

DIFFUSE FASCIITIS WITH EOSINOPHILIA: HISTOLOGICAL AND ELECTRON MICROSCOPIC STUDY

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Abstract. A female case of diffuse fasciitis with eosinophilia (or eosinophilic fasciitis) is reported. This disease is characterized by suddenly developed circumscribed subcutaneous indurations on the extremities, hyalinized fibrosis of the fascia and peripheral eosinophilia. Our patient further displayed Raynaud's phenomenon preceded by thrombophlebitis, and histological and electron microscopical features of her subcutaneous hyalinized area centering at the fascia closely resembled those of morphaea.

Key words: Fasciitis; Morphaea; Histopathology; Electron microscopy

In 1974, Shulman (21) reported two patients with scleroderma-like, underlying tissue-bound taut skin, which was particularly marked on the legs and arms. Both of them showed peripheral blood eosinophilia, elevated ESR and hypergammaglobulinemia. Histologically there was a marked thickening of the fascia with a striking inflammation. However, according to Shulman, it differed from scleroderma by the absence of Raynaud's phenomenon and by the lack of any evidence of visceral manifestations of scleroderma. Furthermore, the biopsy specimen failed to disclose any sclerodermatous changes in the corium. The syndrome was designated "diffuse fasciitis with eosinophilia". Since then, similar cases have been described (1, 2, 3, 4, 5, 6, 10, 16, 20, 22, 23, 24, 25, 26), but recent reports have occasionally suggested an intimate relationship between the fasciitis and scleroderma (1, 3, 4, 5, 20, 26). In one of Rodnan's cases (20), dermal sclerosis with subcutaneous fibrosis was distinguished. Caperton and Hathaway (5) mentioned that the syndrome may be that of scleroderma with eosinophilia, as a biopsy taken from the late lesion revealed a typical picture of scleroderma.

In the present communication, we report a case of diffuse fasciitis with eosinophilia, in which light and electron microscopic features of the hyalinized

subcutaneous tissue including the fascia resembled those of morphaea. Furthermore, Raynaud's phenomenon was observed in our patient, as earlier described by Bennett and co-workers (3).

CASE HISTORY

This 46-year-old woman was first seen in March 1976 at our clinic because of her skin hardness. There was no particular matter in the family history. At the age of 28, 42 and 43 years, she underwent surgery because of otitis media, breast cancer and lung abscess, respectively. At the age of 40 years, she was admitted to the Department of Medicine, Tokyo University for recurrent thrombophlebitis of the skin and peripheral eosinophilia (16%). A biopsy of skin taken from the left hand confirmed the clinical diagnosis along with perivascular eosinophilia. In February 1973, she first noticed pain in the knee joints. Four months later, pallor of fingers of both hands in cold weather was noted. About the same date, an erythematous swelling with tenderness suddenly developed on the extensor aspects of the thighs and then also on the upper arms. Ten days later, when the erythema and pain disappeared, the lesional skin became indurative. These attacks leading to skin induration were at first observed only a few times during the course of a year. The number of attacks had increased year by year up to her first visit to our clinic. In the meanwhile, joints of the elbow and fingers of the left side were gradually contracted in a flexed position, and the dorsum of the left hand was often ulcerated. Stiffness of the right knee and both shoulders also began. A corticosteroid was administered orally for a while, but it appeared ineffective at that time.

Examination

Around both thighs and upper arms, particularly on the extensor aspects, the skin showed a marked, localized induration with irregular skin surface composed of depressions and ridges (Fig. 1). The left elbow, when slightly flexed, was not fully extensible. Livedo reticularis was observed on the lower extremities. Furthermore, a marked edematous swelling with subcutaneous induration as well as deformity following chronic ulcerations was observed around the left hand. In the lower part of the abdomen there was a sharply-outlined, egg-sized indurative area of skin with a clinical resemblance to morphaea. The face, feet and right hand were spared. Systemic signs were not noted.



Fig. 1. Clinical picture. Irregular skin surface due to subcutaneous indurations on the left upper arm.

Investigations

Normal white blood cells counts with 14 to 19% eosinophils. No microlilaria or worms' eggs were found in the blood or feces, respectively. Neither hemorrhagic diathesis nor coagulation disturbance was observed. ESR 28 mm/h. Urinalysis showed no pathological alteration. Serum protein electrophoresis, immunoglobulins and fibrinogen concentrations and complement levels as well as serum glucose, creatine phosphokinase, aldolase, GOT, GPT and lactic dehydrogenase were all in the normal range. Rheumatoid factor, STS, antinuclear antibody (immunofluorescent), anti-DNA antibody (latex) and Mantoux reaction proved negative. The patient was not sensitized to DNCB. Electromyography revealed an interference pattern with low amplitude NMU voltage. Roentgenography of the chest and esophagus did not give any findings indicative of systemic scleroderma, although the pulmonary function test revealed a mild restrictive-obstructive change.

Treatment

The patient was initially treated with 20 mg of prednisolone per day with gradually decreased dosage over the next 2 years. Sclerosis-inducing attacks were com-

pletely inhibited and the hardness of the skin was considerably improved. The morphaea-like lesion on the lower abdomen disappeared after the treatment, although peripheral eosinophilia has persisted.

MATERIAL AND METHODS

Skin biopsies were obtained from the indurative skin of the left upper arm in 1976 (specimen A) and the left thigh in 1978 (specimen B). A part of the specimen was fixed in a formaldehyde-ethanol (1:9) solution containing 1% cetyltrimethylammonium bromide for 24 h at 4°C. After dehydration, the material was embedded in paraffin. Sections were stained with H. E., colloidal iron-PAS, van Gieson, and Weigert. For electron microscopic examinations, a part of the remaining skin specimen was fixed in 2.5% glutaraldehyde, 2% OsO₄ in 0.14 M Veronal acetate buffer (pH 7.4) at 4°C for 2 h, dehydrated with ethanol, and embedded in Epon 812, then fine-sectioned and double-stained with uranyl acetate-lead citrate. Observed with a JEOL JEM 100 C electron microscope. In addition, the remaining specimen was stained with ruthenium red following the Luft's procedure (18).

RESULTS

1. Histopathological findings

Specimen A showed considerable interstitial edema between normal-appearing collagen bundles of the dermis, while specimen B revealed moderately swollen collagen bundles in the middle and lower corium. There was no increase in acid mucopolysaccharide reaction. The pilosebaceous structure and sweat gland appeared normal. In both of the specimens, marked changes were observed in the underlying subcutaneous tissue (Fig. 2a): the adipose tissue showed evidence of new collagen formation, with increased fine collagen bundles between fat cells. Furthermore, specimen A demonstrated a picture of panniculitis with a moderate cellular infiltrative around a fat cell group composed of many fat-phagocytotic histiocytes and a few lymphocytes. Eosinophils were not present. The deeper tissue was replaced by markedly hyalinized connective tissue. The hyalinization was seen rather as spotty or nodular than as diffuse form (Fig. 2b), as in morphaea (11). The strongly hyalinized area (the centre of the nodular sclerosis) showed an increase in PAS reaction with diminished number of elastic fibres, whereas in its peripheral area one could see an increase in colloidal iron-positive mucopolysaccharide reaction and aggregated coarse elastic fibres (Fig. 2c). The connective tissue cells tended to decrease with pro-

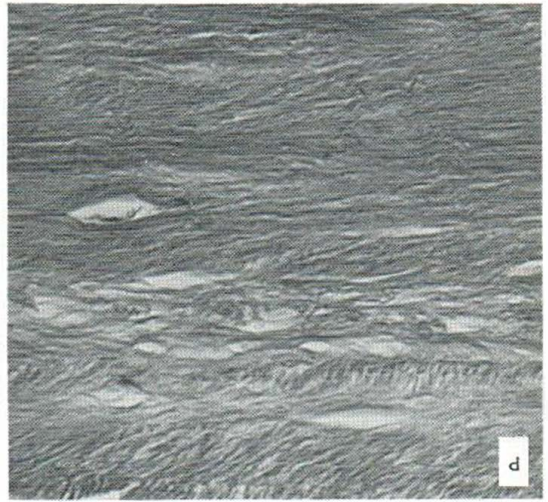
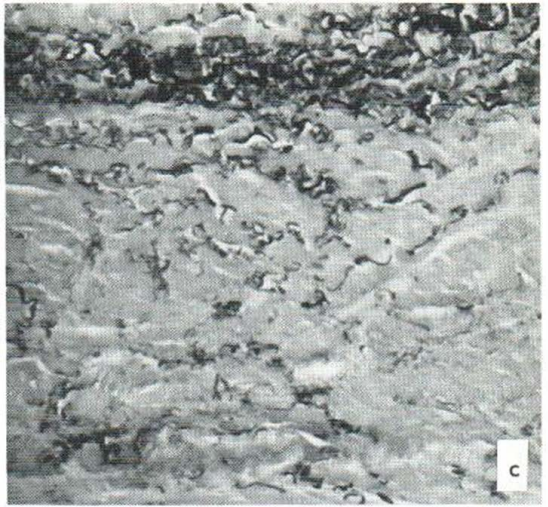


Fig. 2. Skin specimen taken from the left thigh. (a) General view. Skin (1), subcutaneous tissue (2) and fascia (3). HE stain, $\times 3$. (b, c) Subcutaneous tissue, showing nodular-shaped sclerotic fibrosis. (b) HE stain, (c) Weigert stain, $\times 130$. (d) Markedly thickened fascia. HE stain, $\times 130$.

gression of the hyalinization. The walls of the blood vessels here were thickened, and the lumen was frequently found to be occlusive. The fascia furthermore demonstrated a marked fibrotic thickening: it was rather diffusely changed and nearly

acellular (Fig. 2d). Fragmented elastic fibres were rarely found. The PAS stain proved positive, but the hyalinized fascia showed no positive acid mucopolysaccharide reaction. Furthermore, there were large quantities of calcium deposits in the fas-

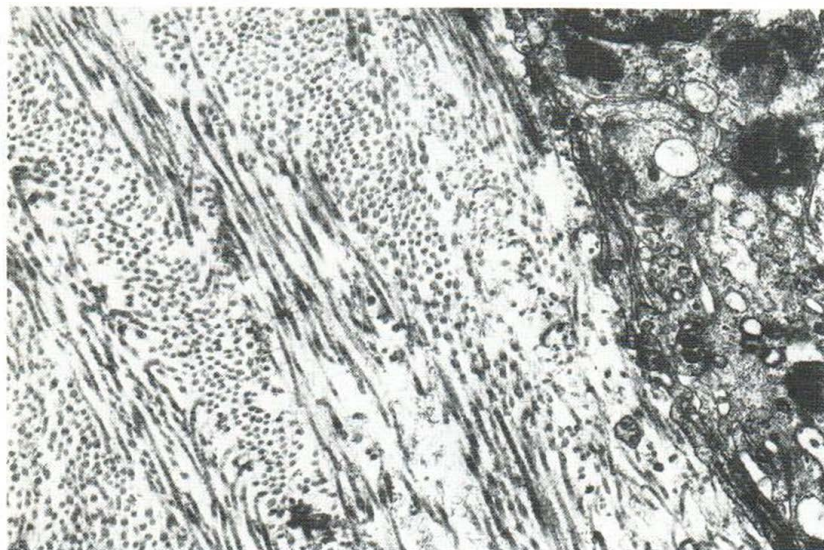


Fig. 3. Electron micrograph of the subcutaneous tissue showing bundles of collagen fibrils arranged in a plywood fashion. Uranyl acetate-lead citrate stain. $\times 15\,040$.

cia. By routine immunofluorescence technique, human immunoglobulins and C3 were not detected in any examined areas of the skin, subcutaneous tissue, or fascia.

Electron microscopic features

The hyalinized subcutaneous, sclerodermatous area demonstrated an increase in thin collagen fibrils, ranging from $250\text{ \AA}$ to $300\text{ \AA}$ in diameter, and generally presented random arrangements scarcely with a compact bundle formation, while in some areas the collagen fibrils were densely arranged in a

plywood fashion (Fig. 3). There were few aggregates of filaments attached to the collagen fibrils, in contrast to systemic scleroderma (9, 12). Fibroblasts revealed a cystic dilatation of endoplasmic reticulum. The ultrastructure of elastic fibres appeared normal. Ruthenium red staining of this area showed a poor picture due to a technical error. The fascia demonstrated virtually the same changes as the overlying tissue. As compared with the normal fascia, that of the patient showed irregular arrangements of collagen fibrils, sometimes abnormally bent, as well as an increase in thin fibrils of

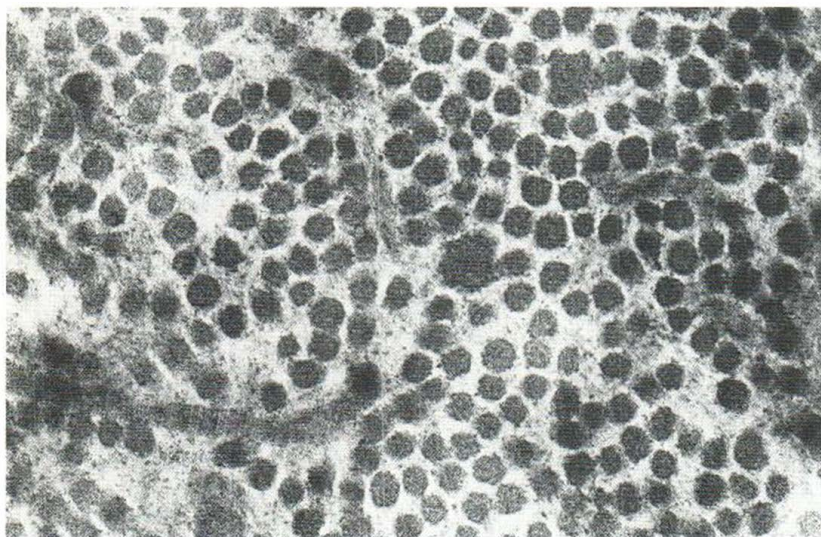


Fig. 4. Electron micrograph of the fascia showing increased fine collagen fibrils as well as appearance of abnormal thick fibrils. Uranyl acetate-lead citrate, $\times 65\,680$.

Table I. Ultrastructural features of eosinophilic fasciitis, morphaea and systemic scleroderma

+: actually observed, -: scarcely or not present

	Eosinophilic fasciitis	Morphaea	Systemic scleroderma
Arrangement of collagen fibrils in random fashion	+	+	+
Increase in thin collagen fibrils	+	+	+
Appearance of abnormal thick collagen fibrils	+	-	-
Irregular contours of collagen fibrils on cross sections due to aggregations of filaments attached to the fibrils	-	-	+
Increase in ruthenium red-positive granules around the collagen fibrils	-	+	+
Increase in small elastic fibres	+	+	+
Enlarged rough endoplasmic reticulum in fibroblasts observed	+	+	+

350–450 Å in diameter (Fig. 4). In addition, in the fascia, thick fibrils about 1800 Å in diameter were observed here and there. Fibroblasts, however, were rarely found. There were many small elastic fibres. Concerning ruthenium red-positive components, no increase was seen in granules around collagen fibrils or threads with knobs in the intercellular matrix. Table I summarizes the electron microscopic features of the hyalinized tissue in this disease.

DISCUSSION

Since the first description by Shulman (21), more than 20 cases have been reported to date. In all of them the extremities were bilaterally affected. Also the trunk was sometimes involved. The face, hands and feet were generally spared. After a transient inflammatory redness, a scleroderma-like skin hardness firmly bound to the underlying tissue suddenly developed to produce irregular skin surface. The skin changes occurred frequently following unaccustomed exercise (10, 22, 25). Clinical features and laboratory findings in our patient were nearly identical with those of previous cases. The differences consisted in involvement of the left hand, the presence of Raynaud's phenomenon and lack of hypergammaglobulinemia in our patient, although Caperton and co-workers (6) described how the hypergammaglobulinemia may spontaneously resolve in the clinical course. Besides, our patient had no unusual exercise immediately before the de-

velopment of the skin hardness, since she was hospitalized at the time. In spite of these differences, the clinical features of our patient were certainly unique and confirmed this disease immediately, as indicated unanimously in the previous reports. Nevertheless, we simultaneously considered the possibility of scleroderma: particularly generalized morphaea was at first considered because of her bilaterally involved localized skin indurations and the presence of Raynaud's phenomenon (27). Furthermore, morphaea-like lesion was seen on the lower abdomen, as also observed in the cases of Rodnan and co-workers (20) and Caperton and co-workers (5, 6). As for alterations in the visceral organs, most patients reported were devoid of manifestations characteristic of systemic scleroderma, but Caperton and co-workers noted pulmonary fibrosis and esophageal dysmobility in one of their patients (6). A patient with Raynaud's phenomenon and mild pulmonary restrictive changes was also described by Bennett and co-workers (3).

Our patient showed a mild restrictive-obstructive disturbance in the pulmonary function test. However, peripheral eosinophilia is very unusual for morphaea (14), whereas all patients with fasciitis have shown persistent peripheral eosinophilia. Although peripheral eosinophilia might be seen in the allergic reaction of the Arthus phenomenon type (7) and in our patient was preceded by thrombophlebitis accompanied by tissue- and peripheral eosinophilia, the significance of peripheral eo-

sinophilia in this fasciitis remained obscure in the present study. Concerning the histological picture, a marked hyalinized fibrosis was observed in the subcutaneous tissue and fascia of our patient in accordance with the description of previous reports. Further, the deep corium showed a slightly sclerotic change, as also noted in some papers (1, 5, 20, 26). Tissue eosinophilia was not present, whereas Shulman and others (21, 23, 25) described an eosinophilic infiltration in the lesion. Moreover, in the present study, the subcutaneous tissue superior to the fascia indicated a nodular-formed sclerotic pattern, and PAS-positivity was increased toward the centre of each of the sclerotic areas. The elastic fibres were reversely diminished in number toward the centre of hyalinized area. The blood vessels showed a thickening of the walls, frequently with occlusive lumen. These features may coincide with the sclerotic changes observed in morphea or generalized morphea (11, 17, 19). Although the hyalinization of the fascia was recognized as diffuse rather than as nodular form, the behaviour of the PAS-reaction or Weigert stain of the fascia was the same as that of the overlying subcutaneous tissue and, on the basis of the histochemical findings, it would appear that the hyalinized changes affected the fascia most strongly, leaving no initial sclerotic change.

On the other hand, there are no available data regarding the ultrastructural features of diffuse fasciitis with eosinophilia. The present work demonstrated that the hyalinized tissue—inclusive of the fascia—was characterized by randomly arranged collagen fibrils and an increase in fine fibrils. These findings also may indicate the change in morphea or generalized morphea rather than a simple fibrosis (9, 15). Occasionally, the collagen fibrils of the subcutaneous tissue were arranged in a plywood fashion as noted by Fleischmajer and Prunieras in the skin of generalized morphea (9). The significance of the appearance of thick collagen fibrils in the hyalinized fascia is unknown, however.

To summarize, diffuse fasciitis with eosinophilia is a distinct syndrome characterized by its unique skin-hardening process, a marked hyalinization of the subcutaneous tissue centering at the fascia and peripheral eosinophilia. However, the morphological resemblance of the hyalinized connective tissue to morphea should be attentively considered and further examined in connection with the pathogenesis of this disease.

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