Clinical and pathologic features and therapeutic management of eosinophilic fasciitis

Yun Li[1,2], Xing Chang[3], Xu-Ming Mao[4], Wei Du[2], Yue-Ping Zeng[2], Xie Yuan[2], Jun Li[1], Li Jia[2], Tao Zhang[2], Yong Xie[2], Qing Li[1], Qiu-Ning Sun[2]

[1]Department of Dermatology, Beijing Tian Tan Hospital, Capital Medical University, Beijing 100070, China;
[2]Department of Dermatology, Chinese Academy of Medical Sciences, Peking Union Medical College, Peking Union Medical College Hospital, Beijing 100730, China;
[3]Department of Education, Chinese Academy of Medical Sciences, Peking Union Medical College, Peking Union Medical College Hospital, Beijing 100005, China;
[4]Department of Dermatology, University of Pennsylvania, Philadelphia, PA, USA.

To the Editor: Eosinophilic fasciitis (EF) is a rare scleroderma-like syndrome of diffuse fasciitis and eosinophilia with unknown etiology, and occurs almost equally in both sexes. At onset, the mean age of patients is 40 to 50 years. Pinal-Fernandez *et al*[1] and Jinnin and Yamamoto[2] proposed criteria for EF diagnosis, including sclerotic lesions, cutaneous induration, and typical fascial thickening with inflammatory infiltration. The skin lesions may progress from edema of the extremities to peau d'orange with hyperpigmentation, the "groove" sign, and woody induration with skin tightness. Various extracutaneous manifestations, such as synovitis, contractures, and arthritic, pulmonary, hematologic, and neoplastic manifestations, may occur. Recently, magnetic resonance imaging has been used for the diagnosis of EF. Laboratory analysis usually reveals an elevated erythrocyte sedimentation rate, peripheral eosinophilia, and hypergammaglobulinemia. The therapeutic management of EF remains a challenge; the current mainstay, steroids, is effective in just over 60% of patients.[3] In some cases, immunosuppressive drugs (acetazolamide, cyclophosphamide, methotrexate, and ciclosporin) and anti-tumor necrosis alpha inhibitors, such as infliximab and photochemotherapy, are also used. To the best of our knowledge, our study will be the most extensive retrospective study to report the demographics, risk factors, disease patterns, clinical, pathologic, and morphologic features, and therapeutic management to allow a greater understanding of the clinical characteristics and achieve effect EF therapy in the Chinese Han population.

By employing a retrospective chart review, we included all patients who were referred to our scleroderma clinic within a 7-year span with a diagnosis of EF. This study was approved by the Institutional Ethics Committee of Peking Union Medical College Hospital (No. S-K1020) and oral informed consent was obtained from each patient. These patients had clinical presentations of a scleroderma-like illness and were diagnosed based on clinical presentation, laboratory findings, and biopsy-proven fascia involvement at our scleroderma center.[4] We collected data, including demographics, the duration and quality of presenting symptoms, laboratory and imaging results, therapeutic management, follow-up, and clinical response for each patient, and potential triggers. Thirty patients underwent biopsies in our hospital, and the characteristic morphologic changes of EF were seen. The biopsies were specifically evaluated for the evidence of epidermal atrophy, as well as fibrosclerosis of the dermis, subcutis, fascia, and muscle. In addition, the location, components, and intensity of the inflammatory reaction were noted.[5] Data were collected regarding treatment regimen, clinical and biologic responses, and any clinical changes found at follow-up visits. The prescribed treatments included oral steroids and Chinese herbs, called fusong or fusu tablets, vitamin B and E, topical tacrolimus, hirudoid cream, tretinoin ointment, compound heparin sodium, and allantoin gel. Response to therapy was measured based on the total body surface involvement and the activity of the limbs. A complete laboratory response was defined as the normalization of peripheral eosinophil count. A multinomial logistic regression analysis was used to assess independent associations based on the results of univariate analyses, such as age at onset, type and duration of disease, sex, joint involvement, and hypereosinophilia ($P < 0.1$). A fitted model was used to evaluate the odds ratio associated with the type of disease. All tests were two-tailed, and a P value of <0.05 was considered to indicate statistically significance. All statistical analyses were performed using the SPSS software version 18 (SPSS, Chicago, IL, USA).

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Correspondence to: Dr. Qiu-Ning Sun, Department of Dermatology, Chinese Academy of Medical Sciences, Peking Union Medical College, Peking Union Medical College Hospital, Beijing 100730, China
E-Mail: sunqnzhy@yahoo.com

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Of the 78 Chinese patients with EF, 47 (60%) were females and 31 (40%) males. The mean age at onset was 31.88 ± 17.04 years. The average time of diagnosis from the first symptoms of EF was 4.84 ± 6.20 years. For patients with a failed treatment, the median time was 8 (4, 20) years. In contrast, for patients that experienced remission, it was 2 (1, 4) years. In general, the disease was diagnosed sooner in men (average 3.33 years) than in women (average 6.82 years). The duration of the disease before the initial biopsy varied from 2 months to 26 years, but was ≤1 year in only ten cases. Five (6.4%) patients had a fever lasting from days to weeks, and six patients experienced fatigue. Six patients had a history of surgery or trauma preceding the onset of EF. One female patient was breastfeeding. The majority of patients experienced swelling and induration of the forearms and legs at the onset, followed by hyperpigmentation. The patients eventually developed severe induration of the skin and subcutaneous tissues, with marked motor limitations of the hands and feet. Upper extremity involvement was identified in 44 patients, and 57 patients had lower extremity involvement. Thirty patients (38%) had a groove sign on the limbs [Figure 1A], 39 patients (50%) had morphea-like lesions [Figure 1C], and nine patients (12%) had a peau d'orange appearance [Figure 1B]. We found that the type of disease was associated with the duration of disease (odds ratio = 0.007; $P = 0.03$) and the duration of groove sign and morphea was longer than that of the peau d'orange appearance. In 59 cases, the induration of skin and the subcutis was limited to the extremities; in 19 patients, it extended variably to the trunk. Joint contractures were the most common extracutaneous manifestations that affected 19 patients. The lesions involved the hand (2/78), the wrist (3/78), the elbow (7/78), knee (11/78), ankle (3/78), and shoulder (1/78). Ten patients (13%) had arthralgia, one patient (1.3%) had chronic hepatitis, and one patient (1.3%) had frequent diarrhea; two (2.6%) patients had a significant family history. Five patients with disease duration less than 10 years and who had flexion contractures complained of short stature, and the affected limb appeared different from the other extremity. High C-reactive protein was found in six out of 20 patients and hypereosinophilia was found in 14 patients. The mean initial peripheral eosinophil count was 9.42 ± 4.59% (range: 0.2–17.9%). Hypereosinophilia in the patients diagnosed within 12 months after initial symptoms was 8.07%, as compared with 9.79% in the patients diagnosed more than 12 months after their initial symptoms. The total eosinophil count was $>1 \times 10^9$ cells/L in six patients. Twenty patients (20/51, 39%) were tested positive for anti-nuclear antibodies. Six patients (6/44, 13.6%) had positive ds-DNA, and three patients (3/44, 6.8%) had positive extractable nuclear antigens. Patients with high anti-nuclear antibody titers were usually younger with more diffuse lesions.

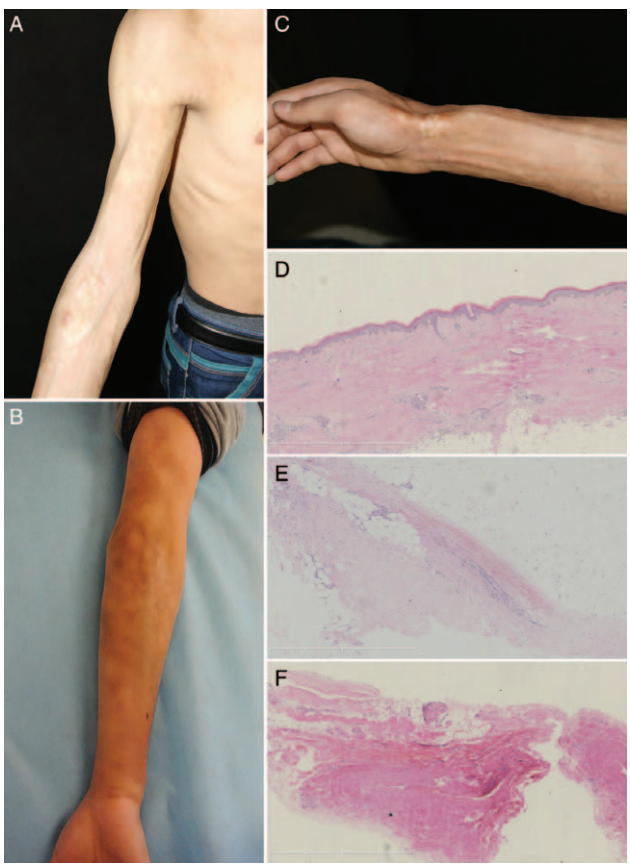

Figure 1: The patient with a groove sign on the limbs (A), Peau d'orange appearance (B), morphea-like lesions (C), severe dermis sclerosis (D, hematoxylin-eosin staining, scale bar = 2 mm), markedly sclerotic interlobular fibrous septums (E, hematoxylin-eosin staining, scale bar = 1 mm), and markedly fascial sclerosis (F, hematoxylin-eosin staining, scale bar = 2 mm).

Thirty patients underwent full-thickness skin to fascia biopsy; the epidermis was normal in five cases, showed mild atrophy in 16 cases, moderate atrophy in nine cases, with no cases of severe atrophy. Increased melanin deposits were present in the basal layer of the epidermis in all 30 patients. The dermis was normal in two cases, whereas 25 patients exhibited sclerosis: seven severe cases [Figure 1D], seven moderate cases, and 11 cases of mild disease. There was infiltration of lymphocytes, plasma cells, histiocytes, and occasionally eosinophils, in patchy periappendageal, and circumvascular locations in 19 cases (18 mild, one moderate) and the interstitium in four cases. The interlobular fibrous septums of the subcutis, particularly in the lower limbs, were markedly sclerotic in three biopsies [Figure 1E], moderately sclerotic in nine biopsies, and mildly sclerotic in seven biopsies. An infiltrate of lymphocytes, plasma cells, histiocytes, and eosinophils occupied the fibrous septums (marked infiltration in one biopsy, moderate infiltration in one biopsy, and mild infiltration in seven biopsies) or the periphery of the fat lobules (marked infiltrate in one biopsy, moderate infiltration in four biopsies, and mild infiltration in five biopsies), or both (three biopsies). As the disease progressed, the thick sclerotic septums often fused with the fascia and occasionally the reticular dermis. Severe fascial thickening and sclerosis were observed in ten patients [Figure 1F], moderate in 13 patients, and mild in seven patients. The components of the inflammatory infiltrate were the same as subcutis (marked infiltrate in two biopsies, moderate infiltrate in four biopsies, and mild infiltrate in 14 biopsies). Tissue eosinophils were quantitated according to the scale described by Barnes *et al*[5]: three biopsies showed grade 1+ eosinophilia, one biopsy showed grade 2+ eosinophilia, and there were no cases of

grade 3+ eosinophilia. Only one of the 30 cases had grade 2+ or higher eosinophilia, and these cells were very focal in distribution. They were more often found in the fibrous septums and fascia. Treatment regimens were evaluated in 78 patients; however, only 35 patients had been followed up at the time of writing. Only 16 patients received corticosteroids (with an initial dose of 30 mg/d prednisone equivalent), whereas all the patients received Chinese herbs called fusong or fusu tablets. The patients were followed up for an average period of 20 months (range: 3–60 months). We prescribed patients who had rapid progression of the disease oral corticosteroids and patients who had relatively stable disease with Chinese herbal medicine. After treatment, eosinophil counts were reduced in all patients. Remission with disability occurred in 31 patients (89%), and treatment failure occurred in four patients (11%). Remission was achieved all four patients who received steroids and Chinese herbs and in 31 of the 35 patients who received Chinese herbs. Patients with treatment failure tended to have a longer diagnosis time delay (8 years *vs*. 15 years) and symptoms located in distal limbs. One case in a child quickly progressed to atrophy and joint contractures within 4 months. The effect of Chinese herbs was shown by the remission of induration, hyperpigmentation, and activity of the limbs.

Few similar studies have been performed in Asian patients. We discovered that biopsy results of only one of the 30 patients showed grade 2+ or higher eosinophilia. Hypereosinophilia of leukocyte differential was found in 14 patients, which was lower than in previous reports.[3] A potential explanation is that eosinophilia may be transient; the duration of study for our patients was generally longer than in other studies, and tissue collections of these cells were quite focal. We found that eosinophilia may disappear more quickly than blood eosinophilia. Some biases, including a retrospective design and the lack of standardized criteria for the evaluation of treatment response, may have impacted the results of the present study. Nevertheless, our study can offer valuable information on the clinical practice relating to EF with regard to the clinical, biologic, and histologic features and disease management.

Conflicts of interest

None.

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