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Clinicopathological profile of eosinophilic fasciitis: a retrospective cohort study from a neuromuscular disorder center in China

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Abstract

Objectives To characterize the clinical and myo-fascial histopathological features, along with long-term treatment outcomes of patients with eosinophilic fasciitis (EF).

Methods We performed a retrospective analysis of the clinical, serological, myo-fascial pathological features, as well as the long-term follow-up outcomes of EF patients between January 2011 and August 2023 at our neuromuscular disorder (NMD) center.

Results Seventeen patients were included, and a male predominance (12/17, 70.6%) was identified. The most common clinical manifestation was skin thickening (100%), always distal to the elbow and knee joints, occupied by limited joint mobility (12/17, 70.6%). The "prayer sign" was observed in 7 (41.2%) patients. Eosinophilia was identified in only 7 (41.2%) patients, including 6 in the blood and 3 in tissue. Anti-Ha antibody was confirmed in one patient (P17). Typical fascial edema with or without involvement of the adjacent subcutaneous tissues was exhibited on magnetic resonance imaging (MRI) in all 9 patients. The perifascicular pattern of MHC-I and/or MHC-II upregulation without MxA expression was identified in 56.3% (9/16) of the patients' muscle specimens. Typical perifascicular atrophy was identified in 4 patients. Complete recovery was noted in 5 patients, including 4 patients treated with prednisone as monotherapy, and 1 patient treated with prednisone combined with D-penicillamine.

Conclusions The "prayer sign" might be an important clinical feature of EF. Perifascicular upregulation of MHC-I and/or MHC-II but negative expression of MxA, with or without PFA, represents a unique pathological phenotype of EF. Most patients show favorable outcome following steroid monotherapy or in combination with immunosuppressants, underscoring the autoimmune pathogenic nature of this disease.

Keywords Eosinophilic fasciitis, Prayer sign, Muscle pathology, MRI, Long-term prognosis

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Introduction

Fasciitis, as the name implies, is a collective name for fascial disorders caused by a variety of inflammatory conditions. Necrotizing fasciitis is a life-threatening diffuse soft tissue infection that primarily affects the superficial fascia, which often requires prompt surgical management and aggressive antibiotics [1]. Macrophagic fasciitis is a localized long-lasting granulomatous response induced by the injection of aluminum-adjuvant vaccines [2]. Nodular fasciitis is a benign, self-limiting fibroblast proliferation of uncertain etiology, often occurs in the fascia or other soft tissues, which could occasionally be accompanied by calcification (known as "ossifying fasciitis") [3, 4]. As an initial and isolated presentation, fasciitis was also described in a IgG4-related case [5]. Lastly but most importantly, eosinophilic fasciitis (EF) is a common type of fasciitis, characterized by swelling and tightness of the skin, restricted joint mobility, and sometimes associated with peripheral eosinophilia, tissue eosinophilic infiltration and polyclonal hypergammaglobulinemia [6, 7].

EF was firstly described in two male patients by Shulman in 1974. Since then, there have been more than 300 reported cases, most of which were presented as scarce case reports or case series by the dermatologists or rheumatologists [8–13]. As it became more well-studied, it was found that blood eosinophilia or eosinophilic infiltration in tissue was present in only some patients or only during certain period of the disease [14]. The American College of Rheumatology has recommended in 1983 that it should be named as "diffuse fasciitis with or without eosinophilia" [15]. However, EF is still by far the most used name and will continue to be applied in this study.

A full thickness biopsy that demonstrates thickening and inflammatory infiltration in the skin and fascia is important supportive evidence for the diagnosis of EF [16, 17]. However, it will be difficult to distinguish EF from other scleroderma-like diseases if there are no eosinophils present on pathology, particularly at the late fibrosis stage [7]. It has been suggested that a surgical biopsy, including skin, subcutis, fascia and muscle, is the most ideal procedure for a comprehensive evaluation and diagnosis of EF [6, 11]. In fact, skeletal muscle involvement might not be rare in EF if open muscle biopsy is routinely performed, as shown in a few previous studies [14, 18, 19]. However, the conclusions of these studies varied. In addition, magnetic resonance imaging (MRI) could readily show fascial or muscle edema, and it is recommended as an effective tool for the diagnosis and monitoring of EF [9, 16, 20].

To expand the understanding of this cross-disciplinary disease, we analyzed the detailed clinicopathological characteristics and long-term treatment outcomes of 17 patients with EF diagnosed mainly through open muscle biopsy at our Neuromuscular Disorder (NMD) Center. We evaluated the myo-fascial pathological and MRI features and discussed the pathogenic mechanism of EF.

Methods

Patients

This is a retrospective observational study. Seventeen patients who were diagnosed with EF based on the commonly used diagnostic criteria [17] at our NMD center between January 2011 and August 2023 were consecutively enrolled. The clinical and laboratory information was collected from the medical notes. Medication adherence and treatment outcomes were obtained from both telephone follow-up and outpatient records. Treatment response criteria was adapted and modified from those employed in previous studies on EF and myositis [13, 21]: complete recovery (with no symptoms or signs of skin and joint involvement), marked improvement (by ≥ 60% improvement compared to the severest condition), moderate improvement (by ≥ 40% improvement compared to the severest condition), mild improvement (by ≥ 20% compared to the severest condition), no improvement (by < 20% improvement or lack of improvement in both skin and joint symptoms or signs).

Laboratory and instrumental examinations

Thirteen patients underwent blood cell count and creatine kinase (CK) tests. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) could be obtained in 13 and 16 patients, respectively. Fourteen patients have gone through the rheumatology screening. A complete panel of myositis-specific antibodies (MSAs) were also examined by immunoblot (Autoimmune Myositis Profile Antibody IgG Detection Kit, MyBiotech Co., Ltd, Xi'an, China, MT559) in 7 patients. Electromyography (EMG) was performed in all 17 patients. Bilateral muscle MRI was performed in 9 patients, including seven in the calf, four in the forearm, three in the thigh and two in the pelvic levels.

Histopathological examinations

Open muscle biopsies have been performed for diagnostic purpose in 16 patients, and 15 of the tissues contained fascia, while only 2 contained skin. Serial frozen sections of the muscle and fascia specimens were stained with hematoxylin and eosin (HE), anti- major histocompatibility complex class (MHC)-I rabbit monoclonal antibody (mAb, clone EP1395Y; Abcam), anti-MHC-II mouse mAb (clone CR3/43; Dako), anti-C5b-9 (MAC) mouse mAb (clone aE11; Dako), and anti-myxovirus resistance protein (MxA) rabbit polyclonal antibody (ab95926; Abcam), anti-CD3 mouse mAb (clone LN10; Zhongshan Golden Bridge Biotechnology), anti-CD4 mouse mAb (clone ZM-0418; Zhongshan Golden Bridge Biotechnology), anti-CD8 rabbit mAb (clone SP16; Zhongshan

Golden Bridge Biotechnology), anti-CD68 rabbit mAb (clone KP1; Zhongshan Golden Bridge Biotechnology), anti-CD31 mouse mAb (3528 S, Cell Signaling Technology). Formalin-fixed, paraffin-embedded skin tissue sections were stained with HE and anti-CD3 antibody, anti-CD4 antibody, anti-CD8 antibody and anti-CD68 antibody.

In regard to the pathological evaluation, the DM scoring system in previous studies was applied in the inflammatory domain [22]. Myofiber MHC-I and MHC-II expression was defined as sarcolemma staining, associated or not associated with sarcoplasmic staining. Four expression patterns were identified: (1) perifascicular pattern if the staining is limited to the perifascicular area; (2) diffuse pattern if the proportion of positive myofibers exceeded 80% of the entire slice field; (3) focal pattern if there was no specific localization; (4) mixed pattern if two or more patterns coexisted in one sample. Myofiber MxA expression was defined as sarcoplasmic staining of nonnecrotic myofibers. MAC deposition on the capillaries and sarcolemma of nonnecrotic myofibers was also recorded.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 10.2.0. Categorical variables are presented as frequencies and percentages. Continuous variables with a normal distribution are expressed as the mean ± standard deviation, while those with a skewed distribution are represented as the median and interquartile range [M(Q1, Q3)]. Fisher's exact two-tailed test was used to compare the categorical variables, and Mann-Whitney U test was applied to compare the inflammatory infiltration scores (CD3, CD4, CD8, CD68). Statistical analyses were carried out using GraphPad Prism version 10.2.0. P values of <0.05 were considered statistically significant.

Result

Clinical and laboratory findings

The detailed clinical and laboratory data of the 17 patients with EF were summarized in Table 1. There was a male predominance in this EF cohort (12/17, 70.6%). The mean age of onset was 38.8 ± 17.7 years, including 2 juvenile patients (P11 and P17).

The median time from the disease onset to muscle biopsy was 6 months with a range from 1 to 36 months. Predisposing factors could be traced back in none of our patients. Concomitant diseases were identified in 3 patients: Churg-Strauss syndrome (CSS) in P4, thrombocytopenia in P7 and papillary thyroid cancer in P12.

Skin thickening, often distal to the elbow and knee joints, could be observed in all of the patients, either bilateral (82.3%, 14/17) or unilateral (17.6%, 3/17). Limited joint mobility was always accompanied by skin thickening and could be noted in 12 (70.1%) cases, respectively. Upper extremities involvement (82.4%, 14/17, Fig. 1A) were more common than lower extremities involvement (64.7%, 11/17, Fig. 1B) in this cohort. The "prayer sign" could be identified in 7 (41.2%) patients (Fig. 1C, D), whereas the characteristic cutaneous manifestations, such as "groove sign" or "orange peel" were recorded in none of our patients. Myalgia was also complained by 82.3% (13/17) of the EF individuals. Peripheral eosinophilia was only identified in 6 out of 15 (40%) patients. ESR and CRP were elevated in 62.5% (10/16) and 53.8% (7/13) of the patients. CK was only mildly elevated in one patient (P12). Anti-nuclear antibodies (ANA) tested positive in 8 out of 14 individuals (57.1%), of whom one patient (P4) was identified with anti-perinuclear neutrophil cytoplasmic antibody (p-ANCA) and two patients (P8 and P16) with rheumatoid factor (RF) concomitantly. Anti-Ha antibody, one of the autoantibodies against the aminoacyl tRNA synthetase (anti-ARS), was identified in 1 (P17) of the 7 patients, which was further confirmed by the immunoprecipitation test (Supplemental Fig. 1). The EMG showed a normal pattern in 13 patients (76.5%), a myogenic pattern in 3 patients (17.6%), and a neuropathic pattern in only 1 patient (5.9%) with CSS. Typical fascial edema with or without involvement of the adjacent subcutaneous tissues could be observed with hyperintense short TI inversion recovery (STIR) signal in all nine patients (100%). The fascia just beneath the subcutis was usually preferentially involved rather than that lying between the muscle bundles (Fig. 2A-D). MRI could exhibit not only the symptomatic fascial inflammation, but also the non-symptomatic lesion sites as seen in P13 at the pelvic and thigh levels (Fig. 2A, B). In addition, the resolution of fascial and subcutaneous inflammation could be explicitly demonstrated on MRI as seen in P10 (Fig. 2E-H).

Histopathological features

The histopathological features of muscle biopsies from 16 patients (except P11) were summarized in Table 2. On skin pathology, both of the two patients (P8 and P12) showed sclerosis of the reticular dermis with excessive collagen deposition and scarce lymphocyte infiltration, but the papillary dermis and the epidermis were not affected (Fig. 3A). On muscle pathology, necrotic and regenerative fibers were only seen in 2 out of the 16 patients (12.5%, Fig. 3B). Perivascular inflammation was a common finding in this cohort (14/16, 87.5%), and transmural vasculitis could also be seen in 1 patient (P4, Fig. 3C). The inflammatory infiltrate was dominated by T lymphocytes (Fig. 3D) and macrophages, while eosinophils could only be observed in 3 cases (3/16, 18.8%, Fig. 3E). There were no significant differences among the total scores of the $CD4^+$ T helper cells, $CD8^+$ cytotoxic

Table 1 Clinical and laboratory characteristics of 17 patients with eosinophilic fasciitis

	Sex/age of onset, y	Disease duration, mo	Clinical presentations					Laboratory examinations						Concomitant disorder
			Skin thickening	Arthralgia	Limited joint motility	Bilateral/Symmetrical	Myalgia	Eo%	Rheumatology	ESR (mm/h)	CRP (mg/l)	CK (U/L)	EMG	
P1	M/45	6	Calf	Interphalangeal, knee	Knee, ankle	Y/Y	+	/	-	NL	NL	/	NL	-
P2	M/26	2	Forearm, calf	Interphalangeal	Interphalangeal	Y/Y	+	15.5%	/	54	/	80	NL	-
P3	M/22	4	Forearm, calf	Elbow, wrist, ankle, knee,	Interphalangeal, ankle, knee	Y/Y	+	/	/	38	/	54	Myogenic	-
P4	M/59	1	Forearm, calf	Interphalangeal, wrist, ankle	-	N/N*	+	22.4%	ANA, p-ANCA	110	53	/	Neurogenic#	CSS
P5	M/59	1	Forearm	Interphalangeal, ankle	Interphalangeal, ankle	Y/Y	-	NL	-	24	14	33	NL	-
P6	M/26	2	Forearm	Interphalangeal, wrist	Interphalangeal, wrist	N/N*	+	/	ANA	NL	NL	76	NL	-
P7	F/63	6	Forearm, calf	-	-	Y/Y	+	9.6%	ANA	NL	NL	36	NL	Thrombocytopenia
P8	M/37	36	Forearm, calf	Interphalangeal, wrist, ankle, knee	Interphalangeal, ankle	Y/Y	+	NL	ANA, RF	NL	NL	42	NL	-
P9	M/37	12	Calf	-	-	N/N**	+	NL	/	20	NL	94	NL	-
P10	M/27	4	Forearm, calf	Interphalangeal, wrist, ankle	Interphalangeal, wrist, ankle	Y/Y	-	22.3%	ANA	27	46	27	NL	-
P11	F/16	4	Forearm	Interphalangeal, wrist	Interphalangeal, wrist	Y/Y	-	11.9%	-	NL	NL	/	NL	-
P12	M/37	24	Forearm, calf	Interphalangeal, wrist	Interphalangeal, wrist	Y/Y	+	NL	ANA	21	43.6	305	NL	Papillary thyroid cancer
P13	M/61	12	Forearm, calf	-	Interphalangeal, wrist	Y/Y	+	15.5%	ANA	NL	11.1	28	NL	-
P14	F/20	24	Forearm, foot	Interphalangeal, wrist, toe	Interphalangeal, wrist, toe	Y/Y	+	/	-	/	/	42	Myogenic	-
P15	M/69	6	Forearm, calf	-	-	Y/Y	-	NL	-	23	9.2	22	NL	-
P16	F/40	2	Forearm	-	Interphalangeal, wrist	Y/Y	+	NL	ANA, RF	34	10.8	/	Myogenic	-
P17	F/16	36	Calf	-	-	N/N*	+	NL	Ha	87	/	38	NL	-

Abbreviations: Eo = Eosinophils; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; CK = creatine kinase; EMG = electromyography; NL = normal; CSS = Churg-Strauss syndrome; p-ANCA = anti-perinuclear neutrophil cytoplasmic antibody; ANA = antinuclear antibody; RF = rheumatoid factor; Ha = anti-tyrosyl-tRNA synthetase antibody. * Right side, ** Left side, / not recorded, # Multiple mononeuropathy. Normal reference ranges: Eo% = 0.4-8%; CRP = 0-8 mg/l; ESR = 0–15 mm/h

Fig. 1 Typical clinical manifestations. (**A**) Skin thickening and hyperpigmentation of the bilateral distal upper extremities in P8. (**B**) Skin thickening and hyperpigmentation of the bilateral distal lower extremities in P6. (**C**) The "prayer sign" of P12 before treatment. (**D**) The "prayer sign" of P12 significantly improved after treatment with prednisone

T cells and $CD68^+$ macrophages in our patients ($P>0.05$). Typical perifascicular atrophy (PFA), which was always adjacent to the inflammatory fascia or perimysium, could be identified in four cases (4/16, 25%, Fig. 3F). MAC deposition on the subfascial capillaries and sarcolemma of myofibers could also be observed in 1 and 3 patients, respectively (Fig. 3G). Vascular endothelial cells in the fascia and perifascicular endomysium were largely preserved (Fig. 3H). Most of the muscle biopsies showed upregulation of MHC-I (15/16, 93.8%) and/or MHC-II (10/16, 62.5%), while none of them expressed MxA (Fig. 3I-L). MHC-I expression showed pure perifascicular pattern in 8 patients (8/16, 50%), diffuse or focal pattern in 6 patients (6/16, 37.5%), and mixed pattern with both PF enhancement and diffuse expression in 1 patient (1/16, 6.3%). MHC-II expression showed pure perifascicular pattern in 5 patients (5/16, 31.3%), focal pattern in 1 patient (1/16, 6.3%), and mixed pattern with both PF enhancement and focal (3) or diffuse (1) expression in 4 patients (4/16, 25%).

Treatment and outcomes

In the present study, 88.2% (15/17) of the patients were followed up. The detailed medication regimen and treatment outcomes of 15 patients are summarized in Table 3; Fig. 4. The median follow-up time was 16 months, with a range of 4–76 months.

Eleven of the fifteen patients received monotherapy with prednisone: four of them (4/11, 36.3%) achieved complete recovery, three of them (3/11, 27.3%) achieved marked improvement, two (2/11, 18.2%) achieved moderate improvement, one patient (P16) who discontinued the medication himself after only one month of treatment achieved neither improvement nor progression, and the last patient (P4) who was concomitant with CSS died of "multiple organ failure" 13 months after the muscle biopsy. Four patients received combined therapy: three of them were treated with prednisone and methotrexate (MTX), of whom two achieved moderate improvement and one only reached mild improvement; the other patient who was treated with prednisone and D-penicillamine achieved complete recovery. Six patients (6/15, 40%) have successfully maintained a drug-free status for a median duration of 26 months (from 6 to 52 months), including 5 patients treated with monotherapy of prednisone, and 1 patient treated with a combination regimen of prednisone and D-penicillamine. Recurrence of myalgia and skin thickening was reported in one patient (P17) after drug withdrawal for 1.5 months, while complete recovery was achieved again after re-treatment with prednisone.

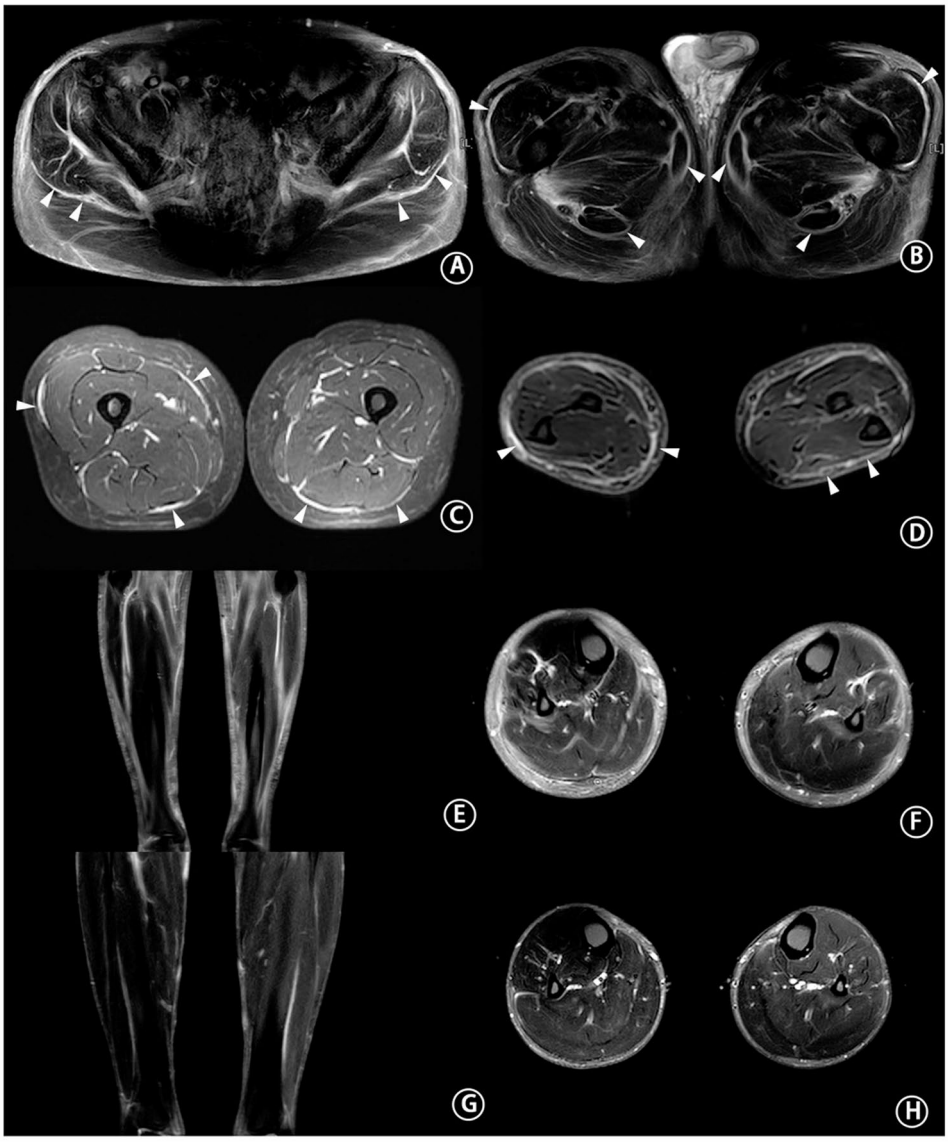

Fig. 2 Representative MRI on hyperintense short TI inversion recovery (STIR) sequence. (**A**, **B**) Apparent edema of the fascial and the adjacent subcutaneous tissue in P13 at the pelvic level. (**C**) Fascial edema without involvement of adjacent subcutis in P16 at the thigh level. (**D**) Fascia edema of bilateral forearm in P5. The fascia beneath the subcutis was usually preferentially involved rather than that lying between the muscle bundles (**A**-**D**, arrowheads). (**E**-**F**) Apparent edema and inflammation of fascia and the adjacent subcutaneous tissue in P10 before treatment. (**G**-**H**) The edema and inflammation of P10 were significantly alleviated after treatment with prednisone and methotrexate

Discussion

This study presents a retrospective analysis of 17 patients who met the diagnostic criteria for EF from a large NMD center in Eastern China [16, 17]. We report the detailed clinical and histopathological features, as well as the long-term follow-up outcomes of these patients. Additionally, we discussed the immune-pathogenic mechanism of EF based on both previous and current studies.

In accordance with previous experience [6, 23, 24], the major clinical manifestations of our EF patients included skin thickening and limited joint mobility of the bilateral distal limb extremities with a subacute or chronic progression pattern. Although lower extremity was reported to be more commonly affected than upper extremity in previous studies [13, 25], upper limb extremities were more frequently and typically involved in this cohort. The "prayer sign", which might result from fascial fibrosis or tendon retraction of the wrist [6, 17, 26], was reported in nearly half of our patients and became the most characteristic manifestation of them, whereas the classic cutaneous "groove sign" or "orange peel" appearance was not recorded in any of them. We could not exclude the recall bias, but this phenomenon was also reported in a recent juvenile EF cohort [8]. A possible

Table 2 Muscle pathological features of 16 patients with eosinophilic fasciitis

	PFA	Necrotic fibers	Fasciitis	Perivascular inflammation	Eosinophils infiltration	CD3	CD8	CD4	CD68	MHC-I	MHC-II	MxA	MAC
P1	+	-	+	+	+	2	2	2	2	Diffuse	Focal + PF	-	-
P2	-	-	+	+	+	2	2	2	2	PF	PF	-	-
P3	+	+	+	+	-	2	2	2	2	PF	PF	-	Cap + Sarco
P4	+	-	+	+	-	2	2	2	2	-	-	-	-
P5	-	-	+	+	-	2	2	2	2	PF	PF	-	-
P6	-	-	+	+	-	2	1	2	2	PF	PF	-	-
P7	-	-	+	+	-	2	2	1	2	PF	PF	-	-
P8	-	-	+	+	-	2	2	1	2	PF	-	-	-
P9	-	-	+	+	-	1	1	1	2	Diffuse	-	-	-
P10	-	+	+	+	+	2	2	2	2	Diffuse	Focal + PF	-	Sarco
P12	-	-	+	+	-	2	1	2	2	Diffuse	Focal + PF	-	-
P13	+	-	+	+	-	2	2	2	2	Diffuse + PF	Diffuse +PF	-	Sarco
P14	-	-	+	-	-	1	1	1	2	PF	-	-	-
P15	-	-	+	+	-	2	2	2	2	Diffuse	Focal	-	-
P16	-	-	NA	-	-	0	0	0	1	PF	-	-	-
P17	-	-	+	+	-	2	2	1	2	Focal	-	-	-

Abbreviations: PFA = perifascicular atrophy; NA = not available; MHC = major histocompatibility complex; MxA = myxovirus resistance protein; MAC = membrane attack complex; PF = perifascicular; Cap = capillary deposition; Sarco = sarcolemma deposition

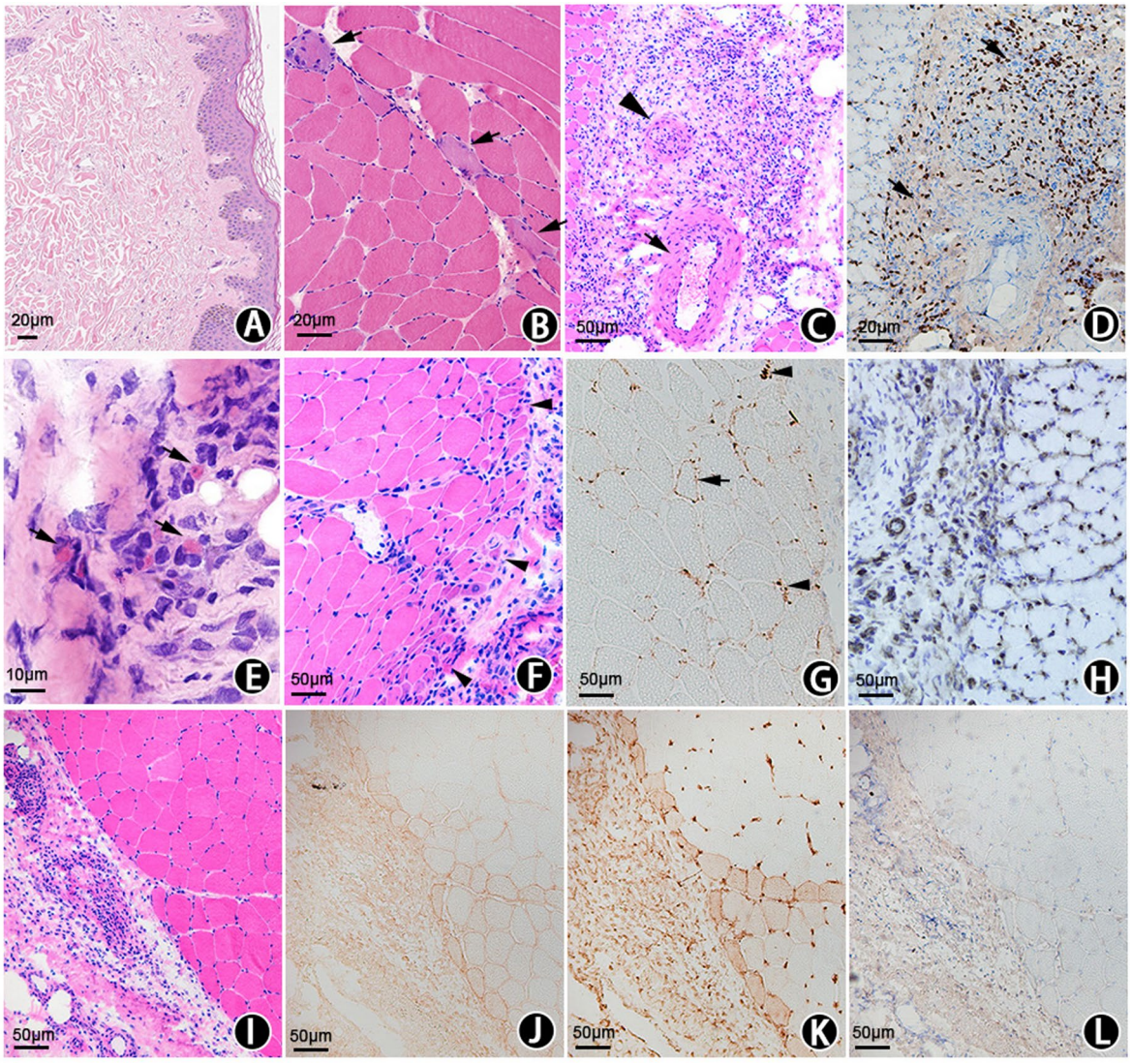

Fig. 3 Histopathological findings. (**A**) Skin pathology in P12 showed sclerosis of the reticular dermis with excessive collagen deposition and scarce lymphocyte infiltration, but the papillary dermis and the epidermis were not affected (HE staining). (**B**) Scattered regenerative myofibers in P10 (HE staining, arrows). (**C**) Perivasculitis (arrow) and transmural vasculitis with an occluded lumen (arrowhead) in skeletal muscle of P4 (HE staining). (**D**) Prominent fascial and perivascular T lymphocytes infiltration in P4 (CD3 staining, arrows). (**E**) Eosinophils scattered in the fascia (E, HE staining), extending to the adjacent endomysium in P2 (F, HE staining). (**F**) Typical perifascicular atrophy adjacent to the inflammatory perimysium in P3 (arrows, HE staining). (**G**) MAC deposition on the sarcolemma of nonnecrotic myofibers and the intramuscular capillaries which were underlying the fascia in P3. (**H**) Vascular endothelial cells in the fascia and perifascicular endomysium was preserved in P3 (CD31 staining). (**I**-**L**) Perifascicular MHC-I (**J**) and MHC-II (**K**) expression but without perifascicular atrophy (I, HE staining) and MxA staining (**L**). MAC = membrane attack complex; MHC = major histocompatibility complex class; MxA = myxovirus resistance protein

explanation is that the inflammation and fibrosis process often begins from the fascia and later extends to the adjacent subcutaneous fat and deep dermis in EF [6, 27], so the "prayer sign" may be more sensitive to the cutaneous signs in some EF patients. Additionally, we suggested that the presence of "prayer sign" without sclerosis of the fingers might be an important clue for distinguishing EF from the most confusing disease-systemic sclerosis (SSc), in which the fingers distal to the metacarpophalangeal joints are often preferentially involved [28].

There were no specific laboratory findings for the diagnosis of EF. Peripheral eosinophilia was only identified in 40% of our EF patients, which is less than previous studies (63–93%) [14, 17]. As a non-infectious inflammatory disease, fever is rarely reported and the inflammatory markers such as CRP or ESR are usually elevated in EF patients, but always at a mild or moderate level, as shown in our study. This might be helpful in differentiating an EF patient from polymyalgia rheumatica [29], especially when muscle pain is the predominant complaint of the patient, as seen in our two patients (P9 and

Table 3 Treatment and outcomes of 15 patients with eosinophilic fasciitis

	Duration before treatment, mo	Treatment at beginning	Treatment course, mo	Therapy at last/ Lasting time, mo	Follow-up time, mo	Outcomes
P2	2	Pred 80 mg qd	24	None/52	76	Marked improvement
P4	1	Pred 60 mg qd	13	None/-	37	Death
P5	1	Pred 60 mg qd, D-penicillamine 250 mg qd	6	None/16	22	Complete Recovery
P6	2	Pred 30 mg qd	8	None/40	48	Moderate improvement
P7	6	Pred 60 mg qd	6	None/36	42	Complete Recovery
P8	36	Pred 35 mg qd	12	Pred 5 mg qd, MTX 15 mg qw /3	12	Moderate improvement
P9	12	Pred 60 mg qd	7.5	None/6	13.5	Complete Recovery
P10	4	Pred 60 mg qd	11	Pred 10 mg qd, MTX 20 mg qw/1	11	Moderate improvement
P11	4	Pred 60 mg qd	10	None/12	22	Complete Recovery
P12	24	pred 60 mg qd	12	Pred 15 mg qd/2	12	Marked improvement
P13	12	Pred 60 mg qd	4	Pred 30 mg qd/1	4	Moderate improvement
P14	24	Pred 60 mg qd	14	Pred 5 mg qd/1	14	Marked improvement
P15	6	Pred 45 mg qd, MTX 15 mg qw	16	Pred 10 mg qd/4	16	Mild improvement
P16	2	Pred 60 mg qd	1	None/4	5	No improvement
P17*	36	Pred 40 mg qd	7.5	Pred 15 mg qd/2.5	27	Complete Recovery

Abbreviations: Pred = prednisone; MTX = methotrexate; qd = per day; qw = per week; * relapse was reported in this patient

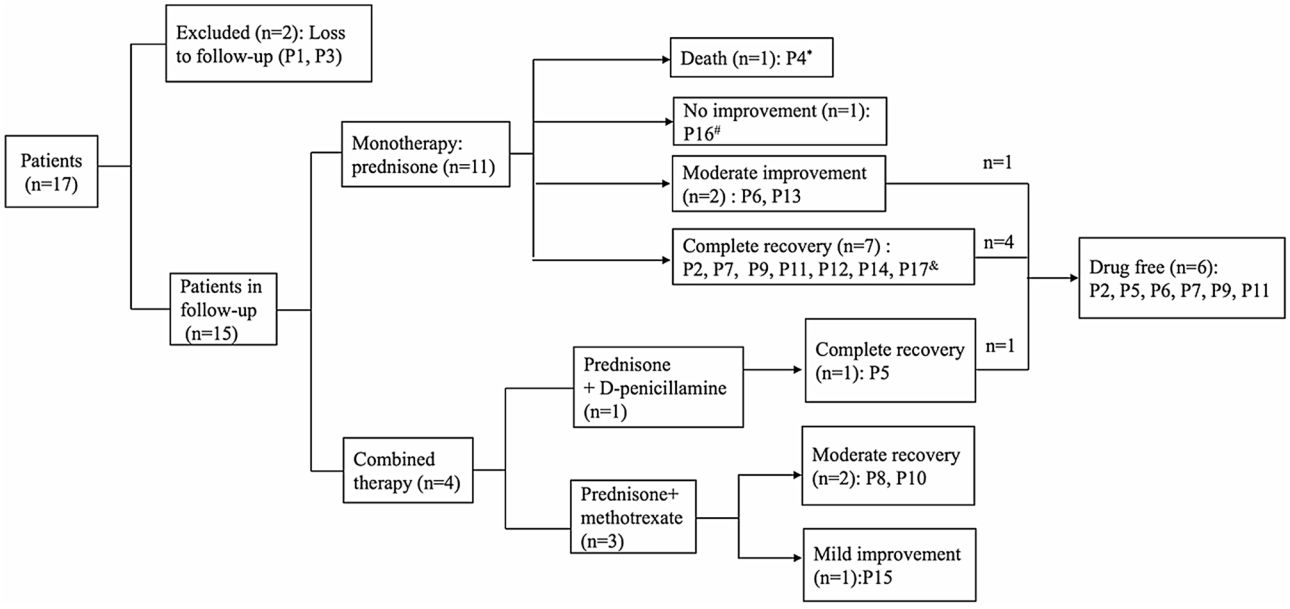

Fig. 4 Treatment and outcomes. *The patient was concomitant with Churg-Strauss syndrome and died from multiple organ failure 13 months after the muscle biopsy. # This patient discontinued the medication himself after only one month of treatment and reached neither improvement nor progression. & Relapse was reported in this patient after drug withdrawal for 1.5 months, while complete recovery was achieved again after re-treatment with prednisone

P17). No specific autoantibodies have ever been reported in EF [6, 7], whereas the anti-Ha antibody was identified in one of our patients (P17). This indicates that there might be a crossover or linkage between EF and antisynthetase syndrome or other subtypes of myositis [30], and MSAs should be routinely screened in those "idiopathic" EF patients. Clinically, CK levels are usually normal or mildly elevated, and myogenic changes on EMG are rarely observed in an active EF patient. This can be easily understood as there is no sarcolemma breakage of skeletal myofibers in EF. On MRI, we found that the fascia, located just beneath or continuous with the subcutaneous tissue, would be preferentially involved than the interfascicular ones in patients with fasciitis, and this phenomenon is also indicated in other studies [9, 31, 32]. It suggests that the fascia-subcutis conjunction might be

the place where inflammation starts in EF. Skeletal muscle edema or fibrosis, which was reported to be highly prevalent in SSc [33], is not apparent in our EF patients.

Histopathological findings of early EF usually show massive infiltration of various inflammatory cells in the fascia and lower subcutis, with a largely normal epidermis and dermis [6, 27]. However, when fibrosis of the full tissue predominates at the late stage, it is difficult to distinguish EF from other sclerosing disorders based solely on the skin and/or fascia pathology [27]. The presence of eosinophil infiltration would help give a diagnosis of EF but it is usually absent in the biopsy tissues [14], and it was only identified in 3 samples of our patients. Consistent with a recent study from Germany [14], we confirmed the unique muscle pathological manifestations of EF: frequent upregulation of MHC-I and/or MHC-II but negative expression of MxA in the perifascicular region, with or without typical PFA. This is similar but definitely different from that of dermatomyositis (DM), for which MxA, the signature of type I interferon (IFN-I), is a pathognomonic pathological marker [34]. This specific muscle immune-pathological phenotype has also been described in graft-versus-host disease [35, 36], but it has not been described in other sclerosing diseases, such as SSc-related myopathy [37, 38]. Therefore, a muscle biopsy might be helpful in distinguishing these mimicking diseases in a specific clinical context. In addition, the two mainstream theories of PFA in DM are IFN-I inducible injury and hypoxia-ischemia secondary to the microvascular abnormalities [39, 40]. However, this could not apparently explain the development of PFA in EF, as there is no significant upregulation of IFN-I or dropout of capillaries in EF, both in the present and the previous study [14]. We hypothesized that damage to the collagen in the fascia and perimysium would disrupt the cross-linking and structural support of the endomysium from the adjacent fascia and perimysium [41], which could potentially contribute to the formation of PFA in EF.

Until now, there is still no standardized therapeutic regimen for EF. The initial treatment for EF is generally oral prednisone 0.5-1 mg/kg daily [16]. Consistent with the previous observation, complete remission could be achieved by the majority of patients treated by the monotherapy of prednisone [12]. MTX (15-25 mg once a week) is the most favored add-on treatment for the refractory patients and is reported to be associated with a higher rate of complete remission [8]. However, it is not always the case as none of the three patients in this cohort treated with a combination therapy of prednisone and MTX achieved complete recovery. Clinical outcome could be influenced by various factors, such as disease duration, severity, individual response to treatment, etc. The efficacy of D-penicillamine, as shown in P5, has also been observed in other studies and could be an alternative option for EF individuals [6]. The overall prognosis for EF patients is optimistic, as most patients would achieve different degrees of improvement with standard immunotherapy, and drug-free status could be achieved in nearly half of them. However, life-threatening events might happen in patients concomitant with other diseases, such as systemic necrotizing vasculitis in P4, hematologic malignancies and other autoimmune systemic diseases [6]. Methylprednisolone pulses at the initial stages are reported to be associated with a better outcome and a lower need for immunosuppressant use [42], which might be considered for the severe cases.

The etiology and pathogenesis of EF is still largely unknown. Several factors, such as strenuous exercise, trauma, radiation therapy, and neoplasms, have been suggested to promote the onset of EF, while no definite triggers could be identified in most EF cases [7]. Eosinophilia is suggested to play an important role in the pathogenesis of EF through the release of toxic granule products or other mediators that can damage tissue [7]. However, none of the cytokines and chemokines involved in activation and chemoattraction of eosinophils is significantly elevated in the tissue of EF patients [14]. Moreover, eosinophil infiltration could also be present in various hereditary, and inflammatory myopathies and even in amyotrophic lateral sclerosis [43], so it might be a nonspecific histological finding secondary to some unknown upstream responses. In fact, peripheral eosinophilia or tissue eosinophilic infiltration is neither consistent and nor essential for diagnosing EF according to the existing criteria [16, 17]. Although the exact pathogenesis remains uncertain, a specific autoimmune mechanism, potentially activating various types of leukocytes and inducing the synthesis of collagen, is supposed to be involved in EF. This condition is characterized by immune-mediated inflammation of the fascia, with notable infiltration of inflammatory cells, including eosinophils and lymphocytes [44]. T-cell activation and release of various cytokines such as IL-5, IL-6 and TGF-β are believed to promote the fibrosis and thickening of the fascia [45]. Our study further provided other evidence including obvious perivascular lymphocytic infiltrates, and the unique expression pattern of MHC-I and MHC-II in muscle pathology. Previous studies also suggested EF might overlap with other autoimmune disorders, such as systemic sclerosis or systemic lupus erythematosus, due to shared immune dysregulation patterns [12]. Based on the above typical immunopathological features observed in muscle pathology, along with the favorable response to prednisone and immunosuppressive treatment in most of the EF patients reported in both previous literatures and this present cohort [6, 7, 12, 14], we propose that "autoimmune fasciitis" might serve as an alternative term to describe this confounding entity, emphasizing

its autoimmune nature, regardless of the presence of eosinophilia.

Our study has several limitations. Firstly, this is a retrospective analysis with a limited number of patients. Recalling bias and missing clinical data are inevitable during the information collection process. Secondly, the level of gamma-globin was not recorded due to insufficient awareness at that time. Thirdly, the MSAs were only detected in a minority of patients, as no serum was stored for the others. Fourthly, muscle MRI was not performed in all patients, and experience with follow-up MRI is still limited. Lastly, we didn't further phenotype the infiltrated macrophages and lymphocytes, while this has been done in the recent pathological study [14].

In conclusion, the "prayer sign" without sclerosis of the fingers might be an important clinical clue for distinguishing EF from the mimicking disease SSc. Fascia located just beneath or continuous with the subcutaneous tissue is preferentially involved on MRI. Perifascicular upregulation of MHC-I and/or MHC-II but negative expression of MxA, with or without PFA represents a unique muscle immune-pathological phenotype of EF. Most patients show favorable outcome following steroid monotherapy or in combination with immunosuppressants, underscoring the immune-pathogenic nature of this disease.

Abbreviations

EF	Eosinophilic fasciitis
MRI	Magnetic resonance imaging
NMD	Neuromuscular Disorder
VAS	Visual analogue scale
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
MSAs	Myositis-specific antibodies
EMG	Electromyography
HE	Hematoxylin and eosin
MHC-I/II	Major histocompatibility complex class-I/II
MxA	Myxovirus resistance protein
MAC	Membrane attack complex
CSS	Churg-Strauss syndrome
CK	Creatine kinase
ANA	Anti-nuclear antibodies
p-ANCA	Perinuclear neutrophil cytoplasmic antibody
RF	Rheumatoid factor
ARS	Aminoacyl tRNA synthetase
STIR	Short TI inversion recovery
PFA	Perifascicular atrophy
MTX	Methotrexate
SSc	Systemic sclerosis
DM	Dermatomyositis

Supplementary Information

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Supplementary Material 1

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Author contributions
Xiaoyuan Wang, Lining Zhang: data curation, writing-original draft preparation. Ying Hou, Tingjun Dai, Kai Shao: validation and statistical analysis. Xiaotian Ma: methodology and statistical analysis. ChuanZhu Yan: conceptualization, methodology and funding acquisition. Bing Zhao: Writing, reviewing and editing.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Standard protocol approval and patient consent
This study was approved by the Ethics Committee of Qilu Hospital (Qingdao), Shandong University, China (KYLL-KS-2022054). Written consent for muscle biopsy, laboratory tests and article publication were obtained from all the patients or their parents in the present study. The study was performed in accordance with the Declaration of Helsinki.

Competing interests
The authors declare no competing interests.

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