

Urticarial lesions: If not urticaria, what else? The differential diagnosis of urticaria

Part II. Systemic diseases

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There are a number of systemic disorders that can manifest with urticarial skin lesions, including urticarial vasculitis, connective tissue diseases, hematologic diseases, and autoinflammatory syndromes. All of these conditions may enter into the differential diagnosis of ordinary urticaria. In contrast to urticaria, urticarial syndromes may manifest with skin lesions other than wheals, such as papules, necrosis, vesicles, and hemorrhages. Lesions may have a bilateral and symmetrical distribution; individual lesions have a long duration, and their resolution frequently leaves marks, such as hyperpigmentation or bruising. Moreover, systemic symptoms, such as fever, asthenia, and arthralgia, may be present. The most important differential diagnosis in this group is urticarial vasculitis, which is a small-vessel vasculitis with predominant cutaneous involvement. Systemic involvement in urticarial vasculitis affects multiple organs (mainly joints, the lungs, and the kidneys) and is more frequent and more severe in patients with hypocomplementemia. Clinicopathologic correlation is essential to establishing a correct diagnosis. (J Am Acad Dermatol 2010;62:557-70.)

Learning objectives: After completing the learning activity, participants should be able to distinguish urticarial lesions suggesting diagnoses other than common urticaria; assess patients with urticarial lesions, and suspect systemic diseases presenting with urticarial skin lesions.

Key words: autoinflammatory syndromes; hypereosinophilic syndromes; neutrophilic urticarial dermatosis; Schnitzler syndrome; urticaria; urticarial vasculitis.

Urticaria is a common disorder that is classically distinguished into acute and chronic forms, which are similar clinically but differ substantially in etiology, epidemiology, patient approach, therapy, and prognosis.¹⁻³ Ordinary urticaria does not have systemic implications, with the exception of the association with autoimmune thyroid diseases,⁴ and does not present with systemic symptoms. The diagnosis of urticaria may not always be straightforward. The differential diagnosis between common urticaria and urticarial diseases limited to

Abbreviations used:

CINCA:	chronic infantile neurologic cutaneous and articular syndrome
CMRO:	chronic recurrent multifocal osteomyelitis
COPD:	chronic obstructive pulmonary disease
DIF:	direct immunofluorescence
FCAS:	familial cold autoinflammatory syndrome
FMF:	familial Mediterranean fever
HIDS:	hyperimmunoglobulinemia D with periodic fever syndrome
MWS:	Muckle-Wells syndrome
PAPA:	pyogenic arthritis-pyoderma gangrenosum-acne syndrome
SLE:	systemic lupus erythematosus
TRAPS:	tumor necrosis factor receptor-associated periodic fever
UV:	urticarial vasculitis
HUV:	hypocomplementemic UV
NUV:	normocomplementemic UV

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the skin was discussed in part I of this two-part series. The presence of systemic symptoms—in particular, fever, asthenia, and arthralgia—and neurologic, respiratory, or cardiovascular signs should alert physicians about the possibility that an urticarial rash is not ordinary urticaria but rather a systemic syndrome with urticaria-like skin lesions. Systemic urticarial

syndromes are very heterogeneous and may involve many organs and systems (Table I). The objective of this article is to discuss the major clinical features of such systemic conditions resembling urticaria.

SYSTEMIC URTICARIAL SYNDROMES

The most important and common differential diagnosis with common urticaria is urticaria vasculitis (UV), which can be the cutaneous expression of a systemic disorder. Other systemic diseases that manifest with urticarial skin lesions are more rare but nonetheless very important to suspect. Systemic urticarial syndromes include other vasculitides (Churg–Strauss syndrome and polyarteritis nodosa), neutrophilic urticarial dermatosis, hematologic diseases (Schnitzler syndrome, Waldenström macroglobulinemia, and hypereosinophilic syndromes), and autoimmune-inflammatory diseases (Table II).

Urticarial vasculitis and other vasculitides

Key points

- UV is a small-vessel vasculitis with predominant skin involvement that represents the main differential diagnosis with chronic urticaria
- It manifests with urticarial skin lesions persisting for more than 24 hours, burning rather than itching, and resolving with hyperpigmentation or bruising. Other skin lesions (purpura or necrosis) may be associated
- UV is often associated with systemic diseases, particularly connective tissue diseases, and therefore systemic symptoms can be present
- Rarely, Churg–Strauss syndrome and polyarteritis nodosa may be associated with cutaneous urticarial lesions
- A biopsy for histologic examination is necessary in order to establish the diagnosis

Vasculitis is a pathologic process characterized by inflammation and necrosis of the blood vessels that may or may not be accompanied by fibrin deposits and leukocytoclasia; red blood cell extravasation and perivascular inflammatory cell infiltrates are also present. Cutaneous small-vessel vasculitis is the most

common type of vasculitis, and primarily affects cutaneous postcapillary venules. UV is a small-vessel vasculitis with predominant skin involvement manifesting with urticarial lesions. The clinical course of UV is characterized by exacerbations and remissions.⁵ The duration of UV tends to be limited to several months, although there is a reported duration of 23

years.⁶ Moreover, recurrences are reported.⁶ UV is clinically characterized by wheals lasting for more than 24 hours and accompanied by burning or painful sensations and pruritus (Fig 1, A).^{5,7,8} Wheals frequently resolve with residual hyperpigmentation or bruising. More rarely, other skin lesions (eg, purpura, necrosis, and ulcers) can be seen either simultaneously or in different phases (Fig 1, B and Fig 2, A).^{7,9,10} In some cases, with the diascopy technique, previously unapparent purpura can be revealed as a dark red or brown macule in the center of an erythematous lesion.¹¹ Moreover, a large number (up to 40-60%) of patients may present only with wheals.^{7,12} Therefore, a skin biopsy should be obtained in all cases of

CAPSULE SUMMARY

- The presence of systemic symptoms should signal the possibility that an urticarial rash is not ordinary urticaria but rather a systemic syndrome with urticaria-like skin lesions.
- A thorough clinical evaluation is fundamental; particular attention should be paid to osteoarticular, neurologic, respiratory, or cardiovascular signs and symptoms.
- Systemic urticarial syndromes may manifest with skin lesions other than wheals. Lesions are more likely to have a bilateral and symmetrical distribution, individual lesions have a long duration, and their resolution frequently leaves marks, such as hyperpigmentation or bruising.
- Clinicopathologic correlation is essential to making the diagnosis.

otherwise clinically typical chronic urticaria, especially if the urticaria is resistant to antihistaminic treatment, in order to exclude UV.^{5,12} Angioedema is present in less than half of the patients.^{5,7,8,12} Other cutaneous findings may include digital infarction, Raynaud phenomenon, photosensitivity, erythema gyratum repens–like eruption, and hemorrhagic vesicles.^{6-8,13-15} The diagnosis always requires histologic confirmation. As for other vasculitides, the choice of the lesion to biopsy is essential. Full blown lesions reveal a vasculitis of the small dermal vessels, usually leukocytoclastic, which is characterized by a neutrophilic perivascular infiltrate, endothelial cell injury and swelling, neutrophil fragmentation, nuclear dust, erythrocyte extravasation, and fibrin deposition in and around the vessels (Fig 2, B and C).^{6,8,10} More rarely, histology reveals a predominance of mononuclear (lymphocytes) cells with only a few granulocytes.^{9,10} A major concern is that it is not always easy to detect true vasculitic changes.¹¹ Furthermore, a continuum of histologic changes exists between common urticaria and UV.¹⁶ In addition, some patients may

Table I. Distinguishing features between urticaria and systemic urticarial syndromes

Common urticaria	Urticarial lesions (one or more of the following)
Only typical wheals: Erythematous edematous lesions Transient (<24-36 hrs) Asymmetric distribution Resolution without signs	Atypical "wheals": Infiltrated plaques Persistent (>24-36 hrs) Symmetric distribution Resolution with signs (hypo/hyperpigmentation, bruising, or scarring)
No associated different elementary lesions (papules, vesicles, purpura, or crustae, etc)	Associated different elementary lesions (papules, vesicles, purpura, scaling, or crustae, etc)
Pruritic (rarely stinging/burning)	Not pruritic; rather painful or burning
Possibly associated with angioedema	Usually no associated angioedema
No associated systemic symptoms	Often associated with systemic symptoms (ie, fever, malaise, arthralgia, abdominal pain, weight loss, acral circulatory abnormalities, or neurologic signs)

Table II. Principal systemic diseases or syndromes that can manifest with urticarial lesions

Vasculitides and immunologic disorders Urticarial vasculitis Systemic lupus erythematosus Sjögren syndrome Dermatomyositis Mixed connective tissue disease Juvenile rheumatoid arthritis Churg–Strauss disease Wegener granulomatosis Polyarteritis nodosa Neutrophilic urticarial dermatosis	Autoinflammatory syndromes Hereditary periodic fever syndromes Familial Mediterranean fever Tumor necrosis factor receptor–associated periodic fever Hyperimmunoglobulinemia D with periodic fever syndrome
Hematologic diseases Non-Hodgkin lymphoma (B-cell) Waldenström macroglobulinaemia Schnitzler syndrome Monoclonal gammopathies of uncertain significance Cryoglobulinemia Hypereosinophilic syndromes Episodic angioedema with eosinophilia (Gleich syndrome) Polycythemia vera	Cryopyrin-associated periodic syndromes Familial cold autoinflammatory syndrome Muckle–Wells syndrome Neonatal onset multisystem inflammatory disease (chronic infantile neurologic cutaneous and articular syndrome) Others Pyogenic arthritis-pyoderma gangrenosum-acne syndrome Blau syndrome Chronic recurrent multifocal osteomyelitis and Majeeed syndrome

concomitantly have UV and common urticaria. The incidence of UV is about 5% to 10% of those with chronic urticaria (up to 15% in antihistamine-resistant cases), and the majority of these are women (57-70%), with a peak age in the fourth decade of life.^{7,8,11,12} Fewer than 10 pediatric cases of UV have been reported in the last 20 years, with a female predominance (about two thirds) and an age varying from 9 months to 12 years; the principal associated manifestations were renal involvement (3 cases), pulmonary disease (2 cases), and systemic lupus erythematosus (SLE; 2 cases), with hypocomplementemia in the majority of cases (5 of 7 cases).¹⁷⁻²³ Although UV is a sporadic

disease, a pair of identical twins with hypocomplementemic UV (HUV) has been reported.²⁴

UV is believed to result from the deposition of immune complexes on the blood vessel wall. Immune complexes have been found in the circulation of 30% to 75% of patients with UV.²⁵ The antigens eliciting the formation of antibodies are often not known. UV is more often idiopathic, but in some cases eliciting stimuli have been identified. One such stimulus may be drugs, including antifolate agents (methotrexate and pemetrexate),^{26,27} antidepressants (paroxetine and fluoxetine),^{28,29} appetite suppressants,³⁰ infliximab,³¹ procainamide,³²



Fig 1. Urticarial vasculitis. **A**, Typical wheals on the trunk and upper limbs coexist in the same patient with **(B)** figurate hemorrhagic, livedoid lesions in the lower limbs subsequent to urticarial lesions.

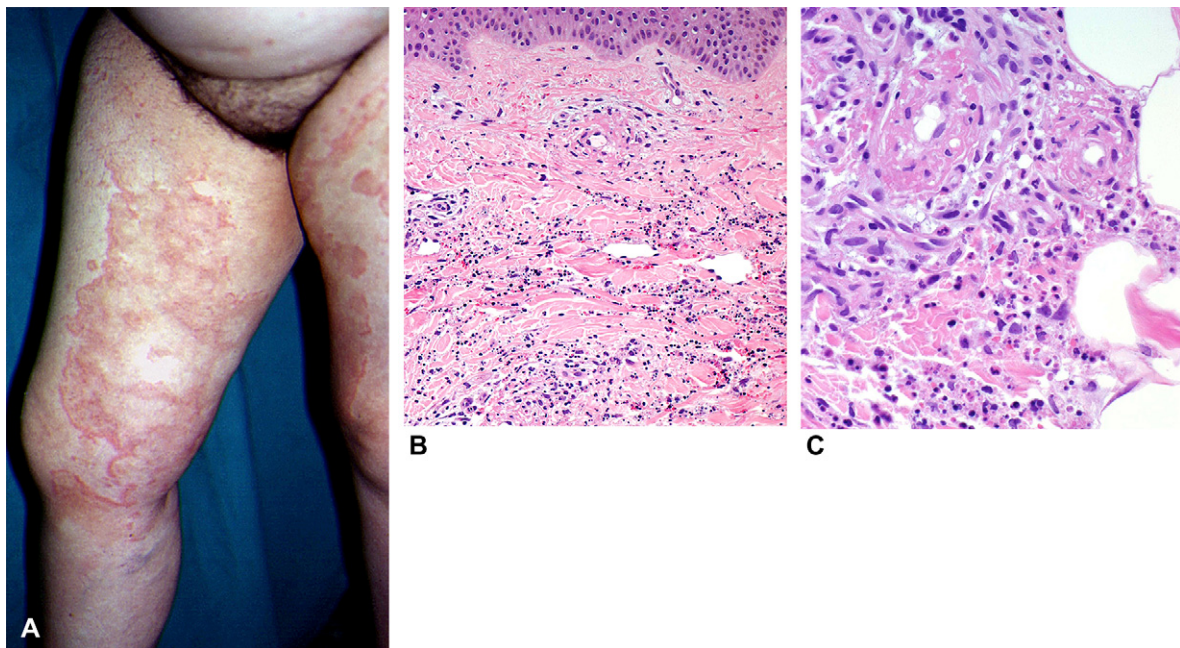


Fig 2. Urticarial vasculitis. **A**, Urticarial purpuric lesions in the lower limbs leaving residual hyperpigmentation. **B** and **C**, Leukocytoclastic vasculitis with fibrinoid necrosis of the vessel wall and abundant infiltrate of neutrophils and nuclear dust. (Hematoxylin–eosin stain; original magnifications: **B**, ×100; **C**, ×250.)

cimetidine,³³ sulfamethoxazole-trimethoprim,³⁴ and other substances (herbs, cocaine, bacillus Calmette-Guérin vaccine, and formaldehyde).^{35–38} Moreover, rare cases induced or exacerbated by

physical stimuli have been reported, including sun or ultraviolet light exposure,^{39,40} cold,^{41,42} and physical exercise.⁴³ In some UV patients, a collagen-like region of the complement fragment C1q has been

implicated as the target antigen.^{10,44} Indeed, a portion of the patients with HUV also have anti-C1q antibodies. These anti-C1q antibodies have been described to be very common in HUV and in SLE, hepatitis C, rheumatoid arthritis, and particularly in patients with glomerulonephritis.⁴⁵ Anti-C1q antibodies are reported to be predictive of active renal involvement.⁴⁴ Furthermore, patients with UV and anti-C1q antibodies frequently have chronic obstructive pulmonary disease¹¹ and other symptoms, such as arthritis or arthralgia, uveitis/episcleritis, recurrent abdominal pain, and glomerulonephritis, as first described by McDuffie et al⁴⁶ and Schwartz et al⁴⁷ and proposed by Wisniewski¹⁰ to be a separate entity (hypocomplementemic urticarial vasculitis syndrome).

UV can be a local process unassociated with an underlying disease or it can be the presenting manifestation of a systemic disease. Among these, the most common are autoimmune connective tissue diseases (particularly SLE,^{19,20,48-55} but also systemic sclerosis,⁵⁶ Gougerot–Sjögren syndrome,⁵⁷ and paraneoplastic dermatomyositis⁵⁸), followed by infections (mainly chronic or acute viral hepatitis⁵⁹⁻⁶⁴ and sporadic reports of Epstein–Barr virus,⁶⁵ *Mycoplasma pneumoniae*,⁶⁶ and Lyme disease⁶⁷) and inflammatory bowel diseases.⁶⁸ In some cases, UV can be a paraneoplastic manifestation, mainly associated with hematologic malignancies, including mostly non-Hodgkin B-cell lymphomas,⁶⁹⁻⁷¹ monoclonal gammopathies/myeloma,⁷²⁻⁷⁴ anecdotal cases of Castleman disease,⁷⁵ and polycythemia rubra vera,⁷⁶ but also with various solid neoplasms (non–small cell lung cancer,⁷⁷ renal cancer,⁷⁸ testicular teratoma,⁷⁹ colon adenocarcinoma,⁸⁰ and nasopharyngeal carcinoma⁵⁸). Finally, the vasculitic process that causes skin lesions can also involve internal organs, particularly the joints, kidneys, and lungs, and also the gastrointestinal tract and central and peripheral nervous systems.

It is noteworthy to mention that UV can be further divided into two groups according to classical pathway complement levels (mainly total complement, CH50, or C3 and C4 fragments): normocomplementemic UV (NUV) and HUV. These two subtypes of UV have significantly different clinical characteristics, as shown in Table III, which summarizes data from the four major case series published in the English literature in the last 20 years.^{5,7,8,12} HUV is strongly associated with female gender (60–100%), the presence of purpura and/or residual hyperpigmentation after skin lesions have faded, and the diagnosis of SLE.^{5,7,8} Moreover, 40% to 80% had arthralgias and 71% to 78% had antinuclear antibodies, suggesting that HUV is a subset of SLE.^{5,8,12} Patients with HUV

also more frequently show renal and pulmonary involvement.^{5,7,8,12} In contrast, patients with normal complement levels on repeated determinations tend to have less frequent systemic involvement. They also show a higher prevalence of females (52–60%), although to a lesser extent. NUV patients possibly have systemic manifestations or the presence of antinuclear antibodies, but only a minority of them meet the criteria for SLE.^{5,8,9} Patients with NUV have a more benign prognosis than HUV patients, but in both cases death as a result of the primary disease is rare, mostly secondary to pulmonary involvement.^{9,81} Articular involvement, either arthralgia or arthritis, is the most frequent finding in both groups, although significantly more prevalent in HUV compared to NUV. Articular manifestations tend to be migratory and transient, mostly affecting peripheral joints.⁹ Jaccoud arthropathy (chronic deforming synovitis, without loss of cartilage or bone erosion of the joints of hands and feet and deviation of the fingers) is rarely reported in patients with HUV, and tends to be associated with valvular heart disease.⁸²⁻⁸⁷ Cardiac involvement is reported also without Jaccoud arthropathy, in the form of valvular heart disease,^{88,89} recurrent pericarditis with tamponade,^{90,91} and myositis involving the heart and proximal muscles⁹² exclusively in HUV patients. Lung involvement occurs frequently in HUV and is more severe in smokers.⁴⁷ The predominant pulmonary manifestation is chronic obstructive pulmonary disease (COPD).^{5,7,47} It is characterized histopathologically by capillaritis⁹³ or leukocytoclastic vasculitis of pulmonary venules,⁹⁴ causing an increase in the number of neutrophils that release elastases, leading to tissue destruction that eventually results in emphysema.^{9,95} Other rare findings include pleural effusion⁹⁶ and a restrictive functional pattern⁶³; in pediatric patients, pulmonary hemosiderosis and hemorrhages have been reported.^{18,23} Disease response to therapy and severity are variable, leading in very rare cases to lung transplantation or death.^{93,97} Renal disease is frequent, and may include a variety of processes, such as glomerulonephritis (the most frequent form), interstitial nephritis, and necrotizing vasculitis.^{5,7,8,9,11} According to isolated case reports, it affects HUV patients almost exclusively, with only rare cases reported in NUV patients in the larger case series.^{8,7,12} Two cases of renal involvement are reported also in pediatric HUV patients.^{22,23} In very rare cases, renal disease led to nephrotic syndrome, kidney transplant, or death.⁹⁷⁻¹⁰⁰

Gastrointestinal symptoms occur often and more frequently in HUV; they include nausea, vomiting, abdominal pain, and diarrhea, but usually not gastrointestinal bleeding or ischemia.^{9,101} Occurring

Table III. Differences between hypocomplementemic and normocomplementemic urticarial vasculitis*

	Hypocomplementemic UV						Normocomplementemic UV						<i>P</i> [†]
	Merhegan et al ⁷	Davis et al ⁵	Dincy et al ⁸	Tosoni et al ¹²	Total	%	Merhegan et al ⁷	Davis et al ⁵	Dincy et al ⁸	Tosoni et al ¹²	Total	%	
Total no. of patients in cohort	72	132	68	47			72	132	68	47			
No. of patients with the specific UV type	23	24	14	5	66		49	108	54	42	253		
Females	NS	24	11	NS	35/38	92	NS	65	28	NS	93/162	57	.000
Fever	1	3	6	3	13/66	20	3	12	9	14	38/253	15	.462
Arthralgias/arthritis	18	18	6	4	46/66	70	21	26	16	14	77/253	30	.000
Abdominal pain	8	NS	0	1	9/42	21	7	NS	6	1	14/145	10	.075
Renal involvement	2	3	3	1	9/66	14	2	0	1	10	13/253	5	.031
Lung involvement	6	4	1	0	11/66	17	3	5	0	6	14/253	6	.006
Purpura/residual hyperpigmentation	15	NS	NS	3	18/28	64	10	NS	NS	0	10/91	11	.000
Systemic lupus erythematosus	5	13	NS	NS	18/47	38	3	2	NS	NS	5/157	3	.000
Increased sedimentation rate	NS	12	NS	2	14/29	48	NS	26/89	NS	18	44/131	34	.202
Antinuclear antibodies presence	NS	17	11	NS	28/38	74	NS	26/97	7/46	NS	33/143	23	.000
Fluorescent deposits at DEJ [‡]	16	NS	1/10	NS	17/33	52	9	NS	0/3	NS	9/51	18	.002
Fluorescent deposits around dermal vessels [‡]	20	NS	2/10	NS	22/33	67	14	NS	2/3	NS	16/51	31	.003
Fluorescent deposits at DEJ + dermal vessels [‡]	NS	23	5/10	NS	28/33	85	NS	1	1/3	NS	2/111	2	.000
Neutrophilic predominance (interstitial)	16	19	12	NS	47/61	77	21	11	34	NS	66/211	31	.000
Eosinophil presence	NS	1	11	NS	12/38	32	NS	7	47	NS	54/162	33	.988

DEJ, Dermoepidermal junction; NS, absolute number not specified or data not recorded; UV, urticarial vasculitis.

*Data derived from the four studies indicated have been aggregated and compared by using the χ^2 test.

[†]Differences between hypocomplementemic and normocomplementemic urticarial vasculitis.

[‡]Fluorescent deposits mainly of immunoglobulin G and C3.

more often in HUV, neurologic complications are not frequent but are possible in both HUV and NUV. They include pseudotumor cerebri, seizure, transverse myelitis, and lower cranial nerve palsies or peripheral neuropathy.^{8,102-105} Ocular involvement is severe, but infrequent, with conjunctivitis, recurrent uveitis, scleritis, or optic disc and retinal vasculitis occurring almost exclusively in patients with HUV.^{5,9,106-108} Therefore, UV associated with systemic involvement is more likely to be hypocomplementemic, but lower than normal levels of complement may not result following a single determination, and may require multiple testings. Patients with UV and mild or no systemic symptoms but hypocomplementemia need a careful follow-up. Interestingly, a correlation has emerged between the dermal interstitial neutrophilic predominance and the presence of hypocomplementemia.^{5,7,8,109} Direct immunofluorescence (DIF) may show deposits of immunoglobulins, complement or fibrin around blood vessels in about 70% to 80% of patients with active lesions in both HUV and NUV.^{6,11} DIF positivity for IgG and/or C3 (especially at the basement membrane) is much more frequent in HUV.^{5,7,8}

Treatment of UV is aimed first at controlling any underlying condition and second at controlling symptoms. No controlled trials are available on UV therapy. Antihistamines are useful for the symptomatic control of pruritus, but are rarely used alone. Corticosteroids of varying dosages are the mainstay of treatment, particularly in patients with HUV or a systemic disease; typically, systemic corticosteroids are initially administered at the dosage of 1 mg prednisone equivalent/kg daily until clinical remission is achieved, then slowly tapered off.²⁵ Because many patients have relapses after steroid tapering, it is often necessary to proceed to a maintenance treatment and add a steroid-sparing agent.²⁵ In these cases, dapsone may be the drug of choice, either alone^{51,110-112} or in association with other agents^{51,113,114}; in particular, it is effective in patients with a SLE-like presentation of UV.²⁵ Colchicine^{112,115-118} and hydroxychloroquine¹¹⁹ have also been used with some success. Mycophenolate mofetil has also been effective in the treatment of UV and as maintenance therapy.^{106,120} Methotrexate is not considered to be particularly effective, although some patients may respond well.¹²¹ Treatment with interferon-alfa could be considered in patients with UV and a hepatitis virus C infection.^{61,62} Other treatments reported include cyclosporine A,⁹⁸ azathioprine,¹²² cyclophosphamide with pulse dexamethasone,^{106,123} rituximab,⁴⁹ intravenous immunoglobulins,¹²⁴ anakinra,¹²⁵ and plasmapheresis.^{9,25}

Churg–Strauss syndrome, also known as allergic granulomatous angiitis, mostly affects middle-aged men and is characterized by a long multistep progression; in the initial years, patients have respiratory manifestations, such as rhinitis, nasal polyps, and asthma; then blood and tissue eosinophilia with Löffler infiltrates appears, followed by pneumonia and gastroenteritis, and finally multiorgan vasculitis may emerge.¹²⁶ Cutaneous manifestations are present in about half of the patients, including palpable purpura, petechiae, nodules, maculopapules, and livedo reticularis; urticarial lesions are present in less than 10% of patients.¹²⁷⁻¹²⁹ Upon histologic examination, urticarial lesions may only reveal abundant eosinophil perivascular infiltration, whereas different cutaneous lesions show extravascular granulomas, small-vessel leukocytoclastic vasculitis with predominantly eosinophilic infiltrate, or cutaneous polyarteritis nodosa.¹²⁷ Approximately 6% of cases of polyarteritis nodosa have urticarial manifestations.¹³⁰

Neutrophilic urticarial dermatosis

Key points

- **Neutrophilic urticarial dermatosis is a rare condition characterized by a transient urticarial eruption with a rich neutrophilic dermal infiltrate, both perivascular and interstitial**
- **It is a reaction pattern associated with connective tissue diseases and autoinflammatory syndromes**

Neutrophilic urticarial dermatosis is characterized clinically by an urticarial rash and histopathologically by a neutrophilic dermatosis. About 50 cases have been reported.¹³¹ Skin lesions appear as erythematous macules, papules, or plaques that may resolve within 24 hours. Histologic examinations reveal an intense perivascular and interstitial neutrophilic infiltrate with leukocytoclasia but without vasculitis or dermal edema. Neutrophils also have a peculiar linear deposition between the dermal collagen fibers; necrobiotic isolated collagen fibers can be found in some cases. These features differentiate neutrophilic urticarial dermatosis with neutrophil dominated common urticaria. The absence of edema is useful in differentiating neutrophilic urticarial dermatosis from Sweet syndrome, whereas the absence of vasculitis can help in excluding UV. Finally, early stages of interstitial granulomatous dermatitis can be difficult to distinguish from neutrophilic urticarial dermatosis.¹³¹ In the majority of patients, skin lesions are associated with systemic symptoms, such as fever and polyarthritides, or laboratory abnormalities, such as increased erythrocyte

sedimentation rate and leukocytosis.¹³¹ Indeed, neutrophilic urticarial dermatosis is often associated with a systemic disease, most often adult-onset Still disease, lupus erythematosus, Schnitzler syndrome, paraproteinemia, or an autoinflammatory genetic disease.¹³¹ The rash is chronic or recurrent and difficult to treat. It is usually unresponsive to antihistamines. The nosographic position of neutrophilic urticarial dermatosis is still debated, and it may eventually be found that this condition is not a separate condition but rather a reaction pattern common to different diseases.

Hematologic diseases

Key points

- **Urticarial lesions may be the manifestation of a variety of hematologic disorders**
- **Schnitzler syndrome presents as chronic urticarial lesions, immunoglobulin M (IgM) gammopathy, fever, and arthralgia**
- **Waldenström macroglobulinemia and cryoglobulinemia may be also associated with urticarial lesions and urticarial vasculitis**
- **Hypereosinophilic syndromes, particularly the lymphocytic variant, often show skin manifestations along with internal organ damage. Cutaneous findings include either angioedematous and urticarial lesions, or erythematous, pruritic papules and nodules**
- **Gleich syndrome is also characterized by recurrent episodes of angioedema and urticaria, eosinophilia, elevated serum IgM, fever, and increased body weight; however, it is not associated with internal organ damage**

Schnitzler syndrome is a rare and often misdiagnosed disease that is characterized by the simultaneous occurrence of monoclonal IgM gammopathy and chronic urticaria with at least two additional minor symptoms: arthralgia, bone pain, fever of uncertain origin, hepato- or splenomegaly, lymphadenopathy, increased erythrocyte sedimentation rate, leukocytosis/thrombocytosis, and increased bone density.^{132,133} Monoclonal gammopathy can be detectable even some years after the onset of the cutaneous manifestations. No spontaneous remissions have been reported to date.¹³³ Schnitzler syndrome usually has a benign course and patients show no increased mortality during the follow-up periods, but there is a 10-year 15% risk of developing a lymphoproliferative disorder, most notably Waldenström macroglobulinemia.^{133,134} Skin manifestations of Schnitzler syndrome include persistent urticarial lesions, frequently with figurate lesions, leaving a brown hyperpigmentation. Histologic

examination reveals a perivascular mixed inflammatory infiltrate with leukocytoclasia, nuclear dust without fibrinoid necrosis, and extravasated red blood cells. IgM deposits can be seen at the dermoepidermal junction. Current treatment is often unsatisfactory, and includes high systemic doses of corticosteroids and antihistamines.¹³⁵ Recent evidence has demonstrated positive responses to oral cyclosporine, intravenous pulse cyclophosphamide, pefloxacin mesylate, and anakinra, the latter suggesting a possible autoinflammatory pathogenetic mechanism for this syndrome.^{132,133,135}

Waldenström macroglobulinemia is a low-grade chronic B-cell lymphoproliferative disorder characterized by bone marrow infiltration with small lymphocytes, lymphoplasmacytoid cells, and plasma cells associated with an elevated circulating level of IgM paraprotein. It can be associated with cutaneous manifestations, such as purpura, edema, urticaria, and ulceration, which are the consequence of hyperviscosity, cryoglobulinemia, and/or tissue depositions of immunoglobulins; direct cutaneous infiltration by neoplastic lymphoid cells is less common and usually skin changes occur in later stages of the disease.¹³⁶

Hypereosinophilic syndromes constitute a heterogeneous group of disorders, defined as persistent and marked blood eosinophilia ($>1.5 \times 10^9/L$ for more than 6 consecutive months) associated with evidence of eosinophil-induced organ damage, where other causes of hypereosinophilia—such as allergic and parasitic disorders, solid and hematologic malignancies, Churg–Strauss disease, and HTLV infection—have been excluded.¹³⁷⁻¹³⁹ Once these criteria are fulfilled, further testing for eventual pathogenic classification is warranted using the appropriate cytogenetic and functional approach.^{137,138} The classification of these disorders is complex and still in progress, though it is possible to grossly divide them into intrinsic eosinophil disorders (myeloproliferative form), secondary to the clonal expansion of cells of the myeloid lineage with preferential eosinophilic differentiation, and extrinsic eosinophil disorders (lymphocytic form), secondary to an increased eosinophilopoietic cytokines production by other cell types, mainly TH₂ lymphocytes.^{137,138} Hypereosinophilic syndromes occur most frequently in young to middle-aged patients, but they may affect any age group. There is a clear but still unexplained male predominance (male to female ratio, 4-9:1) in the myeloproliferative form, but not in the lymphoproliferative one.^{137,140} Target-organ damage mediated by eosinophils is highly variable among patients, with involvement of the skin, heart, lungs, and central and peripheral

nervous systems in more than 50% of cases. Other frequently observed complications include hepato- and/or splenomegaly, eosinophilic gastroenteritis, and coagulation disorders.¹³⁷ Cutaneous manifestations are common and nonspecific and generally consist of angioedematous and urticarial lesions, very itchy erythematous papules and nodules, or eczematous lesions. In patients with the extrinsic lymphocytic variant, skin lesions are often the predominant clinical presentation. Mucosal ulcerations are possible, particularly in patients with the clonal myeloproliferative variant associated with the FIP1L1-PDGFR fusion gene, and are an index of a poorer prognosis.^{137,139} Therapeutic management should be adjusted according to the disease severity and variants and include corticosteroids, hydroxyurea (also named hydroxycarbamide), interferon- α , and imatinib mesilate.¹³⁷ Episodic angioedema with eosinophilia, or Gleich syndrome, also belongs to eosinophilic diseases, because it is characterized by recurrent episodes of angioedema and urticaria, eosinophilia, elevated serum IgM levels, fever, increased body weight, and a benign course.¹⁴¹ Gleich syndrome does not show involvement of internal organs and could therefore be considered a clinical entity distinct from the hyper-eosinophilic syndromes,¹⁴⁰ although recent evidence of clonal T-helper lymphocytes and elevated interleukin-5 levels suggests its inclusion in the spectrum of the lymphocytic form of hyper-eosinophilic syndromes.¹⁴²

Autoinflammatory syndromes

Key points

- **Autoinflammatory syndromes are a group of heterogeneous monogenic diseases that are characterized by recurrent episodes of multisystemic and seemingly unprovoked inflammation, most commonly caused by an excessive activation of the IL-1 β pathway**
- **Skin lesions, fever, and arthralgia/arthritis are the most common symptoms. Cutaneous lesions frequently have an urticarial appearance, especially in the cryopyrinopathies and in familial Mediterranean fever, whereas erythematous macules and papules predominate in the other diseases of this group. Skin lesions are temporally associated with relevant systemic symptoms**
- **Histologically, cutaneous lesions generally show a perivascular neutrophilic infiltrate, sometimes with lymphocytes**

Autoinflammatory syndromes are a group of heterogeneous monogenic diseases that are clinically

characterized by recurrent episodes of multisystemic, seemingly unprovoked inflammation. Indeed, these diseases are caused by variations, mostly missense mutations, in very few genes encoding for innate immune system components (mainly parts of the inflammasome), with the activation of the IL-1 β pathway as the final unifying pathogenetic mechanism.¹⁴³ This latter fact explains the positive results obtained with anakinra, a recombinant human interleukin 1 receptor antagonist, in treating these patients; furthermore, a more specific anti-IL-1 β antibody (canakinumab) proved to be effective in these patients and is awaiting approval from regulatory agencies.¹⁴³ This category traditionally includes the hereditary periodic fever syndromes, namely familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic fever (TRAPS), hyperimmunoglobulinemia D with periodic fever syndrome, and the cryopyrinopathies: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal onset multisystemic inflammatory disease (NOMID, also called chronic infantile neurologic cutaneous and articular syndrome, or CINCA syndrome).¹⁴⁴ The detailed description of these diseases is beyond the purpose of this work, and they have recently been reviewed.¹⁴⁴ Moreover, other classifications have been proposed that include other diseases such as Blau syndrome, pyogenic arthritis-pyoderma gangrenosum-acne (PAPA) syndrome, chronic recurrent multifocal osteomyelitis (CRMO; Fig 3, A), hereditary angioedema, Behçet disease, Gaucher disease, and gout.^{145,146} Particularly for this latter disease, there is evidence that monosodium urate crystals are specifically detected via the NALP3 inflammasome, resulting in a stimulation of IL-1 β secretion.^{147,148}

Autoinflammatory diseases present clinically with recurrent episodes of inflammation (fever, rashes, and elevation of acute phase reactants) in the absence of an infectious, neoplastic, or autoimmune etiology. Fever is always present, with variable duration and severity, along with different types of joint and skin involvement. Other variably associated systemic symptoms include abdominal pain, ocular findings, amyloidosis, serositis, myalgias, and neurologic signs.¹⁴⁴ These diseases are usually familial, but there is a growing number of identified sporadic cases.¹⁴⁹ Most cases present in childhood or infancy; few cases are first detected in adulthood. Cutaneous lesions have an urticarial appearance (“urticarial rash”), especially in the cryopyrinopathies and in FMF, whereas in the other diseases previously mentioned erythematous macules and papules predominate; other skin lesions, such as purpura, vasculitis,

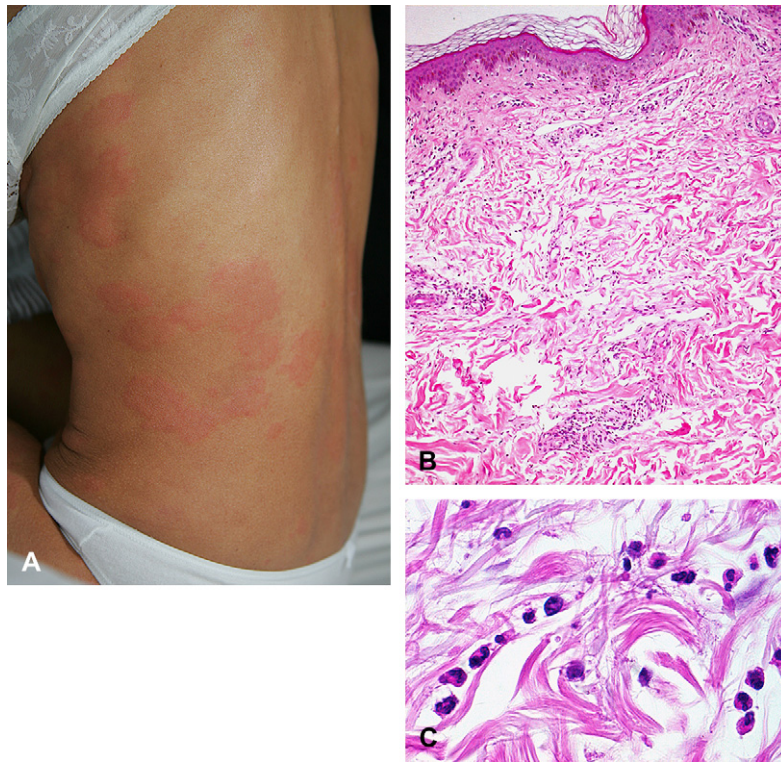


Fig 3. Chronic recurrent multifocal osteomyelitis. **A**, Urticarial lesions on the trunk. Lesions appeared and disappeared simultaneously with fever. **B**, Mild dermal interstitial and perivascular infiltrate composed of mononuclear cells and neutrophils. **C**, Linear aggregates of neutrophils along collagen fibers. (**B** and **C**, Hematoxylin–eosin stain; original magnifications: **B**, $\times 100$; **C**, $\times 1000$ [oil immersion].)

or pyoderma gangrenosum–like ulcers, can be seen.¹⁴⁴ On histology, cutaneous lesions show a perivascular and interstitial infiltrate dominated by neutrophils, frequently with the pattern described in neutrophilic urticarial dermatosis (Fig 3, *B* and *C*); sometimes the appearance is that of a leukocytoclastic vasculitis.^{144,146} In the cryopyrinopathies, urticarial skin lesions usually appear within the sixth month of life and are always associated with relevant systemic symptoms; in FMF, skin lesions are mostly erysipelas-like plaques of the lower extremities, begin in childhood or adolescence, and are simultaneously associated with systemic symptoms.¹⁴⁴ HIDS usually appears on the skin with erythematous macules, but also with urticarial lesions.¹⁴⁴ Very recently, it has been shown that the urticarial rash in cryopyrin-associated periodic syndrome (CAPS) is caused by the excessive constitutional production of IL-1 β by skin mast cells.¹⁵⁰ A recent study on a large cohort of patients with periodic fever demonstrated that young age at onset, positive family history for periodic fever, thoracic pain, abdominal pain, diarrhea, and oral aphthosis are all independently

correlated with a positive genetic test result for autoinflammatory syndromes.¹⁵¹

CONCLUSION

A variety of systemic conditions may present with urticaria-like skin lesions, which can be transient or persistent, and may be only a part of a more complex inflammatory process involving other organs and systems. The main features that can be helpful in distinguishing between common urticaria and urticarial syndromes are the long duration of individual lesions, occasional bilateral and symmetrical distribution, their resolution with hyperpigmentation or bruising, the presence of skin lesions other than wheals, and the presence of associated systemic symptoms. Differentiation between common urticaria and urticarial syndromes represents a diagnostic challenge. For these reasons, a comprehensive clinical evaluation often associated with a thorough clinicopathologic correlation is essential for diagnosis, keeping in mind that a correct interpretation by the pathologist may require a high index of suspicion by the dermatologist. In particular, even in the

presence of typical urticarial lesions, a skin biopsy specimen is helpful in confirming the diagnosis or suggesting an alternative one, particularly when lesions are unresponsive to antihistamines or when there are systemic symptoms.

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