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ORPHAN DISEASES (B MANGER, SECTION EDITOR)

Eosinophilic Fasciitis: an Updated Review on Diagnosis and Treatment

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Abstract
Purpose of Review First recognized in 1974, eosinophilic fasciitis (EF) is a fibrosing disorder of the fascia with characteristic cutaneous and hematologic manifestations. This review discusses recent trends in the diagnosis and treatment of EF.
Recent Findings Although fascial biopsy has classically been considered the gold standard for making a diagnosis of EF, radiologic imaging, particularly magnetic resonance imaging, has been increasingly used for both diagnosis and monitoring of treatment response. Systemic corticosteroids remain the first-line treatment for EF; however, their often prolonged use in the treatment of EF has prompted a search for adjunctive therapies. Methotrexate has emerged as the leading corticosteroid-sparing agent for EF.
Summary Since EF was initially described over 40 years ago, important diagnostic and therapeutic progress has been made. Future efforts should be directed at the pursuit of prospective studies including clinical trials and evidence-based guidelines.

Keywords Eosinophilic fasciitis · Shulman disease · Groove sign · Corticosteroids · Methotrexate · Magnetic resonance imaging

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Introduction

Eosinophilic fasciitis (EF) is a rare fibrosing disorder first described by Shulman in 1974 [1], typified by erythema, edema, and induration of the bilateral extremities. Characteristic findings include a pseudocellulite or peau d'orange appearance of the involved skin, as well as the "groove sign," a linear depression along the course of veins, accentuated by limb elevation, due to inward tethering of the skin by fascial fibrosis [2]. Joint contractures occur in 50–56% of patients [3, 4••], accounting for the high morbidity associated with EF. Other findings include benign or malignant hematologic abnormalities, including peripheral eosinophilia (58–85% of patients) [3, 4••, 5], hypergammaglobulinemia (35–46%) [3, 5], and monoclonal gammopathy (16%) [4••]. Rarely, EF is associated with solid malignancies [6••]. The mean age of onset is 47–57 years, and women are 1.3–2.1 times as likely as men to be affected [3, 4••, 5].

The etiology of EF is unknown. Data from 1998 found exercise to be a trigger in 46% of patients [3]; however, a 2016 study reported a history of exercise in only 28% [4••], suggesting that physical stress may be less of a risk factor than previously thought. Also unclear is the relationship between EF and morphea, a disorder with similar clinical and superficial histopathologic features. Twenty-nine to 41% of patients with EF have concomitant plaque morphea [3, 4••, 5], which, in the context of EF, has been hypothesized to represent superficial extension of inflammation from the fascia to the subcutaneous fat and skin [7]. Many experts consider EF to be a variant of or exist along a spectrum with morphea [8–10].

The rarity and likely under-recognition of EF is reflected in the largest EF study to date [4••]. Although the study spanned 20 years at two tertiary care centers and 10 years at a third center, only 63 patients with EF were identified from 1626 patients with fasciitis and more than 20 million total patient

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visits [4••]. Given this rarity, data on diagnosis and treatment of EF are generally derived from case reports and case series, with few retrospective studies and only three prospective studies in the current literature. Here, we provide an updated review focusing on major advancements in the diagnosis and treatment of EF.

Clinical Manifestations and Diagnosis

Clinical Manifestations

Patients with EF typically present with abrupt-onset edema followed by induration of the bilateral extremities, with all four extremities more commonly affected (70–83% of patients) than only the lower extremities (12–25%) or the upper extremities (5–6%) [3, 4••]. Involvement is most often symmetric, but may be asymmetric. Furthermore, the trunk may be involved in extensive cases. As mentioned previously, the "groove sign" and/or a pseudocellulite appearance of the involved skin may be present, but these are not uniform findings [3]. Due to the depth of inflammation and the fibrosing nature of EF, joint contractures develop in 50–56% of patients and are the main determinant of associated morbidity [3, 4••].

EF affects the distal extremities and, as such, is often mistaken for systemic sclerosis (SSc), a more commonly recognized sclerosing disorder (Table 1) [4••]. However, unlike in SSc, the most distal digits are typically spared in EF [3]. In fact, in many patients with EF, edema and induration occur only proximal to the wrists and ankles, whereas in others, the induration may also include the dorsal hands and/or feet, with extension to the proximal digits in some cases. Again, however, a critical distinction from SSc is the lack of involvement of the distal digits in EF. Another feature that helps to distinguish between the two diseases is the typical absence of Raynaud phenomenon in EF [3] (Table 1).

Diagnostic Criteria

In 2014, Pinal-Fernandez et al. proposed diagnostic criteria for EF (Table 2) [6••]. To diagnose EF, the proposed criteria require the presence of both major criteria or one major criterion

Table 1 Differentiating eosinophilic fasciitis from systemic sclerosis

	Eosinophilic fasciitis	Systemic sclerosis
History		
Raynaud phenomenon	Characteristically absent	Universally present
Extracutaneous involvement	Joint contractures in 50–56%; benign or malignant hematologic abnormalities	Possible cardiopulmonary, renal, and gastrointestinal manifestations; may have joint contractures
Physical examination		
Skin tightening of bilateral extremities	Present	Present
Skin tightening of distal digits	Absent	Universally present
Pseudocellulite- or peau d'orange-appearing skin	Characteristically present	Absent
"Groove sign"	Characteristically present	Absent
Concurrent plaque morphea	Present in 29–41%	Absent
Nailfold capillary changes	Absent	Universally present, but may be subtle
Digital ulcers	Absent	May be present
Labs		
Peripheral eosinophilia	Present in 58–85%	Absent
Hypergammaglobulinemia	Present in 35–46%	Absent
Monoclonal gammopathy	Present in 16%	Absent
Antinuclear antibody	Characteristically negative	Positive
Histopathology	Involvement of fascia is universally present; involvement of dermis and subcutaneous fat may occur (can lead to misdiagnosis when biopsy is too superficial); muscle involvement may also occur	Involvement of dermis and subcutaneous fat
Treatment		
Systemic corticosteroids	First-line therapy	Usually avoided or dosed at < 15 mg/day given potential association with scleroderma renal crisis

The following characteristics help distinguish EF from SSc, which EF is commonly misdiagnosed as, resulting in unnecessary systemic workup and delays in appropriate treatment [3, 4••, 5]

Table 2 Proposed diagnostic criteria for eosinophilic fasciitis

1. Major criteria
   (a) Symmetric or asymmetric, diffuse (i.e., on the extremities, trunk, and abdomen) or localized (i.e., on the extremities) swelling, induration, and thickening of the skin and subcutaneous tissues
   (b) Full-thickness wedge biopsy of clinically affected skin showing fascial thickening with accumulation of lymphocytes and macrophages with or without eosinophils
2. Minor criteria
   (a) Peripheral eosinophilia > 0.5×10^9/L
   (b) Serum hypergammaglobulinemia > 1.5 g/L
   (c) Muscle weakness and/or elevated serum aldolase levels
   (d) "Groove sign" and/or peau d'orange-appearing skin
   (e) T2-weighted MRI showing hyperintense fascia
3. Exclusion criterion
   (a) Diagnosis of systemic sclerosis

According to criteria proposed by Pinal-Fernandez et al. in 2014, the diagnosis of EF requires the presence of both major criteria or one major criterion and two minor criteria, as well as the exclusion of SSc [6••]. Reprinted from Autoimmunity Reviews vol. 13, 2014, I. Pinal-Fernandez, A. Selva-O′ Callaghan, J.M. Grau, Diagnosis and classification of eosinophilic fasciitis, 379–382, Copyright (2014), with permission from Elsevier

and two minor criteria, as well as the exclusion of SSc [6••]. Notably, in practice, many experts now use a wedge biopsy *or* MRI to fulfill the second major criterion (Table 2).

Eosinophilic Fasciitis Versus Systemic Sclerosis

The requirement that SSc be excluded in the diagnostic criteria for EF proposed by Pinal-Fernandez et al. stresses the importance of distinguishing EF from SSc. Despite their similar presentation with symmetric induration of the extremities, the two conditions portend different prognoses and are managed differently (Table 1). Whereas systemic corticosteroids are first-line therapy for EF, they are usually avoided or dosed at less than 15 mg/day in SSc given their potential association with scleroderma renal crisis [11]. Furthermore, unlike SSc, EF does not require an extensive systemic workup, as extracutaneous involvement is generally limited to hematologic abnormalities and joint contractures.

The need to differentiate EF from SSc and other potential mimickers is highlighted by a 2016 retrospective study, which found that 79% of patients with EF were initially misdiagnosed, most frequently with SSc [4••]. The patients misdiagnosed with SSc underwent unneeded, often extensive systemic workup and experienced a delay in the initiation of systemic corticosteroids [4••]. In addition, four patients misdiagnosed with hypereosinophilic syndrome or eosinophilic leukemia underwent unnecessary bone marrow biopsies, and one patient was inappropriately treated with chemotherapy [4••]. Other misdiagnoses in the study included deep vein thrombosis and cellulitis [4••]. The mean diagnostic delay in this and another study was 11 and 7.4 months, respectively [4••, 5].

Although both EF and SSc are characterized by induration of the extremities, in the authors' experience, the two conditions can be distinguished by careful history and physical examination (Table 1). Unlike in SSc, EF is not associated with Raynaud phenomenon or extracutaneous involvement beyond hematologic abnormalities and joint contractures. On physical examination, unlike SSc, EF is characterized by the absence of nailfold capillary changes and lack of skin tightening of at least the distal digits, but often of the entire digits, hands, and/or feet. Additional features that may help to distinguish EF from SSc are the "groove sign," pseudocellulite- or peau d'orange-appearing skin, and possibly concurrent plaque morphea.

Diagnostic Role of Histopathology and Radiology

Histopathology Fascial biopsy has classically been considered the gold standard for confirming a diagnosis of EF. Fascial thickening and fibrosis are characteristic findings, and a lymphocytic infiltrate may be present [3]. Tissue eosinophilia is neither often seen nor required for diagnosis. Associated muscle and fat involvement may be present [3]. Adequate sampling requires a full-thickness incisional biopsy including the fascia, as evidenced by cases in which superficial biopsies of EF were misconstrued as morphea [12, 13•]. In these cases, EF was ultimately diagnosed after a subsequent full-thickness biopsy and/or the overall clinical picture suggested EF was more likely than morphea [12, 13•]. As these cases show, confirming a diagnosis of EF requires not only a biopsy demonstrating fascial inflammation, but also the appropriate clinical context [14].

Given the potential for sampling error, as well as the technical difficulties associated with obtaining an adequate sample in suspected EF (especially given that the incision usually occurs through indurated skin with poor wound healing potential), alternative diagnostic modalities have been explored and are viable options for patients in whom a fascial biopsy is not preferred.

Magnetic Resonance Imaging (MRI) Although fascial biopsy remains the gold standard for the diagnosis of EF, the role of magnetic resonance imaging (MRI) has greatly expanded since 1989, when the MRI characteristics of EF were first reported [15••, 16]. In fact, recently proposed criteria for the diagnosis of EF list hyperintense fascia on T2-weighted images as a minor diagnostic criterion [6••]. Moreover, many experts now use MRI in place of a wedge biopsy to fulfill the second major diagnostic criterion (Table 2).

A retrospective study of six patients with biopsy-proven EF who underwent MRI before and after therapy delineates the

MRI characteristics of EF [17]. Eight pre-therapy MRI studies of the thighs, calves, or arms were performed and identified symmetric thickening (on T1-weighted images), increased signal intensity (on T2-weighted images), and contrast enhancement (on T1-weighted images following gadolinium injection) in superficial muscle fascia in 100% (8/8) of cases and deep muscle fascia in 88% (7/8) [17]. These findings clinically correlated with areas of skin thickening and induration on physical exam [17], and were interpreted as consistent with fascial inflammation given that normal fascia is dark on all MRI sequences [18]. In addition to these principal findings, 38% (3/8) of pre-therapy MRI studies showed signal hyperintensity and contrast enhancement in perifascial muscle, and 25% (2/8) showed hyperintensity in the subcutaneous fat, which correlated with panniculitis on biopsy [17]. These findings were speculated to reflect extension of inflammation from affected fascia to neighboring muscle and fat [17]. Another retrospective study of six patients with biopsy-proven EF confirmed these findings, with 12 magnetic resonance images performed within 6 months of symptom onset showing fascial thickening, signal hyperintensity, and enhancement, as well as an edema-like signal in perifascial muscle [19].

There are several situations in which MRI has been reported to be useful as an adjunctive diagnostic tool in EF. Firstly, MRI has been used to guide selection of a biopsy site in one case series [20] and four case reports [18, 21, 22]. The case series is particularly illustrative, as its three patients were confirmed to have EF by MRI-guided biopsies after initial biopsies performed without MRI guidance were false negatives [20]. A second circumstance in which MRI has played a role is in lieu of biopsies that are inadequate or non-diagnostic [13•, 23]. In one case, MRI was used to diagnose EF after multiple fascial biopsies revealed non-specific fibrotic changes without eosinophils [23]. MRI also confirmed the suspicion of EF in another patient who was initially misdiagnosed with morphea due to inadequate fascial sampling [13•]. A third setting in which MRI has facilitated diagnosis is in atypical cases of EF, such as that of a 56-year-old woman who had bilateral thigh tenderness but no associated skin findings [13•]. Subsequent MRI demonstrated fascial enhancement, after which an incisional biopsy confirmed the diagnosis of EF [13•]. The ability of MRI in this case to facilitate a diagnosis of EF prior to the onset of cutaneous manifestations is uniquely important, given the association of early treatment with improved outcomes [4••, 5, 7]. Lastly, MRI may replace an incisional biopsy when the latter is not possible due to patient preference, as occurred in one reported case [23], when a biopsy cannot be obtained rapidly in order to initiate treatment, or when the degree of induration in an affected extremity confers a risk of poor wound healing.

Ultrasound The ultrasonographic features of EF have been described by one prospective study [24•] and two case reports [21, 25]. The two case reports describe EF as exhibiting thickening and abnormal echotexture of the skin, subcutaneous fat, tendons, and fascia on ultrasound [21, 25]. In both cases, these ultrasonographic findings correlated with thickening and contrast enhancement on MRI [21, 25] and, in one case, guided selection of the biopsy site [21]. In the prospective study, ultrasound was used to measure compressibility of the subcutaneous tissues at the mid-dorsal forearm in patients with various fibrosing conditions, including EF [24•]. The median subcutaneous compressibility was significantly lower in the 12 patients with EF compared to the 23 patients with diffuse SSc and the eight normal controls. Subcutaneous compressibility was also lower in EF than in diabetic cheiroarthropathy, albeit not significantly. The authors hypothesized that tissue compressibility was lowest in EF because the fibrotic process is deeper than in the other fibrosing and sclerosing disorders studied [24•]. Despite these findings, the study found no statistically significant difference in mean dermal thickness or mean subcutaneous tissue echogenicity among the groups, suggesting that decreased subcutaneous compressibility may be the most specific ultrasonographic feature of EF [24•].

Positron Emission Tomography-Computed Tomography (PET-CT) Four case reports demonstrate the utility of PET-CT in the diagnosis of EF [26–28, 29•]. In three cases, PET-CT showed uptake of fluorodeoxyglucose (FDG) by fascia in areas corresponding to clinically affected skin [26–28]. In two cases, MRI was also performed and showed fascial abnormalities corresponding to FDG-avid fascia on PET-CT [26, 27]. Fascial biopsy confirmed the diagnosis of EF in all three cases [26–28]. In the fourth case, PET-CT facilitated the diagnosis of EF prior to the development of skin findings [29•]. In this case, a 69-year-old woman presented with a 2-month history of stiffness in her forearms without skin findings, prompting a PET-CT, which showed FDG uptake in the fascia of the bilateral upper extremities and pectoral and pelvic girdles. Biopsy of an FDG-avid area confirmed the diagnosis of EF, and the patient was successfully treated with systemic corticosteroids [29•]. Despite the paucity of evidence for PET-CT in the diagnosis of EF as compared to MRI, PET-CT has been proposed to have the advantage of excluding the rare chance of an underlying solid malignancy [28]. PET-CT may also be preferred in situations where MRI is contraindicated or unavailable.

Treatment

Timing

Most studies support the notion that early treatment of EF results in improved outcomes [4••, 5, 7, 30]. A retrospective, multivariate analysis of 34 patients found that a diagnostic

delay of greater than 6 months was significantly associated with a 14.7 times greater risk of a poor treatment response [5]. Another retrospective study and systematic review also reported a positive association between early diagnosis or treatment and improved outcomes among 47 and 77 patients, respectively, but these findings were not statistically significant [4••, 7]. Similarly, a review of 19 pediatric patients with EF found that mean time to diagnosis was longer in those who developed residual fibrosis compared with those who achieved complete resolution (8 vs. 5 months) [30]. However, the same review found no statistically significant association between diagnosis within or after 5 months of EF onset and treatment response [30]. Finally, a retrospective study of 52 patients showed no difference in outcomes between patients treated within 6 months of EF onset and those treated thereafter [3]. However, treatment was suboptimal in this study, with only 65% of patients receiving first-line therapy with systemic corticosteroids, possibly limiting the study's ability to detect an association between treatment timing and response [3]. Despite some of the discrepancies in these results, the overall findings, as well as the authors' experience, correlate with the observation that the initial inflammatory or edematous phase of EF is more treatment-responsive than the later phase characterized by skin induration [3]. As a result, at the authors' institutions, systemic therapy is initiated immediately upon diagnosis.

Risk Factors for Treatment Resistance

Concurrent Plaque Morphea A review of 88 cases of EF found concurrent plaque morphea to be associated with a 1.9-fold greater risk of corticosteroid resistance [7]. In cases where the presence of morphea was confirmed histologically, the risk of treatment resistance was 1.4 times higher compared to patients without dermal fibrosclerosis on biopsy [7]. Another study of 34 patients with EF found that those with concurrent plaque morphea were three times as likely to require immunosuppressive medications in addition to systemic corticosteroids [5].

Pediatric Age of Onset In a review of 88 published cases, age less than 12 years at EF onset was associated with a 1.6-fold greater risk of corticosteroid resistance [7]. In addition, a review of 21 pediatric patients found that age less than 7 years at EF onset was associated with twice the risk of progression to cutaneous fibrosis as compared with age over 7 years at EF onset [30].

Trunk Involvement In extensive cases of EF, the trunk may be involved. Such involvement has been associated with a 1.4-fold greater risk of corticosteroid resistance [7].

Underlying Disease The association of EF with hematologic disorders in about 10% of patients [3] and with solid malignancies in rare cases [6••] seems to confer treatment resistance unless the underlying disorder is successfully managed. In a review of nine patients with EF and aplastic anemia, 67% experienced remission or improvement of their EF after receiving first-line therapies for aplastic anemia, compared with no patients treated with corticosteroids for their EF without also receiving therapy for aplastic anemia [31]. In another review of six patients with EF and lymphoma, the EF went into complete or partial remission in 100%; however, in 50% this occurred only following bone marrow transplant and/or chemotherapy for the lymphoma [32].

Other disorders associated with EF that, when treated, have been reported to result in improvement of EF include myelodysplastic syndrome [33], acute myeloid leukemia [34], chronic lymphocytic leukemia [35], multiple myeloma [36], metastatic bladder cancer [34], breast cancer [3], and metastatic colorectal cancer [37]. One example includes a 57-year-old man with EF refractory to systemic corticosteroids, methotrexate (MTX), and photopheresis [38]. Two years after EF diagnosis, the patient was found to have paroxysmal nocturnal hemoglobinuria (PNH). Treatment with eculizumab, a humanized monoclonal antibody against complement component C5 that is FDA-approved for PNH, led to improvement of both PNH and EF [38]. In another case, a patient with EF and aplastic anemia-PNH syndrome experienced substantial improvement in skin thickening and remission of aplastic anemia following allogeneic peripheral blood stem cell transplantation, despite prior progression of EF and transfusion dependence while on high-dose corticosteroids, MTX, cyclophosphamide, anti-thymoglobulin, and cyclosporine [39]. Given these findings, it is imperative that patients with EF be screened for an associated hematologic disorder, especially in the setting of refractory disease. At the authors' institutions, initial workup includes a complete blood count with differential, serum and urine protein electrophoresis and immunofixation, and age- and sex-appropriate malignancy screening. In patients in whom an underlying condition is not initially identified, thorough review of systems and complete physical examination guide additional testing.

Factors Unrelated to Treatment Resistance

Characteristics not associated with treatment resistance include sex [7, 30], preceding physical stress [30], peripheral or tissue eosinophilia [7, 30], hypergammaglobulinemia or elevated IgG level [7, 30], elevated erythrocyte sedimentation rate (ESR) [7, 30], and positive antinuclear antibody [7, 30].

Discrepancy Between Clinical and Laboratory Response

In the majority of patients, laboratory abnormalities, such as peripheral eosinophilia, elevated ESR, and hypergammaglobulinemia, normalize with systemic

corticosteroid therapy, as evidenced by two retrospective studies including 32 and 34 patients treated with prednisone [3, 5]. However, these same studies identified patients with progressive skin induration despite normalization of laboratory studies [3]. Therefore, it is important to note that clinical improvement of EF may not accompany improvement in associated laboratory abnormalities. Thus, therapeutic monitoring should be based upon clinical examination with or without radiologic imaging.

Radiologic Monitoring of Treatment Response

Magnetic Resonance Imaging (MRI) One retrospective study [17] and multiple case reports [18, 23, 40–44] have shown that disease activity in EF correlates with the degree of abnormalities seen on MRI, supporting the use of MRI in the assessment of therapeutic response (Fig. 1). In the retrospective study, complete clinical remission in five patients correlated with complete resolution of the fascial abnormalities seen on pre-treatment MRI, whereas poor clinical response in the sixth patient correlated with only partial remission of MRI abnormalities [17]. Similarly, in several reported cases, MRI has been used to monitor treatment response in patients with EF, with post-therapy images showing reduction or resolution of the abnormalities detected on initial MRI and correlating with clinical improvement in skin induration, joint range of motion, muscle strength, and pain [18, 23, 40–44]. Lastly, it has been proposed that MRI may be used to help determine whether new symptoms in treated patients are due to an EF flare or are unrelated to fascial inflammation [19].

Ultrasound Ultrasonography has been used to monitor treatment response in two reported cases of EF, revealing improved compressibility after prednisone in one patient [24•]. In the second patient, ultrasound detected a significant reduction in skin thickness after ultraviolet A1 (UVA1) phototherapy and methylprednisolone, correlating with clinical improvement [45].

Treatment

Treatment of EF is challenging, and the best existing data regarding therapy are in the form of retrospective reviews, one open-label, single-arm trial, and one open-label, double-arm, non-randomized trial. Furthermore, assessment of clinical response is also extremely challenging given the lack of a validated skin index to accurately evaluate for extent of disease. Assessment of clinical response is further compounded by the fact that EF has both inflammatory and damage components. Therefore, our clinical understanding is that in patients who do not receive early treatment, fibrosis and induration may become permanent and fail to respond to immunosuppressive therapy. Hence, early treatment while the disease is in the edematous or inflammatory stage is considered imperative. Along these lines, physical therapy is considered an important aspect of therapy.

Oral Corticosteroids

Systemic corticosteroids are first-line treatment for EF, as supported by the largest three studies on EF to date [3, 4••, 5].

In 1988, a retrospective study of 52 patients performed at Mayo Clinic identified 34 patients initially treated with prednisone monotherapy starting at 40–60 mg/day [3]. Prednisone monotherapy led to complete remission in 15%, partial response (> 25% improvement but not total resolution) in 59%, and poor response (< 25% improvement) in 26%. These responses usually occurred after 3 to 6 months of prednisone therapy. Regardless of the clinical response, the peripheral eosinophil count, ESR, and gamma globulin level normalized in almost all patients treated with prednisone [3].

In 2012, a retrospective study of 34 patients found that 32 received prednisone monotherapy (beginning at 52.7 ± 22.6 mg/day or 0.77 ± 0.29 mg/kg/day) as first-line treatment [5]. Fifty-three percent achieved complete remission, 3% experienced remission with disability (such as persistent joint contractures, tendon retraction, or subcutis sclerosis), and 44% had an unsatisfactory clinical response requiring treatment beyond systemic corticosteroids. Regardless of the clinical response, the eosinophil count normalized in all patients [5].

Most recently, in 2016, a retrospective study of 63 patients was published in which 89% were treated with oral corticosteroids (mean highest dose of 51 ± 20 mg/day) as monotherapy or for at least 3 weeks prior to the initiation of additional therapies [4••]. The rates of complete response (defined as resolution of erythema and/or edema with no or minimal persistent induration) and partial response (defined as incomplete

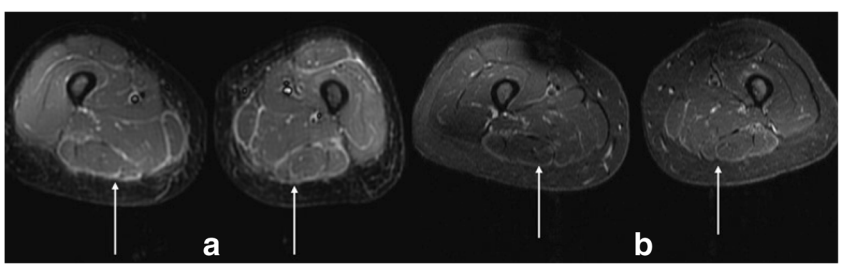

Fig. 1 MRI showing fascial enhancement of thighs affected by EF (**a**, arrows), with resolution after 5 months of treatment with systemic corticosteroids and methotrexate (**b**, arrows)

improvement of erythema, edema, and/or induration) were 30 and 67%, respectively. Only one patient in the study did not respond to systemic corticosteroids [4••].

Although these studies show that the ratio of patients with EF receiving first-line therapy has increased from 1988 to 2016, the lack of systemic corticosteroid use in 11% of patients in the most recent study suggests that EF remains undertreated [4••]. Furthermore, despite the responsiveness of EF to systemic corticosteroids, their prolonged use in these studies (18–45.7 ± 26–31.2 months), the associated adverse effects, and the risk of disease relapse upon their discontinuation underscore the need for corticosteroid-sparing agents in the management of EF [4••, 5].

Pulse Methylprednisolone

In a retrospective study of 34 patients with EF, 44% were treated with intravenous methylprednisolone pulses (500–1000 mg/day) for three consecutive days prior to the initiation of prednisone [5]. Compared to patients who did not receive pulse methylprednisolone, those who did were significantly more likely to achieve complete remission (87 vs. 53%) and less likely to require additional treatment beyond systemic corticosteroids (20 vs. 65%) [5].

Oral Methotrexate (MTX)

Previously limited to case reports [46, 47], evidence for the treatment of EF with oral methotrexate (MTX) now includes two retrospective studies supporting its use in combination with systemic corticosteroids [4••] and as a corticosteroid-sparing agent [48••]. In 2016, a retrospective study of 63 patients with EF, 42 of whom were treated with MTX, found that the rate of complete response was significantly higher with the combination of systemic corticosteroids and MTX (64%) compared to systemic corticosteroid monotherapy (30%) or to other treatment combinations (29%) [4••]. In 2015, another retrospective study showed that 87% (13/15) of patients with prednisone-dependent EF were able to discontinue prednisone after receiving MTX for a mean of 14.5 months [48••]. Moreover, nine of the 13 patients achieved complete remission after an average of 31.4 months of MTX therapy; three of these nine remained in remission after 1–3 years of follow-up; the other 6 relapsed after a mean of 27.1 months off MTX. All patients who relapsed responded to re-initiation of MTX thereafter [48••].

Pulse Methotrexate (MTX)

In a 2016 open-label, single-arm trial, 12 patients with biopsy-proven EF were treated with high-dose intravenous (IV) MTX pulses (4 mg/kg/month) for 5 months [49]. Sixty-seven percent (8/12) of patients also received up to 15 mg/day of systemic corticosteroids. At 5 months of follow-up, clinical response was observed in all but one patient, with a significant reduction in median skin induration. Interestingly, this improvement was not significantly affected by the concomitant use of corticosteroids or prior failure of oral, subcutaneous, or intramuscular MTX. Significant improvements also occurred in median physician- and patient-rated visual analog scale scores for disease activity; median range of motion in the wrists, ankles, and knees; and the physical functioning domain in the 36-Item Short Form Survey (SF-36) health questionnaire. On the other hand, the median durometer score (a measure of skin hardness) and elbow range of motion did not improve [49].

Two to 5 months after the study, six patients flared and responded to an additional 3 months of IV pulse MTX [49]. To limit side effects during the trial, patients received up to 25 mg/day of folinic acid 24 h after MTX administration. Nausea occurred in 75% (9/12) of patients; eight were managed with anti-emetics, while one required a one-time MTX dose reduction. Other side effects were mild stomatitis in five patients, alopecia in four, and an elevated alanine aminotransferase level in one that normalized after study withdrawal. Given these findings, the study authors concluded that high-dose pulse MTX may be considered for EF with or without systemic corticosteroids and regardless of previous response to non-IV forms of MTX [49].

Mycophenolate Mofetil (MMF)

Despite the dearth of existing data in the literature, many EF experts utilize MMF as the second-line corticosteroid-sparing agent in EF given its use in various morphea subtypes when MTX fails or is contraindicated. In the case of a 9-year-old boy with EF who developed Cushing's syndrome from prolonged systemic corticosteroid use, mycophenolate mofetil (MMF) was titrated to 1800 mg/day while a prednisone taper was initiated [50]. After 6 and 12 months of MMF, respectively, the patient discontinued systemic corticosteroids and MRI of his lower extremities, which previously showed fascial enhancement, normalized. After a total of 2 years of MMF, the patient's affected body surface area decreased from 80 to 12% and modified Rodnan skin score (a measure of skin induration validated in SSc) decreased from 39/51 to 6/51. Additionally, the severe joint contractures in the patient's ankles, knees, and elbows markedly improved [50].

Ultraviolet A1 (UVA1) Phototherapy

Two case series with four total patients describe the treatment of EF with ultraviolet A1 (UVA1) phototherapy [45, 51]. In one patient, monotherapy with UVA1 phototherapy improved skin elasticity on the forearms but not the trunk after a cumulative dose of 1750 J/cm^2 [45]. The other three patients were

given UVA1 phototherapy in combination with oral corticosteroids ($n = 3$), isotretinoin ($n = 2$), continuous compression ($n = 2$), physical therapy ($n = 2$), and ceftriaxone ($n = 1$) [45, 51]. All three patients experienced corticosteroid-sparing effects [45, 51]. After a cumulative UVA1 dose of 1930–3940 J/cm^2, one patient had significant reduction in skin thickness on the thighs and improved skin elasticity on the abdomen but no improvement of the forearms [45], and another patient with erosive EF had healing of erosions, near-complete cutaneous softening, and complete return of joint mobility [51]. The third patient had induration that completely cleared on the legs and partially improved on the arms after an unspecified total UVA1 dose [51].

Psoralen Plus Ultraviolet A (PUVA)

One case report describes a 56-year-old man with EF complicated by upper extremity joint contractures who was refractory to high-dose prednisolone and chloroquine [52]. After 35 sessions of psoralen plus ultraviolet A (PUVA) bath photochemotherapy, the patient's induration greatly improved and he regained the ability to completely close his fists. After 50 sessions, his induration resolved [52]. In another report, a 58-year-old woman with EF who partially responded to methylprednisolone and doxycycline experienced disease remission following 42 sessions of oral PUVA therapy [53].

Extracorporeal Photopheresis (ECP)

Two case series [54, 55] and one case report [56] describe the use of extracorporeal photopheresis (ECP) in six patients with EF. ECP was used due to refractory disease in four patients [54–56], a contraindication to high-dose systemic corticosteroids in one patient [54], and as first-line therapy in another patient [55]. When specified, ECP was dosed over two consecutive days every 2 weeks for 3 months, after which an initial clinical response was noted and the interval was increased to every 4 weeks [54, 56]. Three patients went into remission: two patients after 7 and 11 months of ECP monotherapy [55], and another patient, who had EF complicated by ulcers, after 12 months of ECP in combination with bosentan [56]. The other three patients improved after 1 year of treatment with ECP in combination with cyclosporine and/or corticosteroids [54]. All three of these patients experienced a cyclosporine- and/or corticosteroid-sparing effect [54].

Intravenous Immunoglobulin

The treatment of EF with intravenous immunoglobulin (IVIG) is supported by the case of a 39-year-old man who partially responded to prednisone, MTX, and cimetidine, but flared upon attempted taper of prednisone below 20 mg/day [57]. IVIG was added to the patient's regimen, dosed at 0.5 g/kg/day for 3 consecutive days every month for a total of 5 months. Substantial cutaneous and functional improvement was noted as early as 1 month after initiation of IVIG. Two years after IVIG was discontinued, the patient was symptom-free on prednisone 2.5 mg/day and MTX [57].

Cyclosporine

Four case reports support the treatment of EF with cyclosporine as monotherapy [58–60] or in combination with systemic corticosteroids [61]. In three cases, cyclosporine monotherapy (3.7 or 5 mg/kg/day or 100 mg/day) led to an initial response within 1 month and remission within 6 months [58–60]. Ultimately, two patients were maintained on 2.5 mg/kg/day and the third patient discontinued cyclosporine due to side effects, without recurrence of EF in any patient after 8 months to 12 years of follow-up [58–60]. Another case report describes the treatment EF with cyclosporine (300 mg/day) in conjunction with pulse methylprednisolone (1 g/day for 5 days) [61]. Within 3 weeks, skin induration significantly decreased and joint range of motion improved [61].

Dapsone

In one report, a 38-year-old woman with EF who partially responded to prednisolone noted improvement 2 weeks after the addition of dapsone 50 mg/day [62]. Dapsone was then titrated to 150 mg/day while prednisolone was tapered from 30 to 5 mg/day. At 5 and 8 months of follow-up, respectively, the patient had regained the ability to make complete fists with both hands and completely extend her fingers. Occasional mild aches in her lower extremities persisted [62].

Azathioprine (AZA)

Two case reports describe the treatment of EF with azathioprine (AZA) [63, 64]. One patient, a 66-year-old man described as having EF/generalized morphea overlap intolerant of oral corticosteroids, was treated with AZA monotherapy 200 mg/day, which markedly reduced induration and increased skin flexibility after 2 months [63]. At 18 months of follow-up, the patient was in complete remission on AZA 100 mg/day [63]. The other patient achieved complete remission after an unspecified number months on AZA 100 mg/day and D-penicillamine 1 g/day, and remained in remission off all treatments at 2 years of follow-up [64].

Infliximab

One retrospective study [65], one case series [66], and two case reports [67, 68] describe the treatment of refractory EF with infliximab in six patients in total. One patient with prednisone-resistant EF was treated with infliximab

monotherapy for 8 months, after which he remained in remission off therapy for 1.5 years [66]. In the other five patients, infliximab was added after failure of treatments including MTX and/or systemic corticosteroids, and led to corticosteroid-sparing effects in 80% (4/5) of patients [65–68]. Three patients achieved drug-free remission after 1–3 years of infliximab [66, 67]. The fourth patient had marked cutaneous improvement after an unspecified number of months [68]. The fifth patient experienced marked improvement within 1 week of starting infliximab in combination with prednisone and MMF [65].

Rituximab

In a retrospective study of 29 patients with autoimmune diseases treated with rituximab, one patient had EF and an associated hypergammaglobulinemia [69]. After receiving rituximab at an unspecified dose for an unspecified duration, the patient's cutaneous involvement resolved, and peripheral eosinophilia and IgG level normalized [69].

Sirolimus

In one case report, a patient with EF complicated by joint contractures and refractory to prednisone (up to 20 mg/day), MTX, and physical therapy was treated with prednisone 5 mg/day and sirolimus 2 mg/day [70]. After 6 weeks of this regimen, the patient had decreased skin thickening and pain, and after 9 months, further functional improvement was reported. Despite these improvements, the patient noted persistent arthralgias [70].

Tocilizumab

Tocilizumab is a humanized monoclonal antibody against the interleukin-6 receptor approved by the US *Food and Drug Administration* for rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis. In 2015, a case of EF treated with tocilizumab was published [71]. The patient was described as having EF-associated oligoarthritis in addition to cutaneous disease, which flared during a prednisone taper and failed to respond to MTX and etanercept. After 3 months of tocilizumab (8 mg/kg/month), prednisone could be discontinued, and after 6 months, remission of both cutaneous and articular disease occurred. The patient remained in remission at 3 years of follow-up [71].

D-Penicillamine

In an open-label, double-arm, non-randomized trial, 16 patients with severe EF (defined as more than 15% affected body surface area [BSA] or 10%–15% affected BSA with joint contractures) received prednisone and D-penicillamine for an average of 13.5 months (n = 10) or prednisone monotherapy for an average of 19 months (n = 6) [72•]. Despite the lack of randomization, the treatment groups were similar in terms of demographics, interval from symptom onset to diagnosis, affected BSA, and presence of joint contractures. The D-penicillamine group experienced significantly greater reduction in affected BSA (29.5 to 8.9%) compared to the prednisone monotherapy group (28 to 22.8%). In addition, 70% of patients in the D-penicillamine group had improved joint range of motion versus no patient in the prednisone monotherapy group. Forty percent (4/10) of patients in the D-penicillamine group developed adverse effects (proteinuria in three, bullous pemphigoid in one) requiring transition to another corticosteroid-sparing agent [72•]. In addition, a case series and literature review of 18 patients with EF treated with D-penicillamine found that remission occurred in seven, partial remission in one, marked improvement in eight, and mild improvement in two [73]. Treatment ranged from 28 days to 2 years. Side effects included leukopenia, vitiligo, myasthenia gravis, and bullous dermatitis in one patient each [73].

Physical Therapy

Joint contractures have been reported to occur in 50–56% of patients with EF due to involvement of the fascia overlying joints [4••, 5]. Despite the high prevalence of joint contractures in EF, one study found that only 37% of patients with EF were referred for physical therapy [4••]. At the authors' institutions, physical therapy is routinely recommended in combination with systemic treatment to help prevent and/or improve joint contractures and related functional limitation.

Conclusion

Although first identified in 1974 [1], EF remains underrecognized and under-treated. In the largest study on EF to date, 79% of patients were initially misdiagnosed, with accurate diagnosis of EF delayed by almost 1 year on average [4••]. Moreover, the same study found that 11% of patients were not given the standard-of-care treatment with systemic corticosteroids, and only 37% were referred for physical therapy even though joint contractures were highly prevalent [4••]. Despite these shortcomings, important diagnostic and therapeutic advancements in EF have occurred. Recently proposed diagnostic criteria [6••] and radiologic imaging options, particularly MRI, assist in distinguishing EF from its potential mimickers, most commonly SSc [4••]. In regards to therapy, the literature supports the concept that early treatment of EF is critical [4••, 5, 7, 30]. Data from retrospective studies increasingly favor the combination of systemic corticosteroids and MTX as the initial treatment of choice [4••, 48••]. In addition to pharmacotherapy, physical therapy should be recommended to all

patients with involvement of EF over a joint. As EF becomes increasingly recognized, clinical trials and evidence-based guidelines for management should be pursued.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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