Eosinophilic Fasciitis

A Pathologic Study of Twenty Cases

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This report presents a detailed light-microscopic evaluation of biopsies obtained from 20 patients with eosinophilic fasciitis, a newly recognized disorder characterized by inflammation and thickening of the deep fascia, hypergammaglobulinemia, and peripheral and tissue eosinophilia. Early in the course of the disease, the deep fascia and lower subcutis are edematous and infiltrated with lymphocytes, plasma cells, histiocytes, and eosinophils; these features are associated with impressive peripheral eosinophilia. As the illness progresses, these structures and eventually the dermis become collagenized, thickened, and sclerotic. Tissue eosinophilia may be focal or diffuse and is usually observed in the fascia and/or lower subcutis. Extracutaneous involvement has been limited to a chronic synovitis and tenosynovitis, the latter frequently associated with the carpal tunnel syndrome. Deposits of immunoglobulin and/or complement were found in five of eight biopsies studied by direct immunofluorescence, which suggests that an immunologic stimulus may be responsible for initiating this syndrome. Differential diagnoses are discussed. (Am J Pathol 96:493–518, 1979)

IN 1974, SHULMAN described a new scleroderma-like disorder in two men, ages 19 and 53 years, who presented with firm, taut, "bound down" skin on the extremities and were found to have peripheral eosinophilia and marked hypergammaglobulinemia.[1] Biopsies revealed a sclerotic, thickened deep fascia heavily infiltrated with lymphocytes and plasma cells, but no evidence of dermal sclerosis or myositis. Although both developed flexion contractures of the elbows and knees, neither patient exhibited Raynaud's phenomenon nor any of the visceral manifestations characteristic of progressive systemic sclerosis (PSS). One patient experienced a remission following treatment with prednisone, while the second showed only minimal improvement with this drug.

In 1975, Rodnan et al reported 7 similar patients and proposed the term eosinophilic fasciitis (EF) to be used for this syndrome because of the presence of striking peripheral eosinophilia (often 30% or more of the total leukocytes) and the finding of large numbers of these cells in the inflamed deep fascia and subcutis.[2] While additional articles have since

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appeared, enumerating the clinical and laboratory features of this disease,[3-14] a detailed description of the morphologic findings has been documented only in a few reports.[11,12,15,16] We have now seen 30 patients with eosinophilic fasciitis and in this paper wish to describe the histopathologic changes in 20 of these cases in which adequate biopsy material is available.

Materials and Methods

Ten of the 20 patients included in this report were referred to us as having either PSS (8) or PSS with atypical features (2). Five were thought to have various other disorders, including rheumatoid arthritis, dermatomyositis, mixed connective tissue disease, arthritis, and lymphoma. In only five instances was the diagnosis of EF made before referral.

All 20 individuals had biopsies showing the characteristic morphologic changes of EF to be described below. With the exception of one specimen that did not include skin and subcutis and three which did not contain muscle, all biopsies included skin, subcutis, fascia, and muscle, usually removed intact through a surgical incision. The biopsies were all obtained from areas of active disease in the following sites: forearm (12), arm (3), and leg (8). (Two patients had a second biopsy after treatment, and in one individual tissue was obtained from both forearm and arm.)

In addition to routine hematoxylin and eosin, selected specimens were stained with May–Grünwald Giemsa, Verhoef–van Gieson's elastic, Masson's trichrome, Gomori's reticulin, alcian blue, and colloidal iron with and without hyaluronidase (pH 1.0, 2.5, 4.0). Frozen sections of eight biopsies were studied by direct immunofluorescence for the presence of IgG, IgM, IgA, IgE, C3, and C4.

The biopsies were specifically evaluated for evidence of epidermal atrophy as well as fibrosclerosis of the dermis, subcutis, fascia, and muscle. In addition, the location, components, and intensity of the inflammatory reaction were noted. These features were subjectively graded as normal (0), mild (1+), moderate (2+), or severe (3+). Microscopic slides were meticulously scanned for the presence or absence of eosinophils. In the area of greatest concentration, using an American Optical microscope with a ×40 high dry objective and ×10 widefield ocular lens, eosinophils were quantified according to the following scale: 1+ = 0–2/high-power field (HPF); 2+ = 3–5/HPF; 3+ =6–9/HPF; 4+ = 10 or more/HPF.

Results

Clinical Features

The age of the 20 patients at the time of biopsy ranged from 20 to 68 years with a median of 42 years (average 43.5 years). There were 11 females and 9 males. With the exception of 1 black patient, all were white. In general, the disease was diagnosed earlier in men (average 36 years, median 35 years) than in women (average 49.5 years, median 54 years). The duration of the disease prior to the initial biopsy varied from 2 months to 2 years but was 1 year or less in 15 instances (Table 1).

The onset of illness in the great majority of these patients was marked by the occurrence of pain, swelling, and tenderness of the hands, fore-

Table 1—Summary of Clinical Features

Case	Patient	Age/race/sex	Duration of illness at time of biopsy	Biopsy site (date)	Highest recorded eosinophil count		Eosinophil count at time of biopsy		Corticosteroid treatment at time of biopsy
					%	Absolute	%	Absolute	
1	RC	61wf	1 yr	LF*	15	1275	13	1014	None
2	BA	52wf	4 mos	RA (7/70)	16	1536	4	?	Prednisone
			5 yr	RA (7/75)			0	0	Prednisone, 30 mg/d
			5 yr	RF (7/75)			0	0	Prednisone, 30 mg/d
3	WG	35wm	9 mos	RF	13	1138	1	83	?
4	AM	55wf	1 yr	LL	57	3200	17	867	None
5	SG	43wf	3 mos	RL	30	3450	26	2418	None
6	WF	40wm	4 mos	LF	—	—	8	416	None
7	HC	29wm	5 mos	RF	34	3300	34	3300	None
8	EL	23wm	2 yr	LF	30	1980	12	1044	None
9	MM	27wf	1 yr	LF	35	6066	24	2376	None
10	AH	56wf	1 1/2 yr	LF	—	—	—	320	None
11	MR	68wf	8 mos	RF	14	840	6	294	None
12	LC	26wf	6 mos	RL	53	9434	53	9434	None
13	DD	20wm	2 yr	RF	10	660	10	610	None
14	MB	68wf	—	RL	8	776	8	776	None
15	AS	58wm	2 mos	RF	7	805	7	805	None
16	GW	29wm	3 mos	LA	18	1836	18	1836	None
17	LM	35wf	1 3/4 yr	LL	21	2775	4	256	None
18	HS	54wf	4 mos	LL (8/77)	22	3412	26	2288	None
			16 mos	RF (8/78)			—	0	Prednisone, 30 mg/d
19	HR	50wm	3 mos	LL	25	2725	25	2725	None
20	RR	41bm	1 yr	LL	18	1134	15	1005	None

* LF = left forearm; RA = right arm; LL = left leg.

arms, feet, and legs. This was soon followed by the development of severe induration of the skin and subcutaneous tissues of these parts with marked limitation of motion of the hands and feet. Flexion contractures of the fingers were present in 14 cases. In 11 cases the induration of skin and the subcutis was limited to the extremities, but in 9 instances variably extensive portions of the trunk were also affected. Carpal tunnel syndrome was an early feature in 7 of these individuals. Raynaud's phenomenon, difficulty with esophageal function and other visceral manifestations of PSS were conspicuously lacking. In 8 (possibly 9) of these patients there was a record of unusual, severe exertion during a period of days to weeks preceding the onset of these complaints; in the remaining patients, however, careful questioning failed to yield any history of unusual physical activity or other trauma prior to the illness.

Eosinophilia

Peripheral eosinophilia, with total eosinophil counts ranging from 660/cu mm to a high of 9434 cells/cu mm were recorded at some time early in the clinical course in all but two cases. The total eosinophil count was greater than 1000 cells/cu mm in 14 instances. In 1 of 2 patients without proven eosinophilia but with otherwise typical clinical and histologic features of the disease, the single leukocyte and differential count done early in the course of the disease had been lost; in the other patient no counts had been obtained until after the institution of treatment with prednisone.

At the time of biopsy, 14 of the patients had peripheral eosinophilia (>600 eosinophils/cu mm) with total eosinophil counts ranging from 610 to 9434 cells/cu mm. In the remaining 6 cases the total eosinophil count was less than 600/cu mm at the time of biopsy; one of these individuals was taking prednisone (30 mg/day); two others had discontinued the use of prednisone 1–2 weeks prior to biopsy, and in one additional case without eosinophilia the patient may also have been receiving such treatment. In the remaining 2 cases in which the total eosinophil count was normal at the time of biopsy, no corticosteroid was being used.

Pathologic Examination

Gross Pathology

The most striking changes were found in the fascia, which was usually 2–15 times the normal fascia in thickness; sclerotic; gray–white, yellow–tan, or red–pink; and well demarcated but firmly adherent to the subjacent skeletal muscle. In contrast, the fascial–subcutaneous tissue inter-

face was frequently irregular, firm, and fixed due to bands of fibrocollagenous tissue radiating from the fascia into the pannicular adipose tissue. Though occasionally normal, the dermis more often appeared thickened.

Microscopic Pathology

The following microscopic observations were based upon the initial diagnostic biopsy performed on each patient (Table 2).

Epidermis

Present in 19 biopsies, the epidermis was normal in 14 and mildly atrophic in 5. In two of the latter, the atrophic changes were probably related to chronic solar exposure and/or aging rather than EF, while the remaining 3 were associated with varying degrees of dermal sclerosis. With mild dermal sclerosis, rete ridges remained intact; but with increasingly severe dermal changes, there was focal and/or diffuse loss of these structures. Areas of increased melanin deposits were occasionally present in the basal layer of the epidermis. There was no follicular keratosis or liquefactive degeneration of the basement membrane.

Dermis

The dermis was normal in 6 cases, while 13 exhibited sclerosis (4 mild, 4 moderate, and 5 severe). This fibrotic change was limited to the reticular dermis and was generally accompanied by an infiltrate of lymphocytes, plasma cells, histiocytes, and occasionally eosinophils either in a patchy periappendageal location or at the dermosubcutaneous junction. As the sclerosis increased in severity, the reticular dermis became progressively thick and hyalinized, with an associated decrease in size and number of appendages (Figures 5 and 6). Neither calcium nor mucin deposits were seen.

Subcutaneous Tissue

The interlobular fibrous septums of the subcutis, particularly in the lower half, were markedly sclerotic in eight biopsies, moderately so in four, and mildly sclerotic in four. In another three, they were inflamed and edematous but not sclerotic. The edematous appearance was due in part to an accumulation of extracellular acid mucopolysaccharides. An infiltrate of lymphocytes, plasma cells, histiocytes, and eosinophils occupied the fibrous septums or the periphery of the fat lobules or both (Figure 8). Only infrequently did the infiltrate extend into the center of the lobule. Lymphoid nodules with and without germinal centers were sometimes noted. A small lipid granuloma was identified in two biopsies;

Table 2—Summary of Pathologic Findings

Case	Patient	Epidermal atrophy (0–3+)*	Dermal (D) fibrosclerosis (0–3+)*	Subcutaneous (S) fibrosclerosis (0–3+)*	Fascial (F) fibrosclerosis (0–3+)*	Muscle (M) fibrosclerosis (0–3+)*	Site and intensity of inflammation (0–3+)*				Tissue eosinophilia (1–4+)†
							D	S	F	M	
1	RC	1+	2+	2+	2+	NPE‡	1+	3+	1+	NPE	1+
2	BA	1+ (solar)§	0	1+	1+	0	0	3+	3+	1+	2+
		1+ (solar)	0	1+	0	0	0	0	0	0	1+
		1+ (solar)	0	1+	0	0	0	0	0	0	1+
3	WG	1+	2+	2+	2+	0	0	0	1+	2+	1+
4	AM	0	3+	3+	3+	1+	1+	2+	3+	1+	4+
5	SG	0	0	0	1+	1+	0	1+	0	1+	1+
6	WF	0	2+	3+	3+	1+	1+	2+	2+	1+	2+
7	HC	0	3+	3+	3+	1+	1+	3+	3+	1+	4+
8	EL	0	0	2+	2+	0	1+	1+	3+	1+	2+
9	MM	0	3+	1+	3+	1+	1+	1+	2+	1+	4+
10	AH	0	0	2+	3+	0	0	1+	1+	0	1+
11	MR	1+ (solar)	0	0	0	0	0	1+	1+	1+	1+
12	LC	0	0	0	0	0	0	1+	1+	3+	4+
13	DD	0	1+	3+	3+	NPE	1+	3+	3+	NPE	1+
14	MB	0	1+	3+	3+	0	1+	2+	3+	0	4+
15	AS	0	2+	3+	2+	0	1+	3+	3+	0	4+
16	GW	1+	3+	3+	3+	0	1+	3+	3+	1+	4+
17	LM	0	1+	3+	3+	1+	1+	3+	3+	1+	2+
18	HS	0	1+	1+	1+	1+	1+	1+	1+	2+	4+
		0	1+	2+	3+	0	0	0	0	0	1+
19	HR	NPE	NPE	NPE	0	1+	NPE	NPE	1+	2+	4+
20	RR	0	3+	1+	3+	NPE	0	1+	1+	NPE	1+

* 0 = normal; 1+ = mild; 2+ = moderate; 3+ = marked.
† See Materials and Methods section for quantification of eosinophilia.
‡ NPE = not present for evaluation.
§ (solar) = atrophy secondary to sun exposure and/or aging.

otherwise, excessive neutrophils, fat necrosis, giant cells, and a xanthomatous reaction were not present. As the disease progressed, the thick sclerotic septums, often with entrapped lipocytes, fused with the fascia and occasionally the reticular dermis (Figure 2). As a net effect, the overall thickness of the subcutis was diminished (Figure 5).

Fascia

Fascial thickening and/or sclerosis was marked in 10 patients, moderate in 4, and mild in 3 (Figures 2, 3, 5, and 6). In 3, the deep fascia was of normal thickness but inflamed and edematous (Figure 7). The components of the inflammatory infiltrate were as noted above in the subcutis. In general, the fascia was sharply demarcated but firmly attached to the epimysium of the subjacent muscle; however, the boundary between the fascia and subcutis was frequently irregular, particularly when the sclerotic septums of the latter fused with the fascia.

Muscle

Muscle was available for examination in 17 patients. In 3 of these, the muscle was entirely normal, and 1 showed a marked diffuse interstitial infiltrate of eosinophils with focal necrosis and regeneration of myocytes. The majority (13 biopsies) contained only mild (10 cases) to moderate (3 cases) perivascular accumulation of lymphocytes, plasma cells, histiocytes, and eosinophils (Figure 10). Eight of these 13 specimens demonstrated mild (generally focal) interstitial fibrosclerosis or atrophy or both. While occasionally related to the scarred fascia, fibrosclerosis was also present in small random areas remote from the fascia. There was focal necrosis of myocytes in one of the three biopsies with moderately severe inflammation (Figure 10). As noted above, the epimysium subjacent to the fascia was frequently sclerotic and inflamed as a result of what appeared to be spillover from the fasciitis.

Vessels

Marked dermal sclerosis was occasionally accompanied by mild vascular telangiectasia or mural fibrosis or both. Capillaries, small veins, and infrequently arteries of the lower subcutis, fascia, and muscle were usually surrounded by a cuff of lymphocytes and plasma cells (Figure 9). In 10 cases, the inflammatory cells extended into the vascular cells and were associated with edema and endothelial cell hypertrophy or hyperplasia or both (Figure 9). In no instance, however, was vascular necrosis or thrombosis identified.

Eosinophils

Tissue eosinophils were quantitated according to the scale described above. Seven biopsies had 1+, four 2+, and nine 4+ eosinophilia (Figure 4). Since 0–2 eosinophils per HPF might be expected in any inflammatory lesion, 1+ eosinophilia was not regarded as significant. Tissue eosinophilia was therefore considered to be present only when there were three or more of these cells per high-power microscopic field. In 5 of the 13 cases with 2+ or greater eosinophilia, these cells were very focal in distribution, requiring a diligent search and high-quality tissue stains to distinguish them from mast cells and occasionally from neutrophils. They were more often found in the lower subcutis and fascia. However, in one biopsy they were present only in the dermis, while in another case they were found only in the interstitium of the muscle. Intravascular collections of eosinophils were frequently noted and considered to be a reflection of peripheral, not tissue, eosinophilia.

Tenosynovium

Tenosynovium from the flexor tendon sheaths at the wrist was available from two patients who had undergone surgery for relief of carpal tunnel syndrome. In Case 11, the mildly hyperplastic and fibrotic synovium was diffusely infiltrated with lymphocytes and scattered plasma cells and histiocytes. There was 1+ eosinophilia. In Case 14, the synovium was edematous, hyperplastic, villous, and fibrotic with focal 4+ eosinophilia and a diffuse infiltrate of plasma cells and lymphocytes (Figure 11). Lymphoid aggregates were not present in either case.

Immunofluorescent Studies

Of 8 patients who had tissue examined immunohistologically, 3 (Cases 7, 11, and 17) had no detectable immunoglobulins or complement. Two (Cases 8 and 10) had IgG and C3 deposits in the fascia. One patient (Case 19) had IgG, IgM, and C3 in the interstitial tissue of muscle, while another individual (Case 18) had only deposits of IgG in a similar location. IgM and C3 were identified at the epidermal–dermal junction in Case 9. IgA, IgE, and C4 were not observed in any of the specimens.

Differential Diagnosis

There are several conditions to be considered in the differential diagnosis of EF.

Progressive Systemic Sclerosis and Localized Scleroderma

The distinction between EF, progressive systemic sclerosis (PSS), and various forms of localized sclerodema (LS) may be the most challenging

and clinically significant. In the early stages of EF, the epidermis and dermis are usually normal, as opposed to both PSS and LS, in which one finds varying degrees of edema and sclerosis.[17,18] However, it should be stressed that dermal sclerosis is of frequent occurrence in EF and has been confirmed by weighing skin cores of fixed surface diameters (7 mm) obtained from the dorsum of the forearm midway between the wrist and the elbow.[19] The location and severity of the inflammatory reaction are also diagnostically significant, for in EF the inflammation is heavier in the fascia and lower subcutis, while in PSS the inflammation, when present, is greatest in the dermis or dermosubcutaneous junction or both. The presence of a significant number of eosinophils in any location favors EF, as does fascial sclerosis, because the latter most often occurs late in the course of PSS and localized linear scleroderma (LLS).

In addition, calcinosis cutis and extensive muscle fibrosclerosis [20,21] are most suggestive of PSS and LLS, respectively (Figure 13). With the exception of the epimysium subjacent to the fascia, interstitial muscle fibrosclerosis was never marked in our examples of EF. Although calcinosis has been described in the late phase of EF, [15] we did not observe it. In the advanced stages of EF and PSS, the distinction may be impossible to make by biopsy alone (Figures 5 and 12).

Dermatomyositis

Hyalinization and sclerosis of dermal collagen with atrophy or disappearance of dermal appendages is rare in dermatomyositis (DM). The presence of mucin deposits in association with noninflammatory poikiloderma (epidermal atrophy, liquefactive degeneration of the basal layer, and vascular telangiectasia) has been considered almost diagnostic of DM.[22] This combination of changes was not found in our EF series. Focal panniculitis is described in a small minority of DM cases,[22] yet is almost always present to some degree in EF. Calcinosis is also a prominent sequela of DM but rare in EF. As far as the authors are aware, fascial sclerosis is not a significant component of DM.

Depending upon the stage of the disease, the muscle may show the most striking and diagnostic changes of DM. There is usually muscle fiber degeneration and regeneration with inflammatory cells not only in the interstitium but in and between individual muscle fibers. The infiltrate is usually composed of lymphocytes, histiocytes, and few plasma cells. Eosinophils are rare. Late stages reveal fatty replacement and extensive fibrosis; these changes, especially the former, are not common to EF.

Disseminated Eosinophilic Collagenosis

Disseminated eosinophilic collagenosis (DEC), a poorly understood entity, is described as being characterized by peripheral eosinophilia,

hypergammaglobulinemia, and an eosinophilic infiltration of many organs including the heart, lungs, brain, spleen, liver, lymph nodes, skin, and muscle.[23,24,25,26] The infiltrates are frequently associated with focal necrosis and vascular lesions that vary from a mild endarteritis to necrotizing arteritis. The multisystem involvement, transient pulmonary infiltrates, extensive vascular lesions, and focal tissue necrosis are all alien to EF.

Proliferative Fasciitis

In 1975, Chung and Enzinger described an entity that they called proliferative fasciitis [27] (as opposed to nodular fasciitis [28]), which is characterized by a pseudosarcomatous reaction involving the fascia and fibrous septums of the subcutis. It occurs predominantly in the extremities of adults. As with EF, trauma is suggested as a possible etiologic factor. There was no mention of associated eosinophilia in this report. While resembling EF both grossly and at low magnification, the lesion is composed of large ganglion-like giant cells and proliferating fibroblasts frequently associated with a myxoid stroma and inconspicuous inflammatory cells. These features are not seen in EF.

End Stage of Various Panniculitides

There are many disease entities that primarily affect the panniculus adiposus.[29,30] Conceivably the healing or end stages of such disorders might be confused with EF. In such cases, the finding of residual foci of xanthoma cells, more than a rare granuloma or giant cell, vascular necrosis or thrombosis, frequent neutrophils, and fat necrosis are evidence against the diagnosis of EF.

Scleredema (of Buschke)

Scleredema is a disease of unknown etiology that most often occurs in adults. Its onset is abrupt and frequently follows an acute infectious disease. Characterized by a diffuse induration of the skin primarily affecting the neck, shoulders, upper trunk, and proximal portions of the upper extremities, it has been confused with EF.[31] Pathologically, there is an increase in the thickness of the dermis and subcutis due to an increase in connective tissue and deposition of hyaluronic acid between collagen bundles.[32] There is minimal inflammatory reaction and no eosinophilia, vasculitis, or significant atrophy of the epidermis, dermal appendages, or muscles [33] (Figure 14). These factors, together with the sparing of the hands and feet in scleredema,[33] allow one to differentiate this disorder from EF.

Discussion

Since the pathologic findings in EF are found predominately in the fascia and lower subcutis, the tissue provided by the usual cutaneous punch biopsy is generally inadequate for diagnostic purposes. In fact, in those cases of EF associated with dermal sclerosis, such a biopsy could easily be misinterpreted as scleroderma. Therefore, it is essential to obtain an *en bloc* surgically incised biopsy (about 3.0 cm in length) including skin, subcutis, fascia, and muscle. Another potential problem in arriving at a conclusive diagnosis is the failure to realize that peripheral eosinophilia may be transient and tissue collections of these cells quite focal. Treatment with corticosteroids (received by most patients) leads to a rapid fall and often complete disappearance of eosinophils from the peripheral blood; in other cases, we have noted the eventual spontaneous (ie, not drug-induced) reduction in blood eosinophils to normal levels during the natural course of this illness. When this occurs, eosinophils may no longer be detected in tissue. A review of past blood counts for unexplained eosinophilia may be helpful in those patients who fail to demonstrate peripheral and tissue eosinophilia at the time of biopsy. In the case of biopsies, eosinophils may be present in only one or two high-power microscopic fields even in those patients with impressive peripheral eosinophilia.

Eosinophilia has been variously defined as a total eosinophil count in excess of 400,[34] 500,[35] or 700 [36] cells/cu mm. We considered eosinophilia to be present when there were more than 600 cells/cu mm in the peripheral blood and, in the case of tissue, when 3 or more cells/HPF were seen. In this study (excluding those patients receiving prednisone), there was a close correlation between blood and tissue eosinophilia, ie, when the absolute eosinophil count exceeded 600 cells/cu mm at the time of biopsy, 3 or more eosinophils/HPF were found in the tissue of 71% of cases.

In our experience, the majority of patients with EF eventually enjoy a complete or nearly complete remission of their illness, with or without corticosteroid therapy, usually after periods of two to four years of disease. A more detailed clinical analysis of our patients will be the subject of another report. It is appropriate, however, to comment on two of our patients who had more than one biopsy performed during the course of their illness (Tables 1 and 2). Case 2, a 52-year-old woman, was receiving corticosteroid therapy at the time of her initial right-arm biopsy; this revealed marked inflammation and mild sclerosis of the subcutis and fascia, together with 2+ eosinophilia. Five years later (while still receiving prednisone), tissue samples were obtained from the right arm and fore-

arm. Both of these demonstrated a persistence of mild subcutaneous fibrosclerosis; however, inflammation and eosinophilia had subsided, and fascial sclerosis and thickening were no longer apparent. This case provides morphologic evidence for the reversibility of fibrosclerosis of EF. Case 18, a 54-year-old woman who was not taking prednisone at the time of her original biopsy, had tissue removed from her left leg during the fourth month of her disease; this biopsy showed mild sclerosis and inflammation of the dermis, subcutis, fascia, and muscle as well as 4+ eosinophilia. A second biopsy, obtained one year later from the right forearm, revealed that the subcutaneous and fascial sclerosis and thickening had increased in severity despite steroid therapy while the dermal sclerosis remained stationary and the inflammation, eosinophilia, and muscle fibrosclerosis were reversed. This case indicates that even with steroid therapy, some patients with EF may have temporary progression of their disease.

Corticosteroid therapy may mask the tissue diagnosis of EF, since this class of drugs has anti-inflammatory and eosinopenic effects. Therefore, it is highly desirable that biopsies be obtained before institution of this therapy; or if the patient has been receiving these drugs, it is essential that this information be available to the pathologist.

Our observations suggest that EF begins as an accumulation of lymphocytes, plasma cells, histiocytes, and eosinophilia predominantly in the fascia and fibrous septums of the lower subcutis. This is followed by the deposition of new collagen in these sites. This seems to be at least one of two mechanisms by which the fascia becomes thickened. The other is by fusion of the broad subcutaneous fibrous septums with the fascia frequently entrapping adipose tissue between them. As the disease advances, the upper subcutis and reticular dermis become progressively inflamed and sclerotic with subsequent loss of dermal appendages and epidermal atrophy. Muscle involvement is usually limited to mild (occasionally moderate) interstitial perivascular inflammation and fibrosclerosis. In our experience with EF thus far, extracutaneous involvement has been limited to occasional mild oligoarticular joint inflammation (synovitis) and relatively frequent carpal tunnel syndrome resulting from tenosynovitis of the flexor tendon sheath at the wrist.

The histogenesis of EF, therefore, seems to be similar in some respects to that described by Fleischmajer et al for PSS [37] and morphea.[38] In the latter two conditions, he describes an initial panniculitis at the dermosubcutaneous interface followed by the formation and deposition of pale-staining weak-to-absent birefringent collagen with increased reticulin and

few elastic fibers. Histologically the difference between these conditions lies in the more frequent presence of eosinophils and the location of the inflammatory infiltrate at the junction of deep fascia and subcutis in EF. The stimulus for the accumulation of inflammatory cells in the fascia and surrounding structures is unknown. The presence of eosinophils and plasma cells, hypergammaglobulinemia, and occasional tissue deposits of immunoglobulins and C3, are suggestive of an immunologic mechanism. Shulman has hypothesized that strenuous physical exertion or other trauma in a susceptible host might be instrumental in releasing an antigen which could initiate such a reaction.[4,10] As previously indicated, a history of such vigorous physical activity prior to the onset of the disease was obtained in almost half our patients.

Recently there have been several reports describing eosinophilia in association with PSS or its localized variants. Rodnan et al [39] found peripheral eosinophil counts ranging from 7% to 14% in 9 of 14 patients with localized linear scleroderma. In 6 of these the absolute count exceeded 600/cu mm. Defining eosinophilia as greater than 400 cells/cu mm, Fleischmajer and associates [16] noted blood eosinophilia in 13 of 67 patients with PSS and 3 of 15 individuals with localized scleroderma. They also observed 3 or more eosinophils/HPF in six of 20 PSS biopsies and in two of eight examples of localized scleroderma. It is not clear, however, whether some of their biopsies were obtained from the same group of patients who had blood eosinophilia. Such findings have led Caperton et al [7] to suggest that morphea, fasciitis, and PSS with eosinophilia may represent a broad spectrum of a single disease. In contrast to the above experience, Shulman has examined 180 cases of scleroderma and could not find a single case associated with eosinophilia [4]; he also quotes a study of 150 patients with polymyositis in which, with the possible exception of two who had transient eosinophil counts of 5% to 6%, none had eosinophilia.[4] In our own experience with more than 600 patients with PSS, normal peripheral eosinophil counts have been the rule.

While we have enumerated histologic details that in most instances will allow one to differentiate EF from scleroderma, there is undeniable evidence that these two entities do share certain morphologic features that in the late stages of these diseases may make their separation difficult. However, there remain significant differences between the clinical and laboratory findings and the natural history of EF, PSS, and localized scleroderma. The question, therefore, regarding the relationship of EF, if any, with the various forms of scleroderma will have to await further study and long-term follow-up of these patients.

References

1. Shulman LE: Diffuse fasciitis with hypergammaglobulinemia and eosinophilia: A new syndrome? (abstr). J Rheumatol 1 (Suppl):46, 1974
2. Rodnan GP, DiBartolomeo AG, Medsger TA Jr, Barnes EL Jr: Eosinophilic fasciitis: Report of 7 cases of a newly recognized scleroderma-like syndrome (abstr). Arthritis Rheum 18:122–423, 1975
3. Shulman LE: Diffuse fasciitis with eosinophilia: A new syndrome? (abstr). Clin Res 23:443A, 1975
4. Shulman LE: Diffuse fasciitis with eosinophilia: A new syndrome? Trans Assoc Am Physicians 88:70–86, 1975
5. Caperton EM, Hathaway DE: Scleroderma with eosinophilia and hypergammaglobulinemia. The Shulman syndrome (abstr). Arthritis Rheum 18:391, 1975
6. Schumacher HR: A scleroderma-like syndrome with fasciitis, myositis, and eosinophilia. Ann Intern Med 84:49–50, 1976
7. Caperton EM, Hathaway DE, Dehner LP: Morphea, fasciitis, and scleroderma with eosinophilia: A broad spectrum of disease (abstr). Arthritis Rheum 19:792–793, 1976
8. Talbott JH, Cusani BA: Fasciitis (eosinophilic) with scleroderma-like changes in the skin. J Fla Med Assoc 63:702–705, 1976
9. Gray RG, Poppo MJ: Eosinophilic fasciitis: A scleroderma-like illness. JAMA 237: 529–530, 1977
10. Shulman LE: Diffuse fasciitis with eosinophilia: A new syndrome. Arthritis Rheum 20:S205–S215, 1977
11. Krauser RE, Tuthill RJ: Eosinophilic fasciitis. Arch Dermatol 113:1092–1093, 1977
12. Torres VM, George WM: Diffuse eosinophilic fasciitis: A new syndrome or variant of scleroderma? Arch Dermatol 113:1591–1593, 1977
13. Weinstein D, Schwartz RA: Eosinophilic fasciitis. Arch Dermatol 114:1047–1049, 1978
14. Fu TS, Soltani K, Sorenson LB, Levinson D, Lorincz AL: Eosinophilic fasciitis. JAMA 240:451–453, 1978
15. Dehner LP, Caperton EM, Hathaway DE: Fasciitis, morphea-scleroderma, and eosinophilia: A unique clinicopathologic entity (Abstr). Lab Invest 36:336, 1977
16. Fleischmajer R, Jacotot AB, Shore S, Binnick SA: Scleroderma, eosinophilia, and diffuse fasciitis. Arch Dermatol 114:1320–1325, 1978
17. O'Leary PA, Montgomery H, Ragsdale WE Jr: Dermatohistopathology of various types of scleroderma. Arch Dermatol 75:78–87, 1957
18. Reed RJ, Clark WH, Mihm MC: The cutaneous collagenoses. Hum Pathol 4:165–186, 1973
19. Rodnan GP, Lipinski E, Luksick J: Skin thickness and collagen content in progressive systemic sclerosis and localized scleroderma. Arthritis Rheum 22:130–140, 1979
20. Medsger TA Jr, Rodnan GP, Moossy J, Vester JW: Skeletal muscle involvement in progressive systemic sclerosis (scleroderma). Arthritis Rheum 11:554–568, 1968
21. D'Angelo WA, Fries JF, Masi AT, Shulman LE: Pathologic observations in systemic sclerosis (scleroderma): A study of 58 autopsy cases and 58 matched controls. Am J Med 46:428–440, 1969
22. Janis JF, Winkelmann RK: Histopathology of the skin in dermatomyositis. Arch Dermatol 97:640–650, 1968
23. Engfeldt B, Zetterström R: Disseminated eosinophilic "collagen disease": A clinical and pathological study of a clinical entity related to Löffler's syndromes. Acta Med Scand 153:337–353, 1956
24. Odeberg B: Eosinophilic leukemia and disseminated eosinophilic collagen disease—a disease entity? Acta Med Scand 177:129–144, 1965

25. Sparrevohn S: Disseminated eosinophilic collagenosis and familial eosinophilia. Case report. Acta Paediatr Scand 56:307–312, 1967
26. Chusid MJ, Dale DC, West BC, Wolff SM: The hypereosinophilic syndrome: Analysis of fourteen cases with review of the literature. Medicine 54:1–27, 1975
27. Chung EB, Enzinger FM: Proliferative fasciitis. Cancer 36:1450–1458, 1975
28. Price EB Jr, Silliphant WM, Shuman R: Nodular fasciitis: A clinicopathologic analysis of 65 cases. Am J Clin Pathol 35:122–136, 1961
29. Reed RJ, Clark WH, Mihm MC: Disorders of the panniculus adiposus. Hum Pathol 4:219–229, 1973
30. Lever WF, Shaumburg-Lever G: Histopathology of the Skin. Fifth edition. Philadelphia, J. B. Lippincott, 1975, pp. 225–238
31. Atherton DJ, Wells RS: Scleredema of Buschke? Eosinophilic fasciitis. Br J Dermatol 95 (Suppl 14):36–37, 1976
32. Graham JH, Johnson WC, Helwig EB: Dermal Pathology. First edition. Hagerstown, Md, Harper & Row, 1972, pp 760–762
33. Leinwand I: Generalized scleredema: Report with autopsy findings. Ann Intern Med 34:226–238, 1951
34. Miale JB: Laboratory Medicine: Hematology. Fifth edition. St. Louis, C. V. Mosby, 1977, p 774
35. Davidsohn I, Henry JB: Todd–Sanford Clinical Diagnosis by Laboratory Methods. 15th edition. Philadelphia, W. B. Saunders, 1974, p 255
36. Wintrobe MM, Lee GR, Boggs DR, Bithell TC, Athens JW, Foerster J: Clinical Hematology. Seventh edition. Philadelphia, Lea & Febiger, 1974, pp 1282–1283
37. Fleischmajer R, Damiano V, Nedwich A: Alteration of subcutaneous tissue in systemic scleroderma. Arch Dermatol 105:59–66, 1972
38. Fleischmajer R, Nedwich A: Generalized morphea. I. Histology of the dermis and subcutaneous tissue. Arch Dermatol 106:509–514, 1972
39. Rodnan GP, Lipinski E, Rabin BS, Reichlin M: Eosinophilia and serologic abnormalities in linear localized scleroderma (abstr). Arthritis Rheum 20:133, 1977

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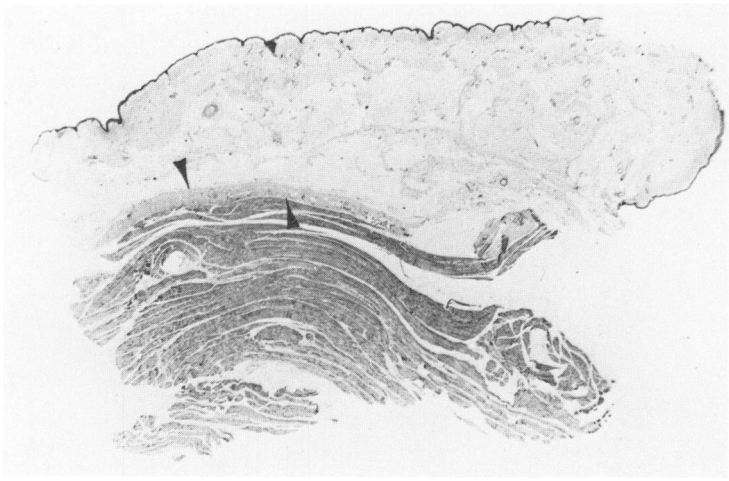
[*Illustrations follow*]



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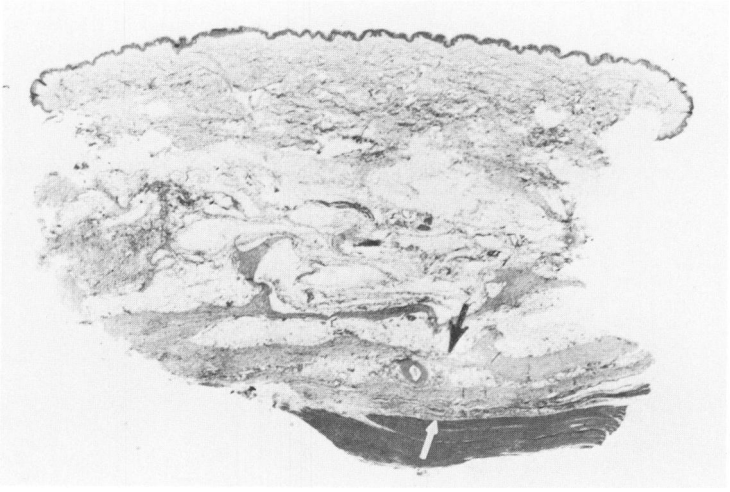

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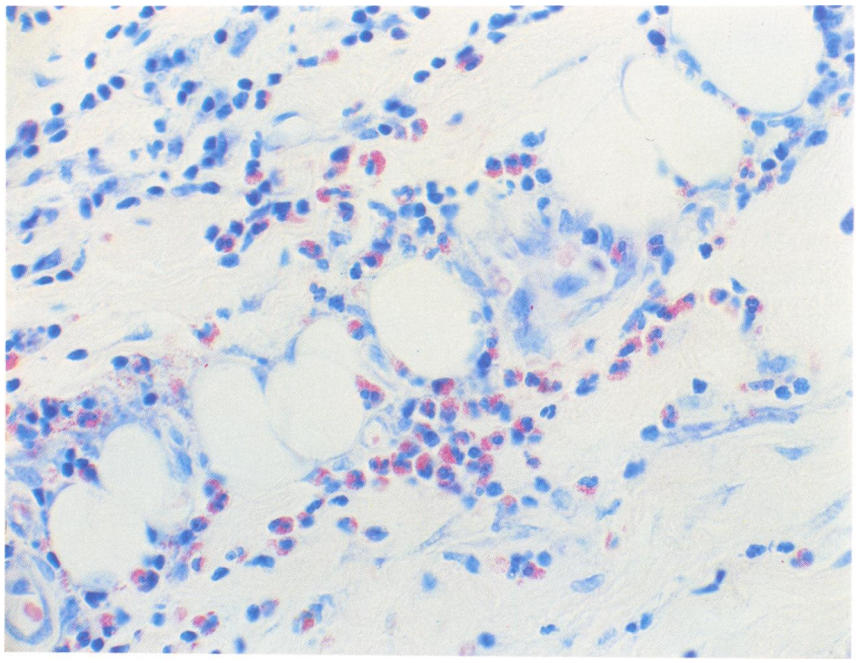
Figure 1—Normal biopsy obtained from the forearm. Observe the relative thickness of the dermis and fascia (*arrows*) and the thin delicate fibrous septums of the subcutis. Interstitial tissue of skeletal muscle is barely visible. (H&E, ×8) **Figure 2**—EF (Case 8), showing moderate sclerosis of the fascia and lower subcutis. Dermis and skeletal muscle are normal. Note the sclerotic subcutaneous septums with entrapped adipose tissue (*arrows*) fusing with the thick fascia. (H&E, × 8) **Figure 3**—EF (Case 17), showing marked collagenous thickening of the fascia and lower subcutis in conjunction with mild dermal sclerosis. Lymphoid aggregates are visible (*arrow*). (H&E, × 8) (With a photographic reduction of 15%)

Figure 4—EF (Case 16) showing a marked accumulation of eosinophils in the fascia and lower subcutis. (Giemsa, × 400)



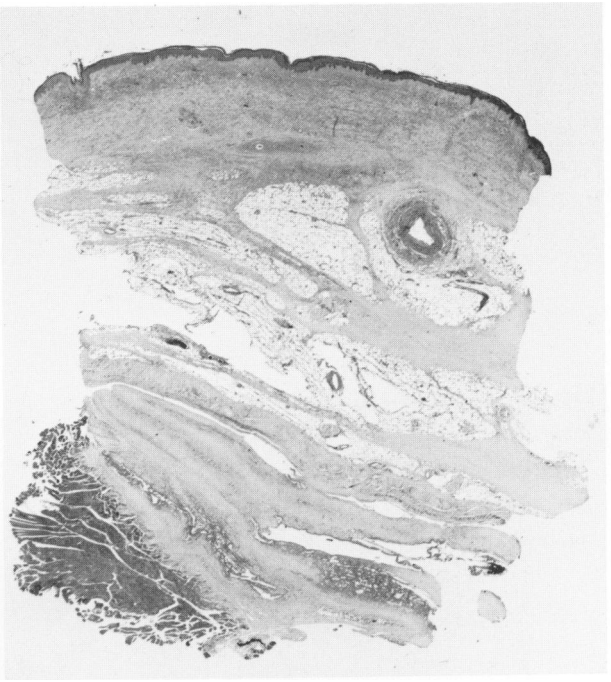


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Figure 5—An advanced case of EF (Case 4) with marked sclerosis and thickening of the dermis, subcutis, and fascia. In this instance it may be impossible histologically to separate EF from PSS, particularly if there has been prior corticosteroid therapy. Compare with Figure 12. (H&E, × 8)

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Figure 6—An unusual example of EF (Case 20) with relative sparing of the subcutis but marked collagenous thickening of the dermis and fascia. (H&E, × 8)

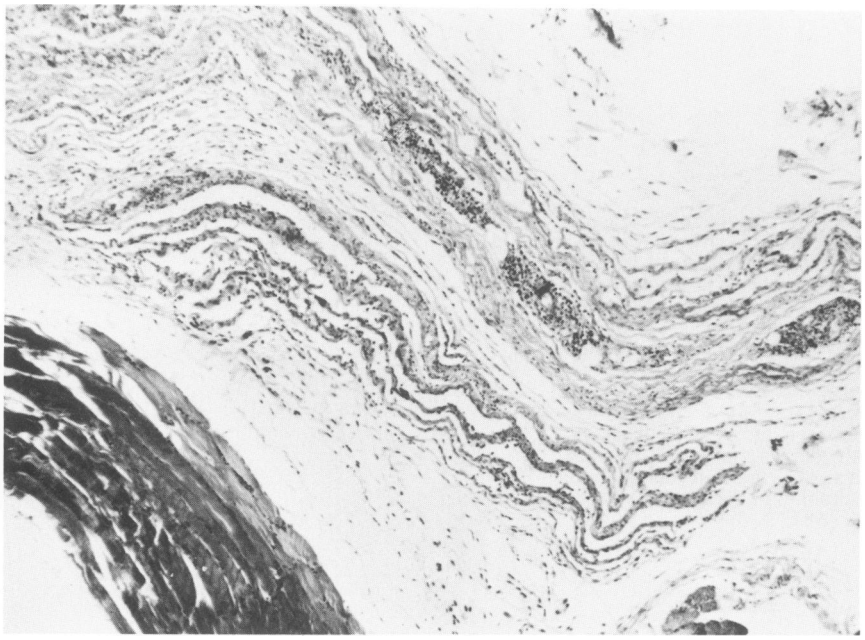
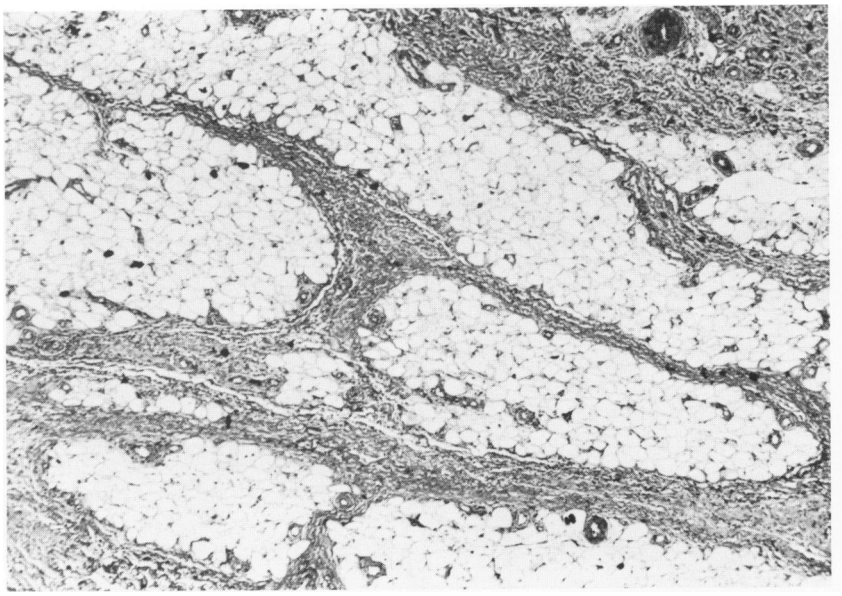


Figure 7—Early stage of EF (Case 2). The deep fascia is inflamed and has an edematous appearance, the latter frequently due to an extracellular accumulation of acid mucopolysaccharides. As the disease progresses, the fascia becomes collagenized and thickened. Skeletal muscle is present in the lower left corner. (H&E, × 40)



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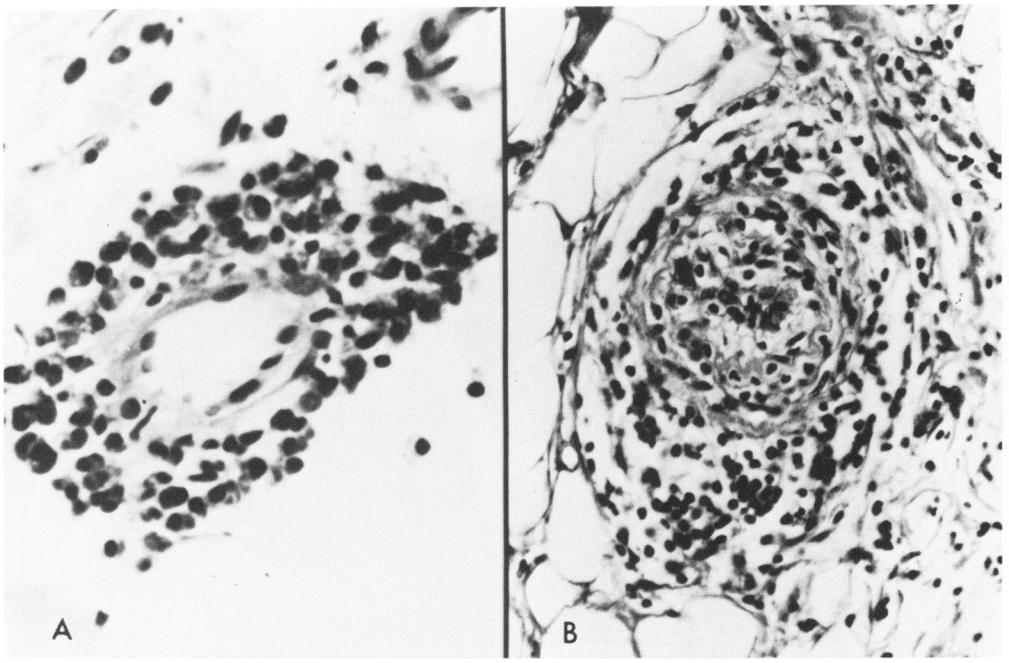

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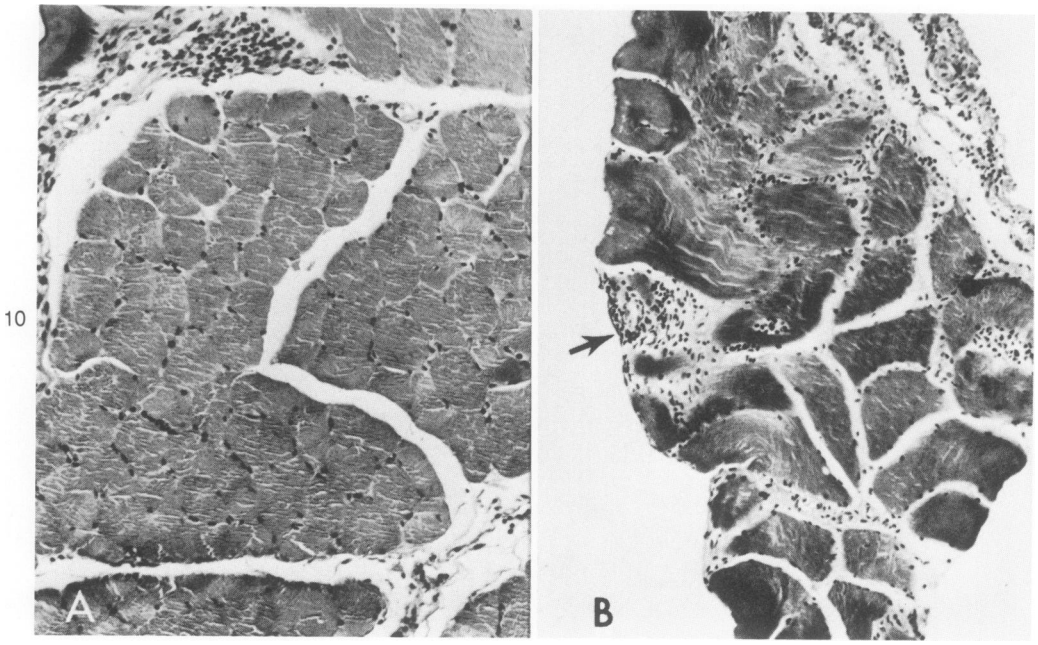
Figure 8—Subcutaneous tissue in EF (Case 14). The inflammatory infiltrate is generally confined to the septums or periphery of the fat lobule (so-called septal panniculitis); only infrequently does the inflammation extend more deeply into the lobule. (H&E, × 40) **Figure 9**—Vessels in EF **A**—Perivascular concentration of lymphocytes and plasma cells around capillaries (as illustrated), small veins, and infrequently arteries is commonly observed (H&E, × 400). **B**—In half our cases, inflammatory cells not only surrounded vessels but infiltrated their walls, as in the case of this vein. This was frequently associated with mural edema and endothelial cell hypertrophy or hyperplasia; vascular necrosis or thrombosis were not seen. (H&E, × 250) (Both with a photographic reduction of 6%)



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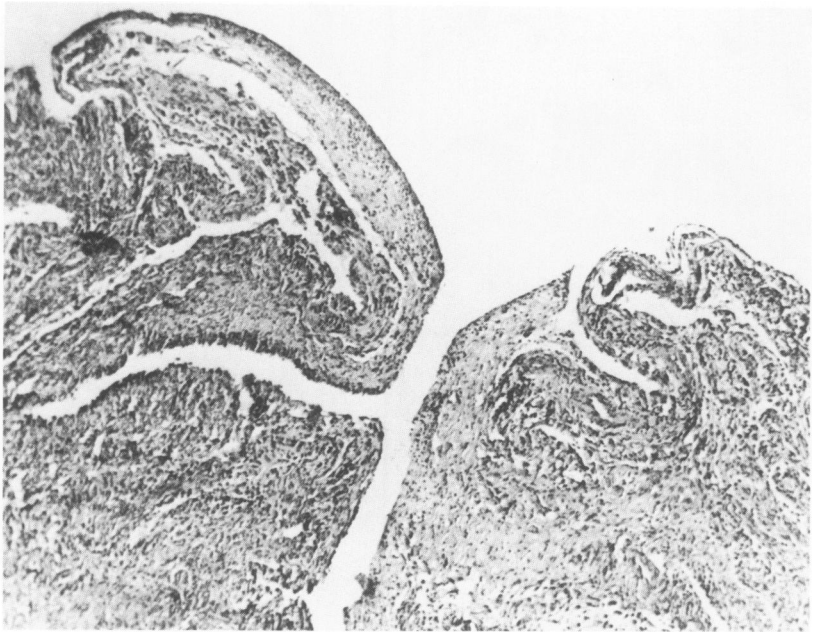

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Figure 10—Skeletal muscle in EF. **A**—Generally there is only a mild focal interstitial perivascular accumulation of inflammatory cells that may be associated with mild fibrosclerosis (Case 6). (H&E, × 100) **B**—There is diffuse inflammation, mild fibrosclerosis, and focal myocyte necrosis (*arrow*). Rarely is skeletal involvement more severe than this. (Case 18). (H&E, × 125) **Figure 11**—Hyperplastic, villous, fibrotic, and diffusely inflamed tenosynovium with focal 4+ eosinophilia obtained from the flexor tendon sheaths at the wrist in a patient with EF and carpal tunnel syndrome. (Case 14). (H&E, × 100) (Both with a photographic reduction of 7%)

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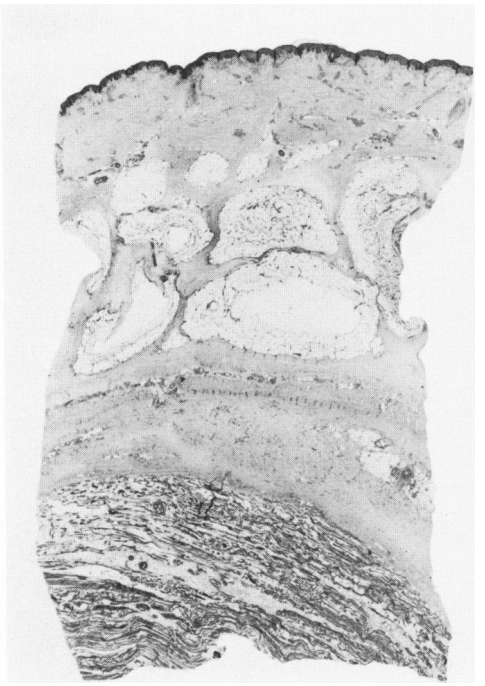

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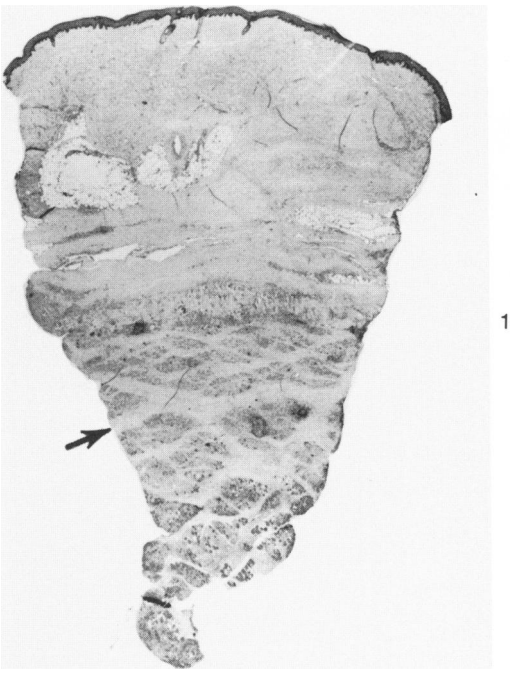

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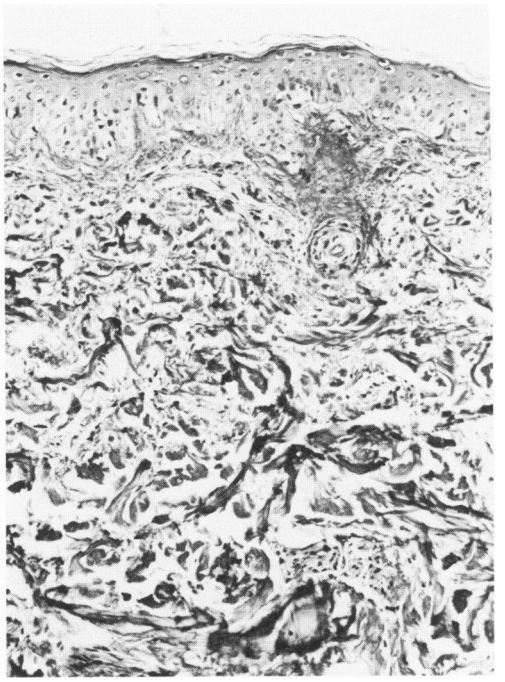

Figure 12—Tissue obtained from the leg of a 58-year-old man with a 4-year history of PSS. Observe the markedly thickened and sclerotic dermis, subcutis, and fascia. The skeletal muscle is atrophic and largely replaced by adipose tissue with only focal fibrosclerosis. Refer to Figure 4. (H&E, × 8) **Figure 13**—Biopsy of localized linear scleroderma (LLS) obtained from the arm of a 15-year-old girl. A solid bridge of dense acellular collagen connects the dermis to the fascia. There is extensive fibrosclerosis of muscle (*arrow*). This degree of muscle sclerosis was never observed in our examples of EF and is rarely seen in PSS. It is, therefore, an important microscopic feature that allows one to separate EF and generally PSS from LLS. (H&E, × 8) **Figure 14**—Biopsy of scleredema (of Buschke) obtained from the back of a 43-year-old man with adult onset diabetes mellitus, and a 3-year history of nonpitting edema of the neck, shoulders, upper back, and chest. Dermal collagen bundles are thickened, nonhyalinized, and widely separated by large clear spaces, the latter due to extracellular accumulation of acid mucopolysaccharides. Inflammation is lacking. (H&E, × 100) (All with a photographic reduction of 19%)

[*End of Article*]