

Interstitial and Granulomatous Drug Reaction Presenting as Erythema Nodosum-like Lesions

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Sir,

Interstitial granulomatous drug reaction (IGDR) is a rare entity presenting as erythematous to violaceous plaques or generalized pruritic scaly eruptions resembling cutaneous T-cell lymphoma or pigmentary purpura (1, 2). The implicated drug classes include calcium-channel blockers, lipid-lowering agents, anti-histamines, anticonvulsants and antidepressants. Histopathologically, IGDR shows an interstitial granulomatous dermatitis pattern with or without an interface change and lymphoid atypia. The lack of degenerated collagen and the presence of "granulomatous rosettes" can be subtle clues supporting interstitial granulomatous dermatitis triggered by a drug (2). We describe a case of IGDR presenting as multiple erythema nodosum-like lesions on the legs, which histopathologically showed the changes of interstitial granulomatous dermatitis.

CASE REPORT

A 25-year-old woman presented with erythematous papulonodules on the lower extremities. She complained of itching and of a painful sensation of the skin lesions. The skin lesions appeared within 2 weeks of her taking a herb medication of unknown compositions for the promotion of health. Physical examination showed multiple, erythematous, smooth-surfaced, slightly indurated, papulonodules distributed on the lower legs (Fig. 1). The complete blood cell count, liver function test and urine analysis were normal. The results of rheumatoid factor, antistreptolysin O, antinuclear antibody, anti-ssA and anti-ssB antibody were negative or non-reactive. A biopsy specimen showed interstitial infiltrates mainly composed of small histiocytes intermingled with eosinophils and neutrophils in the dermis (Fig. 2). In some areas, small "granulomatous rosettes" were present in the dermis. These consisted of a cluster of small histiocytes, neutrophils and eosinophils arrayed in a palisade around a thick collagen bundle (Fig. 2, inset). Clefts between the histiocytes and the central core of thick collagen were often seen. There were no changes of panniculitis in the subcutaneous fat tissue. Features of leukocytoclastic vasculitis or lymphoid atypia were not seen. Mucin was absent as stained by Alcian blue at pH 2.5. Cutaneous lesions disappeared within a week of discontinuation of the herb medication and initiation of oral prednisolone 30 mg/day, but identical papulonodules subsequently appeared on the thigh and lower legs after re-challenge of the same medication.

DISCUSSION

IGDR was first described by Magro et al. (1) in 1998. They described microscopic features such as the



Fig. 1. Erythematous, smooth-surfaced, slightly indurated, papulonodules distributed on the lower legs.

interstitial and palisaded array of histiocytic cell infiltrations, absence of complete collagen necrobiosis, the presence of interface dermatitis and variable lymphoid atypia. The cases presented by Perrin et al. (2) revealed only the changes of interstitial granulomatous dermatitis, and not those of the interface dermatitis or lymphoid atypia. They considered the lack of degenerated collagen and the presence of collagenous rosettes to be a subtle clue supporting interstitial granulomatous dermatitis caused by a drug. Our case showed collagenous rosettes, i.e. small rosettes composed of clusters of histiocytes surrounding thick central collagen bundles, and did not reveal any changes of interface dermatitis and lymphoid atypia. IGDR therefore presents variable histologic features, interstitial granulomatous dermatitis patterns with or without an interface dermatitis and lymphoid atypia (1, 2).

Histopathologic differential diagnoses of IGDR include interstitial granulomatous dermatitis with

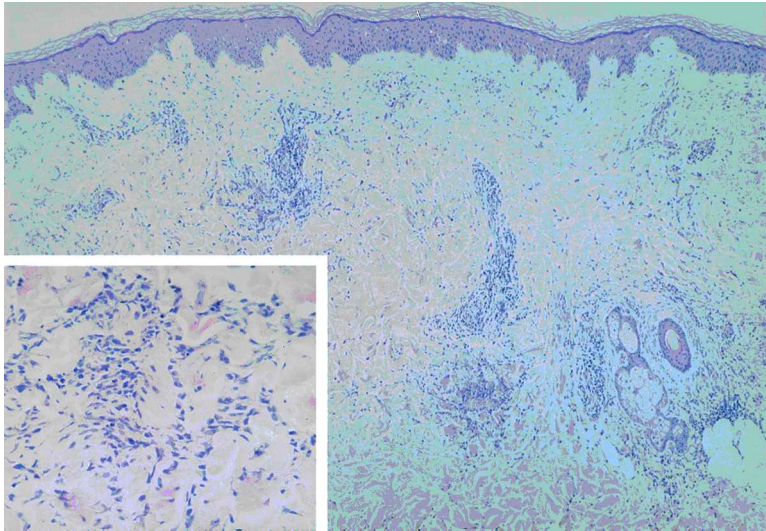


Fig. 2. Perivascular and interstitial inflammatory cell infiltrates in the dermis (H&E, $\times 100$). In some foci, a thick collagen bundle is surrounded by histiocytes, neutrophils and eosinophils forming a "rosette-like configuration" (Inset) (H&E, $\times 400$).

plaque and/or arthritis, erythematous variants of granuloma anulare, palisaded neutrophilic granulomatous dermatitis and methotrexate-induced papular eruption.

Interstitial granulomatous dermatitis with arthritis is an uncommon disorder and was first described by Ackerman et al. (3). Histopathologically, it is characterized by a dense, diffuse inflammatory infiltrate composed mainly of histiocytes distributed interstitially and in palisaded array within the reticular dermis. In some tiny foci, a few bundles of degenerated collagen are enveloped by a large number of neutrophils and eosinophils with the formation of structures resembling "Churg-Strauss granuloma" in miniature or "flame figure". The authors also used the "rope sign" to describe the prominent, linear cutaneous bands occurring on the trunk or proximal parts of upper extremities, which, when present, were believed to be pathognomonic for this disorder. However, interstitial granulomatous dermatitis can present many clinical expressions, including papules, annular plaques; in addition, in some patients, the plaques were not linked to arthritis (4, 5). Therefore, Aloï et al. (4) proposed the name "interstitial granulomatous dermatitis with plaques" for this condition.

In IGDR, complete collagen necrobiosis, which was a characteristic phenomenon of idiopathic granuloma anulare, is usually absent (2–4). In granuloma anulare, deposition of mucin is evident, and neutrophils and eosinophils are usually absent.

Palisaded neutrophilic granulomatous dermatitis (Churg-Strauss granuloma) is seen in cutaneous lesions of patients with systemic vasculitis and diseases of an autoimmune nature (6). The lack of leukocytoclastic vasculitis and extravascular neutrophils rules out the

palisaded neutrophilic granulomatous dermatitis in our case.

Methotrexate-induced papular eruption is a distinctive cutaneous adverse reaction that appears shortly after administration of methotrexate therapy in patients with acute bouts of collagen vascular diseases (7). The lesions are most commonly located on the proximal areas of the extremities and the histopathologic features show the same changes of IGDR.

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