Institute of Experimental Morphology, Pathology and Anthropology with Museum
Bulgarian Anatomical Society

Acta Morphologica et Anthropologica, 29 (3-4)
Sofia ● 2022

Interstitial Granulomatous Dermatitis Associated with Systemic Lupus Erythematosus

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Interstitial granulomatous dermatitis is a rare skin condition that presents with erythematous violaceous plaques mostly associated with pruritus and pain. The etiopathogenesis remains obscure, hence, it is often associated with autoimmune systemic diseases and systemic infections. Herein, we present an anecdotal case of interstitial granulomatous dermatitis in a male patient with immune constellation of systemic lupus erythematosus. A comprehensive review of the literature on the possible pathogenetic pathways and clinical peculiarities is also highlighted.

Key words: interstitial granulomatous dermatitis, connective tissue disease, lupus erythematosus

Introduction

Interstitial granulomatous dermatitis (IGD) is a rare disease that clinically presents with a symmetric, erythematous, and violaceous plaques over the lateral trunk, buttocks, and thighs [11]. Fewer than 70 cases have been documented in the literature [6]. Diagnosed via skin biopsy, it is characterized by the infiltration of the mid-to-deep reticular dermis with palisadic histiocytes, linearly distributed among the thick collagen bundles. Variable evidence of phagocytosis may be seen. Neutrophils and eosinophils may also be present in the infiltrate [3].

A clinical entity of unknown etiology, IGD is associated with autoimmune triggers, which include connective tissue disease (lupus erythematosus (LE), rheumatoid arthritis), vitiligo, thyroiditis, and diabetes [4]. It has been hypothesized that the deposition of immune complexes in the dermal vessels induce complement

and neutrophil activation, which leads to dermal collagen damage and evokes palisading granulomatous inflammation in response to the insult [12]. Various medications, particularly calcium channel blockers, lipid-lowering agents, angiotensin-converting enzyme inhibitors, antihistamines, anticonvulsants, and antidepressants have been claimed to induce IGD. Most recently, anti-TNF agents such as etanercept, infliximab, and adalimumab are also implicated [4,7,8,11]. We report a case of histologically verified IGD, associated with systemic lupus erythematosus.

Case report

A 47-year-old man presented to our dermatology department with a history of asymptomatic, symmetric, erythematous plaques with annular configuration, distributed over his inner parts of the arms and lateral trunk with a 8-month duration (**Fig. 1**). He also suffered from photosensitivity, malaise, arthralgia, and non-specific myalgia since the onset. There was no history of drug intake or malignancy. His mother was diagnosed with systemic lupus erythematosus five years ago. A history of a tick bite one year ago in the area of the left thigh was also reported. Due to persistently positive IgM Borrelia burgdorferi titers, the patient experienced a series of beta-lactam antibiotics therapeutic courses, which did not alleviate his symptoms and did not affect the dermatological status. The Borrelia burgdorferi IgG antibodies showed constant negative trend. In the last two weeks, topical tacrolimus reduced the intensity of the erythema, but did not succeed to resolve the skin changes.

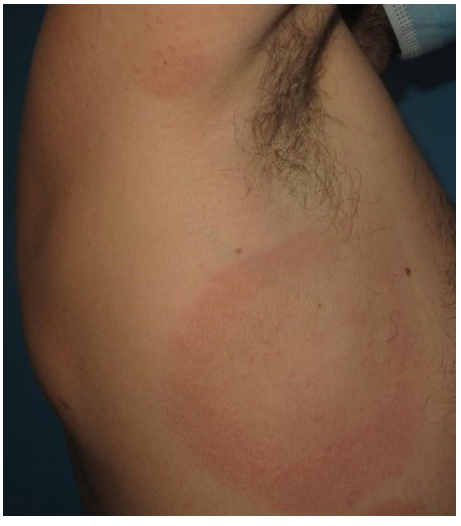

Fig. 1. Erythematous plaques with annular configuration over his left lateral part of trunk.

The laboratory results were in normal values except the increased levels of antinuclear screening titer and dsDNA antibodies. The level of Borrelia burgdorferi IgM was also positive 2.63 (value <1.1) in contrast to IgG level that was proved negative. A punch biopsy specimen taken from a skin lesion on the trunk showed deep dermal inflammation presented by palisading of lymphocytes and histiocytes along the collagen fibres (**Fig. 2**) and around foci of necrobiosis with mucin deposition (**Fig. 3**). Edematous endothelial cells with subsequent lumen obturation of small-to-middle-sized vessels in the deep dermis and leukocytoclasia as an epi-phenomenon was also demonstrated (**Fig. 4**). The histological picture was consistent with IGD.

Taken in consideration the patient's photosensitivity, arthralgia, positive antinuclear, and dsDNA antibody titers, we coined the diagnosis of systemic lupus erythematosus in association with IGD.

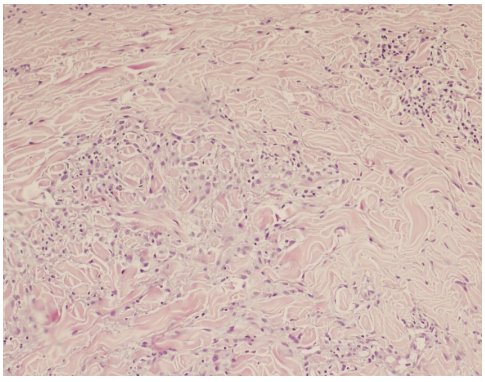

Fig. 2. Deep dermal interstitial granulomatous inflammation, presented with large epithelioid cells, lymphocytes and a few eosinophils around foci of necrobiosis and along the parallel orientated thick and edematous collagen bandles (H&E, ×200).

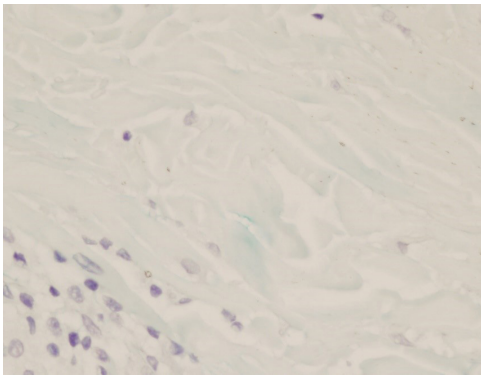

Fig. 3. Deposits of mucin in the deep dermial necrobiotic foci (Alcian blue staining, ×400).

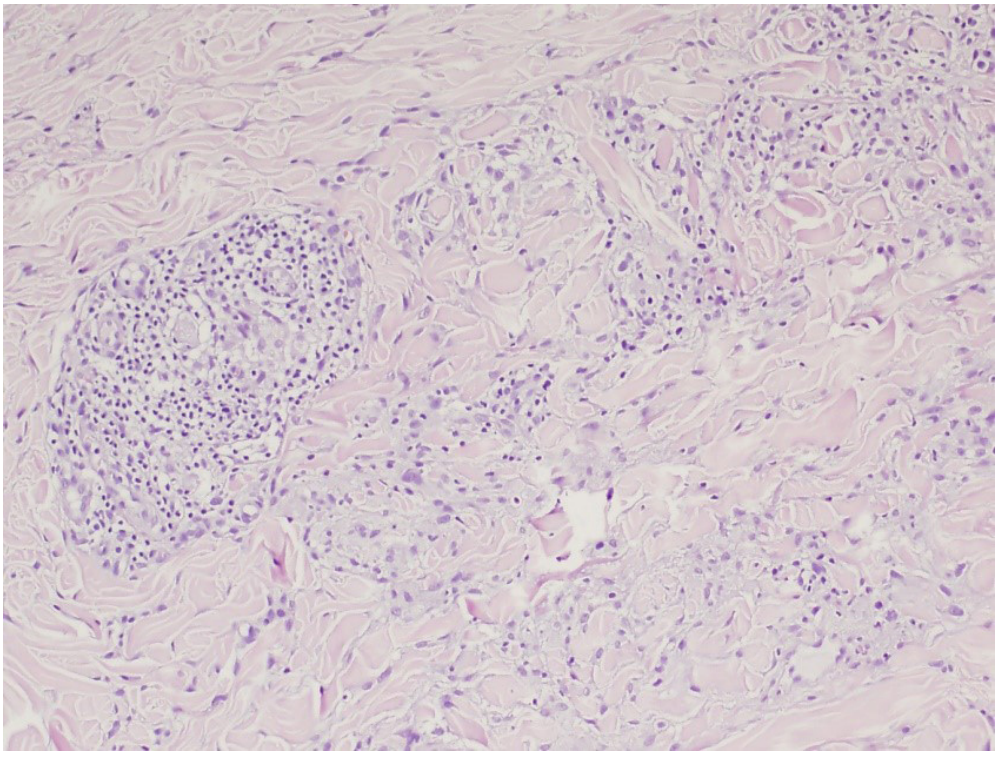

Fig. 4. Mixed perivascular inflammatory infiltrate with leukocytoclasia and nuclear dust surround the small-to-middle sized vessels in the deep dermis. Edematous endothelial cells with lumen obliteration is also presented (H&E, ×100).

Discussion

IGD is a rare skin disorder, presented with asymptomatic skin coloured or erythematous lesions, varying from linear cords, typically seen in patients with rheumatoid arthritis, to patches, papules and plaques, symmetrically distributed on the trunk and proximal extremities [10]. The morphological heterogeneity encompass its histological characteristics [2]. The most typical findings reveal lower dermis perivascular and interstitial infiltrate of epithelial cells, lymphocytes and neutrophils with a variability of leukocytoclasia and nuclear dust. Foci of necrobiosis with mucin deposition are often present. Inflammation may extend to the hypodermis. Late stages show fibrosis and parallel orientation of collagen bundles [3]. The diagnosis of IGD relies on typical histological findings, corresponding to suggestive skin changes. Our patient showed erythematous annular plaques with elevated margins and pityriasiform desquamation located to the trunk and upper extremities, a characteristic clue to IGD. The pathology skin findings of interstitial palisading inflammation with mucin deposits coined the diagnosis.

The etiology of IGD remains obscure. Most commonly, it occurs in patients with underlying immune-reactive predisposition and various forms of humoral autoimmune dysregulation, which easily initiate a profound formation of circulating immune complexes [9]. Thus, enhanced neutrophilic hemotaxis and complement activation evoke dermal collagen damage and final granulomatous responses, forming the classic clinic-pathological constellation of IGD. The key player that induces and perpetuates the granulomatous inflammation is a subtype of human macrophages, which belongs to M2b, expressing CD163 [14]. These cells are inducible by the circulating immune complexes and suppress lipopolysaccharide-regulated immune responses by inducing cell apoptosis. They inhibit tissue repair progression and remodeling to form permanent fibrosis and tumor progression. Remarkably, the same cell clone is over activated in patients with systemic lupus erythematosus and is the dominant subpopulation in lupus nephritis. The predominance of CD163-positive M2b human macrophages in the pathogenesis of both IGD and systemic lupus erythematosus proves common autoimmune humoral dysregulation in the two diseases, and finally give some light to their often clinical associations.

The persistent elevation of IgM Borrelia burgdorferi titer in our patient can also correspond to the enhanced immune complex formation under the influence of M2b macrophages. The negative seroconversion trend indirectly proves the lack of active Lyme disease, which is also supported by the therapeutic irresponsiveness towards specific antibiotic treatment. Our empiric observations on patients with undifferentiated connective tissue diseases often demonstrate high levels of IgM Borrelia burgdorferi antibodies in the absence of other clinical or laboratory clues to Lyme disease. We believe this phenomenon is immunologically defined and requires a thorough scientific exploration.

IGD treatment is not well established. The majority of documented cases have been treated with systemic and topical glucocorticoids [6, 8, 2]. In cases of drug-induced IGD, the withdrawal of the offending agent can resolve the cutaneous lesions [13, 9]. Narrow-band ultraviolet B phototherapy in conjunction with topical steroids has also been used successfully [10]. Alghamdi et al. described treatment with IVIG therapy [1]. Gerbing et al. and Wollina et al. reported treatment with

hydroxychloroquine and cyclosporine, respectively [5,13]. In conjunction with the underlying pathogenesis, biological agents have been the topic of recent discussion for the treatment of IGD.

Conclusions

We present an anecdotal case of IGD in association with systemic lupus erythematosus in a male patient. Interstitial granulomatous inflammatory reaction should always evoke a specific diagnostic interest since it can serve as a clinical clue to underlying immunological disorders. This suggestion relies on the dominant role of CD163 – positive M2-like macrophages in the pathogenesis of both diseases and gives some insights on the future therapeutic modalities that can be introduced. A high index of suspicion for connective tissue disease is needed at any case of interstitial granulomatous dermatitis.

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