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# Eosinophilic fasciitis (Shulman disease)

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The eosinophilic fasciitis (EF) is a rare connective tissue disease characterized by symmetrical and painful swelling with a progressive induration and thickening of the skin and soft tissues. The diagnosis of EF is often based on the association of characteristic skin or subcutaneous abnormalities and a thickened fascia with an inflammatory infiltration, mostly composed of lymphocytes and eosinophils. A peripheral eosinophilia is frequently present, but is not mandatory for the EF diagnosis. The diagnosis might be helped by a muscle magnetic resonance imaging which typically may evidence an increased signal intensity within the fascia and marked fascia enhancement after gadolinium administration at the acute phase of the disease.

Differential diagnoses should be ruled out, including eosinophilia-myalgia syndrome (EMS) after L-tryprophane ingestion, hypereosinophilic syndromes (HES), systemic sclerosis, Churg-Strauss syndrome, and/or peripheral T cell lymphomas with cutaneous involvement.

Due to the scarcity of the EF disease, there is no consensual therapeutic strategy. However, oral corticosteroids remain the mainstay treatment and may be associated to an immunosuppressive drug such as methotrexate in patients with morphea-like lesions or an unsatisfactory response to corticosteroids alone.



## Introduction

Eosinophilic fasciitis (EF) is a rare connective-tissue disease characterised by symmetrical and painful swelling with a progressive induration and thickening of the skin and soft tissues [1]. In 1974, Shulman described the first cases of EF and reported them as a new syndrome defined by

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scleroderma-like skin changes associated with peripheral eosinophilia, hypergammaglobulinaemia and elevated erythrocyte sedimentation rate (ESR) [2]. There are no international diagnostic criteria and the diagnosis of EF is often based on the association of characteristic skin or subcutaneous abnormalities and a thickened fascia with an inflammatory infiltration, mostly composed of lymphocytes and eosinophils [3–5]. After the first publication of Shulman, more than 300 cases have been reported but the largest retrospective study comprised 52 patients and was published in 1988 [4]. The therapeutic management of EF is now one of the most significant challenges, as the clinical–biological and pathological features are yet well defined. Its evaluation is hampered by the lack of standardised criteria for the treatment modalities and responses [3,4,6]. Recently, we have reported our experience of 34 patients with a biopsy-proven EF with a detailed analysis of clinical, biological, pathological and morphological features and a specific focus on the therapeutic management [5].

The main goals of this review will be first to report the clinical, biological, pathological and morphological features that may lead to the diagnosis of EF and second to define a therapeutic strategy.

## Clinical manifestations of EF

The onset of the disease may be featured by weight loss (26%), asthenia (38%) and spontaneous or provoked myalgia (67%) [5]. The anamnesis may also evidence a recent preceding history of intense physical exertion or trauma in 30–46% of patients [3–6].

### *Cutaneous manifestations of EF*

At diagnosis, a cutaneous involvement is reported in up to 90% of patients [4,5] including pitting oedema, induration and '*peau d'orange*' aspect with hyperpigmentation [4]. Initially, swelling and stiffness might affect distal extremities before evolving to induration [4,6]. Noteworthily a depressed vein aspect, also called the 'groove sign', can be present in up to half of patients and seems to be highly suggestive of a deep fibrosis or a fasciitis involvement (Fig. 1). The upper extremities are quite almost involved (88%) and the lower limbs are involved in up to 70% of patients [5]. Other localisations are possible even less frequent, including the neck (6–18%) and the trunk (17–32%) [4,5].

Morphea (localised scleroderma) is present in about one-third of patients [3–5]. A Raynaud phenomenon is rare and capillaroscopy is usually normal [4–7]. Although EF is mainly symmetrical, unilateral disease is possible [8]. Virtually, any part of the body might be involved but distality is more frequently concerned, mainly on the lower extremities [6]. Other parts of the body are less frequently involved: abdomen 12/52 (23%), chest 9/52 (17%), back 3/52 (6%), face or neck 3/52 (6%) of patients [4].

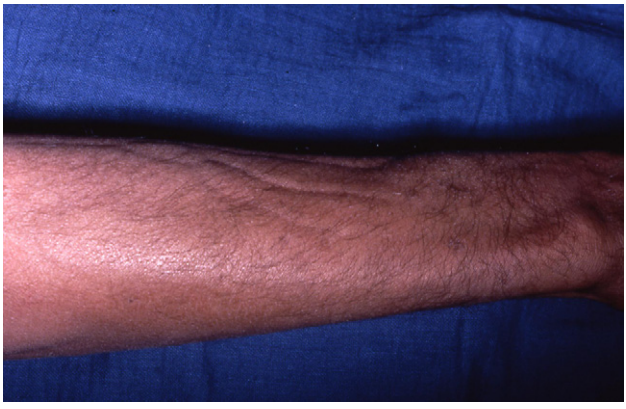

**Fig. 1.** Typical depressed veins aspect ("groove sign") of the left forearm of a patient with an eosinophilic fasciitis (EF).

*Muscular and articular manifestations of EF*

Myalgias, spontaneous or provoked, are present at the onset of the disease in up to 67% of patients and up to 86% of patients at diagnosis.

An articular involvement is frequently reported including joint contracture and inflammatory arthralgia in up to 40% of patients [4,5]. Distal synovitis is reported in 3–11.5% of patients. Morning stiffness may also be present in about 23% of patients. Carpal tunnel syndrome is present in about 23% of patients [4,5]. Tendon retraction and joint contracture might be assessed by the prayer sign, the inability to close fist or restricted joint movement but mostly occurs at a late stage of the disease, reflecting the severity of the fascia fibrosis [4,6,9,10].

*Visceral involvement of EF*

In the main retrospective series, none of the patients exhibited renal, pulmonary or heart involvement [4,5]. Nevertheless, few case reports described the following visceral involvement:

- Pulmonary and bilateral pleural involvement. This patient exhibited eosinophilia with cutaneous lesions and histologic findings consistent with EF [11]. Pleural effusion punction revealed inflammatory cells, mostly eosinophils. High-resolution computed tomography (CT) of the chest showed nodular interstitial thickening but no distortion. Pulmonary and cutaneous lesions improved after prednisolone treatment.
- Pericarditis associated with pleural effusion [12].
- Renal involvement in a 17-year-old boy with EF. Proteinuria led to a renal biopsy, which revealed ischaemic collapse of glomerular capillaries and atrophy of tubules of the cortex [13]. Another patient exhibited EF-associated with a focal segmental glomerulosclerosis [14]. Immunofluorescence was negative.

In summary, a visceral involvement is not expected with a typical EF, and should lead us to exclude other systemic diseases such as hypereosinophilic syndrome and Churg–Strauss vasculitis.

*Associated malignancies*

Haematological disorders might be associated with EF in less than 10% of patients [4–6,15], including thrombocytopaenia, myelomonocytic leukaemia, chronic lymphocytic leukaemia and myeloproliferative disorder. Severe aplastic anaemia (SAA) has been described with EF with a good response to cyclosporine A and antithymocyte globulin [16,17] or allogeneic haematopoietic stem cell transplantation (HSCT) [17,18]. Other reports of EF-associated haematological diseases are anecdotic including multiple myeloma [19], B-cell lymphoma [20],Hodgkin's disease [21] and peripheral T-cell lymphoma [22–24].

Nevertheless, it is difficult to assess the precise link between EF and haematological disorder. Whether EF is considered as a paraneoplastic syndrome associated with the haematological disorder or as the direct trigger of an initial haematological event is unknown. In the rare cases of EF-associated T cell lymphoma, the potential role of interleukin (IL)-5 producing T lymphocytes might be hypothesised as IL-5 is known to induce eosinophil proliferation.

Solid malignant tumours are scarcely reported with EF including a breast cancer with a complete resolution of EF after mastectomy [4], a choroidal melanoma with bone metastases [25], a prostatic cancer [26] and a bronchopulmonar cancer [27]. In view of the scarcity of these cases, there is no need to investigate an underlying malignancy in patients with EF, unless a suggestive manifestation is evidenced.

## Biological features of EF

A peripheral eosinophilia is present in 63–93% of patients, but is not mandatory for the EF diagnosis [3–5]. Furthermore, the level of the eosinophilia does not correlate with disease severity and some

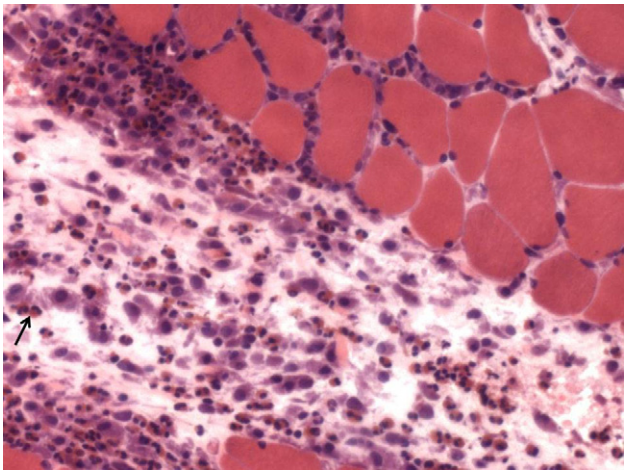

**Fig. 2.** Skin-fascio-muscular biopsy of a patient with EF: the haematoxylin-eosin staining shows intense, diffuse and perivascular inflammatory infiltrates within the fascia, composed mainly of lymphocytes, but also eosinophils (arrows).

patients may experience progressive skin induration despite normal laboratory data [3,4,6]. An inflammatory syndrome is frequent with raised C-reactive protein in 55% of patients, elevated ESR in 29–63% of patients and a hypergammaglobulinaemia in more than one-half of patients. Antinuclear antibodies may be detected in 15–20% of patients, but anti-DNA and anti-extractable nuclear antigen (ENA) antibodies are expected negative [3–5]. To avoid a Churg–Strauss vasculitis misdiagnosis, anti-neutrophil cytoplasmatic antibodies should be negative. Serum creatinine kinase is rarely elevated (4–6%) and might reflect a moderate muscle involvement [4,5]. No human leucocyte antigen (HLA) status was found to be associated with this disease [4].

## Pathological features of EF

A pathological confirmation is mandatory for EF diagnosis and a full skin-to-muscle biopsy should be realised whenever possible. Typically, the diagnosis can be assessed by the evidence of a fasciitis with a thickened fascia and inflammatory infiltrates composed of lymphocytes and/or eosinophils [4,5] (Fig. 2). Perivascular infiltrates of lymphocytes are quite almost present (>95%) [4,5] and are mainly composed of CD8+ lymphocytes (CD4/CD8 ratio <1) [28]. Eosinophil infiltrates are present in 69–75%

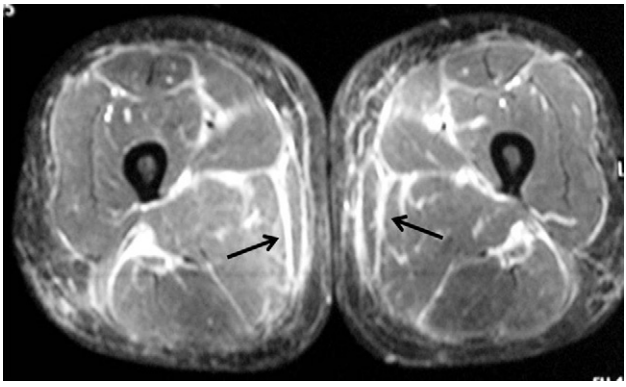

**Fig. 3.** Thigh muscle magnetic resonance imaging (MRI) of a patient with EF: the axial fat-suppressed, T2-weighted fast spin-echo MR image shows a markedly increased signal intensity within superficial and deep fascial layers and a mildly increased T2 signal intensity within superficial muscle fibres adjacent to the fascia (arrows).

of patients but not mandatory for EF diagnosis [3–5]. They can be absent at a chronic stage of the disease [29] or after corticosteroid treatment [30]. Other cells such as macrophages and plasma cells are frequently present in less than half of patients and polymorphonuclear cells in less than 10% of patients [5]. An interstitial myositis can be evidenced in 8–68% of patients [5] but a muscle necrosis is rarely reported. The epidermis is normal or slightly atrophic and the dermis shows mild accumulation of cells (mainly lymphocytes). Dermal collagen may be mildly sclerotic but is often normal unless in cases of associated morphea, which can be highlighted in up to 37% of patients [5].

## Morphological investigations in EF

*Muscle magnetic resonance imaging*

The muscle MRI is now considered the best morphological procedure for EF diagnosis [5,31]. Typically, the muscle MRI evidenced a markedly increased signal intensity within the fascia on fluid-sensitive sequences and marked fascia enhancement after gadolinium administration at the acute phase of the disease in up to 80% of patients (Fig. 3). It might also be useful in indicating the optimal location for muscle biopsy [31] and in the therapeutic re-evaluation of patients after treatment by evidencing a rapid relief of MRI abnormalities after corticosteroid treatment [31–35]. 5.2 Ultrasounds.

Preliminary studies reported a possible correlation between ultrasonography and MRI findings in EF [33]. Another report described correlation between ultrasonography and clinical improvement with treatment of EF, suggesting the use of this method for patients follow-up under treatment [9].

## Differential diagnosis of EF

The diagnosis of EF might be delayed because of initial aspecific signs such as muscular or joint pain. Furthermore, several differential diagnoses might be difficult with the following conditions:

A: An eosinophilia–myalgia syndrome (EMS) after L-tryprophane ingestion [36]. The Centres for Disease Control definition includes peripheral blood eosinophils count greater than 1000 $mm^{-3}$, generalised myalgia (severe enough to affect patient's ability to pursue daily activities) and the absence of infection or neoplasm to account for the first two criteria. The acute phase of EMS starts with generalised myalgia, dyspnoea, cough, fever, cutaneous hyperaesthesia, rash, pruritus and swelling of the extremities [37]. The chronic phase associates scleroderma-like cutaneous changes and progresses to multi-organ system involvement.

B: The hypereosinophilic syndromes (HES). They are characterised by a peripheral eosiniphilia, a systemic organ involvement (cardiac, pulmonary and neurological) and include a myeloproliferative and a lymphocytic variant with different clinical, histologic, cytogenetic or molecular patterns [38].

C: Systemic sclerosis (SS) as EF and SS may be both responsible for an extensive cutaneous fibrosis. However, SS is associated with neither a peripheral eosinophilia, nor satisfying response to corticosteroids and more frequently leads to a visceral involvement (pulmonary or oesophageal). The capillaroscopy is usually normal in EF [7] contrary to SS.

D: A Churg–Strauss syndrome should be excluded in any case of EF-associated visceral involvement. An actual fasciitis is rare in Churg–Strauss syndrome and inversely, typical features of Churg–Strauss syndrome, which include a steroid-dependent asthma with sinusal and/or neurologic, cardiac, dermatologic and renal involvement [39], are absent in EF. Moreover, antineutrophilic cytoplasmic antibodies, which are present in 38–48% of cases of Churg–Strauss syndrome [40,41], are absent in EF patients.

E: Peripheral T-cell lymphomas may have a cutaneous and sometimes a fascia involvement, but are easily excluded by the muscle biopsy pathological examination.

## Aetiology and pathophysiology of EF

The precise nature and mechanisms of EF are still unknown but eosinophil granule products such as eosinophil-derived neurotoxin may contribute to the development of fascia fibrosis. In EF patients, fibroblast cells produce more collagen and are a chemoattractant for eosinophils, therefore increasing production of reactive oxygen species [10,42]. The disease can be triggered by treatment, toxic

exposure or physical exertion. Cases have been described after the use of simvastatin [43], atorvastatin [44], phenytoin [45], ramipril [46], subcutaneous heparin [47] and trichloroethylene exposure [48]. Some cases are reported associated with bacterial infections such as borreliosis [49,50], or more recently *Mycoplasma arginini* [51]. The role of muscle trauma is hypothesised, as approximately 30–46% of EF patients have a history of intense physical exertion or trauma prior to EF onset [3,4,6].

Cases of EF have also been reported after allogeneic HSCT: two patients over 189 allogeneic HSCT, 21 and 9 months after this treatment [52]. These two patients had an autoimmune background: Hashimoto's thyroiditis for one and association with antinuclear antibodies, anti-ENA and antigliadin antibodies for the other. Both were treated with extracorporeal photochemotherapy with clinical improvement. Fasciitis has also been reported as a rare form of graft-versus-host disease [53]. In this latter series, none of the patients responded to corticosteroids.

## Treatment of EF

The evaluation of the therapeutic management is made difficult by the lack of standardised criteria for the treatment and the clinical response [3–6]. In the largest retrospective study, three categories were defined: poor response (<25% improvement), partial response (>25% improvement but not total resolution) and complete remission [4]. Another systematic review of 88 cases [3] and the more recent study in the field [5] defined three outcome groups based on the response to therapy: cure (free from symptoms at the end of the reported follow-up), remission (improvement and did not have symptoms because of residual fibrosis) and persistent (symptoms due to fibrosis at the end of the follow-up). Beyond the treatment outcome definition, there is no consensual time duration to define treatment failure or success, and some reports of unsuccessful corticosteroid treatment are probably due to a too short course of treatment [6]. Noteworthy is that some patients experienced spontaneous improvement without any treatment [4], although this spontaneous evolution is very scarce.

It is now well defined that the mainstay of treatment of EF is based on corticosteroids with mostly a good response, as 70–90% of patients experienced a partial to complete response [4,5]. The mean initial dose of oral corticosteroids is usually between 0.5 and 1 mg $kg^{-1}$ $day^{-1}$, followed by a progressive tapering of the dose according to the clinical response. The mean duration of the corticosteroid treatment is not consensual duration and is reported ranging from few months to several years. In our experience, the mean treatment duration with corticosteroids alone was $45 \pm 31$ months with a median duration of 31 months [5]. In our experience, there is an actual benefit of using methylprednisolone pulses (0.5–1 g $day^{-1}$ for 3 consecutive days) prior to oral corticosteroid treatment, as it was significantly associated with a better outcome. Indeed, 47% of our patients received methylprednisolone pulses at treatment initiation, and compared to patients who did not, they were more likely to have a complete remission (87% vs. 53%, $P = 0.06$) and less frequently required an additional immunosuppressive drug (20% vs. 65%, $P = 0.02$) [5].

Another issue in EF treatment remains the use of immunosuppressive drugs (ISDs). The use of ISDs such as azathioprine, cyclophosphamide, methotrexate, cyclosporine and more recently anti-tumour necrosis factor alpha and rituximab is not codified, and is mostly justified by the failure of, or the dependency to high-doses of corticosteroids [4,6,10,54–62]. Here are the different treatments that have been proposed for cases of resistance or dependency to corticosteroid treatment reported before our study [5]:

- D-Penicillamine. One patient in the main retrospective study received D-penicillamine without response [4]. Two other patients have been recently reported [63].
- Azathioprine. In a series of six patients, two received this treatment. One recovered and the other improved [61]. Complete remission under azathioprine and D-penicillamine has also been reported [55].
- Cyclophosphamide. One patient received this treatment because of the progression of the disease under azathioprine: he experienced cutaneous improvement allowing corticosteroid tapering [57]. Another patient received corticosteroids and cyclophosphamide. He presented the unusual association of clinical and histological findings consistent with EF and cytoplasmic-antineutrophil cytoplasmic antibodies (c-ANCA) (with negative proteinase 3 antibodies). Evolution after 6

months of treatment (corticosteroids and cyclophophamide) was favourable (clinically and radiologically on MRI) [59].

- Methotrexate. It has been used in three patients among a series of 12 patients with three good responses (defined as marked clinical improvement of cutaneous or extracutaneous manifestations) [6]. Two other patients experienced clinical improvement under this treatment [14,64].
- Cyclosporine. One patient (without SAA) was successfully treated with cyclosporine after failure of high-dose systemic corticosteroids [54].
- Anti-tumour necrosis factor alpha. Three case of corticoresistant EF were treated with infliximab (3 mg $kg^{-1}$ every 8 weeks). All patients noticed improvement of their symptoms within 8 weeks of starting infliximab, leading to a drug-free remission (range 1–3 years) [60]. Another case of a good response to infliximab has been reported in a paediatric context [65].
- One patient received rituximab for refractory EF with cutaneous remission [62].
- Dapsone. A 38-year-old woman experienced corticosteroid-resistant disease and intolerance to cyclosporine. Dapsone was initiated at 50 mg $day^{-1}$ and then increased to 100 mg $day^{-1}$ with a rapid improvement (2 weeks) [10].
- PUVA therapy (psoralen-ultravolet A bath photochemotherapy). In this case of biopsy-proven EF, prednisolone and chloroquine failed to stop progression of the disease. PUVA bath photochemotherapy was therefore initiated and the patient experienced improvement after 35 irradiation sessions [9]. Two other patients were successfully treated with PUVA therapy [66]. This treatment has also been shown to be effective in treating morphea (localised scleroderma) [67].
- Extracorporeal photochemotherapy. Three patients experienced this treatment (2 consecutive days at 2-weeks interval for the first 3 months and thereafter every 4 weeks) with improvement of quality of life. Two of them showing improvement evaluated on skin elastometry after 1 year of treatment [68].
- Allogeneic HSCT. In this case, SAA was associated with EF. Although clinical finding were consistent with this latter diagnosis, no deep biopsy was performed (because of thrombopenia) [18]. Signs of this so-called EF completely disappeared on day + 29 after allogeneic HCST. Another patient with SAA associated with EF received allogeneic HSCT with prompt remission of EF and SAA [17].
- Antithymocyte globulin and cyclosporine A. In this case, the patient experienced SAA (proven on a bone-marrow biopsy) associated with EF (proven on fascia biopsy). The haematological condition improved with this treatment and 2 years later, the blood examination remained normal and the skin was almost completely normal [16]. Another patient with SAA associated with EF received antithymocyte globulin and cyclosporine A with prompt remission of EF and SAA [17].
- Physical therapy should be initiated early in order to limit joint contracture and to maintain mobility but no study have evaluated this therapeutic [6].

In our experience [5], due to an unsatisfactory clinical response, an ISD was required in more of oral corticosteroids in up to 44% (14/32) of patients. Methotrexate, with a 10–20 mg weekly dose, was mostly given as a second-line therapy (12/14 patients) and azathioprine in only 2/14 patients, with a 24.7 (±23.3)-month mean duration (median = 19.5 months; range: 5–93). Whereas these patients failed to an initial treatment with corticosteroids alone, a complete remission could be achieved for 36% of patients under the combined regimen.

We have shown that the relative risk of requiring an ISD was 5 times higher in patients with clinical and/or histological morphea (95% confidence interval (CI) = 2–23; $P = 0.007$) and 4 times higher in patients who did not receive methylprednisolone pulses at treatment initiation (95%CI = 1–16; $P = 0.02$). Finally, taking account of all outcome results, the factors that were associated with the lack of complete resolution were a diagnosis delay above 6 months (odds ratio (OR) = 15; $P = 0.02$) and the absence of methylprednisolone pulses at treatment initiation (OR = 13; $P = 0.04$). The presence of morphea-like skin lesions, an involvement of the trunk, an age under 12 years and dermal fibrosclerosis at cutaneous biopsy were also found associated with a poor outcome and a residual cutaneous fibrosis [3,5].

Taking account of our data and previous reviews, some practical suggestions regarding the approach to EF management can be summarised by the following take-home messages: 1) corticosteroid treatment (0.5–1 mg $kg^{-1}$ $day^{-1}$) remains the standard therapy for EF, taken alone or in

association with an ISD; 2) methylprednisolone pulses (0.5–1 g $day^{-1}$ for 3 consecutive days) at initiation of treatment may be associated with a better outcome and a lower need of ISD use, and their use may be considered for a certain number of patients; 3) an ISD, mostly methotrexate, should be combined to steroids as a first-line therapy for patients with morphea-like lesions or an unsatisfactory response to corticosteroids alone. Evidently, there is a great need of confirming these messages by a prospective and multicentre study.

## Conclusions

EF is a rare connective-tissue disease featured by symmetrical and painful swelling with a progressive induration and thickening of the skin and soft tissues. The pathological findings at skin-to-muscle biopsy are characterised by a fasciitis with a thickened fascia and perivascular inflammatory infiltrates composed of lymphocytes and/or eosinophils. A peripheral eosinophilia is frequent but not mandatory for the diagnosis. Due to the scarcity of the disease, there is no consensual therapeutic strategy. However, oral corticosteroids remain the mainstay treatment and may be associated to an ISD such as methotrexate in patients with morphea-like lesions or an unsatisfactory response to corticosteroids alone.

## References


*[1] Shulman LE. Diffuse fasciitis with hypergammaglobulinemia and eosinophilia: a new syndrome? Journal of Rheumatology 1984;11:569–70.
*[2] Shulman LE. Diffuse fasciitis with eosinophilia: a new syndrome? Transactions of the Association of American Physicians 1975;88:70–86.
*[3] Endo Y, Tamura A, Matsushima Y, Iwasaki T, Hasegawa M, Nagai Y, et al. Eosinophilic fasciitis: report of two cases and a systematic review of the literature dealing with clinical variables that predict outcome. Clinical Rheumatology 2007;26:1445–51.
*[4] Lakhanpal S, Ginsburg WW, Michet CJ, Doyle JA, Moore SB. Eosinophilic fasciitis: clinical spectrum and therapeutic response in 52 cases. Seminars in Arthritis and Rheumatism 1988;17:221–31.
*[5] Lebeaux D, Frances C, Barete S, Wechsler B, Dubourg O, Renoux J, et al. Eosinophilic fasciitis (Shulman disease): new insights into the therapeutic management from a series of 34 patients. Rheumatology (Oxford) 2012;51:557–61.
*[6] Bischoff L, Derk CT. Eosinophilic fasciitis: demographics, disease pattern and response to treatment: report of 12 cases and review of the literature. International Journal of Dermatology 2008;47:29–35.
[7] Herson S, Brechignac S, Piette JC, Mouthon JM, Coutellier A, Bletry O, et al. Capillary microscopy during eosinophilic fasciitis in 15 patients: distinction from systemic scleroderma. American Journal of Medicine 1990;88:598–600.
[8] Daniel RS, Lavery S, Maize Jr JC, Brown AN, Bolster MB. Unilateral eosinophilic fasciitis: an under-recognized subtype? Journal of Clinical Rheumatology 2009;15:247–9.
[9] Schiener R, Behrens-Williams SC, Gottlober P, Pillekamp H, Peter RU, Kerscher M. Eosinophilic fasciitis treated with psoralen-ultraviolet A bath photochemotherapy. British Journal of Dermatology 2000;142:804–7.
[10] Smith LC, Cox NH. Dapsone treatment for eosinophilic fasciitis. Archives of Dermatology 2008;144:845–7.
[11] Killen JW, Swift GL, White RJ. Eosinophilic fasciitis with pulmonary and pleural involvement. Postgraduate Medical Journal 2000;76:36–7.
[12] Rizzo S. Eosinophilic pleuropericarditis and fasciitis. A new case. Monaldi Archives For Chest Disease 2002;57:311–3.
[13] Kirschstein M, Helmchen U, Jensen R, Kuster RM, Lehmann H. Kidney involvement in a 17-year-old boy with eosinophilic fasciitis. Clinical Nephrology 1999;52:183–7.
[14] Janzen L, Jeffery JR, Gough J, Chalmers IM. Response to methotrexate in a patient with idiopathic eosinophilic fasciitis, morphea, IgM hypergammaglobulinemia, and renal involvement. Journal of Rheumatology 1995;22:1967–70.
[15] Blaser KU, Steiger U, Wursch A, Speck B. Eosinophilic fasciitis with aplastic anemia and Hashimoto's thyroiditis. Review of the literature and report of a typical example. Schweizerische Medizinische Wochenschrift 1989;119:1899–906.
[16] Bonnotte B, Chauffert B, Caillot D, Martin F, Lorcerie B. Successful treatment with antithymocyte globulin and cyclosporin A of a severe aplastic anaemia associated with an eosinophilic fasciitis. British Journal of Rheumatology 1998;37:1358–9.
[17] Kim SW, Rice L, Champlin R, Udden MM. Aplastic anemia in eosinophilic fasciitis: responses to immunosuppression and marrow transplantation. Haematologia (Budap) 1997;28:131–7.
[18] Cetkovsky P, Koza V, Cetkovska P, Svojgrova M. Successful treatment of severe Shulman's syndrome by allogeneic bone marrow transplantation. Bone Marrow Transplantation 1998;21:637–9.
[19] Khanna D, Verity A, Grossman JM. Eosinophilic fasciitis with multiple myeloma: a new haematological association. Annals of the Rheumatic Diseases 2002;61:1111–2.
[20] Naschitz JE, Misselevich I, Rosner I, Yeshurun D, Weiner P, Amar M, et al. Lymph-node-based malignant lymphoma and reactive lymphadenopathy in eosinophilic fasciitis. American Journal Of the Medical Sciences 1999;318:343–9.
[21] Michaels RM. Eosinophilic fasciitis complicated by Hodgkin's disease. Journal of Rheumatology 1982;9:473–6.
[22] Eklund KK, Anttila P, Leirisalo-Repo M. Eosinophilic fasciitis, myositis and arthritis as early manifestations of peripheral T-cell lymphoma. Scandinavian Journal of Rheumatology 2003;32:376–7.
[23] Kim H, Kim MO, Ahn MJ, Lee YY, Jung TJ, Choi IY, et al. Eosinophilic fasciitis preceding relapse of peripheral T-cell lymphoma. Journal of Korean Medical Science. 2000;15:346–50.
[24] Chan LS, Hanson CA, Cooper KD. Concurrent eosinophilic fasciitis and cutaneous T-cell lymphoma. Eosinophilic fasciitis as a paraneoplastic syndrome of T-cell malignant neoplasms? Archives of Dermatology 1991;127:862–5.

[25] Veyssier-Belot C, Zuech P, Lumbroso-Le Rouic L, Recanati G, Dendale R. Eosinophilic fasciitis and metastatic choroidal melanoma: a paraneoplastic syndrome? Revue De Medecine Interne 2008;29:1013–6.
[26] Naschitz JE, Yeshurun D, Zuckerman E, Rosenbaum M, Misselevitch I, Shajrawi I, et al. Cancer-associated fasciitis panniculitis. Cancer 1994;73:231–5.
[27] Blanche P, Abad S, Barete S, Beuzeboc P, Sicard D. Fasciitis with eosinophilia and bronchial cancer. Annales De Medecine Interne (Paris) 1996;147:62–4.
[28] Toquet C, Hamidou MA, Renaudin K, Jarry A, Foulc P, Barbarot S, et al. In situ immunophenotype of the inflammatory infiltrate in eosinophilic fasciitis. Journal of Rheumatology 2003;30:1811–5.
[29] Ohno M, Nagaoka S, Onari K, Kitamura H, Hachiya M, Kondo S, et al. Remitting fasciitis without eosinophilia: a new disease entity? A case report. Rheumatology (Oxford) 2001;40:1428–30.
[30] Antic M, Lautenschlager S, Itin PH. Eosinophilic fasciitis 30 years after - what do we really know? Report of 11 patients and review of the literature. Dermatology 2006;213:93–101.
*[31] Moulton SJ, Kransdorf MJ, Ginsburg WW, Abril A, Persellin S. Eosinophilic fasciitis: spectrum of MRI findings. American Journal of Roentgenology 2005;184:975–8.
[32] Desvignes-Engelbert A, Sauliere N, Loeuille D, Blum A, Chary-Valckenaere I. From diagnosis to remission: place of MRI in eosinophilic fasciitis. Clinical Rheumatology. 29: p. 1461–464.
*[33] Dybowski F, Neuen-Jacob E, Braun J. Eosinophilic fasciitis and myositis: use of imaging modalities for diagnosis and monitoring. Annals of the Rheumatic Diseases 2008;67:572–4.
[34] Ronneberger M, Janka R, Schett G, Manger B. Can MRI substitute for biopsy in eosinophilic fasciitis? Annals of the Rheumatic Diseases 2009;68:1651–2.
[35] Baumann F, Bruhlmann P, Andreisek G, Michel BA, Marincek B, Weishaupt D. MRI for diagnosis and monitoring of patients with eosinophilic fasciitis. American Journal of Roentgenology 2005;184:169–74.
*[36] Silver RM, Heyes MP, Maize JC, Quearry B, Vionnet-Fuasset M, Sternberg EM. Scleroderma, fasciitis, and eosinophilia associated with the ingestion of tryptophan. New England Journal of Medicine 1990;322:874–81.
[37] Swygert LA, Maes EF, Sewell LE, Miller L, Falk H, Kilbourne EM. Eosinophilia-myalgia syndrome. Results of national surveillance. Journal of the American Medical Association 1990;264:1698–703.
[38] Roufosse F. Hypereosinophilic syndrome variants: diagnostic and therapeutic considerations. Haematologica 2009;94:1188–93.
[39] Noth I, Strek ME, Leff AR. Churg-Strauss syndrome. Lancet 2003;361:587–94.
[40] Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. Medicine (Baltimore) 1999;78:26–37.
[41] Sinico RA, Di Toma L, Maggiore U, Bottero P, Radice A, Tosoni C, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. Arthritis and Rheumatism 2005;52:2926–35.
[42] Varga J, Kahari VM. Eosinophilia-myalgia syndrome, eosinophilic fasciitis, and related fibrosing disorders. Current Opinion in Rheumatology 1997;9:562–70.
[43] Choquet-Kastylevsky G, Kanitakis J, Dumas V, Descotes J, Faure M, Claudy A. Eosinophilic fasciitis and simvastatin. Archives of Internal Medicine 2001;161:1456–7.
[44] DeGiovanni C, Chard M, Woollons A. Eosinophilic fasciitis secondary to treatment with atorvastatin. Clinical and Experimental Dermatology 2006;31:131–2.
[45] Buchanan RR, Gordon DA, Muckle TJ, McKenna F, Kraag G. The eosinophilic fasciitis syndrome after phenytoin (dilantin) therapy. Journal of Rheumatology 1980;7:733–6.
[46] Serratrice J, Pellissier JF, Champsaur P, Weiller PJ. Fasciitis with eosinophilia: a possible causal role of angiotensin converting enzyme inhibitor. Revista De Neurologia (Paris) 2007;163:241–3.
[47] Cantini F, Salvarani C, Olivieri I, Padula A, Senesi C, Bellandi F, et al. Possible association between eosinophilic fasciitis and subcutaneous heparin use. Journal of Rheumatology 1998;25:383–5.
[48] Hayashi N, Igarashi A, Matsuyama T, Harada S. Eosinophilic fasciitis following exposure to trichloroethylene: successful treatment with cyclosporin. British Journal of Dermatology 2000;142:830–2.
[49] Granter SR, Barnhill RL, Duray PH. Borrelial fasciitis: diffuse fasciitis and peripheral eosinophilia associated with *Borrelia* infection. American Journal Of Dermatopathology 1996;18:465–73.
[50] Hashimoto Y, Takahashi H, Matsuo S, Hirai K, Takemori N, Nakao M, et al. Polymerase chain reaction of Borrelia burgdorferi flagellin gene in Shulman syndrome. Dermatology 1996;192:136–9.
[51] Sillo P, Pinter D, Ostorhazi E, Mazan M, Wikonkal N, Ponyai K, et al. Eosinophilic Fasciitis associated with Mycoplasma arginini infection. Journal Of Clinical Microbiology 2012;50:1113–7.
[52] Minciullo PL, Morabito F, Mandaglio R, Iacopino P, Gangemi S. Eosinophilic fasciitis associated with autoimmune phenomena after bone marrow transplantation: report of two cases. Clinical Rheumatology 2006;25:80–2.
[53] Janin A, Socie G, Devergie A, Aractingi S, Esperou H, Verola O, et al. Fasciitis in chronic graft-versus-host disease. A clinicopathologic study of 14 cases. Annals of Internal Medicine 1994;120:993–8.
[54] Bukiej A, Dropinski J, Dyduch G, Szczeklik A. Eosinophilic fasciitis successfully treated with cyclosporine. Clinical Rheumatology 2005;24:634–6.
[55] Caspi D, Fishel R, Varon M, Yona E, Baratz M, Yaron M. Multisystem presentation of eosinophilic fasciitis. Rheumatology and Rehabilitation 1982;21:218–21.
[56] Chaudhary UB, Eberwine SF, Hege KM. Acquired amegakaryocytic thrombocytopenia purpura and eosinophilic fasciitis: a long relapsing and remitting course. American Journal of Hematology 2004;75:146–50.
[57] De Jonge-Bok JM, Steven MM, Eulderink F, Cats A. Diffuse (eosinophilic) fasciitis. A series of six cases. Clinical Rheumatology 1984;3:365–73.
[58] Drosou A, Kirsner RS, Welsh E, Sullivan TP, Kerdel FA. Use of infliximab, an anti-tumor necrosis alpha antibody, for inflammatory dermatoses. Journal of Cutaneous Medicine and Surgery 2003;7:382–6.
[59] Haiduc VF, Erkan D, Kirou K, Birchansky S, Park J, Danon MJ. Anti-neutrophil cytoplasmic antibody (c-ANCA) positive recurrent eosinophilic fasciitis responsive to cyclophosphamide: a clinical pathology conference held by the division of rheumatology at hospital for special surgery. Hospital for Special Surgery Journal 2008;4:81–6.

[60] Khanna D, Agrawal H, Clements PJ. Infliximab may be effective in the treatment of steroid-resistant eosinophilic fasciitis: report of three cases. Rheumatology (Oxford) 2010;49:1184–8.
[61] Nassonova VA, Ivanova MM, Akhnazarova VD, Oskilko TG, Bjelle A, Hofer PA, et al. Eosinophilic fasciitis. Review and report of six cases. Scandinavian Journal of Rheumatology 1979;8:225–33.
[62] Scheinberg M, Hamerschlak N, Kutner JM, Ribeiro AA, Ferreira E, Goldenberg J, et al. Rituximab in refractory autoimmune diseases: brazilian experience with 29 patients (2002-2004). Clinical and Experimental Rheumatology 2006;24:65–9.
[63] Manzini CU, Sebastiani M, Giuggioli D, Manfredi A, Colaci M, Cesinaro AM, et al. D-penicillamine in the treatment of eosinophilic fasciitis: case reports and review of the literature. Clinical Rheumatology 2012;31:183–7.
*[64] Pouplin S, Daragon A, Le Loet X. Treatment of eosinophilic fasciitis with methotrexate. Journal of Rheumatology 1998;25: 606–7.
[65] Poliak N, Orange JS, Pawel BR, Weiss PF. Eosinophilic fasciitis mimicking angioedema and treatment response to infliximab in a pediatric patient. Annals of Allergy Asthma & Immunology 2011;106:444–5.
[66] Silny W, Osmola-Mankowska A, Czarnecka-Operacz M, Zaba R, Danczak-Pazdrowska A, Marciniak A. Eosinophilic fascitis: a report of two cases treated with ultraviolet A1 phototherapy. Photodermatology Photoimmunology & Photomedicine 2009;25:325–7.
[67] Kerscher M, Meurer M, Sander C, Volkenandt M, Lehmann P, Plewig G, et al. PUVA bath photochemotherapy for localized scleroderma. Evaluation of 17 consecutive patients. Archives of Dermatology 1996;132:1280–2.
[68] Romano C, Rubegni P, De Aloe G, Stanghellini E, D'Ascenzo G, Andreassi L, et al. Extracorporeal photochemotherapy in the treatment of eosinophilic fasciitis. Journal Of the European Academy of Dermatology and Venereology 2003;17:10–3.