Delayed diagnosis of eosinophilic fasciitis: a case report and review of the literature

Aydin E, Turan Y, Yildirim C, Tataroğlu C, Çullu E, Sendur OF

ACTA REUMATOL PORT. 2015;40:179-184

ABSTRACT

Eosinophilic fasciitis (EF) is an uncommon entity characterized by edema, skin thickening and hyperpigmentation of extremities. Laboratory findings are variable and may include peripheral eosinophilia, hypergammaglobulinaemia, and elevated acute phase reactants. A full-thickness skin/fascia/muscle biopsy is the gold standard for diagnosis. Since EF is an uncommon disorder and the clinic presentation mimics scleroderma, it takes a long time to make definitive diagnosis. We present a case diagnosed two years after its onset and responded well to the treatment. We also include here-in the results of our literature survey regarding delayed diagnosis of Eosinophilic fasciitis.

Keywords: Case report; Delayed diagnosis; Eosinophilic fasciitis; Peripheral eosinophilia.

INTRODUCTION

Eosinophilic fasciitis (EF) is a rare rheumatic disorder of unknown etiology. It is characterized by an inflammatory edema, scleroderma-like skin changes and hyperpigmentation in involved limbs. The disease is more common in females than males and diagnosed more frequently in middle age.

Although the pathophysiology of the disease is still unknown, severe physical activity, infections (Borrelia burgdorferi, Mycoplasma arginini), toxicity (trichloroethylene, denatured fats, L-tryptophan), medications (statins, lansoprazole, phenytoin), hematological diseases (lymphoma, leukemia, multiple myeloma, aplastic anemia, pernicious anemia) have been suggested to have a pathogenic role. The onset of the symptoms usually present with acute edema and pain in the limbs, followed by thickening of the dermis or subcutaneous fascia and hyperpigmentation. Skin tightness may present with woody induration, “peau d’orange” appearance, and groove sign. Laboratory analysis reveals increased eosinophilia, hypergammaglobulinemia and elevated acute phase reactants in peripheral blood samples. The definitive diagnosis is based on the presence of inflammatory cell infiltration in the fibrotic fascia, as assessed by a full-thickness skin/fascia/muscle biopsy. Morphea, systemic sclerosis and eosinophilia-myalgia syndrome should be considered in the differential diagnosis. The clinical manifestations of EF may suggest systemic sclerosis although patients with systemic sclerosis have sclerodactyly, visceral organ involvement or Raynaud’s phenomenon. Today, the first line treatment is with high-dose steroids and these are effective in most of the cases. Immunosuppressant drugs and methotrexate (MTX) can be added in refractory cases.

As the clinical manifestations of EF mimic systemic sclerosis, the biopsy is often neglected, resulting in difficult or delayed diagnosis. In this article, we present a case with EF who was diagnosed two years after the onset of the symptoms and responded to the treatment well.

CASE REPORT

A 65-year-old female patient, who had a history of two-month-pain in her left arm, was admitted to our outpatient clinic. She had complained about a painless swelling and stiffness in her left forearm for two years, accompanied by subsequent pain. The patient visited our outpatient clinic with the complaint of increasing pain lasting for two months. The history of the patient revealed hypertension. Physical examination showed non pitting edema and stiffness beginning from the left
elbow to the wrist (Figure 1). There was a groove sign between muscle groups. Dorsiflexion and palmar flexion of the left wrist was slightly limited and painful. Neurological examination was normal. The visual analogue scale (VAS) score for pain was 9 cm. Laboratory analysis showed an erythrocyte sedimentation rate (ESR) of 31 mm/h, C-reactive protein (CRP) of 5.23 mg/L, rheumatoid factor (RF) (-), anti-nuclear antibody (ANA) (-), anti-smooth muscle antibody (ASMA) (-), anti-mitochondrial antibody (AMA) (-), and normal complete blood count (CBC), routine biochemical tests, and hepatic biomarkers. Serum IgE level was slightly over the borderline. Abdominal ultrasound and echocardiography demonstrated normal findings. Magnetic resonance imaging (MRI) of the left forearm showed increased heterogeneous T2 signal indicating edema and inflammation in the fascial planes involving extensor and partially flexor carpi ulnaris muscle and tendon. The examination of the skin/fascia/muscle biopsy samples taken from the left forearm revealed perilobular mononuclear cell infiltration in the subcutaneous adipose tissue. There was an increased acellular collagen matrix, capillary endothelial swelling and perivascular mononuclear cell infiltration in the fascia and lymphocytic cell infiltration in the adjacent adipose tissue (Figure 2). The patient was diagnosed as EF based on the clinical signs and histopathological findings. A treatment of fluocortolone 40 mg/day and MTX 20 mg/week was initiated. A prophylactic treatment for preventing osteoporosis was also added. The patient was administered physical therapy for 10 sessions including transcutaneous electrical nerve stimulation (TENS) (30 min/day) and cold pack (4 x 10 min/day) on her left wrist and exercises for range of joint motion and stretching. At the first month, the VAS score for pain was found to be 1 cm with decreased swelling and stiffness in the left upper extremity. Methotrexate was maintained while corticosteroid treatment was discontinued, with a gradually reduction after one year of treatment, in which the pain and swelling was fully recovered.

DISCUSSION

Eosinophilic fasciitis was first described by Shulman as a variant of scleroderma and it was defined as “eosinophilic fascitis” by Rodnan in 1975.10 Most patients are in their third to sixth decades, however pediatric cases also have been reported.11,12 Although the etiopathogenesis of the disease is still unknown, there are some reports showing EF accompanied by hematological diseases including aplastic anemia, hemoly-
tic anemia, leukemia, and lymphoma, other malignancies and autoimmune diseases including Hashimoto's thyroiditis, systemic sclerosis and Sjogren's syndrome. The onset of the disease is triggered by severe physical activity in more than half of the patients and there are also some case reports showing EF associated with trauma, hemodialysis, insect bite, phenytoin use, exposure to trichloroethylene, and Borrelia burgdorferi. A study investigating the cytokine profile in EF demonstrated increased cytokine abnormalities and transforming growth factor β-1 levels similar to patients with atopic diseases, suggesting that autoimmune mechanisms may also play a role in the pathogenesis of EF. The major symptoms include usually symmetrical acute or subacute pain and edema in the limbs, limited range of joint motion and thickened skin. Review of literature revealed case reports with unilateral presentation similar to our case. The disease is characterized by “peau d’orange” appearance and woody induration, as well as edema and erythema. Face and hands are rarely involved. A groove sign due to skin indurations on superficial veins is a specific characteristic of the disease. In our case, symptoms were unilateral and the groove sign was also present. We could not find any triggering factor, as no detailed information was obtained from the patient since the complaints started two years ago. The diagnosis was made in the late stage, as the patient visited our outpatient clinic two years after the onset of swelling.

Laboratory tests reveal increased eosinophilia, increased ESR and polyclonal hypergammaglobulinemia in peripheral blood samples. The result of ANA, anti ds-DNA and RF are usually negative. In our case, the patient had no eosinophilia in peripheral blood samples with a slightly increased acute phase reactants. The laboratory parameters, which partially returned to normal levels, may be explained by chronic phase of the disease. This suggests that imaging techniques and biopsy samples are more reliable for the diagnosis of patients with chronic disease, than laboratory tests.

The MRI findings are also highly valuable in the diagnosis of EF which reveals thickening and hyperintensity in the superficial muscular fascia in the T1, T2-weighted and STIR sequences without contrast enhancement, while severe contrast enhancement was observed in the fascia in the T2-weighted and STIR sequences following the administration of IV contrast agent. The majority of the patients had deep muscular fascia involvement. The MRI has a critical role in the differential diagnosis of EF and myositis. In addition, MRI is a useful imaging technique in the selection of biopsy site and monitorization of the treatment process. In consistency with the literature data, in our case MRI of the upper extremity showed increased heterogeneous T2 signal indicating edema and inflammation in the fascial planes involving extensor and partially flexor carpi ulnaris muscle and tendon, reduced adipose tissue, and signal loss in T1-weighted series. In these adjacent regions, increased subcutaneous adipose tissue was observed. However, there is a limited data on the sensitivity and specificity of MRI in the diagnosis of EF.

The definitive diagnosis is based on the full-thickness skin/fascia/muscle biopsy. The biopsy findings often show normal but rarely atrophic epidermis. Although half of the patients had sclerosis in the dermis, there are cases without sclerosis. Sclerosis is accompanied by lymphocyte, eosinophilia, plasma cells and histiocytic infiltration. The fascia beyond dermis is thickened by 2-15 folds. Eosinophilic infiltration which is disease-specific in fascia is rarely seen. Muscular biopsy results usually show lymphocyte, plasma cell and histiocytic infiltration. The pathological findings of skin/fascia/muscle biopsy in consistent with all these findings suggested definitive diagnosis of EF in our case.

The initial treatment in EF is high dose corticosteroids with a success rate of 70% among patients. Other beneficial options include MTX, hydroxychloroquine, cyclosporine, D-penicillamine and photochemotherapy. In recent years, tumor necrosis factor antagonists, such as infliximab, have been tested in steroid-refractory EF patients and revealed beneficial results. Although our case was diagnosed two years after the onset of the symptoms, she responded well to high dose steroids in combination with MTX. Her pain and swelling were substantially recovered. No recurrent disease occurred during the follow-up visits.

Bischoff et al. reported that the mean time to diagnosis of EF was 8.8 months. The authors observed that patients with poor outcome had a longer time gap between initiation of first symptoms and diagnosis, when compared to patients with good outcome. We have screened a total of 60 reports on EF which has full texts published in English in Pubmed-MEDLINE from 1974 to the present. Among these, in seven cases the mean time of diagnosis was >1 year (Table I). Only five of these cases had eosinophilia in peripheral blood samples, while five had increased ESR and only two studies
### Table I. Clinical Characteristics of Cases in the Literature

<table>
<thead>
<tr>
<th>Time to diagnosis</th>
<th>Laboratory results</th>
<th>MRI findings</th>
<th>Biopsy results</th>
<th>Treatment</th>
<th>Response to the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Islam et al. [34]</td>
<td>12 months</td>
<td>ESR: 28 mm/s WBC: 17.1x10^9/l Eo: 36% Serum Ig: N</td>
<td>Ø</td>
<td>+</td>
<td>20 mg prednisolone+ hydroxychloroquine (400 mg/day)</td>
</tr>
<tr>
<td>Khanna et al. [33]</td>
<td>15 months</td>
<td>ESR: not available WBC: 7.9/µl Eo: 18%</td>
<td>Ø</td>
<td>+</td>
<td>40 mg prednisolone Infliximab (3 mg/kg/8 hft)</td>
</tr>
<tr>
<td>Danis et al. [21]</td>
<td>36 months</td>
<td>ESR: 3 mm/h WBC: 22.8x10^9/l Eo: 60%</td>
<td>+</td>
<td>+</td>
<td>1mg/kg/day methylprednisolone</td>
</tr>
<tr>
<td>Silny W [35]</td>
<td>&gt;12 months</td>
<td>ESR: increased Eo: 5%</td>
<td>Ø</td>
<td>+</td>
<td>1000-500-250 mg IV methylprednisolone followed by 32 mg P.O. methylprednisolone +cylosporine (150 mg/day) UVA1 phototherapy (60J/cm^2, three times a week, 31 irradiation, total dose: 1750 J/cm^2)</td>
</tr>
<tr>
<td>Tahara et al. [36]</td>
<td>12 months</td>
<td>ESR: 66 mm/s WBC: 5500/µl Eo: 500/µl Serum IgG: 3550 mg/dl</td>
<td>Ø</td>
<td>+</td>
<td>Cylosporine (100 mg/day)</td>
</tr>
<tr>
<td>Khanna et al. [5]</td>
<td>12 months</td>
<td>ESR:100 mm/s Total blood count: normochromic normocytic anemia IgG Monoclonal gammopathy in the protein electrophoresis (also diagnosed with multiple myeloma) Serum IgG: 36.00g/l (N: 6.87-16.30)</td>
<td>Ø</td>
<td>+</td>
<td>High dose dexamethasone and pamidronate (multiple myeloma treatment)</td>
</tr>
<tr>
<td>Flamen et al. [37]</td>
<td>48 months</td>
<td>ESR: 44mm/s WBC: N Moderate eosinophilia Polyclonal IgG hypergammaglobulinemia in the protein electrophoresis</td>
<td>Ø</td>
<td>+</td>
<td>Glucocorticosteroids + D- penicillamine (dose not available)</td>
</tr>
<tr>
<td>Rosenfeld et al. [38]</td>
<td>12 months</td>
<td>ESR: 61mm/s WBC: 25x10^9 Eo: 80%</td>
<td>Ø</td>
<td>+</td>
<td>45 mg prednisolone</td>
</tr>
</tbody>
</table>

Agreement was voted on a scale from 1 to 10 (fully disagree to fully agree) by 36 voting rheumatologists.

ASAS, Assessment of Spondyloarthritis international Society. ASDAS, Ankylosing Spondylitis Disease Activity Score. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index. SD, standard deviation.
showed increased serum IgG level. These results suggest obscure laboratory findings in late stages of disease. The definitive diagnosis was based on full-thickness skin/fascia/muscle biopsy in all these seven cases. The MRI was performed only in one case, suggesting findings consistent with EF. The treatment modalities varied, however the majority of the patients responded well to medication\(^\text{21,33-36}\).

In conclusion, EF should be considered in differential diagnosis in case of unknown swelling and pain. Although laboratory parameters may be reduced in cases with late diagnosis, a full-thickness skin/fascia/muscle biopsy and MRI may significantly contribute to the diagnosis. Despite late diagnosis, patients may still benefit from a high dose steroid therapy.

CORRESPONDENCE TO
Elif Aydin
Adnan Menderes University Hospital Department of Physical and Rehabilitation
09100 Aydin, Turkey
E-mail: drebulak@yahoo.com

REFERENCES


