

# Eosinophilic fasciitis (Shulman's disease): review and comparative evaluation of seven patients

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## Abstract

**Objectives:** Eosinophilic fasciitis (EF) was described in 1974 by Shulman as a rare fibrosing connective tissue disease of unknown etiology. An undetermined trigger is thought to lead to the degranulation of eosinophils that interact with fibroblasts and express fibrogenic cytokines including the transforming factor of tumor growth  $\alpha$  and  $\beta$  and interleukins 1 and 6. The purpose of this study was to summarize seven cases of EF in a central hospital.

**Material and methods:** This was a retrospective and descriptive study of a population with EF of a central hospital. All patients diagnosed with EF in a hospital unit were admitted to the study between January 1, 2005, and April 30, 2018.

**Results:** A total of seven patients diagnosed with EF were analyzed. The median age of the population at the time of diagnosis was 56 years, and 57% of the patients were women. All patients had elevated peripheral eosinophilia and sedimentation rate, and only one patient had hypergammaglobulinemia. All patients had edema and cutaneous thickening of the limbs, 57% had constitutional symptoms, and 57% had inflammatory arthritis with joint contracture. Prednisolone (PDN) therapy was initiated in all patients, and only in two was the association of PDN with methotrexate (MTX) initially performed. In one patient triple therapy of PDN, MTX, and cyclosporine was required. At the time of this publication, only one patient maintains active disease, and tocilizumab has been initiated.

**Conclusions:** Recent studies show a more favorable response from the combination of PDN and MTX than from PDN alone. Considering the rarity of the disease, more long-term studies are needed regarding the etiopathogenetics, progression, recurrence of EF, and new effective therapies.

**Key words:** eosinophilic fasciitis, Shulman disease, groove sign, corticosteroids.

## Introduction

In 1974 Shulman [1] described a rare scleroderma-like syndrome designated as eosinophilic fasciitis (EF). Eosinophilic fasciitis is rare disease characterized by subacute onset of erythema, edema, and induration of the skin and soft tissues of the limbs and trunk [2]. These manifestations are replaced by fascial fibrosis, leading to a cobblestone appearance or *peau d'orange*, as well as the “groove sign,” a linear depression along the course of veins, accentuated by limb elevation, due to inward

tethering of the skin. Concurrent plaque morphea can be present in 29–41% of cases. Extracutaneous involvement includes muscle pain and weakness [3], neuropathies such as carpal tunnel syndrome (23%) [4], articular symptoms like joint contractures (50–56%) [5], and arthritis (40%) [6], with a high impact of morbidity related to EF. Visceral involvement is rare, but some cases have been reported as pericarditis [7], pleural effusions [8], and renal involvement.

Laboratory evaluation often reveals peripheral eosinophilia (58–85%) [9], hypergammaglobulinemia (36–46%) [7] monoclonal gammopathy (16%) [8], and an elevated

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Submitted: 23.01.2019; Accepted: 9.04.2019

erythrocyte sedimentation rate (ESR), although it is not mandatory for the diagnosis.

The incidence of EF is uncertain. It occurs most commonly in middle-aged individuals, with peak incidence between 40 and 50 years of age.

The pathogenesis of EF is not well understood. Eosinophils degranulate and induce tissue damage, which results in fibrosis via accumulation of extracellular matrix. Various studies have indicated that eosinophils interact with fibroblasts and express fibrogenic cytokines including tumor growth factor (TGF)  $\alpha$ , TGF- $\beta$ , interleukin (IL) 1, and IL-6 [10].

There are some possible triggering factors or factors associated with EF, such as infections [11], initiation of hemodialysis [12], radiotherapy, graft-versus-host disease, hematological disorders, as well as autoimmune diseases [13] (primary biliary cirrhosis, systemic lupus erythematosus, Sjögren's syndrome). Other reasons for EF are also taken into account, such as: exposure to certain medications [14] (ramipril, phenytoin, subcutaneous heparin, statins), strenuous exercise, or trauma. However, most cases are considered as idiopathic. Rarely, EF can be associated with solid or hematological neoplasms [15]. Hematological abnormalities associated with EF include the following: multiple myeloma, lymphoma, myelodysplastic syndromes, myeloproliferative disorders, acquired amegakaryocytic thrombocytopenia, aplastic anemia, and paroxysmal nocturnal hemoglobinuria.

The diagnosis of EF is based on clinical features complemented by laboratory findings; however, universally accepted international diagnostic criteria are lacking. A full-thickness skin biopsy including the fascia usually confirms the diagnosis by demonstrating characteristic lymphocytic and eosinophilic infiltrate with thickened collagen bundles in the fascia. Magnetic resonance imaging (MRI) should be performed when the biopsy is non-diagnostic or cannot be obtained. Findings on MRI show an increased T2 signal in subcutaneous and deep fascia and enhancement of these structures on fat-suppressed T1 images after gadolinium administration. If MRI cannot be performed, 18-F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) [16] or ultrasound should be performed [17].

There are a variety of other disorders that should be considered in the differential diagnosis of EF. Systemic sclerosis (SSc) is the main differential diagnosis of EF. Sometimes EF can be misdiagnosed and there are some features that can help clinicians distinguish these two entities. In EF there is no skin tightening of distal digits, nailfold capillary changes, digital ulcers, or Raynaud's phenomenon. Histopathology in EF universally involves fascia and involvement of the dermis, subcutaneous fat,

and muscle may occur, whereas in SSc only dermis and subcutaneous fat are involved [18].

Localized scleroderma includes morphea and linear scleroderma. These entities have a slowly progressive course and are not associated with significant eosinophilia.

In scleroderma-like disorders we can find skin thickening and decreased pliability. Scleromyxedema can occur alone or in association with malignancies. Scleroderma is associated with diabetes, plasma cell disorder, and monoclonal gammopathy. In the skin biopsy of scleroderma there is no evidence of inflammation.

Early treatment of patients with EF showed better outcomes in some studies, but these findings were not statically significant [19].

Currently, systemic corticosteroids (SCS) are the cornerstone of treatment. In those patients who develop a steroid-resistant disease the introduction of an immunosuppressive drug is essential. The most common agent used is methotrexate (MTX), especially in patients with morphea-like skin lesions. Other treatment options include hydroxychloroquine, azathioprine, cyclophosphamide, cyclosporine, or an anti-TNF agent (etanercept). There are some recent studies showing the efficacy of a therapy targeting IL-6 cytokine, tocilizumab (TCZ), in EF refractory to steroids and other immunosuppressive drugs [20].

## Material and methods

This was an observational, retrospective, and descriptive study based on the population of Clinical Immunology Unit (CIU) in a single central hospital between January 1, 2005, and April 30, 2018.

### Population

All adult patients diagnosed with EF followed in CIU. EF diagnosis was based on suggestive clinical, laboratory findings and with a biopsy-proven fascia involvement.

### Data collection

We collected demographic and clinical data registered on the clinical software (SCLINICO®) of all patients. Age and gender were used as demographic variables.

Clinical variables included evolution time of disease, anatomic localization of disease, and personal and familiar medical history. Other considered variables related to extracutaneous involvement were constitutional symptoms, history of edema, inflammatory arthritis, morning stiffness, hyperpigmented lesions, Raynaud syndrome, dysphagia or gastroesophageal reflux disease, and carpal tunnel syndrome.

The laboratory variables considered were peripheral eosinophilia, gammaglobulinemia, complement, antinuclear antibodies, and erythrocyte sedimentation rate.

Series of EF are rarely published. The purpose of this study was to summarize seven cases, showing the clinical findings, laboratory results, histological characteristics, and immunosuppressive treatment used.

## Results

### Study sample

A total of seven patients were followed in CIU between January 2005 and April 2018. Mean age at diagnosis was  $56 \pm 21.1$  years, and four patients were women. At the time of the study, patients had an average of 11 (1–41) years of disease progression.

Table I shows patients' characteristics such as anatomic localization of EF, and signs and symptoms and laboratory findings.

Regarding the anatomic localization, arms, forearms, and thighs were the most affected. Only one patient had familiar and personal history of autoimmune disease.

The immunological laboratory results such as antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA) were negative. Thyroid function (TSH, ft4, and ft3), thyroid peroxidase antibody (TPO), thyroglobulin antibody (TGA), and thyroid stimulating hormone receptor antibody (TSHRab) were negative.

In laboratory findings, all patients had peripheral eosinophilia and elevated ESR, and only one patient had hypergammaglobulinemia. None of the patients presented abnormalities in complement component levels. All patients had history of edema and skin induration. Constitutional symptoms and inflammatory arthritis with joint contracture were present in 57% of patients. Raynaud phenomenon and visceral involvement were not present in the described patients.

Nailfold capillaroscopy was performed in three patients, two of them were normal picture of nailfold capillaries and one showed nonspecific alterations. A full thickness incisional skin biopsy was performed in all pa-

**Table I.** Patients' characteristics

Feature	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Diagnosis age (years)	5	60	28	56	36	56	61
Current age (years)	19	67	69	63	42	58	62
Gender	Female	Female	Female	Male	Male	Male	Female
Anatomic localization							
Face	–	–	+	–	–	–	–
Trunk	–	+	–	–	–	–	+
Arms	–	–	+	+	+	+	+
Forearm	–	–	–	+	+	+	+
Hands	+	–	+	–	–	–	–
Abdomen	–	+	–	+	–	–	+
Thighs	–	–	+	+	+	–	+
Ankle	+	–	–	–	–	–	–
Familiar history autoimmune disease	+	–	–	–	–	–	–
Personal history autoimmune disease	Vitiligo	–	–	–	–	–	–
Laboratory findings							
Eosinophilia	10.4%	8.3%	9.2%	10%	9.1%	9.2%	10.3%
Gammaglobulinemia	–	–	+	–	–	–	–
Antinuclear antibodies	1/160	1/80	1/80	1/60	1/80	1/160	1/80
Erythrocyte sedimentation rate (mm/h)	80	60	65	60	54	65	68
Signs and symptoms							
Constitutional symptoms	+	+	–	–	+	–	+
Inflammatory arthritis	+	+	–	–	+	–	+
Morning stiffness	–	+	–	–	+	–	+

tients, and histopathological assessment revealed infiltrated lymphocytes, plasma cells, histiocytes, and eosinophils. MRI was performed in one patient and showed thickening and global hypersignal of the forearm.

### Immunosuppressive treatment

Table II shows the immunosuppressive treatment used in the treatment of analyzed patients. Prednisolone (PDN) was initiated in all patients with a 0.5–1 mg/kg/day initial dose. In this study, in only two patients was the combination of PDN with MTX initially performed (patients 4 and 7). The median time between disease onset and MTX initiation was three months, and the maximum dose was 20 mg/week. One patient required triple therapy of PDN, MTX, and cyclosporine (initial dose 200 mg). Disease recurrence was observed only in one patient. Only one patient maintains active disease, and due the exuberant extension of fasciitis, subcutaneous tocilizumab 162 mg/week was initiated eight months after the disease onset. Six patients (86%) achieved disease remission after a median time of 12 months (range, 3–24 months). No patient underwent psoralen and ultraviolet A therapy.

### Discussion

Shulman's disease is rare, and high clinical suspicion is needed for the diagnosis, which can be difficult because of the differential diagnoses that should be considered.

Typical clinical manifestations include edema and skin thickening, with orange peel skin texture, and groove sign, with more common involvement in the extremities, neck, and trunk. Complaints of myalgias and

muscle weakness are common. Inflammatory arthritis is only present in a minority of patients. In these patients, sclerodactyly and Raynaud's syndrome are absent, as well as visceral involvement, and hence they are compatible with this study [21].

Rarely, some conditions can accompany the disease like compartment syndrome [22], esophageal dysmotility [23], reactive hepatitis [24], contractures in the joints due to edema [25], and peripheral polyneuropathy [26]. Contractures in the joints were found in 57% of patients, which can be very disabling and drastically reduce the quality of life.

Frequent analytical findings include peripheral eosinophilia, which may be transient, increased ESR, and polyclonal hypergammaglobulinemia. The laboratory abnormalities can be transitory and are not mandatory for the diagnosis. In this study, peripheral eosinophilia was present in all patients.

In most cases, the diagnosis is confirmed by skin biopsy (thickening of the fascia with accumulation of lymphocytes and macrophages with or without eosinophilic infiltrate) [18], and in this study the result of the biopsy was consistent with the suspected disease. Magnetic resonance imaging may be performed in atypical cases or if the biopsy does not confirm the diagnosis.

The differential diagnoses include neoplasia, infections, systemic sclerosis and other scleroderma subsets such as morphea, and epidemic fasciitis syndromes caused by toxic agents such as myalgia-eosinophilia syndrome and toxic oil syndrome [27]. Neoplasia should be suspected when corticosteroid therapy is refractory. In our study, none of the patients had an underlying disease diagnosed.

**Table II.** Immunosuppressive treatment

Therapeutics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
PDN initial dose (mg)	20	40	30	20	60	80	60
PDN maximum dose (mg)	20	40	30	20	60	80	60
Time for introduction of another (months)	14	3	1	0	1	–	0
MTX initial dose (mg)/week	17,5	5	10	10	5	–	7.5
MTX maximal dose (mg)/week	25	15	20	20	17.5	–	20
Time for introduction of another (months)	–	–	–	3	–	–	8
Current therapeutics	MTX 12.5 mg/week	PDN 5 mg + MTX 15 mg/week	MTX 17.5 mg/week	CCP 100 mg/daily + PDN 5 mg/daily	MTX 7.5 mg/week	PDN 5 mg	PDN 20 mg/daily + MTX 20 mg/week + TCZ 162 mg/week
Active disease	–	–	–	–	–	–	+
Disease recurrence	–	–	+	–	–	–	–

The standard treatment is systemic corticosteroid therapy [28]. Recent studies show a more favorable response of the combination of PDN and MTX than of PDN alone [29].

Currently there are new therapies that can improve the outcome of these patients, and it is fundamental to establish effective therapy as early as possible, to obtain a better prognosis. The introduction of a therapy targeting IL-6 cytokine in the case of EF refractory to steroids and other immunosuppressive drugs has been described [30]. In this study, TCZ at 162 mg for three months showed softening of the skin with a significant reduction of skin hardness.

Limitations of our study include its retrospective design and small study size.

## Conclusions

Eosinophilic fasciitis is a rare disease that may present a variable spectrum of clinical manifestations.

The variability of the age, presentation form, and laboratory changes make the EF challenging from the point of view of the possible differential diagnoses, as well as the therapeutic management.

Considering the rarity of the disease, more long-term studies are needed regarding the etiopathogenesis, progression, recurrence of EF, and new effective therapies.

*The authors declare no conflict of interest.*

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