Clinicopathologic and immunophenotypic features of eosinophilic fasciitis and morphea profunda: A comparative study of 27 cases

Oluwakemi Onajin, MD,[a] Carilyn N. Wieland, MD,[a,b] Margot S. Peters, MD,[a,b] Christine M. Lohse, MS,[c] and Julia S. Lehman, MD[a,b]
Rochester, Minnesota

Background: Eosinophilic fasciitis (EF) and morphea profunda (MP) are inflammatory and sclerosing disorders of the subcutis that can exhibit clinical and pathologic presentations that overlap.

Objective: To identify clinicopathologic features that can be used to distinguish EF from MP.

Methods: We performed a retrospective review of 16 patients with EF and 11 patients with MP. Hematoxylin-eosin, CD123, CD34, and Verhoeff-Van Gieson stains were evaluated on skin biopsies that included the fascia.

Results: EF patients were more likely than MP patients to be men ($P = .047$), have forearm involvement ($P = .003$), and have peripheral eosinophilia ($P < .01$). Compared with MP patients, patients with EF were more likely to have fascia that contained eosinophils ($P = .003$), although eosinophils were absent in 3 (19%) patients with EF. Focal absence of CD34 staining was more prominent in the fascia of EF patients ($P = .04$). The extent of Verhoeff-Van Gieson staining did not differ between the 2 groups. Dermal sclerosis was not detected in many cases of EF and MP (56% and 36%, respectively).

Limitations: This was a retrospective study at a single institution.

Conclusion: Although EF and MP share clinical and pathologic features, our results indicate that the presence of eosinophils in the blood and fascia and focal loss of CD34 staining might be more suggestive of EF than MP. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2017.06.148.)

Key words: dermatopathology; eosinophilic fasciitis; eosinophils; histopathology; immunohistochemistry; morphea profunda; sclerosing disorder.

Eosinophilic fasciitis (EF) and morphea profunda (MP) are inflammatory and sclerotic disorders of the subcutis that exhibit overlapping clinical and pathologic presentations. There is controversy as to whether EF and MP are distinct disorders or whether they fall within a spectrum.

Abbreviations used:

EF:	eosinophilic fasciitis
IL:	interleukin
MP:	morphea profunda
TGF:	tumor growth factor

From the Department of Dermatology,[a] and the Department of Laboratory Medicine and Pathology,[b] Mayo School of Graduate Medical Education, Mayo Clinic, Rochester; and Division of Biomedical Statistics and Informatics, Mayo School of Graduate Medical Education, Mayo Clinic, Rochester.[c]

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Correspondence to: Julia S. Lehman, MD, Department of Dermatology, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail: lehman.julia@mayo.edu.
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EF is a rare disorder involving sclerosis first described by Shulman in 1974.[1] It is classically characterized by acute onset of cutaneous edema and induration, often following vibrational or other repetitive trauma.[1,2] Laboratory evaluation often reveals peripheral eosinophilia, hypergammaglobulinemia, and an elevated erythrocyte sedimentation rate. The typical histopathologic finding for EF is lymphoplasmacytic inflammation involving subcutaneous fat septa, fascia, and sometimes muscle. Eosinophils might be a component of the inflammatory infiltrate but are not necessary for diagnosis of EF. The dermis often appears spared[3-6]; however, morphea-like plaques have also been described in patients with EF.[2,7-9]

MP is a type of morphea that primarily affects the deep dermis and subcutaneous fat but can extend into the fascia and muscle. During the inflammatory stage, perivascular, interstitial dermal, and subcutaneous septal spaces exhibit lymphocytes, plasma cells, and sometimes eosinophils. During the sclerotic stage, there might be minimal inflammation.[10-13]

We sought to describe the clinicopathologic features that distinguished cases of EF from those of MP. The features evaluated included the $CD123^{+}$ plasmacytoid dendritic cell population, expression of CD34, and elastic fiber patterns.

CAPSULE SUMMARY

- Distinguishing between eosinophilic fasciitis and morphea profunda can be difficult due to their similar clinical and histopathologic features.
- Our results indicate that the presence of eosinophils in the blood and fascia and focal loss of CD34 staining might be more suggestive of eosinophilic fasciitis.
- Accurate diagnosis of these diseases is needed because they might exhibit differing clinical courses, prognoses, and responses to treatment.

MATERIALS AND METHODS

Study design

With the approval of our institutional review board, we retrospectively reviewed the electronic medical records of patients clinically diagnosed with EF and MP from January 1992 through November 2015. We searched our electronic pathology (CoPath) database for the terms "eosinophilic fasciitis," "deep morphea," "morphea profunda," and "scleroderma" and found 235 cases. We reviewed the clinical charts of the 235 cases without reviewing the pathology, and identified 16 patients with EF and 11 with MP who had clinical features that fit well with classical descriptions of these diseases recorded in the electronic medical records. To avoid circular reasoning, we did not consider the histopathologic diagnosis when selecting the cases for this study.

The clinical criteria used to select EF cases included acute onset, erythema, edema, induration, peripheral blood eosinophilia, elevated inflammatory markers, polyclonal hypergammaglobulinemia, and associated vibrational or strenuous exercise. The clinical criteria used to select MP cases included indolent onset of skin tightening and lack of clinical evidence of systemic sclerosis, sclerodermoid graft-versus-host disease, or EF.

We excluded patients with scleroderma and cases with ambiguous or overlapping clinical features. A board-certified dermatopathologist reviewed all available hematoxylin-eosin stained slides and excluded cases in which the biopsy specimen did not include the fascia.

Data collection

We collected data on patient demographics, clinical presentation, and laboratory data including peripheral blood eosinophilic count, erythrocyte sedimentation rate, serum protein electrophoresis, and antinuclear antibodies whenever available.

Histopathologic, histochemical, and immunophenotypic data

Hematoxylin-eosin stained sections 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. The slides were reviewed by a board-certified dermatopathologist (Dr Lehman) who was blinded to the clinical diagnoses.

Statistical analysis

Features of EF and MP were compared by using *P* values obtained from 2-sample t, Wilcoxon rank sum, chi-square, or Fisher's exact tests. Statistical analyses were performed with statistical analysis software (SAS) package version 9.4 (SAS Institute Inc, Cary, NC). All tests were 2-sided and *P* values $<.05$ were considered statistically significant.

RESULTS

Patient demographics and clinical presentations

Twenty-seven patients were included in the study: 16 with EF and 11 with MP (Table I). The

Table I. Comparison of clinical features of patients with eosinophilic fasciitis and morphea profunda

	Eosinophilic fasciitis, N = 16	Morphea profunda, N = 11	
Feature	**N (%)***	**N (%)***	***P* value**
Age at diagnosis, years, mean ± SD	60.6 ± 12.4	49.4 ± 16.9	.057
Duration of symptoms, months, mean ± SD	6.4 ± 8.2	24.7 ± 34.5	**.035**
Sex			
Female	6 (38)	9 (82)	**.047**
Male	10 (63)	2 (18)	
History of increased activity	5 (31)	0 (0)	.060
History of edema	15 (94)	6 (55)	**.027**
Anatomic location†			
Lower legs	15 (94)	9 (82)	.55
Hands	2 (13)	3 (27)	.37
Trunk	7 (44)	4 (36)	1.0
Thighs	4 (25)	2 (18)	1.0
Forearms	15 (94)	4 (36)	**.003**
Arms	4 (25)	1 (9)	.62
Feet	1 (6)	3 (27)	.27
Hands, feet, or face	3 (19)	4 (36)	.39
Clinical appearance biopsy site†			
Induration	15 (94)	10 (91)	1.0
Erythema	4 (25)	1 (9)	.62
Hyperpigmentation	2 (13)	5 (45)	.084
Edema	3 (19)	3 (27)	.66
Sclerosis	1 (6)	3 (27)	.27
Hypopigmentation	0 (0)	2 (18)	.16
Peripheral eosinophilia	16 (100)	2 (18)	**<.001**
Elevated ESR (N = 16; N = 9)‡	7 (44)	5 (56)	.69
Hypergammaglobulinemia (N = 13; N = 9)‡	2 (15)	2 (22)	1.0
ANA positive (N = 14; N = 10)‡	2 (14)	3 (30)	.61
Dysphagia or GERD	3 (19)	3 (27)	.66
Raynauds	1 (6)	4 (36)	.13
Inflammatory arthritis	1 (6)	1 (9)	1.0
Steroid response (N = 12; N = 6)‡	11 (92)	5 (83)	1.0
History of autoimmune disease	3 (19)	1 (9)	.62
History of hematologic malignancy	4 (25)	2 (18)	1.0

Statistically significant *P* values are in bold.
ANA, Antinuclear antibodies; *ESR*, erythrocyte sedimentation rate; *GERD*, gastroesophageal reflux disease; *SD*, standard deviation.
*N (%) except where indicated.
†Patients might be listed in >1 category.
‡Feature contained missing data. Sample sizes for the 2 groups are listed in parentheses.

mean duration of symptoms before skin biopsy was significantly shorter in EF patients than in MP patients (EF 6.4 months, MP 24.7 months; $P = .035$). Ninety-four percent (15/16) of patients receiving a diagnosis of EF had edema as an initial presenting symptom compared with 55% (6/11) of patients receiving a diagnosis of MP. The most commonly affected anatomic locations were forearms and lower legs for EF (94%, 15/16) and lower legs for MP (82%, 9/11).

All 16 patients with EF had peripheral blood eosinophilia compared with only 18% (2/11) of patients with MP ($P < .001$). The erythrocyte sedimentation rate was elevated in 7 of 16 (44%) EF patients and 5 of 9 (56%) MP patients ($P = .69$). Hypergammaglobulinemia was present in 2 of 13 (15%) EF patients and 2 of 9 (22%) MP patients ($P = 1.0$). Antinuclear antibodies were present in 2 of 14 (14%) EF patients and 3 of 10 (30%) MP patients ($P = .61$).

Histopathologic and immunophenotypic analysis

The histopathologic and immunophenotypic features are summarized in Table II and Fig 1. The degree of inflammation was higher with EF than with MP ($P = .023$); abundant inflammation was found in 10 (63%) EF cases compared with 2 (18%) MP cases.

Table II. Comparison of histopathologic and immunophenotypic features among patients with eosinophilic fasciitis and morphea profunda

Feature	EF, N = 16, N (%)	MP, N = 11, N (%)	*P* value
Degree of inflammation			
Sparse	3 (19)	6 (55)	**.023**
Scattered	3 (19)	3 (27)	
Abundant	10 (63)	2 (18)	
Distribution of inflammation			
Perivascular	5 (31)	6 (55)	.26
Interstitial	11 (69)	5 (45)	
Level of inflammation*			
Fascia	15 (94)	7 (64)	.13
Fat	14 (88)	11 (100)	.50
Deep dermis	6 (38)	4 (36)	1.0
Mid-dermis	5 (31)	1 (9)	.35
Sup dermis	1 (6)	1 (9)	1.0
Any of the above	16 (100)	11 (100)	NA
Nature of inflammation			
Eosinophils only	1 (6)	0 (0)	.65
Mixed	12 (75)	7 (64)	
Plasmacytic	3 (19)	4 (36)	
Eosinophils in fascia			
None	3 (19)	7 (64)	**.003**
Sparse	4 (25)	4 (36)	
Scattered	4 (25)	0 (0)	
Abundant	5 (31)	0 (0)	
Plasma cells in fascia			
None	3 (19)	3 (27)	.49
Sparse	1 (6)	2 (18)	
Scattered	9 (56)	4 (36)	
Abundant	3 (19)	2 (18)	
Fascial edema			
Mild	8 (50)	6 (55)	.82
Prominent	8 (50)	5 (45)	
Level of sclerosis*			
Fascia	13 (81)	6 (55)	.21
Fat	12 (75)	7 (64)	.68
Deep dermis	7 (44)	7 (64)	.31
Mid-dermis	6 (38)	4 (36)	1.0
Sup dermis	1 (6)	1 (9)	1.0
Any of the above	14 (88)	9 (82)	1.0
Eccrine trapping			
No	10 (63)	6 (55)	.69
Focal	5 (31)	4 (36)	
Prominent	1 (6)	1 (9)	
CD123 fascia (N = 15; N = 11)†			
Sparse	6 (40)	8 (73)	.051
Scattered	4 (27)	3 (27)	
Abundant	5 (33)	0 (0)	
CD123 fat (N = 15; N = 11)†			
Sparse	10 (67)	10 (91)	.16
Scattered	4 (27)	1 (9)	
Abundant	1 (7)	0 (0)	
CD34 fascia			
Areas of negative staining	13 (81)	4 (36)	**.040**
Within normal limits	3 (19)	7 (64)	
VVG fascia			
Areas of near-complete absence	7 (44)	3 (27)	.53
Diminished elastin	4 (25)	4 (36)	
Normal elastin	5 (31)	4 (36)	
VVG fat			
Areas of near-complete absence	9 (56)	2 (18)	.066
Diminished elastin	5 (31)	6 (55)	
Normal elastin	2 (13)	3 (27)	

Statistically significant *P* values are in bold.
EF, Eosinophilic fasciitis; *MP*, morphea profunda; *NA*, not applicable; *VVG*, Verhoeff-Van Gieson.
*Patients might be listed in >1 category.
†Feature contained missing data. Sample sizes for the 2 groups are listed in parentheses.

The fascia from EF patients were more likely to contain eosinophils (Fig 2) than the fascia from MP patients ($P = .003$), although eosinophils were absent in the fascia from 3 (19%) EF patients. The focal absence of CD34 staining was more prominent in the fascia from EF ($P = .04$) than the fascia from MP patients (Figs 3 and 4). Fascia with inflammation, sclerosis, and CD123-positive cells were more often features of EF than MP, although the differences were not statistically significant. Sclerosis was more prominent in the deep dermis and subcutaneous fat septa of MP patients. There was no difference in elastic fiber staining patterns between EF and MP patients.

We checked to see if peripheral eosinophilia was associated with any histopathologic and immunophenotypic feature (Table III). Patients with peripheral blood eosinophilia were more likely to have a higher degree of tissue inflammation ($P = .001$) (which was predominantly in the fascia, $P = .03$), eosinophils in the fascia ($P = .004$), and focal loss of CD34 expression in the fascia ($P = .039$).

DISCUSSION

A widely used classification of localized scleroderma considers EF and MP to represent subtypes of deep morphea.[11] Whether these 2 diagnoses are distinct or fall along a spectrum remains unclear. Localized morphea-like lesions can be seen in one-third of patients with EF.[2,7-9]

The pathogenesis of EF is not well understood. Eosinophils degranulate and induce tissue damage,

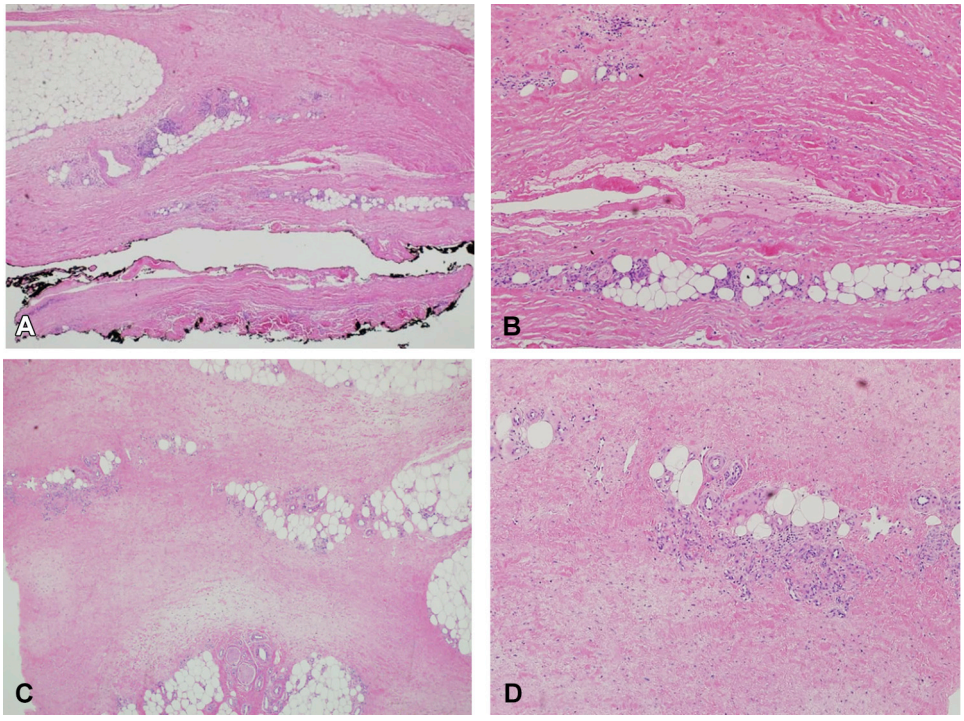

Fig 1. Eosinophilic fasciitis and morphea profunda. Low-power (**A**) and high-power (**B**) photos of eosinophilic fasciitis. Low-power (**C**) and high-power (**D**) photos of morphea profunda. (**A**-**D**, Hematoxylin-eosin stain; original magnifications: **A** and **C**, ×4; **B** and **D**, ×20.)

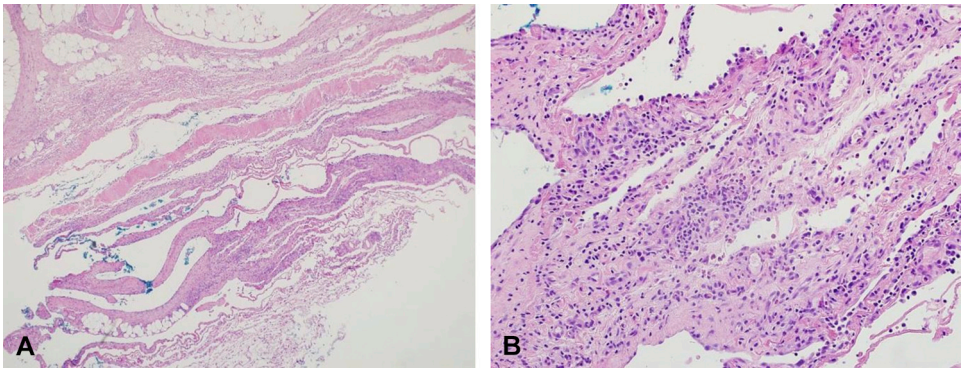

Fig 2. Eosinophils within the fascia of a patient with eosinophilic fasciitis. Low-power (**A**) and high-power (**B**) photos. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×4; **B**, ×40.)

which results in fibrosis via accumulation of extracellular matrix. Various studies have indicated that eosinophils interact with fibroblasts and express fibrogenic cytokines including tumor growth factor (TGF) α, TGF-β, interleukin (IL) 1, and IL-6.[14,15] Gomes et al proposed a model for the role of eosinophils in fibrogenesis through a study demonstrating that in vitro coculture of eosinophils with fibroblasts stimulates fibroblast production of IL-6, resulting in increased production of tissue inhibitor of metalloproteinase and inhibition of matrix metalloproteinases.[15] One study demonstrated higher levels of tissue inhibitor of metalloproteinase 1 in EF patients than in healthy controls.[16] Increased levels of TGF-β1 and IL-5 have been reported in a patient with EF.[17]

The pathogenesis of MP appears to be multifactorial, with implicated factors including trauma, therapeutic radiation, infection, autoimmunity, and microchimerism.[13]

Immunohistochemical studies using CD123 and CD34 antibodies have been performed with lesional skin from patients with morphea. These studies reported abundant expression of CD123 in the deep dermis and subcutis,[18] and decreased numbers of CD34-positive dendritic cells in the dermis.[19-22]

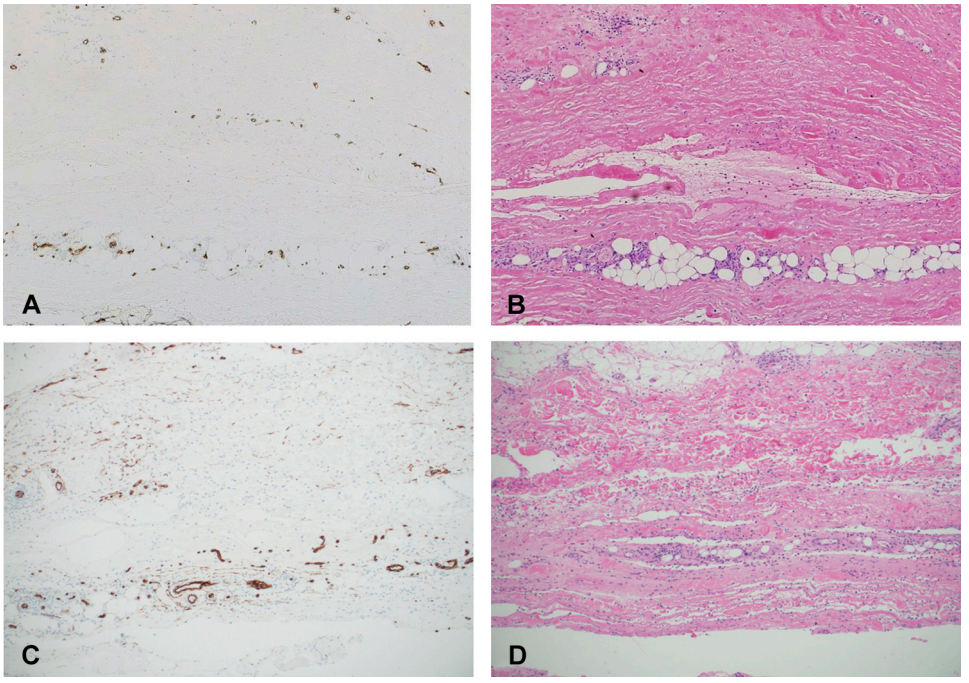

Fig 3. CD34 expression in 2 cases of eosinophilic fasciitis. High-power photo showing loss of cells expressing CD34. (**A** and **C**; original magnifications: **A**, ×20; **C**, ×20.) (**B** and **D**, Hematoxylin-eosin stain; original magnifications: **B**, ×20; **D**, ×20.)

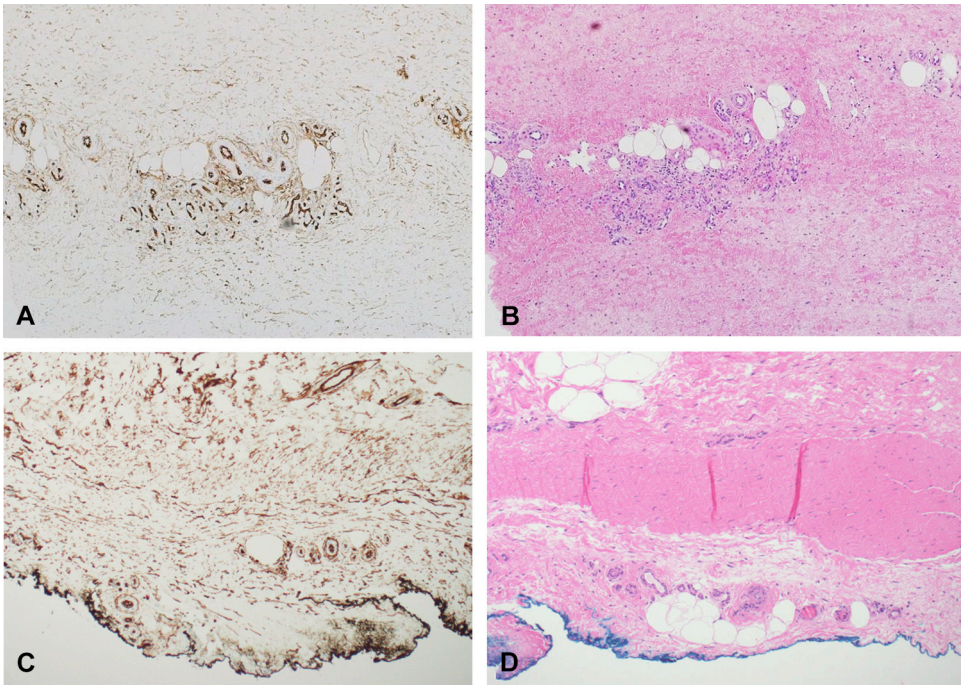

Fig 4. CD34 expression in 2 cases of morphea profunda. High-power photo showing CD34-positive cells. (**A** and **C**; original magnifications: **A**, ×20; **C**, ×20.) (**B** and **D**, Hematoxylin-eosin stain; original magnifications: **B**, ×20; **D**, ×20.)

Verhoeff-Van Gieson staining has demonstrated preservation of the elastic fibers in lesional skin of morphea.[22]

In our study, the mean duration of symptoms before obtaining a skin biopsy was shorter in patients with EF (6.4 months) than in patients with

Table III. Comparison of select features of patients with eosinophilic fasciitis or morphea profunda with and without peripheral eosinophilia

Feature	Peripheral eosinophilia: No, N = 9, N (%)	Peripheral eosinophilia: Yes, N = 18, N (%)	*P* value
Degree of inflammation			
Sparse	6 (67)	3 (17)	**.001**
Scattered	3 (33)	3 (17)	
Abundant	0 (0)	11 (67)	
Level of inflammation			
Fascia	5 (56)	17 (94)	**.030**
Eosinophils in fascia			
None	7 (78)	3 (17)	**.002**
Sparse	2 (22)	6 (33)	
Scattered	0 (0)	4 (22)	
Abundant	0 (0)	5 (28)	
Eosinophils in fascia			
None	7 (78)	3 (17)	**.004**
Sparse, scattered, abundant	2 (22)	15 (83)	
CD34			
Areas of negative staining	3 (33)	14 (78)	**.039**
Within normal limits	6 (67)	4 (22)	

Statistically significant *P* values are in bold.

MP (24.7 months). This might be due to the abrupt onset of symptoms in EF compared with MP. As a result, patients with EF might be more likely to seek medical care earlier in the course of their disease than patients with MP do. Patients given a diagnosis of EF were also more likely than those given a diagnosis of MP to have edema and involvement of the forearms. An early known symptom of EF is edema of the dermis, which eventually becomes *peau d'orange* in appearance and displays dimpling and induration.[2,6,23] Peripheral eosinophilia is a hallmark feature of EF, but in some cases, eosinophilia only transiently appears.[2] Although not a diagnostic requirement, all EF patients in our study had peripheral eosinophilia compared with only 2 of 11 (18%) MP patients.

In 1979, Barnes et al described the histopathologic features of 20 EF cases. They reported that in early phases of EF, the subcutis and deep fascia were edematous with a mixed inflammatory infiltrate consisting of lymphocytes, plasma cells, histiocytes, and eosinophils. As EF progressed, the subcutis, deep fascia, and even the dermis became sclerotic. They also observed that tissue eosinophilia occurred mostly in the lower subcutis and deep fascia.[4] In our study, skin biopsies from patients with EF showed a higher degree of tissue inflammation and eosinophilia in the fascia than the skin biopsies from patients with MP. It is important to note that tissue eosinophils were absent in 3 (19%) of the EF cases. Sclerosis of the fascia was more often found in cases of EF than MP. Because there was no dermal sclerosis in many cases of EF and MP (56% and 36%, respectively), our data emphasize the importance of obtaining deep biopsies that include the fascia for microscopic evaluation.

Immunohistochemical studies have previously been performed on lesional skin in patients with morphea. CD123, a marker for plasmacytoid dendritic cells, was found to be more abundant around blood vessels and between collagen bundles in the deep dermis and subcutis in lesional skin compared with nonlesional skin in patients with morphea.[18] A decreased number of $CD34^+$ dermal dendritic cells[19-22] and preservation of elastic fibers have also been demonstrated in the lesional skin of patients with morphea.[22] In our study, $CD123^+$ cells in the fascia was more likely to be a feature of EF than MP (although this was not statistically significant), and the focal decrease in the number of $CD34^+$ cells in the fascia was more prominent in skin biopsies from EF patients. In addition, peripheral blood eosinophilia was associated with a higher degree of tissue inflammation in the fascia, presence of eosinophils in the fascia, and decreased number of $CD34^+$ cells in the fascia. There was no difference in elastic fiber staining between patients with EF and MP. Our results do not support using these stains to differentiate between these 2 conditions.

The results from this study indicate that the presence of eosinophils in the blood and fascia and the focal loss of CD34 staining might be more suggestive of EF. In summary, a history of abrupt onset of symptoms coupled with histopathologic features of fascial sclerosis, lymphoplasmacytic inflammation, eosinophils in fascia and peripheral blood, and focal loss of CD34 favor a diagnosis of EF over MP. Accurate diagnosis is needed because these disease entities might have different natural histories, prognoses, and responses to treatment.

Limitations of our study include its retrospective design and small study size. Also, our study was based on subjective comparisons between EF and MP cases. Nevertheless, our observations demonstrate the importance of certain clinicopathologic features in the diagnosis of EF and MP.

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