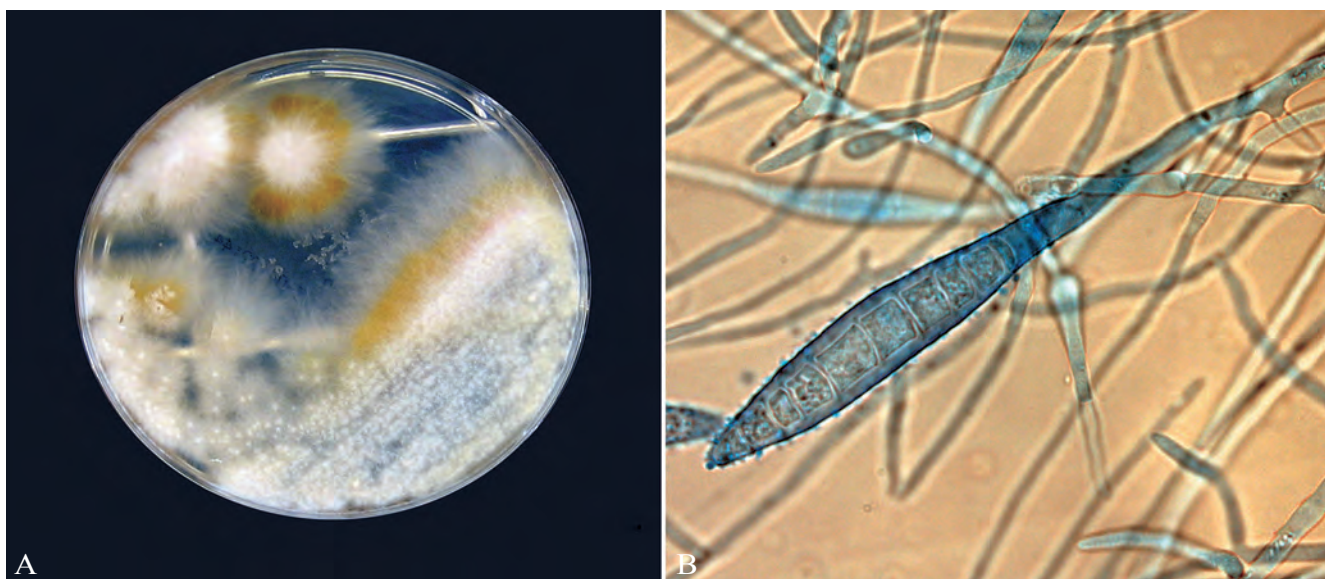


Figure 3.—*M. canis*. Colony on SDA: surface (A). Macroconidia (100x Original Magnification) (B).

poor hygienic standards. Infections in healthy adults are held to be quite rare, but a review of the recent literature highlights an increase number of reported cases, mainly

involving elderly postmenopausal women,^{1,3} whose sebum production decrease due to lower oestrogen levels.⁴

The most common cause of *Tinea capitis* is *Microspo-*

rum canis, an infection that in Mediterranean countries, like Italy, has the highest incidence. Other dermatophytes like *T. violaceum* and *T. tonsurans* are described, being related to immigration from African countries⁵ ways of contagion involve direct contact with natural animal reservoirs, mostly cats and dog, healthy carriers, but also other mammals. Less often, dermatophytes can pass from human to human. Interestingly, a transmission through hairdresser brushes or other tools has been reported,² suggesting an alternative source of potential infection when others (contact with animals or infected children) have been ruled out, a possibility to consider in an environmental eradication attempt.

Our case, like others reported in literature, was initially treated for a bacterial folliculitis but other diagnostic hypotheses were then considered, due to missed response to therapy. In particular, an autoimmune disease or a skin tumour were taken into account.

In conclusion our case highlights how *Tinea capitis* should be considered in patients with any scalp inflammatory disease and alopecia, also in adult, even if contact with children or animal is excluded, not only to better treat the patient and avoid delay in the treatment but also to eradicate a potential source of epidemic infection. Histopathological examination is the appropriate tool for a correct differential diagnosis, since it allowed to exclude both hypotheses (skin neoplasia or autoimmune disease) and, due to identification of characteristic PAS positive fungal spores, to achieve the correct diagnosis further refined by microbiologic investigation.

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Dermatomyositis accompanying nasopharyngeal carcinoma in a caucasian patient

TO THE EDITOR: Dermatomyositis (DM) is a multisystemic inflammatory disease primarily affecting the skin and muscles. It is well known to be associated with malignancies. Nasopharyngeal carcinoma has been reported in DM patients but particularly in the Far East Asian population.¹ We presented a Caucasian patient with DM and nasopharyngeal carcinoma (NPC).

A 46-year-old female patient was admitted to derma-

tology clinic with complaint of rash on her face and arms persisting for 10 days. She complained of tiredness and muscle weakness on her upper and lower extremities for 2 months but her daily activities were not affected. Dermatologic examination revealed red violaceous maculopapular lesions on dorsal surface of the hands, extensor surface of the upper extremities and upper part of her trunk. Periorbital edema and violaceous erythema of the eyelids,



Figure 1.—Periorbital edema and violaceous erythema of the eyelids, red violaceous maculopapular lesions on the upper chest.



Figure 2.—Red violaceous maculopapular lesions on dorsal surface of the hands, extensor surface of the upper extremities.

erythematous areas at the bases of the finger nails were present (Figures 1, 2). On physical examination muscle strength were normal. Laboratory examination showed an increase in creatine kinase (680.1[35-195] U/L), aldolase (9.4[2.7-5.3] U/L), lactate dehydrogenase (684[90-240] IU/L). Antinuclear antibody was positive (1/100 dilution), anti-Jo-1 and anti SS-A, anti SS-B, anti Sm antibodies were negative. Her erythrocyte sedimentation rate was slightly elevated (31 mm/h). The patient was consulted to obstetrics and gynecology and internal medicine departments for possible associated malignancy. Tumor markers (CA125, CA 15-3, CA 19-9, CEA), liver function tests, chest radiography, mammogram, cervical smear, pelvic ultrasonography were normal. Abdominal ultrasonography was also normal except cholelithiasis. Fecal occult blood test was resulted negative for three times. Electromyography demonstrated myopathic motor unit potentials at left biceps brachii muscle and spontaneous potential at left tibialis anterior muscle, which were accepted as early phase of myopathic involvement. The skin biopsy from the lesion revealed vacuolar alteration of basal keratinocytes and perivascular lymphoid infiltration in the dermis. Patient was diagnosed as dermatomyositis and no associated malignancy was detected. Oral methylprednisolone 60 mg/day was given initially, and then methotrexate 10 mg/week was added and dose was increased to 25 mg/week. Her lesions decreased but remission had never been complete.

Seven months after her first admission, she started to complain about nasal obstruction while on methotrexate and steroid treatment. She was evaluated by an ear, nose and throat specialist. Endoscopic assessment demonstrated an ulcerative granulomatous tissue which had obstructed the choanas. Histologic examination showed a non-keratinized carcinoma of the nasopharynx. So, NPC was also diagnosed in the patient.

A series of agents and factors have been implicated in the etiology of DM. An autoimmune process was suggested to have a role in the mechanism. It may be initiated by viral or bacterial agents in genetically susceptible people or may represent a paraneoplastic event.² An association of DM with malignancies has been widely reported in the literature. The reported neoplasms seen in DM patients of Far East Asian countries were different from those in Caucasians. Breast and lung carcinomas are the most common cancers reported to be associated with dermatomyositis in whites, whereas nasopharyngeal cancer was identified commonly in DM patients from the Far East Asia.² The high frequency of pharynx malignancies in the Far East is attributed to carcinogens of tobacco, racial, hereditary factors, viruses and common chronic sinusitis seen in those countries.² Strong association of NPC with Epstein-Barr virus has been reported as well.³ EBV infection is one of the factors suggested to have role in the pathogenesis of DM. Molecular mimicry, EBV-induced expansion of autoreactive B cells,

and altered T cell response against EBV are the hypotheses for explaining this possible role.³ So, EBV seems to have a role in NPC and DM etiology. It was already recommended to suspect an occult NPC in PM/DM patients with IgA anti-EBNA-1 or increased EBV DNA loads.³

Although the association of DM and NPC is a common condition in the Far East, it is rare in Caucasians. To our knowledge, the association between DM and NPC was only reported in one Israelite, two Italian, 8 Tunisian patients apart from Far East.^{2, 4, 5} By this report, we presented one more DM patient with nasopharyngeal carcinoma outside of the Far East. The risk of cancer in DM patients should be kept in mind and screening for malignancy is necessary. Detailed laboratory evaluation directed by findings on medical histories, physical examinations, screening laboratory tests, chest X-ray, whole abdominal ultrasound, upper gastrointestinal endoscopy and colonic endoscopy, mammography, breast ultrasonography and Papanicolaou test had been suggested in the malignancy assessment.¹ Besides these, we want to emphasize the importance of the ear, nose and throat examination and nasopharyngeal endoscopy in necessary conditions, not only for patients of Far East but also for Caucasian patients.

Nasopharyngeal carcinoma could be the associated malignancy in dermatomyositis patients regardless of geographic area, lifestyle and environmental factors. So, a detailed ear, nose and throat examination is important for all dermatomyositis patients.

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