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Invited Review Article

Eosinophilic fasciitis: From pathophysiology to treatment

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ABSTRACT

Eosinophilic fasciitis is a disease originally proposed as “diffuse fasciitis with eosinophilia” by Shulman in 1974. The patients with this disease often have history of strenuous exercise or labor a few days to 1–2 weeks before the onset.

The chief symptoms are symmetrical, full-circumference swelling and plate-like hardness of the distal limbs. This is accompanied by redness and pain in the early stages, with many cases exhibiting systemic symptoms such as fever or generalized fatigue. The lesions have been observed extending to the proximal limbs, though never on the face or fingers.

En bloc biopsies from the skin to the fascia show marked fascial thickening and inflammatory cell infiltration by the lymphocytes and plasma cells. Eosinophilic infiltration is useful for the diagnosis but is only seen in the early stages of the disease.

Recently, “Diagnostic criteria, severity classification, and clinical guidelines for eosinophilic fasciitis” were published.

This review article discusses about eosinophilic fasciitis in detail, from its pathophysiology to the treatment.

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Introduction

In 1974, Shulman proposed a new disease concept called “diffuse fasciitis with eosinophilia” in a report of 2 cases presenting with scleredema-like hardening of the skin on the limbs, hypergammaglobulinemia, eosinophilia in the peripheral blood, and diffuse fasciitis on histology.¹

Both cases were adult men presenting with bilateral, symmetrical, diffuse, scleroderma-like hardening of the skin on the limbs, accompanied by joint contracture, which appeared after vigorous exercise. They had no signs of Raynaud's phenomenon or internal organ lesions and responded positively to oral corticosteroid therapy. The report mentioned peripheral eosinophilia but no eosinophilic tissue infiltration.

In 1975, Rodnan reported about similar cases, proposing the name “eosinophilic fasciitis” because of the presence of peripheral eosinophilia and eosinophilic infiltration in the hypertrophied fascia.² This name was commonly used, and the condition is now considered a relative of scleroderma, because of the characteristic sclerotic lesions. Depending on the stage or location, this condition

does not always present with eosinophilia or eosinophilic tissue infiltration. For this reason, the American College of Rheumatology has used the name “diffuse fasciitis with or without eosinophilia” in recent times for conditions that present with sclerotic lesions of the fascia, in addition to the characteristic clinical image. While some believe that the name “Shulman syndrome” or “diffuse fasciitis” should be used, “eosinophilic fasciitis” is the most widely accepted. Many cases are misdiagnosed as systemic sclerosis, rheumatoid arthritis, carpal tunnel syndrome, or unclassified collagen disease. A close examination of the skin and histological findings is essential.

Epidemiology

Although this condition is considered relatively rare, with only about 100 case reports from Japan, many cases go unreported, leading to lack of clarity about its prevalence. It often occurs in adults in the age group of 20–60 years, though it has been reported in children and elderly people as well. It is slightly more common in men, with a male–female ratio 1.5:1.

Etiology and pathophysiology

The cause of this condition is unclear, although an auto-immunological mechanism is presumed. This is due to the presence

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of hypergammaglobulinemia and complications similar to those seen in autoimmune diseases; response to steroids; and the presence of rheumatoid factor, antinuclear antibodies, and immune complexes in some cases.^{3,4} It is induced by strenuous exercise or labor, which might provoke an autoimmune response targeting the damaged fascia.

The dermal fibroblasts of eosinophilic fasciitis patients exhibit greater expression of type I collagen and fibronectin than healthy dermal fibroblasts.⁵ In addition, fibrosis is generated by the increased production of tissue inhibitor of metalloproteinase-1 (TIMP-1), an inhibitor of the extracellular matrix degrading enzyme matrix metalloproteinase-1 (MMP-1, collagenase).⁶

Elevated levels of eosinophilic cationic protein and serum interleukin-5 (IL-5),⁷ and increased eosinophilic migration capacity,⁸ which are consistent with an increased eosinophil count have been reported, suggesting that eosinophils contribute to the mechanism of onset of this condition. The involvement of mast cells has also been indicated, with an increase in plasma histamine levels.⁹ There have also been reports of increased production of IL-2, interferon- γ (IFN- γ), and leukemia inhibitory factor (LIF) by peripheral mononuclear cells in the blood¹⁰; overexpression of CD40 ligands,¹¹ and elevated superoxide dismutase (SOD) levels.¹² The percentage of Th17⁺ cells was reported to be increased in this disease.¹³ However, focal absence of CD34 staining was prominent in the fascia of eosinophilic fasciitis patients.¹⁴ These findings suggest an involvement of these cytokines and other substances in the pathology.

There have also been reports of increased expression of transforming growth factor- β 1 mRNA in fibroblasts derived from the fascia,¹⁵ and increased expression of connective tissue growth factor genes in fibroblasts in the fascia of affected areas.¹⁶ These fibrosis-related cytokines are thought to contribute to the pathophysiology.

Clinical symptoms

In typical cases, there is a history of strenuous exercise or labor a few days to 1–2 weeks before the onset. The disease appears suddenly in about 50% of the cases, with gradual onset seen in many cases.

The chief symptoms are symmetrical, full-circumference swelling and plate-like hardness of the distal limbs (forearms and lower legs). This is accompanied by redness and pain in the early stages, with many cases exhibiting systemic symptoms such as fever or generalized fatigue. The lesions have been observed extending to the proximal limbs (upper arms and thighs), though never on the face or fingers.

The skin of the affected areas shows unevenness, deep fibrosis, and prominent hair follicles, which appear like the skin of an orange (peau d'orange). In the areas of plate-like hardness, only the blood vessels remain soft, which creates grooves (groove sign).

The joints of the limbs have a restricted range of motion, and patients become unable to sit on the floor with their buttocks on their heels (*seiza* style). The fingers do not harden, though hardness of the forearms can cause flexion contracture of the fingers. Carpal tunnel syndrome is often seen due to pressure on the median nerve.

"Diagnostic criteria, severity classification, and clinical guidelines for eosinophilic fasciitis" were published in 2016¹⁷ as part of a 2014 policy research project on intractable diseases, funded by the Japanese Ministry of Health, Labor, and Welfare. The research topic was "Diagnostic criteria, severity classifications, and clinical guidelines for scleroderma and fibrotic skin diseases" (principal investigator Prof. Hironobu Ihn).^{17–20} These guidelines now serve

as the diagnostic criteria and a reference for assessing the severity (Table 1, 2).

Histopathological findings

En bloc biopsies from the skin to the fascia are necessary. Marked fascial thickening is sometimes confirmed while performing the biopsy. The hypertrophied fascia primarily shows inflammatory cell infiltration by the lymphocytes and plasma cells. Eosinophilic infiltration is useful for the diagnosis but is only seen in the early stages of the disease. Eosinophilic infiltration of the fascia is seen in about 50% of the cases that are investigated. Lesions in this condition mainly involve the fascia, though fibrosis can reach the dermis, which can be accompanied by swelling and proliferation of the dermal collagen fibers and mild infiltration by inflammatory cells, mainly lymphocytes.

Examination findings

Eosinophilia, elevated sedimentation rate, and hypergammaglobulinemia are observed, though eosinophilia often totally disappears during the course of the disease or only appears temporarily during the early stages and then disappears. Elevated sedimentation rate and hypergammaglobulinemia are observed in about 60% of the cases. Many cases have elevated serum aldolase, which is known to reflect the disease activity.²¹ Serum type III procollagen peptide (PIIIP) levels also reflect the disease activity, which makes it a highly useful marker for this condition.²² About 10% of the cases are positive for antinuclear antibodies or rheumatoid factor.

As a noninvasive examination, MRI is useful for determining the site for biopsy, monitoring the course and assessing the outcomes of treatment.²³

Differential diagnosis

It is often difficult to differentiate eosinophilic fasciitis and localized scleroderma histologically; hence, a clinical differentiation is necessary.

Table 1
Diagnostic criteria of eosinophilic fasciitis.

Major criterion: Symmetrical plate-like sclerotic lesions are present on the four limbs. However, this condition lacks Raynaud's phenomenon, and systemic sclerosis can be excluded.
Minor criteria 1: The histology of a skin biopsy that incorporates the fascia shows fibrosis of the subcutaneous connective tissue, with thickening of the fascia and cellular infiltration of eosinophils and monocytes.
Minor criteria 2: Thickening of the fascia is seen using imaging tests such as magnetic resonance imaging (MRI).

A definitive diagnosis is made when a patient has the major criterion and one of the minor criteria, or the major criterion and two of the minor criteria.

Table 2
Severity classification of eosinophilic fasciitis.

- Joint contracture (upper limbs): 1 point - Joint contracture (lower limbs): 1 point - Limited movement (upper limbs): 1 point - Limited movement (lower limbs): 1 point - Expansion and worsening of skin rash (progression of symptoms): 1 point

A total of 2 or more points is classified as severe.

Localized scleroderma exhibits fibrosis mainly in the dermis, while eosinophilic fasciitis does so mainly in the fascia. However, as the localized scleroderma lesions progress, fibrosis can be seen not only in the dermis and subcutaneous layers, but also in the underlying fascia, muscle, and bone. Moreover, as eosinophilic fasciitis progresses, fibrosis can extend from the fascia to the dermis. Finally, eosinophilic tissue infiltration is not observed in many cases of eosinophilic fasciitis. These factors make a histological differentiation difficult.

Eosinophilic fasciitis presents with bilateral, symmetrical, and diffuse swelling of the limbs, whereas localized scleroderma can be unilateral or bilateral, though predominantly unilateral, with a well-defined border. This can make differentiation easier, though atypical cases of eosinophilic fasciitis can be difficult to differentiate from linear scleroderma or from some cases of subcutaneous localized scleroderma (morphea profunda).

Therapy, course, and prognosis

The 2016 "Diagnostic criteria, severity classifications, and clinical guidelines for eosinophilic fasciitis"¹⁷ mentioned above, also contain detailed descriptions of the treatments, which can be used as a reference.

Oral corticosteroid therapy is the first choice, starting at 20–30 mg/day. Improvement in hardness of the skin and infiltration, range of motion, and other clinical symptoms, along with the various investigations described above, can be used as markers for gradually lowering the dose. If the course is favorable, therapy can be terminated in 1–2 years. Oral corticosteroid therapy is effective in more than 90% of the cases. The prognosis for survival is good, but there might be remnant hardness or joint contracture if treatment is delayed. Therefore, it is important to start treatment immediately after reaching a definitive diagnosis.

Patients who do not respond to corticosteroid therapy can be checked to see if they respond to cyclosporin,²⁴ cyclophosphamide,²⁵ or methotrexate.²⁶ Psoralen and ultraviolet A (PUVA) therapy and other ultraviolet therapies are also known to be effective.²⁷

Complications

Eosinophilic fasciitis is complicated by localized scleroderma in 20–30% of cases.²⁸ Several other autoimmune complications have been reported, including systemic lupus erythematosus,²⁹ rheumatoid arthritis,³⁰ Sjögren's syndrome,³¹ and autoimmune thyroiditis.³²

Other reported complications include aplastic anemia,³³ autoimmune hemolytic anemia,³⁴ idiopathic thrombocytopenic purpura,³⁵ leukemia, malignant lymphoma,³⁶ and myelodysplastic syndrome.³⁷ Many patients who are resistant to steroid therapy may have complicated neoplastic diseases.

Conflict of interest

The author has no conflict of interest to declare.

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