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GUIDELINE

Guideline for diagnostic criteria, severity classification and treatment of eosinophilic fasciitis

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ABSTRACT

We established diagnostic criteria and severity classification of eosinophilic fasciitis because there is no established diagnostic criteria or widely accepted severity classification of the disease. Also, there has been no clinical guideline for eosinophilic fasciitis, so we established its clinical guideline ahead of all over the world. In particular, the clinical guideline was established by clinical questions based on evidence-based medicine according to the New Minds Clinical Practice Guideline Creation Manual (version 1.0). We aimed to make the guideline easy to use and reliable based on the newest evidence, and to present guidance as specific as possible for various clinical problems in treatment of eosinophilic fasciitis.

Key words: **collagen, eosinophils, fibrosis, guideline, skin.**

DIAGNOSTIC CRITERIA

The diagnostic criteria of eosinophilic fasciitis are as follows.

Major Criterion:

Symmetrical plate-like sclerotic lesions are present on the four limbs.

However, this condition lacks Raynaud's phenomenon, and systemic sclerosis can be excluded.

Minor Criteria 1:

The histology of a skin biopsy that incorporates the fascia shows fibrosis of the subcutaneous connective tissue, with thickening of the fascia and cellular infiltration of eosinophils and monocytes.

Minor Criteria 2:

Thickening of the fascia is seen using imaging tests such as magnetic resonance imaging (MRI).

A definitive diagnosis is made when a patient has the major criterion and one of the minor criteria, or the major criterion and two of the minor criteria.

SEVERITY CLASSIFICATION

Severity classification of eosinophilic fasciitis

- Joint contracture (upper limbs): 1 point
- Joint contracture (lower limbs): 1 point
- Limited movement (upper limbs): 1 point
- Limited movement (lower limbs): 1 point
- Expansion and worsening of skin rash (progression of symptoms): 1 point.

A total of 2 or more points is classified as severe.

TREATMENT GUIDELINE

CQ1 What are the causes of eosinophilic fasciitis?

Recommendation: Exercise and labor are suggested as related to the onset of eosinophilic fasciitis.

Recommendation level: 1D.

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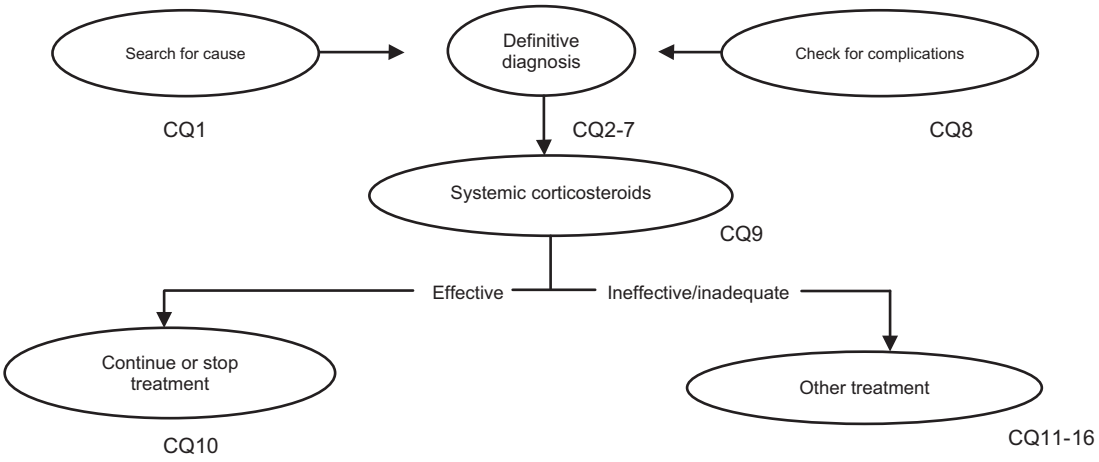

Figure 1. Clinical algorithm for treating eosinophilic fasciitis.

Explanation: This disease is sometimes suspected to have a causative factor; for example, 30–46% of patients with eosinophilic fasciitis have engaged in harsh exercise and work, or have a history of trauma, including bruising, immediately before the onset. Therefore, one of the pathogenic mechanisms is thought to be non-specific inflammation of the injured fascia and the resulting autoimmune response against antigens that are released from the tissue.[1–3] The evidence level is low, but the recommendation level is set as 1D, based on the consensus of the committee that created this guideline (Tables 1–3, Fig. 1).

In addition, similar to localized scleroderma, some cases are positive for *Borrelia burgdorferi* antibody, and *Borrelia* infection may be involved.[4] Mycoplasma infection is also implicated in the onset of the disease.[5]

The onset of this disease is suspected to be related to the use of statins,[6,7] phenytoin,[8] an angiotensin-converting enzyme inhibitor called ramipril[9] and heparin.[10] Similar symptoms are known to develop due to impurities in the manufacturing process of L-tryptophan[11] and through contact with organic solvents such as trichloroethylene and trichloroethane.[12–14]

The disease is also reported to be caused by hemodialysis[15] or radiotherapy[16] and graft-versus-host disease.[17]

CQ2 What clinical findings are useful for diagnosis?

Recommendation: An "orange peel-like appearance" and "groove sign" are recommended as clinical findings that are useful for the diagnosis of this disease (Fig. 2).

Recommendation level: 1D.

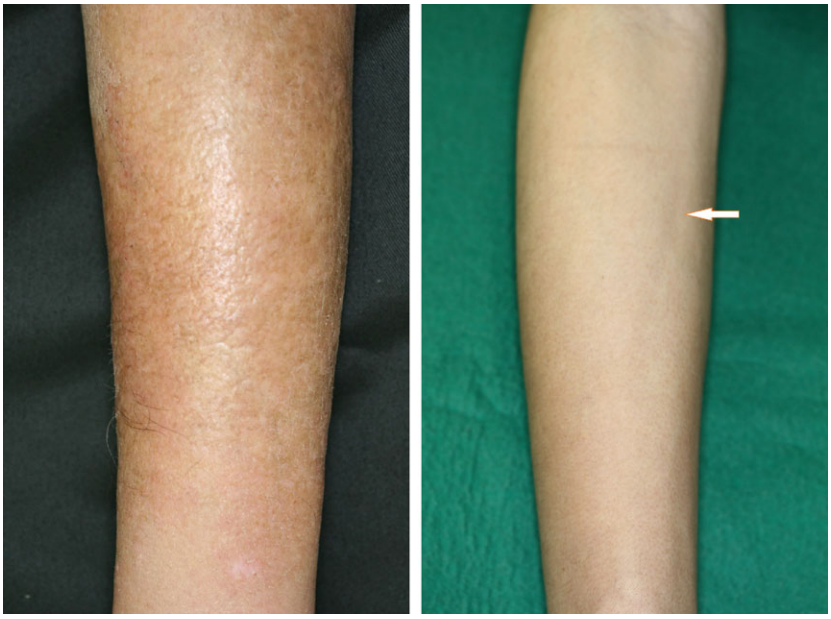

Figure 2. Clinical findings of the orange peel-like appearance and groove sign of eosinophil fasciitis.

Explanation: This disease is characterized by symmetrical swelling, induration and thickening, resulting in limited joint mobility. Normally, the face or fingers are not involved. Additionally, the disease presents with a characteristic orange peel-like appearance (peau d'orange appearance) that is caused by swelling and puckering of the affected skin (Fig. 2). In a report by Berianu *et al.*,[18] eight out of 16 (50%) patients presented with this finding, and the disease duration of these patients was long. Furthermore, the groove sign is a depression along the course of the superficial veins, which is more pronounced on elevation of the affected limb. The epidermis and upper layer of the dermis may be less affected by the fibrosis of this disease and more mobile than the deep dermis and perivascular area. Therefore, the superficial layers of the vessels are pulled inwards when the blood flow decreases in the peripheral blood vessels, creating the characteristic indentation. In a report by Lebeaux *et al.*,[19] 18 of 34 patients (53%) presented with the groove sign.

No studies have a high evidence level regarding the effectiveness of these clinical findings for diagnosis, but the recommendation level is set as 1D, based on the consensus of the committee that created this guideline.

Table 1. New Minds recommendation grades

Presentation of the strength of recommendation	
Recommendation grade	
1	Strongly recommended
2	Advocated
None	When undecided
Evidence level classification	
A	Strong conviction about the estimated effect
B	Moderate conviction about the estimated effect
C	Limited conviction about the estimated effect
D	Almost no conviction about the estimated effect

CQ3 Are blood tests useful for diagnosis and determining disease activity?

Recommendation: The peripheral blood eosinophil count, erythrocyte sedimentation rate and serum aldolase levels are recommended for utilizing as diagnostic or disease activity marker.

Recommendation level: 1D.

Explanation: One of the blood test abnormalities seen in this disease is peripheral eosinophilia, and although the criteria differs depending upon the report, this finding is present in approximately 63–86% of cases.[20–22] This is often transient and only seen during the acute phase, and it reportedly correlates with disease activity, because the levels decrease after treatment.[23] Because peripheral eosinophilia is rare in systemic sclerosis (~7%), and it is useful for the differential diagnosis.[20,24]

The serum immunoglobulin G levels are elevated in approximately 3–72% of cases, and in some patients, these levels correlate with disease activity. However, an investigation by Seibold *et al.* found that it is not statistically significant.[20,22,25–27] On the other hand, an accelerated erythrocyte sedimentation rate is seen in approximately 29–80% of cases, and it correlates with disease activity.[20,26,27]

The serum creatine kinase levels are usually normal, but elevated serum aldolase levels are seen in approximately 60% of cases, and in some reports, the levels decrease with treatment and become elevated again when there is relapse of the skin symptoms. Thus, serum aldolase is effective as an indicator of disease activity.[18,23,28,29] There are also reports that these levels normalize later than other abnormal findings of blood tests, and increase most sharply during relapse.[23]

In addition, serum soluble interleukin-2 receptor levels, serum type III procollagen amino peptide levels, serum immune complexes and serum tissue inhibitor of matrix metalloproteinase-1 levels are reported to be effective as disease activity markers in eosinophilic fasciitis.[26,27,30,31]

Thus, based on the above information, although there are no reports with a high evidence level, peripheral eosinophil

Table 2. Evidence level correspondence

Old evidence level classification		Evidence level classification used in this guideline	
I	Evidence from systematic review/randomized controlled trial/meta-analysis	A	I, II
II	Evidence from at least one randomized controlled trial	B	III
III	Evidence from at least one controlled study without randomization	C	IV
IVa	Evidence from analytical epidemiological studies (cohort study)	D	V, VI
IVb	Evidence from analytical epidemiological studies (case–control study, cross-sectional study)		
V	Evidence from descriptive studies (case reports, case series)		
VI	Evidence from expert committee reports or opinions or clinical experience of respected authorities, not based on patient data		

Also state the strength of evidence in the strength of endorsements or recommendations (A, B, C, D)
(Example) (1) Recommend implementing therapy I for patient P (1A) = (strong recommendation, based on strong evidence)
(2) Propose implementing therapy I compared to therapy C for patient P (2C) = (weak recommendation, based on weak evidence)
(3) Propose not implementing therapy I or therapy C for patient P (2D) = (weak recommendation, based on very weak evidence)
(4) Strongly recommend not implementing therapy I for patient P (1B) = (strong recommendation, based on moderate evidence)

Table 3. Summary of clinical questions

Clinical question	Recommendation Level	Recommendation
CQ1 What are the causes of eosinophilic fasciitis?	1D	Exercise and labor are suggested as related to the onset of eosinophilic fasciitis
CQ2 What clinical findings are useful for diagnosis?	1D	An orange peel-like appearance and groove sign are recommended as clinical findings that are useful for the diagnosis of this disease
CQ3 Are blood tests useful for diagnosis and determining disease activity?	1D	The peripheral blood eosinophil count, erythrocyte sedimentation rate and serum aldolase levels are recommended for utilizing as diagnostic or disease activity marker
CQ4 Are imaging tests effective for diagnosis, finding biopsy sites and evaluating disease activity?	1D–2D	Magnetic resonance imaging (MRI) is recommended as an effective imaging test for the diagnosis of eosinophilic fasciitis, and the use of ultrasound scans has also been proposed. Depending upon the patient, MRI has also been proposed as an effective test for determining biopsy sites and evaluating disease activity or therapeutic response
CQ5 Are skin biopsies effective for diagnosis?	1D	Skin biopsies are effective for diagnosing eosinophilic fasciitis, and performing an en bloc biopsy from the skin to fascia is recommended
CQ6 Are peripheral eosinophilia and histopathological eosinophil infiltration in the fascia essential for diagnosis?	1D	Peripheral eosinophilia and histopathological infiltration of eosinophils in the fascia are effective but not essential for diagnosing eosinophilic fasciitis. Comprehensively diagnosing this disease based on the patient's clinical pictures, laboratory findings and pathohistological characteristics is recommended
CQ7 What findings are useful for differentiating eosinophilic fasciitis from systemic sclerosis?	1D	Eosinophilic fasciitis lacks the digital and facial skin sclerosis that are characteristic of systemic sclerosis, as well as nail fold capillary abnormalities, antinuclear antibodies and disease-specific autoantibodies, but it presents with an orange peel-like appearance and peripheral eosinophilia. Therefore, these findings are recommended as effective for differentiating these two diseases
CQ8 What complications should be noted?	2D	Autoimmune diseases, including localized scleroderma, and hematological malignancies have been reported as complications. Therefore, checking for these complications in patients with eosinophilic fasciitis is proposed
CQ9 Are systemic corticosteroids effective for treating eosinophilic fasciitis?	Oral corticosteroids, 1D; steroid pulse therapy, 1C	Oral corticosteroids and steroid pulse therapy are effective for treating eosinophilic fasciitis, and are recommended
CQ10 Is it possible to stop treatment after remission?	2D	The long-term prognosis of this disease is unknown and some cases relapse; therefore, there is insufficient evidence for ceasing the use of oral steroids. However, there are many reports on cases that could stop treatment. Accordingly, stopping treatment after confirming that the progression of the disease has sufficiently eased has been proposed as an option
CQ11 Is topical therapy effective?	2D	There is insufficient evidence to support the efficacy of topical treatment, but it has been proposed as a treatment option, depending upon the patient. Topical monotherapy is not expected to be effective, and combining topical therapy with an appropriate systemic therapy is preferable
CQ12 Are immunosuppressants effective for treating steroid-resistant cases?	2D	The efficacy of methotrexate, mycophenolate mofetil, cyclosporin, azathioprine and cyclophosphamide for treating eosinophilic fasciitis has been reported; therefore, their use has been proposed as a treatment option
CQ13 Is phototherapy effective?	2D	Phototherapy has been reported to be effective for treating the skin lesions that are seen in patients with eosinophilic fasciitis, and phototherapy has been proposed as a treatment option
CQ14 Is rehabilitation effective?	2D	Rehabilitation is reportedly effective for improving limb contractures, and it is a proposed treatment option
CQ15 Are there any effective therapies other than the aforementioned?	2D	Some reports have found that dapsone, ketotifen, cimetidine, infliximab, chloroquine and hydroxychloroquine have therapeutic effects on eosinophilic fasciitis, and these drugs have been proposed as adjuvant therapy options for refractory cases. However, it is essential to carefully consider using these drugs
CQ16 Does this disease ever resolve spontaneously?	2D	This disease has been reported to resolve spontaneously in some cases; therefore, considering this possibility during treatment is proposed

count, erythrocyte sedimentation rate and serum aldolase levels are regarded as blood test abnormalities that are effective for diagnosis and evaluation of disease activity in eosinophilic fasciitis; therefore, the recommendation level is set as 1D based on the consensus of the committee that created this guideline.

CQ4 Are imaging tests effective for diagnosis, finding biopsy sites and evaluating disease activity?

Recommendation: MRI is recommended as an effective imaging test for the diagnosis of eosinophilic fasciitis, and the use of ultrasound scans has also been proposed. Depending upon the patient, MRI has also been proposed as an effective test for determining biopsy sites and evaluating disease activity or therapeutic response.

Recommendation level: MRI for diagnosis, 1D; MRI for identification of biopsy sites and evaluating disease activity, 2D; ultrasound scans for diagnosis, 2D.

Explanation: MRI is a non-invasive imaging test that may be useful for the management of eosinophilic fasciitis, because MRI can identify the presence of fascia edema and inflammation,[32–34] and it can be effective for diagnosis in cases where biopsy is not possible. The evidence level is low, but the recommendation level is set as 1D, based on the consensus of the committee that created this guideline. There have also been reports of cases in which MRI was effective for determining biopsy sites and evaluating the disease activity or therapeutic response.[32–34]

Subcutaneous thinning has been seen on ultrasound scans (12-MHz/B-mode) in patients with eosinophilic fasciitis, compared with control subjects.[35] Subcutaneous tissue compressibility when the skin is compressed with a probe has been reported as significantly lower in patients with eosinophilic fasciitis than in those with other fibrotic diseases such as systemic sclerosis; therefore, this finding is useful for diagnosis.[35]

There is little evidence, but computed tomography scans may be considered when MRI scans cannot be taken.

CQ5 Are skin biopsies effective for diagnosis?

Recommendation: Skin biopsies are effective for diagnosing eosinophilic fasciitis, and performing an en bloc biopsy from the skin to fascia is recommended.

Recommendation level: 1D.

Explanation: In the initial stage of the disease, edema in the fascia and deep subcutaneous tissue, and infiltration of various inflammatory cells including lymphocytes, plasma cells, histiocytes and eosinophils are characteristic pathohistological findings.[36,37] As the disease progresses, the main pathohistological findings are atrophy of the epidermis, thickening of the fascia, and increase of thickened collagen bundles in the subcutaneous tissue and lower layers of the dermis. Investigations of many cases indicate that epidermal atrophy is seen in 16% of cases, increase of thickened collagen bundles in 40–70%, eosinophil infiltration in 65–80%, thickening of fat septum in more than half and fascia thickening in almost all.[19,23,37,38]

According to the published work, almost all cases with suspected eosinophilic fasciitis are diagnosed using skin biopsies. En bloc biopsies in which the full thickness from the epidermis to fascia and muscle surface is incorporated are particularly useful for the diagnosis of this disease. On the other hand, while the dermis is the principal location of fibrosis in patients with systemic sclerosis or localized scleroderma, in those with eosinophilic fasciitis, fibrosis starts from the fascia and subcutaneous tissue and spreads to the deep layer of the dermis;[37] therefore, a normal biopsy that does not incorporate the fascia and muscle has little value for diagnosis. A punch biopsy does not allow collection of tissue at an adequate depth, and in one report, this type of biopsy did not lead to a diagnosis in three patients.[23] Therefore, using en bloc biopsy to collect tissue at an adequate depth is necessary for patients with eosinophilic fasciitis. The evidence level is low, but the recommendation level is set as 1D, based on the consensus of the committee that created this guideline.

CQ6 Are peripheral eosinophilia and histopathological eosinophil infiltration in the fascia essential for diagnosis?

Recommendation: Peripheral eosinophilia and histopathological infiltration of eosinophils in the fascia are effective but not essential for diagnosing eosinophilic fasciitis. Comprehensively diagnosing this disease based on the patient's clinical pictures, laboratory findings and pathohistological characteristics is recommended.

Recommendation level: 1D.

Explanation: Eosinophilic fasciitis was first reported in 1974, when Shulman described two patients who presented with peripheral eosinophilia, as well as swelling and induration of skin and soft tissue with joint contractures on the limbs, and he named the condition "diffuse fasciitis with eosinophilia".[1] Thereafter, Rodnan *et al.*[39] reported six similar cases, but they found that these cases not only had peripheral eosinophilia, but a large number of eosinophils had also infiltrated the fascia, and the authors called the disease "eosinophilic fasciitis". In this way, the disease name "eosinophilic fasciitis" has been in general use, because it was originally considered a disease that was characterized by involvement of eosinophils. However, other studies have subsequently clarified that a certain number of cases did not have peripheral eosinophilia and there were also cases that did not have significant histopathological infiltration of eosinophils in the fascia; therefore, the condition also became known as diffuse fasciitis with or without eosinophilia. In reality, although the criteria for peripheral eosinophilia differs depending upon the report, approximately 63–86% of cases present with peripheral eosinophilia, and it is not present in all cases.[20–22,24,40] Furthermore, it is often transitory and is only seen at the acute stage.[23] In other reports, histopathological infiltration of eosinophils in the fascia was found in 13 out of 20 cases, and the infiltration was only localized and transitory.[23,37] In a compilation report by Endo *et al.*,[38] 61 out of 76 patients (80.2%) presented with infiltration.

Based on the above information, peripheral eosinophilia and histopathological infiltration of eosinophils in the fascia is useful

but not essential for diagnosis, and comprehensively diagnosing the disease based on the patient's clinical pictures, laboratory findings and pathohistological characteristics is recommended. The evidence level is low, but the recommendation level is set as 1D, based on the consensus of the committee that created this guideline.

CQ7 What findings are useful for differentiating eosinophilic fasciitis from systemic sclerosis?

Recommendation: Eosinophilic fasciitis lacks the digital and facial skin sclerosis that is characteristic of systemic sclerosis, as well as nail fold capillary abnormalities, antinuclear antibodies and disease-specific autoantibodies, but it presents with an orange peel-like appearance and peripheral eosinophilia. Therefore, these findings are recommended as effective for differentiating these two diseases.

Recommendation level: 1D.

Explanation: Eosinophilic fasciitis and systemic sclerosis have many commonalities, but the two diseases are fundamentally different; therefore, differentiation of them is important. Unlike systemic sclerosis, eosinophilic fasciitis normally lacks digital and facial skin sclerosis, and presents with the characteristic orange peel-like appearance (peau d'orange appearance), which is caused by swelling and puckering of the affected skin. In a report by Berianu *et al.*, eight out of 16 subjects (50%) presented with these signs, and the disease duration of these patients was long.[18,24] Furthermore, the nail fold capillary abnormalities, antinuclear antibodies and systemic sclerosis-specific autoantibodies (anti-topoisomerase I antibodies, anticentromere antibodies and anti-RNA polymerase antibodies) do not appear in eosinophilic fasciitis, but instead patients with eosinophilic fasciitis experience elevated levels of peripheral eosinophils.[41,42] Eosinophilic fasciitis is not normally associated with Raynaud's phenomenon, but there has been a report of patients with accompanying Raynaud's phenomenon.[43]

The evidence level is low, but the recommendation level is set as 1D, based on the consensus of the committee that created this guideline.

CQ8 What complications should be noted?

Recommendation: Autoimmune diseases, including localized scleroderma, and hematological malignancies have been reported as complications. Therefore, checking for these complications in patients with eosinophilic fasciitis is proposed.

Recommendation level: 2D.

Explanation: Multiple reports have evaluated the complications that are associated with eosinophilic fasciitis, including: autoimmune diseases such as localized scleroderma (30%),[44] autoimmune thyroiditis,[45] systemic lupus erythematosus,[45] and rheumatoid arthritis;[20,45] blood diseases such as aplastic anemia,[45] thrombocytopenic purpura,[45] autoimmune hemolytic anemia,[45] malignant lymphoma,[45] leukemia,[45,46] multiple myeloma[44,47] and myelodysplastic syndrome;[45,46] peripheral neuropathy[20,40,48]; and visceral malignant tumors including prostate cancer[45,46] and breast cancer.[20,45] Muscle pain and weakness can sometimes occur due to perimyositis with the spread of fasciitis, but myositis is not normally seen.[49]

It is unknown whether the incidence of the aforementioned diseases increases in patients with eosinophilic fasciitis, and the causal relationship is not proved, but there are reports of patients who developed multiple complications.[46,50] Therefore, checking for these complications in patients with eosinophilic fasciitis is proposed.

CQ9 Are systemic corticosteroids effective for treating eosinophilic fasciitis?

Recommendation: Oral corticosteroids and steroid pulse therapy are effective for treating eosinophilic fasciitis, and are recommended.

Recommendation level: Oral corticosteroids, 1D; steroid pulse therapy, 1C.

Explanation: The initial treatment for eosinophilic fasciitis is generally oral prednisolone 0.5–1 mg/kg per day. There are no randomized studies on steroid therapy, but in a study by Endo *et al.*[38] 24 subjects were cured, 13 went into remission and 15 were unchanged with a mean dose of 39.7 mg/day of prednisolone. In a report on 52 subjects, 34 of the patients were initially treated with 40–60 mg/day of oral prednisone. The symptoms eased in 20 of the patients and disappeared in five, and nine patients were resistant to treatment.[20] Similarly, Bischoff *et al.*[40] reported that skin symptoms improved in eight out of 12 patients who took 20 mg/day or more of oral prednisone.

In a report by Lebeaux *et al.*,[19] 15 out of 32 patients were treated with steroid pulse therapy. There was a higher rate of complete remission in the treated group than in the non-treated group (87% vs 53%, $P = 0.06$), and the rate of concomitant immunosuppressant use was significantly lower in the treated group than in the non-treated group (20% vs 65%, $P = 0.02$).

Based on the above information, oral steroid or steroid pulse therapy is effective for treating eosinophilic fasciitis. The evidence level is low, but the recommendation level is set as 1D or 1C, respectively, based on the consensus of the committee that created this guideline.

CQ10 Is it possible to stop treatment after remission?

Recommendation: The long-term prognosis of this disease is unknown and some cases relapse; therefore, there is insufficient evidence for ceasing the use of oral steroids. However, there are many reports of cases in whom treatment could not be stopped. Accordingly, stopping treatment after confirming that the progression of the disease has sufficiently eased has been proposed as an option.

Recommendation level: 2D.

Explanation: Many reports have been published on patients who tapered and then stopped pharmacotherapy based on the improvement of skin lesions and serological tests, and maintain full remission.[6,51] Furthermore, Lebeaux *et al.*[19] retrospectively investigated the clinical course of 34 patients with eosinophilic fasciitis and reported that 53% of the patients who were treated with concomitant oral steroids and immunosuppressants were able to stop treatment, which suggests that depending

upon the patient, some people may be able to discontinue steroid and immunosuppressant treatment. Conversely, other cases experienced relapsed after the steroid dose was tapered,[18,52] and in one report, 70% of cases relapsed after stopping methotrexate once they achieved remission.[18] Thus, there is insufficient evidence to indicate that treatment can be stopped. Therefore, while it is essential to carefully investigate the applicability of stopping treatment, it is proposed as a treatment option.

CQ11 Is topical therapy effective?

Recommendation: There is insufficient evidence to support the efficacy of topical treatment, but it has been proposed as a treatment option, depending upon the patient. Topical monotherapy is not expected to be effective, and combining topical therapy with an appropriate systemic therapy is preferable.

Recommendation level: 2D.

Explanation: A search for reports revealed that only one study used topical steroids to treat skin lesions that were associated with eosinophilic fasciitis, and topical steroids were used concurrently with an anti-allergic agent; but the treatment was ineffective.[53] In another report, a patient used tacrolimus ointment, but it was not effective.[40] These results probably reflect the pathology of eosinophilic fasciitis that the fascia is mainly affected, and there is insufficient evidence to show that topical drugs are effective for treating eosinophilic fasciitis. However, topical therapy may be effective for patients in whom the fibrosis extends as far as the upper dermis. With the consensus of the committee that created this guideline, topical therapy is proposed as a possible adjuvant therapy once the patient has had appropriate systemic treatment.

CQ12 Are immunosuppressants effective for treating steroid-resistant cases?

Recommendation: The efficacy of methotrexate, mycophenolate mofetil, cyclosporin, azathioprine and cyclophosphamide for treating eosinophilic fasciitis has been reported; therefore, their use has been proposed as a treatment option.

Recommendation level: 2D.

Explanation: There is a comparatively large number of reports on methotrexate, and the first patient who was successfully treated with methotrexate was reported in 1995.[54] Subsequently, Lebeaux *et al.*[19] treated 12 steroid-resistant patients with methotrexate, and reported that four patients achieved complete remission, but there was little effect in the remaining eight patients. Berianu *et al.*[18] treated 16 patients, including steroid-resistant patients, with methotrexate, and reported that three patients achieved complete remission and seven had partial remission.

No reports have a high level of evidence to support the use of mycophenolate mofetil, cyclosporin, azathioprine and cyclophosphamide, but a number of case reports have described successful treatments with these immunosuppressants.[55–59] Based on the above information, immunosuppressants may be effective for refractory cases, and these drugs may be considered as a treatment option. However, immunosuppressants are not currently covered by insurance.

CQ13 Is phototherapy effective?

Recommendation: Phototherapy has been reported to be effective for treating the skin lesions that are seen in patients with eosinophilic fasciitis, and phototherapy has been proposed as a treatment option.

Recommendation level: 2D.

Explanation: There are a number of reports on the use of phototherapy for the skin lesions that are seen in patients with eosinophilic fasciitis, and psoralen plus ultraviolet A therapy was effective within 6 months for a patient who was unresponsive to steroids and chloroquine.[60] Weber *et al.*[61] achieved good results with ultraviolet A1 along with retinoids and oral corticosteroids. Based on the above information, although few reports have a high level of evidence, phototherapy may be considered as a treatment option for eosinophilic fasciitis.

CQ14 Is rehabilitation effective?

Recommendation: Rehabilitation is reportedly effective for improving limb contractures, and it is a proposed treatment option.

Recommendation level: 2D.

Explanation: Patients with eosinophilic fasciitis are prone to limb contracture; therefore, rehabilitation may be effective and its efficacy has been shown in multiple case reports. A specific rehabilitation program has not been established, but Dozono *et al.*[62] implemented exercise therapy (after warming the joints with a hot pack, the patients performed joint range of motion exercises with active assistance using a pulley for the shoulder joint, passive range of motion exercises for major joints and leg muscle strength training using wall bars) and occupational therapy (muscle strength training for the intrinsic hand muscles using Celloplast, sanding and daily activity training exercises) five times per week for approximately 2 h per session before starting steroid therapy, and found that patients' range of motion improved. O'Laughlin *et al.*[63] reported on the efficacy of physical therapy with paraffin baths, active/passive movement and walking in a pool after pharmacotherapy, 8 months after the onset of the disease. Two reports from Japan also found that rehabilitation was effective for treating residual joint contractures after pharmacotherapy was administrated.[14,64]

On the other hand, it is known that eosinophilic fasciitis can develop due to excessive exercise, and one of the four patients mentioned above had an increased eosinophil count and C-reactive protein levels after starting rehabilitation.[14] The clinical symptoms did not worsen in all patients. Although the evidence level is low, the benefit of rehabilitation may outweigh its risk, but it is essential to fully consider the possibility that symptoms may worsen due to rehabilitation.

CQ15 Are there any effective therapies other than the aforementioned?

Recommendation: Some reports have found that dapsone, ketotifen, cimetidine, infliximab, chloroquine and hydroxychloroquine have therapeutic effects on eosinophilic fasciitis, and these drugs have been proposed as adjuvant therapy options for refractory cases. However, it is essential to carefully consider using these drugs.

Recommendation level: 2D.

Explanation: To date, various treatments for eosinophilic fasciitis have been tried. The treatments listed below have been evaluated in a small number of patients, and they have a low evidence level, but these treatments may be considered as options while carefully evaluating patients for adverse drug reactions.

Dapsone (4,4′-diaminodiphenylsulfone) is expected to reduce eosinophil-related inflammation through the inhibition of eosinophil peroxidase, and in one case report, the patient's symptoms improved after 2 weeks of treatment, resulting in the successful reduction of the steroid dose.[65] Ketotifin may also have an inhibitory effect on eosinophils, and in one report, this drug was effective at preventing relapse.[66] Other reports have found that there were responders and non-responders to the H_1 blocker cimetidine.[66–68]

Furthermore, while the role of tumor necrosis factor-α in eosinophilic fasciitis is not yet clear, in a number of reports infliximab was effective for patients who responded poorly to other treatments.[69,70] Penicillamine is thought to have an inhibitory effect on collagen expression or immune response, and some patients have responded to this treatment. However, there are also non-responders, and it is vital to be aware of adverse reactions due to penicillamine.[71–73] The efficacy of chloroquine or hydroxychloroquine has also been suggested,[74,75] but there have also been non-responders to this treatment.[18,60] In one study, 12 out of 14 patients who concurrently used colchicine with steroids and immunosuppressants were reported to have achieved complete remission.[44] In the other study, some cases achieved partial remission with the concomitant use of colchicine and prednisolone at 30 mg/day,[45] but the efficacy of colchicine itself is unknown. Similarly, there are also examples of the use of sulphasalazine, but the treatment is used in combination with multiple drugs, and it is difficult to evaluate its own efficacy.[40,76] A case report described that eosinophilic fasciitis improved by treating aplastic anemia with bone marrow transplantation,[77,78] which suggests that treating the underlying disease may be effective.

Further investigation into the efficacy of rituximab, i.v. immunoglobulin, anti-thymocyte globulin and fasciectomy is desired.[43,45,56,79–81]

Many of the treatments described above have been combined with corticosteroids; therefore, they are proposed as options for adjuvant therapy in refractory cases, but it is essential to carefully consider the use of these treatments. These treatments are currently not covered by insurance companies in Japan, and chloroquine is not available in Japan.

CQ16 Does this disease ever resolve spontaneously?

Recommendation: This disease has been reported to resolve spontaneously in some cases; therefore, considering this possibility during treatment is proposed.

Recommendation level: 2D.

Explanation: This disease has been reported to resolve spontaneously without treatment in some cases.[82,83] Lakhanpal *et al.*[20] reported that the symptoms resolved without treatment in two out of five patients with eosinophilic fasciitis, and the symptoms improved by 50% in two other cases. Michet *et al.*[84] also reported that the condition spontaneously resolved without treatment in one of two patients; only ankle and elbow contracture remained.

On the other hand, other reports have found that some cases repeatedly experienced relapse after the symptoms spontaneously resolved,[85] and caution is needed. However, when treating patients with eosinophilic fasciitis, considering the possibility that this condition may spontaneously resolve is recommended.

CONFLICT OF INTEREST: None declared.

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