Eosinophilic fasciitis

Case report and review of the literature

ROBERT M. BENNETT, ANNE HERRON, AND LOUISE KEOGH

From the Department of Medicine, University of Chicago, Chicago, Illinois, USA

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 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

Table 1 Previous reports of eosinophilic fasciitis

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Clinical and pathological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shulman (1974) 2</td>
<td>Localized induration of skin and subcutaneous tissue associated with a blood eosinophilia and hypergammaglobulinaemia; biopsies showed thickened fascia with lymphocyte and plasma cell infiltration</td>
<td></td>
</tr>
<tr>
<td>Shulman (1975) 2 original + 2 new cases</td>
<td>Similar clinical and histological features 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</td>
<td></td>
</tr>
<tr>
<td>Rodnan et al. (1975a) 7</td>
<td>Sudden onset of skin oedema with a hidebound appearance with patches of morphea; similar blood and biopsy findings to other reports</td>
<td></td>
</tr>
<tr>
<td>Rodnan et al. (1975b) 6</td>
<td>Localized subcutaneous induration in thighs, calves, and forearms; biopsy showed fasciitis with perivascular mononuclear cell infiltrate and a superficial myositis</td>
<td></td>
</tr>
<tr>
<td>Caperton et al. (1975) 5</td>
<td>Stresses that eosinophilia and hypergammaglobulinaemia may be transient; synovitis may persist and restrictive skin disease may develop</td>
<td></td>
</tr>
<tr>
<td>Schumacher (1975) 1</td>
<td>Caperton et al. (1976) Follow-up of 5 original + 3 new cases</td>
<td></td>
</tr>
</tbody>
</table>
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 × 10⁹/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 1.0–3.0), 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...
leading the disease of unknown cause. In the other disease concept, one of the strictest and most dramatic examples is gammaglobulinaemia (12), within which lymphocytes may be affected. The lymphocytes may be involved in a main perivascular distribution.

**Fig. 2** High power view of thickened subcutaneous fascia, showing infiltration with plasma cells and lymphocytes in a mainly perivascular distribution. ×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, 1934; 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 (Schinke et al., 1967; Rowell, 1966), 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 Weisenbach, 1912; Brooks, 1934), visceral involvement without skin changes (Crown, 1961; Rodnan and Fennell, 1965; 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

<table>
<thead>
<tr>
<th>Morphea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrosclerosis</td>
</tr>
<tr>
<td>Rapidly progressive systemic sclerosis</td>
</tr>
<tr>
<td>Overlap syndromes with other rheumatic diseases</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
</tr>
<tr>
<td>CRS (or Thibierge-Weisenbach) syndrome</td>
</tr>
<tr>
<td>Systemic sclerosis without skin involvement</td>
</tr>
<tr>
<td>Scleroderma and pneumoniosus</td>
</tr>
<tr>
<td>Scleroderma and malignancy</td>
</tr>
<tr>
<td>Childhood scleroderma</td>
</tr>
<tr>
<td>Scleroderma-like changes in Werner's syndrome, cutaneous amyloid and carcinoid tumours</td>
</tr>
<tr>
<td>Eosinophilic fasciitis</td>
</tr>
</tbody>
</table>
Eosinophilic fasciitis 357

(iv) association with eosinophilia and hypergamma-
globulinaemia, and (v) beneficial response to
corticosteroids.

Localized skin involvement, within the sclero-
derma 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 myxoedematous). The
biopsy in this condition shows a mucinous, meta-
chromatic 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 diagnosis 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 eosino-
philic fasciitis, are not routine in the usual investiga-
tion of scleroderma. When such biopsies are per-
formed they show that the most striking histological
changes in early scleroderma occur in the sub-
cutaneous 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 fibro-
blasts and lymphocytes. These findings resemble the
histological features of eosinophilic fasciitis and
raise the question of their usefulness as a differenti-
tiating 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
cue that the patient may have eosinophilic fasciitis.
There are no well documented reports of an associa-
tion of scleroderma and eosinophilia, only one paper
reporting normal eosinophil counts in both pro-
gressive systemic sclerosis and localized scleroderma
(Roder and Pinzer, 1972). The nomenclature of
disease states associated with eosinophilia is some-
what 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 hypergamma globulinaemia in
eosinophilic fasciitis is a less specific feature,
occuring in 25% to 50% of patients with sclero-
derma (Rodnan et al., 1957; Corcos et al., 1961;
Clark et al., 1971), as well as in other rheumatic and
nonrheumatoid conditions (Swartz, 1959, Fleisch-
majer, 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 anti-
nuclear 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.

This work was supported by the Illinois chapter of the Arthritis Foundation and by clinical centre grant from the National Arthritis Foundation.

Addendum


References


