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CASE BASED REVIEW

# The use of tocilizumab in the treatment of refractory eosinophilic fasciitis: a case-based review

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**Abstract**
Eosinophilic fasciitis (EF) is a rare disorder involving chronic inflammation of the fascia and connective tissue of unknown aetiology and poorly understood pathogenesis. We present the case of a 60-year-old man diagnosed with eosinophilic fasciitis with extensive cutaneous involvement and severe functional repercussion, which appeared weeks after suffering from pneumonia due to *Legionella pneumophila*. The patient did not experience any clinical response with high-dose corticosteroids, subcutaneous methotrexate, and intravenous immunoglobulins. Consequently, tocilizumab was initiated at 8 mg/Kg monthly achieving clinical response measured by a control MRI at the fifth dose. Response in terms of cutaneous thickness has been slower however favourable, therefore, more months of follow-up are necessary to assess the complete remission at skin level. EF treatment still constitutes a challenge, and experience with tocilizumab in the management of the disease is very limited. Through a systematic search of medical literature, we retrieved two cases describing EF treated with tocilizumab and several cases using another monoclonal antibody or Janus kinase inhibitor. We report the third case to our knowledge of the efficacy of tocilizumab in a refractory EF to corticosteroids and other immunosuppressive drugs.

**Keywords** Eosinophilia · Eosinophilic fasciitis · Fibrosis · Monoclonal antibodies · Scleroderma-like disorders · Tocilizumab

## Introduction

Eosinophilic fasciitis (EF) is an uncommon connective tissue disease first described by Shulman in 1974 as a new syndrome defined by scleroderma-like induration associated with an elevated erythrocyte sedimentation rate (ESR), hypergammaglobulinemia and peripheral eosinophilia [1]. It is characterized by acute or subacute onset of symmetrical swelling with progressive induration and thickening of the skin and soft tissues, followed by fascial fibrosis which leads to a pseudo-cellulite or "peau d'orange" appearance of the involved skin and a linear depression along the course of veins known as "groove sign" which is more accentuated by limb elevation. Thickening is similar to that seen with the scleroderma-spectrum disorders, however, sclerodactyly is absent [2–4].

The pathogenesis is not well understood; however, it was observed that eosinophils degranulation induces tissue damage, which results in fibrosis via the accumulation of extracellular matrix [2, 5]. Some studies suggest that eosinophils interact with fibroblasts which exhibit greater expression of type I collagen and fibronectin [2, 4] and express fibrogenic cytokines including tumour growth factor β (TGF-β), interleukin 1 (IL-1) and interleukin 6 (IL-6) [2, 5].

The diagnosis of EF is confirmed with a skin-muscle-fascia biopsy [3]. Magnetic resonance imaging (MRI) is useful as a non-invasive examination to confirm fascial inflammation, determine the site for biopsy, monitor the diseases' course and assess the outcomes of treatment [6]. Diagnostic criteria and severity classification was published in guidelines in 2016 [4, 7]. In addition, Endo et al. analysed clinical variables associated with prognosis of EF, in particular, incidence of morphea-like skin lesions were significantly higher in patients with refractory fibrosis, younger age at onset was associated with more risk of residual fibrosis, trunk involvement was associated with a higher likelihood of residual fibrosis and

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the presence of dermal fibrosclerosis was associated with greater risk of refractory fibrosis. These clinical characteristics were considered an important risk factor for developing residual fibrosis in EF patients [8].

Systemic glucocorticoids are the mainstay of treatment being the majority of patients who respond to oral corticosteroids' first choice [9, 10]. However, a relapse often occurs during the dose-tapering process and many patients do not respond to glucocorticoids [3, 4]. Because of this, other immunosuppressive or immunomodulatory agents are required to obtain a therapeutic response, such as D-penicillamine [11, 12], methotrexate [3, 13], mycophenolate mofetil [13, 14], azathioprine [15, 16], cyclosporine [3], or intravenous immunoglobulin [17]. To date, the effective treatment of EF still constitutes a challenge. No randomized trials have evaluated therapies for EF and the success of other therapies is based on case series and reports.

**Case report** A 60-year-old man was referred to presenting a subacute onset of non-pitting peripheral oedema, myalgias and progressive skin stiffness with extensive cutaneous involvement. Clinical manifestations appeared weeks after suffering from pneumonia due to *Legionella pneumophila*.

The initial physical examination showed extensive symmetrical skin thickening involving the arms, anterior chest, abdomen, thighs, legs and feet whilst respecting the face and fingers. The evaluation of skin involvement was performed by applying the modified Rodnan Skin Score (mRSS) [18]. Although mRSS is not a validated outcome measurement in eosinophilic fasciitis, we used it due to lack of any other validated tool. The examination also showed a depressed vein aspect (groove sign) located on the volar surface of both forearms and a "peau d'orange" appearance on the patient's arms and legs (Fig. 1). Joint contractures and limitation of motion predominantly in the elbows, knees and ankles were apparent because of the extensive skin involvement with no evidence of arthritis. Range of motion was measured with a goniometer by two expert rheumatologists. No Raynaud phenomenon, tendon friction rubs and sclerodactyly were associated. Initial blood test showed an increase in C-reactive protein (CRP) 5.88 mg/dL (0–0.5 mg/dL), eosinophilia 1000/microL (20–500/microL) and increase in muscle enzymes with lactate dehydrogenase at 541 UI/L (135–225 UI/L), aldolase at 15.7 UI/L (0.1–7.6 UI/L) and normal creatine kinase. No hypergammaglobulinemia was observed. Parasitic serologies and a stool parasite study were negative. The initial autoimmunity study did not show autoantibodies positivity. Additionally, no capillaroscopy abnormalities were found.

A magnetic resonance imaging (MRI) of both legs was performed, showing an increased signal and diffuse thickening of muscle fascia associated with trabeculation and a discrete signal increase of subcutaneous cellular tissue at the STIR sequence (Fig. 2). Subsequently, a skin-to-muscle biopsy from the right leg was performed (Fig. 3) evincing degranulate infiltrating eosinophils, which confirmed the initial suspected diagnosis of eosinophilic fasciitis.

A steroid-based treatment with three pulses of methylprednisolone followed by oral prednisone at 1 mg/Kg/day was initiated. After 3 months of follow-up, no clinical improvement was evident, however, analytically, a decrease in inflammatory markers was observed. Due to the severity and extent of the disease with generalized cutaneous thickness and the severe functional repercussion secondary to stiffness and joint limitation, a concomitant administration of subcutaneous methotrexate at 20 mg weekly was initiated, without any additional benefit. Afterwards, we decided to start intravenous immunoglobulins at doses of 2 g/Kg monthly.

After 6 months of follow-up with the combined therapy (oral prednisone at 0.5 mg/Kg daily, intravenous immunoglobulins 2 g/Kg monthly and methotrexate at 20 mg weekly) the patient did not experience any change in the assessment of the skin score or in range of motion, evidently becoming a refractory disease with severe functional repercussion.

Because of this, intravenous tocilizumab (an inhibitor of Il-6 receptor) was initiated at 8 mg/Kg/month after discontinuing intravenous immunoglobulins but maintaining subcutaneous methotrexate and oral prednisone, with progressive tapering. After the administration of five doses of intravenous

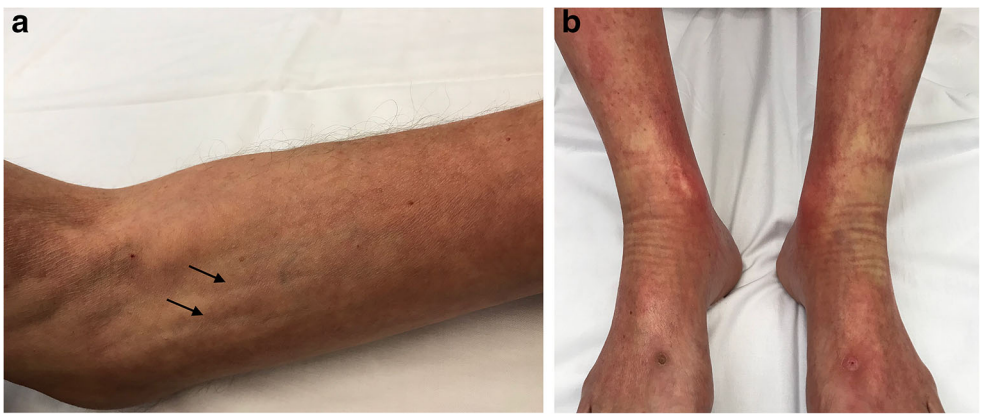


**Fig. 1** Skin furrowing along the course of veins (groove sign) which occurs secondary to fascial sclerosis and is accentuated by limb elevation (a). Severe and diffuse thickening of the skin affecting leg and foot (b)

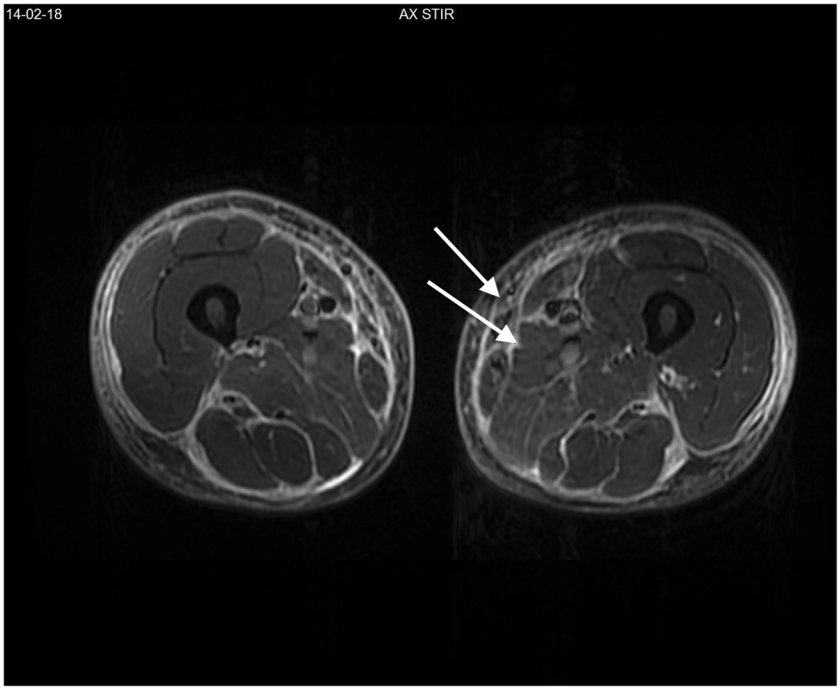


**Fig. 2** Extensive thickening (> 3 mm) and diffuse hyperintensity of the superficial and deep fasciae of both legs with symmetric and diffuse appearance (arrows). There is no involvement of the underlying musculature which suggests the existence of myositis. Slight inflammatory changes in the adjacent subcutaneous tissue, reactive in appearance. The findings are compatible with fasciitis

tocilizumab, clinical improvement in terms of skin thickening (Fig. 4) and range of motion were evident. Initial modified Rodnan Skin Score was 40/51 and 29/51 after the fifth dose. In terms of functionality, the patient achieved an average of 83.11% of his global range of motion (being of 67.55% before starting the treatment). A control MRI of both legs was performed showing a total resolution of the findings observed at the initial imaging study (Fig. 5). Oral prednisone was tapered progressively at 3 months of tocilizumab introduction and methotrexate was discontinued. Ten months after tocilizumab initiation, no adverse effects were observed, and partial disease remission was achieved. Because of global health improvement, the patient was able to go back to work after more than 1 year of sick leave.

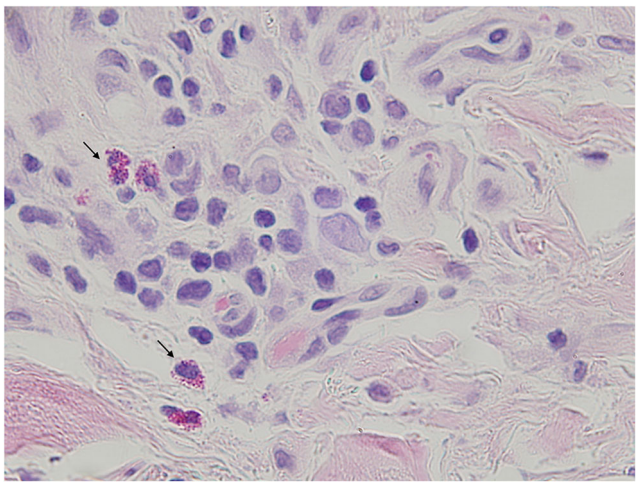

**Fig. 3** High-power view of haematoxylin and eosin-stained skin-fascia-muscle biopsy, showing infiltrating eosinophils in the fascia degranulate locally (arrows)

**Search strategy** The search strategy for writing review articles proposed by Gasparyan et al. [19] was followed. Inclusion criteria were cases of eosinophilic fasciitis in MEDLINE/PubMed, EMBASE and SCOPUS, describing disease in adults (over 18 years old) and treated with monoclonal antibodies or Janus kinases if refractory disease to first-line treatment or other immunosuppressive or immunomodulatory agents.

Articles available on MEDLINE/PubMed, published up to July 2019 in the English language, were reviewed using search words ("TNF" [All fields] AND "eosinophilic fasciitis" [All fields]); ("monoclonal antibody" [All fields] AND "eosinophilic fasciitis" [All fields]); ("Janus kinase" [All fields]

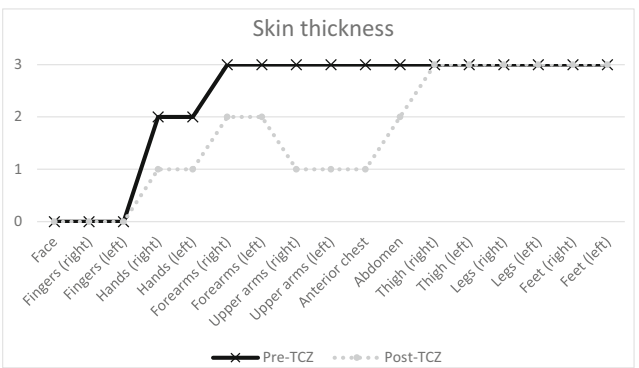


**Fig. 4** Evolution of skin involvement before and after starting tocilizumab, modified Rodnan Skin Score (mRSS) was applied during the follow-up

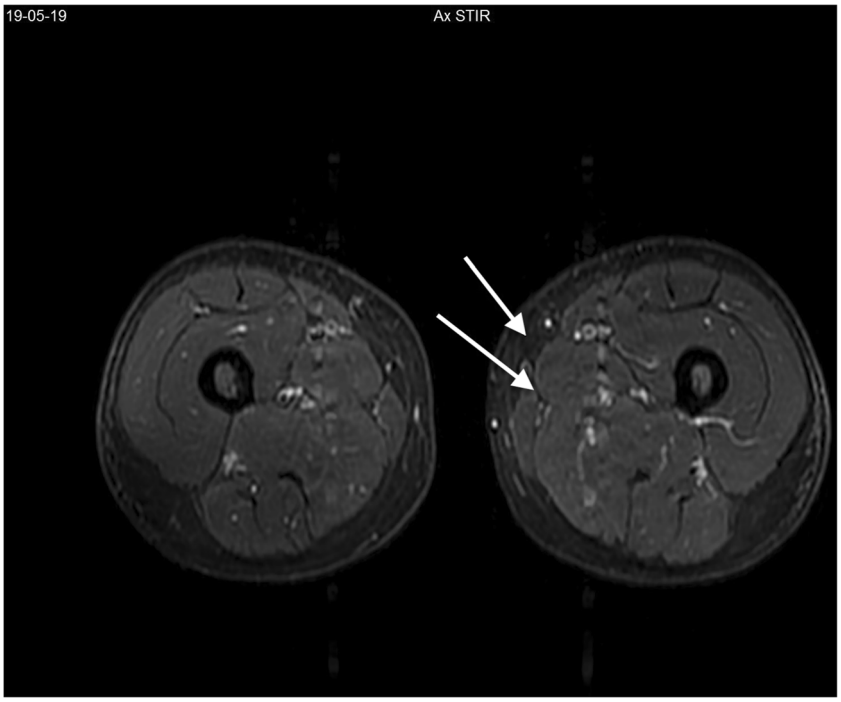


**Fig. 5** Control imaging study after the fifth dose of tocilizumab shows complete resolution of the initial findings, with morphology and fascia signal within normality

AND "eosinophilic fasciitis" [All fields]); ("tocilizumab" [All fields] AND "eosinophilic fasciitis" [All fields]); ("Interleukin 6" [All fields] AND "eosinophilic fasciitis" [All fields]). Seventeen articles were obtained. Articles describing EF developed under treatment with monoclonal antibodies (a total of five) or describing the disease in paediatric patients (two of them) were excluded. On reviewing these articles, we found eight case reports amounting to ten cases. Nine cases described refractory EF treated with monoclonal antibodies and one case described treatment with a Janus kinase inhibitor. A similar search was done in EMBASE and SCOPUS and we did not find any new article. Table 1 summarizes case reports of EF treated with the mentioned therapy.

## Discussion

Eosinophilic fasciitis is a rare scleroderma-like disorder with unclear pathogenesis, although, some fibrogenic cytokines including tumour growth factor β (TGF-β), interleukin 1 (IL-1) and interleukin 6 (IL-6) seem to be related in the development of the disease [2, 5, 27]. The pleiotropic activity of IL-6 leads to multiple effects on inflammation and immune response. The patients' dysregulated production results in different biological effects, such as increasing collagen by stimulation of dermal fibroblasts leading to fibrosis [28]. In recent years, tocilizumab has been used as an inhibitor of IL-6 to treat fibrotic disease [2, 24, 29, 30].

The aetiology is unknown, but possible triggers have been suggested as associated with EF, such as infection, being *Borrelia burgdorferi*'s as the most described infectious agent [20–22]. In our case, the clinical onset appeared weeks after suffering from pneumonia due to *Legionella pneumophila*. Nevertheless, a cause-effect on the disease's course due to infection by *Legionella* is not known and no data are available in the medical literature.

EF treatment still constitutes a challenge. The best approach remains yet unclear and no randomized trials have evaluated therapies. Initial treatment consists of the use of systemic glucocorticoids [9, 10]. Nevertheless, relapses may occur, and many patients do not respond. Other therapeutic alternatives are necessary to obtain a response or to act as glucocorticoid-sparing agents such as methotrexate [3, 13], mycophenolate mofetil [13, 14], azathioprine [15, 16], D-penicillamine [11, 12] or intravenous immunoglobulins [17]. The success of other therapies is based on case reports, describing the use of monoclonal antibodies and Janus kinase inhibitors [2, 23–26, 31–33].

Whereas the use of tocilizumab is well-described and consolidated in some rheumatic diseases such as rheumatoid arthritis [34], juvenile idiopathic arthritis [35] and giant cell arteritis [36], the experience with this drug to treat eosinophilic fasciitis is very limited due to its rare occurrence and the lack of clinical trials. The effectiveness of tocilizumab in patients with EF was first reported in 2015 by Espinoza et al., publishing the results of a case report in a refractory EF patient with clinical remission within 36 months of starting tocilizumab [24]. Later in 2019, Urzal et al. reported a case series of seven patients with EF, of which one was treated with tocilizumab because of the persistence of active disease,

**Table 1** Use of target therapy in refractory eosinophilic fasciitis

| Author | Year | Number of cases | Age | Gender | Initial therapy | Active disease | Target therapy | Adjunctive therapy | Response | Side effects |
|---|---|---|---|---|---|---|---|---|---|---|
| Drosou A et al. [20] | 2003 | 1 | 69 | Female | Mycophenolate mofetil, methotrexate, cyclosporine A, prednisone | N/A | Infliximab | Mycophenolate mofetil, prednisone | Moderate | N/A |
| Scheinberg M et al. [21] | 2006 | 1 | 20 | Male | N/A | N/A | Rituximab | N/A | Complete | N/A |
| Khanna D et al. [22] | 2010 | 3 | 46 | Female | Prednisone, methotrexate | Yes | Infliximab | Prednisone | Complete | N/A |
| | | | 61 | Female | Prednisone, methotrexate | Yes | Infliximab | Prednisone, methotrexate | Complete | N/A |
| | | | 61 | Female | Prednisone | Yes | Infliximab | No | Complete | N/A |
| de Masson A et al. [23] | 2013 | 1 | 57 | Male | Prednisone, cyclosporine A | Yes | Rituximab | Cyclosporine A | Complete | N/A |
| Espinoza F et al. [24] | 2015 | 1 | 43 | Male | Prednisone, methotrexate, etanercept | Yes | Tocilizumab | Prednisone | Complete | No |
| Frumholtz L et al. [25] | 2016 | 1 | 57 | Male | Prednisolone, prednisone, methotrexate | Yes | Eculizumab | N/A | Moderate | N/A |
| Kim SR et al. [26] | 2018 | 1 | 66 | Female | Prednisone | Yes | Tofacitinib | Prednisone, methotrexate | Moderate | N/A |
| Urzal J et al. [2] | 2019 | 1 | 61 | Female | Prednisone, methotrexate | Yes | Tocilizumab | Prednisone, methotrexate | Moderate | N/A |

N/A, not available

showed softening of the skin with a significant reduction of skin hardness [2].

According to the mentioned search, the reviewed case reports were published between 2003 and 2019. In all the reported cases the disease was refractory to systemic corticosteroids and classic immunosuppressive drugs. The most common agent used as immunosuppressive drug after corticosteroid-resistance was methotrexate and other treatment options included mycophenolate mofetil and cyclosporine A. Due to the disease activity, the authors decided to start treatment with monoclonal antibodies; specifically, we found four cases with infliximab [23, 25], two cases using rituximab [26, 31], two cases with tocilizumab [2, 24] and a case with eculizumab [32]. Additionally, one case reported the use of a Janus kinase inhibitor, specifically tofacitinib [33]. In all of them, the most frequent adjunctive therapy was oral corticosteroids and methotrexate. In most cases, combined therapy was performed maintaining the monoclonal antibody or Janus kinase inhibitor with one of the initial immunosuppressant. Progressive clinical response was achieved in all cases after starting the targeted therapy. All data is summarized in Table 1 [2, 23–26, 31–33].

Our patient fulfilled classification criteria for EF [4, 6] and importantly, other rheumatic and immune-mediated diseases were ruled out after a careful diagnostic workup. In our case, the patient was affected with a corticosteroid refractory disease characterized by progressive severe skin thickening and limitation of range of motion secondary to extensive skin involvement, which was translated into an overall functional repercussion with a non-clinical response to first-line treatment nor to subcutaneous methotrexate or intravenous immunoglobulins. This fact and the lack of evidence in the therapeutic management of the disease and also, considering the cytokines involved in the pathophysiology, we decided to opt for the use of tocilizumab as a therapeutic alternative. Our patient showed marked clinical improvement at the fifth dose, with a total response at the fascia level, although more months of follow-up will be necessary to assess the complete response at the skin and joint level.

We report the third case to our knowledge of the efficacy of tocilizumab in a refractory EF to corticosteroids and other immunosuppressive drugs. The experience with tocilizumab in the treatment of EF is very limited, nevertheless, ideally, more case reports and randomized trials are needed to assess the impact over the natural history of the disease using targeted therapies such as tocilizumab.

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## Compliance with ethical standards

**Disclosures** None.

**Statement of informed consent** Informed consent has been obtained from the patient to access and collect data from the medical record to be used in scientific publications.

## References

1. Shulman LE (1984) Diffuse fasciitis with hypergammaglobulinemia and eosinophilia: a new syndrome? J Rheumatol 11:569–570
2. Urzal J, Cimbron M, Mendoça T, Farinha F (2019) Eosinophilic fasciitis (Shulman's disease): review and comparative evaluation of seven patients. Reumatologia 57:85–90

3. Mazori DR, Femia AN, Vleugels RA (2017) Eosinophilic fasciitis: an updated review on diagnosis and treatment. Curr Rheumatol Rep 19:74
4. Ihn H (2019) Eosinophilic fasciitis: from pathophysiology to treatment. Allergol Int 68:437–439
5. Gomes I, Mathur SK, Espenshade BM, Mori Y, Varga J, Ackerman SJ (2005) Eosinophil-fibroblast interactions induce fibroblast IL-6 secretion and extracellular matrix gene expression: implications in fibrogenesis. J Allergy Clin Immunol 116:796–804
6. Kirchgesner T, Dallaudiere B, Omoumi P et al (2015) Eosinophilic fasciitis: typical abnormalities, variants and differential diagnosis of fasciae abnormalities using MR imaging. Diagn Interv Imaging 96: 341–348
7. Jinnin M, Yamamoto T, Asano Y et al (2018) Diagnostic criteria, severity classifications, and clinical guidelines of eosinophilic fasciitis. J Dermatol 45:88
8. Endo Y, Tamura A, Matsushima Y, Iwasaki T, Hasegawa M, Nagai Y, Ishikawa O (2007) Eosinophilic fasciitis: report of two cases and a systematic review of the literature dealing with clinical variables that predict outcome. Clin Rheumatol 26:1445–1451
9. Lebeaux D, Francès C, Barete S, Wechsler B, Dubourg O, Renoux J, Maisonobe T, Benveniste O, Gatfossé M, Bourgeois P, Amoura Z, Cacoub P, Piette JC, Sène D (2012) Eosinophilic fasciitis (Shulman disease): new insights into the therapeutic management from series of 34 patients. Rheumatology (Oxford) 51:557–561
10. Bischoff L, Derk CT (2008) Eosinophilic fasciitis: demographics, disease pattern and response to treatment: report of 12 cases and review of the literature. Int J Dermatol 47:29–35
11. Mendoza FA, Bai R, Kebede AG, Jimenez SA (2016) Severe eosinophilic fasciitis: comparison of treatment with D-penicillamine plus corticosteroids vs. corticosteroids alone. Scand J Rheumatol 45:129–134
12. Manzini CU, Sebastiani M, Giuggioli D, Manfredi A, Colaci M, Cesinaro AM, Ferri C (2012) D-penicillamine in the treatment of eosinophilic fasciitis: case reports and review of the literature. Clin Rheumatol 31:183–187
13. Tull R, Hoover WD 3rd, De Luca JF et al (2018) Eosinophilic fasciitis: a case series with an emphasis on therapy and induction of remission. Drugs Context 7:212529
14. Loupasakis K, Derk CT (2010) Eosinophilic fasciitis in a pediatric patient. J Clin Rheumatol 16:129–131
15. Alonso-Castro L, de las Heras E, Moreno C et al (2014) Eosinophilic fasciitis/generalized morphea overlap successfully treated with azathioprine. Int J Dermatol 53:1386–1388
16. Caspi D, Fishel R, Varon M, Yona E, Baratz M, Yaron M (1982) Multisystem presentation of eosinophilic fasciitis. Rheumatol Rehabil 21:218–221
17. Pimenta S, Bernardes M, Bernardo A, Brito I, Castro L, Simões-Ventura F (2009) Intravenous immunoglobulins to treat eosinophilic fasciitis: a case report. Joint Bone Spine 76:572–574
18. Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L, Distler O, Foeldvari I, Kuwana M, Matucci-Cerinic M, Mayes M, Medsger T Jr, Merkel PA, Pope JE, Seibold JR, Steen V, Stevens W, Denton CP (2017) Standardization of the modified Rodnan skin score for the use in clinical trials of systemic sclerosis. J Scleroderma Relat Disord 2:11–18
19. Gasparyan AY, Ayvazyan L, Blackmore H, Kitas GD (2011) Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. Rheumatol Int 31:1409–1417
20. Hashimoto Y, Takahashi H, Matsuo S et al (1996) Polymerase chain reaction of Borrelia burgdorferi flagellin gene in Shulman syndrome. Dermatology 192:136
21. Mosconi S, Streit M, Brönimann M, Braathen L (2002) Eosinophilic fasciitis (Shulman syndrome). Dermatology 205:204
22. Granter SR, Barnhill RL, Duray PH (1996) Borrelial fasciitis: diffuse fasciitis and peripheral eosinophilia associated with Borrelia infection. Am J Dermatopathol 18:465
23. Khanna D, Agrawal H, Clements PJ (2010) Infliximab may be effective in the treatment of steroid-resistant eosinophilic fasciitis: report of three cases. Rheumatology (Oxford) 49:1184–1188
24. Espinoza F, Jorgensen C, Pers YM (2015) Efficacy of tocilizumab in the treatment of eosinophilic fasciitis: report of one case. Joint Bone Spine 82:460–461
25. Drosou A, Kirsner RS, Welsh E, Sullivan TP, Kerdel FA (2003) Use of infliximab, an anti-tumor necrosis alpha antibody, for inflammatory dermatoses. J Cutan Med Surg 7:382–386
26. Scheinberg M, Hamerschlak N, Kutner JM, Ribeiro AA, Ferreira E, Goldenberg J, Kiss MH, Chahade WH (2006) Rituximab in refractory autoimmune diseases: Brazilian experience with 29 patients (2002-2004). Clin Exp Rheumatol 24:65–69
27. Viallard JF, Taupin JL, Ranchin V, Leng B, Pellegrin JL, Moreau JF (2001) Analysis of leukemia inhibitory factor, type 1 and type 2 cytokine production in patients with eosinophilic fasciitis. J Rheumatol 28:75–80
28. Tanaka T, Narazakin M, Kishimoto T (2014) IL 6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. https://doi.org/10.1101/cshperspect.a016295
29. Zacay G, Levy Y (2018) Outcomes of patients with systemic sclerosis treated with tocilizumab: case series and review of the literature. Best Pract Clin Rheumatol 32:563–571
30. Khanna D, Denton CP, Lin CJF, van Laar J, Frech TM, Anderson ME, Baron M, Chung L, Fierlbeck G, Lakshminarayanan S, Allanore Y, Pope JE, Riemekasten G, Steen V, Müller-Ladner U, Spotswood H, Burke L, Siegel J, Jahreis A, Furst DE (2018) Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomized controlled trial (faSScinate). Ann Rheum Dis 77:212–220
31. de Masson A, Bouaziz JD, Peffault de Latour R, Benhamou Y, Moluçon-Chabrot C, Bay JO, Laquerrière A, Picquenot JM, Michonneau D, Leguy-Seguin V, Rybojad M, Bonnotte B, Jardin F, Lévesque H, Bagot M, Socié G (2013) Severe aplastic anemia associated with eosinophilic fasciitis: report of 4 cases and review of the literature. Medicine (Baltimore) 92:69–81
32. Frumholtz L, Sebert M, de Masson A et al (2017) Efficacy of eculizumab against eosinophilic fasciitis associated with paroxysmal nocturnal haemoglobinuria. J Eur Acad Dermatol Venereol. https://doi.org/10.1111/jdv.13819
33. Kim SR, Charos A, Damsky W, Heald P, Girardi M, King BA (2018) A treatment of generalized deep morphea and eosinophilic fasciitis with Janus kinase inhibitor tofacitinib. JAAD Case Rep 4: 443–445
34. Kremer JM, Blanco R, Brzosko M, Burgos-Vargas R, Halland AM, Vernon E, Ambs P, Fleischmann R (2011) Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheum 63:609–621
35. De Benedetti F, Brunner HI, Ruperto N et al (2012) Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med 367:2385–2395
36. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, Brouwer E, Cid MC, Dasgupta B, Rech J, Salvarani C, Schett G, Schulze-Koops H, Spiera R, Unizony SH, Collinson N (2017) Trial of tocilizumab in giant-cell arteritis. N Engl J Med 377:317–328