CASE BASED REVIEW





Eosinophilic fasciitis in a pregnant woman with corticosteroid dependence and good response to infliximab

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Abstract

Eosinophilic fasciitis (EF) is characterized by symmetrical thickening of subcutaneous muscular fascia, causing skin induration with wrinkles and prominent hair follicles: the classic *peau d'orange*. Eosinophilia is a characteristic—albeit not universal—finding. We present the case of a 43-year-old pregnant woman diagnosed with EF during pregnancy who had extensive cutaneous involvement and severe functional repercussions, including worsening of lung function and intrauterine growth restriction as a possible complication. Treatment with prednisone was initiated during gestation and it was necessary to increase the dose. After delivery, methotrexate treatment was initiated and the corticosteroid dose progressively decreased, with progressive worsening in the torso and abdomen and secondary dyspnea due to thoracic pressure. Treatment with infliximab was then initiated, with favorable progress, though residual ankle and tarsal joint stiffness and significant muscular atrophy in the limbs continued. The triggering factor of EF was not identified. In a systematic search of the medical literature, three cases of EF in pregnant woman without clear triggers were found. Interestingly, all three cases progressed favorably with steroid treatment. Apart from this case, there are only seven published cases of infliximab use in the literature, all with moderate or complete response. Infliximab could be an option for corticosteroid-dependent EF with no response to other options.

 $\textbf{Keywords} \ \ Eosinophilic \ fasciitis \cdot Infliximab \cdot Methotrexate \cdot Corticosteroid \ dependence \cdot Pregnancy \cdot Intrauterine \ growth \ restriction$

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Introduction

Eosinophilic fasciitis (or Shulman's syndrome) was first described in 1975 [1]. This pathology is characterized by an early phase of erythema and non-pitting edema in the limbs, neck, or torso followed by symmetrical thickening of the subcutaneous muscular fascia, causing skin induration with wrinkles and prominent hair follicles, giving an appearance similar to an orange peel or *peau d'orange*. Eosinophilia is a characteristic—albeit not universal—finding and eosinophil percentages 30% higher than normal values may be observed [2]. Among the multiple triggering factors are toxic substances and drugs (statins, phenytoin, ramipril, subcutaneous heparin), infections (Borrelia burgdorferi and afzelii, Mycoplasma arginini), hematologic pathologies (thrombocytopenia, chronic myelomonocytic leukemia, chronic lymphocytic leukemia, lymphomas, myeloproliferative disorders, etc.), solid neoplasms (breast, melanoma, prostate, and bronchopulmonary neoplasms), autoimmune pathology



(Hashimoto's or Graves' disease, primary biliary cholangitis, systemic lupus erythematosus, vasculitis, etc.), and physical triggers (burns, radiotherapy) [3, 4]. It affects both genders and the average age of onset is between 40 and 50 years. Onset is sudden in 50% of cases, though it can also occur gradually [3, 4].

Only three cases of eosinophilic fasciitis in a pregnant woman without other clear triggers have been published in the literature. All three cases progressed favorably with steroids. In this work, we present the case of a woman diagnosed during pregnancy and describe the diagnostic approach, therapeutic management during pregnancy, and complications.

Presentation of the clinical case

The case presented is a 43-year-old woman who was 16 weeks pregnant after conceiving through in vitro fertilization. She had no known allergies, was a former smoker, and had mild intermittent asthma. She had undergone surgery for papillary thyroid carcinoma and had been treated with radioactive iodine 3 years earlier. Her habitual medication included levothyroxine, formoterol/budesonide, and salbutamol as needed, and since the beginning of the pregnancy, folic acid and acetylsalicylic acid were added.

She consulted for the appearance of an indurated plaque on the right cheek, without traumatic antecedents, that had been present for 2 months. The only antecedent of interest she reported was infiltration of hyaluronic acid in the lips 6 months before. It was diagnosed as a possible focal panniculitis. In a consultation for follow-up on the lesion when the patient was 16 weeks pregnant, she reported a sensation of tightness in the skin of the hands and forearms, with difficulty in bending the fingers. A physical examination showed skin induration on the forearms, lower limbs, and torso with difficulty in pinching the skin, which had an "orange peel" appearance. When the arm was elevated, there was a depressed furrow in the skin that corresponded to the vein path (Fig. 1). She did not report systemic symptoms.

The initial clinical suspicion was diffuse scleroderma or scleredema. A biopsy was performed in the forearm, in which a slight thickening of the dermis collagen fibers and a slight inflammatory periadnexal infiltration were described, without evidence of mucin deposits or loss of appendage or periadnexal adipose tissue. It was thus inconclusive for the suspected diagnosis. Treatment with UVA phototherapy was initiated. On a blood test, the autoimmunity study was negative (ANA; RF; antiRNA polymerase III; antisynthetase antibodies; and a panel of antibodies typical of myopathies: Ro52, anti-OJ, anti-EJ, PL-12, PL-7, SRP, Jo-1, PM75, PM100, Ku, SAE-1, NXP2, MDA5, TIF1g, Mi-2b, and Mi-2a). Glucose values, a renal function test, an electrolyte



Fig. 1 Composition showing (right to left) orange peel d on both thighs, fold sign in the forearm, and atrophic scleroderma changes in upper and lower limbs

panel, a liver function test, and a lipid profile showed no abnormalities and a complete blood count indicated normochromic anemia (hemoglobin 10.8 g/dL) and an eosinophil percentage of 24% (2600/ml). The erythrocyte sedimentation rate (ESR) was 79 mm/h (0–20 mm/h) and the PCR value was 62.2 mg/L (0–5 mg/L). Tumor markers (CEA, CA 15-3, CA 125, CA 19-9, and alpha-fetoprotein) were normal and serologic tests for hepatitis B, hepatitis C, and human immunodeficiency virus were negative. The urinalysis was normal.

Despite treatment with phototherapy, the patient reported worsening of skin rigidity, which was becoming generalized and affected both the torso and limbs. The skin presented with greater induration to the touch in the abdomen and dented plaques in the dorsal area and limbs. The patient also presented with scleroderma cutaneous trophic changes in the hands and feet (Fig. 2) with joint mobility affected in the hands, wrists, shoulders, knees, and ankles as well as a subjective decrease in muscle mass. Given the findings, treatment with 10 mg/day of prednisone was initiated in the 25th week of gestation.

In light of the laboratory values (eosinophilia, elevation of acute phase reactants, and negative autoimmunity) and lack of conclusive findings compatible with scleroderma in the biopsy, the diagnosis was reconsidered and eosinophilic fasciitis was suspected. A deep biopsy of the quadriceps muscle and fascia was performed, in which hypodermic tissue with chronic inflammatory infiltration accompanied by eosinophils and fibrosis was observed in the fascia. In the skin, hypodermic tissue with chronic inflammatory infiltration accompanied by eosinophils in the deeper areas of hypodermis and focal fibrosis was observed (Fig. 3). The



prednisone dose was increased to 1 mg/kg/day (60 mg/day) in the 26th week of gestation and a progressive decrease in eosinophils was observed until the value reached 70 eosinophils/ml and ESR reached 9 mm/h. The diagnostic study was completed with a normal transthoracic echocardiogram and a spirometry (Table 1). Creatine kinase and aldolase levels were normal, though they were measured while the patient was taking steroids.

With the increase in the prednisone dose, the patient presented with hypertension of up to 160/90 mmHg, for which treatment with labetalol was warranted. Finally, an emergency Caesarian section was performed at 31 weeks of

pregnancy due to mixed intrauterine growth restriction and mild preeclampsia.

After delivery, treatment with methotrexate (starting at 12.5 mg/week and increasing up to 25 mg/week subcutaneous) and progressive decrease of corticosteroids at a rate of – 5 mg of prednisone every 2 weeks was initiated, with associated treatment with colchicine, hydroxychloroquine, and prophylactic cotrimoxazole. The patient began physical therapy. She presented with a progressive improvement in skin elasticity and limb functionality, improved gate, and was able to perform tasks for which she was previously limited. However, she had progressive worsening in the torso

Fig. 2 Composition showing marked atrophic sclerodermiform changes in various body regions with dented plates in the described regions. Progression of atrophic sclerodermiform changes during evolution from the previous image

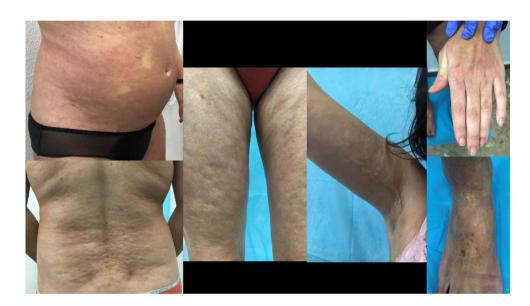


Fig. 3 Fascia tissue (left): hypodermal tissue with chronic inflammatory infiltration accompanied by eosinophils and with fibrosis. Skin tissue (right): hypodermal tissue with chronic inflammatory infiltration accompanied by eosinophils in the deeper areas of hypodermis and focal fibrosis

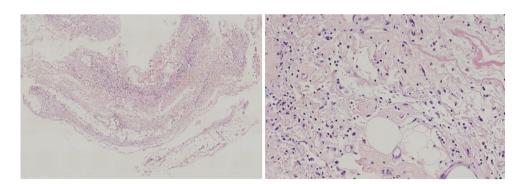


Table 1 Respiratory function tests during the evolution

	Forced expiratory volume in 1 s (FEV1) in ml (% of the theoretical value)	Forced vital capacity (FVC) in ml (% of the theoretical value)	FEV1/ FVC ratio (%)	Single-breath diffusing capacity of the lung for CO (DLCO SB)
26th week of gestation	2430 ml (82%)	3030 (88%)	80	Not done
Two months postpartum	2224 ml (76%)	2720 (80%)	82	66% (77% with AV correction)
Five months postpartum	1880 ml (64%)	2410 ml (71%)	97	57% (83% with AV correction)

A marked worsening can be seen



and abdomen areas, with secondary dyspnea due to thoracic pressure.

At 2 months postpartum, respiratory function test were repeated (Table 1). At 3 months postpartum, the dose of prednisone had to be increased from 35 to 60 mg/day again due to the worsening. In view of the progressive worsening in the torso, which was similar to a corset that prevented made breathing difficult, respiratory function tests were repeated 3 months later (Table 1). A high-resolution CT scan of the lungs showed no signs of interstitial lung involvement. Patchy inflammatory involvement of subcutaneous abdominal cellular tissue and mild edema of both vastus lateralis were described in an abdominal and lower limb MRI.

The appearance of facies cushingoides and severe corticoid steatohepatitis occurred. In spite of high doses of methotrexate, it was not possible to lower prednisone of 30 mg/day, due to persistent elevation of acute phase reactants (CPR and ESR) and lack of clinical improvement. At this time, 6 months after the delivery, it was decided to initiate treatment with infliximab at a dose of 3 mg/kg following the rheumatoid arthritis treatment schedule (day 0, week 2, week 6, and then every 8 weeks). The third dose of infliximab allowed for prednisone to be discontinued and the patient continued with methotrexate 15 mg/week subcutaneously. The subsequent progress was slow, but the patient progressed favorably, especially in regard to the torso. She had residual joint stiffness in the ankles and tarsi and significant muscular atrophy of the limbs, but had functional recovery of the shoulders, wrists, metacarpophalangeal and interphalangeal joints, and knees.

Search strategy

Inclusion criteria were cases of eosinophilic fascitis in MEDLINE/PubMED, Scopus and Web of Science, describing disease (1) in pregnant women; and (2) patients who had been treated with infliximab or other anti TNF-alfa drugs.

Articles available on MEDLINE/PubMed, published up to December 2020 in the English language were reviewed using search words, were reviewed using search words ["infliximab" (all fields) AND "eosinophilic fascitis" (All fields)]; ["golimumab" (all fields) AND "eosinophilic fascitis" (All fields)]; ["adalimumab" (all fields) AND "eosinophilic fascitis" (All fields)]; ["etarnecept" (all fields) AND "eosinophilic fascitis" (All fields)]; ["pregnancy" (all fields) AND "eosinophilic fascitis" (All fields)]. A total of three articles were found describing a total of three cases of eosinophilic fasciitis during pregnancy. Furthermore, a total of eight articles were found about the use of infliximab; two review articles were excluded, one cause of eosinophilic fasciitis triggered by infliximab was found and explained in this review; and a total amount of seven cases were explained in five papers, as we can see in Table 3.

Discussion

As mentioned, only three cases of eosinophilic fasciitis in pregnancy were found in the literature, two of which were during gestation and one following the birth. The first case [5] described a 27-year-old Caucasian woman with mild arthritis who was in the 16th week of gestation. She presented with skin induration and eosinophilia (23%), with histological confirmation 9 weeks later. In this case, the patient was able to continue with a prednisone dose of 10 mg per day and reached a full-term pregnancy of 40 weeks, giving birth to a healthy newborn. The second case [6] was a 42-year-old woman who presented with pain, weakness, and edema of the hands as well as eosinophilia (23%) 3 months after delivery. She responded well to 10 mg/day of prednisone and the dose was decreased at 8 months, with no subsequent symptoms. The third case [7] was a 23-year-old Caucasian woman in the 12th week of gestation who experienced symmetrical and progressive rigidity, induration and edema of the arm and thighs, and the characteristic peau d'orange. Eosinophilia was much lower (3%), though she presented with mild hypergammaglobulinemia (1.6 g/dL) and a positive ANA of 1/320. The rapid progression of symptoms made it necessary to start prednisone at a dose of 1 mg/kg/day, which was decreased to 10 mg per day until delivery (week 40). She experienced no complications with prednisone treatment or the birth. Treatment with prednisone at low doses was then maintained for 2 years. The extensiveness of our case, with trunk involvement, differs from these three cases, with only extremities affection, and with good response by lower doses of steroids. A summary of these cases can be seen in Table 2.

Eosinophilic fasciitis cases have several common characteristics. Skin involvement is practically universal [8, 9] with a typical peau d'orange appearance; non-pitting edema; and symmetrical, progressive induration. Both upper and lower limbs are affected in > 70\% of cases. Other structures such as the face, abdomen, chest, back, and neck are less frequently affected [10]. Another characteristic of these cases is the groove sign. Elevation of an affected limb reduces the venous pressure and as a consequence, a marked groove is produced along the path of the superficial veins. This occurs as a result of the epidermis and superficial dermis remaining static in addition to the immobility and fixation of the perivascular connective tissue, keeping the tissue around the vessel stationary as the vessel retracts due to a drop in venous pressure. Arthritis in joints near affected fascia has been described in some case series, but limited mobility of the joints related to thickening and loss of flexibility of the skin and fascia is a more common finding. All the cases in



pregnant women described in the literature had joint involvement, as did the case described in this work.

Other symptoms that have been described include myalgia and muscular weakness as well as cranial and peripheral neuropathies (characteristic of carpal tunnel syndrome). Inflammatory myositis or organ involvement (pleural effusion, pericarditis, or renal involvement with proteinuria and tubular atrophy) are very rare [9, 11–14].

The fundamental diagnostic test for eosinophilic fasciitis is a deep tissue elliptical biopsy down to the muscle that includes epidermis, dermis, hypodermis, fascia, and muscle tissue. In the early phase of the disease, the deep fascia and subcutaneous tissue are edematous and infiltrated by inflammatory cells (lymphocytes, plasma cells, histiocytes, and eosinophils) [8–10], coinciding with peripheral eosinophilia. Eosinophilic infiltrates are possible, but not universal, occurring in 69–75% of cases [15]. The epidermis is normal or slightly atrophic and extension into the dermis is possible in more advanced cases [4]. As the disease progresses, fascia become thicker, collagen bundles increase, and inflammatory infiltration disappears.

The role of magnetic resonance imaging (MRI) in the diagnosis of this pathology is gaining importance, as a support for the biopsy. The usefulness of PET–CT scans and ultrasound are also being explored [16, 17].

In terms of laboratory findings, eosinophilia is characteristic in early stages, occurring in 63–93% of cases. It is unrelated to the degree of disease activity [7]. In 50% of cases, abnormal ESR and C-reactive protein (CRP) levels and even hypergammaglobulinemia (3–72%) are found [9, 18, 19]. ANA are usually negative, though they have been found to be positive in 10% of cases [4]. These values are not related to the clinical course [18]. Creatinine kinase levels are usually normal despite myalgia, but aldolase levels are typically elevated (60% of cases) [19] and reflect the course of the disease, with early normalization with treatment and a sharp rise observed during relapses [20]

Given clinical entity's frequent association with hematological abnormalities (observed in 10% of cases), it is essential to request a complete blood count with blood smear, a protein electrophoresis, and immunoglobulins blood test. As for other possible triggers, thyroiditis and autoimmune thyroid diseases have often been associated with this entity, but the same is not true of neoplastic thyroid diseases or treatment with radioactive iodine. In the case presented in this work, other triggers were ruled out, including severe muscle trauma; drugs or toxins; infections (lack of clinical or analytical data); solid tumors (based on appropriate clinical, radiological, and analytical screening corresponding to the age and risk group); autoimmune pathology; and physical factors.

An important aspect in this case is the history of hyaluronic acid injection in the lips. A greater presence of

connective tissue diseases was found [21] in patients with implants, including dermatomyositis, polymyositis, sclero-derma, and Raynaud's phenomenon. There is also a case published in the literature of an overlap syndrome between morphea and eosinophilic fasciitis after breast prosthesis implantation, considered to be a form of ASIA [22]. No cases of eosinophilic fasciitis associated with hyaluronic acid were found in the literature.

No cases of eosinophilic fasciitis associated with in vitro fertilization were found in the literature, and no information regarding the possible relationship between gestation hormones and its pathogenesis.

With respect to the pregnancy, we hypothesize that restriction caused by intense skin rigidity is what led to the intrauterine growth restriction. This is similar to what is described in pregnant women with systemic sclerosis, in which the presence of adverse events has been demonstrated to be greater (odds ratio 3.2; 95% CI 2.21–4.53) and, most relevant to our case, notably includes intrauterine growth restriction [23].

There are two sets of eosinophilic fasciitis diagnostic criteria and severity classification guidelines [3, 15], which are summarized in Table 3. The case described in this work met the major criterion and one minor criterion of the Jinnin et al. diagnostic criteria [15] and the two major criteria and one minor criterion of the Pinal-Fernández et al. guidelines [3]. With respect to severity, according to Jinnin et al. guidelines [15], one point would be scored for: (a) joint contracture of the upper limb; (b) joint contracture of the lower limbs; (c) limited movement of the upper limbs; (d) limited movement of the lower limbs; and (e) expansion and worsening of the rash (symptom progression). The disease is considered severe if a score of two or more is obtained. In our case, the score was four.

A differential diagnosis must be made with all scleroderma syndromes, though mainly with systemic sclerosis [24] as well as with morphea and linear scleroderma. Other entities with which a differential diagnosis should be made include nephrogenic systemic fibrosis, scleromyxedema, scleredema, eosinophilia and myalgia syndrome, toxic oil syndrome, and graft-versus-host disease. The diagnosis of eosinophilic fasciitis is difficult to make and up to 79% of cases are initially misdiagnosed [24], with an average time to final diagnosis of 11 months.

The treatment of choice is corticosteroids at doses equivalent to 1 mg/kg/day of prednisone (up to 1.5 mg/kg/day), though no clinical trials have been carried out on this matter. Treatment is usually followed by rapid resolution of the eosinophilia in addition to normalization of the ESR, as occurred in our case. Most patients respond to steroids (70–90%) [7, 24] and 50% can even achieve remission with this treatment alone. With good progress, treatment can be discontinued in 1 or 2 years [4]. Indicators of



Table 2 Published cases of eosinophilic fasciitis in pregnant women

Author	Year	Year Age Relation with the pregnancy Pathology features		Pathology features	Treatment	Gestation result	
Amdur et al. [5]		27 yo	Synchronous—week 16 of gestation	Mild arthritis, skin induration, eosinophilia (23%)	10 mg/d prednisone with good response	Full-term pregnancy at 40 weeks with a healthy newborn	
Strosberg et al. [6]		42 yo	Three months after the delivery	Pain, weakness and edema of the hands. 25% eosinophilia	10 mg/d prednisone with good response-tapering in 8 months	Healthy newborn	
Fonseca et al. [7]		23 yo	Synchronous—week 12 of gestation	Symmetrical and progressive rigidity, induration and edematization of the arm and thighs; <i>peau d'orange</i> . Eosinophilia (3%), hypergammaglobulinemia (1.6 g/dL), ANA positive at 1/320	Starting dose of prednisone at a dose of 1 mg/kg/d and decreasing to 10 mg until delivery. Low doses maintained for 2 years	Full-term pregnancy at 40 weeks with a healthy newborn	

Table 3 Diagnostic criteria according to the 2018 guidelines by Jinnin et al. [15] and the 2014 guidelines by Pinal-Fernández et al. [3]

	Jinnin et al. guidelines, 2018 [15]	Pinal-Fernández et al. guidelines, 2014 [3]
Major criteria	Plate-like sclerotic lesions in extremities, without Raynaud's phenomenon	Diffuse or localized symmetrical or asymmetrical swelling, induration and thickening of skin and subcutaneous tissues Full-thickness wedge biopsy of clinically affected skin with fascial thickening and accumulation of lymphocytes and macrophages, with or without eosinophils
Minor criteria	Histology in fascial biopsy showing fascia thickening and infiltration of eosinophils and monocytes Fascia thickening on MRI	 Peripheral eosinophilia > 0.5 × 10^9/L Hypergammaglobulinemia > 1.5 g/L Muscle weakness and/or high serum aldolase Groove sign and/or peau d'orange MRI in T2 showing hyperintense fascia
Needed for diagnosis	Major criterion + 1 or 2 minor criteria	No exclusion criteria: diagnosis of systemic sclerosis Presence of: +1 major criterion + 2 minor criteria 2 major criteria

poor prognosis and corticoid resistance are a delay in starting treatment with corticoids [10], coexistence with plaque morphea, onset in a pediatric age, advanced age, a torso or neck condition, underlying pathology (especially hematological and solid neoplasms), prolonged time of treatment until remission, and high CRP [8, 10, 25, 26]. In patients with a lack of response to steroids or difficulty in reducing doses, subcutaneous methotrexate can be associated at doses of 15–25 mg per week and good results [27]. Once a response is achieved, treatment is usually maintained for 6 months. Results published in the literature [24] show a response rate of 64% for the combination of corticoids and methotrexate compared to 30% with steroids in monotherapy or 29% with steroids and other combination treatments (mainly mycophenolate and hydroxychloroquine.

As an alternative to methotrexate, there are a limited number of reports on the use of mycophenolate mofetil (MMF) and hydroxychloroquine [10], with good results for MMF (71% of patients had a partial response after 6 months, the steroid was discontinued in 69% after a median of 13 months of treatment), which could be an alternative to methotrexate [28–30].

There are only seven published cases of infliximab use in the literature. A description of the cases is provided in Table 4, although information in the most recent case is limited. All were patients with a partial response to first-line treatment (corticosteroids, methotrexate, or MMF) with corticosteroid dependence. Other biological therapies used in isolated cases include tocilizumab [31–33], rituximab [34–36], or tofacitinib [37, 38], all of which were used in cases that were refractory to systemic corticoids and classic immunosuppressants (methotrexate, mycophenolate mofetil, and cyclosporine A). Finally, there are individual cases and small series in which other therapeutic options are used, such as sulfasalazine,



Table 4 Published cases of refractory eosinophilic fasciitis with infliximab use

Author	Year	No. of cases	Age	Sex	Initial therapy	Additional therapy	Response	Time using infliximab	Posterior remission
Drosou et al. [51]	2003	1	69	Female	MMF, MTX, CsA, Predn	MMF, Predn	Moderate	1 dose	-NA-
Khanna et al. [52]	2010	3	46	Female	Predn, MTX	Predn	Complete	36 months	2 years
			61	Female	Predn., MTX	Pred., MTX	Complete	36 months	-NA-
			61	Female	Predn	No	Complete	7 months	1.5 years
Poliak et al. [53]	2011	1	5	Male	Predn., MTX, MPN	Predn., MTX, MPN	Moderate	-NA-	-NA-
Tzaribachev et al. [54]	2008	1	12	Male	Predn., MPN	Predn., MTX	Complete	12 months	1 year
Yamamoto et al.	2020	1	NA	NA	NA	NA	NA	NA	NA

CsA cyclosporin A, MMF mycophenolate mofetil, MPN methylprednisolone pulses, MTX methotrexate, Predn. prednisone

azathioprine, immunoglobulins, dapsone, cyclosporine A, D-penicillamine, psoralen plus ultraviolet A (PUVA), sirolimus, and antithymocyte globulin. All were used once the possibilities described above were exhausted [25, 39–48]. Rehabilitation is important for all patients, regardless of medical treatment [15] as well as the surgical release of joint contractures [49] or fasciotomies [50] in the most severe cases with greater functional limitation

In conclusion, eosinophilic fasciitis is a rare pathology that is described in pregnant women in an almost anecdotal way and as such, pregnancy as a trigger of this pathology has not been conclusively established. Furthermore, in our case, there were possible confounding factors (possible hyaluronic acid ASIA syndrome). There is very little experience with infliximab in corticosteroid-resistant cases, but an increasing amount of evidence is being published and shows good clinical results.

Author contributions All the authors whose names appear on the submission: (1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; (2) drafted the work or revised it critically for important intellectual content; (3) approved the version to be published; and (4) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest All the authors declare that they have no conflict of interest.

Ethical approval (Include appropriate approvals or waivers) Not applicable.

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