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Eosinophilic fasciitis in the context of autoimmune skin diseases: a case report

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Abstract

Eosinophilic fasciitis (EF) is a rare autoimmune disorder affecting the connective tissue. It is characterized by painful inflammation and fibrosis, leading to sclerosis of fascia concerning limbs. Diagnosis is mostly based on clinical findings and confirmed by histopathological examination. Its rare occurrence and non-obvious course of this disease, mimicking more common syndromes, often causes diagnostic problems. During the diagnostic process, a number of diseases must be excluded: systemic scleroderma (SS), nephrogenic systemic fibrosis,

eosinophilia-myalgia syndrome, or Churg-Strauss syndrome (EGPA). The following case report features a 67-year-old female and identifies the characteristic clinical and laboratory features that allow the differentiation of EF from systemic sclerosis and other autoimmune skin diseases, which is useful in everyday clinical practice. The patient complained of increasing swelling of the lower limbs, forearms, and induration in the subcutaneous tissue without involvement of the hands and feet. Based on the biopsy and additional tests, she was diagnosed with EF and treated primarily with oral glucocorticoids (GC). Due to the present side effects of steroid therapy, the decision was made to reduce the doses of GSs with the introduction of methotrexate (MTX). This modification proved successful, and after 23 weeks of treatment, remission of symptoms was observed without further progression of the disease.
Key words: eosinophilic fasciitis; systemic sclerosis; methotrexate; case report

Introduction

Eosinophilic fasciitis (EF) is a rare connective tissue disease of undetermined etiology. The disease primarily affects Caucasians, with a peak incidence at 40–50 years of age [1]. Men suffer from this disease almost 2 times more often than women, and cases in children have been described sporadically, mainly in girls [2, 3]. The characteristic feature is the presence of symmetrical oedema and erythema of the skin, together with a wood-like induration of the fasciae. Secondary to sclerotization of the skin, contractures limiting mobility of the limbs and torso develop [1]. Diagnosis is confirmed through the histopathological examination of a dermo-muscular section. Treatment is mainly conducted using oral GC and disease-modifying anti-rheumatic drugs (DMARD) such as methotrexate (MTX), which, if included, reduce the side effects of steroid therapy and ensure long-term remission of the disease [1].

Etiology and pathophysiology

The etiology of EF remains unknown. However, predisposing factors have been identified as most commonly appearing in patients' history. These include trauma and intense exercise, as well as excessive cold exposure [2, 4]. Cases of patients in whom the presence of infections such as *Mycoplasma arginini*, *Borrelia burgdorferi* or parasitial infections were identified, have also been described [5]. Certain drugs have been identified whose intake has been linked to EF: simvastatin, atorvastatin, phenytoin, heparin, intravenous iron, and some of the checkpoint inhibitors [6]. It has been observed that EF may coexist with autoimmune diseases such as Graves' disease, Hashimoto's disease, Sjögren's syndrome, spontaneous thrombocytopenia, hemolytic anemia, and pernicious anemia [1]. Studies also indicate the presence of immunoglobulin deposits and factor C3 of the complement system in the fascia and skin, suggesting an essential role of autoimmune conditions in pathomechanism. In addition, EF was classified as a paraneoplastic syndrome that resolved after successful tumor curation [7].

Clinical manifestations

The development of eosinophilic fasciitis is usually sudden [8]. Initial symptoms include pain and swelling in both upper and lower extremities. Accompanying general symptoms include fever, weakness, weight loss, and malaise. This is followed by the development of induration of the skin and subcutaneous tissue. Apart from the extremities, the trunk and neck are rarely affected, and the lesions are symmetrical. The skin sometimes takes on the characteristic appearance of the so-called orange peel, and the affected venous vessels cause the so-called furrow sign characterized by linear depressions in the skin [9–11].

Further, the development of sclerosis can lead to contractures in the limbs, as well as restricted mobility in the joints, which develop over weeks or months. Patients report morning stiffness,

and 20% have symptoms of carpal tunnel syndrome or compression of other peripheral nerves [9]. Occasionally, internal organ lesions may appear, such as restrictive changes in the lungs, pleuritis with effusion, pericarditis, splenomegaly, esophageal peristalsis, liver or renal involvement, and lymphadenopathy [11–13].

Additional tests

Histopathological examination of a deep dermal-muscular biopsy slice is fundamental in the diagnosis of eosinophilic fasciitis. The biopsy should include skin, subcutaneous tissue, fascia, and muscle [1]. The prevailing cells found in the inflammatory infiltration are eosinophils, plasma cells, macrophages, and histiocytes. As the disease develops, tissue fibrosis and thickening of the fascia are observed. In the affected muscles, findings include inflammatory changes without signs of necrosis.

Due to the invasive nature of biopsy, attempts have been made to replace it with magnetic resonance imaging (MRI). To date, however, MRI is mainly used to select the site to be used as a dermo-muscular slice and to monitor treatment progress [14].

Differential diagnosis

EF should first be differentiated from diseases that also involve fibrosis or eosinophilia. Most commonly, EF needs to be distinguished from systemic sclerosis. A characteristic of EF is the lack of involvement of the face, feet, and hands. Additionally, the absence of sclerodactyly, Raynaud's phenomenon, and telangiectasia argue against a diagnosis of scleroderma [1]. Specific antibody testing and assessment of internal organ involvement are also utilized, as well as abnormalities in capillaroscopy. Ultimately, histopathological examination remains decisive.

Another condition to consider is nephrogenic systemic fibrosis, affecting patients with severe kidney failure. In this case, fibrosis, in addition to skin, may also involve muscles and internal organs: heart, lungs, and kidneys. In the case of eosinophilia-myalgia syndrome, which is induced by tryptophan preparations, generalized muscle pain, joint pain, cough with dyspnea, skin hypersensitivity, itching, and rash occur. In the chronic phase of this condition, skin and subcutaneous tissue become hardened, and internal organs are affected.

In contrast to EF, elevated liver enzyme levels and aldolase activity are observed. In the case of peripheral eosinophilia, hypereosinophilic syndrome should be differentiated. In addition to changes in peripheral blood, organ involvement is present without the characteristic skin and subcutaneous tissue changes seen in EF [1]. Scleromyxoedema is a syndrome characterized by skin changes localized to the face, neck, upper limbs, and trunk. Histopathological examination revealing mucin deposits, fibroblast proliferation, and collagen deposits argues against EF. Pulmonary and neurological symptoms exclude EF and the presence of ANCA antibodies. Lastly, cutaneous lymphoproliferative disorders should be considered in differential diagnosis. Primary cutaneous proliferative center lymphoma (PCFCL), primary cutaneous marginal zone lymphoma (PCMZL), and primary cutaneous diffuse large B-cell lymphoma of the limb type (PCLBCL LT) may be responsible for skin lesions involving upper and lower extremities, occasionally mimicking EF. Characteristics of lesions include multifocal macules, discs, and nodules. Histopathological evaluation and appropriate immunohistochemical staining are essential for diagnosis [15].

Treatment

Due to the unknown etiological factor, causal treatment is not available. Symptomatic therapy aims to slow down and reduce the inflammatory process. In pharmacological treatment, glucocorticoids are the first-line therapy. Initially, prednisone is used at a dose of 1 mg/kg/day or methylprednisolone at 0.5–1 g/day intravenously [2]. After four to eight weeks, a reduction of the dose is recommended at a 10 mg per month rate until reaching a maintenance dose of 5–10 mg per day. This treatment is maintained for many years or even lifelong. If a satisfactory effect is not achieved after 4–6 weeks, DMARD should be considered [2]. Among them, the following are used: methotrexate, azathioprine, cyclosporine, and cyclophosphamide.

In some cases, human immunoglobulins of 0.4 g/kg per day for 5 days, then once a month for 3–7 months, are recommended [8]. In case of refractory eosinophilic fasciitis or contraindication to traditional medications, biologic treatment may be useful. Tocilizumab, infliximab, and rituximab provide the highest frequency of improvement in this group of medications, ensuring sustained remission [16, 17].

Non-pharmacological treatment includes rehabilitation to reduce and prevent contractures [2]. In advanced cases, surgical treatment may be considered to relieve symptoms associated with peripheral nerve compression [1].

Case report

A 67-year-old female patient was admitted to the rheumatology ward, referred after a prolonged diagnostic process in the internal medicine department due to increasing swelling of the lower limbs and forearms and hardening of the subcutaneous tissue. During that stay, echocardiography, abdominal computed tomography (CT) scan, and lung scan were performed without a specific identification of the cause. With the referral of the patient, laboratory results

with the following abnormalities were included: C-reactive protein (CRP) 84 mg/L, thrombocytosis 452,000/L, eosinophilia in peripheral blood smear 1716/μL (12%) with leukocytosis of 14 300/μL.

In a physical examination, an impaired gait was observed due to “tightness of the lower extremities”. Raynaud’s sign was absent, and there was no sclerodactyly and no facial involvement of the skin lesions. In capillaroscopy, no significant changes were observed. The following series of laboratory tests were performed (Tab. 1).

Eosinophilia is a characteristic feature of eosinophilic fasciitis and is present in 80–90% of patients. A high eosinophil count in the peripheral blood smear, exceeding 500/μL, is most notable in the initial stage of the disease [1]. Despite its high occurrence, eosinophilia is not essential for EF diagnosis, and its severity does not necessarily correlate with the severity of the disease [2, 7]. Some patients may show increased creatine kinase (CPK) and aldolase enzymes, indicating muscle damage. Hypergammaglobulinemia, typically polyclonal in nature, often involves immunoglobulin A (IgA) and immunoglobulin G (IgG) [14, 18]. The absence of specific antibodies is utilized in differential diagnosis [14].

Based on the findings, systemic scleroderma was excluded, and further diagnostic steps were directed towards EF. First, a dermo-muscular biopsy was taken, and symptomatic treatment was administered: prednisone 60 mg daily. Histopathological diagnosis confirmed the suspicion of EF: Multiple lymphocytic inflammatory infiltrates in the medium-density subepithelial layer of the dermis. The structure of the epidermis and dermis, the number of dermal appendages, and the structure of subcutaneous adipose tissue were within normal limits. Focal high-density lymphocytic inflammatory infiltrates are seen within the fascia and skeletal muscle. The above picture is consistent with chronic fasciitis and skeletal muscle inflammation. Given the diagnosis,

prednisone 55 mg daily was used in the treatment. Because of the side effects of prednisone – agitation and sleep disturbance, the decision was made to start methotrexate at a dose of 15 mg weekly and to reduce prednisone. In the 8 weeks between the next outpatient visit, the patient was hospitalized in the psychiatry department, where a diagnosis of mixed dementia was made, and psychotropic and antidepressant medications were started. The reduction of medication dose continued: prednisone finally to 7,5 mg daily, and methotrexate was increased to 25 mg weekly (Fig. 1).

Discussion

EF is a rare entity that poses a diagnostic challenge due to the nature of its symptoms, which are similar to the course of other diseases. In the first instance, it may mimic systemic scleroderma, where the nature of the skin lesions, although resembling orange peel, also involves the fingers, which is not characteristic of EF. The absence of ulceration of the fingers, Raynaud's sign, and the presence of eosinophilia in the peripheral blood will also argue against the diagnosis of scleroderma. It should be remembered that topoisomerase I (Scl-70) and anti-centromere antibodies (ACA) may be determined, which are present in generalized and limited forms of scleroderma in approximately 90% of patients, respectively. Despite the many differences, the diagnosis of EF is problematic, and a definitive diagnosis can be made after histopathological examination of a dermo-muscular slice, where the characteristic changes of EF are visible. Other conditions considered in the differential diagnosis are nephrogenic systemic fibrosis, eosinophilia-myalgia syndrome, and sclerosing myxedema. Since EF can be, in some cases, classified as a paraneoplastic syndrome, an appropriate diagnostic process should be made to exclude neoplasms as a potential cause.

EF, when treated, has a good prognosis, but treatment targets only symptoms, with no causal options available. Additionally, due to its rarity, therapy is based exclusively on case reports and retrospective analyses. The first-line treatment is with corticosteroids: prednisone and methylprednisolone. In most patients, this leads to regression of the lesions and halting of the disease progression. Nevertheless, in some cases, including our patient, GC is inconvenient due to many possible side effects of long-term therapy. In this case, the MTX proved to be an adequate substitute for the GC, reducing adverse effects and ensuring the remission of the disease.

Conclusions

The non-obvious course of EF, which may mimic more common diseases, can be problematic, sometimes delaying diagnosis and implementation of appropriate treatment. During the diagnostic process it in necessary to exclude systemic scleroderma, and the presence of certain neoplasm, which may cause EF. After a successful diagnosis, MTX proved to be effective, safe, and well-tolerated, allowing for a quick reduction in the dose of GC.

Ethics statement

The authors declare that the work which is a case report does not disclose personal information about the patient. The anonymity of the patient is preserved in the case of publication of the attached photos.

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Conflict of interest

The authors declare no conflict of interest with respect to the submitted article. The paper was written independently, without external funding or sponsorship.

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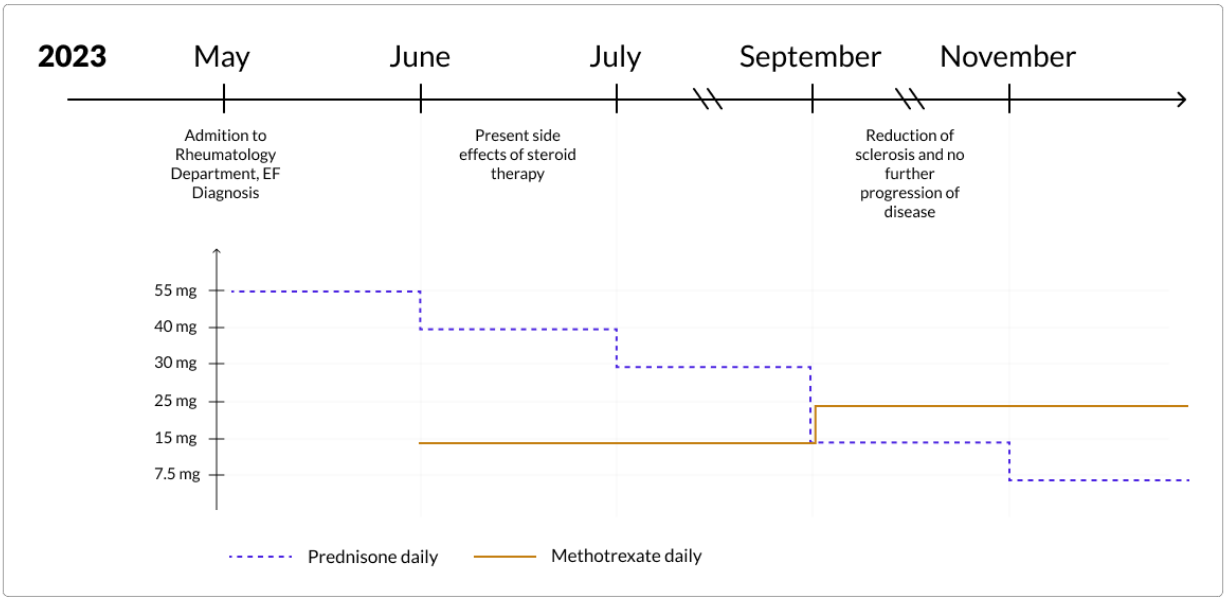
Table 1. Laboratory tests, performed on the admission to the rheumatology department

Test	Results
CRP	57 mg/l
ESR	20 mm
Eosinophilia	1712 /µl or 12,5% (normal up to 500 /µl or 5%)
Leukocytosis	13 700 /µl
Aldolase	11 U/l (normal 2.2-8.5 U/l)
Protein electrophoresis	increased alpha 1 and alpha 2 globulins
LDH	normal
CPK	low
Complement components	normal levels
HBsAg, anti-HCV and HIV Ab/Ag	negative
ANCA antibodies	absent
ANA antibodies	titer 1:160, granular luminescent type

CRP — C-reactive protein; ESR — erythrocyte sedimentation rate; LDH — lactate dehydrogenase; CPK — creatine kinase; HbsAg — hepatitis B surface antigen; anti-HCV — hepatitis C virus antibody; HIV Ab/Ag — human immunodeficiency virus antibody/antigen; ANCA — antineutrophil cytoplasmic antibodies; ANA — Anti-nuclear antibodies

Figure 1. Timeline of the administered treatment


2023
May
June
July
September
November
Admition to Rheumatology Department, EF Diagnosis
Present side effects of steroid therapy
Reduction of sclerosis and no further progression of disease
55 mg
40 mg
30 mg
25 mg
15 mg
7.5 mg
Prednisone daily
Methotrexate daily