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Review

Diagnosis and classification of eosinophilic fasciitis ☆

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ABSTRACT

Eosinophilic fasciitis (EF) is a rare scleroderma-like syndrome with an unknown etiology and pathogenesis that should be considered an immune-allergic disorder. Painful swelling with progressive induration and thickening of the skin and soft tissues of the limbs and trunk are the clinical hallmarks of the disease. Peripheral blood eosinophilia, hypergammaglobulinemia, and elevated erythrocyte sedimentation rate are the main laboratory findings. Full-thickness wedge biopsy of the clinically affected skin showing inflammation and thickening of deep fascia is essential to establish the diagnosis. The differential diagnosis includes systemic sclerosis and other scleroderma subsets such as morphea, and epidemic fasciitis syndromes caused by toxic agents such as the myalgia–eosinophilia syndrome and toxic oil syndrome. Peripheral T cell lymphomas should also be ruled out. The diagnosis of EF can be established by clinical, laboratory and histological findings, but universally accepted international diagnostic criteria are lacking. Corticosteroids are efficacious and remain the standard therapy for EF, although some patients may improve spontaneously.

Contents

1. Introduction

Eosinophilic fasciitis (EF) is an uncommon scleroderma-like disorder first described by Shulman [1] in 1974 and characterized by induration of the skin, peripheral eosinophilia, hypergammaglobulinemia, and elevated erythrocyte sedimentation rate (ESR). The disease is present almost equally in both sexes [2–4], in sporadic rather than in epidemic form. The mean age at onset has consistently been reported as between 40 and 50 years, with a wide range from childhood to advanced age [5]. It remains unclear whether race and family history are risk factors for developing eosinophilic fasciitis; anecdotal evidence suggests familial aggregation with a predominance of HLA-A2 [5–7].

2. Etiology and pathogenesis

The etiology of EF remains uncertain. Hematological, infectious, and autoimmune diseases, as well as intense physical exertion, chemical compounds, drugs, solid neoplasms, and physical factors have been proposed as possible triggers and associated factors [2,5,6] (Table 1). Some authors have proposed an aberrant immune response as the main

Abbreviations: CRP, C-reactive protein; EF, Eosinophilic fasciitis; ESR, Erythrocyte sedimentation rate; MRI, Magnetic resonance imaging; TIMP-1, Tissue inhibitor of metalloproteinase-1; SSc, Systemic sclerosis.

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Table 1
Reported triggers and factors associated with eosinophilic fasciitis.

Muscle trauma	30%–46% of EF patients have a history of intense physical exertion or trauma before EF onset.
Drugs	Statins: simvastatin, atorvastatin.
	Phenytoin
	Ramipril
	Subcutaneous heparin
	Trichloroethylene exposure.
Infections	*Borrelia burgdorferi* and *B. afzelii*
	Mycoplasma arginini
Hematologic disorders	Present in less than 10% of patients
	Thrombocytopenia
	Myelomonocytic leukemia
	Chronic lymphocytic leukemia
	Myeloproliferative disorders
	Aplastic anemia
	Allogenic hematopoietic stem cell transplantation
	Graft versus host disease
	Multiple myeloma
	B cell lymphoma
	Paroxysmal nocturnal hemoglobinuria.
Solid neoplasms	Rarely associated with EF
	Breast cancer
	Choroidal metastatic melanoma
	Prostatic cancer
	Bronchopulmonary cancer
Autoimmune diseases	Thyroid: Hashimoto and Graves disease
	Primary biliary cirrhosis
	Lupus erythematous
	Vasculitis
	Hemolytic anemia
	Idiopathic thrombocytopenic purpura
	Sjögren syndrome
Physical factors	Radiotherapy
	Burns

pathogenetic mechanism, a notion supported by findings of hypergammaglobulinemia in peripheral blood and IgG and C3 deposition in fascia of some patients [2,8]. Infiltrating eosinophils in the fascia degranulate locally, resulting in release and tissue accumulation of cationic granule proteins with toxic and potentially fibrogenic properties. Tissue inhibitor of metalloproteinase 1 (TIMP-1) has also been implicated in the pathogenesis of EF [9]. IL-5 plays a role related to the production, survival, activation, adhesion, and degranulation of eosinophils. Peripheral blood mononuclear cells of patients with EF have demonstrated an increased capacity to produce IFN-gamma, IL-5, and IL-10 [10]. CD8 + T lymphocytes containing granzyme B were detected as part of the inflammatory infiltrate of fascia and muscle in patients with EF, which suggests a cytotoxic cellular immune response [11]. Abnormal expression of CD34 and CD40 antigens has been linked with tissue fibrosis in these patients [12].

3. Clinical manifestations

EF is characterized by abrupt onset of painful and erythematous swelling of the affected extremities. Although the condition is mainly symmetrical, unilateral disease also occurs [13]. Involvement of the extremities is the rule, but any other skin areas can be affected [2,5,6]. Trunk involvement is a recognized risk factor for refractory fibrosis [4]. Edema is progressively replaced by thickening of the skin, which is firmly bound to the underlying tissue. *Peau d'orange* appearance (Fig. 1) and the "groove" sign (Fig. 2) are characteristic findings in these patients. Restrictive respiratory disease due to extensive trunk skin fibrosis (Fig. 3), myalgia, and even some degree of proximal muscle weakness caused by extended inflammation from fascia to perimysium (Fig. 4) may been seen in the most generalized forms [14,15].

The skin induration can lead to joint contractures and tendon retraction, evidenced by the prayer sign, which reflects the severity of fascia fibrosis [6]. Morphea-like lesions are present in about one-third of patients. These are likely due to more superficial involvement of the dermis, which is a risk factor for residual fibrosis, requiring more intensive treatment [16]. Inflammatory polyarthritis of small and large joints is seen in up to 40% of patients. Myalgia, weight loss, asthenia, morning stiffness, and carpal tunnel syndrome are also common manifestations [2,3,6]. Visceral involvement is rare and should lead to exclusion of other diseases; however, restrictive lung disease and pleural effusion [17], as well as pericardial [18] and renal involvement [19] have been reported in association with EF.

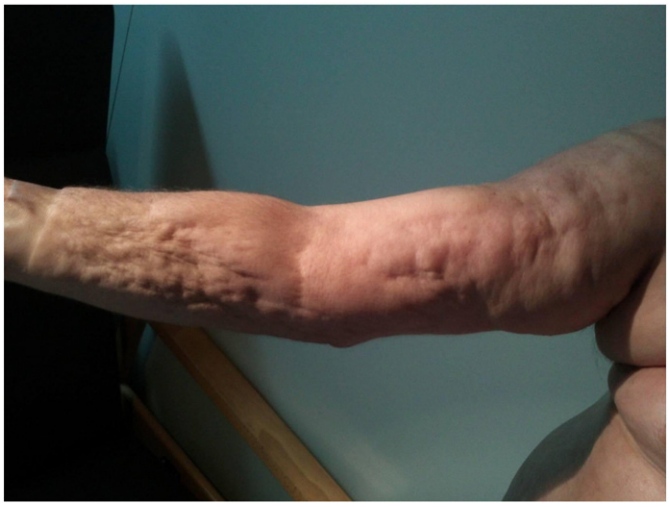

Fig. 1. *Peau d'orange.*

EF can be easily differentiated from systemic sclerosis (SSc), because of the absence of sclerodactylia. The muscle fascia is respected in SSc and the typical features of SSc, such as microstomia, telangiectasis, and sclerodactylia, are not observed in EF. The Raynaud phenomenon and abnormal capillaroscopy findings seen in SSc are usually absent in EF [2,3,6,20].

4. Additional examinations

The following complementary tests can be of help in the diagnosis of EF.

4.1. Biological features

The most characteristic laboratory finding in EF is peripheral eosinophilia. It is present in 63% to 93% of patients, but it is not mandatory for

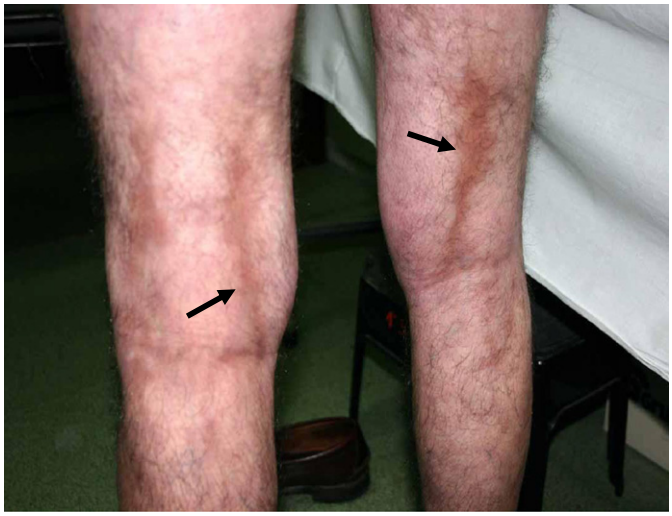

Fig. 2. Groove sign (arrows).

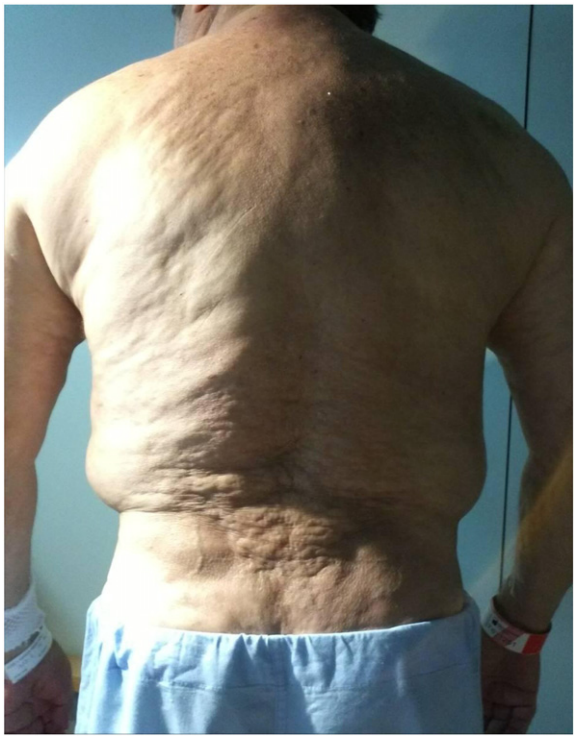

Fig. 3. Eosinophilic fasciitis (trunk involvement).

the EF diagnosis, does not correlate with disease severity, and is not useful for follow-up of disease activity [2–4,6]. Inflammatory markers such as CRP, ESR and hypergammaglobulinemia can be found in more than half of patients [6]. Antinuclear antibodies may be detected at low titers in less than one-quarter of patients, but anti-DNA or anti-extractable nuclear antigen antibodies are negative [2–4]. TIMP-1 is experimentally postulated to be a good serological marker for assessing disease activity [9]. Serum creatinine kinase is rarely elevated and might reflect moderate muscle involvement [2,3], while aldolase, another muscle enzyme, is reported to be increased in EF, and therefore, a useful indicator of disease activity [21].

4.2. Imaging procedures

MRI is considered the best imaging modality for diagnosing EF [22], showing markedly increased signal intensity within the fascia.

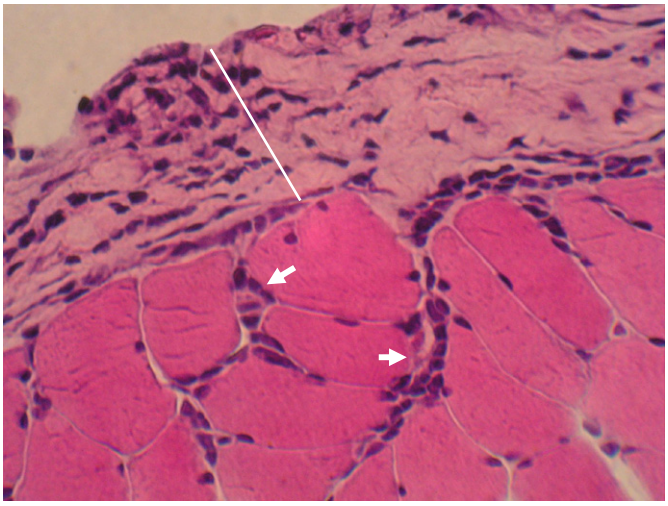

Fig. 4. Thickened fascia (barr), with perimyositis (arrowheads).

Table 2
Proposed criteria for the diagnosis of patients with eosinophilic fasciitis.

Major criteria
1. Swelling, induration, and thickening of the skin and subcutaneous tissue that is symmetrical or non-symmetrical, diffuse (extremities, trunk and abdomen) or localized (extremities)
2. Fascial thickening with accumulation of lymphocytes and macrophages with or without eosinophilic infiltration (determined by full-thickness wedge biopsy of clinically affected skin)

Minor criteria
1. Eosinophilia $> 0.5 \times 10^9$/L
2. Hypergammaglobulinemia > 1.5 g/L
3. Muscle weakness and/or elevated aldolase levels
4. Groove sign and/or *peau d'orange*
5. Hyperintense fascia on MR T2-weighted images

Exclusion criteria: diagnosis of systemic sclerosis.
Presence of both major criteria, or one major criterion plus 2 minor criteria, establishes the diagnosis of eosinophilic fasciitis.

This technique is also useful for determining the optimal location of muscle biopsy and for follow-up purposes. Use of positron emission tomography/computed tomography (PET-CT) for diagnosing EF when biopsy is not available, and ultrasonography for clinical follow-up, are reported alternatives [22,23].

5. Pathological features

A full-thickness wedge biopsy of the affected skin usually reveals characteristic findings. The muscle fascia shows accumulation of lymphocytes, mainly CD8 + lymphocytes (CD4/CD8 ratio < 1) [11], macrophages, and plasma cells. Eosinophils or major basic eosinophilic proteins are not always present in affected tissues [24]. The fascia is usually 2 to 15 times thicker than normal and firmly adherent to the subjacent skeletal muscle, whereas the dermis and epidermis are usually normal. Nevertheless, dermal involvement may occur as morphea-like plaques. Frequently, the epimysium near the fascia and the perimysium among muscle fibers are inflamed, a situation known as perimyositis (Fig. 4) [14,15].

6. Diagnosis and differential diagnosis

Universally accepted diagnostic criteria in patients with EF are lacking. Most physicians consider that the diagnosis of EF can be established when characteristic skin lesions are present, after excluding the various subsets of scleroderma, toxic oil syndrome, silica exposure, gadolinium administration in patients with renal failure, and L-tryptophan-induced eosinophilia–myalgia epidemic syndrome [4,24,25]. It is our opinion that some of the features related to EF are more important than others. We suggest that some of them, such as cutaneous induration respecting acral zones and typical fascial thickening with inflammatory infiltration, should be considered major diagnostic criteria, whereas others, such as elevated ESR, hypergammaglobulinemia or even peripheral eosinophilia, can help the diagnosis, but cannot, in themselves, establish a correct diagnosis of EF (Table 2). SSc should be excluded by clinical, immunologic, and capillaroscopy studies.

7. Treatment

Some EF patients improve spontaneously without treatment, but in those who do not, glucocorticoids (0.5–1 mg/kg/d) are the mainstay therapy. Clinical improvement can take weeks or months and is heralded by resolution of peripheral blood eosinophilia. Methotrexate at low doses (15–25 mg once weekly) is probably the most favored second-line treatment, especially in patients with morphea-like skin lesions [2,3].

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