

EOSINOPHILIC FASCIITIS (SHULMAN'S SYNDROME): CASE REPORTS AND REVIEW OF THE LITERATURE

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In 1974, Shulman et al. reported two patients with scleroderma-like skin changes, peripheral eosinophilia and hypergammaglobulinemia.¹ This disorder was initially distinguished from progressive systemic sclerosis by the absence of Raynaud's phenomenon, visceral involvement, and a favorable response to corticosteroid therapy. Histologically, there was marked thickening of the fascia with striking inflammation.¹ The term eosinophilic fasciitis (EF) was suggested by Rodnan et al. due to the presence of the striking peripheral eosinophilia and the finding of large numbers of these cells in the inflamed deep fascia and subcutis.² However, further studies showed that eosinophils are not a consistent component of the inflammatory infiltrate in the fascia and can be absent.³ One patient with localized eosinophilic fasciitis from Saudi Arabia has been reported.⁴ In this paper, we further report 2 cases with generalized EF. The etiology of Shulman's syndrome is still unknown, although a hypersensitivity reaction and autoimmune processes have been suggested.

Case Reports

Case 1

A 27-year-old male Saudi soldier was referred to our hospital because of progressive tightness of the skin with proximal weakness of upper and lower limbs for 5 months. The tightness affected the skin of the abdomen, chest, upper and lower limbs, with consequent impaired mobility of joints but spared the face, hands and feet. He gave a history of cough with a small amount of whitish sputum, associated with shortness of breath on exertion, but no history of fever or chest pain. He reported no history of heavy exercise, Raynaud's phenomenon, skin rash, hair loss, joint pain or stiffness. He had no significant drug history or exposure to unusual chemicals or toxins. The patient is neither asthmatic nor a smoker.

On examination, the patient looked healthy, with stable vital signs. He had no lymphadenopathy, skin rash, telangectasia, cyanosis, sclerodactyly, microstomia, digital

infarcts or gangrene. The skin was tight and indurated over the abdomen, chest, upper and lower limbs. Groove sign was obvious in both forearms (Figure 1). Gross nailfold examination was unremarkable. Chest examination was normal except for bilateral restriction of chest movement. Cardiovascular and abdominal examinations were normal. Higher mental function and cranial nerves were intact, however, there was proximal weakness (4/5) in upper and lower limbs. Muscle tone, deep tendon reflexes, sensation and coordination were all normal. Laboratory investigations included hemoglobin (Hb) 121 g/L (normal range: 130-180 g/L), white blood cell (WBC) $8.5 \times 10^9/L$ (normal $4-11 \times 10^9/L$) with eosinophils 11.9% (absolute eosinophil count 1020 cells/L), platelets $332 \times 10^9/L$ (normal $140-450 \times 10^9/L$) and erythrocyte sedimentation rate (ESR) 27 mm/hr (normal 0-10 mm/hr). Urinalysis, prothrombin time (PT), partial thromboplastin time (PTT), midstream urine (MSU), urea and electrolyte (U&E), liver function test (LFT), calcium, phosphorus, alkaline phosphatase, creatinine phosphokinase (CPK), serum immunoglobulins and chest x-ray (CXR) were all normal. Hepatitis surface antigen (HbsAg) and antinuclear antibodies (ANA) were negative. Pulmonary function test (PFT) showed mild restrictive and obstructive ventilatory impairment, however, diffusion capacity was normal. Computerized tomography (CT) scan of the chest showed a picture suggestive of early obliterative bronchiolitis. Electromyogram (EMG) and muscle biopsy were normal. Incisional skin biopsy from the right forearm showed normal dermal layers, but the subcutis and underlying fascia contained areas of increased collagen with inflammatory cells infiltration consisting of plasma cells and many scattered eosinophils. The patient was started on oral prednisolone 40 mg in the morning and 10 mg in the evening, and oral cimetidine 400 mg twice daily. Within two weeks, he showed good response with softening of the skin and lessening of the limitation of his activity.

Case 2

A 34-year-old Saudi policeman presented with a history of progressive skin tightness and swelling of the extremities for 6 months. It initially started in left forearm then spread to left and right arms, forearms, legs and thighs. This led to marked limitation of his daily activities. Because of the pain and paresthesia in the hands and forearms, he saw an

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FIGURE 1. Patient's forearms showing groove sign.



FIGURE 2. Skin biopsy showing marked eosinophilic infiltration.

orthopedic surgeon who performed a left carpal tunnel release but without any improvement. There was no history of numbness, digital discoloration, Raynaud's phenomenon, dysphagia or similar illness in the family. The patient gave a history of arthralgia in both knees but with no history of joint stiffness, swelling, fever or hair loss.

The patient had normal cardiovascular, chest, abdomen and CNS examinations. He had mild effusions of both knees with decrease in the range of movement of fingers, wrists and elbows on both sides. His skin showed swelling, tightness and severe induration of right and left forearms and arms. Groove sign was obvious on the forearms. The skin of the lower limbs had similar but milder changes. The face, hands and feet were spared. Gross nailfold exam was unremarkable.

His investigations showed Hb 150 g/L (normal 130-180 g/L), WBC $16 \times 10^9/L$ (normal $4-11 \times 10^9/L$) with 34% eosinophils (5440 cells/L absolute count), platelets $346 \times 10^9/L$ (normal $140-450 \times 10^9/L$) and ESR 23 mm/hr (normal 0-10 mm/hr). Urinalysis, liver, renal profiles and CPK were all normal. Hepatitis B and C, HIV, ANA and rheumatoid factor were all negative. Immunoglobulin G (IgG) was elevated at 27.4 g/L (normal 8 to 18 g/L). IgM and IgA were normal. EMG, PFT, CXR, and capillary microscopy were all normal. His skin biopsy (incision from right forearm) showed similar changes to that in Case 1, but with marked eosinophilic infiltration extending to the subcutis (Figure 2). The patient was put on oral prednisolone 40 mg in the morning and 20 mg in the evening, and hydroxychloroquine 200 mg once daily. The patient showed marked skin softening and improved limb mobility when he was seen six weeks later.

Discussion

Both of our patients had characteristic skin changes, leading to severe tightness of the skin and subsequent impaired mobility of joints. Groove sign was evident in both cases. Face, hands and feet were spared. There was

peripheral and tissue eosinophilia and elevated ESR. Hypergammaglobulinemia was present in one patient. Histopathological changes were characteristic of the condition in both patients.

EF (diffuse fasciitis with eosinophilia or Shulman's syndrome) is a rare syndrome characterized clinically by symmetric skin induration, swelling of the extremities and joint contractures, leading to impaired mobility. These changes affect extremities, neck and trunk. However, face, hands and feet are usually spared. In some cases, muscle groups are separated by a distinct line of demarcation because of fascial involvement.⁵ Raynaud's phenomenon and internal organ involvement is very unusual. Abnormal nailfold capillaroscopy is one of the connective tissue disease signs and it is usually normal in EF. Important laboratory findings include peripheral eosinophilia, elevated ESR and hypergammaglobulinemia, and elevated aldolase even with normal CPK.

Skin biopsy usually shows primary fascial infiltration with lymphocytes, plasma cells, mast cells and eosinophils through eosinophilic-triggered fibroblast activation mediated by transforming growth factor B. As the disease process continues, the fascia becomes fibrotic and collagen fibers replace the subcutaneous tissue. Degranulation of eosinophils leads to stimulation of fascial fibroblast to produce increased amounts of collagen and to display elevated levels of MRNAs for types I, III and VI collagens *in vitro* compared with fibroblast derived from the adjacent dermis.⁶ Stimulation of fascial fibroblasts by transforming growth factor B (TGF- B_1), which leads to activation of TGF- B_1 mRNA expression, suggests a role for this growth factor in EF.⁷

The etiology of EF is still speculative. Shulman suggested a hypersensitivity reaction to muscle tissue precipitated by the damage induced by a preceding strenuous exercise.¹ However, it became clear later on that only 50% of the cases worldwide had a history of heavy exercise prior to the presentation.⁸

The evidence supporting an autoimmune mechanism includes the detection of hypergammaglobulinemia and

circulating immune complexes in active EF,⁹ the association of EF with other autoimmune diseases,¹⁰ and the occurrence of EF in chronic graft versus host disease (GVHD).¹¹ Recently, Reitamo et al.¹² demonstrated elevation of interleukin-8 and autoantibodies to interleukin-8 in the serum of patients with eosinophilic fasciitis. EF has been associated with exposure to drugs and toxins, such as phenytoin,¹³ trichloroethylene,¹⁴ antituberculous drugs,¹⁵ subcutaneous heparin¹⁶ and fosinopril.¹⁷ Trauma has been reported as a cause and accepted for workers' compensation in France.¹⁸ L-tryptophan is known to be associated with EMS (eosinophilia myalgia syndrome),^{19,20} however, 8 patients with a history of L-tryptophan ingestion have been reported in 1990 to have EF.¹⁹ Interestingly, L-tryptophan became available in the United States in 1974, the year in which EF was first described.²¹ Eosinophilia myalgia syndrome (EMS) is a multisystem toxin-induced disorder, and 98% of all patients have a history of ingesting L-tryptophan.²² The main differences from EF are:^{3,23}

1. EMS is preceded by acute episodes of "flu-like" illness, with malaise, fatigue, severe myalgia, characteristic muscle cramps with respiratory symptoms or pneumonitis.
2. The pathology is pan-cutaneous-subcutaneous in EMS, in contrast to EF, which mainly involves the subcutis alone.
3. The presence of objective evidence of systemic involvement (including muscles, nerves, heart and/or lungs), which is lacking in EF.

Unfortunately, some authors use the term EF to represent the skin changes of EMS, although there are clinical differences between these two entities, which have led to some degree of confusion.

The association between EF and Lyme disease has remained speculative for a number of years. However, *Borrelia burgdorferi* was documented for the first time in lesional tissue of EF in 1994, where two cases were described in which the serum IgG against *Borrelia burgdorferi* was borderline positive.²⁴ The organism was visualized by microscopy using silver staining technique (in one patient) and immunoperoxidase technique (in the other one). *Borrelia burgdorferi* specific DNA was detected by PCR amplification in one patient. The authors then concluded that some of the cases of what has previously been described as eosinophilic fasciitis may be an expression of Lyme disease. They also proposed the term "Borrelia fasciitis" to describe such lesions.¹⁷

One of our cases showed mild restrictive pulmonary function but both patients showed normal gross nailfold examination, as reported by others.²⁵ Chalker et al. reported one case of extrapulmonary thoracic restriction (hidebound chest) complicating eosinophilic fasciitis. However, there was no evidence of parenchymal lung disease.²⁶

Carpal tunnel syndrome (CTS) has been reported in 20% of patients with EF.²⁷⁻³⁰ One of our patients had a carpal tunnel release but with no improvement.

Lakhanpal et al. reported CTS in 12 patients out of 51 (23%).²⁵ Arthritis was seen in 44% of the patients reported in that study, and may be the presenting symptom in some patients.²⁵ Joints of the hands, knees, wrists, elbows, ankles, feet and shoulders were involved, in that order. Peripheral eosinophilia is also frequently reported with EF.^{19,25} It is defined as eosinophils >7% of total WBC or >760 cells/microliter absolute count.²⁵ Muscle weakness was reported in 11 out of 15 cases and was judged to be due to mild eosinophilic myositis.²⁵ Lakhanpal et al. reported nonspecific changes in EMG, showing motor unit potentials of reduced duration and amplitude, but fibrillation potentials were not seen.²⁵ CPK was elevated only in one patient out of 23 (4%), while a low-grade myositis along with fasciitis was seen in 4 cases out of 52. Fujimoto et al.³¹ reported 3 cases of EF in which the serum aldolase level was a useful indicator of disease activity. In these 3 cases, the aldolase level was elevated, whereas the CPK level was normal. The serum aldolase level returned to normal with treatment, and became elevated with reactivation of the disease. Nelson³² reviewed the earlier literature and found elevation of serum aldolase in several cases, but many others had normal serum aldolase level. He suggested that serum aldolase level in a laboratory measure of activity will be useful to follow if abnormal in the active phase of the disease, but will be of no clinical benefit if normal at the beginning of the treatment.

Bennet et al. reviewed 20 cases from 1974 to 1976, and found them all to be negative for antinuclear antibodies (ANA) and rheumatoid factor (RF).³³ Others found 2 out of 52 patients to be positive for RF and 3 out of the 52 positive for ANA.²⁵ Lakhanpal et al.²⁵ reported 15 patients out of 52 with elevated ESR (>29 mm/1 hr), and hypergammaglobulinemia in 17 out of 49 (35%). EF is not known to involve the kidneys. However, 2 cases of EF were reported to be associated with renal disease.^{34,35}

Skin biopsy is the cornerstone of the diagnosis. Epidermis and dermis are basically normal but the main changes are in the subcutis (panniculus and deep fascia). Initially, there will be fascial infiltration with lymphocytes, plasma cells, mast cells and eosinophils but, later on, the fascia will be severely fibrotic and excessive collagen is eventually deposited in the subcutaneous tissue and dermis with an eosinophilic infiltrate. Sometimes, extension to subjacent muscle (in the form of low-grade myositis) does occur.^{25,27} Deposits of immunoglobulins and/or complement were found in 5 of 8 biopsies studied by direct immunofluorescence.²⁷ Magnetic resonance imaging (MRI) has been demonstrated to be of value for the localization of potential biopsy sites and to follow the course of therapy.³⁶

Multiple hematological conditions are associated with EF, including aplastic anemia, thrombocytopenia, myelomonocytic leukemia, chronic lymphocytic leukemia, myeloproliferative syndrome, monoclonal gammopathy and Hodgkin's and non-Hodgkin's lymphomas.^{25,37-39} Solid tumors such as carcinoma of the breast^{25,37,40} and prostate³⁷ have also been seen with EF. EF, when associated with

hematological or malignant disorders, appears to carry a poor prognosis.²⁵ Recently, an EF patient with renal involvement responded very well to fasciotomy and methotrexate.³⁵ Lakhanpal et al.²⁵ reported 52 cases of EF, and only 59% of them had a satisfactory response to prednisolone alone (40 to 60 mg/day in divided daily doses). Laboratory abnormalities, including elevated ESR, peripheral eosinophilia and hypergammaglobulinemia reverted to normal with prednisolone therapy in almost all patients.²⁵ However, corticosteroid resistance has been encountered in the setting of paraneoplastic³⁷ and GVH EF.¹¹ Two patients were treated with colchicine, but showed no benefit.²⁵ The value of cimitidine and D-penicillamine²⁵ in the treatment of EF is unknown because of the small number of patients treated. The fact that out of five untreated EF patients, 2 had complete spontaneous resolution and 2 had some spontaneous improvement of their disease, questions the validity of the use and efficacy of any mode of treatment for EF.²⁵ Physiotherapy in the form of active and passive range of movement should be an essential part of management of severe function-limiting disease to prevent contractures.^{41,42}

Long-term follow-up is recommended, as EF has been associated with some hematological disorders and solid malignancies.

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