Janus kinase inhibitor tofacitinib is a potential therapeutic option for refractory eosinophilic fasciitis

Sirs,

Eosinophilic fasciitis (EF) is a rare connective tissue disorder. The clinical manifestations are featured by progressive sclerosis of the skin and subcutaneous tissues in distal limbs. Glucocorticoids (GCs) are the mainstay of treatment. Various immunosuppressants, including cyclophosphamide (CTX) and methotrexate, are also used in clinical practice. However, the curative effect has been found to vary (1, 2). We documented a refractory EF case resistant to GCs and CTX. After treatment with tofacitinib, the clinical symptoms were markedly improved.

A 68-year-old man was hospitalised on June 11, 2018. He exhibited skin-pitting oedema and erythema affecting bilateral forearms and calf which initially developed on July 2017. The mucocutaneous itching and desquamation were concomitant. Gradually, the lesions were replaced by sclerosis. Proximal limbs, neck, and trunk were affected. The patient denied Raynaud's phenomenon.

Constitutional symptoms included weight loss and asthenia. Laboratory tests revealed peripheral eosinophilia with an absolute count of eosinophil 2.43×10^9/L. The erythrocyte sedimentation rate was 34 mm/h, and hypersensitive C-reactive protein was 7.9mg/L. Routine screening for anti-nuclear, anti-Smith, anti-Scl70, anti-centromere, and anti-PM/Scl antibodies and malignant disorders was negative. There was no evidence of visceral organ involvement. The diagnosis of EF was made. Oral prednisone 30 mg daily was prescribed for 1 month and tapered at the rate of 10% dosage reduction per week. Unfortunately, skin induration continued to progress. Numbness of extremities beyond the bilateral knee and elbow joint developed. MRI of bilateral calves was performed in February 2018, which demonstrated linear increased signal intensity on fat saturated T2 weighted imaging (T2WI) in the subcutaneous fascia. In March 2018, oral CTX 100 mg was administered every other day due to old age. However, in May 2018, the patient reported a new complaint, difficulty in dorsiflexion of the left foot.

On admission, a peau d'orange appearance, "groove sign," and "prayer sign" were prominent. Electromyography revealed impaired peripheral nerves, abnormal sympathetic skin response, and weak contractility of left tibialis anterior muscle, which indicated exacerbation of skin induration. The results of skin and muscle biopsy were consistent with EF (Fig. 2). The patient agreed to off-label therapy involving oral tofacitinib and was given tofacitinib at a dose of 5 mg twice daily. CTX was discontinued, and GCs were tapered quickly. After five months of treatment, the skin sclerosis and paresthesia dramatically resolved. The skin could be pinched on palpation. The patient could straighten his fingers and flex his left foot smoothly. The inflammatory markers returned to normal and eosinophilia resolved. Repeated MRI of bilateral calves revealed marked remission of the subcutaneous fascial lesions (Fig. 1), which further confirmed the efficacy of tofacitinib.

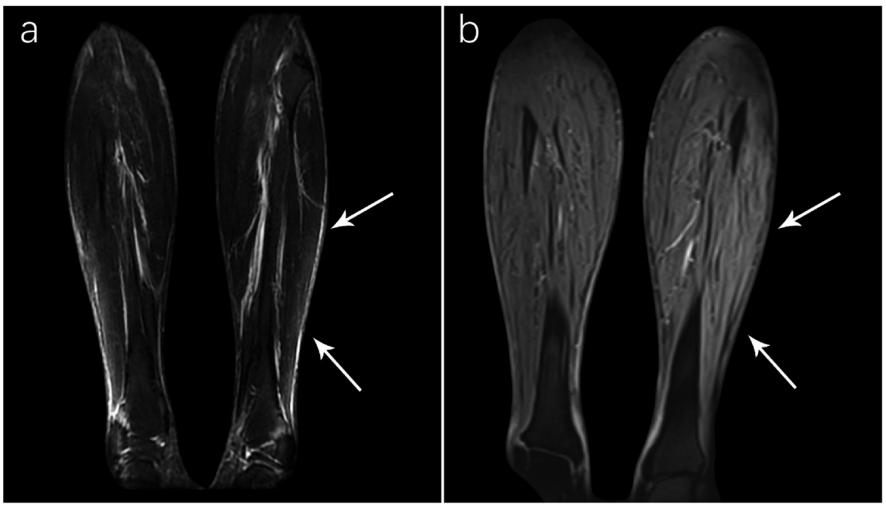

Fig. 1. Coronal fat saturated T2 weighted images (T2WI) of bilateral calves initially in February 2018 (**a**) and follow-up in November 2018 (**b**).
a. There is linear increased signal intensity on T2WI in the subcutaneous fascia (arrows), indicating fascial inflammation.
b. After a five-month treatment with tofacitinib, the high signal of subcutaneous fascia disappeared (arrows), in accordance with clinical improvement.

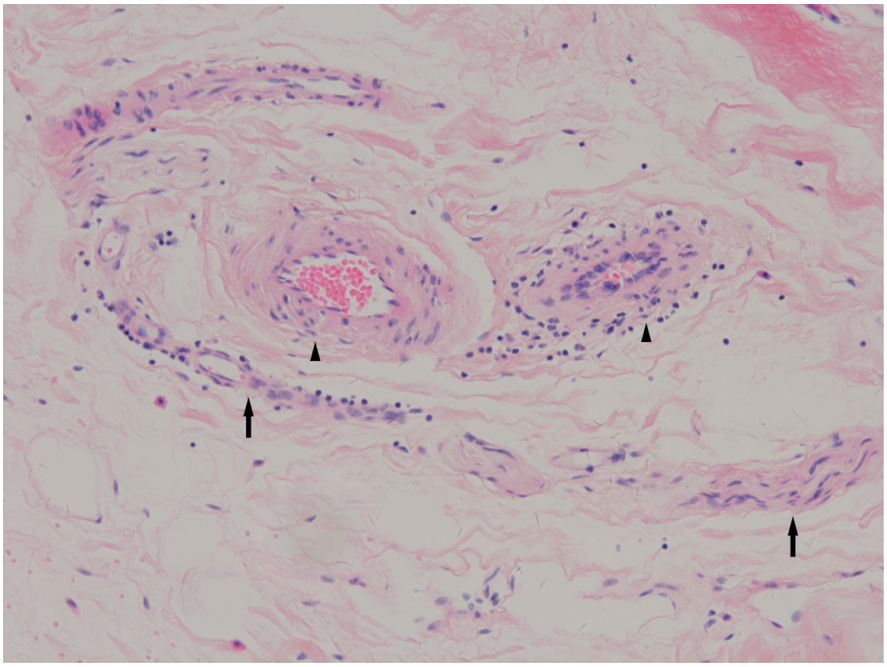

Fig. 2. The histopathology of left quadriceps femoris demonstrated the inflammation of fascia, with an infiltrate composed of lymphocytes in perivascular areas (arrowheads) and mesenchyme (arrows). (haematoxylin and eosin, ×100).

Under certain conditions, the increased production of interleukins (IL)-2, IL-5, IL-10, and interferon (IFN)-gamma has been reported in EF (3). IFN-alpha has been shown to be involved in the aetiology of EF (4). Tofacitinib, the Janus kinases (JAK) inhibitor, can block the signal transduction of the aforementioned cytokines (5). Additionally, the recent research showed JAK participated in the activation of signal transducer and activator of transcription 3,which integrated profibrotic signals to promote fibrosis (6). Systemic sclerosis could overlap with EF, which possibly reflected the common pathogenesis between these two diseases (7). Previous reports have indicated the effectiveness of tofacitinib in treating EF and scleroderma (8). Hypereosinophilic

syndrome with cutaneous involvement also responds well to tofacitinib (9). Our report not only confirmed the efficacy of tofacitinib in EF, but also further revealed the positive effect for refractory EF. On the whole, we speculated the tofacitinib could be a suitable therapeutic option for refractory EF.

Our study complied with the Declaration of Helsinki. The present work was approved by the Ethics Committee of Peking Union Medical College Hospital – approval number S-191 – and informed consent was obtained from the patient.

Key message

Janus kinase inhibitor was effective in treating refractory eosinophilic fasciitis.

X.-Y. CAO[1] *MD*
J.-L. ZHAO[1], *MD*
Y. HOU[1], *MD*
F.-D. WANG[2], *MD*
Z.-H. LU[3], *MD*

[1]Department of Rheumatology and Clinical mmunology, [2]Department of Radiology, [3]Department of Pathology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China.

Please address correspondence to:
Jiu-liang Zhao,
Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Graduate School of Peking Union Medical College,
Beijing 100730, China.
E-mail: zjlpumc@163.com

Yong Hou,
(address as above)
E-mail: houyongjia@hotmail.com

Funding: this work was supported by the National Natural Science Foundation of China [grant no. 81671614, website: www.nsfc.gov.cn/) to Y. Hou; and Chinese Academy of Medical Sciences Initiative for Innovative Medicine [grant no. 2017-12M-3-001] to Y. Hou.

Competing interests: none declared.

References

1. FETT N, ARTHUR M: Eosinophilic fasciitis: Current concepts. *Clin Dermatol* 2018; 36: 487-97.
2. MAZORI DR, FEMIA AN, VLEUGELS RA: Eosinophilic fasciitis: An updated review on diagnosis and treatment. *Curr Rheumatol Rep* 2017; 19: 74.
3. VIALLARD JF, TAUPIN JL, RANCHIN V, LENG B, PELLEGRIN JL, MOREAU JF: Analysis of leukemia inhibitory factor, type 1 and type 2 cytokine production in patients with eosinophilic fasciitis. *J Rheumatol* 2001; 28: 75-80.
4. FRENCH LE, SHAPIRO M, JUNKINS-HOPKINS JM, WOLFE JT, ROOK AH: Eosinophilic fasciitis and eosinophilic cellulitis in a patient with abnormal circulating clonal T cells: Increased production of interleukin 5 and inhibition by interferon alfa. *J Am Acad Dermatol* 2003; 49: 1170-4.
5. O'SHEA JJ, SCHWARTZ DM, VILLARINO AV, GADINA M, MCINNES IB, LAURENCE A: The JAK-STAT pathway: Impact on human disease and therapeutic intervention. *Annu Rev Med* 2015; 66: 311-28.
6. CHAKRABORTY D, ŠUMOVÁ B, MALLANO T *et al.*: Activation of STAT3 integrates common profibrotic pathways to promote fibroblast activation and tissue fibrosis. *Nat Commun* 2017; 8: 1130.
7. ZAMPELI E, PANTELIDAKI A, MOUTSOPOULOS HM: Evolution of one systemic rheumatic disease into another: scleroderma evolving to eosinophilic fasciitis with myositis. *Clin Exp Rheumatol* 2019; 37 (Suppl. 119): S149-50.
8. KIM SR, CHAROS A, DAMSKY W, HEALD P, GIRARDI M, KING BA: Treatment of generalized deep morphea and eosinophilic fasciitis with the Janus kinase inhibitor tofacitinib. *JAAD Case Rep* 2018; 4: 443-5.
9. KING B, LEE AI, CHOI J: Treatment of hypereosinophilic syndrome with cutaneous involvement with the JAK inhibitors Tofacitinib and Ruxolitinib. *J Invest Dermatol* 2017; 137: 951-4.