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Baseline characteristics and long-term outcomes of eosinophilic fasciitis in 89 patients seen at a single center over 20 years

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Abstract

Aim: Eosinophilic fasciitis (EF) is a rare, fibrosing disorder of skin and subcutaneous tissue. This study was undertaken to describe its clinical and laboratory features and identify prognostic factors associated with outcome.

Methods: We conducted a retrospective review of all EF patients evaluated at our institution from 1 January1997 to 30 December 2016. Kaplan-Meier methods were used to determine treatment response rates over time. Potential associations between baseline characteristics and complete response were examined using Cox models adjusted for age and sex. Time-dependent covariates were used to examine treatment effects.

Results: We identified 89 EF patients, with a female-to-male ratio of 1:1. Clinical features included groove sign in 26 (29%), peau d'orange/dimpling in 22 (25%), inflammatory arthritis in 9 (10%) and muscle weakness in 9 (10%). Aldolase was elevated in 11/36 (31%). Complete response rate was 60% (95% confidence interval [CI]: 35-75) at 3 years. Diagnostic delay was inversely associated with treatment response (hazards ratio: 0.84 per 1 month increase; 95% CI: 0.73-0.98). No baseline characteristics correlated with treatment response, but a trend toward positive association of elevated aldolase, hypergammaglobulinemia and presence of hematologic disorders was noted. Methotrexate was the most commonly used immunosuppressant in 79%, hydroxychloroquine in 45%, mycophenolate mofetil in 18% and azathioprine in 8%. No single immunosuppressant agent was associated with a superior response during treatment.

Conclusions: EF is characterized by relatively high response rates. Consensus diagnostic criteria, standardized management algorithms, and large prospective multi-center cohorts are needed to develop an evidence-directed approach to this challenging condition.

KEYWORDS
eosinophilia, eosinophilic fasciitis, sclerosing disorder, thickened skin

1 | INTRODUCTION

Eosinophilic fasciitis (EF), first described by Shulman et al in 1974,[1,2] is a rare disorder characterized by erythema and edema of skin and subcutaneous tissues, followed by induration of the affected areas. Symmetric induration of bilateral extremities is the typical presentation, but unilateral and/or truncal disease may occur. The etiology is unknown but onset may be preceded by strenuous exercise, trauma, infection, medication, systemic autoimmune condition, and even malignancy.[3-6] Absence of systemic involvement, sclerodactyly, and Raynaud phenomenon differentiate EF from systemic sclerosis. Although in the spectrum of fibrosing skin disorders along with morphea profunda, the presentation of EF is clinically distinct, and there are histopathologic features that may help differentiate the 2 disorders.[7] Diagnosis generally depends on biopsy confirmation of the clinical impression, but there are no widely accepted diagnostic or classification criteria. Most published data on EF consist of retrospective case series. We undertook the present study to describe the clinical and laboratory features of EF and identify prognostic factors associated with disease outcomes in a large cohort of patients seen at our tertiary referral center.

2 | METHODS

We identified study subjects by searching the medical records of patients for the term "eosinophilic fasciitis" and who were seen at our institution between 1 January 1997, and 31 December 2016. Patients were included only if they authorized their inclusion in retrospective research studies. Diagnosis of EF was made on suggestive clinical and laboratory findings and supported by biopsy or imaging abnormalities. Patients with systemic sclerosis, graft-versus-host disease, or radiation-induced skin fibrosis were excluded. Patients with concurrent morphea were included, provided that clinical features of EF also were present at the time of evaluation.

A standardized data collection form was used to record clinical features, laboratory and histopathologic findings at the time of initial evaluation at our institution. Baseline variables included age, gender, pertinent physical exam findings and the extent of skin involvement: upper and lower extremities (proximal to elbows or distal to wrists; proximal to knees or distal to ankles respectively), chest, upper, lower abdomen, back and face. Presence of peau d'orange/dimpling (induration of the skin with a dimpling/rippling/puckering or "pseudo-cellulite" appearance) and groove sign (linear depression where veins appear to be sunken within the indurated skin) were recorded. The methods of diagnosis, by biopsy, imaging, or clinical evaluation, were assessed. Laboratory studies abstracted included complete blood count, peripheral eosinophilia, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), muscle enzymes and serum autoantibodies if performed. Magnetic resonance imaging (MRI) showing presence of myositis, with thickening of fascia with increased T2 signal and enhancement after contrast administration, was noted. Skin biopsies were examined for: the degree, nature, and distribution of inflammation; presence of eosinophils, plasma cells, and edema in the fascia; sclerosis; and eccrine trapping. Newly cut sections obtained from the formalin-fixed, paraffin-embedded tissue blocks were stained with CD34, CD123, and Verhoeff-Van Gieson. All medications used for treatment of EF, glucocorticoids or other immunosuppressive medication used prior to initial evaluation at our institution were recorded. The progress of the disease was determined at each subsequent visit based on evaluation by the treating physician.

Complete response was defined as complete resolution of skin thickening per clinical evaluation, and normalization of acute phase reactants and eosinophilia. Partial response was defined as improved skin thickening in some areas but not all, and worsening or no improvement was recorded as resistant disease. Prognostic analyses were performed in patients who were seen within 1 year of diagnosis at our institution.

The study was approved by our institution's Institutional Review Board.

2.1 | Statistical analysis

Descriptive statistics (means, percentages, etc) were used to summarize the data. Kaplan-Meier methods were used to determine response and recurrence rates over time. Potential associations between baseline characteristics and complete response were examined using Cox models adjusted for age and gender. Time-dependent covariates were used to examine treatment effects. Analyses were performed using SAS version 9.4 (SAS Institute Inc) and R 3.4.2 (R Foundation for Statistical Computing).

3 | RESULTS

EF was diagnosed in 89 patients. The mean age at diagnosis was 51.5 years (range 12-78 years) (Table 1). The female-to-male ratio was 1:1. Median time to diagnosis from symptom onset was 6 months (range 1-45 months). The majority of patients (79; 89%) were diagnosed on the basis of clinical features and biopsy, 3 on clinical and MRI abnormalities, and 7 (8%) on clinical presentation alone. Suspected initial triggers for the diseases were serious illness (n = 1), L-tryptophan (n = 1) and vigorous exercise (n = 19). There were no patients who reported exposure to adulterated oil or infectious triggers. The disease course was rapidly progressive in 64 (83%).

Coexistent morphea was seen in only 3% of patients. Hematologic disorders were diagnosed in 9 patients (10%), including angio-immunoblastic T-cell lymphoma (2), T-cell large granular lymphocytic leukemia (1), acute lymphoblastic leukemia (1), chronic lymphocytic leukemia (1), aplastic anemia (1), lymphocytic-variant hypereosinophilia (1), low-grade lymphoproliferative disorder (1) and T-cell clonal arrangement (1). Diagnosis of hematologic disorder and EF was concurrent in 3 patients, made prior to EF in 3 patients (mean 28 months, range 1-48 months) and followed the diagnosis of EF in 3 (mean 19 months, range 14-26 months). One patient with angio-immunoblastic T-cell lymphoma treated 4 years earlier developed EF concurrent with recurrence of the disease.

TABLE 1 Baseline characteristics of 89 patients with eosinophilic fasciitis

Characteristic	Follow-up cohort (N = 38)	Total cohort (N = 89)
Age at diagnosis, y, mean (SD)	52.8 (14.8)	51.5 (16.2)
Gender, female	23 (61%)	44 (49%)
Length of follow-up, y, median (range)	2.2 (0.4-18.5)	2.2 (0.2-18.5)
Time from symptom onset to diagnosis, mo, median (range)	6.0 (1.0-45.0)	6.0 (1.0-45.0)
Groove sign, specifically mentioned in documentation	13 (34%)	26 (29%)
Peau d'orange, specifically mentioned in documentation	11 (29%)	22 (25%)
Myalgias	7 (18%)	10 (11%)
Muscle weakness	4 (11%)	9 (10%)
Inflammatory arthritis	6 (16%)	9 (10%)
Skin involvement of upper extremity	35 (92%)	82 (92%)
Skin involvement of lower extremity	34 (89%)	77 (87%)
Skin involvement of the trunk	13 (34%)	33 (37%)
Associated malignancy	7 (18%)	10 (11%)
Associated hematologic disorder	7 (18%)	11 (12%)
Laboratory values, n positive/n tested (%)		
Elevated ESR, >29 mm/1 h for females, >22 mm/1 h for males	11/33 (33%)	19/76 (25%)
Abnormal CRP, ≥8 mg/L	18/28 (64%)	36/61 (59%)
Eosinophilia, ≥0.5 × 10^9/mL or ≥7% of total leukocytes	21/36 (58%)	40/79 (51%)
Elevated aldolase, >7.7 units	6/15 (40%)	11/36 (31%)
Polyclonal hypergammaglobulinemia	9/29 (31%)	16/56 (29%)
Elevated ANA, titer ≥1:320 and/or ELISA ≥3 units	4/38 (11%)	7/72 (10%)
Anti-dsDNA	0/11 (0%)	1/23 (4%)
Anti-SSA	1/36 (3%)	2/68 (3%)
Anti-SSB	1/36 (3%)	2/67 (3%)
Anti-Smith	0/36 (0%)	1/66 (2%)
Anti-RNP	1/36 (3%)	2/66 (3%)
Anti-Scl-70	1/38 (3%)	2/71 (3%)
ACPA	1/13 (8%)	4/22 (18%)
EMG consistent with inflammatory myositis	4/11 (36%)	6/18 (33%)

Abbreviations: ACPA, anti-citrullinated protein antibodies; ANA, antinuclear antibodies; CRP, C-reactive protein; dsDNA, double-stranded DNA; ELISA, enzyme-linked immunosorbent assay; EMG, electromyelogram; ESR, erythrocyte sedimentation rate; RNP, ribonuclear protein; SCL-70, scleroderma 70; SSA, Sjögren's syndrome A; SSB, Sjögren's syndrome B.

Other malignancies seen in 7 cases were melanoma (1), testicular seminoma (1), bladder (1), skin cancer (1), prostate (2), and thymoma (1). Concurrent autoimmune diseases occurred in 5 patients, namely, rheumatoid arthritis (2), eosinophilic enteritis (1), Sjögren's syndrome, Hashimoto and celiac disease (1), autoimmune neuropathy and Raynaud phenomenon (1).

3.1 | Physical exam, laboratory features and imaging

The upper extremities were involved in 82 (92%), and lower extremities in 77 patients (87%); truncal involvement was noted in 33 (37%). Isolated upper extremity involvement was seen in 8 (9%) and lower extremity involvement alone in 5 (6%). Groove sign was noted in 26 (29%), (Figure 1) and peau d'orange/dimpling-like changes in 22 (25%) patients. Nine patients (10%) had active inflammatory arthritis (oligoarticular in all) at the time of initial EF evaluation. Joint contractures occurred in 42 (47%).

The median absolute eosinophil count was 0.4 × 10^9/mL (range 0.0-14.4) and peripheral eosinophilia (defined as greater than 0.5 × 10^9/mL or 7% of total leukocytes) was noted in 40 patients (51%). Eleven patients (12%) received steroids prior to diagnosis. Eosinophil counts were available for 8 of these patients and elevated in all. Median ESR was 12.0 mm/1 h (range 0.0-122.0) and CRP 11.6 mg/L (range 0.0-108.3). Elevated ESR was seen in 19/76 (25%) and elevated CRP in 36/61 (59%). Creatine kinase and aldolase were elevated in 2/45 (4%) and 11/36 (31%), respectively. Serum protein electrophoresis (SPEP) showed hypergammaglobulinemia (gamma globulin >1.6 g/dL) in 19/56 (34%). Three of these patients had a monoclonal gammopathy. The monoclonal protein was IgM kappa in 1 patient and IgG kappa in 2 patients.

Low complement C3 (<75 mg/dL) was seen in 1/19 (5%) and low C4 (<14 mg/dL) in 2/20 (10%) patients. High titer positive antinuclear antibodies (≥1:320 or ≥3 units by enzyme-linked immunosorbent assay) was seen in 7/72 (10%), 2 of whom had a positive scleroderma-70 (Scl-70) and 2 had positive Sjögren's syndrome A (SSA) and Sjögren's syndrome B (SSB) antibodies. The titer of anti-Scl-70 was low at 1.4 units (normal <1). The treating physician did not feel there were any features of scleroderma and the clinical examination, biopsy and treatment response supported a diagnosis of EF. Anti-cyclic citrullinated protein antibody was tested in 22 patients and positive in 4 (including 1 with known rheumatoid arthritis).

MRI was performed on 18 patients. Findings included increased T2 signal in the superficial and deep fascia (16/18) and in the muscle (10/18). Electromyogram (EMG) was performed in 18 patients, and showed inflammatory myopathy in 6/18 (33%). Skin biopsies were available in 76 patients and only muscle biopsies in 3 patients. Histopathologic evidence of eosinophilia in subcutaneous tissue was noted in biopsy specimens from 42 patients (47%). Eleven patients had muscles biopsies, 9 consistent with inflammatory myopathy.

The mean time from symptom onset to diagnosis was 6.2 months (range 2-15) in patients with muscle weakness and not different from those without (8.6 months, range 1.0-45.0, P = .33).

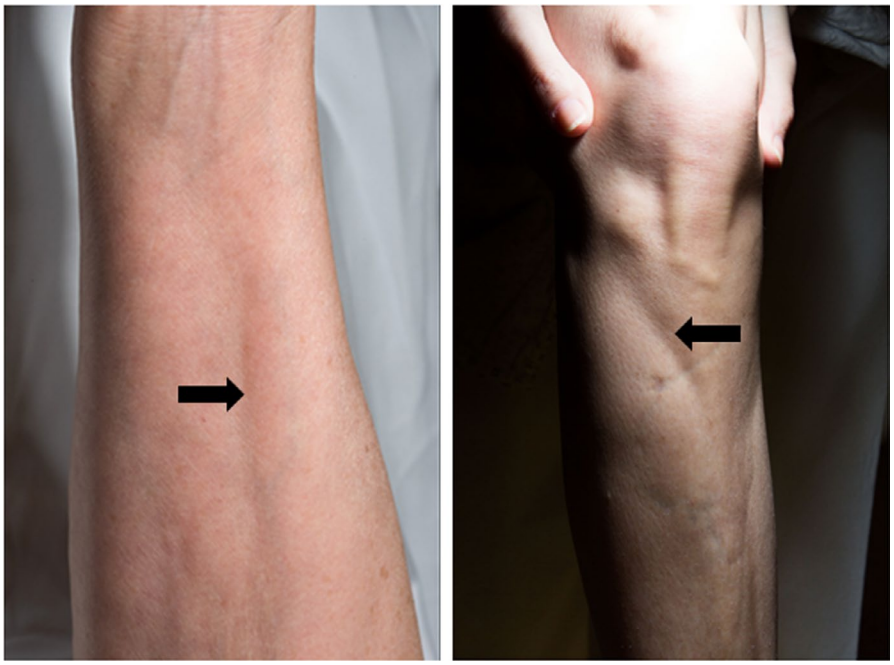

FIGURE 1 Groove sign: Fibrosis of connective tissue around the veins which spares the dermis and epidermis results in superficial layers of skin bowing inward (arrow) which is pronounced when the limb is elevated causing venous pressure to fall

3.2 | Treatment and follow-up

The median follow-up was 2.2 years (interquartile range 0.2-18.5) among 89 patients with at least 1 return visit. Of those, 38 were initially seen at our institution within 1 year of diagnosis, and were included in outcome and prognosis analysis. By 3 years, 60% (95% confidence interval [CI] 35-75) had achieved a complete response with resolution of skin thickening (Figure 2). Treatment included glucocorticoid monotherapy in 4 patients. Methotrexate was the most commonly used immunosuppressant in 79%, hydroxychloroquine in 45%, mycophenolate mofetil in 18% and azathioprine in 8%. The maximum dose of methotrexate was 20 mg once weekly (median, range 7.5-30 mg). At the last follow-up visit, complete response was seen in 39% on methotrexate, 44% on hydroxychloroquine, 67% on mycophenolate mofetil and 25% on azathioprine. No single immunosuppressant agent was associated with a superior response during treatment (Table 2).

Other agents that were used included imatinib (4), cimetidine (3), lefluonamide (2), sulfasalazine (2), and adalimumab, rituximab, intravenous immunoglobulin, dapsone, cyclosporine, thalidomide, everolimus and cyclosporine (1 each). Psoralen and ultraviolet A (PUVA) therapy were administered to 2, UVA-1 to 2 patients and extracorporeal photopheresis to 2. Of the patients treated with imatinib, 1 patient had no response, 1 patient stopped due to abdominal side effects, and 1 reportedly had a complete response.

Table 3 shows the prognostic factors tested for correlation with treatment remission. Elevated aldolase (hazards ratio [HR] 9.37, 95% CI 0.94-93.28), polyclonal hypergammaglobulinemia (HR 5.65, 95% CI 1.37-23.22) and h/o hematologic malignancy (HR, 10.20, 95% CI 2.08-49.93) showed a positive association with complete response with HR > 3, but this did not reach statistical significance. Symptom duration prior to diagnosis was inversely

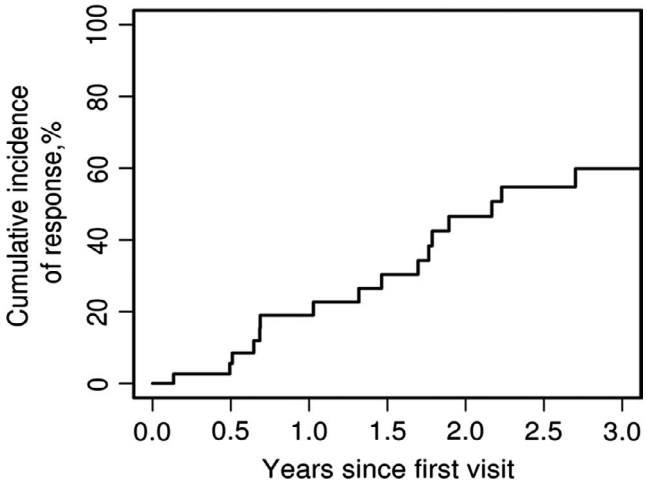

FIGURE 2 Cumulative incidence of complete response

associated with treatment response (HR 0.84 per 1 month increase; 95% CI: 0.73-0.98; P = .022). We did not find any association between the outcomes and age, arthritis, extent or type of skin involvement, elevated acute phase reactants, eosinophilia, and complement levels (data not shown). Eight patients died during the follow-up period. One patient died of a bowel perforation, and another from an apparent reaction to blood. Cause of death was not known for 6 patients.

4 | DISCUSSION

Prior to this study, most information about the features of EF was derived from small retrospective series, and disease rarity

TABLE 2 Association between treatments (time-dependent covariates) and first complete response/resolution (n = 18 events), first complete or partial response (n = 36 events) among 38 patients with follow-up at Mayo and initial presentation within 1 year of diagnosis of eosinophilic fasciitis

	Complete response		Complete or partial response	
Treatment	Hazard ratio[a] (95% CI)	*P* value	Hazard ratio[a] (95% CI)	*P* value
Exposure				
MTX	0.41 (0.14-1.19)	.10	1.01 (0.46-2.24)	.98
HCQ	0.75 (0.28-2.04)	.58	0.84 (0.41-1.72)	.63
MMF	0.74 (0.14-4.11)	.74	0.55 (0.19-1.64)	.29
AZA	0.43 (0.06-3.31)	.41	1.86 (0.54-6.42)	.33
Current use				
MTX	0.43 (0.16-1.15)	.09	0.75 (0.36-1.54)	.38
HCQ	0.59 (0.20-1.74)	.34	0.60 (0.27-1.33)	.21
MMF	1.01 (0.12-8.95)	.99	0.23 (0.03-1.81)	.16
AZA	—	.99	1.86 (0.54-6.42)	.33
MTX, HCQ, MMF or AZA	0.31 (0.10-0.91)	.033	0.55 (0.22-1.36)	.20

Abbreviations: AZA, azathioprine; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; MTX, methotrexate.

[a]Adjusted for age and gender.

TABLE 3 Association between risk factors of interest at initial presentation and first complete response (n = 18 events) among 38 patients with initial presentation within 1 year of diagnosis of eosinophilic fasciitis

Characteristic	Complete response Hazard ratio[a] (95% CI)
Age, per 10 y increase	1.01 (0.70-1.46)
Symptom duration from onset to diagnosis, per 1 mo increase	0.84 (0.73-0.98)
Inflammatory arthritis	2.30 (0.72-7.39)
Elevated ESR	1.46 (0.46-4.65)
Abnormal CRP	0.95 (0.34-2.63)
Eosinophilia[b]	0.87 (0.32-2.34)
Elevated aldolase >7.7 units	9.37 (0.94-93.28)
Polyclonal hypergammaglobulinemia	
vs normal SPEP – excluding not tested	3.25 (1.03-10.24)
vs normal – adjusted for testing ordering	5.65 (1.37-23.22)
EMG consistent with inflammatory myositis	1.67 (0.06-47.21)
Inflammatory myopathy on muscle biopsy	2.32 (0.61-8.84)
History of hematologic malignancy	10.20 (2.08-49.93)

Abbreviations: CRP, C-reactive protein (≥8 mg/L); EMG, electromyogram; ESR, erythrocyte sedimentation rate (≤29 mm/1 h for females, ≤22 mm/1 h for males); SPEP, serum protein electrophoresis.

[a]Adjusted for age and gender.

[b] ≥0.5×10^9/mL or ≥7% of total leukocytes.

makes identification of prognostic factors difficult. The present study, the largest EF cohort to date, was undertaken to describe clinical and laboratory features and determine prognostic factors for outcomes in EF. Although we did not find any features that significantly predicted complete response, a trend toward association of good outcome with polyclonal hypergammaglobulinemia, elevated aldolase and the presence of hematologic malignancy was noted. Hypergammaglobulinemia seen earlier in disease course normalizes during treatment; it can be speculated that elevated aldolase from muscle involvement may also cause patients to seek early attention. Alternately, these features may identify a subset of patients with heightened immune activation or biologic pathways associated with greater response to immunosuppressive (IS) therapy.

Some studies have shown treatment resistance in patients with hematological disorders unless the underlying blood disorder is corrected.[8] Hematologic malignancies that have been described include thrombocytopenic purpura, myelodysplastic syndrome, myeloproliferative disorder, multiple myeloma, Hodgkin disease, peripheral T-cell lymphoma, chronic lymphocytic leukemia, aplastic anemia and myelomonocytic leukemia. Aplastic anemia, the most common hematologic disorder associated with EF, is usually seen in older men. In a series of 23 patients, none achieved remission of EF when treated with corticosteroid monotherapy without also receiving therapy for aplastic anemia; 67% experienced remission or improvement of their EF after receiving first-line therapies for aplastic anemia.[9] However, not all studies have found an adverse prognostic implication of underlying hematological disorder.[10] In a review of 88 patients, no association of residual fibrosis with hematological disorder was noted.[11] How hematological disorders contribute to EF pathogenesis or resistance to recovery is not known. Postulated mechanisms include elaboration of cytokines by T cells like interleukin (IL)-3, IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF) that induce eosinophilia, common immune-mediated pathology with antibodies against hematopoietic stem cells and colony-forming

GM (CFU-GM), burst-forming unit-erythroid and CFU-erythroid and so on.

We show that diagnostic delay is associated with lower likelihood of response. Several series have shown adverse outcomes with delayed diagnosis. A diagnostic delay of >6 months was 14.7 times more likely to be associated with poor outcomes and in another study correlated negatively with physician assessment of damage (but did not reach statistical significance).[6,12] Wright et al[13] showed that treatment within 6 months of diagnosis generally led to better outcomes. The early inflammatory stage of EF may be treatment responsive, while late-stage fibrosis may be treatment resistant. Therefore, we interpret from the known pathogenesis and the observation that early diagnosis correlates with better outcomes that early disease recognition may improve patient outcomes. Imaging modalities like ultrasound, positron emission tomography (PET) and MRI may provide early diagnosis and assessment of disease activity.[14] Berianu et al reported a patient who had symptoms and signs affecting only the left side of the body, but MRI showed bilaterally symmetrical disease.[15] This indicates that MRI may show changes before they are clinically apparent and that the disease can be more extensive than appreciated on clinical exam. PET-computed tomography may have the advantage of excluding the rare chance of an underlying malignancy. The role of imaging in early diagnostic workup warrants further study. Dermal and subcutaneous sclerosis may be reversible in some patients and aggressive therapy should not be withheld even in patients presenting late.[16]

EF is usually treated with a combination of corticosteroids and IS or immunomodulatory medications. Steroid monotherapy and methylprednisolone pulses have been used with good responses.[6] However, a large study that included 64 patients from 3 centers showed more complete responses with the combination of glucocorticoids and methotrexate (64%) vs glucocorticoid monotherapy (30%) or with other combinations (29%).[13] We are unable to comment on responses to steroid monotherapy as the majority of our patients were on combination IS therapy. Methotrexate, hydroxychloroquine, azathioprine and mycophenolate mofetil were the commonly used IS agents and we did not find any particular agent to be superior. Use of any combination therapy showed a lesser likelihood of response which was not statistically significant. However, this finding is potentially influenced by channeling bias where patients with severe conditions tend to receive stronger therapy. Similar to our findings, in a retrospective series, treatment failures were higher in the IS group at 29% vs 12% in glucocorticoids alone and confounding by indication as discussed by the authors, could not be excluded.[6] Prospective studies are needed, guided by standardized protocols and better risk stratification, to determine the optimal combination therapy.

Two other studies have looked at factors affecting outcomes.[11,12] Increased CRP levels, neck and truncal involvement, prolonged time to remission, presence of dermal sclerosis, age <12 years and concurrent morphea, were associated with adverse outcomes. The presence of concurrent morphea is significantly lower in our series compared to others. This likely reflects differences in practice and diagnostic assessment. Our study included only adult patients. We did not find any prognostic associations with age, extent or type of skin involvement, elevated acute phase reactants, eosinophilia, or complement levels.

Our cohort is similar to previously described series in many ways. The average age of onset, prolonged time from symptom onset to diagnosis, and frequency of eosinophilia align with all other previously published cohorts.[4,6,12,13,15] The 1:1 female-to-male ratio seen here approximates the ratios reported by some,[4,6,15] although others have reported a female predominance closer to 2:1.[5,12,13,17] Inflammatory arthritis has been described as a clinical feature seen in EF, and was also seen in this cohort, although at a lower rate than in some previous reports.[4,5] Peripheral blood eosinophilia is not a consistent feature even in patients who have not been treated with glucocorticoids. CRP was elevated in a greater proportion than ESR. The reported rate of complete response is 60%-69% and similar in our study.

The histological features of a subset of these patients have previously been described in detail.[7] This study noted there were no pathognomonic histopathologic features of EF but rather features that may be supportive in the right clinical setting. There is considerable variability in biopsy features, which is based on the age of the clinical lesion biopsied, anatomic location from which it was derived, whether the patient has been treated or not, and so on. The present study was focused on clinical features, treatment and outcomes and it was beyond the scope of this study to assess histopathologic features.

Our study has limitations. The natural heterogeneity of the EF disease course and differences in treatment potentially obscure prognostic signals and conclusions regarding management. The lack of objective measures of disease activity for EF also made determination of disease trajectory ambiguous in some cases. In addition, the nature of our tertiary referral practice may have imparted selection bias. The rarity of EF has made it difficult to describe its full breadth of presentation, and to rigorously evaluate potential treatments. Prospective studies with standardized algorithms may decrease some of the heterogeneity, and allow for definition of additional prognostic factors.

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AUTHOR CONTRIBUTIONS

Robert L Mango, Kubra Bugdayli: study design, data acquisition, data analysis, manuscript writing. Cynthia S. Crowson: study design and data analysis. Lisa A. Drage, David A. Wetter, Julia S. Lehman, Margot S. Peters and Mark D Davis: study design, manuscript writing. Vaidehi R. Chowdhary: study design, data acquisition, data analysis, manuscript writing.

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