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ORIGINAL ARTICLE

Characteristics of Japanese patients with eosinophilic fasciitis: A brief multicenter study

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ABSTRACT

Eosinophilic fasciitis is a relatively rare cutaneous fibrotic condition affecting the deep fascia of the extremities, with or without peripheral blood eosinophilia. To examine the characteristics of Japanese patients with eosinophilic fasciitis, we conducted a brief, multicenter, retrospective survey at seven university hospitals. In total, 31 patients were identified as having eosinophilic fasciitis, among whom 30 patients fulfilled the Japanese diagnostic criteria. The male : female ratio was 2.3:1, and the mean age was 47.7 years. Three of the patients were under 20 years old. The possible triggering factors included muscle training, sports, walking or sitting for a long time, physical work, insect bite and drug. Co-occurrence of morphea was observed in nine cases (29%), and malignancies were associated in three (two hematological malignancies and one internal malignancy). Immunological abnormalities in the serum showed positive antinuclear antibody, positive rheumatoid factor, increased aldolase levels and increased immunoglobulin G levels. The patients were treated with either monotherapy or combination therapy by oral prednisolone (20–80 mg/day), methotrexate (6–10 mg/week), cyclosporin (100–150 mg/day), mizoribine, infliximab and phototherapy. Methylprednisolone pulse therapy was performed in six cases. By contrast, spontaneous improvement due to resting only was observed in two cases, and skin hardening was improved by withdrawal of the anticancer drug in one case. This study suggests several characteristics of Japanese patients with eosinophilic fasciitis, namely male predominance, rare pediatric occurrence, immunological abnormalities and coexistence with morphea. Systemic prednisolone is the first-line therapy, but pulse therapy is occasionally required for severe cases. The triggering events of physical stress are not so frequent as have previously been reported, and various factors or even unknown factors may be associated with the induction of eosinophilic fasciitis.

Key words: eosinophil, fasciitis–panniculitis syndrome, fibrosis, paraneoplastic, therapy.

INTRODUCTION

Eosinophilic fasciitis is a rare fibrotic disorder presenting as wooden or plate-like symmetrical hardening of the upper and lower extremities.[1–4] It was originally described by Shulman[5] as scleroderma-like changes associated with peripheral eosinophilia, hypergammaglobulinemia and a raised erythrocyte sedimentation ratio. Eosinophilic fasciitis resembles systemic sclerosis but usually lacks either Raynaud's phenomenon or finger swelling. Some regard eosinophilic fasciitis as a subtype of deep morphea,[6,7] but whether eosinophilic fasciitis is morphea profundus or not remains controversial.

Eosinophilic fasciitis is occasionally induced by vigorous exercise, as well as trauma, leading to the hardening of the skin and limited range of movement in the joints. Moreover, cases of drug-induced or paraneoplastic eosinophilic fasciitis have also been reported. An en bloc biopsy typically reveals an inflammatory infiltrate of mononuclear cells and eosinophils in the thickened fascia. Eosinophilic fasciitis is sometimes

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associated with several autoimmune conditions, and morphea is the most frequent skin disease. Recently, diagnostic criteria, severity classification and clinical guidelines for eosinophilic fasciitis have been also proposed in Japan.[8] To determine the characteristics of Japanese eosinophilic fasciitis patients, we conducted a multicenter, retrospective survey, and herein report the current status of eosinophilic fasciitis in Japan.

METHODS

This study was a multicenter, non-interventional, retrospective study, conducted using electronic medical records. Patients with eosinophilic fasciitis, who newly presented at seven university hospitals (Kumamoto University, Tokyo University, Kanazawa University, Gunma University, Tsukuba University, Wakayama Medical University and Fukushima Medical University) over a period of 5 years were included. All of the patients underwent histological examination and fulfilled the criteria recently proposed in Japan.[8] The evaluation items obtained from the patients' medical records were: age, sex, duration of disease, triggering factors, occupation, comorbidities, serum antinuclear antibody, rheumatoid factor, aldolase, immunoglobulin (Ig)G and therapies. This retrospective study was approved by the institutional review board of each institute.

RESULTS

In total, 31 patients with eosinophilic fasciitis were identified from seven institutes. Among them, one case did not fulfill the Japanese diagnostic criteria[4] because of unilateral onset and was thus excluded. The remaining 30 cases were from Tokyo University (n = 10), Kanazawa University (n = 5), Gunma University (n = 5), Fukushima Medical University (n = 5), Kumamoto University (n = 3), Tsukuba University (n = 1) and Wakayama Medical University (n = 1). The study population comprised 21 (70%) males and nine females (30%) (male : female, 2.3:1), with an age range of 8–80 years and a mean age of 47.7 years. Skin biopsy was carried out in all patients. The possible triggering factors included muscle training (n = 2), sports (n = 3), walking or sitting for a long time (n = 3), physical work (n = 2), insect bite (n = 1) and drug (n = 1). Co-occurrence of morphea was observed in nine cases (29%) and associated malignancies were present in three cases (two hematological malignancies and one internal malignancy). Laboratory examination showed immunological abnormalities in the serum, such as positive antinuclear antibody (n = 11), positive rheumatoid factor (n = 1), increased aldolase levels (n = 11) and increased IgG levels (n = 4). Patients were treated with either monotherapy or combination therapies of oral prednisolone (20–80 mg/day) (n = 27), methotrexate (6–10 mg/week) (n = 6), cyclosporin (100–150 mg/day) (n = 2), mizoribine (n = 1), infliximab (n = 1) and/or phototherapy (n = 2). Pulse therapy was performed in six cases (methylprednisolone 500–1000 mg/day for a consecutive 3 days). By contrast, spontaneous improvement due to resting only was observed in two cases, and skin hardening was improved by withdrawal of an anticancer drug in one case.

DISCUSSION

This is the first multicenter study of eosinophilic fasciitis in Japan, although it is a brief study without detailed examination. The characteristics of the study population are summarized in Table 1. Eosinophilic fasciitis is sometimes regarded as deep morphea histologically; however, clinically, characteristic features such as symmetrical profound sclerosis are typically exhibited on the extremities. To highlight the distinct differences in systemic sclerosis, the Japanese guidelines used the description of "plate-like", instead of "edematous", sclerotic lesions. To accurately diagnose eosinophilic fasciitis, systemic sclerosis must first be excluded.

The relationship between eosinophilic fasciitis and deep morphea (morphea profundus) is still unclear. Morphea profundus involves subcutaneous tissues as well as deeper tissues, even without eosinophil infiltration. Indeed, morphea, either solitary, multiple or generalized, is sometimes observed in association with eosinophilic fasciitis. In a previous series of 34 cases, morphea was clinically present in 41% of the patients.[9] In the present study, morphea was observed in 29% of the patients, which suggests a possible relationship with similar pathogenesis; however, there also may be differences such as eosinophil infiltration and CD34 expression between the local lesions even in a single individual,[10] and thus further studies are necessary. Previously, Endo *et al.*[11] reviewed 88 cases of eosinophilic fasciitis, which included two of their own cases and a published work review; they found that morphea was observed in 19.3% (17/88) of those cases. They separated those cases into three groups according to outcome: cure, remission and permanent. The presence of morphea-like lesions was associated with refractory fibrosis. In addition, younger age of onset and trunk involvement were also associated with residual fibrosis.

Table 1. Clinical characteristics of 30 patients with eosinophilic fasciitis

	n
Male : female	21:9 (2.3:1)
Age, years (mean)	8–80 (47.7)
Triggering events	
Muscle training	2
Sports	3
Walking/sitting for a long time	3
Physical work	2
Insect bite	1
Drug (chemotherapy)	1
Associated diseases	
Malignancy	2
Lower leg varix	1
Diabetes mellitus	3
Hyperlipidemia	1
Hypertension	4
Atrial fibrillation	1
Gastric ulcer	1
Morphea	9

Another similar condition is fasciitis–panniculitis syndrome, which was described by Naschitz *et al*.[12] as a paraneoplastic syndrome related to eosinophilic fasciitis. In their series of 12 cases, hematological malignancies were most common (n = 9), with solid internal cancers (n = 3) being less common.[13] They speculate that eosinophilic fasciitis is a wider and more general prototype of fasciitis–panniculitis syndrome. Eosinophilic fasciitis is sometimes seen in patients with hematological malignancies.[14,15] In the present study, associated malignancies were detected in three cases (two hematological malignancies and one internal malignancy).

Eosinophilic fasciitis is occasionally induced by vigorous exercise as well as trauma, leading to the hardening of the skin and limited range of movement in the joints. Trauma or intense exercise preceded the onset of eosinophilic fasciitis in 28% of 29 patients.[16] Among our patients, 10 cases (33.3%) had prior episodes of physical stress. The triggering events of physical stress were not so frequent as had previously been reported, and other factors such as malignancy, drugs or even unknown factors may be associated with the induction of eosinophilic fasciitis.

Laboratory findings in eosinophilic fasciitis include peripheral blood eosinophilia, hypergammaglobulinemia and increased levels of inflammatory markers, such as C-reactive protein and erythrocyte sedimentation rate. In addition, several immunological abnormalities have been reported, such as antinuclear antibody and rheumatoid factor, whereas specific autoantibodies are absent. Previous reports showed that 2–20% of patients with eosinophilic fasciitis had positive antinuclear antibodies.[1] In the present study, antinuclear antibodies were present in over 30% of the patients. Occasionally, muscle enzymes such as creatinine kinase and aldolase are elevated, and aldolase may serve as a useful indicator of disease activity.[17] The cases in the current study showed increased aldolase levels, but its association with disease course was unknown. In addition, the serum levels of tissue inhibitors of metalloproteinase (TIMP)-1, TIMP-2, matrix metalloproteinase 13, CD40 and manganese superoxide dismutase have been reported to be elevated in patients with eosinophilic fasciitis.[18–21] A recent study from Japan showed that serum thymus and activation-regulated chemokine levels may be a marker of eosinophilic fasciitis,[22] and may be a new biomarker of eosinophilic fasciitis.

Usually, treatment was started with prednisolone in small to moderate amounts (0.5–1 mg/kg per day). Additional treatment with methotrexate, azathioprine, cyclophosphamide, cyclosporin, mycophenolate mofetil, D-penicillamine, biologics (tumor necrosis factor blocker, interleukin-6 receptor inhibitor, rituximab), hydroxychloroquine, dapsone, colchicine, iv. Ig, extracorporeal photopheresis, as well as phototherapy and physical therapies are sometimes necessary depending on the case severity.[1,23] Extensive skin induration of eosinophilic fasciitis can lead to joint contractures and tendon retraction, which reflect the severity of fascia fibrosis. A previous study showed that 29 of 52 patients (55.8%) had flexion contractures,[24] and another study showed 50% (31/62) had joint contractures.[16] In cases of severe joint contracture, methylprednisolone pulse therapy should be considered. In our study, oral prednisolone was used as a first-line therapy in 90% of the cases, and methotrexate was also used in six cases. Methylprednisolone pulse therapy was carried out in six severe cases. Treatment modalities are summarized in Table 2.

Table 2. Therapy of eosinophilic fasciitis

Therapy	*n*
Corticosteroid	
Oral	27
Pulse	6
Immunosuppressive drug	
Cyclosporin	2
Mizoribine	1
DMARDs	
Methotrexate	6
Biologics	
Infliximab	1
Chemotherapy	
CHOP therapy	1
Phototherapy	2
Spontaneous improvement	2

The current study has some limitations. First, the study was retrospective in design, and may therefore have some biases. Second, detailed examinations were not carried out. Third, the treatment regimens may differ depending on the institution. Lastly, long-term follow up is lacking. Nonetheless, we evaluated the characteristics of the highest number of Japanese patients with eosinophilic fasciitis in multicenter studies. Further studies are necessary to determine the similarities and differences between Asian and Western populations regarding the characteristics of patients with eosinophilic fasciitis.

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CONFLICT OF INTEREST: None declared.

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