International Journal of
Rheumatic Diseases

International Journal of Rheumatic Diseases 2015; **18:** 91–98

ORIGINAL ARTICLE

Eosinophilic fasciitis: clinical characteristics and response to methotrexate

Florentina BERIANU, Marc D. COHEN, Andy ABRIL and William W. GINSBURG

Department of Rheumatology, Mayo Clinic, Jacksonville, Florida, USA

Abstract

Aim: To describe our experience with 16 patients with eosinophilic fasciitis (EF) treated in our clinic over 14 years.

Methods: We retrospectively reviewed the charts of all patients with biopsy-proven EF. We collected data regarding demographics, clinical presentations, possible triggers, labs, imaging, treatment and response to therapy on follow-up.

Results: Eight women and eight men with a mean age of 52 years were included in the study. Three patients related the onset to prior strenuous exercise and one was exposed to vibratory machinery. Fourteen patients had a gradual onset and presented with induration of the skin. Two other patients presented with acute-onset and significant edema and weight gain. All patients required immunosuppressive therapy. Methotrexate (MTX) was used in all of our patients. The rate of complete remission was ~60%. Although the recurrence rate after stopping MTX was 70%, these patients responded well to re-treatment with MTX.

Conclusion: We believe that MTX represents an effective treatment option for EF. The rarity of this disease would make a double-blind controlled trial study difficult to perform.

Key words: eosinophilic fasciitis, methotrexate.

INTRODUCTION

Eosinophilic fasciitis (EF) was first described in 1974 by Shulman in patients who presented with a scleroderma-like disease.[1] Since then, more than 300 cases have been reported. The largest retrospective study included 52 patients and was published in 1988.[2] More recently, smaller case series have been reported; one included 34 patients.[3] There is limited data in the literature regarding the response to therapy in patients with EF. The objective of this study is to describe the clinical features and the response to therapy of a series of patients with EF seen at a tertiary care center. We report our experience with 16 patients who were followed in the rheumatology department over 14 years.

Correspondence: William W. Ginsburg, MD, (Associate Professor of Medicine, Emeritus) 4500 San Pablo Road, Jacksonville, FL 32224, USA.
Email: Ginsburg.william@mayo.edu

PATIENTS AND METHODS

This study was approved by the Mayo Clinic Institutional Review Board. We used our institution's medical record diagnostic link system to identify patients treated at Mayo Clinic in Jacksonville, Florida, USA. We retrospectively reviewed the charts of all patients who were diagnosed with EF from January 1998 to December 2012. Sixteen patients with biopsy-proven EF who were followed and treated during that time were included. All patients underwent full-thickness skin to muscle biopsy to confirm the diagnosis. All patients were seen and followed by rheumatologists. The amount of skin involvement was clinically documented. We collected data regarding demographics, clinical presentations, possible

triggers, laboratory results, imaging, treatment and response to therapy.

Data collection

A data collection form was completed on all cases containing information on presenting symptoms and physical findings at the initial visit and at follow-up. All relevant laboratory investigations, radiological data and pathological results were recorded. Information on therapy, response to different medications, remission and relapses were all documented. Response to therapy was assessed as per treating physician and as documented in the charts. Complete remission was defined as a complete recovery, without any physical findings or symptoms. Relapses were defined as a recurrence of the disease on clinical grounds requiring reinitiation of therapy.

Statistical analysis

Descriptive statistics were used to summarize the data: percentage means. Response to therapy was reported in percentages of patients who went into remission and mean time until relapse.

RESULTS

We studied eight women and eight men aged 30–75 (mean age 52). None of the patients reported tryptophan intake. Three patients related the onset to prior strenuous exercise; one was exposed to heavy machinery and contact with vibrating surfaces associated with his work. No other potential triggers were identified in the rest of the patients.

Clinical characteristics

Fourteen patients described having a gradual onset with achiness, itching and swelling over the affected areas. Two patients reported a more acute onset over 1–2 weeks, and these cases were remarkable for significant weight gain: 14lbs and 17lbs = 6.35kg and 7.71kg respectively, in addition to peripheral edema. Half the patients reported fatigue and non-specific arthralgias with early morning stiffness; otherwise there were no other constitutional symptoms. Cutaneous involvement was reported in all patients. Ten patients had peripheral edema at presentation. Fourteen patients had induration of the skin. Eight had typical peau d'orange with dimpling of the skin and this was usually associated with long-standing disease. The demographics and clinical characteristics are shown in Tables 1 and 2. Seven patients had involvement of the dorsum of the hands with relative sparing of the fingers. In seven patients, the dorsa of the feet were involved. Fourteen patients had both arm and leg involvement. One patient had only arms and another had involvement of only his legs. One patient presented initially with limited involvement of the arms, and after initial remission, had a recurrence involving only the legs. The majority

Table 1 Patient characteristics

Patient	Sex	Age at onset	Time to diagnosis (months)	Type of onset	Peripheral edema	Induration/ peau d'orange	Raynaud's phenomena	Extent of skin involvement
1	F	75	8	Gradual	–	+/+	–	Arms, legs, chest, hands, feet
2	F	57	3	Gradual	+	+/–	–	Arms, legs, abdomen, hands, feet
3	F	75	12	Gradual	–	+/+	–	Arms, legs, chest, abdomen
4	M	33	5	Gradual	–	+/+	–	Arm, legs, hands, feet
5	M	62	2	Gradual	+	+/–	–	Arms, legs, chest, abdomen, feet
6	M	61	6	Gradual	+	+/+	–	Arms, legs, hands
7	F	53	3	Gradual	+	+/–	–	Arms, legs, neck, chest, abdomen
8	F	46	< 1	Acute	++	–/–	–	Arms, legs
9	M	36	4	Gradual	+	+/–	–	Arms, legs, abdomen, hands, feet
10	M	59	7	Gradual	+	+/+	–	Arms, legs, chest, feet
11	M	45	< 1	Acute	++	–/–	–	Arms, legs
12	M	41	8	Gradual	+	+/+	–	Arms, hands, abdomen, hands, feet
13	M	59	9	Gradual	–	+/+	–	Arms, legs, chest
14	F	30	1	Gradual	+	+/–	–	Arms, legs
15	F	51	2	Gradual	–	+/–	–	Arms, legs, abdomen
16	F	52	7	Gradual	–	+/+	+	Legs

Table 2 Clinical features

Patient	Localized morphea	Synovitis	Tendon contracture	Visceral involvement	Fatigue	Arthralgia
1	+	–	Wrist, elbow	–	+	–
2	–	–	Wrist	–	+	–
3	+	–	Wrist	–	–	–
4	–	–	–	–	–	+
5	+	–	–	–	+	+
6	–	–	Elbow	–	–	+
7	+	–	–	–	+	–
8	–	–	–	–	–	–
9	+	–	–	–	+	+
10	+	–	Knee, ankle	–	–	–
11	–	–	–	–	+	+
12	–	–	–	–	+	–
13	+	–	–	–	–	+
14	–	+	–	–	–	+
15	+	–	–	–	+	+
16	–	+	Achilles	–	–	–

of the patients had asymmetric involvement of the extremities. One patient had symptoms and skin findings limited to the left side of the body. Seven patients had involvement of the abdominal wall and six had chest lesions. Localized morphea lesions were also described in eight patients. Morphea presented as circumscribed areas of plaques involving one or two areas of the body. Morphea could be present at the time of diagnosis or appear later on. The diagnosis was made on the clinical features. Only one patient had Raynaud's phenomena without telangiectasia or sclerodactyly, and nailfold capillaroscopy was normal. None had visceral involvement. Flexion contraction with limited range of motion were noted at wrists in three patients, elbows in two patients, ankles in one patient, knees in one patient, and severe contraction of Achilles tendon was reported in one patient. Synovitis of the small joints of the fingers which presented in similar fashion as rheumatoid arthritis (RA) was noted in two patients. Five patients had clinical symptoms and electromyograph indicating carpal tunnel syndrome, and one had severe bilateral ulnar neuropathy.

Laboratory, imaging and pathological results

Although non-specific for EF, the majority of patients had elevated peripheral eosinophils. In nine patients, the absolute eosinophils values ranged from 1050 to 4800 cells/μL (normal less 350 cells/μL). In three patients, these values were within the normal limits, and in four patients, the values were not documented prior to steroid therapy. Inflammation markers were mildly elevated in half the patients; these are outlined in Table 3. With therapy, the absolute eosinophil count and the inflammation marker values had normalized in all affected patients before clinical improvement became obvious. Most of the patients had negative serology for a connective tissue disease (CTD) or vasculitis. However, two patients were noted for low titer anti-nuclear antibodies (ANA). One had mild elevation of citric citrullinated peptide (CCP) and mild positive rheumatoid factor (RF). This patient had synovitis and was also diagnosed with RA. Eight patients had documented polyclonal hyper-gammaglobulinemia, but no monoclonal gammopathy. Lyme serology was negative in 11 patients and were not checked in five patients. Aldolase values of 9.3–18 units/L (normal < 8 units) were documented in four patients and all of them had normal creatine kinase (CK) values. Only one patient had an elevated CK. It was 1000 units/L (normal: 38–176 units/L) on one occasion, but that occurred after vigorous exercising.

Magnetic resonance imaging (MRI) of the affected extremities was performed in all 16 patients, and all had fascial enhancement. Interestingly, the patient with only left-side involvement clinically had MRI findings that were remarkable for bilateral symmetric involvement (Fig. 1).

Biopsy was positive for fasciitis in all 16 cases with a lymphocytic infiltrate, and 10 of the cases also had an eosinophilic infiltrate (Fig. 2).

Treatment

Thirteen patients were initially placed on prednisone: eight patients on prednisone alone, three on predni-

Table 3 Laboratory values

Patient	Peripheral eosinophils (normal < 350 cells/μL)	CTD serology (ANA < 1 units, RF < 14 units)	Markers of inflammation (normal CRP < 8 units; ESR < 29 mm/h)	Aldolase (normal < 7.6 units/L)	Hyper gamma-globulinemia	Lyme serology	MRI fascial enhancement	Biopsy-proven
1	1050	Negative	CRP 30.6; ESR 9	12.3	+	NA	+	+
2	1258	ANA 1.4	CRP 38.8	8.7	+	–	+	+
3	Normal	Negative	Normal	Normal	–	NA	+	+
4	NA	NA	NA	NA	NA	NA	+	+
5	1450	Negative	CRP 8.2	Normal	+	–	+	+
6	1150	Negative	Normal	Normal	+	–	+	+
7	Normal	Negative	Normal	Normal	–	–	+	+
8	2100	Negative	CRP 40.3;ESR 63	13	+	–	+	+
9	1989	Negative	CRP 27	Normal	+	–	+	+
10	1920	ANA 2.4	Normal	Normal	+	–	+	+
11	4800	Negative	CRP 26	9.8	–	–	+	+
12	NA	NA	NA	NA	NA	NA	+	+
13	NA	Negative	NA	NA	NA	NA	+	+
14	1356	Negative	Normal	Normal	+	–	+	+
15	NA	CCP 35.1; RF 18	CRP 24.8	Normal	–	–	+	+
16	Normal	Negative	Normal	Normal	–	–	+	+

CTD, connective tissue disease; ANA, antinuclear antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; NA, not available; CCP, cyclic citrullinated peptide.

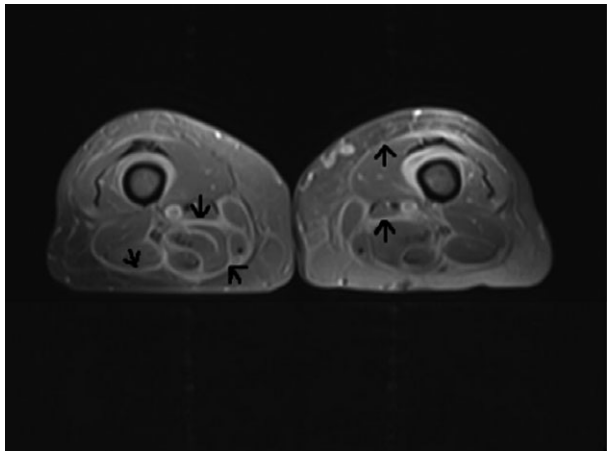

Figure 1 Axial T1-weighted post-contrast magnetic resonance imaging with fat-saturation obtained through the level of the mid-thighs. Abnormal diffuse thickening and enhancement of fascial planes is evident bilaterally, consistent with fasciitis. The closed arrows show the thick and enhanced fascia surrounding the muscles.

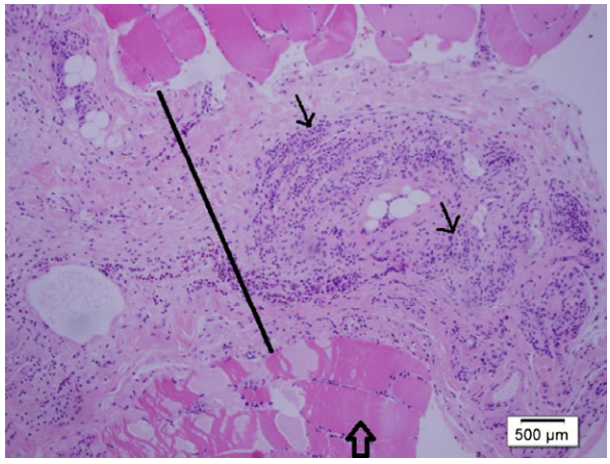

Figure 2 Photomicrograph of fascia–skeletal muscle junction shows markedly thickened fascia with heavy inflammatory infiltration. At the closed arrow, mononuclear inflammatory infiltrate is seen primarily in the fascia. The open arrow shows muscle spared of inflammation. The line shows thick, inflammed fascia.

sone in combination with azathioprine and two patients on a combination of prednisone and hydroxychloroquine. These patients had an initial response to prednisone, but it could not be tapered without recurrence of the symptoms, so they were then placed on methotrexate (MTX). Two patients were initially started on MTX and prednisone. One patient with diabetes was started on MTX alone. Thirteen patients were able to taper off their prednisone treatment within 10–33 months (mean 14.5 months) after starting MTX.

A clinical response with decrease in skin induration was usually not seen until about 6 months of therapy. Regrowth of hair sometimes was first noted prior to loosening of the skin, although the edema in the extremities responded quickly to prednisone.

After initiation of MTX therapy, nine patients achieved complete remission within 12–84 months of therapy (mean 31.4 months). Three patients maintained complete remission and were off all medication at 12–36 months follow-up. Six patients had relapse of the disease after stopping MTX therapy within 7–36 months (mean 27.1 months); these are outlined in Table 4. All of the relapses responded to MTX therapy once it was restarted.

DISCUSSION

In patients who present with skin induration that resembles a scleroderma-like disorder, without Raynaud's phenomena or internal organ involvement, a clinician should consider the diagnosis of eosinophilic fasciitis.

In its early phase, the disease is characterized by edema. In a few patients with acute onset, a significant weight gain over the course of 1–2 weeks has been noted. These patients were also noted to have significant hypereosinophilia and a quick response to the initiation of steroid therapy with weight loss and improvement of the edema. Cellulitis and angioedema are in the differential diagnoses in this early phase of acute onset with edema. Clinical course, response to appropriate therapy and ultimately the full thickness skin to muscle biopsy will help to establish the correct diagnosis.

In patients with insidious onset or in whom therapy was not initiated, the skin changes usually evolved from edema to induration of the skin and later to the appearance of peau d'orange appearance. At these stages, a significant number of patients can present with tendon contracture and entrapment neuropathy as outlined in our study and noted in previous publications.[2,4]

The disease has a symmetric involvement in the majority of cases, but clinically we have seen a case of asymmetric presentation. Interestingly, MRI fascial enhancement in this patient involved the limbs in a symmetric fashion. Fifty percent of our patients presented with concomitant morphea plaques. This association has been described in the literature with morphea lesions noted in about 30% of patients with EF.[2,3,5] There is controversial literature classifying EF under the

Table 4 Medications

Patient	Medication prior to MTX	Steroids dose when MTX was started (mg)	Off steroids (months)	Complete remission on MTX (months)	Off/on MTX (months)	Clinical response	Other medications added
1	HCQ/prednisone	30	10	24	Off at 36	Complete remission	
2	Prednisone	40	10		On at 24	Improved	
3	Prednisone	40	24	30	Off at 36	Complete remission	
4	Prednisone started the same time with MTX	60	4	12	Off at 22	Complete remission	
5	AZT/prednisone	5	22	7 years	On at 14 years for recurrence	Recurrence after 3 years	
6	HCQ/prednisone	20	12	48	On for recurrence	Recurrence after 7 months	
7	HCQ/prednisone	30	11	24	On at 10 years for recurrence	Recurrence after 2 years	
8	Prednisone	30	13	18	On for recurrence	Recurrence after 2 years	
9	Prednisone	20	On at 8 months		On at 8	Improved	
10	Prednisone	40	33		On at 5 years	Improved	
11	Prednisone	40	6	19	On for recurrence	Recurrence after 2 years	
12	Prednisone	40	25	24	On for recurrence	Recurrence after 3.5 years	
13	Prednisone started the same time with MTX	40	9		On at 4 years	Improved	
14	None				On at 24	Improved	Enbrel
15	Prednisone	30	10		On at 38	Improved	Humira
16	AZT/prednisone	10	On at 4 years		On at 4 years	Improved	

MTX, methotrexate; HCQ, hydroxychloroquine; AZT, azidothymidine.

spectrum of morphea. Terms like generalized morphea or deep morphea have been used sometimes to describe patients with EF, especially in dermatology. Also, there are case reports of patients with co-existent lesions of EF and deep morphea.[5–8] All our patients presented with superficial morphea lesions and they responded to therapy with steroids and MTX used to treat EF. The two conditions can be differentiated easily on the clinical ground that EF has a more acute, symmetric onset and, if left untreated, will turn to the appearance of peau d'orange in contrast to morphea that starts as white plaques and evolves to hyperpigmented lesions in later stages. The histology in morphea will demonstrate sclerosis and collagen deposition involving the skin. Deep morphea may show inflammation in the fascia and muscle with characteristics found in EF. Clinical features of EF histology consistent with fasciitis that spare the skin will help to differentiate the two conditions.

There are no specific laboratory abnormalities for EF, but it has been reported that significant eosinophilia can occur early at the onset in the majority of patients.[2,3] Eosinophilia resolves quickly with the initiation of therapy. Hypereosinophilia was noted prior to the recurrence of the disease in only one patient. The eosinophil count was not elevated prior to recurrence in the other cases. When hypereosinophilia occurs it may be a useful marker to predict recurrence. Polyclonal hypergammaglobulinemia was also a common finding. Previous publications have found other hematologic disorders associated with EF in 10% of patients.[2] Other laboratory findings include normal serologies for CTD. Two of our patients presented with polyarthritis and had objective synovitis on clinical examination. One of these patients also had positive anti-CCP and was also diagnosed with RA. In these two patients, we added anti-tumor necrosis factor therapy to better control the arthritis, which resulted in a significant improvement of EF symptoms. Aldolase was increased in four of our patients with normal CK values. These patients did not report myalgias and MRI findings were not suggestive of an inflammatory myopathy.[9]

Magnetic resonance imaging is helpful in assessing patients with EF. Increased T2 signal in fascia with enhancement, and increased signal on fat-suppressed T1 images after gadolinium administration are highly suggestive of EF.[10,11]

CONCLUSION

When EF is clinically suspected, the MRI findings will support the diagnosis, but it should always be confirmed by a fascial biopsy. This will require an elliptical full thickness biopsy of skin and subcutaneous tissue down to the muscle surface.

The best therapy known remains steroids and the majority of cases require immunosuppressive therapy.[2,3,12,13] In our experience MTX seems a viable option for EF. The rate of complete remission in our cohort was about 60%, but the recurrence rate was high at 70%. These patients responded well to re-treatment with MTX. These findings are in agreement with the French experience in a cohort of 34 patients: 86% of patients were treated with MTX and a remission rate of 69% was reported.[3] Ours is a small-scale cohort study and it is retrospective. The rarity of this disease would make a double-blinded randomized controlled trial difficult to perform.

ACKNOWLEDGEMENTS

The authors would like to thank Kelly Viola, ELS and Alison Dowdell for their editorial assistance.

CONFLICTS OF INTEREST

None.

FUNDING

None.

AUTHOR CONTRIBUTIONS

All authors participated in all stages of the study and preparation of the manuscript and approved the final draft.

REFERENCES

1 Shulman LE (1975) Diffuse fasciitis with eosinophilia: a new syndrome? *Trans Assoc Am Physicians* **88**, 70–86.
2 Lakhanpal S, Ginsburg WW, Michet CJ, Doyle JA, Moore SB (1988) Eosinophilic fasciitis: clinical spectrum and therapeutic response in 52 cases. *Semin Arthritis Rheum* **17** (4), 221–31.
3 Lebeaux D, Frances C, Barete S *et al.* (2012) Eosinophilic fasciitis (Shulman disease): new insights into the therapeutic management from a series of 34 patients. *Rheumatology (Oxford)* **51** (3), 557–61.
4 Huppke P, Wilken B, Brockmann K, Sattler B, Hanefeld F (2002) Eosinophilic fasciitis leading to painless contractures. *Eur J Pediatr* **161** (10), 528–30.

5 Bielsa Marsol I (2013) Update on the classification and treatment of localized scleroderma. *Actas Dermosifiliogr* **104** (8), 654–66.
6 Peterson LS, Nelson AM, Su WP (1995) Classification of morphea (localized scleroderma). *Mayo Clin Proc* **70**, 1068–76.
7 Miller JJ 3rd (1992) The fasciitis-morphea complex in children. *Am J Dis Child* **146** (6), 733–6.
8 Odhav A, Hoeltzel MF, Canty K (2014) Pansclerotic morphea with features of eosinophilic fasciitis: distinct entities or part of a continuum? *Pediatr Dermatol* **31** (2), e42–7.
9 Nakajima H, Fujiwara S, Shinoda K, Ohsawa N (1997) Magnetic resonance imaging and serum aldolase concentration in eosinophilic fasciitis. *Intern Med* **36** (9), 654–6.
10 Ronneberger M, Janka R, Schett G, Manger B (2009) Can MRI substitute for biopsy in eosinophilic fasciitis? *Ann Rheum Dis* **68** (10), 1651–2.
11 Moulton SJ, Kransdorf MJ, Ginsburg WW, Abril A, Persellin S (2005) Eosinophilic fasciitis: spectrum of MRI findings. *AJR Am J Roentgenol* **184**, 975–8.
12 Bischoff L, Derk CT (2008) Eosinophilic fasciitis: demographics, disease pattern and response to treatment: report of 12 cases and review of the literature. *Int J Dermatol* **47** (1), 29–35.
13 Khanna D, Agrawal H, Clements PJ (2010) Infliximab may be effective in the treatment of steroid-resistant eosinophilic fasciitis: report of three cases. *Rheumatology (Oxford)* **49** (6), 1184–8.