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Case Report

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Shulman's Syndrome (Eosinophilic Fasciitis): Case Report

Mourabiti AY, Sqalli M, El Bouardi N, Haloua M, Alaoui Lamrani MY, Boubbou M, El Maaroufi M and Alami B*

Department of Radiology, CHU HASSAN II de Fez, Faculty of Medicine Fez, University Sidi Mohamed Ben Abdellah, Morocco

***Corresponding author**: ALAMI BADREEDDINE, Department of Radiology, CHU HASSAN II de Fez, Faculty of Medicine Fez, University Sidi Mohamed Ben Abdellah, Fez, Morocco, Tel: 212669073208, E-mail: BADR.ALAMI@YMAIL.COM

Abstract

Eosinophilic fasciitis is a rare disease that is classified by some authors to scleroderma-like syndromes. It is characterized by symmetrical induration of skin and subcutaneous tissue associated with eosinophilia in peripheral blood. We report the case of 37-year-old man who presented with a 6-month history of bilateral myalgia of the lower limbs, rapidly worsening with painful swelling of legs. Physical examination revealed induration of the skin with irreducible dorsiflexion of Both ankles. Laboratory examination showed peripheral eosinophilia associated with moderate elevation of both the erythrocyte sedimentation rate and C-reactive protein. No infectious, neoplastic, hemopathic, or immunological abnormality was detected. Magnetic resonance imaging (MRI) showed thickening of the muscular fascias of both legs in high signal intensity on T2-weighted images, slightly enhanced after contrast agent injection on T1 images. Histological analysis showed sclerosis and eosinophilic infiltration of the fascia. A diagnosis of eosinophilic fasciitis was confirmed and the patient was successfully treated with systemic corticotherapy. A short review of the clinicopathological and radiological features of the lesions is presented.

Keywords: Eosinophilic fasciitis; MRI; Sclerotic skin

Introduction

Eosinophic Fasciitis (EF) is an uncommon connective tissue disease of unknown etiology and unclear pathophysiology. It is characterized by scleroderma-like cutaneous changes (erythema, swelling, induration of the extremities), peripheral eosinophilia, hypergammaglobulinemia and elevated Erythrocyte Sedimentation

Rate (ESR) [1]. MRI is the modality of choice for the diagnosis and monitoring of this entity, by showing typically signal abnormalities and thickening of deep fasciae [2]. The diagnosis is confirmed by a deep skin biopsy which revels chronic inflammatory infiltration affecting deep fascia with lymphocytes, histiocytes, and occasionally eosinophils. In this report, we aimed to present the clinical features, MRI appearance and therapeutic management of an EF case with short review of the literature.

Case History

A 37-year-old man presented with a history of six months of severe fatigue with myalgia, rapidly worsening with painful swelling of legs. Physical examination revealed stiffening of the skin in the lower limbs, both ankles were fixed at 90 degrees' dorsiflexion with no sign of arthritis in the joints. Neurological examination of the patient was normal. Laboratory investigations revealed white blood cell count at 12000/mm3, with eosinophilia of 19%. ESR was 77 mm/hour and C-Reactive Protein (CRP) level 51 mg/dl. Liver, renal and thyroid function tests were normal. Uric acid level was normal. Rheumatoid factor and Antinuclear Antibodies (ANA) agglutination tests were negative. Oligoclonal hypergammaglobulinemia was found in protein electrophoresis. MRI scan revealed increased signal intensity within superficial and deep fascial layers on T2WI (Figure 1) with moderate fascial enhancement after contrast administration (Figure 2).

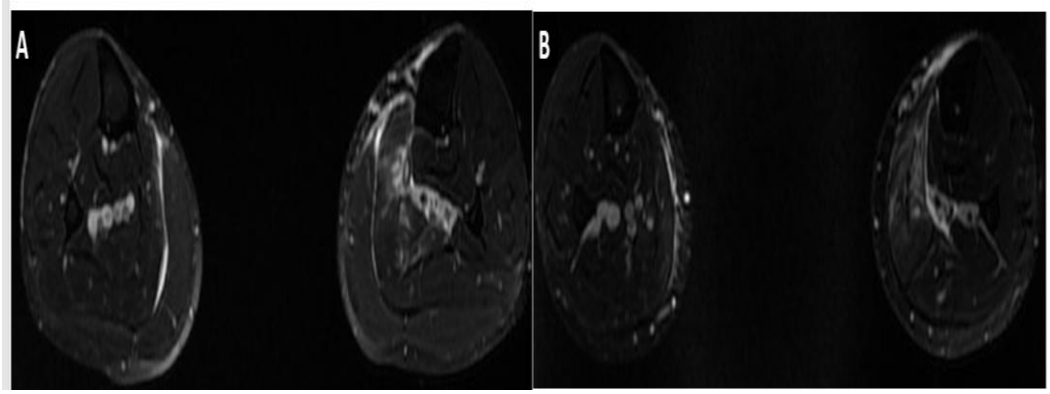

Figure 1: Axial T2-weighted fast spin-echo MR images (A, B) show increased signal intensity within superficial and deep fascial layers.

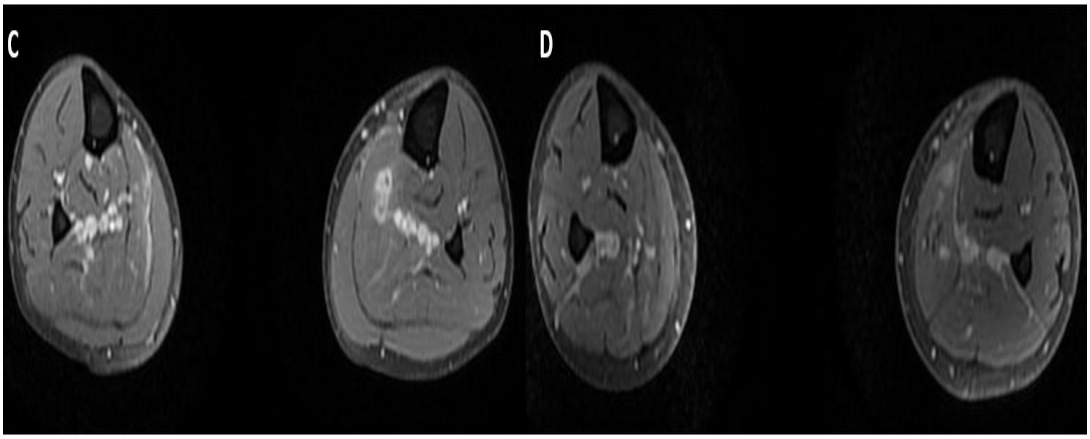

Figure 2: Axial enhanced, fat-suppressed T1-weighted spin-echo MR images (C, D) show moderate fascial enhancement corresponding to T2 signal abnormalities.

Histologic examination of a deep wedge biopsy taken from the left leg revealed thickened fascia with eosinophilic and lymphocytic infiltration. The diagnosis of eosinophilic fasciitis (Schulman's syndrome) was done. Treatment with oral prednisolone was started at 60 mg daily for two months with no clinical benefit. Therefore, methotrexate (0.3 mg/kg/week) was added to prednisolone treatment. Two months later, the eosinophil count was returned to normal. The edematous changes and skin induration of both legs gradually improved.

Discussion

Eosinophilic Fasciitis (EF) is a rare connective tissue disease that was first described in 1975 by Shulman [1,2]. It appears to be a variant of scleroderma, with which it differs by the absence of Raynaud's phenomenon, telangiectasia's and extra-cutaneous manifestations [3]. The average age of onset is approximately 40-50 years [3], with no gender predilection, but probably affecting men earlier [4]. The pathophysiology of the EF remains largely unclear. However, an autoimmune mechanism is suspected given the presence of immune deposits (IgG, IgM, C3, C4) in fascia, circulating immune complexes, and the possible but inconstant presence of antinuclear antibodies and rheumatoid factor [5]. Immune cells accumulated in the fascia and dermis (lymphocytes, histiocytes, plasma cells and eosinophils) are also found. Lymphocytes, through the production of cytokines, and eosinophils by their degranulation and release of TGF beta, are responsible for an increase in the proliferation of fibroblasts and their synthesis of more collagen and extracellular matrix proteins [6]. On the other hand, the pathogenesis of MP appears to be multifactorial: intense physical effort or muscle trauma prior the onset of symptoms is often among the main risk factors reported [7,8]. Some cases have been reported to occur after taking the following drugs (simvastatin, atorvastatin, phenytoin, ramipril, subcutaneous heparin, fosinopril, alpha-methyldopa, and antituberculous treatment, and more recently nataluzimab) or after chemical exposure [9,10]. In other cases, the condition was found to be associated with bacterial infection (borreliosis, mycoplasma) [10]. Clinical manifestations of EF have been described as progressive [7]. Up to 90% of patients present with cutaneous manifestations, including edema of the extremities, followed by "peau d'orange" with hyperpigmentation, and finally induration [2,7]. Venous furrowing along the veins within the infiltrated area, also called the ''groove sign'', is observed in nearly half of the patients and is highly evocative of fasciItis or deep fibrosis [2]. Topographically, cutaneous involvement is usually bilateral and symmetrical, even if unilateral forms have been reported [10]. It concerns the forearms and arms in 85 to 90% of patients, the hands in 30 to 54% of patients and the lower limbs in more than 70% of patients as in our patient [8,11]. The cutaneous manifestations can also concern other localizations including the cervical region (6 to 19%), the abdomen (23 to 44%), the chest and the back (6 to 38%), more exceptionally the face [8,11]. The head is generally not affected, the hands and feet are rarely involved [2]. At the time of diagnosis, skin manifestations are associated with myalgia in up to 86% of patients and joint involvement with inflammatory arthralgia in up to 40% of patients [8]. Eosinophilic fasciitis has been frequently associated with hematological disorders (in nearly 10% of patients), such as aplastic anemia, hemolytic anemia, thrombocytopenia, leukemias, lymphomas and other myeloproliferative disorders [9,10]. However, it is still not clear whether these blood disorders cause the

fasciitis (paraneoplastic syndrome) or whether, on the contrary, fasciitis serves as the initial trigger for hematological disorders [2]. Some autoimmune diseases such as systemic sclerosis, antiphospholipid antibody syndrome, sjögren's syndrome, and systemic lupus erythematosus have also been reported in patients with EF [12]. In our case, there was no evidence of autoimmune or hematological disease. Furthermore, there are scarce reports linking EF with solid malignant tumors such as colorectal carcinoma, prostate cancer, bladder cancer, bronchopulmonary cancer, choroidal melanoma and breast cancer. Given the rarity of these cases, it does not appear necessary to perform a systemic assessment for solid neoplasia during FE in the absence of suggestive symptoms [3,10]. In our case, there was no evidence of collagen tissue or hematological disease. Laboratory investigations may reveal peripheral eosinophilia in 60 to 90% of patients [8,10,11]. However, it is not indispensable for the diagnosis of EF and its counts are not associated with disease prognosis [4,10]. An inflammatory syndrome is frequently reported with elevated C-reactive protein (50-64%), an increase in erythrocyte sedimentation rate (30-60%) and generally polyclonal hypergammaglobulinemia (35 to 60%), similar to findings in our case [8,10]. Elevation of aldolase has also been reported in 31% of patients [10]. The elevated serum creatinine phosphokinase is rarely present (4-10%), and may reflect a moderate muscle involvement during the EF [8,10]. The antinuclear antibody test is positive in 15 to 20% of cases, but without anti-DNA antibodies or ANCA [8,10]. MRI is now considered as the better imaging tool for the morphological diagnosis of EF. Typically, MRI shows a thickening of deep fasciae on T1-weighted sequences that appears with increased signal intensity on fluid-sensitive sequences (fat-saturated T2-weighted sequences), and a marked enhancement after gadolinium injection in the acute phase of the disease [2,8,10,13], less frequently MRI signal abnormalities may be observed in the muscle and hypodermic tissue adjacent to the fascia [2], the same appearance was found in our patient. MRI can be found normal when done very early or after the start of corticosteroid therapy [10]. MRI is useful also in directing the surgeon to the optimal location for biopsy, thus reducing the possibility of sampling error and false-negative results [13]. MRI also helps to monitor the therapeutic response on corticosteroid treatment [10,13,14]. The differential diagnosis of EF includes morphea, systemic sclerosis and eosinophilia-myalgia syndrome [1]. In morphea, the lesions consist of a thickening of the dermis and a variable degree of subcutaneous tissue infiltration. Fascia thickening is however limited compared to that observed in the EF [2]. Systemic sclerosis is not associated with peripheral eosinophilia or significant corticosteroid response and is often accompanied by visceral (pulmonary or digestive) involvement and capillaroscopic abnormalities that are absent during EF [10]. Eosinophilia-myalgia syndrome has similar findings, both clinically and histologically, with EF, but has a history of L-tryptophan ingestion, polyneuropathy and pulmonary symptoms [1]. Deep skin biopsy (skin and muscle) is the gold standard for diagnosis of EF [12]. Typically, anatomopathological examination reveals a thickened fascia with inflammatory infiltrates WHICH are usually perivascular and include lymphocytes [8,10] (predominantly CD8 + T cells, CD4 / CD8 ratio <1) [10], with a varying percentage of eosinophil granulocytes. eosinophils are not essential for diagnosis [8,15]. Indeed, they may be absent at the late stage of the disease or shortly after the start of corticosteroid treatment [10], for this reason, it seems preferable to designate the condition as ''fasciitis with eosinophilia'' rather than ''eosinophilic fasciitis [2]. Inflammatory infiltrates may also include macrophages (41%) and plasma cells (44 to 50%) and more rarely polymorphonuclear cells (6 to 10%). At a later stage, the fascia is less inflammatory and invaded by collagen fibrosis in up to 40% of cases [8]. Regarding the treatment of EF, it is now well

established that the gold standard is high-dose corticosteroids with a complete or partial response in 70 to 90% [1,8]. The initial loading dose ranges from 0.5 to 1 mg/kg/day, followed by a progressive decreased dose of prednisone. The average duration of treatment is not consensual and varies from a few months to several years depending on the clinical and laboratory course of the condition [8,9]. Another non-consensual issue concerns the use of immunosuppressive drugs such as azathioprine, cyclophosphamide, methotrexate, ciclosporin and more recently biotherapies (anti-TNF, rituximab) [8,10,11,15]. Their prescription is essentially justified by the failure of treatment or steroid-dependence at a high level. In the patient population studied by Lebeaux all of the 32 patients followed in the long-term, have received steroids, for a period average of 45.7 months. because of an unsatisfactory clinical response, 44% of them (14 patients) have required a second-line treatment including adjunctive immunosuppressive therapy for an average of 24.7 months (methotrexate in 86% of cases, azathioprine in 14% of cases and hydroxychloroquine in 6% of cases). 94% (17/18) of patients treated with steroids alone achieved complete remission, compared to only 36% (5/14) of patients who received steroids with adjunctive immunosuppressive therapy and which had a more severe disease. These authors also show that the use of high doses of steroids as induction treatment (Solu-Medrol 0.5 g to 1 g / day for three days) seems to be associated with more complete remissions [8]. On the other hand, some recent publications report the efficacy of anti-TNF-alpha (tumor necrosis factor) (infliximab) in cases resistant to steroids and immunosuppressants [16]. FE is a disease of good prognosis, if it is not associated with severe hematological disorders.

Endo et al. [15] have reviewed the various factors associated with the absence of complete remission, which include.

- The diagnostic delay greater than 6 months;
- No bolus of methylprednisolone at the start of treatment;
- The presence of clinical or histological morphea lesions;
- Trunk involvement;
- Young age of onset (under 12 years).

Finally, as mentioned above, treatment with high doses of steroids at diagnosis appears to decrease the need for immunosuppressive therapy later and improve skin prognosis in the long term [8].

Conclusion

Eosinophilic fasciitis is a rare connective tissue disease characterized by symmetrical oedematous induration of the skin and soft tissues predominant in the upper and lower limbs. MRI is a very important diagnostic tool showing characteristic fascial abnormalities, it is useful also in directing the surgeon to the optimal location for biopsy. Oral corticosteroids remain the gold standard treatment and may be associated with an immunosuppressive therapy such as methotrexate, particularly in patients with unsatisfactory corticosteroid response. The fact that certain aspects of this disease are close to other more frequent inflammatory pathologies suggests that FE is probably underdiagnosed. It is important to think about it because the prognosis and the response to the treatment are better than for these other connectives.

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