

Papular and annular fixed urticarial eruption: A characteristic skin manifestation in patients with relapsing polychondritis

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Background: Skin manifestations of relapsing polychondritis (RP) are usually nonspecific.

Objective: We report a series of patients with RP who presented with annular skin lesions.

Methods: The clinical and histologic features and follow-up data of patients with RP and an annular urticarial eruption were retrospectively reviewed.

Results: Ten patients (9 male, 1 female) (mean age 63.7 years) were included. All patients had tense, fixed, urticarial papules with an annular configuration predominantly located on the upper part of the trunk. Skin lesions occurred before the chondritis in 7 of 10 cases with a mean delay of 23 ± 13 months. Histologic examination consistently showed a lymphocytic vasculitis with no leukocytoclastic vasculitis, even when biopsies were repeated during the evolution ($n = 7$). Hematologic abnormalities were found in all cases. A myelodysplastic syndrome was found in 4 patients. Oral corticosteroids were effective in all cases, although skin lesions recurred during the decrease of corticosteroid doses in 4 cases. Five patients died during the evolution.

Limitation: Retrospective case series design is a limitation.

Conclusion: Annular and papular fixed urticarial eruption may represent a characteristic skin manifestation of RP. It is frequently associated with hematologic abnormalities and may auger a poor prognosis. (J Am Acad Dermatol 10.1016/j.jaad.2010.09.007.)

Key words: annular lesion; blood abnormalities; lymphocytic vasculitis; myelodysplastic syndrome; relapsing polychondritis.

Relapsing polychondritis (RP) is a rare inflammatory disorder of the cartilage, which mainly involves the ear, nose, larynx, and trachea.¹ Moreover, RP can occasionally involve other proteoglycan-rich tissues, such as the eyes, blood vessels, heart, and skin.² Cutaneous features have been reported in 17% to 37% of patients with RP.³ The most frequent skin manifestations are

aphthosis, limbs nodules, purpura, and papules, which are usually considered as poorly specific.^{3,4} They most often occur simultaneously or after chondritis during the course of RP. We report 10 patients with RP along with papular and annular fixed urticarial skin lesions corresponding histologically to a lymphocytic vasculitis. Interestingly, these lesions occurred several months to several years before the

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onset of chondritis, and seem to represent a characteristic early skin manifestation of RP.

METHODS

Patients

Inclusion criteria in this study were, first, the diagnosis of RP according to the criteria proposed by McAdam et al.⁴ The diagnosis of RP was established in patients who fulfilled 3 or more of the following criteria: ear chondritis; nonerosive inflammatory polychondritis; nasal chondritis; ocular inflammation; laryngeal, tracheal, or bronchial chondritis; and cochlear or vestibular damage. The second criterion was presence of papular and annular urticarial skin lesions.

Clinical characteristics

The main clinical characteristics of patients were retrospectively assessed. Photographs of patients were retrospectively examined. The dates of occurrence of cutaneous and extracutaneous features were obtained from the patient's medical records. Biopsies of skin lesions for histologic analysis and direct immunofluorescence (DIF) were performed in all patients at the onset of urticarial lesions. In addition, 7 patients had two or more skin biopsies during their follow-up. All biopsy specimens were re-examined by one of the authors (P. C.). Blood cell count, erythrocyte sedimentation rate, C-reactive protein, CH50, C3, C4, and search for antinuclear antibodies (anti-DNA, anti-Sjögren's syndrome A [anti-SSA], and anti-Sjögren's syndrome B [anti-SSB] antibodies) were performed in all patients. In addition, plasma levels of folic acid, B12 vitamin, creatinine, and thyroid-stimulating hormone were measured in patients with nonregenerative anemia.

RESULTS

Population of patients

Main clinical and biological features of the 10 patients are indicated in [Table I](#). Ten patients, 9 men (mean age 67.6 ± 5.9 years) and one woman (age 30 years), were referred during a 10-year period to two dermatology departments in France and fulfilled the inclusion criteria. Main clinical features of these 10 patients were the following: all patients had ear

chondritis; in addition, 5 patients had other chondritis affecting the nose ($n = 4$) or cricoid cartilage ($n = 1$). All patients had systemic symptoms, including arthritis ($n = 6$), conjunctivitis and/or uveitis ($n = 3$), cerebral thrombophlebitis ($n = 1$), respiratory symptoms ($n = 3$), or necrotizing glomerulonephritis ($n = 1$).

CAPSULE SUMMARY

- Tense, fixed, urticarial papules and plaques with an annular configuration on the trunk of male patients may represent a unique manifestation of relapsing polychondritis.
- The lesions occurred before the chondritis in most cases.
- Histologically a lymphocytic vasculitis was observed.
- Blood abnormalities, especially myelodysplastic syndrome, were common and the prognosis seemed to be poor.

Clinical and histologic features of cutaneous lesions

All patients presented with tense fixed erythematous and urticarial papules ([Fig 1](#)). An annular configuration with a tense erythematous shape was observed at least once during the follow-up of patients. Skin lesions were predominantly located on the upper part of the body in all patients. Upper part of the trunk was involved in all cases, particularly the shoulders and neck. Proximal part of the limbs was involved in 5

cases. Only one patient had lesions on the hands and feet. Lesions were itchy and painful in 3 patients.

Skin biopsy was performed at the onset of skin lesions in all patients. Eight patients were not receiving a corticosteroid treatment at time of biopsy, whereas the skin biopsy was performed in patients previously treated with corticosteroid in the last two patients who had chondritis before skin lesions. Analysis of skin biopsy specimens showed a dermal infiltrate of small lymphocytes with few neutrophils and erythrocytes around small vessels, associated with vascular damage, and endothelial cell swelling in all cases, and fibrin deposits in the vessel walls in some cases ([Fig 2](#)). Lesions were primarily in the papillary and mid dermis. In addition, skin biopsies were performed during the follow-up of 7 patients. A histologic picture of lymphocytic vasculitis was still observed in all these 7 cases, with no evidence of leukocytoclastic vasculitis. DIF analysis revealed negative findings in all cases.

Skin lesions occurred before the chondritis in 7 of 10 cases with a mean delay of 23 ± 13 months. Skin lesions and chondritis occurred simultaneously in two patients. Finally, skin lesions occurred 12 months after the chondritis in only one patient. Interestingly, the particular clinical features of these skin lesions lead us to suspect the diagnosis of RP-associated annular urticarial lesions in the remaining

Table I. Clinical and biological findings and outcomes of 10 patients with relapsing polychondritis—associated annular urticarial lesions

Patient No./ age, y/ sex	Location of skin lesions	Timing of skin lesions in relation to onset of chondritis (delay, mo)	Location of chondritis	Hematologic abnormalities	Myelodysplastic syndrome	Treatment	Complications during follow-up	Outcome
1/69/M	Trunk	Before (47)	Ear, nose	Anemia, lymphopenia	+	Dapsone (100 mg/d), prednisone (0.5 mg/kg/d)	Pneumonia	Death
2/30/F	Trunk/limbs	After (12)	Ear	—	—	Prednisolone (0.5 mg/kg/d)	Pulmonary embolism	Alive
3/69/M	Trunk	Before (17)	Ear, nose	Anemia, lymphopenia	—	Dapsone (100 mg/d), prednisone (1 mg/kg/d)	—	Alive
4/70/M	Trunk, limbs, hands, and feet	Simultaneously	Ear	Anemia, lymphopenia	—	Prednisone (0.5 mg/kg/d)	Pulmonary embolism	Death
5/57/M	Trunk	Before (23)	Ear, cricoid cartilage	Anemia, lymphopenia	+	Dapsone (100 mg/d), hydroxychloroquine (200 mg/d), thalidomide (100 mg/d), prednisone (1 mg/kg/d)	Pneumonia	Death
6/58/M	Trunk	Before (4)	Ear	—	—	Dapsone (100 mg/d), prednisolone (0.75 mg/kg/d)	—	Alive
7/73/M	Trunk, limbs	Simultaneously	Ear, nose	Anemia	+	Prednisone (1 mg/kg/d)	Leukemia, pneumonia	Death
8/73/M	Trunk, limbs	Before (29)	Ear	—	—	Dapsone (100 mg/d), indomethacin (150 mg/d), prednisone (0.75 mg/kg/d)	Polyneuritis, cerebral thrombophlebitis, uveitis, glomerulonephritis, pneumonia	Death
9/70/M	Trunk, limbs	Before (21)	Ear	Anemia, lymphopenia	—	Dapsone (100 mg/d), hydroxychloroquine (200 mg/d), thalidomide (100 mg/d)	—	Alive
10/70/M	Trunk	Before (20)	Ear, nose	Anemia	+	Dapsone (100 mg/d), colchicine (1 mg/d), indomethacin (150 mg/d), prednisone (1 mg/kg/d)	—	Alive

F, Female; M, male.



Fig 1. Tense fixed erythematous and urticarial papules and plaques, some in an annular configuration.

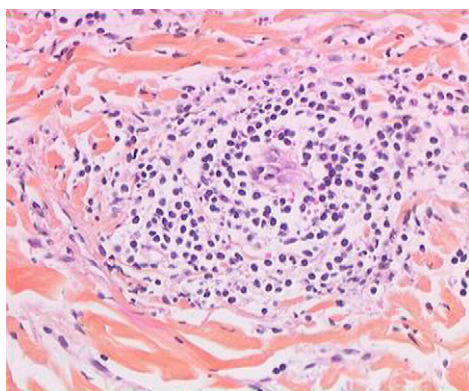


Fig 2. Analysis of initial skin biopsy specimens showed a dermal infiltrate of small lymphocytes with few neutrophils and erythrocytes around small vessels, associated with vascular damage, endothelial cell swelling, and fibrin deposits in the vessels.

3 patients of this series, who secondarily developed chondritis during their evolution.

Associated hematologic disorders

Nine patients had blood cell abnormalities: increased mean corpuscular volume ($n = 9$), non-regenerative anemia ($n = 7$), and lymphopenia ($n = 5$). Folic acid, B12 vitamin, thyroid-stimulating hormone, and creatinine plasma levels were within normal range in all cases. A myelodysplasia was found on bone-marrow biopsy specimen in 4 of 10 patients. The 6 other patients had a chronic macrocytic anemia, which was not explained by vitamin deficiency, hypothyroidism, or renal failure. Because these patients had a moderate anemia, a bone-marrow biopsy was not performed. Four patients had a lymphopenia, including two patients with an associated myelodysplasia (Table I). The associated myelodysplasia was found after the occurrence of cutaneous lesions in 3 of the 4 cases.

Treatment and follow-up

Mean follow-up of patients was 54 ± 19 months. Visceral involvement occurred in 3 patients. One patient had peripheral polyneuritis, cerebral thrombophlebitis, uveitis, and necrotizing glomerulonephritis; two additional patients had a pulmonary embolism. Five of 10 patients died; 4 patients died from infections, in particular pneumonia, which were possibly related to an associated myelodysplasia, and oral corticosteroid treatment. The last patient died from the evolution of myelodysplastic syndrome to an acute myeloid leukemia.

The 7 patients who had skin lesions without chondritis were treated with one or more of the following drugs: dapsone 100 mg/d ($n = 7$), colchicine 1 mg/d ($n = 1$), hydroxychloroquine 200 to 400 mg/d ($n = 2$), indomethacin 150 mg/d ($n = 2$), and thalidomide 50 to 100 mg/d ($n = 2$). Of these drugs, thalidomide was the only effective treatment on skin lesions. Six patients were secondarily treated with prednisone at an initial dose from 0.5 to 1 mg/kg/d, because of the association with severe chondritis and/or arthritis. Skin lesions and chondritis rapidly resolved in all cases. However, urticarial lesions recurred in 4 of 6 patients during the decrease of corticosteroid doses.

DISCUSSION

Cutaneous features described in this report seem to correspond to a particular disorder associated with RP, characterized by the occurrence of tense urticarial papules frequently with an annular shape predominantly located on the upper part of the trunk, shoulders, neck, and less frequently on the proximal part of the limbs. These lesions occurred predominantly in male patients (90%) (Table II). Interestingly, these lesions seem to correspond to an early manifestation of RP, because they occurred before the diagnosis of RP in 7 of 10 cases with a mean delay of 23 months, whereas cutaneous features of RP, which have been previously reported, occurred either simultaneously, or after the chondritis in more than 95% of cases.^{3,5}

Histologic analysis of urticarial lesions showed a lymphocytic vasculitis with negative DIF findings. In fact, this histologic picture was consistently observed both on biopsy specimens taken initially on recent skin lesions, and on the 7 biopsy specimens that were taken later on during the evolution. Therefore, it is likely that a lymphocytic vasculitis was associated with cutaneous lesions in these patients. Two cases of patients with RP and annular urticarial eruption preceding chondritis have been reported in the literature.^{6,7} Interestingly, their skin lesions were very similar to those of patients from the

Table II. Main characteristics of 12 patients with relapsing polychondritis—associated annular urticarial eruption reported in the literature

	Ingen-Housz et al, ⁶ 2000 (n = 1)	Watkins et al, ⁷ 2009 (n = 1)	Current series (n = 10)	Total (n = 12) n (%)
Tense fixed urticarial papules	1	1	10	12 (100)
Location on upper part of trunk	1	1	10	12 (100)
Age, y	74	68	63.9 ± 13.1*	65.9 ± 12.3*
Male gender	1	1	9	11 (92)
Arthritis	1	1	6	8 (67)
Onset of skin lesions before chondritis (delay in mo)	1 (30)	1 (18)	7 (23 ± 13)*	9 (75)
Histology	Perivascular infiltrate of lymphocytes, sparse keratinocyte necrosis	Dermal infiltrate of lymphocytes, endothelial swelling	Lymphocytic vasculitis	
Anemia	1	1	7	9 (75)
Myelodysplastic syndrome	1	—	4	5 (42)
Main complications				
Infection	1	—	4	5 (42)
Pulmonary embolism	—	1	2	3 (25)
Leukemia	—	—	1	1 (8)
Death	—	—	5	5 (42)

*Mean ± SD.

current study. These two male patients presented with annular and urticarial lesions of the trunk, which occurred 18 and 30 months before the onset of chondritis, respectively (Table II). Histologic analysis showed a dermal perivascular infiltrate of small lymphocytes with endothelial swelling, sparse keratinocyte necrosis, and a negative DIF finding, suggestive of a drug reaction. These two patients had an anemia and one had a RP-associated myelodysplasia^{6,7} (Table II). The clinical and histologic features described in the current series and in these two case reports are completely different from the infiltrated purpura corresponding to a leukocytoclastic vasculitis, which has been previously reported in patients with RP.^{3,8} To date, these RP-associated papular and annular urticarial lesions have not been accurately described in the various reports of patients with RP and skin involvement.^{3,4,9,10} In a major series by Frances et al,³ the more frequently reported skin lesions were aphthosis, nodules of the limbs, purpura, aseptic pustules, erythema nodosum-like lesions, superficial thrombophlebitis, and livedo reticularis, whereas urticarial papules were reported only in 5% to 13% of patients with RP, depending on the association with a myelodysplasia. Histologic pictures reported in this series were a leukocytoclastic vasculitis (53%), a Sweet-like infiltrate of polymorphonuclear neutrophils (15.5%), or a thrombosis (12.5%), whereas a lymphocytic vasculitis was observed in only 6% of skin biopsy specimens.

Similar histologic lesions have been reported in smaller series of patients with RP.⁴

These RP-associated annular urticarial lesions were frequently associated with hematologic disorders, because abnormalities of blood cell count or a histologically proven myelodysplasia were observed in 100% and 40% of patients from this series, respectively. Skin manifestations with RP have been more frequently reported in patients with RP hematologic disorders, primarily myelodysplastic syndrome and refractory anemia.^{8,11-15} They were reported in 35% of patients with RP and no associated medical records and in 91% of patients with RP and a myelodysplasia in the series by Frances et al.³

One could question whether these RP-associated urticarial lesions may be directly related to an associated myelodysplasia, rather than RP. However, skin lesions reported in patients with myelodysplasia mainly correspond to neutrophilic dermatosis and leukocytoclastic or necrotizing vasculitis.^{8,13,16-18} Therefore, clinical lesions of patients with myelodysplasia mainly consist of infiltrated and/or necrotic purpura, which is predominantly located on the lower aspect of legs, and greatly differs from the annular urticarial lesions mainly located on the trunk, described in this report.

Skin lesions described in this report appeared also rather different from lymphocytic vasculitis with an annular configuration such as Jessner-Kanoff syndrome and subacute lupus erythematosus. Clinically,

lesions of Jessner-Kanoff syndrome are predominantly located on the back. They most often occur in women, whereas lesions of RP-associated urticarial lesions occur quite exclusively in men and are mainly located on the front aspect of the trunk. Moreover, patients with RP and annular urticarial lesions had a negative DIF examination result and neither antinuclear nor anti-RoSSA antibodies, as patients with subacute lupus erythematosus.³ Annular erythematous, indurated plaques similar to the lesions in these patients have been reported in patients with Sjögren syndrome (predominantly Japanese patients), but histologically these lesions showed prominent mucin and had a perivascular mononuclear cell infiltrate and patients typically had positive SSA and SSB antibodies.^{19,20}

RP-associated urticarial lesions were resistant to conventional nonsteroidal treatments, because no patient from this series could be controlled by colchicine, dapsone, hydroxychloroquine, or indomethacin. Interestingly, thalidomide was effective in two cases. Skin lesions rapidly cleared up in patients treated with high doses of oral corticosteroids. Unfortunately, relapses were frequently observed during the decrease of corticosteroid doses or after corticosteroid withdrawal. Interestingly, corticosteroid and/or thalidomide were also reported to be effective in the two cases of RP-associated annular urticarial eruption reported in the literature.^{6,7}

Overall, these annular urticarial eruptions seem to represent a unique and early skin manifestation in patients with RP. Their particular clinical features allowed us to suspect the diagnosis of RP before the occurrence of chondritis in the last 3 patients in this series. Myelodysplasia seems to be frequently associated with these lesions.

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