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Eosinophilic Fasciitis: A Review of Research and Therapeutic Possibilities

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Abstract

Introduction

Eosinophilic fasciitis (EF) is a rare inflammatory disorder marked by elevated eosinophils in tissues and blood. Patients typically present with symptoms such as skin swelling, pain, and

induration, which can be mistaken for other connective tissue diseases. The pathogenesis of EF is not fully understood, though immune and autoimmune mechanisms appear to play significant roles. Diagnosis often involves biopsies, lab analyses, and imaging techniques. Current treatment mainly consists of corticosteroids, but further research is needed to assess various therapeutic strategies. Understanding EF is essential for improving patient outcomes and quality of life.

Purpose

The purpose of this article is to enhance knowledge of eosinophilic fasciitis by examining its pathogenesis, immune mechanisms, and diagnostic challenges, as well as evaluating current diagnostic criteria and treatments. Given the rarity and complexity of EF, the study also seeks to clarify its differentiation from similar diseases and offer insights into effective therapies for early diagnosis and improved treatment outcomes.

Conclusion

EF is a rare disease, and its complexity, due to diverse etiologies and variable treatment efficacy, poses significant challenges in clinical practice. In the near future, the publication of new cases and the initiation of clinical trials should contribute to the development of innovative therapeutic strategies and an effective treatment algorithm.

Materials and methods: Our review is based on an analysis of material collected in 'Pubmed', 'Google Scholar' and other scientific articles using the keywords: Eosinophilic fasciitis, Shulman, fibrosis, hypergammaglobulinemia, eosinophilia.

Keywords: Eosinophilic Fasciitis; Shulman; Fibrosis; Hypergammaglobulinemia; Eosinophilia

Introduction

Eosinophilic fasciitis, also known as Schulman's disease or diffuse fasciitis with eosinophilia, is a rare fibrotic disease of the fascia with unknown etiology and pathophysiology [1]. The condition manifests with peripheral eosinophilia, hypergammaglobulinemia and an elevated erythrocyte sedimentation rate. Skin lesions, such as erythema, edema and induration of the

body's coverings, especially around the extremities and trunk, are also characteristic. Visceral changes are not present [2].

Eosinophilic fasciitis is most common in Caucasians, mostly affecting people aged 30-60. Gender differences in incidence are not clearly established, as reflected in various studies. Some works suggest that the condition is more common in men [3], while others show a predominance of women among patients [4]. There are also studies that show no significant difference in incidence between the sexes [2,4-7].

The syndrome was first described in 1974 by Schulman. Due to the sporadic nature of the disease and difficulties in diagnosis, it is difficult to estimate the number of cases that have been reported since then [8,9].

Pathogenesis and immune mechanisms

Eosinophilic fasciitis (EF) is presumed to have an immunological basis, although its etiology is not fully understood. It is indicated by various immunological factors, such as the presence of hypergammaglobulinemia and deposits of IgG and complement C3 components in the fascia in some patients. A key role in the development of the disease is played by cytokines such as IL-5, IFN-γ and IL-10, and CD8+ lymphocytes, suggesting activation of the immune system. The coexistence of autoimmune and hematologic diseases is also observed, further emphasizing the immune nature of EF.

Eosinophils play a central role in inflammation and fascial fibrosis. Interleukin 5 (IL-5) is responsible for their survival and proliferation, leading to increased numbers of eosinophils infiltrating fascial tissue. Eosinophils, through degranulation products, induce toxic effects on tissues and stimulate fibrogenic processes, which contributes to fibrosis and thickening of fascia. This can lead to reduced joint mobility and, in extreme cases, irreversible changes.

Fibrosis in EF is also associated with overproduction of the enzyme inhibitor of extracellular matrix degradation (MMP-1), namely tissue inhibitor of metalloproteinase-1 (TIMP-1), which interferes with the natural process of collagen breakdown. In EF patients, skin fibroblasts show

increased expression of fibronectin and type I collagen, which further promotes the fibrosis process.

In addition to eosinophils, mast cells are also involved in the pathological process, as evidenced by elevated plasma histamine levels. At the same time, there is increased production of IL-2, IFN-γ and leukemia inhibitory factor (LIF) by peripheral blood mononuclear cells. In addition, Th+ cells and superoxide dismutase (SOD) are also elevated in EF, indicating widespread involvement of the immune system.

Increased expression of transforming growth factor-β1 (TGF-β1) mRNA in fascicle-derived fibroblasts and elevated expression of connective tissue growth factor genes suggest that fibrosis-associated cytokines also play an important role in the physiopathology of the disease. Thus, eosinophils, proinflammatory cytokines, and fibrogenesis processes all work together to induce and sustain inflammation and fascial fibrosis in EF [10-14].

In about 50% of cases, the onset of eosinophilic fasciitis is preceded by overexertion or trauma. There are also cases associated with exposure to certain drugs, such as heparin, statins, phenytoin, ramipril or checkpoint inhibitors, especially pembrolizumab and nivolumab. In addition, the disease can be triggered by contact with toxic substances (e.g., herbicide containing Florasulam and 2,4-D 2-ethylhexyl ester [15]) and associated with infections, such as those caused by Borrelia burgdorferi, B. afzelli or Mycoplasma arginini. Eosinophilic fasciitis also frequently occurs in association with autoimmune diseases, hematologic diseases (e.g. thrombocytopenia, leukemia, lymphomas, plasmocytic myeloma) and solid tumors [16].

Cases of eosinophilic fasciitis as a form of paraneoplastic syndrome that resolved after successful cancer treatment have also been described. A case of eosinophilic fasciitis after local radiation therapy for breast cancer [17]. There are known cases of this syndrome after starting dialysis in a patient with renal failure [18], in a patient with colorectal cancer [19], and in a woman in the perinatal period [20]. A case of eosinophilic fasciitis has been described in a patient with asthma, which went into remission after starting asthma treatment with inhaled corticosteroids [21].

Clinical picture

The onset of the disease may manifest as weight loss , weakness and spontaneous or induced muscle pain. Patients may also have a history of recent intense exercise or trauma [22].

At the time of diagnosis, skin lesions are present in up to 90% of patients, including dimpled edema, induration and an “orange peel” appearance with hyperpigmentation. Initially, the swelling and stiffness may affect the distal parts of the limbs, and then progress to induration. It is worth noting that reduced visibility of veins, referred to as the “groove sign,” may be present in half of the patients and strongly suggests deep fibrosis or fascial involvement. In most patients, the patients' upper extremities and lower extremities are involved. Lesions in other locations, such as the neck and trunk, are much less common. Morphea (localized scleroderma) occurs in about one-third of patients. Raynaud's phenomenon is rare, and capillaroscopy findings usually remain normal [22].

Joint involvement, including joint contracture and inflammatory joint disease, is frequently reported in patients, reaching up to 40%. Distal synovitis occurs in 3-11.5% of individuals. In addition, morning stiffness may be present in about 23% of patients, and carpal tunnel syndrome also affects about 23% of patients [22].

Differentiating eosinophilic fasciitis from other diseases

The diagnosis of eosinophilic fasciitis may be delayed due to initial symptoms that are nonspecific, such as muscle and joint pain. The differential diagnosis should consider several conditions that may present with similar symptoms [22]:

1)Systemic scleroderma- both eosinophilic fasciitis (EF) and scleroderma can lead to significant skin fibrosis, but differ significantly in other clinical features. Scleroderma is not associated with eosinophilia or a positive response to corticosteroids, which are often effective in treating EF. In addition, in systemic scleroderma there is involvement of internal organs such as the lungs and esophagus, which is not typical of EF. In EF, the skin of the hands and feet generally remains intact, and sclerodactyly, characteristic of systemic scleroderma, is absent. This helps in the differential diagnosis between these conditions. In addition, capillaroscopic findings

usually remain normal in EF, making it possible to distinguish this condition from scleroderma [23].

2) Churg-Strauss syndrome should be ruled out in any case of internal organ involvement associated with eosinophilic fasciitis . Actual fasciitis is rare in the context of Churg-Strauss syndrome, which in turn is characterized by symptoms such as asthma, sinus involvement and neurological, cardiac, dermatological and renal problems. EF lacks the typical features of Churg-Strauss syndrome. In addition, patients with EF do not have cytoplasmic antibodies against neutrophils present, which are found in 38-48% of people with the syndrome [24-26].

3) Hypereosinophilic syndromes are characterized by peripheral eosinophilia and involvement of organs such as the heart, lungs and nervous system. HES include various variants, including myeloproliferative and lymphocytic, which differ in clinical, histologic, cytogenetic and molecular patterns [27].

4) Eosinophilia-muscle syndrome after L-tryptophan ingestion. As defined by the Centers for Disease Control and Prevention, a diagnosis of EMS requires a peripheral blood eosinophil level of more than 1,000/mm^3, the presence of generalized muscle pain that impedes the patient's daily functioning enough, and the exclusion of infections and tumors that could explain the symptoms.

The acute phase of EMS begins with generalized muscle pain, and patients may also experience shortness of breath, cough, fever, skin sensitivity, rash, pruritus and swelling of the extremities. The chronic phase, on the other hand, is associated with scleroderma-like skin lesions and can lead to multiple organ involvement [28,29].

5) Peripheral T-cell lymphomas can involve the skin and sometimes the fascia. However, their presence can be easily ruled out by histopathological examination of samples obtained from muscle biopsies [22].

6) Renal systemic fibrosis is a disease entity worth noting in the differential diagnosis. This condition occurs in patients with advanced kidney disease (dialysis-dependent or with glomerular filtration rate <15 ml/min) and can sometimes be associated with gadolinium administration. Unlike eosinophilic fasciitis , renal systemic fibrosis involves different areas

such as the hands and feet; eosinophilia is absent, and the characteristic histopathologic pattern is clearly present [30].

7) Graft versus host disease (GVHD) is also associated with cutaneous sclerosis and fibrotic processes [31].

8) Toxic oil syndrome is a disease entity associated with eosinophilia and skin sclerosis that gained attention in the 1980s due to an epidemic in Spain caused by adulterated canola oil (caused by consumption of canola oil contaminated with aniline 2%). Symptoms of the disease include shortness of breath, muscle and joint pain, as well as swelling and hardening of the skin of the extremities, resembling the symptoms of scleroderma. In addition, there are joint contractures, neuropathy, eosinophilia, elevated serum creatine kinase levels and lung infiltrates [32].

7) Scleroderma edema is a condition characterized by deposition of amorphous mucinous material in the dermis, leading to thickening of the skin. Often, yellow-red, waxy papules also appear. The condition is sometimes associated with monoclonal gammopathy [33].

Diagnosis

Laboratory studies of patients often show transient peripheral eosinophilia, which is not correlated with disease severity. Laboratory analysis also reveals elevated inflammatory markers such as ESR and CRP and hypergammaglobulinemia [1].Electrophoresis should be performed to rule out hematologic diseases that may cause eosinophilic fasciitis. Data indicate that eosinophilia may be transient, and tissue changes may resolve before blood eosinophil levels return to normal. This underscores the need for further diagnostics, such as biopsy or MRI, in patients with highly suspected eosinophilic fasciitis [7]. Disease activity can be assessed by elevated levels of serum aldolase, which is often altered in patients with

eosinophilic fasciitis, and levels of type III procollagen peptide (PIIIP), which reflects disease activity and may be useful in monitoring it [34].

Specific antibodies are usually not present. In 15-20% of patients with eosinophilic fasciitis, antibodies to centromere, antitopoisomerase 1 and anti-RNA polyisomerase III may be present. To rule out eosinophilic granulomatosis with vasculitis, evaluation of anti-neutrophil cytoplasmic antibodies (ANCA) is recommended [11]. 10% of patients with eosinophilic fasciitis have been observed to have antinuclear antibodies and rheumatoid factor [34].

There are no generally accepted diagnostic criteria for eosinophilic fasciitis. Pinal-Fernandez and colleagues proposed criteria for the diagnosis and classification of EF, which include two main criteria:

1. Swelling, induration and thickening of the skin and subcutaneous tissue, which may be symmetrical or asymmetrical, diffuse (involving the limbs, trunk and abdomen) or localized (confined to the extremities).
2. Thickening of the fascia with accumulation of lymphocytes and macrophages with or without eosinophilic infiltration, confirmed by full thickness wedge biopsy of the affected skin.

In addition, five ancillary criteria are distinguished:

a. Eosinophilia $>0.5 \times 10^9/L$,

b. Hypergammaglobulinemia >1.5 g/L,

c. Muscle weakness and/or elevated aldolase levels,

d. Groove sign and/or “peau d'orange”,

e. Hyperintensity of fascicles in T2-dependent MRI images.

The diagnosis of EF can be made with two main or one main and two subsidiary criteria [35].

MRI, which has recently gained prominence in the diagnosis of eosinophilic fasciitis, is now considered, after biopsy, to be one of the most effective diagnostic methods in this field [7].

A biopsy for eosinophilic fasciitis reveals swelling and an inflammatory infiltrate of lymphocytes, plasma cells, histiocytes and, most importantly, eosinophils in the deep fascia and lower layer of subcutaneous tissue. As the disease progresses, the fascia thickens and sclerotizes, and the inflammatory infiltrate gradually disappears. Eosinophils, after degranulation within the fascia, release cytokines, chemokines and growth factors that lead to the accumulation of proteins such as cationic granule protein (ECP), eosinophil-derived neurotoxin (EDN), eosinophil peroxidase (EPX) and major basic protein (MBP). These substances have toxic effects and promote fibrotic processes.

Histamine, released by degranulating mast cells, is present both in affected tissues and elevated in patients' blood. Pathological changes involve not only fascia, but also muscle tissue, affecting structures such as the epimysium, perimysium and endomysium, and in some cases muscle fibers [36].

Although fascial biopsy remains the gold standard for diagnosing eosinophilic fasciitis, the role of magnetic resonance imaging (MRI) has increased significantly. MRI is now considered a secondary diagnostic criterion, indicating characteristic fascial changes. MRI can be useful in selecting a biopsy site, especially in cases where previous biopsies have yielded false-negative results. Also, in situations where biopsy is not possible due to patient preference, MRI can facilitate diagnosis. In addition, it allows EF to be diagnosed before the onset of skin lesions, which is crucial for successful treatment [8]

Positron emission tomography with computed tomography (PET-CT) can also be a useful tool in the diagnosis of eosinophilic fasciitis, particularly in identifying fluorodeoxyglucose (FDG) uptake in altered fascial areas. Although MRI remains the standard method, PET-CT may be preferred in situations where MRI is contraindicated or unavailable. Although it is not a standard diagnostic test, it has the advantage of being able to simultaneously exclude malignancies [37-39].

Treatment, prognosis and complications

10-20% of patients may experience spontaneous resolution of the disease after two to five years of illness. In the rest, treatment should include physiotherapy in combination with immunomodulatory drugs.

First-line treatment includes oral corticosteroids, usually at an initial dose of 20-30 mg/day [34].

In a retrospective study involving 34 patients with eosinophilic fasciitis, intravenous pulse administration of methylprednisolone at a dose of 500-1000 mg daily for three days was used before prednisone therapy. The results showed that patients receiving methylprednisolone were significantly more likely to achieve complete remission (87% versus 53% in patients who did not receive this treatment) and were less likely to require additional therapy beyond systemic corticosteroids (20% in the methylprednisolone group versus 65% in the control group) [40].

Gradual dose reduction is possible based on improvement in skin hardness, reduction in infiltrates, improvement in joint mobility and diagnostic test results. With a favorable course, therapy can be terminated after 1-2 years. Corticosteroids prove to be effective in more than 90% of patients [34].

For patients whose treatment with corticosteroids is not satisfactory, or as corticosteroid-sparing therapy in those who require long-term use of corticosteroids, the inclusion of methotrexate [41,42] or other immunosuppressive drugs in the treatment regimen can be considered (e.g. cyclosporine [43], cyclophosphamide [40], tocilizumab [44,45], rituximab [46]). Therapy with psoralen and UVA radiation (PUVA) has also shown efficacy in the treatment of eosinophilic fasciitis [47-49].

The long-term prognosis of EF is generally good, but recurrence can occur after treatment is discontinued [50].

Physiotherapy, in combination with immunosuppressive treatment, plays a key role in maintaining joint mobility and reducing contractures [51]. Key aspects of physiotherapy include stretching and strengthening exercises, manual therapy, and ultrasound and electrotherapy.

In severe cases with significant movement limitations, surgical interventions may be considered to correct joint contractures. Fasciectomy is also a surgical treatment option, and can be considered in patients in whom conventional treatments have not been beneficial [16].

The prognosis for survival is favorable, but delayed treatment can lead to permanent skin hardness or joint contractures. For this reason, it is crucial to begin therapy immediately after a definitive diagnosis is made.

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