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. Key words: granuloma annulare; diabetes mellitus; scleroderma-like syndrome.

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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 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).

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 palisading 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 lipidica and scleroderma cutaneum of Buschke. Clinically, the absence of lesions on the lower legs, the lack of atrophy, telangiectasia and scarrring 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). Scleroderma cutaneum 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 scleroderma (8), our patient had violet-coloured patches. The eruption was sclerotic rather than indurated and the sites favoured by scleroderma were spared. Scleroderma usually causes little morbidity (8) and could not explain the presence of irreversible joint contractures in our patient. Finally, the histological features of scleroderma 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

1. Dahl MV. Granuloma annulare. In: Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF, eds. Dermatology in general medicine, 4th edn. New York: McGraw-Hill, 1993: 1187–1191.
2. Smith MD, Downie JB, DiCostanzo D. Granuloma annulare. Int J Dermatol 1997; 36: 326–333.
3. Haim S, Friedman-Birnbaum R, Shafir A. Generalized granuloma annulare: relationship to diabetes mellitus as revealed in 8 cases. Br J Dermatol 1970; 83: 302–305.
4. Shapiro PE. Granuloma annulare. In: Elder D, Elenitsas R, Jaworsky C, Johnson Jr. B, eds. Lever’s histopathology of the skin, 8th edn. Philadelphia, PA: Lippincott-Raven, 1997: 328–330.
5. Cunliffe WJ. Necrobiotic disorders. In: Champion RH, Burton JL, Burns DA, Breathnach SM, eds. Textbook of dermatology, 6th edn. Oxford: Blackwell Science, 1998: 2297–2308.
6. Perez MI, Kohn SR. Cutaneous manifestations of diabetes mellitus. J Am Acad Dermatol 1994; 30: 519–531.
7. Jellinek JE. Cutaneous manifestations of diabetes mellitus. Int J Dermatol 1994; 33: 605–617.
8. Rowell NR, Goodfield MJD. The connective tissue diseases. Scleroderma. In: Champion RH, Burton JL, Burns DA, Breathnach SM, eds. Textbook of dermatology, 6th edn. Oxford: Blackwell Science, 1998: 2553–2554.
9. Ogino A, Tamaki E. Atypical granuloma annulare. Dermatologica 1978; 156: 97–100.
10. Gannon TF, Lynch PJ. Absence of carbohydrate intolerance in granuloma annulare. J Am Acad Dermatol 1994; 30: 662–663.
11. Dicken CH, Carrington SG, Winkelmann RK. Generalised granuloma annulare. Arch Dermatol 1969; 99: 556–563.
12. Penas PF, Jones-Caballero M, Fraga J, Sanchez-Perez J, Garcia-Diez A. Perforating granuloma annulare. Int J Dermatol 1997; 36: 340–348.
13. Haim S, Friedman-Birnbaum R, Haim N, Shafir A, Ravina A. Carbohydrate tolerance in patients with granuloma annulare. Br J Dermatol 1973; 88: 447–451.
14. Dabski K, Winkelmann RK. Generalised granuloma annulare: clinical and laboratory findings in 100 patients. J Am Acad Dermatol 1989; 20: 39–47.
15. Rosenbloom AL, Frias JL. Diabetes mellitus, short stature and joint stiffness—a new syndrome. Clin Res 1974; 22: 92A.
16. Haustein UF. Scleroderma-like lesions in insulin-dependent diabetes mellitus. J Eur Acad Dermatol Venereol 1999; 13: 50–53.
17. Schleicher SM, Misten HJ. Resolution of disseminated granuloma annulare following isotretinoin therapy. Cutis 1985; 35–36: 147–148.
18. Botella-Estrada R, Guillen C, Sammartin O, Aliaga A. Disseminated granuloma annulare: resolution with etretinate therapy. J Am Acad Dermatol 1992; 26: 777–778.
19. Daly TJ, Weston WL. Retinoid effects on fibroblast proliferation and collagen synthesis in vitro and on fibrotic disease in vivo. J Am Acad Dermatol 1986; 15: 900–902.