Long-term outcome of eosinophilic fasciitis: A cross-sectional evaluation of 35 patients

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Background: Eosinophilic fasciitis (EF) is a connective tissue disease with an unknown long-term course.

Objective: To evaluate presence and determinants of residual disease damage in patients with EF after long-term follow-up.

Methods: Patients with biopsy-proven EF were included for this cross-sectional study. Outcome measures included the Physician's Global Assessment of Disease Activity, Physician's Global Assessment of Damage (PhysGA-D), skin pliability scores, passive range of motion, and health-related quality of Life (HRQoL) questionnaires.

Results: In total, 35 patients (24 of whom were female [68.6%]) with a median age of 60 years participated. All patients had detectable residual damage. Impairment of HRQoL, assessed by the Dermatology Quality of Life Index and the 36-Item Short-Form Survey, correlated to the extent of residual damage. The PhysGA-D score at participation correlated to signs of severe disease at presentation, such as increased C-reactive protein level (Spearman's rho [r_s] = 0.486, P = .006), involvement of the neck (r_s = 0.528, P = .001) and trunk (r_s = 0.483, P = .003), prolonged time to disease remission (r_s = 0.575, P = .003), and presence of concomitant morphea (r_s = 0.349, P = .040). Lastly, maximum methotrexate dose correlated negatively to PhysGA-D score at study participation (r_s = -0.393, P = .022).

Limitations: Sample size.

Conclusion: All patients with EF had detectable residual damage. Impairment of HRQoL correlated to the extent of residual damage. Advanced age and signs of severe disease at presentation were associated with the severity of residual damage. (J Am Acad Dermatol 2017;77:512-7.)

Key words: disease course; eosinophilic fasciitis; localized scleroderma; morphea; Shulman syndrome.

Eosinophilic fasciitis (EF) is a rare connective tissue disorder characterized by subacute onset of edema, erythema, and induration of the extremities and trunk (Fig 1, *A*). Subsequently, these manifestations are replaced by fibrosis of the fascia, leading to a cobblestone appearance (Fig 1, *B*) and thickening of the overlying skin.[1-3]

In the majority of patients, progression of the disease is halted by administering medium- to high-dose systemic corticosteroids (SCSs), and weekly methotrexate (MTX).[1,2,4,5] Despite adequate treatment, some patients recover with minimal damage, whereas others develop severe damage[6] with consequential functional impairment.[7,8]

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Identification of patients at risk for development of severe residual damage should lead to individualized treatment; these patients could benefit from more aggressive treatment. Currently, however, little is known about determinants for a poor disease outcome. The aim of this cross-sectional study was to evaluate the extent of residual disease damage and the influence on health-related quality of life (HRQoL). A secondary objective was to identify determinants for a poor outcome.

CAPSULE SUMMARY

- Eosinophilic fasciitis is a rare and debilitating connective tissue disease.

- Advanced age and signs of severe disease at presentation, such as truncal involvement, increased inflammatory markers, and presence of concomitant morphea, were associated with the severity of residual damage.

- Impairment of health-related quality of life, scored by the Dermatology Quality of Life Index and the 36-Item Short-Form Survey, correlated with extent of residual damage.

METHODS
Study design and patients

A cross-sectional study was conducted at the tertiary referral center Radboud University Medical Center, Nijmegen, The Netherlands. The study was conducted in accordance with principles of the Declaration of Helsinki and approved by our local ethical board. Eligible patients were at least 18 years old with biopsy-proven EF and visited the outpatient clinics of dermatology and rheumatology between January 1, 1990, and October 1, 2016.

Assessments

The Physician Global Assessment of Disease Activity (PhysGA-A) and Physician Global Assessment of Disease Damage (PhysGA-D) were assessed by the same physician (J.M.) in all patients. Both these global assessments were graded on a 100-mm visual analog scale. Components of the PhysGA-A and PhysGA-D were based on the localized scleroderma (LoS) literature (Supplementary Appendix; available at http://www.jaad.org).[9,10]

Extent of skin fibrosis was assessed by the modified Rodnan skin score (MRSS)[11] and the Localized Scleroderma Cutaneous Assessment Tool (LoSCAT). The LoSCAT is a reliable and valid tool for evaluation of the disease activity and damage of LoS.[9,10] The score is a composite of the modified Localized Scleroderma Skin Severity Index[9] and Localized Scleroderma Skin Damage Index (Supplementary Appendix; available at http://www.jaad.org).[10]

Joint contractures were evaluated by measuring passive range of motion (RoM), and limitations were assessed with a semiquantitative score (0, absent; 1, mild; 2, moderate; and 3, severe).

Patient-reported outcome measures consisted of HRQoL questionnaires. Participants filled out the Dermatology Quality of Life Index (DLQI), a skin-specific health questionnaire.[12,13] For the DLQI, higher scores reflect decreased quality of life. In addition, the 36-Item Short Form Survey (SF-36)[14] general health questionnaire was administered. Results from the SF-36 were scored by using previously reported methods.[15] Overall, physical and mental impairment are summarized in the Physical Component Summary and Mental Component Summary, respectively. For the SF-36, lower scores represent decreased quality of life.

Statistical analyses

Descriptive statistics including median (range) for continuous variables and percentages for categorical data were used. Spearman's correlation was used to explore correlations among different outcome measures and between outcome measures and patient, disease, and treatment characteristics. Correlations were reported by Spearman's rho (r_s) and *P* values. A *P* value of .05 or less was regarded statistically significant. Statistical analyses were performed with SPSS software, version 24 (IBM Corp., Armonk, NY).

RESULTS
Inclusion

In total, 57 adults with biopsy-proven EF were identified (Supplemental Fig 1; available at http://www.jaad.org). Eight patients were deceased at study initiation. Of the remaining 49 patients, 35 (71.4%) consented to study participation. The remaining 14 patients (28.6%) either refused participation (n = 9 [18.4%]) or could not be contacted (n = 5 [10.2%]). The characteristics of the nonparticipants were similar to those of the participants.

Patient and disease characteristics

Two-thirds of the patients (n = 24 [68.6%]) were female (Table I). The median ages at disease presentation and study participation were 54 years [range, 13-68] and 60 years (range, 27-78), respectively. The median disease follow-up at participation was 100 months (range, 9-341). In patient history, 28 patients (80%) had achieved disease remission after a median time of 33 months (range, 9-293). Disease recurrence was noted in 14

patients (40%) at a median of 48 months (range, 9-81) after disease remission. Concomitant morphea was present in 23 patients (65.7%).

Immunosuppressive treatment

Most patients (n = 32 [91.5%]) received a combination of an SCS and weekly MTX during the course of disease (Table II). The median time between SCS initiation and disease onset was 8 months (range, 0-49). The median maximum SCS dose was 30 mg (range, 10-80). The median time between disease onset and MTX initiation was 12 months (range 3-88) and the median maximum weekly dose was 20 mg (range, 15-30 mg). At study participation, 15 patients (42.9%) were still receiving MTX and 16 patients were receiving an SCS (Supplemental Table I; available at http://www.jaad.org).

Outcome measures at study participation

Disease activity and assessment. The majority of patients (n = 25 [71.4%]) were evaluated with inactive or minimally active disease (PhysGA-A score <5). The remaining 7 patients (20%) had not yet achieved disease remission or experienced recurrent disease at participation (n = 3 [8.6%]).

Disease damage. All patients (n = 35 [100%]) had detectable disease damage (PhysGA-D score >0); the extent of disease damage was highly variable (Fig 2, *A*). A major component of damage consisted of residual cutaneous fibrosis. This is reflected in the similar distributions of the cutaneous fibrosis scores on the MRSS (Fig 2, *B*) (a moderate correlation with PhysGA-D [r_s = 0.661, P < .001]) and LoSCAT (Fig 2, *C*) (a strong correlation with PhysGA-D [r_s = 0.706, P < .001]) within the study population. RoM impairment, resulting from cutaneous fibrosis, was frequently observed; 20 patients (57.1%) experienced decreased RoM of the ankles (mild in 14 [40%], moderate in 4 [11.4%], and severe in 2

[5.7%]). RoM of the wrists was impaired in 11 patients (31.4%), of the knees in 11 (31.4%) and of the elbows in 1 patient (2.9%) (Fig 2, *D*).

Patient-reported outcome measures. Patients with more severe residual disease damage at participation demonstrated increased impairment in HRQoL, measured by the DLQI and SF-36. The SF-36 predominantly demonstrated impairment in physical domains (Supplemental Table II; available at http://www.jaad.org). The physical functioning domain of the SF-36 and DLQI scores correlated moderately with the PhysGA-D, MRSS, and LoSCAT scores (Supplemental Table III; available at http://www.jaad.org).

Determinants of residual disease damage

Patient and disease characteristics. Involvement of the neck (r_s = 0.528, P = .001) and trunk (r_s = 0.483, P = .003), increased C-reactive protein level (r_s = 0.486, P = .006), presence of concomitant morphea (r_s = 0.349, P = .040), advanced age at disease presentation (r_s = 0.449, P = .007), and time to disease remission (r_s = 0.575, P = .003) all correlated moderately with PhysGA-D scaore (Table III). In other words, presence of the aforementioned characteristics was associated with a poor outcome.

Immunosuppressive treatment history. Patients who received higher maximum dosages of MTX had lower PhysGA-D scores at study participation (r_s = -0.393, P = .022). Other characteristics of MTX treatment, such as delay of MTX initiation or treatment duration, did not correlate to PhysGA-D score, and neither did any of the characteristics of SCS treatment.

DISCUSSION

The current lack of knowledge on the long-term course of EF propelled us to perform this cross-sectional study. This study encompasses a detailed description of 35 patients with close to 300 patient-years of follow-up.

All patients (100%) experienced disease damage at participation. Damage most often consisted of residual cutaneous fibrosis and consequential decreased RoM of the affected joints. More than half of the participants (57.1%) experienced decreased RoM of the ankles, and one-third experienced decreased RoM in the wrists and knees. In addition, patients with more severe disease damage reported substantially decreased HRQoL, captured by the DLQI and SF-36 questionnaires. Impact on physical functioning was previously reported in the active stage of EF.[8,16] However, this study demonstrates that residual damage still affects HRQoL after many years of quiescent disease.
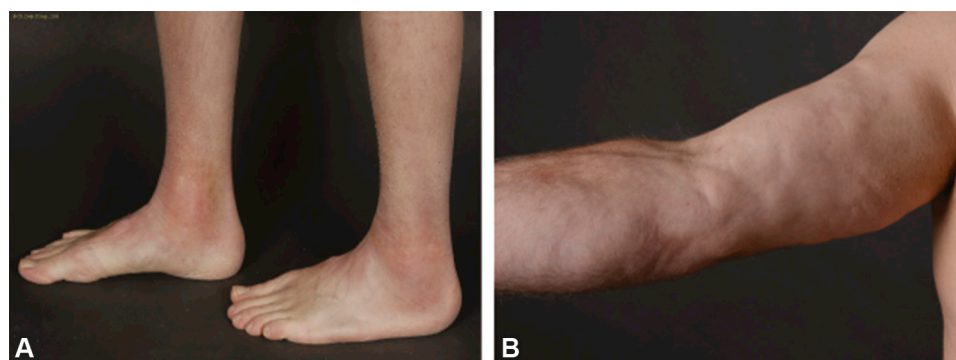
Fig 1. Eosinophilic fasciitis. **A**, Typical image of the lower limbs during the inflammatory phase. **B**, Cobblestone appearance on the right arm.

Table I. Patient and disease characteristics

Characteristic	Value
Total patients, n (%)	35 (100)
Sex, n (%)	
Male	11 (31.4)
Female	24 (68.6)
Median age (range), y	
At disease onset	53 (13-68)
At participation	60 (27-78)
Median diagnostic delay (range), mo	7 (1-122)
Median follow-up at participation (range), mo	100 (9-341)
Concomitant AID, n (%)*	12 (34.3)
Concomitant morphea, n (%)	23 (65.7)
EF secondary to malignancy, n (%)[†]	2 (5.7)
Laboratory results at disease presentation	
Peripheral eosinophilia (absolute count ≥ .5 × 10^9/L), n (%)	22 (62.9)
Increased ESR (>20 mm/h), n (%)[‡]	16 (45.7)[‡]
Increased CRP level (ref >10 mg/L), n (%)[§]	21 (67.7)[§]
ANAs, n (%)[¶]	11 (37.9)[¶]

AID, Autoimmune disease; *ANA*, antinuclear antibody; *CRP*, C-reactive protein; *EF*, eosinophilic fasciitis; *ESR*, erythrocyte sedimentation rate.
*Concomitant AID consisted of rheumatoid arthritis, coeliac disease, Hashimoto's thyroiditis, psoriasis (n = 3), lichen sclerosus (n = 3), Graves' disease, Crohn's disease, Colitis ulcerosa, and alopecia areata.
[†]Malignancies consisted of prostate carcinoma and intestinal carcinoid tumor.
[‡]ESR test results were available for 33 patients.
[§]CRP test results were available for 31 patients.
[¶]ANA test results were available for 29 patients.

Table II. Immunosuppressive treatment history

Characteristic	Value
SCS treatment	
Received	32 (91.4)
Median delay in SCS initiation (range), mo*	8 (0-49)
Median maximum dose (range), mg	30 (10-80)
Median treatment duration (range), wk	90.5 (2-245)
Combination with methotrexate, n (%)	32 (91.4)
MTX treatment	
Received weekly MTX, n (%)	34 (97.1)
Median delay in MTX initiation (range), mo*	12 (3-88)
Median maximum dose (range), mg	20 (15-30)
Median treatment duration (range), wk	122 (1-911)
Route of administration, n (%)	
Oral	23 (67.6)
SC	9 (26.5)
Both oral and SC	2 (5.9)

MTX, Methotrexate; *SC*, subcutaneous; *SCS*, systemic corticosteroid.
*Delay (in months) in initiation of SCS and MTX after first signs or symptoms.

A significant percentage of patients were severely affected by residual disease damage. Additional analysis revealed a relationship between the extent of disease damage and signs of severe disease at presentation, such as increased C-reactive protein level, involvement of the trunk and neck, and a longer time until disease remission. Furthermore, this investigation confirms the concept, postulated by Endo et al,[6] that presence of concomitant morphea represents a subset of EF patients who develop more residual damage. Additionally, a relationship between advanced age at disease onset and a poor outcome was demonstrated. To our knowledge, 1 retrospective study[2] and 1 systematic review[6] have described residual fibrosis in EF and risk factors thereof. However, these studies describe only residual cutaneous fibrosis, and information on the extent of damage is lacking. In conclusion, this study demonstrates that older patients and patients with a severe phenotype at presentation, including presence of concomitant morphea, are at risk for development of more residual disease damage. Identification of this subgroup of patients could lead to improvement in treatment strategies and improved care for them.

History of treatment with lower doses of MTX correlated to a poorer outcome at participation. However, a similar trend, favoring a more aggressive treatment regimen in other treatment parameters,
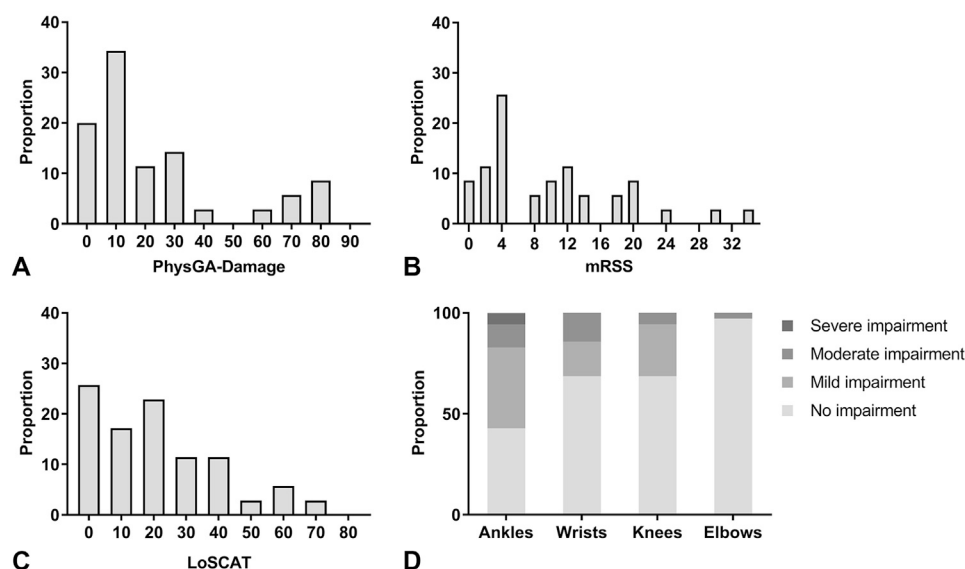
Fig 2. Disease damage in eosinophilic fasciitis. Distribution of results of administration of the Physician Global Assessment of Disease Damage (PhysGA-D) (**A**), the modified Rodnan skin thickness score (**B**), and results of administration of the Localized Scleroderma Cutaneous Assessment Tool (LoSCAT) (**C**) are shown. **D**, Impairment of range of motion of the ankles, wrists, knees, and elbows. *MRSS*, Modified Rodnan skin score.

Table III. Correlation between Physician Global Assessment of disease damage (0-100) at participation and patient, disease, and treatment characteristics

Characteristic	r_s	P value
Age at disease onset, y	**.449**	**.007**
Diagnostic delay, mo	−.011	.951
Follow-up at participation, mo	.176	.313
Concomitant AID	.278	.107
Time to disease remission, mo	**.575**	**.003**
Recurrent episodes of disease activity	.121	.487
Concomitant morphea	**.349**	**.040**
Disease distribution		
Neck	**.528**	**.001**
Trunk	**.483**	**.003**
Upper limbs	−.017	.923
Lower limbs	.128	.465
Laboratory test results		
Peripheral eosinophilia count (abs. count ≥.5 × 109/L)	.010	.569
Increased ESR (>20 mm/h)	.022	.901
Increased CRP (ref >10 mg/L)	**.486**	**.006**
ANA	−.004	.983
Treatment history		
MTX		
MTX delay, mo	.082	.649
Maximum dose, mg/wk	**−.393**	**.022**
Treatment duration, wk	−.107	.553
SCS		
SCS delay	.107	.597
Maximum dose, mg/d	−.118	.536

Bold indicates Spearmans rho's which reached significance (*P* <.05). *AID*, Autoimmune disease; *ANA*, antinuclear antibodies; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *MTX*, methotrexate; *r*$_s$, Spearman's rho; *SCS*, systemic corticosteroids.

could not be demonstrated. Moreover, the correlation of retrospective treatment characteristics with cross-sectional outcome measures is prone to confounding by indication; patients with severe EF received higher dosages of MTX or an SCS for a reason. This limitation illustrates the need for prospective studies to compare different treatment regimens. To date, no standard treatment exists for EF. Recent studies report favorable results for treatment with a combination of an SCS and weekly MTX[4,5] compared with SCS monotherapy. The vast majority of patients in this study were treated with a combination of a medium- to high-dose SCS, followed by tapering, and weekly MTX. Despite these treatment regimens, however, there is still an unmet need in patients with EF. This unsatisfactory treatment result stresses the need for additional treatment approaches and novel antifibrotic therapeutics.

This study is subject to some limitations. First, the rarity of EF led to a limited sample size. In addition, no outcome measures have been validated for EF; all the outcome measures we have reported originated from LoS and systemic sclerosis research.

CONCLUSION

In this study, residual disease damage was demonstrated in all patients with EF through the use of well-defined (patient-reported) outcome measures. Advanced age and signs of severe disease at presentation, such as truncal involvement,

increased inflammatory markers, and presence of concomitant morphea, were associated with the severity of residual damage. Lastly, HRQoL impairment, scored by the DLQI and SF-36, correlated to the extent of residual damage.

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SUPPLEMENTARY APPENDIX. LOCALIZED SCLERODERMA CUTANEOUS ASSESSMENT TOOL

The Localized Scleroderma Cutaneous Assessment Tool (LoSCAT) assesses 18 cutaneous anatomic sites, capturing both disease activity (mLoSSI) and damage (LoSDI) parameters. Scores for each site are based on the most severe score for each parameter. To minimize intersubject variability, all skin changes are compared with the contralateral or ipsilateral skin area.

Modified Localized Scleroderma Skin Severity Index (mLoSSI)

The mLoSSI includes the sums of 3 separate activity scores as follows: (1) erythema, using the color of the lesion's edge with 0 = no erythema, 1 = slight erythema/pink, 2 = red/clearly erythema, and 3 = dark red or marked erythema/violaceous; (2) skin thickness with 0 = normal skin thickness and freely mobile, 1 = mild increase of thickness, 2 = moderate increase of thickness, impaired skin mobility, and 3 = marked increase of thickness or no mobility of skin; and (3) new lesion/lesion extension: new lesion development and/or enlargement of an existing lesion within the past month (score of 3).

Localized Scleroderma Damage Index (LoSDI)

Three cutaneous damage domains are summated to obtain the LoSDI as follows: (1) dermal atrophy with 0 = normal-appearing skin, 1 = mild skin atrophy (ie, shiny skin), 2 = moderate atrophy (ie, visible blood vessels or mild "cliff-drop" sign), and 3 = severe skin atrophy (ie, obvious cliff-drop sign); (2) subcutaneous atrophy with 0 = normal subcutaneous thickness, 1 = flattening or 1/3 fat loss, 2 = obvious concave surface or 1/3 to 2/3 fat loss, a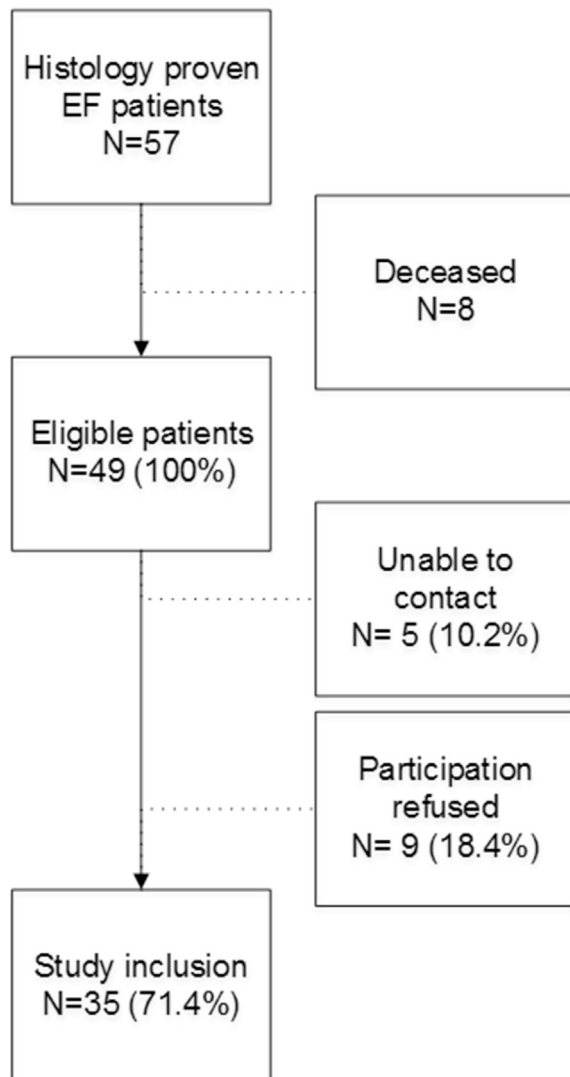nd 3 = severe subcutaneous fat loss (2/3 loss); and (3) dyspigmentation, assessing hyperpigmentation or hypopigmentation, whichever is most prominent with 0 = normal skin pigment, 1 = mild dyspigmentation, 2 = moderate dyspigmentation, and 3 = severe dyspigmentation.

Physician's Global Assessment of Disease Activity (PhysGA-A)

The PhysGA-A was developed based on consensus agreement by pediatric LoS experts and is typically used in conjunction with the mLoSSI. The 100-mm analog scale is anchored by "inactive" at 0 and "markedly active" at 100. The following cutaneous variables were included when scoring the PGA-A: new lesions within the previous month, enlargement of existing lesion within the previous month, and erythema/violaceous color and/or skin thickening/induration at the border of lesion. For the purpose of EF activity assessment, stable skin thickening/induration for multiple years, was not regarded active disease.

Physician's Global Assessment of Disease Damage (PhysGA-D)

The PhysGA-D is anchored by "no damage" at 0 and "markedly damaged" at 100. Based on consensus agreement, both cutaneous and extracutaneous manifestations (ECM) are taken into account when scoring the PGA-D. The cutaneous manifestations include hyperpigmentation or hypopigmentation, and subcutaneous and dermal atrophy. The ECM include musculoskeletal involvement (skeletal muscle atrophy, bone atrophy, facial atrophy, limb length discrepancy, physical disability, joint contracture), neurologic involvement (central nervous system symptoms, abnormal brain magnetic resonance imaging findings, eye involvement), and psychosocial quality-of-life impairment.

Supplemental Fig 1. Participant inclusion. *EF,* Eosinophilic fasciitis.

Supplemental Table I. Immunosuppressive
treatment at participation

Drug	n (% or range)
MTX	
No. of patients	15 (42.9%)
Dose, mg/wk	20 (5-30)
SCS	
No. of patients	16 (45.7%)
Dose, mg/d	8.75 (2.5-60)
Imatinib	1 (2.9%)

MTX, Methotrexate; *SCS*, systemic corticosteroid.

Supplemental Table II. Summary of outcome measures at study participation

Outcome measure	Median (range)
MRSS	8 (0-33)
LoSCAT	17 (1-74)
mLoSSI	9 (0-47)
LoSDI	5 (0-36)
PhysGA	
PhysGA-A	2 (0-30)
PhysGA-D	12 (2-82)
DLQI	3 (0-18)
SF-36	
PCS	45.14 (22.9-58.9)
MCS	54.23 (30.3-65.1)

DLQI, Dermatology Quality of Life Index; *LoSCAT*, Localized Scleroderma Cutaneous Assessment Tool; *LoSDI*, Localized Scleroderma Skin Damage Index; *MCS*, Mental Component Summary; *mLoSSI*, modified Localized Scleroderma Skin Severity Index; *MRSS*, modified Rodnan Skin Score; *PCS*, Physical Component Summary; *PhysGA*, Physician's Global Assessment; *PhysGA-A*, Physician's Global Assessment of Disease Activity; *PhysGA-D*, Physician's Global Assessment of Disease Damage; *SF-36*, 36-Item Short Form Survey.

Supplemental Table III. Correlation between the patient-reported outcome measures and outcome measures scored by the physician

Outcome measure	DLQI		Physical functioning according to SF-36	
	r_s	*P* value	r_s	*P* value
PhysGA				
Damage	.585	.001	−.368	.045
Activity	.465	.007	−.408	.025
LoSCAT	.478	.006	−.475	.006
mLoSSI	.561	.001	−.498	.004
LoSDI	.331	.065	−.359	.044
MRSS	.538	.002	−.511	.003

Spearman's rho (r_s) and *P* values are displayed. Higher DLQI scores reflect more impairment of health-related quality of life. Lower SF-36 scores reflect more impairment of health-related quality of life.

DLQI, Dermatology Quality of Life Index; *LoSCAT*, Localized Scleroderma Cutaneous Assessment Tool; *LoSDI*, Localized Scleroderma Skin Damage Index; *mLoSSI*, modified Localized Scleroderma Skin Severity Index; *PhysGA*, Physician's Global Assessment; *MRSS*, modified Rodnan Skin Score; *SF-36*, 36-Item Short Form Survey.