ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

Rheumatology Forum

OFFICIAL JOURNAL OF THE POLISH SOCIETY OF RHEUMATOLOGY

ISSN: 2720-3921

e-ISSN: 2720-3913

Eosinophilic fasciitis — a case report

Authors: Joanna Zalewska, Tacjana Barczyńska, Małgorzata Węgierska, Daniel Jeka

DOI: 10.5603/rf.96786

Article type: Case report

Submitted: 2023-08-01

Zaakceptowane: 2023-10-08

Published online: 2024-01-24

Eosinophilic fasciitis — a case report

10.5603/rf.96786

Joanna Zalewska[1, 2], Tacjana Barczyńska[1, 2], Małgorzata Węgierska[1, 2], Daniel Jeka[3]

[1]*Department of Rheumatology and Connective Tissue Diseases, Nicolaus Copernicus University Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń (UMK), Poland*

[2]*Clinic of Rheumatology and Connective Tissue Diseases, Jan Biziel University Hospital No. 2, Bydgoszcz, Poland*

[3]*Innovative Clinical Therapies, Toruń, Poland*

Abstract

Eosinophilic fasciitis (EF) is a rare disease. The case of a patient who was treated with immunosuppressive therapy with methotrexate and methylprednisolone was presented. The aetiology of the disease, diagnostic difficulties and treatment were also discussed.

Key words: eosinophilic fasciitis

Introduction

Eosinophilic fasciitis (EF) is a rare disease. It was first described in 1975 by Lawrence E. Schulman as diffuse fasciitis with eosinophilia. The disease occurs predominantly in Caucasians, aged 40–60 years. Researchers do not agree on the prevalence of the disease in either sex. There are reports of increased incidence in both women and men [1–4]. Typical symptoms include symmetrical and painful swelling of the skin, with progressive significant hardening of the skin involving the upper and lower extremities, as well as the trunk. Laboratory tests show elevated acute phase indices such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and peripheral blood eosinophilia. No organ changes are found. Due to the very rare occurrence of the disease, differential diagnosis, as well as treatment, is difficult due to the lack of randomised clinical trials and the absence of therapeutic algorithms [1–7].

Case report

This paper presents the description of a 52-year-old man who was admitted to the Department of Rheumatology in July 2022 due to erythema and increased skin turgor of the back, chest, upper extremities — arms and left forearm and left hand. The symptoms occurred a year earlier. The patient denied Raynaud's phenomenon, dysphagia, dry eyes and mouth, oral ulcers and hypersensitivity to sunlight, and other symptoms of systemic connective tissue diseases. The patient had a history of hypertension, type 2 diabetes, oesophagitis and gastritis, hepatic steatosis, lower limb varicose veins, osteoarthritis. Laboratory tests revealed such abnormalities as elevated acute phase indices: ESR, hyperglycaemia, hypergammaglobulinemia. Immunofixation was assessed — negative result. During hospitalisation, numerous immunological tests were performed, including anti-nuclear antibodies (ANA) — negative result, anti-cardiolipin IgG (ACA-IgG) — negative result, ACA-IgM — positive result, anti-phosphatidylserine IgG — negative result, anti-phosphatidylserine IgM — positive result, anti-β2glycoprotein 1 IgG and IgM — positive results, (anti-)chlamydia trachomatis IgG — positive result, (anti-)chlamydia trachomatis IgM — negative result, (anti-)Yersinia IgG — positive result, (anti-)Yersinia IgM — negative result, anti-cytomegalovirus (CMV) IgG — positive result, anti-CMV IgM — negative result, EBV IgG — positive result, (anti-)Epstein-Barr virus (EBV) IgM — negative result, anti-citrullinated protein (anti-CCP) antibodies, rheumatoid factor (RF) IgM, anti-centromere protein (anti-CENP), anti-topoisomerase I (Scl-70), anti-double stranded DNA (anti-dsDNA), anti-fibrillarin IgG and IgM, anti-beta-2 glycoprotein 1 IgG, antinuclear anti-SS-A (Ro), La, Jo-1, Mi-2, PM-Scl, anti-neutrophil cytoplasmic antigens (ANCA): pANCA, cANCA, Rib-P, Sm, anti-ribonucleoprotein (U1-RNP) — negative results. Ultrasonography (USG) of the abdomen showed features of hepatic steatosis and splenomegaly. A computed tomography (CT) scan of the chest showed no abnormalities. Capillaroscopy showed a reduced capillary count, while densitometry (DXA) revealed osteopenia. Haematology, diabetology, dermatology and surgery consultations were conducted. A colonoscopy was performed and a sigmoid polyp was found (polypectomy was performed), as well as diverticula in the sigmoid colon and hemorrhoids. In the histopathological examination of a skin-muscle biopsy of the left forearm, lymphocytic and histiocytic infiltrates were observed in the dermis around the blood vessels of the superficial plexus, with mild involvement around the glands, predominantly characterised by T lymphocytes (CD3+) over B lymphocytes (CD20+). Scattered and clustered mixed inflammatory infiltrates of single B lymphocytes (CD 20+) and multiple T lymphocytes (CD3+) with a CD4>CD8 ratio were found within the fascia. Eosinophilic fasciitis (EF) was diagnosed. Methotrexate at a dose of 15 mg/week per os (*p.o.*) and methylprednisolone at a total

dose of 1,500 mg intravenously (*i.v.*) were included. Prednisone at a dose of 5 mg/d. *p.o.* was ordered on an outpatient basis . From July 2022, the patient received nine pulses of methylprednisolone *i.v.* at a total dose of 1.5 g *i.v*. each. Treatment was well tolerated and no complications were observed. From October 2022, the dose of methotrexate was increased to 20 mg/week*p.o.* and from December 2022 to 25 mg/week *p.o.* In February 2023, there was improvement in skin lesions. The skin was softer, with less turgor, without swelling or redness. Currently, the patient is hospitalised every 2–3 months for continued treatment with methylprednisolone pulses *i.v.* as part of maintenance therapy.

Aetiopathogenesis

The aetiopathogenesis of EF is unknown. Factors that are responsible for triggering symptoms of EF include intense physical exertion, prolonged exposure to cold, trauma, stress. First symptoms of EF also appeared in patients with *Borrelia burgdorferi* infection and *Mycoplasma arginini* infection, after exposure to fire ant (*Solenopsis invicta*) toxins, as well as after exposure to chemicals — trichloroethylene — and after the use of L-tryptophan preparations. Medicines that can induce the symptoms include simvastatin, atorvastatin, phenytoin, subcutaneous heparin and intravenous iron. Eosinophilic fasciitis (EF) can also coexist with autoimmune diseases such as Hashimoto's disease, Graves' disease, Sjögren's syndrome, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, haemolytic anaemia, pernicious anaemia. Eosinophilic fasciitis (EF) is also described as a comorbidity associated with cancer, post-SARS-CoV-2 infection, and following the use of oncology drugs, including pembrolizumab, ipilimumab, atezolizumab, nivolumab [2, 8–10].

Pathophysiology

Eosinophils play an important role in the fibrotic process. They produce eosinophil-derived neurotoxin (EDN). Eosinophil-derived neurotoxin (EDN), together with transforming growth factor β1 (TGFβ), connective tissue growth factor (CTGF) and cytokines: interleukins (IL) — IL-4 and IL-13 — affect activation of fibroblasts. As a result, fibroblasts produce increased amounts of collagen and also secrete cytokines that are chemoattractants for eosinophils, leading to excessive production of reactive oxygen species. An important role is played by IL-5, which affects the production, activation, adhesion and degranulation of eosinophils. Elevated levels of tissue inhibitor of metalloproteinase 1 (TIMP-1), which could be used as a marker of disease activity, are found in EF patients [2, 11, 12].

During retrospective analysis, patients very often report an increase in physical exertion shortly before the onset of first symptoms. Physical exertion may trigger an antigenic response in the fascia

and subcutaneous tissue. The intake of L-tryptophan preparations is associated with the action of this substance and its metabolites on the aryl hydrocarbon receptor (AHR). Activation of the receptor triggers the differentiation of Th17 lymphocytes and initiates an inflammatory response [3, 10, 13].

Clinical manifestations

EF usually starts suddenly. In the first phase of the disease, there may be general symptoms such as weakness, reduced exercise tolerance, weight loss and fever. Initially, there is pain and swelling, followed by hardening of the skin and subcutaneous tissue. The lesions are usually symmetrical, involving the upper and lower extremities, sometimes the trunk and neck, exceptionally the face. The skin may have an appearance of orange peel with an irregular surface. Sometimes there is a groove sign — linear depressions over the veins in the affected area. Pigmentation changes and hair loss in the area of hardening were also described. Hardening of the skin can lead to reduced joint mobility and contractures in the joints. Signs of arthritis with associated morning stiffness are sometimes found. Symptoms of EF also include carpal tunnel syndrome, muscle pain and weakness, and sometimes an increase in creatine phosphokinase (CPK) and aldolase levels. Raynaud's phenomenon is usually absent, which is helpful in differentiating from systemic sclerosis (SSc). Most authors deny the presence of organ changes in the course of EF. Some describe involvement of internal organs such as restrictive changes in the lungs, pleurisy with effusion, pericarditis, splenomegaly, lymphadenopathy, oesophageal peristalsis, endocolitis, renal involvement or peripheral neuropathy [2, 3, 13, 14].

Laboratory and diagnostic tests

Laboratory tests show peripheral eosinophilia, which does not correlate with disease activity. Elevated acute-phase markers — ESR and CRP — are also found, as well as — occasionally — polyclonal hypergammaglobulinemia, which needs further diagnostic workup for haematological diseases. The degree of disease activity is assessed using serum aldolase assay or type III procollagen peptide (PIIINP) assay. It is thought that PIIINP may be a good marker for monitoring disease activity.

Specific antibodies are usually absent. Some authors confirm the presence of antibodies such as CENP, Scl-70 and anti-RNA polymerase III in 15–20 % of EF patients [8]. Antinuclear antibodies and RF are positive in approximately 10 % of EF patients [3, 10].

Histopathological examination

The most important diagnostic test in the diagnosis of EF is the histopathological examination. It is the gold standard for diagnosis. The material from the skin-muscle biopsy shows inflammatory infiltrates consisting of lymphocytes, histiocytes, plasma cells and eosinophils, which are localised in the deep fascia and subcutaneous tissue. In a further stage, there is thickening and hardening of the fascia with disappearance of inflammatory infiltrates. Degranulation of eosinophils is followed by the release of cytokines, chemokines and growth factors. Proteins, including eosinophil cationic proteins (ECP), EDN, eosinophil peroxidase (EPX) and major basic protein (MBP), are released and accumulate due to their toxic and fibrotic effects on tissues, thereby activating fibrosis. There is also an increase in histamine, which is found in the tissues and blood.

When the histopathological result is unclear or when material cannot be collected for histopathological examination, magnetic resonance imaging (MRI) can be used to confirm the presence of inflammatory infiltrates in the fascia. Inflammatory activity in the fascia is visible and confirmed by T2 signalling in the subcutaneous tissue and deep fascia, with enhancement of fat-suppressed structures at T1 after administration of gadolinium. If MRI is contraindicated, other imaging modalities such as ultrasound (US) or positron emission tomography/computed tomography (PET/CT) can be used [2, 3].

Diagnostic criteria and stage of disease

The latest diagnostic criteria for EF were presented in the Journal of Dermatology in 2018. The classification criteria specify one major criterion — symmetric sclerotic lesions located on the extremities, with the exclusion of SSc and with the absence of Raynaud's phenomenon. Minor criteria include histopathological findings and changes seen on MRI. The patient meets the diagnostic criteria for EF if a major criterion and one or two minor criteria are present [15].

Table 1. Diagnostic criteria for eosinophilic fasciitis (EF)

Major criteria	**Minor criteria**
Symmetric sclerotic lesions located on the extremities, absence of Raynaud’s phenomenon, exclusion of SSc	1. Histopathological findings indicative of fibrosis of fascia, with thickening of the fascia and cellular infiltration of eosinophils and monocytes
	2. Thickening of the fascia in MRI

SSc — systemic sclerosis; MRI — magnetic resonance imaging

For the assessment of the patient's clinical condition, disease severity criteria can be used. The severity of the disease is dependent on the presence of contractures in the upper and lower extremities, limitation of the mobility of the upper and lower extremities, and worsening of the skin lesions.

Differential diagnosis

The differential diagnosis should include localised scleroderma (*morphea*) and SSc. Raynaud's phenomenon is usually absent in EF patients, whereas it is present in 95 % of SSc patients. Capillaroscopy, which is normal in EF patients, is also an important differentiating test. It should be noted that a normal capillaroscopic picture may also be present in SSc patients. Determination of antibodies, including CENP and Scl-70 that are usually absent in EF patients, is also important. The absence of internal organ involvement in EF patients is also an important sign.

Nephrogenic systemic fibrosis, in which deterioration of renal function occurs, should be considered in the differentiation. In contrast to EF, scleroderma involves the hands and feet and no eosinophilia is found. In scleromyxedema (*lichen sclerosus*), the histopathological picture shows deposition of mucin deposits in the skin. In scleredema (otherwise known as Buschke disease), there is extensive induration of the skin, no antibodies and no signs of inflammation on histopathological examination. The disease is most often associated with diabetes mellitus or monoclonal gammopathy.

Eosinophilia-myalgia syndrome (EMS) is also an important condition in the differential diagnosis. The aetiology underlines the importance of previous intake of L-tryptophan and 5-hydroxytryptophan supplements. The predominant symptom is myalgia of greater severity than in EF. In EMS, there is also involvement of internal organs such as the lungs and nervous system.

Eosinophilia and scleroderma also occur in toxic oil syndrome, which was described in 1981 in Spain, in approximately 20,000 people after ingestion of contaminated rapeseed oil. Patients had symptoms such as dyspnoea, myalgia, arthralgia, swelling and hardening of the skin of the extremities, *livedo reticularis*, joint contractures, and neurological symptoms, including neuropathy. Laboratory tests also showed eosinophilia and increased creatine kinase levels. Graft-versus-host disease (GvHD) should also be considered in the differential diagnosis. Symptoms associated with scleroderma and skin fibrosis are present. In the initial phase of the disease, skin lesions are present on the medial side of arms and thighs. Skin involvement along with the presence of fibrosis of fascia

occurs in the chronic phase of the disease. Neoplastic disease should also be excluded during diagnostic workup [2, 3, 8–10, 13].

Treatment

Currently, treatment standards based on randomised clinical trials have not been developed due to the rarity of the disease. Initiating therapy is prednisone at a dose of 1 mg/kg body weight in reducing doses. Normalisation of acute phase indices and reduction of eosinophilia occur earlier than improvement of skin lesions, which takes several weeks to several months. In the absence of improvement, higher doses of prednisone 1.5 mg/kg body weight may be considered for a period of approximately 3 months. Lack of treatment efficacy is an indication for disease-modifying drug therapy. Methotrexate at a dose of 15–25 mg/week is used. Once remission has been achieved, treatment can be maintained for 4–6 months. Another alternative is mycophenolate mofetil or hydroxychloroquine. There are reports of the efficacy of sulphasalazine, azathioprine, cyclosporine, sirolimus and biologics such as tocilizumab, infliximab, rituximab, as well as intravenous immunoglobulins, dapsone, baricitinib and psoralen with UVA phototherapy (PUVA) — in patients with recurrent symptoms. Cases of extracorporeal photopheresis with successful results have also been described, especially in patients who are refractory to therapy with glucocorticosteroids. In patients who have been found to be unable to respond to the aforementioned therapies, monoclonal antibodies for IL-5 inhibitors — reslizumab and mepolizumab — may be considered and are in clinical trials. Physiotherapy also plays an important role [16].

Conclusions

Eosinophilic fasciitis (EF) is a rare disease that requires extensive diagnostic workup. The differentiation – especially with systemic sclerosis – is crucial due to the initiation of appropriate treatment, including glucocorticosteroids, the use of which is contraindicated in systemic sclerosis.

Ethics statement

The collection and evaluation of all patient data – conducted after the confirmation of patient informed consent.

Conflict of interest

Authors declare no conflicts of interests.

Figure 1. Skin lesions on the chest and left upper extremity