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Association of Generalized Granuloma Annulare with Autoantibodies

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Abstract

Granuloma annulare is a degenerative disease of the skin histopathologically characterized by focal degeneration of collagen with a surrounding infiltrate of lymphoid cells, histiocytic cells, and multinucleated giant cells. Immunological abnormalities such as delayed-type hypersensitivity and vasculitic origin are suspected in the pathogenesis. We describe three patients with generalized granuloma annulare, in whom autoantibodies, including antinuclear antibody, anti-thyroid stimulating hormone receptor antibody, and immune complex, were detected.

Key words: generalized granuloma annulare; autoantibody; antinuclear antibody; immune complex

Introduction

Immunological investigations suggest a role for delayed-type hypersensitivity (1–3) or vascular injury (4, 5) in the pathogenesis of granuloma annulare. We recently observed three patients with generalized granuloma annulare, in whom various kinds of autoantibodies were detected.

Report of Cases

Case 1

A 40-year-old woman had a slightly prutitic, symmetrical rash of about 5 years duration. It had begun on the right arm and spread to her other arm, trunk, and both legs. Her past history was unremarkable.

On physical examination, widespread, skin-colored or pink, papulonodular lesions were present on the neck, chest, shoulders, back, arms, and thighs (Fig. 1). Some of these lesions had depressed centers and elevated annular borders. Slight enlargement of her thyroid gland was recognized. She had fine finger tremors.

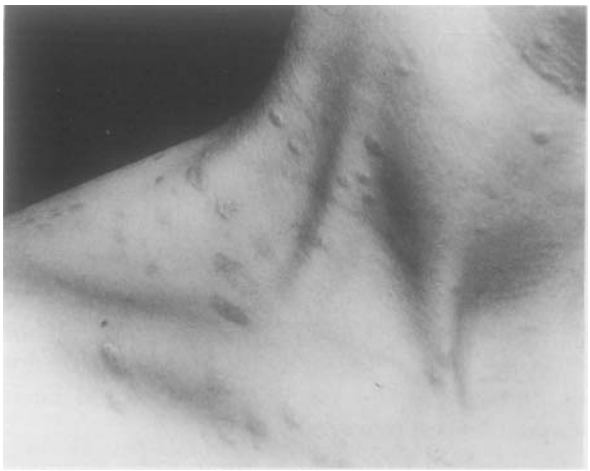

Fig. 1. Case 1, papulonodular eruptions, some of which have depressed centers and elevated annular borders, on the neck and chest.

Routine laboratory results were within normal limits. Serum levels of triiodo-thyronine (normal: 0.75–1.70 ng/ml) and thyroxine (normal: 5.00–12.50 μg/dl) were 3.77 ng/ml and 20.70 μg/dl, respectively, which indicated hyperthyroidism. Anti-thyroid stimulating hormone receptor antibody was positive and antinuclear antibody was detected at a titer of 1/40 with a speckled pattern. She had no antibodies to thyroglobulin, thyroid microsomes, or DNA.

A skin biopsy specimen taken from the shoulder

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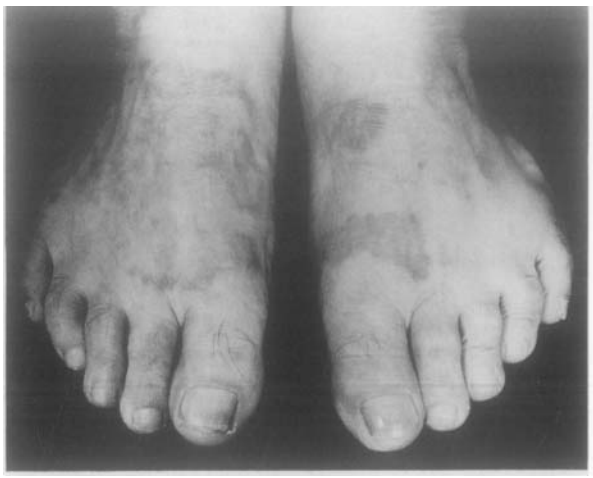

Fig. 2. Case 2, dark-red plaques with circinate borders on the dorsa of the feet.

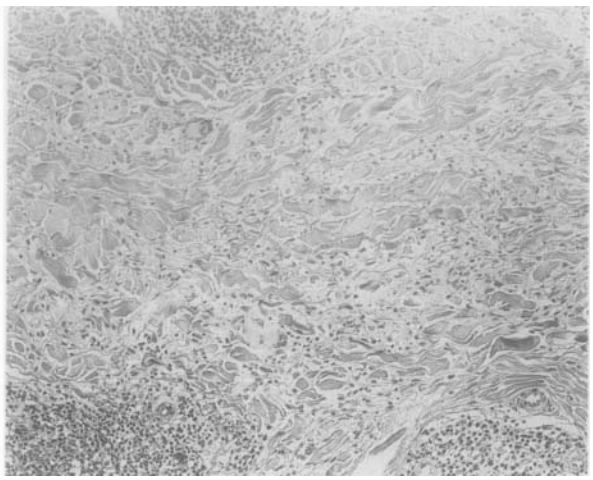

Fig. 3. Case 2, the histological features showing central collagen degeneration with an infiltrate of lymphoid cells, histiocytes, and giant cells (H&E ×80).

showed focal collagen degeneration and a surrounding infiltrate of inflammatory cells, including histiocytes and occasional multinucleated giant cells, consistent with a diagnosis of granuloma annulare.

Treatment with thiamazole improved hyperthyroidism. The skin eruption also disappeared gradually with very high levels of topical corticosteroids.

Case 2

A 65-year-old man had a 5-year history of a generalized pruritic eruption, beginning on the dorsa of both hands and slowly spreading to involve the extremities and trunk. Glycosuria had been detected several years previously.

On physical examination, there were scattered, various-sized, hyperpigmented, dark-red plaques on the dorsa of hands and feet, arms, legs, and trunk. These lesions had atrophic centers and slightly elevated, irregular, ring-like or circinate borders (Fig. 2).

Routine laboratory values were within normal limits except for a mildly impaired glucose tolerance. Antinuclear antibodies were repeatedly detected at titers ranging from 1/40 to 1/20 with a speckled pattern. No other autoantibodies were found.

A biopsy specimen taken from the dorsal aspect of the left hand showed central collagen degeneration, with a surrounding infiltrate of lymphoid cells, histiocytes, and a few giant cells (Fig. 3). Immunophenotyping of T-lymphocyte populations in the inflammatory infiltrate of the specimen demonstrated a predominance of the helper/inducer subset. There was no deposition of immunoglobulins or complement.

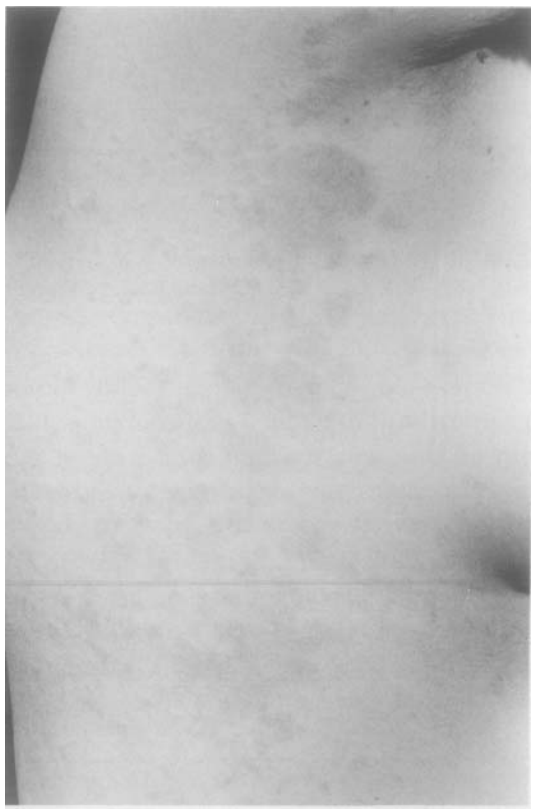

Fig. 4. Case 3, papular eruption and erythematous plaques on the right lateral chest.

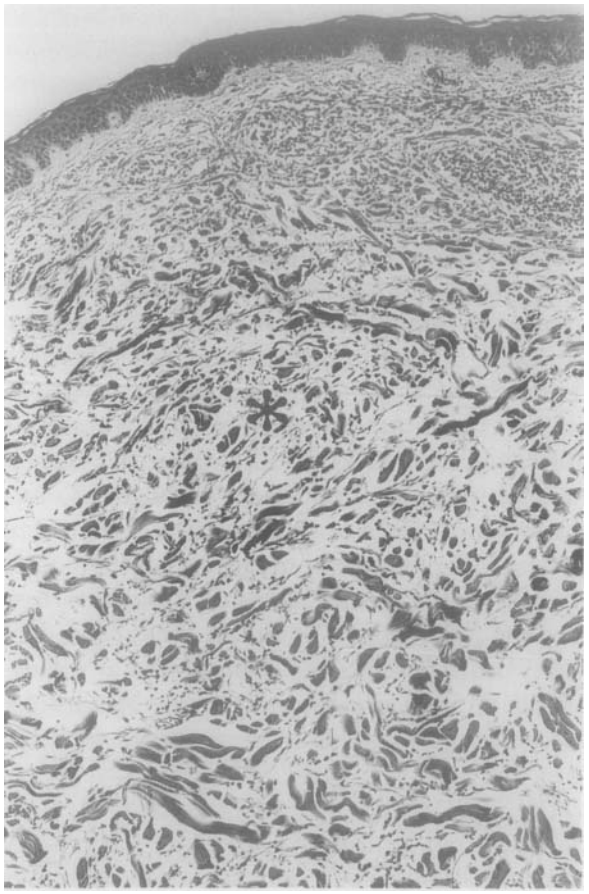

Fig. 5. Case 3, the histological feature showing minimal collagen degeneration (*) with an infiltrate of mononuclear cells (H&E ×150).

Very high levels of topical corticosteroids were effective. Blood glucose level was well controlled by diet.

Case 3

A 60-year-old woman was admitted to our hospital with a one-year history of non-pruritic eruptions, beginning on the thighs and spreading to the trunk and arms. She had gained more than 10 kg in weight in the last ten years and hyperlipidemia had been recently detected.

On physical examination, widespread skin-colored to pink papular lesions were present on the upper arms, back, lateral chest, and thighs. They coalesced from the back to lateral chest, forming large erythematous plaques with an irregular border (Fig. 4). No annular lesions were found. She showed no signs or symptoms of autoimmune diseases including rheumatoid arthritis.

Laboratory tests, including blood cell counts, liver function tests and urinalysis showed no abnormal values. Total cholesterol was 284 mg/dl (normal: 110–267 mg/dl). CRP was 1.2 mg/dl (normal: <0.3 mg/dl) and serum level of rheumatoid factor was 70.5 IU/ml (normal: <18 IU/ml). Antinuclear antibodies were repeatedly detected at titers ranging from 1/1280 to 1/640 with a speckled or homogeneous pattern. Circulating immune complex level was 3.1 μg/ml (normal: <3.0 μg/ml). Ratio of CD4/CD8 of peripheral blood was 6.0 (normal:

Table 1. Clinical, laboratory, and histopathological features in the patients

	Case 1: 40yr Female	Case 2: 65yr Male	Case 3: 60yr Female
Distribution	Neck, Chest, Back, Extremities	Hands, Feet, Extremities, Trunk	Trunk, Extremities
Duration	Five years	Five years	One year
Associated diseases	Hyperthyroidism	Diabetes mellitus	Hyperlipidemia, Obesity
Histopathological changes			
Collagen alteration	Fragmentation Hyalinization, Necrobiosis	Fragmentation Hyalinization	Fragmentation
Elastic tissue	Loss	Loss	Less
Histiocyte	Many, Epithelioid, Multinucleated	Many, Epithelioid, Multinucleated	A few
Alcian blue	Positive	Positive	Positive
Immunohistochemistry	ND	$CD4^+$ T-cell	$CD4^+$ T-cell
Direct immunofluorescence	ND	Negative	Negative
Autoantibodies	Anti-TSHR antibody ANA (×40 Speckled)	ANA (×20~×40 Speckled)	ANA (×640~×1280 Speckled, Homogeneous) Immune complex

TSHR: thyroid stimulating hormone receptor, ANA: antinuclear antibody, ND: not done

1.1–2.2).

Several skin biopsy specimens were taken; they showed similar changes of minimal collagen degeneration with an infiltration of scattered mononuclear cells (Fig. 5). Immunohistochemically, infiltrated lymphocytes showed the phenotype of helper/inducer T-cells. A few giant cells were found. Immunofluorescence study of the specimen revealed no deposits of immunoglobulins or complements. The skin eruptions gradually disappeared in 6 months without any treatment. In parallel with the improvement in cutaneous lesions, abnormal serological findings and deviated subpopulation of peripheral lymphocytes returned almost to their normal ranges.

Clinical, laboratory, and histopathological features of our patients are summarized in Table 1.

Discussion

Generalized granuloma annulare is an uncommon, cutaneous, granulomatous disease. Recently information about generalized granuloma annulare is increasing in the literature (3, 6-8). Recent reports suggest that immunological alterations might play an important role in the pathogenesis of granuloma annulare.

In a study of 30 patients with localized granuloma annulare, circulating immune complexes have been found in 60% and antinuclear antibodies, in 30% at titers ranging from 1/40 to 1/1280 (9). The higher prevalence of circulating immune complexes and antinuclear antibodies in patients with granuloma annulare over those in normal subjects may support a vasculitic origin of granuloma annulare (4, 9). Another analysis of 100 patients with generalized granuloma annulare pointed out the high incidence of antinuclear antibodies, although the authors do not discuss the meaning of such antibodies in the pathogenesis of granuloma annulare (6). In these reports, the prevalence of associated autoimmune diseases was very low. This indicates that positive autoantibodies in patients with granuloma annulare may have a direct relationship with granuloma annulare itself rather than be the consequence of associated autoimmune diseases. Our three patients showed no signs or symptoms of autoimmune diseases such as lupus erythematosus or rheumatoid arthritis. In our third case, circulating immune complex and a high titer of antinuclear antibody were revealed. In adition, the other two patients showed positive antinuclear antibody. Furthermore, the first patient concomitantly had hyperthyroidism with anti-thyroid stimulating hormone receptor antibody. The association of generalized granuloma annulare with thyroiditis and anti-thyroglobulin antibody has been reported (10), although the relationship between dysfunction of thyroid gland and generalized granuloma annulare was obscure. The abnormal laboratory findings returned to their normal ranges after disappearance of skin lesions in the first and third cases. Two of our patients showed low titers of positive antinuclear antibodies. The role of positive antinuclear antibodies should be investigated in many more patients with granuloma annulare, as low titers of positive antinuclear antibodies in a normal population have been reported (11).

Umbert, Dabski, and Winkelmann (1, 3, 6) believed that granuloma annulare is a type IV delayed hypersensitivity reaction to either locally or systemically acting stimuli from the results of histopathologic, immunopathologic, and ultrastructural studies of granuloma annulare. They proposed that sensitized lymphocytes in the dermis release some cytokines which cause macrophages and histiocytes to sequester in the dermis and release various lysosomal enzymes that partially degrade collagen fibers. Kallioinen et al. (12) also speculate that cytokines are important mediators of tissue degeneration in granuloma annulare. T-cell subpopulations in granuloma annulare were predominantly identified as helper/inducer cells (2), and the number of S100 positive dendritic cells within the epidermis and dermis was increased in granuloma annulare (13). In two of our cases, immunohistochemistry showed the predominance of helper/inducer T-cells in the inflammatory infiltrates. Generalized granuloma annulare has also been described in acquired immunodeficiency syndrome, in which helper/inducer T-cells are much impaired (14).

The question of an association between generalized granuloma annulare and diabetes mellitus has been discussed extensively without definite conclusions (6). Our second patient had impaired glucose tolerance and positive antinuclear antibody. Blood glucose values well-controlled by diet had no relationship to the clinical course of his granuloma annulare.

The two above mentioned hypotheses may be inconsistent in some respects. However, many immunological abnormalities in granuloma annulare are reported, such as elevated circulating immune complexes (9), positive antinuclear antibodies (6, 9), and antithyroid antibodies (10) as described in our three cases. These autoantibodies appear to be related to granuloma annulare; their meaning remains to be ascertained.

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