Clinical and Laboratory Investigations

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Eosinophilic Fasciitis 30 Years after – What Do We Really Know?

Report of 11 Patients and Review of the Literature

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Key Words
Eosinophilic fasciitis, pathomechanism · Shulman syndrome · Borreliosis

Abstract
Background: Eosinophilic fasciitis (EF) is a rare fibrosing disorder associated with peripheral eosinophilia and scleroderma-like induration of the distal extremities which affects substantially quality of life. Although the disease has been described 30 years ago, the etiology and pathomechanisms are still obscure, and consensus for therapy is lacking. Numerous case reports of patients with EF exist but series are scarce. ***Patients and Methods:*** Eleven patients with EF from the Department of Dermatology, Kantonsspital Aarau, the University Hospital Basel and the Outpatient Clinic of Dermatology, Triemli Hospital Zurich, Switzerland, were retrospectively studied. ***Results:*** In 4 patients the initial diagnosis was not recognized by the referring nondermatologists. The median age was 55 years, excluding the youngest patient ever diagnosed with EF (age = 1 year). All patients showed an induration of the skin, which led to painful contractures in the joints in 3 cases. All but 2 patients demonstrated edema. A slight predominance of the upper extremities was observed. Sclerodactyly was noticed in 1 patient. Three patients reported an initial trauma at the affected site. Two patients were tested positive for borreliosis. One patient subsequently developed aplastic anemia and Hashimoto thyroiditis. Visceral or extracutaneous involvement was absent. Eight patients had a full or partial recovery under corticosteroids whereas in 2, improvement could be achieved only with cyclosporine, azathioprine or cyclophosphamide. ***Conclusions:*** The diagnosis of EF can be established by clinical, laboratory and histological findings. In general, corticosteroids are highly efficacious in EF and only a minority of patients need other immunosuppressive or cytostatic drugs.

Introduction

Eosinophilic fasciitis (EF) is a rare localized scleroderma-like disorder first described by Shulman [1] in 1974. Until today both the etiology and pathomechanism remain elusive. In general, the skin changes are symmetric and include an initial edema and erythema of the extremities, followed by 'peau d'orange' and woody skin induration in a later phase. The skin induration can lead to joint

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Table 1. Age, sex, differential diagnosis, therapy and outcome

Patient	Age years	Sex	Differential diagnosis	Treatment	Course
1	61	M	Erysipelas	Prednisone 50 mg initially for 2 weeks and then tapered	Marked amelioration within few months
2	72	F	Scleromyxedema	Prednisone 50 mg for 4 weeks	No detail given
3	70	F		Prednisone 40 mg initially for 2 months and then tapered	Clearing within 5 months
4	60	M	Erysipelas	Prednisone 50 mg initially for months, azathioprine, cyclosporine, cyclophosphamide, rocephine	Slow amelioration over months
5	62	F		Prednisone 25 mg for 4 months, cyclosporine, danatrol	Slow amelioration
6	1	F	Dermatomyositis	Prednisone 20 mg (2 mg/kg/body weight) for 8 weeks and then tapered	Amelioration over months
7	35	M		Prednisone 50 mg for 4 weeks	Clearing within 4 weeks
8	60	F		Prednisone initially 20 mg, later 30 mg	Under 20 mg increasing induration, slow amelioration under 30 mg
9	48	F	Scleroderma/ panmorphea	Prednisone 20 mg initially then stopped, 8 sessions of PUVA	Amelioration over months
10	28	M	Phlegmone/ necrotic fasciitis	Prednisone 100 mg for 1 week, then 75 mg	Nearly clearing within 4 weeks
11	48	M		Prednisone 50 mg	Slow amelioration

contractures with limited mobility. Laboratory tests may show hypergammaglobulinemia, peripheral eosinophilia and an elevated erythrocyte sedimentation rate, but these results are not mandatory for the diagnosis, since these are transient. Confirmation of the clinical diagnosis is made by skin biopsy including the fascia. EF might be triggered by vigorous exercise [2], drugs [3], borreliosis [4, 5], arthropod bites [6] and trauma [7, 8]. Numerous treatments with various results have been reported, such as hydroxyzine [9], ibuprofen and cimetidine [10], hydroxychloroquine, prednisone [11], photochemotherapy [12, 13] and cyclophosphamide [6]. In one third of the patients, spontaneous remission can be observed [11].

Series of EF are rarely published. The clinical findings, laboratory results, histological characteristics and course in 11 cases are summarized. Reviewing the world literature our study also includes the youngest patient ever diagnosed as having EF (age = 1 year).

Patients and Methods

From 1987 to 2004 we retrospectively included 11 patients with EF, observed at the Department of Dermatology, Kantonsspital Aarau, the University Hospital Basel and the Outpatient Clinic of Dermatology at the Triemli Hospital in Zurich, Switzerland. One patient has already been described in an earlier report [14].

The patients met the following inclusion criteria:

1 characteristic skin lesions such as cutaneous erythema and induration, cutaneous swelling of the upper and/or lower extremities;
2 fascial biopsy with histopathological findings such as thickening of the fascia with chronic inflammatory infiltrate containing eosinophils.

Results

Age and Sex Distribution

All our patients were Caucasians, 6 (55%) were female. The patients were between 28 and 72 years old with a mean of 54.4 years, excluding the 1-year-old girl (table 1).

Table 2. Spectrum of skin changes in EF

Skin changes	Patients (n = 11)
Induration	11 (100)
Erythema	11 (100)
Edema (lower extremities or forearms)	9 (82)
Groove sign	2 (18)
Hyperpigmentation	1 (9)
Edema face	1 (9)

Figures in parentheses indicate percentages.

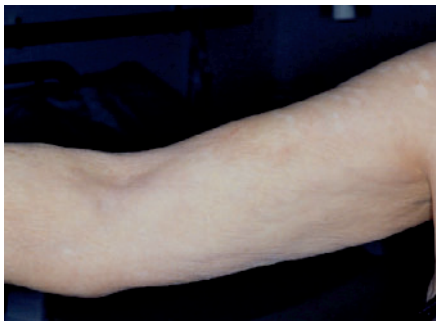

Fig. 1. Patient No. 3: increasing induration of the upper extremities over a period of 8 weeks.

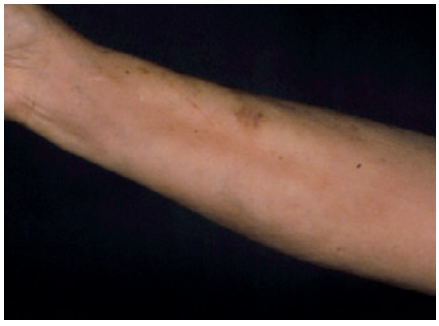

Fig. 2. Patient No. 5: increasing induration of both forearms during 5 months with appearance of furrows along the superficial veins (groove sign).

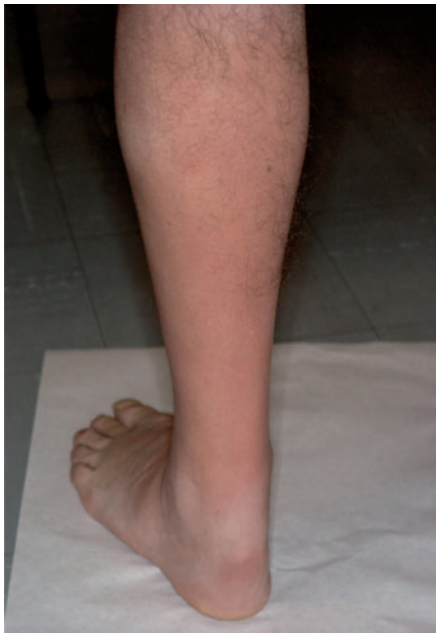

Fig. 3. Patient No. 1: erysipelas-like presentation of EF.

Clinical Manifestations

The main symptoms in all patients were cutaneous erythema and marked induration (fig. 1) associated with weakness and muscle pain with limited motility. Another common symptom was pitting edema found in 9 of 11 patients (82%). Two patients (No. 1, 7) had the classical groove signs (fig. 2) on the upper extremities. The characteristic sparing of fingers and toes was also observed in 10 patients. One patient (No. 5) had sclerodactyly, and in 2 patients (No. 1, 4) the findings were erysipelas-like (fig. 3). Raynaud's phenomenon or abnormal nail fold capillary microscopy was never found. In 3 patients, painful contractures occurred, in 2 (No. 4, 6), the ankle was involved and in another (No. 2) the elbow. None of the patients showed visceral or systemic involvement of EF. Two patients (No. 4, 11) had concomitant active borreliosis and another (No. 5) had aplastic anemia and Hashimoto thyroiditis. In 3 cases there was a preceding trauma including one with a previous stripping of varicose veins. Table 2 shows the pattern of the cutaneous involvement.

Laboratory Investigations

In 7 patients (64%) the laboratory tests revealed elevated eosinophils (ranging from 7.9 to 57.1% of leukocytes). Hypergammaglobulinemia (No. 6, 10) and positive antinuclear antibodies (No. 6, 9) were observed in 2 patients. Only the 1-year-old infant (No. 6) showed an inversed leukocyte count of 56×10^9/l. In 4 patients different autoantibodies were searched and were all negative. An elevated erythrocyte sedimentation rate was observed in 7 patients (No. 2, 4, 5, 7, 8, 10, 11; from 18 up to 59 mm/h). In 2 patients (No. 4, 5) the hemoglobin was decreased to 121 and 95 g/l, respectively. The latter showed also pancytopenia (thrombocytes 6,000/mm^3; leukocytes 1,700/mm^3). A bone marrow biopsy showed aplastic anemia.

The same patient had Hashimoto thyroiditis. The C-reactive protein was elevated in 4 patients (No. 1, 2, 5, 8) ranging from 10 to 59 mg/l. The Waler Rose and latex tests for rheumatoid arthritis were negative in all patients. Two patients (No. 4, 11) had IgG and IgM antibodies against *Borrelia burgdorferi.*

Histopathology

In all patients a deep full-thickness biopsy was done. All biopsies showed lymphoplasmacytic inflammation with histiocytes and eosinophilic granulocytes and a thickened deep fascia caused by sclerosis and fibrosis. The inflammation was mild to moderate in the lower dermis, the fascia and the superficial muscle. No inflammation was observed in the epidermis, papillary dermis and adnexa. In 1 patient (No. 1), the fascia and the superficial muscle were free of inflammation. In this case the infiltration was restricted to the dermal layer consisting of lymphocytes, histiocytes, eosinophils and mast cells. In addition, edema of the connective tissue was observed whereas no fibrinoid necrosis, granulomas or signs of vasculitis were seen in this biopsy. In 1 patient tested positive for borreliosis (No. 4), the Warthin-Starry coloration failed to demonstrate *Borrelia.*

Treatment and Course

Table 1 summarizes patient data and course of each patient. All patients received systemic steroids. The initial dosage varied between 20 and 100 mg/day. The clinical course was variable. Nearly complete healing after 4 weeks was observed in 2 patients (No. 7, 10). However, most patients had a prolonged course, and additional immunosuppressive agents or chemotherapeutic modalities were added. In 2 patients (No. 4, 5), steroids were ineffective. Cyclosporine in 1 of these (No. 5) and cyclosporine, azathioprine and cyclophosphamide in the other (No. 4) led to moderate response. In 1 patient (No. 9) with prolonged course under corticosteroids, adding PUVA therapy was highly beneficial. In 1 patient (No. 2), the outcome of the therapy could not be established.

Discussion

EF is a rare disorder with unknown etiology and pathogenesis [15]. The discussion whether EF is a variant of morphea or a new entity is still ongoing [16]. Jensen et al. [6] reported a patient with EF following localized scleroderma, suggesting a close relationship between the two entities.

An association with vigorous exercise in up to 66% [11, 14], trauma [7, 8, 17], simvastatin [3] and phenytoin [18], arthropod bites [6, 19], *Borrelia* infection [5, 20, 21], hematological malignancies [22–24] and thyroid diseases [25, 26] has been reported.

The differential diagnosis includes eosinophilia-myalgia syndrome and the Spanish toxic oil syndrome. These are part of eosinophilic fibrosing disorders and share clinical and pathological features with EF but may include visceral disease [3, 27, 28]. Eosinophilia-myalgia syndrome in the late eighties was largely induced by ingestion of L-tryptophan [3, 29]. Some cases of EF are reported after L-tryptophan ingestion, suggesting an overlap in the pathogenesis [30, 31].

None of our patients had a history of ingesting L-tryptophan or of offending drugs nor was strenuous exercise before the appearance of the symptoms reported. Two were serologically positive for borreliosis and 3 patients had a previous trauma to the affected site. One had previously had a stripping of her varicose veins and the 2 others had been hit on their legs. Blaser et al. [14] suggested that trauma or marked exercise may trigger antigenicity of the fascia and subcutis. Naschitz et al. [16] noted that similar pathological findings may be encountered in other disorders, such as morphea profunda, lupus panniculitis, lipodermosclerosis of chronic venous insufficiency, chronic lymphedema, graft-versus-host reaction, postirradiation injury, chronic Lyme disease, erysipelas, systemic infections and malignant neoplasms. All these disorders share the finding of an indurated skin due to chronic inflammation and fibrosis of the subcutaneous septa and muscular fascia [16].

On the basis of our study, we think that EF is a unique cutaneous reaction pattern to different stimuli. Since there are recognized etiological agents and an identifiable group of signs and symptoms in EF, we consider it as a disease and not as a syndrome, in view of the fact that the recognizable symptoms and signs of EF do not necessarily occur together.

Pathogenetically an aberrant immune response is proposed by some authors, which is underlined by the findings of hypergammaglobulinemia in the peripheral blood and the IgG and C3 deposition in the fascia of some patients [6, 11, 32]. Recently a study has demonstrated that metalloproteinase 1 (TIMP-1) is involved in the pathogenesis of EF [33]. Patients with EF showed significantly higher serum levels of TIMP-1 than healthy individuals, thus suggesting that TIMP-1 may be a good serological marker for disease activity like gammaglobulins [33]. Kahari et al. [34] reported elevated transforming growth fac-

tor β_1, type I procollagen and cellular fibronectin mRNA from lesional tissue produced in vitro by fibroblasts. In addition, IL-4, IL-13 and connective tissue growth factor contribute to fibrosis in scleroderma-like conditions [35]. Activated and degranulated eosinophils appear implicated in the lesional process. Thus, eosinophils may lead to fibroblast activation.

French et al. [15] reported a patient with EF and eosinophilic cellulitis, who had abnormal circulating clonal T cells and an increased production of the cytokine IL-5. They suggested that the elevated IL-5 caused the peripheral eosinophilia and led to the disease. IL-5 plays an important role regarding production, survival, activation, adhesion and degranulation of eosinophils [15, 36, 37].

Another report showed cytokine abnormalities similar to atopic patients [38] including elevation of IL-5 and a striking elevation of transforming growth factor β_1. In a later step of the cascade, tumor necrosis factor α may also play a role in EF. Indeed, Drosou et al. [39] used infliximab, a monoclonal antibody against tumor necrosis factor α, with encouraging effects.

The immunophenotype of inflammatory cells of fascia and muscle in EF was addressed in the study of Toquet et al. [40] where predominance of macrophages, CD8+ T lymphocytes and few eosinophils was demonstrated; 14% of the CD8+ T lymphocytes contained granzyme B, which suggests a cytotoxic cellular immune response. Altered expression of CD34 and CD40 antigens in eosinophilic fasciitis and scleroderma-like diseases seems also to play a role in tissue fibrosis [27, 41].

Recently Mori et al. [35] have recommended focussing on the role of genetic factors in scleroderma-like conditions. Shakoory et al. [42] observed the role of mast-cell-derived cytokines in eosinophil biology. Apparently the cytokines and chemokines of the mast cell in tissue can regulate the eosinophil hematopoiesis, activation, survival and elaboration of mediators. In addition, the eosinophils can influence mast cell function in a paracrine mode by secretion of stem cell factor. This interaction between mast cells and eosinophils may influence chronic inflammatory responses.

Patients between the second and sixth decade of live are mostly affected [6, 14]. Our 1-year-old girl was, according to the literature, the youngest patient with a diagnosis of EF. Six out of 11 patients in our study (55%) were female. A study by Blaser et al. [14], which reviewed 192 cases from the literature, suggests an equal occurrence of the disease. Mostly Caucasians are affected with only few Afro-Americans [43–45], Africans [46] and Asians [2, 36, 47].

The classical pattern of cutaneous involvement was observed in our patients, though in 1 case the face presented an atypical edema. In a second step, the skin develops a scleroderma-like induration which can lead to joint contractures in up to 55% [11]. All of our patients had firm indurations of the skin, which finally led to painful contractures. Interestingly EF involved the arms in all patients, whereas the legs were spared in 3. Fatigue, fever and loss of weight may also occur [32]. Carpal tunnel syndrome occurs in 20% of the patients, and inflammatory arthritis can be present in as many as 44% of the patients [11]. However, none of our patients showed these symptoms.

Signs and symptoms which are typical of scleroderma as Raynaud phenomenon, sclerodactyly, abnormal nail fold capillaroscopy findings and antinuclear antibodies are not found in EF [48]. In general sclerodactyly is absent in EF. Sclerodactyly is more a marker for systemic sclerosis. Still, one of our patients presented with sclerodactyly. Visceral and extracutaneous involvement in EF is rare with few reports of involvement of the lungs, esophagus, myocardium, kidney, colon and brain [49–51]. One of our patients developed aplastic anemia and Hashimoto thyroiditis during the disease process. Thyroid abnormalities, such as Hashimoto disease and Graves disease are rarely reported in association with EF [25, 26, 52–54].

Serious hematological disorders and malignancies, such as aplastic anemia, immune thrombocytopenia, peripheral T-cell lymphoma, pure red cell aplasia, acquired thrombocytopenic purpura, Hodgkin and non-Hodgkin lymphoma, have been published [21, 36, 55–58]. Patients with EF show a clearly elevated risk for hematological malignancies [59]. In nearly 10% of EF, hematological disorders can be found [11, 24]. EF can also be linked with other malignancies such as breast cancer or prostatic carcinoma [24, 59].

Our youngest patient, who was exactly 1 year old at her admission to the hospital, had previously presented with a *Mycoplasma*-related pneumonia treated with antibiotics. Subsequently she developed edema and flaky skin within the following days and an eosinophilia-myalgia overlap which faded over months under steroid therapy. The initial suspicion of dermatomyositis or graft-versus-host-disease-like dermatopathy was ruled out by clinical, laboratory and histopathological investigation [60].

In the review of Lakhanpal et al. [11], blood eosinophilia was reported in 63% out of 52 patients, hypergammaglobulinemia and elevated erythrocyte sedimentation rate were seen in 35 and 29%, respectively. Blaser et al. [14] documented in 209 patients a remarkably higher percentage with blood eosinophilia (86.2%), hypergammaglobu-

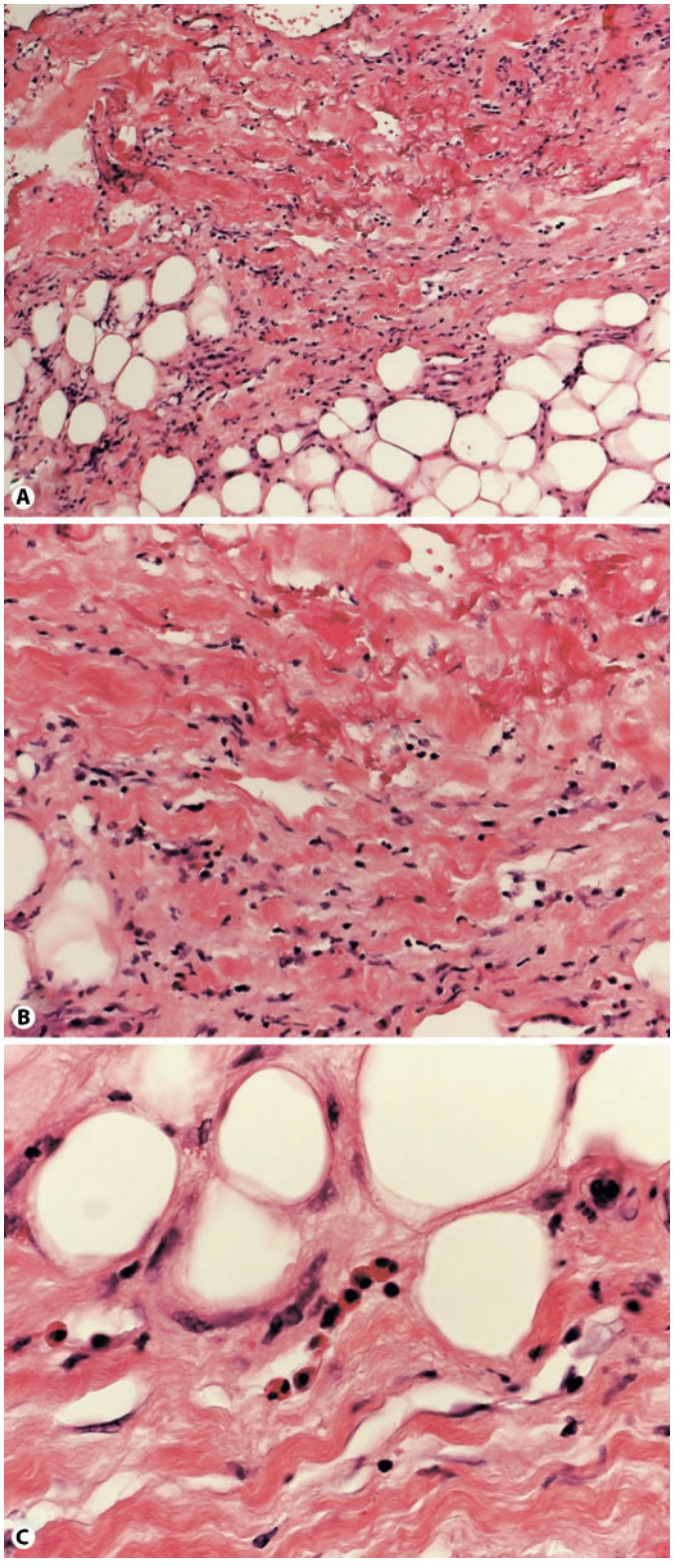

Fig. 4. Lymphohistiocytic inflammation with numerous eosinophilic granulocytes and a focal hypereosinophilic degeneration of the fascia. Biopsy taken before steroid treatment (patient No. 5). Hematoxylin-eosin. **A** ×100. **B** ×200. **C** ×400.

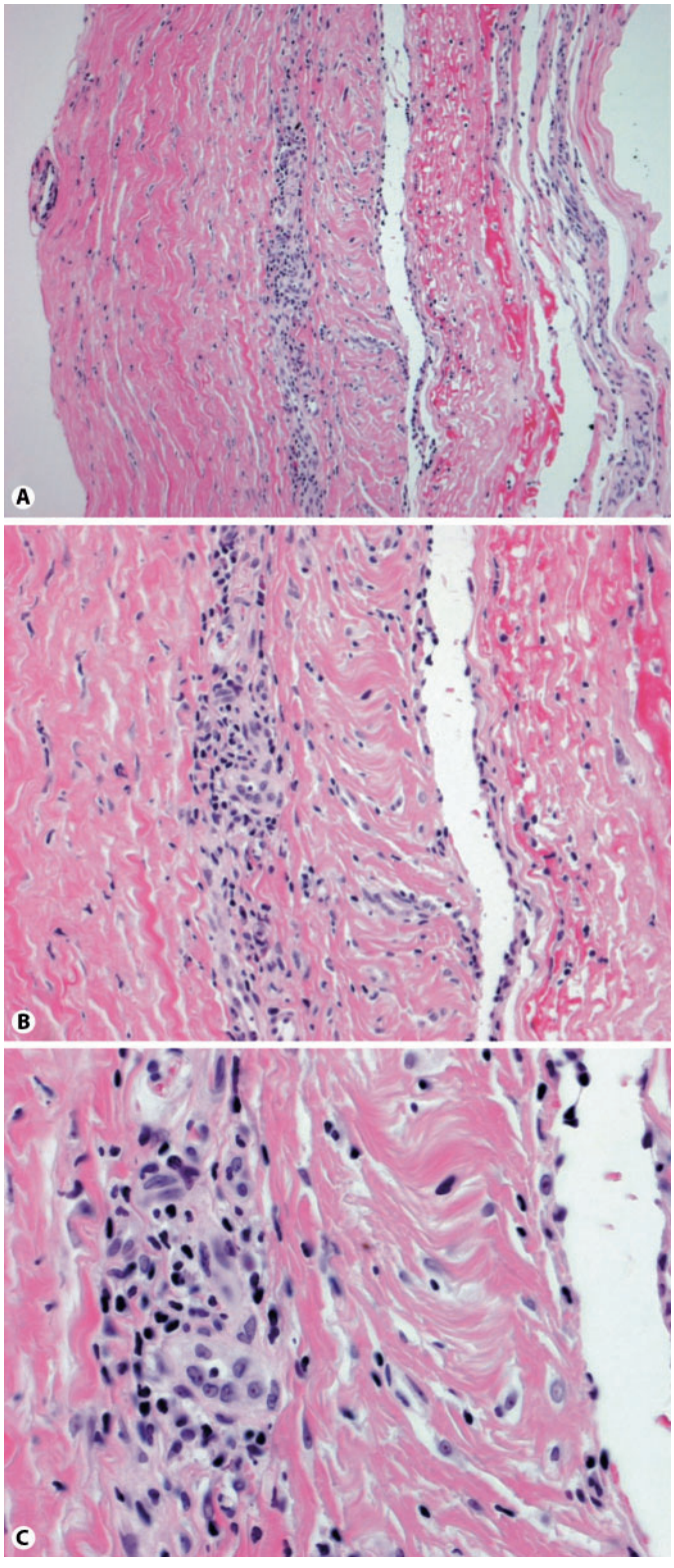

Fig. 5. Fibrinoid necrosis of collagen connective tissue and moderate lymphocytic infiltration predominantly surrounding small vessels and absent eosinophils. Biopsy taken after steroid treatment (patient No. 1). Hematoxylin-eosin. **A** ×100. **B** ×200. **C** ×400.

linemia (72.3%) and elevated erythrocyte sedimentation rate (80.3%). In comparison, 7 of our patients (64%) showed blood eosinophilia, 2 (18%) a hypergammaglobulinemia and 7 (64%) an elevated erythrocyte sedimentation rate. Under steroid treatment, all laboratory findings normalized quickly. Although typical, neither blood eosinophilia nor hypergammaglobulinemia are mandatory for the diagnosis [6, 61]. Even the presence of eosinophils is not required in the fascia for diagnosis. The absence or presence of eosinophils in the fascia seems to correlate with the blood eosinophilia [11].

If EF is suspected, an incisional full-thickness biopsy should be obtained for diagnosis. Typical findings are lymphoplasmacytic inflammation, eosinophils and fibrosis of the deep fascia. In contrast to scleroderma, the dermis is not affected. It is recommendable to take the biopsy prior to steroid therapy, because eosinophils decrease quickly [14, 44] as we can demonstrate in figures 4 and 5. Figure 4 shows the biopsy from patient No. 5 three weeks after the onset of the clinical symptoms and before steroid therapy. Figure 5 with the biopsy of patient No. 1 shows the disappearance of eosinophils within 4 weeks after steroid therapy.

Serology for *Borrelia* should be obtained in every case, as this association was documented repeatedly [4, 5, 20, 21]. The literature also shows several cases, where living *Borrelia* was detected in biopsies [5, 20]. In comparison 2 of our patients were serologically tested positive for borreliosis but living *Borrelia* could not be found in either of their biopsies.

Systemic corticosteroids remain the first-line treatment and are usually followed by a quick response in contrast to scleroderma. The treatment consisted initially in 20–100 mg/day and the drug was tapered as soon as the condition improved. Three patients presented a full or nearly full remission of the symptoms under prednisone within 4 weeks and 5 months, respectively. In 5 patients, partial recovery with remaining induration was observed over months under prednisone. Both patients with borreliosis received adequate antibiotic treatment but only 1 responded clinically to corticosteroids. The other improved under cyclophosphamide after steroids, cyclosporine and azathioprine had failed. The satisfactory response under steroid therapy varies between 59 and 88% [62]. A third of the patients show spontaneous remissions [11] with a protracted course. An early steroid therapy has a positive impact on duration and development of the disease [14]. It may take 3–5 years for full remission of the symptoms without therapy. In the meantime steroid therapy is indicated [13] to prevent symptoms such as joint contractures and carpal tunnel syndrome. Nonresponders and patients with contraindications for corticosteroids have been treated with different therapies which have all been reported to lead to improvement alone or in combination, such as antihistamines (hydroxyzine) [9], histamine 2 antagonists (cimetidine) [10, 16, 63], nonsteroidal antirheumatic drugs (ibuprofen) [10], hydroxychloroquine [11], extracorporeal or bath photochemotherapy [12, 13], cytostatics [4, 6, 64] and immunosuppressive agents [39, 65, 66]. Recently some in vitro data have suggested the use of α-interferon in EF, which could inhibit IL-5 production [17]. Finally for all patients with skin induration, physical therapy should be recommended to prevent or to lessen joint contractures.

Conclusion

Even 30 years after the description of EF, the exact etiology and pathomechanism are still unclear. Further in vivo and in vitro laboratory investigations will be crucial for further understanding the disease. The combination of typical clinical, laboratory and histological findings should easily lead to the correct recognition of the disease.

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