Fasciitis eosinophilica: personal observations and a review of the literature

Danuta Bobrowska-Snarska, Lidia Ostaneck, Marek Brzosko
Clinic of Rheumatology, Pomeranian Medical University, Szczecin, Poland

Abstract: Eosinophilic fasciitis is a rare disease that is classified by some authors to scleroderma-like syndromes. Symmetrical induration of skin and subcutaneous tissue associated with eosinophilia in peripheral blood are characteristic features of the disease. Internal organ involvement is uncommon. It is often difficult to diagnose eosinophilic fasciitis and its course may be variable. Glucocorticosteroids are most commonly used in the treatment but in many cases they are ineffective. Then other immunosuppressive therapy must be considered. Prognosis is rather favorable. The remission is not always achieved and sometimes flares of the disease are observed as evidenced by the described cases. It should be emphasized that a majority of our patients were females. In four out of five patients anti-thyroglobulin antibodies and/or anti-thyroid peroxidase antibodies were present suggesting their involvement in the pathogenesis of eosinophilic fasciitis. Neither indicators of inflammation nor peripheral blood eosinophilia were pathognomonic. Results of glucocorticoid treatment were satisfactory in three patients, but two patients required combined immunosuppressive treatment.

Key words: eosinophilic fasciitis, immunosuppressive treatment

INTRODUCTION

Eosinophilic fasciitis (EF), Shulman’s syndrome, is a rare disease that is classified by some authors to scleroderma-like syndromes [1-3]. Its position in the classification of rheumatic diseases has not been established yet, as concerns the disease entity, syndrome or variant of scleroderma [4-7]. Most authors [8-10] agree that the EF forms a separate disease entity.

This syndrome was described by Shulman et al. [4] as the diffuse fasciitis. The present name was introduced by Rodnan et al. [11] in 1975.

The etiology of the EF is not known. Clinical symptoms may be preceded by strenuous physical exercise [1,12,13], the L-tryptophan ingestion [3,13,14] and the Borrelia burgdorferi infection [14,15].

The EF occurs mainly in men aged 50 to 60 [1,12]. The disease is characterized by a sudden onset. The main symptom is a symmetrical induration of the integument, preceded by swelling which affects extremities, the trunk and the neck, but spares the face, hands, and feet. Only a few described cases presented face affection [1,12]. The induration of skin and subcutaneous tissue is often localized, but in some cases may be presented as diffused [16,17,18]. The skin takes the form of peau d’orange with an irregular, nodular and stiff surface causing the limitation of major joints mobility and minor joints contractures [14,19,20,21]. The hypo- or hyperpigmentation of the skin is observed. Telangiectasies are not presented. A typical feature is a groove sign (appearance of linear furrows along the superficial veins on the affected arm or leg when elevated). The skin is often warm to the touch, sometimes erythematous and finally hyperpigmented.

The Raynaud phenomenon is rarely observed in patients with the EF. A normal result of capillaroscopy test [19] helps to differentiate it from scleroderma and systemic sclerosis [22].

The majority of patients with the EF suffer from leg and arm weakness [23,24]. In some cases a creatinine kinase level was elevated indicating muscle damage [18].

Most patients reported peripheral joints inflammation of different localization [1,16,24]. Carpal tunnel syndrome is often observed [16,25].

Visceral involvement in eosinophilic fasciitis is rarely seen. There were splenomegaly, lung restriction, esophageal dysmotility [3,18], peripheral neuropathy, autoimmune thyroiditis and lymphadenopathy described [8,26].

Hematological symptoms are uncommon. Aplastic anemia, hemolytic anemia, thrombocytopenia, lymphoma and B-cell lymphocytic leukemia were described [2,8,18,27]. The increased risk of myelodysplastic syndrome incidence is observed [5,22].

The C-reactive protein is usually increased. The erythrocyte sedimentation rate (ESR) may remain normal in some cases [23,28], while increased in others [13,22,29,30]. Peripheral eosinophilia (20–30%) occurs usually at diagnosis and relapse [7,23]. Protein electrophoresis usually shows polyclonal hypergammaglobulinemia [18]. The typically rheumatoid
factor (RF) and antinuclear antibodies (ANA) are negative, but may be occasionally positive (titre 1:640, 1:1260) [8,16]. The RF- and ANA- positive patients require careful observation because the EF may turn out to be a symptom of any other systemic disorders such as scleroderma, systemic lupus erythematosus or Sjögren’s syndrome [29]. In some cases immunological complexes were identified in the early stage of the disease [1,31].

The diagnosis is made with a skin-muscle biopsy. The thickening and consecutively fibrosis of the fascia involving more profound skin layers and muscles is observed. Inflammatory infiltrates composed of eosinophils, lymphocytes, plasma cells, and fascia histiocytes may also occur around the blood vessels [5]. The vascular wall infiltration consists mostly of multinuclear cells with a predominance of eosinophils without occlusion [15] or with local vessel occlusion [7]. In a case study analysis by Abeles et al. [23] perivascular infiltrates with lymphocytes, plasmatic cells and eosinophils are associated with mesothelial cells proliferation leading to the vessel lumen occlusion are described.

Eosinophilia was seen in the different forms of pathological fibrosis. It is suggested that it has a causal role in the process of fibrosis. Eosinophils – released fibroblasts activation proceeds in many ways like fibrogene cytokine activation – transforming growth factor β (TGFβ) as well as the potentially toxic major basophilic protein (MBP) abundantly expressed in granulocytes. The BMP protein released in the mechanism of granulocytes activation and degranulation may induce independently, or together with the TGFβ production, of interleukin-6 by fibroblasts. The IL-6 induction of collagen production suggests its role in the pathogenesis of sclerosis [8]:

The EF diagnosis criteria are as follows [12]:
1) soft tissue sclerosis and fibrosis, initially developing in extremities, sparing hands and feet
2) absence of Raynaud’s sign and visceral involvement (unlike in scleroderma)
3) lymphoplasmatic infiltration of the fascia with a variable number of eosinophils without necrotic vascular lesions.

The optimal treatment of the EF is not established yet. Up to now there are no pharmacological standards. Therapy is usually based on the opinion of experts or clinical case studies. The best results were achieved with corticosteroids [10,24]. In the case of a disease unresponsive to corticosteroids – hydrochloroquine, azathioprine [17] and methotrexate [24] are used. Cyclophosphamide, cyclosporine A and antithymocyte globulin are administered [10,27,32]. Reported colchicine and D-penicillamine efficacy is less encouraging [24,33]. Surprisingly, good effects were observed after treatment with histamine receptor antagonists – ceterizine and cimetidine [34]. Cimetidine was demonstrated to act on mast cells, but it may also have influence on peripheral lymphocyte subpopulations which have H1 receptors on their surface. A good response to cimetidine confirms the participation of lymphocyte in the EF pathogenesis [35]. In some cases the good response was achieved with the UVA photochemotherapy with psoralen. [8,36].

We have found 11 cases of the EF in Polish papers [1,26,28,32,37-42]. Here we present 5 cases observed in the Poznań Medical University Rheumatology Clinic with different onsets, courses and treatment responses.

CASE REPORTS

Case 1

A 34-year-old female presenting the pain and edema of skin and subcutaneous tissue of forearms, thighs and calves with “tight skin” feeling. The complaints were accompanied by muscle weakness and weight loss as well as the pain of proximal interphalangeal and metacarpophalangeal joints and fingers paresthesias. For three years she was treated intensively with insulin because of diabetes, and for 2 years with levothyroxine sodium 50 mg/day because of hypothyroidism. Electromyogram revealed the loss of F wave in the right peroneal nerve and the slight increase of F wave value in remaining nerves examined, as well as abounding rest activity and slight neurogenic lesions in the right extensor digitorum brevis muscle.

The skin-muscle biopsy of the calf revealed the fascia inflammatory infiltrate with lymphoid cells, plasmocytes and eosinophils.

The remaining clinical signs and symptoms and results of additional tests are set together in tables 1 and 2.

The patient was treated intravenously with methylprednisolone 500 mg a day over the course of 3 days and consecutively with 8 mg a day as maintaining treatment together with azathioprine 100 mg a day. Previous medications – isophane human insulin (Humulin R and N) and levothyroxine sodium – were administered in the previous doses.

After 5 weeks of treatment peripheral eosinophilia decreased but there was no improvement of skin lesions.

Because of no clinical response and in the presence of coexisting diabetes a decision of methylprednisolone intravenous pulse therapy (500 mg a day over the course of 3 days) every 4 weeks was taken. 5 consecutive treatment cycles were performed. Between intravenous administrations, oral methylprednisolone 8 mg a day and azathioprine 100 mg a day were administered.

The peripheral eosinophilia decrease and the ESR and CRP normalization were obtained as well as the regression of skin symptoms and subcutaneous tissue hypertonia. A slight contracture of the right knee joint persisted. Currently the patient is treated for 25 months with deflazacort 6 mg a day. She remains in a good condition without any symptoms of the disease. The treatment is well tolerated.
Case 2

A 22-year-old female for a couple of years remaining in the medical care of the Outpatient Rheumatology Clinic. In 1988, at the age of five, thighs pains occurred. At the same time an oval, dark brown hyperpigmented foci of skin and hypodermic tissue hardenings with marked edema revealed. In a period of three months it spread over seizing the skin of lower extremities, loins, back, abdomen and upper extremities, sparing hands, feet and the face. The patient reported weakness, fatigue, hypersomnia, appetite loss, abdominal pain and dysphagia.

The skin-muscle biopsy revealed abundant infiltrates with mononuclear cells in the muscle fascia, penetrating in the neighboring fatty tissue.

Remaining clinical signs and symptoms and additional tests results are set together in tables 1 and 2.

The diagnosis of the EF was established in 1989 in the Institute of Rheumatology in Warsaw. She was treated with prednisone 1 mg/kg a day, procaine penicillin, piascledine, vitamin A + E, B<sub>6</sub>, PP and iontophoresis of iodide. After several weeks of treatment skin lesions stopped enlarging and became less dense. Hyperpigmentation started to decline. Abdominal pains and dysphagia resolved. Treatment with constantly reduced doses of prednisolone was continued for 6 months. Treatment with piascledine was continued for 10 years. Currently the patient remains without any pharmacological treatment. The cicatrical hyperpigmentation of abdomen, hips and loins persisted.

Case 3

A 54-year-old female referred to the rheumatology ward with the diagnosis of the EF. The disease began in February 2002 with the pain, edema and induration of skin and the hypodermic tissue of forearms, back, arms, chest, neck and thighs and with muscles pains. The hand and wrist joints were swollen. Periodically ambilateral Achilles' tendon pains occurred. The patient suffered from the loss of appetite, weakness, insomnia and upper abdominal pains. During next several weeks a slight atrophy of lumbrical and interbone muscles of the hand appeared with concomitant painful skin induration. There was the ambilateral symmetric extension restriction of the proximal I and IV interphalangeal hand and knee joints.

The diagnosis based on clinical symptoms and the skin-muscle biopsy was set in the Department of Rheumatology, the University Hospital of Trondheim, in March 2003. Treatment was initiated with low doses of steroids and cyclophosphamide. The cumulative intravenous dose of cyclophosphamide during

<table>
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<tr>
<th>Table 1. Clinical symptoms in eosinophilic fasciitis</th>
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<tr>
<td><strong>Case 1</strong></td>
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<tr>
<td><strong>age</strong></td>
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<td>edema</td>
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<td>hyperpigmentation</td>
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<td>groove sign</td>
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<td>pain</td>
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<td>hypotonia</td>
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<td>edema</td>
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<td>extension restriction</td>
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<td><strong>visceral involvement</strong></td>
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<tr>
<td>history of esophageal dysmotility</td>
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<tr>
<td><strong>others</strong></td>
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<td>peripheral neuropathy</td>
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</table>

8 months came to 7.2 g. During the treatment period skin lesions and general symptoms subsided. However, because of the aminotransferases level elevation, the treatment with cyclophosphamide was withdrawn. During the next two months the patient was treated with low doses of steroids (prednisone 10 mg/day) which were gradually withdrawn because of a good general condition and the lack of symptoms. In December 2003, 6 weeks after prednisone withdrawal skin lesions occurred again. Methylprednisolone 16 mg a day and azathioprine 100 mg a day were introduced. The patient was admitted to the Rheumatology Clinic in January 2004 because of the intensifying muscle pains, skin induration and skin lesions spreading(fig. 1).

Remaining clinical signs and symptoms and additional tests results are set together in tables 1 and 2.

The patient was treated with six pulses of methylprednisolone (500 mg i.v. a day over the course of three days) and cyclophosphamide 800 mg i.v. every 4 weeks. During the treatment period the skin became gradually less tensed and more stretchy, soft and sleek, but the lesions did not resolve completely. The muscle weakness and periodical joints and muscle pains and hyperaesthesia persisted. The combined treatment of low doses of deflazacort, methotrexate and cyclosporine A is continued for 20 months with an excellent general condition and without the clinical signs of the EF. The groove sign on forearms persisted.

### Case 4

A 50-year-old female admitted to the Rheumatology Clinic with the raised tonus of forearms and calves skin and the restricted extension mobility of both hands joints.

The symptoms of transient lower limbs swelling occurred in October 2004. After approximately 12 weeks the “tight skin” symptom developed on forearms and shanks. The groove sign of forearms was present (fig. 2). At the moment of diagnosis the patient was in the course of hormone substitution therapy for five years.

The skin-muscle biopsy from the calf demonstrated abundant perivascular infiltrates with skin and fascia lymphoid cells. Remaining clinical signs and symptoms and additional tests results are set together in tables 1 and 2.

The patient was treated with low doses of steroids, gradually reduced alongside with the clinical improvement.

### Case 5

A 20-year-old male admitted to the Rheumatology Clinic with the raised skin tonus of the left part of the neck, restricting the cervical spine mobility. The symptoms occurred suddenly 6 months before the described here hospitalization, after a rapid cooling. The response to antibiotics was unsatisfactory. The affected skin remained swollen, tough and erythema-

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Table 2. Abnormalities of laboratory tests in EF patients

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
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<th>Case 5</th>
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<tr>
<td>ESR (mm/1h)</td>
<td>25 (↑)</td>
<td>9 (N)</td>
<td>17 (↑)</td>
<td>12 (N)</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>15 (↑)</td>
<td>&lt;1 (N)</td>
<td>&lt;1 (N)</td>
<td>10.06 (↑)</td>
</tr>
<tr>
<td>Peripheral eosinophilia (absolute count/ 1ml)</td>
<td>3290 (↑)</td>
<td>1008 (↑)</td>
<td>1680 (↑)</td>
<td>770 (N)</td>
</tr>
<tr>
<td>Serum IgG (mg/ml)</td>
<td>1847 (↑)</td>
<td>900 (N)</td>
<td>1034 (N)</td>
<td>2533 (↑)</td>
</tr>
<tr>
<td>Serum IgE (IU/ml)</td>
<td>102 (↑)</td>
<td>40.9 (N)</td>
<td>4.5 (N)</td>
<td>39.6 (N)</td>
</tr>
<tr>
<td>ANA</td>
<td>(–)</td>
<td>1:1280 (↑)</td>
<td>(–)</td>
<td>(–)</td>
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<td>ANCA</td>
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<td>aCL</td>
<td>(N)</td>
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<td>Scl-70</td>
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<td>Immunological complexes</td>
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<td>RF</td>
<td>(–)</td>
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<tr>
<td>TSH (m/l)</td>
<td>8.132 (↑)</td>
<td>3.104 (N)</td>
<td>1.32 (N)</td>
<td>0.6 (N)</td>
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<tr>
<td>TgAb (IU/ml)</td>
<td>17.1 (N)</td>
<td>76.0 (↑)</td>
<td>70.8 (↑)</td>
<td>51.4 (↑)</td>
</tr>
<tr>
<td>TPOAb (IU/ml)</td>
<td>75.6 (↑)</td>
<td>4.3 (N)</td>
<td>8.1 (N)</td>
<td>13.1 (↑)</td>
</tr>
<tr>
<td>Borrelia IgM antibody</td>
<td>(–)</td>
<td>(–)</td>
<td>(–)</td>
<td>5.502 (↑)</td>
</tr>
<tr>
<td>Borrelia IgG antibody</td>
<td>(–)</td>
<td>(–)</td>
<td>(–)</td>
<td>2.101 (↑)</td>
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tous. The head mobility was significantly restricted. No other symptoms were present.

The skin-muscle biopsy showed abundant focal inflammatory infiltrates, mainly with plasmocytes and eosinophils of the hypodermic tissue and fascia. Skin and muscle infiltrates were less intense.

Remaining clinical signs and symptoms and additional tests results are set together in tables 1 and 2.

The patient was treated with four cycles of methylprednisolone (500 mg i.v. a day over the course of three days) every 4 weeks and subsequently deflazacort 18 mg a day. At present the pharmacological treatment is continued with the clinical improvement.

The cicatricial lesion of the skin and hypodermic tissue on the left supraclavicular region persisted (fig. 3).

DISCUSSION

Diagnostic criteria of the EF were fulfilled in all cases presented. According to this [12] skin lesions mainly on the trunk and extremities were observed. The face was spared, which is consistent with other authors’ observations [16,18,24].

According to our data, most patients are women, unlike the majority of other investigators data emphasizing the more frequent occurrences of the disease in middle-aged men [1,16,39,43].

In 2 cases visceral involvement in the form of esophageal dysmotility were confirmed. Gastrointestinal symptoms – abdominal pains and appetite loss – are supposed to be connected with chronic active gastritis. Elevated aminotransferase observed in one case is probably caused by the cyclophosphamide therapy. In the second case presented here esophageal dysmotility coexisted with skin lesions, which could indicate an early phase of scleroderma. The diagnosis of the EF was confirmed by the later course of the disease, skin-muscle biopsy, 15-year-long observation and good reaction to steroids. Esophageal dysmotility was observed also in the fourth case but there were no other typical of scleroderma symptoms.

Symptoms from the muscle-skeletal system in three cases were observed. In 1 of these cases the pain and edema of hand joints were observed, while in the other the pain of interphalangeal and metacarpophalangeal joints occurred and the edema of foot joints appeared in the third. Extension restriction in the joints caused by skin lesions and the thickening of the fascia were observed in 3 cases. We have not observed carpal tunnel syndromes, described by some authors [16], however, the first patient presented unspecific peripheral neuropathy symptoms and the third – the symptoms of the right ulnar nerve compression at the level of the wrist. Muscle pains and weakness were described in all cases, however, there were no biochemical markers of muscle damage identified.

Consistent with the findings of other authors [7,16,23], we observed the ESR and the CRP elevation and transient peripheral eosinophilia in all described cases.
We did not documented the ANA in three cases. In the second case antinuclear antibodies occurred two years after remission and it is still present with gradually decreasing titre. The patient does not meet the clinical and serologic criteria for any other than the EF connective tissue disease.

According to available data immunologic disorders in the EF patients were limited to the occasionally confirmed ANA and immune complexes. There are no reports of coexisting thyroid gland disorders or chronic thyroiditis. We confirmed antithyroglobulin antibodies (TGAb) or thyroid peroxidase antibodies (TPOAb) in all cases and in one of them hypothyroidism occurred. Thyroid disorders may be one of the ethicopathologic factors of the EF.

In the fourth case we confirmed the positive IgG and IgM Borrelia antibodies without clinical symptoms of borreliosis. It is necessary to consider the ethicopathologic role of the Borrelia infection in the EF induction, which was previously reported [14,15].

The differential diagnosis of the EF includes scleroderma-like lesions in the course of diabetes, paraproteinemia (multiple myeloma), scleromyxedema and porphyria cutanea tarda as well as genetic scleroderma-like disorders. The skin-muscle biopsy result establishes the diagnosis. There are also differences in clinical course and treatment reactions in other scleroderma-like diseases.

The skin lesions in the first case were very active and responsive to steroids, unlike in sclerodema in the course of diabetes. Paraproteinemic disorders were not the reasons for indurated edema in the presented cases. We have confirmed neither clinical symptoms nor laboratory findings typical of Porphyria cutanea tarda.

The most confusing factors in the differential diagnosis may be symptoms suggesting one of the forms of scleroderma. In the cases presented here we considered the Morphea scleroderma, diffuse systemic scleroderma and linear scleroderma. The skin-muscle biopsy result determines the diagnosis [44-47].

The eosynophilic fasciitis treatment remains an open question. There are suggestions that treatment is not necessary in some cases because the disease may resolve spontaneously [35]. The treatment is based on steroids [12,16,23], but refractoriness to steroids requiring cytostatics or other immunosuppressants remains quite common [10,18,24,27]. Glycocorticoid drugs were administered to all our patients. In the second case antinuclear antibodies occurred two years after remission. There were no clinical effects although in two of them skin lesions did not resolve completely. A small number of reports referring to the disease entity and the lack of data concerning its effective treatment make every new observation useful in clinical practice.

The cases of the EF described here present different clinical pictures, different treatment reactivity and good clinical effects although in two of them skin lesions did not resolve completely. The eosynophilic fasciitis is clinically distinguishable from the eosinophilia-myalgia syndrome and is not associated with L-tryptophan use. J Rheum. 1991; 18: 259-263.

References