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Generalized Morphea with Vascular Involvement

A Case Report and Disaccharide Analysis of the Skin Glycosaminoglycans

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We report a 69-year-old man with severe generalized morphea, who showed over 80% of skin involvement, while the internal organs were not affected. We performed histological examinations and analysis of skin disaccharides constituting chondroitinase-digestible glycosaminoglycans in the center and periphery of the sclerotic lesions and the clinically uninvolved skin. In both the central and peripheral parts of the sclerotic lesions, sclerotic fibrosis and a dense perivascular cell infiltration, consistent with morphea, were seen in the entire dermis and subcutis. Furthermore, various vascular changes were observed, such as endothelial cell swelling, thickened basement membrane and obstruction of vascular lumen in the fat lobules. In the clinically uninvolved skin, interstitial edema was prominent along with a slight perivascular cell infiltration. On disaccharide analysis, the increase in the amount of ΔDi-4S(DS), the main disaccharide unit of dermatan sulphate, ΔDi-6S and ΔDi-6S, the main disaccharide units of chondroitin sulphate, and the decrease in ΔDi-HA, which is derived from hyaluronate, were found not only in the sclerotic lesions but also in the clinically uninvolved skin, though less prominent. These alterations were consistent with systemic sclerosis, suggesting a close relationship between severe forms of generalized morphea and systemic sclerosis. ***Key words: vascular change; interstitial change; systemic sclerosis.***

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Morphea or localized scleroderma is a localized form of scleroderma characterized by sclerotic skin plaques with an ivory-colored center and a surrounding violaceous halo (1). Since Raynaud's phenomenon or sclerodactyly is rare in patients with morphea, it is generally considered to be a different entity from systemic sclerosis (SSc) that features a systemic connective tissue disorder in the skin and other organ systems.

When the lesion is widespread and multiple, the disease is defined as generalized morphea (GM) (2,3). Unlike SSc, GM usually lacks visceral involvement. We here report a severe form of GM with special reference to the histological study and the disaccharide analysis of the skin glycosaminoglycans (GAGs), both in the center and periphery of the sclerotic lesions and in the clinically uninvolved skin.

CASE REPORT

A 69-year-old Japanese male patient visited our department with 16 months' history of multiple sclerotic plaques in April 1994. He had often been exposed to kerosene and petroleum from the age of 22 to 46, and to volatile adhesive agents from 48 to 60. He first noticed an asymptomatic erythema on the abdomen in December 1992. During the subsequent 10 months, multiple erythematous lesions appeared on his trunk and extremities. He had never been aware of Raynaud's phenomenon. He was admitted to our department under the diagnosis of GM. Physical examination revealed multiple sclerotic plaques of variable sizes with a symmetrical distribution involving more than 80% of the body surface. His scalp, face, feet and fingers were spared. Each lesion showed an ivory-white sclerotic plaque surrounded by violaceous erythema with ichthyotic scale. Abnormal results in routine laboratory examination were as follows: WBC count 10400/mm^3, serum complement hemagglutinin test level 60 IU/ml (normal value; 30–45), IgG 2088 mg/dl (770–1700), IgA 515mg/ml (90–450). Tests for antinuclear antibody, anti double-stranded and single-stranded DNA, anti RNP, anti Scl-70, anti centromere, anti SS-A and SS-B antibodies and anti *Borrelia burgdorferi* antibody were all negative. Other hematology tests and blood chemistry tests were normal. On capillary microscopic examination, the patient's nail fold capillary showed a pattern compatible with that of SSc. We could find no abnomality in chest radiograph, pulmonary function test or esophageal function test.

Treatment with bucillamin, 300 mg q.d.s., was started, resulting in the gradual improvement of the sclerotic skin.

Histological examination

Three skin specimens were obtained from the extensor surface of the patient's forearm, exactly from the center and the periphery of the sclerotic lesion and from clinically uninvolved skin. Each specimen was divided into two pieces, one for histology and the other for biochemical analysis. Three site-matched skin samples from healthy individuals or non-SSc patients were studied as controls for biochemical analysis.

Both in the peripheral (Fig. 1b) and central (Fig. 1c) parts, hyalinized collagen bundles in the dermis and subcutaneous fat tissue were noted. Dense perivascular mononuclear cell infiltrations were also observed, which were more prominent in the peripheral part than in the central part. Additionally, remarkable vascular changes were noted. The endothelial cells of the blood vessels in the entire dermis were swollen. There were extravasations of erythrocytes in the upper dermis (Fig. 2a), and furthermore, the lumina of the blood vessels in the residual subcutaneous fat tissue were occasionally obstructed with the proliferation of vessel wall cells (Fig. 2b).

In the clinically uninvolved skin, interstitial edema of the dermis and a slight perivascular cell infiltration were noted, whereas collagen bundles were apparently normal (Fig. 1a). Alcian blue staining (pH 2.5) demonstrated the deposition of GAGs in the interstitial space.

Disaccharide analysis of GAGs

The disaccharide analysis was performed using the previously described method (4–6). ΔDi-6S and ΔDi-4S(CS), the main disaccharide units of chondroitin sulphate, and ΔDi-HA, which is derived from hyaluronate, were determined as unsaturated disaccharides liberated with chondroitinase AC digestion. ΔDi-4S(DS), the main disaccharide unit of dermatan sulphate, was calculated by deducting the above ΔDi-4S (CS) from the total ΔDi-4S liberated with chondroitinase ABC digestion. The values obtained were expressed as amount per 1 mg dry skin.

In the central part, all disaccharide units but ΔDi-HA were increased, and ΔDi-HA was decreased as compared with normal controls, which was consistent with our previous results of SSc (5). In the peripheral part, a similar tendency was found. Although the amount of ΔDi-HA was at the same level, there was less of ΔDi-6S, ΔDi-4S(CS) and ΔDi-4S(DS) than in the central lesion. Subsequently, during the progress of sclerosis, the amount of ΔDi-6S, ΔDi-4S(CS) and ΔDi-4S(DS) increased, while the amount of ΔDi-HA showed no

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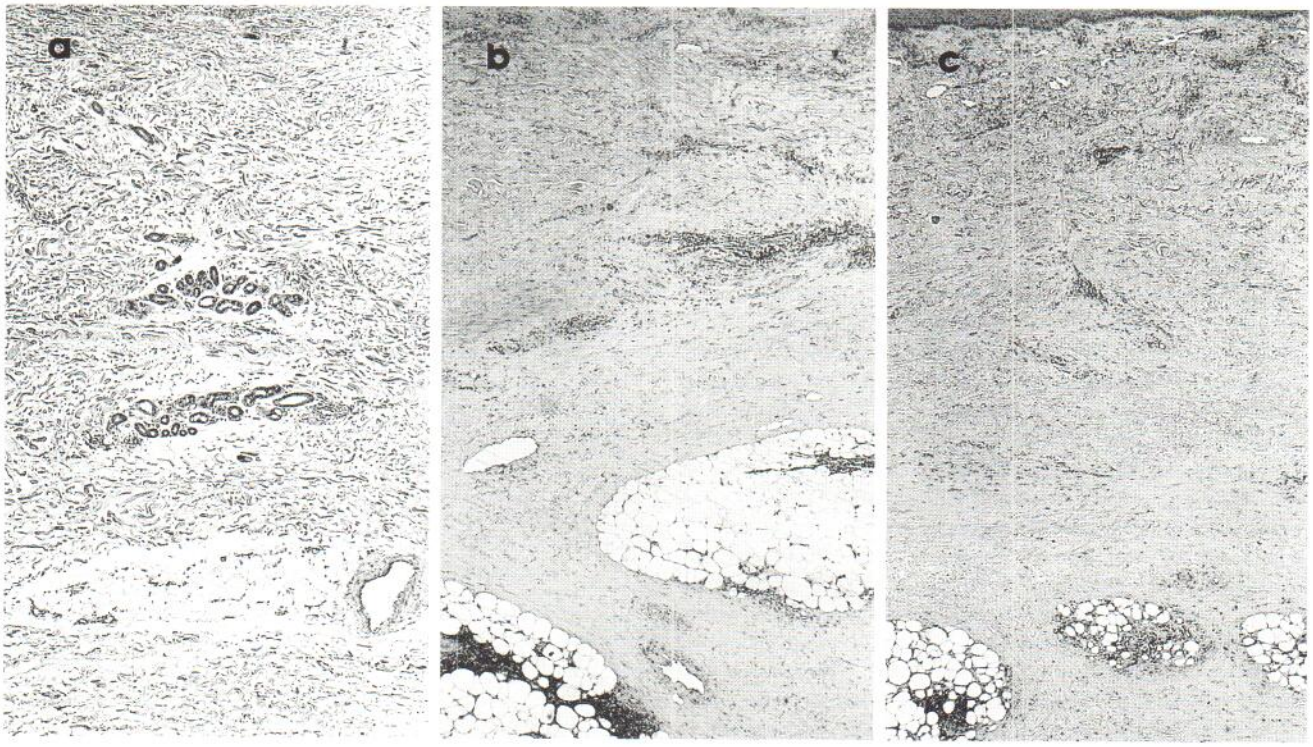

Fig. 1. Histological comparison of involved and uninvolved skin of the forearm. In the clinically uninvolved skin (*a*), the interstitial edema of the dermis and a slight perivascular cell infiltration are noted, whereas collagen bundles are apparently normal. In the peripheral part (*b*) and the central part (*c*) of the sclerotic lesion, homogenized collagen bundles in the dermis and subcutaneous fat tissue are observed. Dense perivascular mononuclear cell infiltrations are prominent (hematoxylin and eosin ×40).

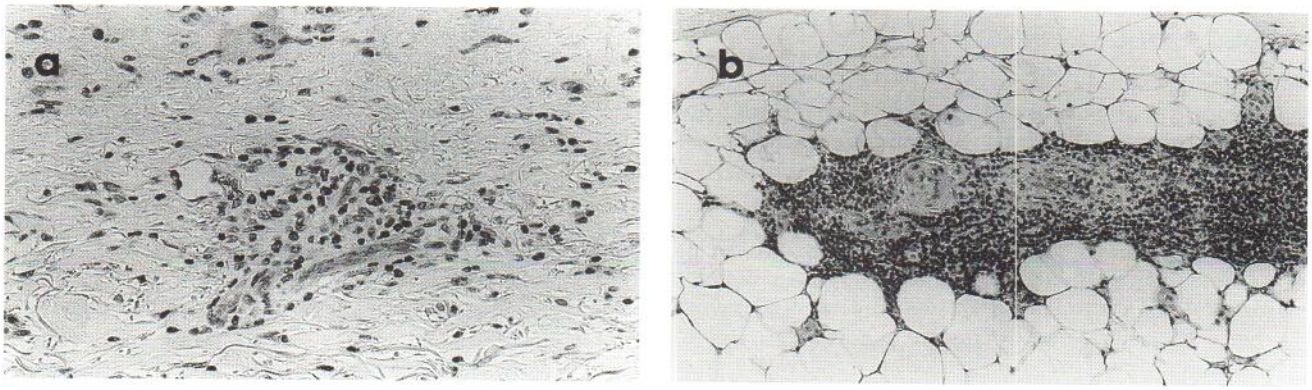

Fig. 2. High magnification of the sclerotic lesion. In the upper dermis (*a*), swollen endothelial cells and extravasated erythrocytes are noted. The lumina of vessels in the subcutaneous fat tissue (*b*) are obstructed with the proliferation of vessel wall cells (hematoxylin and eosin ×400).

change. Even in the clinically uninvolved part, an increase in ΔDi-4S(DS) and a decrease in ΔDi-HA were noted, the values being between the patient's lesions and the control skin (Fig. 3).

DISCUSSION

Endothelial cell injury is thought to be important in the pathogenesis of SSc (8–12). Raynaud's phenomenon, a common feature of SSc and possibly one of the premonitory symptoms of SSc (13), has been supposed to cause endothelial cell injuries (14,15). However, most patients with morphea lack Raynaud's phenomenon. The vascular changes in morphea have rarely been pointed out (3). Ishikawa & Mori (16) reported that the vascular changes in some patients with morphea were similar to SSc. In electron microscopic examination of morphea, Kobayasi & Serup (17) reported the enlargement of endothelial cells and pericytes and the thickening of basal lamina, though endothelial cell destruction was not found. Thus they concluded that the most essential change in morphea was the activation of pericytes transformed into myofibroblasts. They proposed that pericytes capable of regulating blood flow in small vessels might inhibit the ordinary blood flow, with a resultant increase in their secretary function when they are transformed into myofibroblasts. As no electron microscopic examination was performed in our case, we could only demonstrate that the vascular changes were similar to SSc, based on the findings of the routine histopathology and capillary microscopy. However, the obstruction of vascular

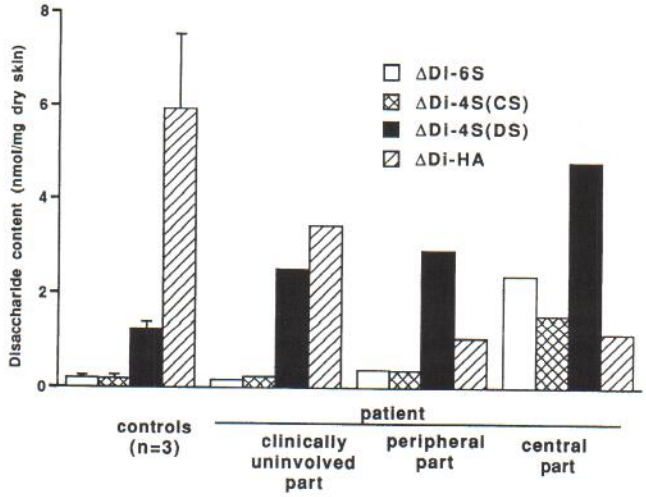

Fig. 3. The composition of main disaccharides in the forearm skin. ΔDi-4S(CS) and ΔDi-6S constitute the main units of chondroitin sulphate. ΔDi-4S(DS) is derived from dermatan sulphate and ΔDi-HA is from hyaluronate. As compared with controls, the decrease in ΔDi-HA and the increase in ΔDi-4S(DS) are remarkable in the sclerotic skin. Clinically uninvolved skin exhibits intermediate changes between the control skin and the sclerotic skin. *Bars* indicate mean ± SD.

lumen in subcutaneous fat lobules, as observed in our case, has rarely been found in SSc. Thus, we assume that these vascular changes are unusual and may play important roles in the development of the disease.

We previously reported that the distribution pattern of the main disaccharide in SSc was different from that of scars or normal controls (4). In the present study, the disaccharide analysis revealed a similar pattern with SSc (4,5). It was of note that the content of ΔDi-4S (DS) increased in accordance with the progression of sclerotic changes. An electron microscopic study revealed that collagen fibrils in normal skin are bridged or anchored by proteoglycans (glycosaminoglycan-protein complex) (18). Vogel et al. demonstrated that small dermatan sulphate proteoglycans of bovine tendon specifically inhibit fibrinogenesis of both type I and type II collagens (19). These results suggest a close interaction of collagen fibrils and proteoglycans. Taking these reports into consideration, we suggest that the altered GAG metabolism may be closely related to the abnormal collagen metabolism, though it remains unclear whether this change is a primary or secondary event. Furthermore, it is of great interest that the clinically uninvolved skin showed abnormal disaccharide contents. This may suggest that systemic skin changes like SSc will occur in GM.

Localized scleroderma is generally assumed to be different from SSc. However, the progression to SSc (20), or the co-existence with SSc (21) in localized scleroderma, suggests a common pathologic background in localized scleroderma and SSc. The two diseases may represent two ends of a continuous spectrum of the disease such as systemic and cutaneous lupus erythematosus. Our case may represent the intermediate case of localized scleroderma and SSc.

Localized scleroderma (22) and SSc (23) have been observed in human patients after exposure to organic solvents. Our patient had been exposed to organic solvents 9 years before the onset of the disease. Although there was a long interval, we cannot deny the possibility that those agents were the provoking factor in our case.

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