Letters

RESEARCH LETTER

Epidemiology and Treatment of Eosinophilic Fasciitis: An Analysis of 63 Patients From 3 Tertiary Care Centers

Eosinophilic fasciitis (EF) is a rare fibrosing disorder of the fascia characterized by erythema, edema, and induration of the bilateral extremities. Joint contractures and related functional limitation commonly occur owing to fascial involvement overlying the joints. Hematologic abnormalities, including peripheral eosinophilia and monoclonal gammopathy, may occur. Systemic corticosteroids are considered first-line therapy; however, prolonged treatment is frequently required in patients with EF, and a standardized therapeutic protocol is lacking.[1,2] Given the dearth of systematic data guiding treatment, we evaluated the presentation and clinical response of EF in 63 patients at 3 tertiary care centers.

Methods | After institutional review board approval from Partners HealthCare and New York University Langone Medical Center, we performed a search of the Partners Research Patient Data Registry (January 1, 1995-May 31, 2015; Brigham and Women's and Massachusetts General Hospitals) and 2 medical record databases at New York University Langone Medical Center (January 1, 2005-May 31, 2015), which together include more than 20 million patient visits. The search was based on the term *fasciitis* and EF-related *International Classification of Diseases, Ninth Revision* codes (728.89, 728.9, and 729.4). Data were extracted on patient demographics, disease presentation, treatment, and clinical response, defined as complete response (resolution of erythema and/or edema with no or minimal persistent induration), partial response (incomplete improvement of erythema, edema, and/or induration), or no response (lack of improvement). Each patient record, along with clinical photographs when available, was reviewed to ensure accurate diagnosis of EF. The 2 senior authors (A.N.F. and R.A.V.) independently confirmed the diagnosis of EF and assessment of clinical response. Categorical variables were compared using 2-tailed χ^2 tests, with $P \leq .05$ considered statistically significant. Analysis was conducted from October 1, 2014, to May 31, 2015.

Results | Of 1626 patients with fasciitis identified, 63 had confirmed EF (**Table 1**). Mean (SD) time from onset of EF to diagnosis was 11 (8) months. Seventy-nine percent of patients (37 of 47) were initially misdiagnosed, most frequently with systemic sclerosis (SSc), deep vein thrombosis, hypereosinophilic syndrome, or cellulitis. Most patients who were misdiagnosed with SSc underwent unnecessary evaluation for internal disease and failed to receive corticosteroids before the correct diagnosis. Four patients who were misdiagnosed with hypereosinophilic syndrome or eosinophilic leukemia underwent bone marrow biopsies and 1 patient received chemotherapy. Fifty percent of patients (31 of 62) had joint contractures, yet only 37% (23 of 62) were referred for physical therapy. In 28% of patients (8 of 29), trauma or intense exercise preceded the onset of EF. During a mean (SD) follow-up of 39 (43) months, complete response was more likely with the combination of corticosteroids and methotrexate (21 of 33 patients [64%]) compared with other treatment combinations (9 of 31 [29%]; $P = .006$), corticosteroid monotherapy (10 of 33 [30%]; $P = .007$), or treatment without corticosteroids (1 of 6 [17%]; $P = .03$) (**Table 2**). Complete response also occurred more frequently in patients diagnosed within 6 months of the onset of EF, but this finding was not statistically significant (10 of 15 [67%] vs 17 of 31 [55%]; $P = .45$).

Discussion | To our knowledge, this study represents the largest cohort to date of patients with EF and underscores the diagnostic and therapeutic challenge that EF presents. Frequent misdiagnoses likely accounted for the mean diagnostic delay of almost 1 year and resulted in unnecessary, invasive procedures and inappropriate treatments. Furthermore, many patients were undertreated; more than 10% of patients did not receive the standard of care with corticosteroids, and only 37% were referred for physical therapy despite the high rate of joint contractures.

The most common misdiagnosis was SSc, likely because both EF and SSc frequently present with induration of the extremities. Distinguishing these 2 conditions is imperative because corticosteroids are first-line therapy for EF, whereas corticosteroids are generally avoided in patients with SSc, given a potential association with renal crisis. Furthermore, visceral involvement in EF is generally limited to hematologic abnormalities, and thus an extensive systemic workup is not indicated as it is in SSc. Clinically, nailfold capillary changes and Raynaud phenomenon are typically absent in EF, unlike in SSc, and skin tightening on the distal digits is lacking. In addition, the groove sign (linear depressions along the course of veins), pseudocellulitic or peau d'orange skin, concurrent plaque morphea, and peripheral eosinophilia may be present in EF. As only 28% of patients in our study had a history of recent trauma or exercise, this criterion may play a more limited role in the etiology and thus diagnosis of EF than traditionally thought.[1,3] Diagnostic criteria for EF incorporating these characteristics have been recently proposed but remain to be validated.[3]

Although corticosteroids remain first-line therapy for EF, their prolonged use in this and 2 other large studies[1,2] demonstrates the need for corticosteroid-sparing therapy. In our study, combination therapy with corticosteroids and methotrexate, which may have corticosteroid-sparing effects,[4,5] portended a higher rate of complete response. Furthermore, our study supports the notion that early treatment of EF results in improved outcomes.[2]

Table 1. Demographics, Clinical Features, and Treatments of 63 Patients With Eosinophilic Fasciitis

Characteristic	Value[a]
Age at diagnosis, mean (SD), y (n = 58)	57 (15)
Sex	
Male	20 (32)
Female	43 (68)
Race (n = 51)	
White	47 (92)
Black	3 (6)
Asian	1 (2)
Method of diagnosis	
Biopsy and/or MRI	44 (70)
Expert clinical opinion	19 (30)
Distribution of disease	
Upper and lower extremities	44 (70)
Lower extremities only	16 (25)
Upper extremities only	3 (5)
Concurrent plaque morphea (n = 60)	21 (35)
Preceding trauma or intense exercise (n = 29)	8 (28)
Joint contractures (n = 62)	31 (50)
History of misdiagnosis (n = 47)	37 (79)
Time from disease onset to diagnosis, mean (SD), mo (n = 48)	11 (8)
Peripheral eosinophilia (n = 57)	33 (58)
Eosinophilia percentage, mean (n = 34)/AEC, mean, /μL (n = 33)	18.4/1500
Monoclonal gammopathy (n = 37)	6 (16)
ANA positivity (n = 46)	8 (17)
Treatment	
Corticosteroids	
Oral corticosteroids	56 (89)
Pulse methylprednisolone	7 (11)
Methotrexate	42 (67)
Mycophenolate mofetil	6 (10)
Hydroxychloroquine	12 (19)
Other[b]	48 (76)
No treatment	1 (2)
Physical therapy (n = 62)	23 (37)
Highest dose of oral corticosteroids, mean (SD), mg (n = 38)	51 (20)
Duration of oral corticosteroid use, mean (SD), mo (n = 34)	18 (26)
Follow-up, mean (SD), mo (n = 59)	39 (43)

Abbreviations: AEC, absolute eosinophil count; ANA, antinuclear antibody; MRI, magnetic resonance imaging.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Includes narrowband UV-B phototherapy (n = 6), doxycycline (n = 4), calcitriol (n = 4), adalimumab (n = 3), cimetidine (n = 3), etanercept (n = 2), imatinib (n = 2), rituximab (n = 2), colchicine (n = 2), extracorporeal photopheresis (n = 2), cyclosporine (n = 2), nonsteroidal anti-inflammatory drugs (n = 2), compression stockings (n = 2), calcipotriol (n = 2), intravenous immunoglobulin (n = 1), azathioprine (n = 1), sulfasalazine (n = 1), penicillamine (n = 1), psoralen UV-A phototherapy (n = 1), clopidogrel (n = 1), triamterene-hydrochlorothiazide (n = 1), clobetasol (n = 1), fluocinolone (n = 1), and halobetasol (n = 1).

Table 2. Clinical Response of Eosinophilic Fasciitis to Therapy

	Response, No. (%)		
Treatment	Complete	Partial	None
Corticosteroid monotherapy[a]	10 (30)	22 (67)	1 (3)
Combination therapy	30 (47)	27 (42)	7 (11)
Corticosteroids and methotrexate	21 (64)	12 (36)	0
Other combinations	9 (29)	15 (48)	7 (23)
No corticosteroids	1 (17)	2 (33)	3 (50)
Duration from disease onset to diagnosis, mo			
≤6	10 (67)	5 (33)	0
>6	17 (55)	14 (45)	0

[a] As only treatment or for at least 3 weeks before the initiation of combination therapy.

This study's limitations include its retrospective nature, the possibility of spontaneous resolution rather than therapeutic effect, and the fact that initial therapeutic intervention occurred at various disease stages, thereby complicating assessment of clinical response. Despite the small sample size, this study represents the largest cohort to date of patients with EF. Further investigation is needed to determine an appropriate treatment algorithm for patients with EF.

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