An Unusual Form of Generalized Granuloma Annulare in a Patient with Insulin-dependent Diabetes Mellitus

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The generalized form of granuloma annulare may be associated with systemic disorders, including diabetes mellitus. We describe here an unusual form of generalized granuloma annulare in a patient with complicated insulin-dependent diabetes mellitus. The cutaneous eruption had been present for decades as non-pruritic, persistent, violet–brown patches with raised edges. There were flexion deformities of the small joints of the hands and feet associated with thickening of the skin over dorsa of the fingers. The patient is currently on isotretinoin therapy, with partial resolution of lesions at 3 months follow-up. Keywords: granuloma annulare; diabetes mellitus; scleroderma-like syndrome.

Granuloma annulare (GA) is a benign, inflammatory, self-limited dermatosis that has no proven etiology or widely accepted theory of pathogenesis. Generalized GA is a rare form of disease and occurs in 15% of GA patients (1, 2). Although GA usually appears to be idiopathic, a number of possible associated diseases have been reported, including diabetes mellitus (2, 3).

We describe here an unusual sclerotic form of generalized GA in a patient with complicated insulin-dependent diabetes.

CASE REPORT

A 48-year-old Caucasian man was referred to our Dermatology Clinic for evaluation of a widespread, non-pruritic, violet–brown rash. The rash had begun 33 years earlier, soon after diagnosis of juvenile-onset diabetes mellitus. The patient had poorly controlled diabetes, manifest as recurrent episodes of ketoacidosis, severe retinopathy and scleroderma-like syndrome involving the hands and feet.

Dermatologic examination revealed widespread, symmetrical areas of violet–brown patches with raised arcuate, annular and linear edges. The lesions were widespread and symmetrically located on the trunk, thighs, buttocks, axillae and the extensor surface of the extremities in a bathing-suit distribution. They were pronounced at sites of pressure, such as under the elastic bands of underclothing (Figs. 1–3). The affected lesional skin was tight, less mobile and somewhat sclerotic, compared with clinically uninvolved skin areas. The non-lesional skin sites were clinically normal. The scalp, face, neck, upper back, forearms, lower legs and mucosa were spared. There was waxy thickening and sclerosis of skin over dorsa of the hands, feet and fingers in association with bilateral and symmetric flexion contractures on hands and feet involving metacarpophalangeal, metatarsophalangeal, proximal and distal interphalangeal joints. The contractures were limited to the skin and spared the flexor tendons. Limited joint mobility was evident on active and passive extension of the involved joints.

Two punch biopsy specimens were taken from the elevated and sclerotic lesional skin of the flexor surface of the right upper arm. Histopathologic examination revealed basket-weave orthokeratosis and perivascular lymphohistiocytic infiltration involving the superficial and deep vascular plexuses and among the collagen bundles. The histiocytes were present in an interstitial pattern and there were no well-developed pallisading granulomas (Fig. 4). Mucin stains of lesional biopsy samples were negative. These findings were consistent with the interstitial type of GA (4).

Except for an elevated blood glucose level (380 mg/dl) and the presence of glucose in urine the results of other laboratory tests, including HIV antibody, tuberculosis skin test, rheumatoid factor, antinuclear and anticientromere antibodies, Lyme screen, venereal disease research laboratory test, serum protein electrophoresis and Pathergy test, were negative or within normal limits. Radiological examination of hands and feet demonstrated generalized osteoporosis and subluxation of some interphalangeal joints.

Although the patient had a history of obvious benefit from systemic corticosteroids for his skin disease, aggressive diabetes precluded their use. Isotretinoin treatment was initiated at a dose of 1 mg/kg/day. At 3-month follow-up, partial healing of lesions was observed, with flattening and fading of colour. The patient himself had noted a softening in sclerotic skin areas and an improvement in his ability to carry out manual work.

DISCUSSION

Generalized GA usually presents with various skin-coloured, discrete or confluent, asymptomatic papules that may form annular plaques on the trunk and extremities (1, 2). Our patient presented with violet–brown infiltrated patches with arcuate, annular and linear palpable edges. The lesions were widespread and symmetrically located on the trunk, thighs, buttocks, axillae and the extensor surface of the extremities in a bathing-suit distribution. They were enhanced at sites of pressure and spared the scalp, face, upper back, forearms, lower legs and mucosa. A particular feature of the lesions was prominent sclerosis inside the patches and indurated elevated edges. Histopathologically, the lesions lacked the palisade of histiocytes and positive mucin staining. However, the interstitial type of GA, in which palisading of histiocytes is not prominent, may not reveal increased mucin (4).

The differential diagnosis of the present case included necrobiosis lipoidica and sclerodema adlutorum of Buschke. Clinically, the absence of lesions on the lower legs, the lack of atrophy, telangiectasia and scarring and the presence of raised arcuate and linear edges favoured the diagnosis of GA. Histologically, the absence of marked, diffuse and complete necrobiosis, lipid-filled giant cells, vascular changes and fibrosis were suggestive of GA (5). Sclerodema adlutorum presents with diffuse symmetric thickening and induration of the skin favouring the back and posterior upper neck.
Fig. 1. Elevated, ring-like, arcuate and annular edges on the flexor surface of the upper arm.

Fig. 2. Sclerotic violet–brown patches on the trunk.

Fig. 3. Sclerotic violet–brown patches on both thighs.

Fig. 4. High-power magnification image of the lymphohistiocytic infiltration among collagen bundles in the dermis (hematoxylin–eosin staining; original magnification × 400).
Classically it occurs in middle-aged and almost invariably obese patients with non-insulin-dependent diabetes mellitus. Histological examination reveals a thick dermis with wide clear spaces or fenestrations between the collagen bundles previously occupied by mucin and an increase in the number of mast cells (6–8). In our patient the cutaneous eruption had initially developed around puberty, simultaneous with the diagnosis of insulin-dependent diabetes mellitus. Although a brown pigmentation may be associated with sclerodema (8), our patient had violet-coloured patches. The eruption was sclerotic rather than indurated and the sites favoured by sclerodema were spared. Sclerodema usually causes little morbidity (8) and could not explain the presence of irreversible joint contractures in our patient. Finally, the histological features of sclerodema were lacking in our case.

Previously an erythematous variant of GA has been described as large, slightly infiltrated erythematous patches with moderately elevated irregular borders on which scattered papules may subsequently arise (4, 9). Ogino & Tamaki (9) reported such a case with non-specific histopathological changes. The authors could diagnose the eruption as GA when multiple papular lesions with typical histological features appeared on the erythematous base. Our case had similarities with the erythematous form of GA. However, the presence of sclerosis and an association with insulin-dependent diabetes mellitus has not been described in erythematous GA. Transition from erythematous patches to disseminated papular lesions had not been noted by our patient since the initial appearance of the eruption. We believe that the present case may represent a new subset of generalized GA occurring in the setting of overt insulin-dependent diabetes mellitus and scleroderma-like syndrome, for which we propose the term sclerodermatous GA.

The relationship between diabetes and GA is controversial. The prevalence of diabetes is reported to be 4–10% in patients with GA (10, 11). A disordered carbohydrate metabolism, with abnormal glucose tolerance tests or overt diabetes, appears to occur particularly in the generalized and perforating forms of the disease (12–14).

Diabetes-associated scleroderma-like syndrome is characterized by painless, progressive, bilateral and symmetric stiffness of the small joints of the hands and feet, in association with thickening and sclerosis of the skin over the fingers. Also known as the limited joint mobility—waxy skin syndrome, it is considered as an early clinical complication of juvenile-onset diabetes heralding the possible development of other complications such as retinopathy (6, 7, 15). Poor glucose utilization may be responsible for the stimulation of fibroblasts to produce abundant amounts of matrix proteins deposited in the skin. In addition, an increased non-enzymatic glycosylation of dermal collagen, with an associated decrease in collagen degradation, may contribute to scleroderma-like syndrome (16). Our patient had a full-blown picture of scleroderma-like syndrome with irreversible contractures and waxy thickening and sclerosis of the overlying skin.

Recently, the use of isotretinoin and etretinate has been reported to be effective in the treatment of generalized GA (17, 18). Isotretinoin was effective in our patient, in terms of both resolution of GA lesions and softening of the sclerotic skin areas. Spontaneous resolution was unlikely as the lesions had been present for decades. We believe that systemic retinoids could be worth trying in patients with persistent generalized GA and complicated diabetes, where the use of systemic steroids or potentially toxic drugs is inconvenient. Our patient also noticed a subjective reduction in joint stiffness and an improvement in his ability to perform manual work during isotretinoin therapy. This may imply that retinoids could also be useful in the treatment of diabetes-associated scleroderma-like syndrome, particularly if initiated before the joint contractures develop. This would not be surprising as retinoids are known to inhibit fibroblast proliferation and collagen synthesis (19), leading to a reduction in the abnormal collagen. Future clinical trials on the use of systemic retinoids in a large population of diabetic patients with scleroderma-like syndrome could test this hypothesis.

REFERENCES