Eosinophilic fasciitis

Case report and review of the literature

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SUMMARY Eosinophilic fasciitis is a recently described rheumatic disease, some 20 cases having been reported in abstract form. Previous descriptions have stressed the localized nature of skin involvement, the absence of visceral changes or Raynaud's phenomenon, an association with hypergammaglobulinaemia and eosinophilia, and a good response to corticosteroid therapy. The most conspicuous feature of this entity has been a massive thickening of the subcutaneous fascia, when an adequate (skin down to muscle) biopsy has been performed. We report another case conforming to these general features, with the exception that Raynaud's phenomenon was a prominent symptom. A critical review of the literature suggests that eosinophilic fasciitis should tentatively be regarded as a variant of scleroderma.

In 1974 Shulman described 2 men with a scleroderma-like disease of the extremities associated with eosinophilia and hypergammaglobulinaemia. Biopsy showed a conspicuous thickening of the fascia, between the subcutis and muscle, with an intense infiltration of lymphocytes and plasma cells. The distribution of the changes, predominantly in the forearms with sparing of the fingers, normal skin, absence of Raynaud's phenomenon and visceral changes, and a good response to corticosteroid therapy, suggested that this was a distinct rheumatic disease syndrome. There have been six other abstracts to date recording a similar disease spectrum (see Table 1). On the basis of the striking histological changes in the subcutaneous fascia, Rodnan has proposed that this condition be termed 'eosinophilic fasciitis' (Rodnan *et al.*, 1975b). We report here a further case conforming to the general features of this syndrome, with the exception that Raynaud's phenomenon was a prominent symptom. A critical review of the literature is presented to explore the justification of regarding eosinophilic fasciitis as a distinct clinical entity.

Case report

A 31-year-old white male store manager was initially

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Table 1 Previous reports of eosinophilic fasciitis

Reference	No. of patients	Clinical and pathological features
Shulman (1974)	2	Localized induration of skin and subcutaneous tissue associated with a blood eosinophilia and hypergammaglobulinaemia; biopsies showed thickened fascia with lymphocyte and plasma cell infiltration
Shulman (1975)	2 original + 2 new cases	Similar clinical and histological features to initial description
Rodnan <i>et al.</i> (1975a)	7	Similar findings to initial description; in 2 cases the lower abdomen was involved, in another the face; biopsy findings included panniculitis and superficial myositis as well as fasciitis
Rodnan <i>et al.</i> (1975b)	6	Sudden onset of skin oedema with a hidebound appearance with patches of morphea; similar blood and biopsy findings to other reports
Caperton <i>et al.</i> (1975)	5	Localized subcutaneous induration in thighs, calves, and forearms; biopsy showed fasciitis with perivascular mononuclear cell infiltrate and a superficial myositis
Schumacher (1975)	1	Stresses that eosinophilia and hypergammaglobulinaemia may be transient; synovitis may persist and restrictive lung disease may develop
Caperton <i>et al.</i> (1976)	Follow-up of 5 original + 3 new cases	

seen in the outpatient clinic at the University of Chicago in May 1976. He gave an 18-month history of progressive aching and burning in his hands and fingers associated with diminished strength. He had been subject to severe Raynaud's phenomenon for

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the past 2 years. Intermittent stiffness and arthralgia in the shoulders, elbows, ankles, and feet had been present for one year. There were no symptoms to suggest a generalized visceral involvement. The past history and family background provided no further relevant information. Onset of the symptoms was insidious and there was no obvious episode of unusual exertion as a preceding event, as has been noted in some cases (Shulman, 1975). He had not been on any medications apart from simple analgesics.

On physical examination he was noted to be of a slim athletic build, notably anxious, with conspicuous Raynaud's phenomenon at room temperature (about 74°F). The most striking change was an induration of the skin over both forearms; the skin was tightly bound to the underlying fascia and appeared pale and relatively devoid of hair. These skin changes did not extend into the hands although there were early flexion contractures of the fingers and both elbows. Similar but less marked changes were seen over the ankles and feet. There was a moderately active synovitis involving several proximal and distal interphalangeal and metacarpal joints. Telangiectasia, calcinosis, or tendon rubs were not present, and apart from the forearms, muscular strength was normal. Blood pressure was 130/80 mmHg and a general physical examination was normal.

Investigations showed haemoglobin 15.5 g/dl; white cells 9400/mm³ ($9.4 \times 10^9/l$) with neutrophils 52%, lymphocytes 26%, eosinophils 10%, monocytes 9%, basophils 1%. Sedimentation rate (Westergren) 10 mm/h; SCAT and latex fixation tests, negative; antinuclear factor negative; complement profile normal. Serum protein electrophoresis, total 81 g/l (normal 65–79), albumin 40.6 g/l (normal 32–50), globulins 40.4 g/l (normal 20–38), alpha₁-globulin 2.7 g/l (normal 1.0–5.0), alpha₂-globulin 8.3 g/l (normal 3.0–11), beta globulin 11.1 g/l (normal 4.0–11), gamma globulin 18.4 g/l (normal 3.0–17); quantitative immunoglobulins, IgA 3.16 g/l (normal 0.8–2.0), IgG 19.3 g/l (normal 0.7–11.13), IgM 0.7 g/l (normal 0.9–1.7). Urinalysis normal; chest x-ray normal; fine detail hand x-rays normal; pulmonary function tests, mild restrictive abnormality (patient smoked 20–30 cigarettes per day), normal carbon monoxide diffusing capacity; vitamin B12 level and a Schilling's test normal; barium swallow and upper gastrointestinal x-rays normal; oesophageal motility studies, reduced high pressure zone in distal portion with normal motility.

In view of the localized nature of the skin involvement, absence of visceral changes, and associated eosinophilia and hypergammaglobulinaemia a 'full thickness' (down to underlying muscle) skin biopsy

was taken from the right forearm. This showed a massive thickening of the deep subcutaneous fascia (Fig. 1) with collagenous hypertrophy and an intense infiltration of lymphocytes and plasma cells (Fig. 2). Cellular infiltration was most prominent in a perivascular distribution; eosinophils were not a prominent feature. Immunofluorescent studies, with fluorescein conjugated anti IgG, IgM, IgA, and C3 showed only a nonspecific staining of collagen bundles and a scattered cytoplasmic staining for IgG (assumed to be in plasma cells).

The clinical and laboratory features, with the exception of Raynaud's phenomenon, were thought

Fig. 1 Full thickness biopsy (skin to deep fascia) from right forearm, showing normal skin and subcutaneous adipose tissue, with a gross thickening of the subcutaneous fascia. $\times 8$.

Fig. 2 High power view of thickened subcutaneous fascia, showing infiltration with plasma cells and lymphocytes in a mainly perivascular distribution. $\times 300$.

to be consistent with what has been termed 'eosinophilic fasciitis', and a trial of corticosteroids was started. Initially prednisone 30 mg/day was given, with dramatic results. The Raynaud's phenomenon, stiffness, and joint pains all regressed completely within 12 hours of starting therapy. The hypergammaglobulinaemia returned to normal, 30 g/l (normal 20–38) after 4 months, and the eosinophilia within one month. Over the course of 6 months of follow-up the affected skin had returned to near normal consistency.

Discussion

The strict categorization of disease is inevitably thwarted by a self-evident law of nature: 'there is an exception to every rule'. This is particularly true in those diseases of undetermined aetiology where no unifying concept can be evoked. Scleroderma is a disease of unknown cause characterized by hardness of the skin with fibrosis and loss of smooth muscle leading to progressive visceral dysfunction. It is

difficult to define succinctly, though its classical form is recognized by relentlessly progressive skin changes.

Review of many case histories shows that there is a wide divergence of symptoms and morbidity. At one end of the spectrum there is acrosclerosis, usually slowly progressive with minimal systemic involvement and a good progress (Sellei, 1936; O'Leary and Waisman, 1943; Stava, 1959); at the other extreme there is a rapidly progressive scleroderma with extensive visceral involvement usually with a fatal fulminant course (Osler, 1892; Goetz, 1945; Tuffanelli and Winkelmann, 1962). Vascular involvement is a common accompaniment: Raynaud's phenomenon is present in about 90% of patients (Goetz, 1945) often antedating the skin and visceral changes by several years (Bennett *et al.*, 1971). Telangiectasia (Schimke *et al.*, 1967; Rowell, 1968), abnormal capillary loops (Redisch *et al.*, 1970), pulmonary hypertension (Conner and Bashour, 1961; Sackner *et al.*, 1964), and renal artery involvement (Moore and Sheehan, 1952; Rodnan *et al.*, 1957; Barbieri *et al.*, 1966) are further manifestations of widespread circulatory disease.

Scleroderma occurs in conjunction with overlap syndromes (Tuffanelli and Winkelmann, 1961; Dubois *et al.*, 1971; Sharp *et al.*, 1972; Dubois, 1974), calcinosis (Thibierge and Weissenbach, 1910; Brooks, 1934), visceral involvement without skin changes (Crown, 1961; Rodnan and Fennell, 1962), pneumonitis (Rodnan *et al.*, 1967), malignancy (Tompkin, 1969), and childhood variants (Jaffe and Winkelmann, 1961; Kass *et al.*, 1966), as well as scleroderma-like changes in Werner's syndrome (Epstein *et al.*, 1966), cutaneous amyloid (Loewenthal and Falkson, 1965) and carcinoid tumours (Fries *et al.*, 1973) (Table 2). The newly recognized syndrome of eosinophilic fasciitis is considered against this broad background.

Five features of eosinophilic fasciitis which have been noted by previous authors are (i) localized nature of the skin involvement, (ii) pronounced thickening of the subcutaneous fascia, (iii) absence of visceral changes and Raynaud's phenomenon.

Table 2 Scleroderma syndromes

Morphea
Acrosclerosis
Rapidly progressive systemic sclerosis
Overlap syndromes with other rheumatic diseases
Mixed connective tissue disease
CRST (or Thibierge-Weissenbach) syndrome
Systemic sclerosis without skin involvement
Scleroderma and pneumoconiosis
Scleroderma and malignancy
Childhood scleroderma
Scleroderma-like changes in Werner's syndrome, cutaneous amyloid and carcinoid tumours
Eosinophilic fasciitis?

(iv) association with eosinophilia and hypergammaglobulinaemia, and (v) beneficial response to corticosteroids.

Localized skin involvement, within the scleroderma diathesis, usually denotes morphea (Crocker, 1880a; Christiansen *et al.*, 1956). This is seen as a sharply localized plaque of sclerotic skin often depressed and demarcated from the surrounding skin by a lilac coloured margin. Morphea is usually associated with an absence of visceral involvement and a correspondingly good prognosis, although progression to a more generalized form has been noted by several authors (Hutchinson, 1822; Crocker, 1880b; Curtis and Jansen, 1958). Localized skin involvement in eosinophilic fasciitis does not have the well demarcated borders or atrophic appearance of morphea, rather there is an initial swelling of one or more limbs and sometimes the face, which progresses to an induration of the skin and subcutaneous tissues with flexion contractions of contiguous joints. Unlike classical scleroderma the hands are not prominently affected. Onset is rapid, often associated with recent muscle exertion, and the changes tend to remain localized to the initial areas of involvement. It is only in this latter respect that eosinophilic fasciitis resembles morphea, the actual skin changes being similar to acute onset diffuse scleroderma.

Pronounced thickening of the subcutaneous fascia is generally considered to be the most distinctive feature of eosinophilic fasciitis. This thickening is due to striking proliferation and hypertrophy of collagen which is densely infiltrated with plasma cells and lymphocytes. The skin itself shows no changes on light microscopy. To make a histological diagnosis it is therefore necessary to take a biopsy which includes skin and all subcutaneous tissues down to muscle. This is important in the differential diagnosis, as a somewhat similar clinical picture is seen in scleromyxoedema (lichen myxoedematosus). The biopsy in this condition shows a mucinous, metachromatic infiltration and fibrosis of the upper dermis; there is often an associated bone marrow plasmacytosis and a unique serum globulin (James *et al.*, 1967). This differentiation is of some practical importance as the prognosis is poor with little tendency to spontaneous improvement or response to steroids. Early in the course of scleroderma skin biopsy is often not diagnostic. Full thickness biopsies, as advocated for the diagnosis of eosinophilic fasciitis, are not routine in the usual investigation of scleroderma. When such biopsies are performed they show that the most striking histological changes in early scleroderma occur in the subcutaneous tissues (Fleischmajer *et al.*, 1971), which are found to be replaced by abnormal connective

tissue consisting of immature collagen, increased ground substance, and a cellular infiltrate of fibroblasts and lymphocytes. These findings resemble the histological features of eosinophilic fasciitis and raise the question of their usefulness as a differentiating feature between the two diseases.

The absence of visceral changes and Raynaud's phenomenon have been stressed in most reports of eosinophilic fasciitis and have obvious prognostic implications. In our case, Raynaud's phenomenon was a prominent feature and, curiously enough, responded to corticosteroid therapy; we are not aware of such a response previously. A few patients with a clinical picture similar to eosinophilic fasciitis have now been reported with the associated visceral changes of restrictive lung disease and pulmonary fibrosis (Caperton *et al.*, 1976). The same author reports two further variations: one case of fasciitis with massive oedema and eosinophilia but no cutaneous induration, the other case with patchy skin induration and eosinophilia without fasciitis. These variations from the 'classical' concept of eosinophilic fasciitis may represent extremes of a wide disease spectrum which will only be fully recognized by the use of full thickness skin biopsies.

The occurrence of eosinophilia is often the first clue that the patient may have eosinophilic fasciitis. There are no well documented reports of an association of scleroderma and eosinophilia, only one paper reporting normal eosinophil counts in both progressive systemic sclerosis and localized scleroderma (Roder and Pinzer, 1972). The nomenclature of disease states associated with eosinophilia is somewhat chaotic (Roberts *et al.*, 1970). A condition characterized by peripheral blood eosinophilia and multisystem infiltration has been termed 'disseminated eosinophilic collagen disease' (Engfeldt and Zetterstrom, 1956; Odeberg, 1965). It is therefore important that patients with eosinophilia and a scleroderma-like syndrome have a full thickness skin biopsy if the diagnosis of eosinophilic fasciitis is to be substantiated.

The occurrence of hypergammaglobulinaemia in eosinophilic fasciitis is a less specific feature, occurring in 25% to 50% of patients with scleroderma (Rodnan *et al.*, 1957; Corcos *et al.*, 1961; Clark *et al.*, 1971), as well as in other rheumatic and nonrheumatoid conditions (Swartz, 1959; Fleischmajer, 1964). All the patients so far described with eosinophilic fasciitis have had negative tests for antinuclear antibodies and rheumatoid factor. This is to be compared with a 60% incidence of antinuclear antibodies (Rothfield and Rodnan, 1968) and a 35% incidence of positive rheumatoid factors (Clark *et al.*, 1971) in scleroderma.

The beneficial response to corticosteroids, the occurrence of spontaneous remission, and the generally favourable prognosis, are good reasons for considering eosinophilic fasciitis as a distinct clinical entity. However, such claims are probably premature in the light of the natural history of progressive systemic sclerosis (Rodnan, 1963). The histological changes in the subcutaneous tissues, the development of flexion contractures, and the presence of Raynaud's phenomenon (present case), and pulmonary and oesophageal involvement (Caperton *et al.*, 1976) are persuasive reasons for considering eosinophilic fasciitis as a variant of scleroderma. The oedematous skin and joint pains of scleroderma often respond to corticosteroids, but over the course of many years the disease progresses relentlessly and no therapy has proved to be effective (Bennett *et al.*, 1971), though spontaneous remission has been reported in a few cases (Tuffanelli and Winkelmann, 1961). Only after many cases of eosinophilic fasciitis have been identified, and its long-term outcome is fully evaluated, will the prognosis of such a diagnosis be known.

It seems reasonable now to consider eosinophilic fasciitis as a distinct rheumatic disease syndrome. Many of its features bear a close resemblance to scleroderma, and it seems logical to classify it tentatively as a scleroderma variant. Whether such a classification is tenable will depend upon careful clinical observation over many years.

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Addendum

Since writing this report another case of eosinophilic fasciitis has been recorded: Ansell, B. M., Nasseh, G. A., and Bywaters, E. G. L. (1976). Scleroderma in childhood. *Annals of the Rheumatic Diseases*, **35**, 189-197.

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