

Eosinophilic Fasciitis (Shulman Syndrome)

Sueli Carneiro, MD, PhD; Arles Brotas, MD; Fabrício Lamy, MD; Flávia Lisboa, MD; Eduardo Lago, MD; David Azulay, MD; Tullia Cuzzi, MD, PhD; Marcia Ramos-e-Silva, MD, PhD

GOAL

To understand eosinophilic fasciitis to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Recognize the clinical presentation of eosinophilic fasciitis.
2. Discuss the histologic findings in patients with eosinophilic fasciitis.
3. Differentiate eosinophilic fasciitis from similarly presenting conditions.

CME Test on page 215.

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We present a case of eosinophilic fasciitis, or Shulman syndrome, in a 35-year-old man and discuss its clinical and histopathologic aspects, as well as its relationship to scleroderma. Although controversial, the tendency is to set

Shulman syndrome apart from all other scleroderma states.

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From the School of Medicine and HUCFF-UFRJ, Federal University of Rio de Janeiro, Brazil. Dr. Carneiro is Associate Professor, Sector of Dermatology; Drs. Brotas, Lamy, Lisboa, and Lago are post-graduation students, Sector of Dermatology; Dr. Azulay is Assistant Professor, Sector of Dermatology; Dr. Cuzzi is Associate Professor, Sector of Pathology; and Dr. Ramos-e-Silva is Associate Professor and Chair, Sector of Dermatology.

Reprints: Sueli Coelho da Silva Carneiro, MD, PhD, Rua Farma de Amoedo, 140/601, Ipanema Rio de Janeiro 22420-020, Brazil (e-mail: sueli@hucff.ufrj.br).

Case Report

A 35-year-old white man visited our Sector of Dermatology complaining about a feeling of increased weight and volume in his arms and legs that had started 2 months previously. The symptoms had begun 48 hours after a vigorous and unusual physical effort—carrying 30- to 40-kg boxes during a more than 2.5-hour period. When the patient sought medical assistance, his problem was diagnosed as rheumatism. He was prescribed a non-steroidal anti-inflammatory drug, with partial



Figure 1. Infiltrated areas in both forearms.



Figure 2. Infiltrated area in right leg, sclerosis of skin, and scarcity of hair in the affected area.

improvement. A few days later, his condition evolved to hand and wrist joint induration lasting more than 2 hours that was associated with a discrete disturbance to his normal way of walking.

The patient did not exercise regularly and denied the use of medication containing L-tryptophan. He did not report any systemic signs and symptoms such as fever, reduced weight, hyporexia, dyspnea, difficulty swallowing solids and liquids, previous upper respiratory tract infections, recent history of hepatitis, diabetes mellitus, or similar cases in the family.

Results of a physical examination showed loss of weight and skin blushing. The patient was hydrated, acyanotic, anicteric, feverless, and eupneic. His arterial pressure was 120×80 mm Hg, with ample peripheral pulses. The patient showed atypical facies without edema, with normal wrinkling for his gender and age and a mouth opening of 4.5 cm. His thorax and abdomen were without abnormalities. His upper and lower limbs had increased volume with infiltration varying from discrete to moderate, without sustained depressions at finger pressure except on the extremities. There was absence of Raynaud phenomenon. Results of an examination of articulations showed absence of edema or synovitis of the knees, ankles, wrists, and hands; mobility was free and painless.

Results of a dermatologic examination revealed visible sclerosis of limb skin, which was more evident at the extremities and diminished in intensity

in the direction of the proximal region; in addition, the affected area had a discrete yellowish color, scarcity of hair, and telangiectasia (Figures 1 and 2).

Results of laboratory tests showed intense eosinophilia (28%: a blood count of 2500 eosinophils in 8900 leukocytes); an increased erythrocyte sedimentation rate; and hypergammaglobulinemia (35.7%). His immunologic profile was evaluated for antinuclear factor, anti-DNA, antitopoisomerase, and anticentromere antibodies; all test results were negative. Antibodies for human immunodeficiency virus and indicators for hepatitis also were negative. Urine sediment and parasitologic stool examinations, as well as an x-ray of the thorax, did not reveal alterations. An incisional biopsy down to the muscular fascia was performed with a scalpel on the anterior surface of the right forearm.

Results of a histopathologic examination with hematoxylin-eosin stain revealed an inflammatory infiltrate of lymphocytes, plasma cells, and eosinophils around dermal vessels, mostly at the muscular fascia and adjacent adipose tissue (Figures 3 and 4). Results of direct immunofluorescence showed immunoreactivity to fibrinogen in some vessels of the superficial dermis; however, the results were negative for IgG, IgM, IgA, and C3, configuring an unspecific pattern of vascular reaction.

The patient was diagnosed with eosinophilic fasciitis (Shulman syndrome), prescribed a therapeutic regimen of prednisone 20 mg/d (0.3 mg/kg) and diclofenac potassium 100 mg/d, and advised

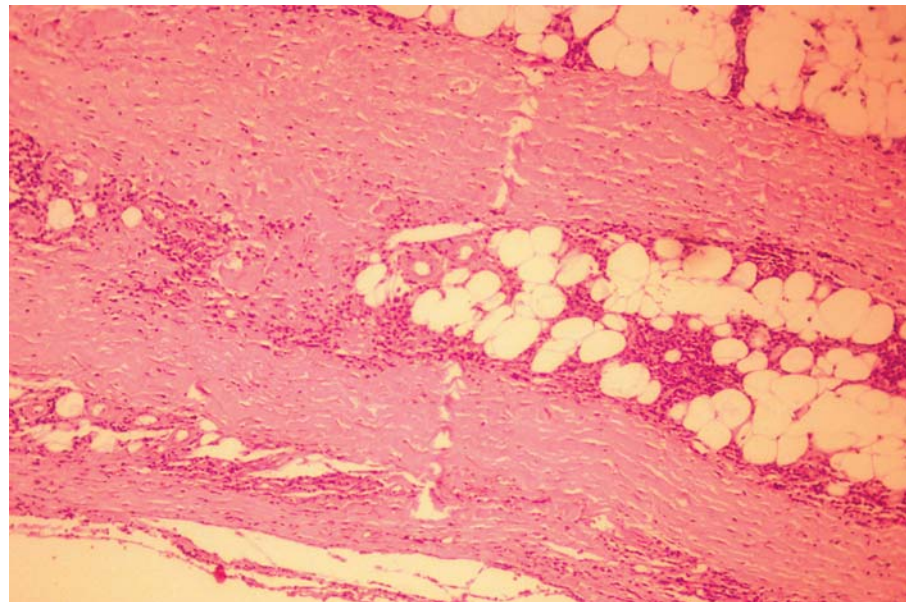


Figure 3. Inflammatory cells at the muscular fascia and adjacent adipose tissue (H&E, original magnification $\times 200$).

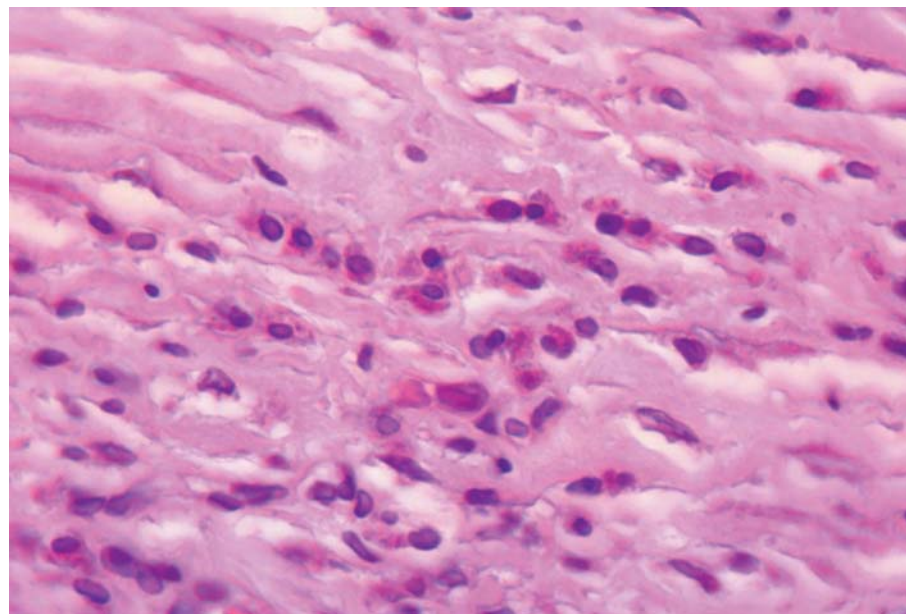


Figure 4. Numerous eosinophils among inflammatory cells (H&E, original magnification $\times 400$).

to avoid exercise and to rest. The patient's condition progressively improved, as did the cutaneous sclerosis, which improved faster in the upper limbs. After 6 months of prednisone with gradual withdrawal, examination results showed only a discrete sclerosis of the arms, forearms, thighs, and legs.

Comment

Shulman syndrome, first described in 1974 by Shulman,¹ is characterized by a sudden onset of a symmetrical edema with induration at the extremities. In 1975, Rodnan et al² proposed the name

eosinophilic fasciitis after evaluating a laboratorial aspect of the disease. At that time, more than 200 cases were reported, some in nonhuman primates such as the rhesus monkey.³

Eosinophilic fasciitis is an inflammatory disease of unknown etiology that affects the muscular fascia and is characterized by a considerable increase of serous and tissue eosinophils, with hypergammaglobulinemia.⁴⁻⁶ This sclerodermiform syndrome presents clinical and histopathologic characteristics that allow a clinical distinction from scleroderma, despite that in some cases such

differentiation may be difficult. Eosinophilic fasciitis mostly affects white men aged 30 to 70 years, frequently after the performance of vigorous and unusual physical effort. Patients complain about pain and edema with sudden onset and centripetal evolution starting at the extremities, evolving to induration that leads to limitation of hand and feet mobility.^{7,8} Occasionally, the face and abdomen also may be involved.⁹ An important dermatologic sign for the diagnosis is called the valley signal, which can be observed during extension and abduction of the arms, and corresponds to the linear depression following the vascular path of the area involved. The description of 6 cases in the presence of hematologic neoplasia has led some authors to believe that eosinophilic fasciitis is a manifestation of a paraneoplastic syndrome.¹⁰

Since the first description of Shulman syndrome in the literature, the condition has appeared in more than 100 articles, mostly of Anglo-Saxon origin. These articles have generated much debate regarding the condition's relation to scleroderma or its existence as an autonomous entity.¹¹ The condition should be set apart from all other sclerodermiform states. Scleredema adultorum (Buschke disease) is related to respiratory infection or to diabetes mellitus of long evolution. Scleredema adultorum presents a centrifugal evolution, beginning at the cervical region and root of the upper limbs, with half of the cases occurring during childhood or adolescence, and is twice as frequent in women.⁸ Mucin is generally evident at the beginning of the disease.¹² Myalgia-eosinophilia syndrome presents respiratory and neurologic symptoms associated with myalgia of sudden onset and is accompanied by a temporary cutaneous eruption that varies from maculopapular to urticarial. Myalgia-eosinophilia syndrome may present intense itching, and is related to the ingestion of the amino acid L-tryptophan.¹³⁻¹⁶ Systemic scleroderma presents a universal induration of the skin accompanied by vasospastic phenomena in several organs with a variety of symptoms. Patients with acroscclerosis, a form of systemic scleroderma, present with calcinosis, Raynaud phenomenon, esophageal alterations, sclerodactyly, and telangiectasis (also known as CREST syndrome) on the face and upper trunk. The circumscribed forms are characterized by several types of cutaneous lesions, which are localized and seldom accompanied by other alterations.¹⁷⁻²⁰

Peripheral eosinophilia is a common finding in patients with eosinophilic fasciitis, presenting in more than 80% of cases; it also may occur in different forms in systemic sclerosis (7%) and in

localized scleroderma (31%).^{17,21} In nonmedicated patients with eosinophilic fasciitis, peripheral eosinophilia was a consistent finding, even in those who had the disease for more than 30 months. Most authors define *eosinophilia* as an eosinophil count of more than 600 cells/cm³; however, others have defined it as 400 or even 300 cells/cm³, with existence of a relationship between the peripheral and tissue count of eosinophils in most cases. In one study, eosinophilia above 1000 cells/mm³ was found in 61% of patients, but only 1% had systemic sclerosis and 8% had the localized form, indicating that peripheral eosinophilia is not only more frequent and intense but also guides the diagnosis.^{17,21} Tissue eosinophilia is more variable than peripheral eosinophilia.

In some cases, the peripheral eosinophils are present in numbers within reference range in a certain blood sample, showing that the finding may be temporary. It is important to make the differential diagnosis between systemic sclerosis, morphea, and eosinophilic fasciitis because they not only have different prognoses but also have different treatments.^{21,22} Eosinophilic fasciitis responds well to systemic corticoid therapy; in scleroderma, steroids are not always useful, and morphea can remit spontaneously. Absence of Raynaud phenomenon and induration of the limbs after intense and unusual exercise help to establish the diagnosis of eosinophilic fasciitis. Fascia damage can be found, though rarely, in the late phases of systemic sclerosis. Proliferative fasciitis represents a pseudo-sarcomatous reaction involving the muscular fascia and the subcutaneous fibrous septum; in addition, despite not presenting eosinophilia, proliferative fasciitis affects the extremities of adults and may have trauma as an etiological factor.¹⁹

The diagnosis of eosinophilic fasciitis may be confirmed by histopathologic examination, results of which show an inflammatory infiltrate with eosinophils extending to the muscular fascia.¹⁹ Tissue eosinophilia is defined as the presence of 3 or more cells in the microscopic field.¹⁶ The eosinophils are present in the entire damaged area from disease onset; however, this must not be confused with disseminated eosinophilic collagenosis, in which the cells infiltrate several organs, leading to focal necrosis and necrotizing endarteritis. When the biopsy result does not reach a diagnosis of hypodermis and fascia, the sclerotic aspect prevails, which is not characteristic of eosinophilic fasciitis. In the initial phases of eosinophilic fasciitis, there are no significant epidermal and dermal alterations; in scleroderma, there are variable degrees of edema and sclerosis,

and the inflammatory process, when present, occurs in the dermis and in the upper portion of the subcutaneous cell tissue.^{8,19,20}

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