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 immuno-suppressants, 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 muco-cutaneous 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 2.43x10^9/L. The erythrocyte sedimentation rate was 34 mm/h, and hypersensitive C-reactive protein was 7.9 mg/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.

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 participation 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

Fig. 1. Coronal fat saturated T2 weighted images (T2WI) of bilateral calves initially in February 2018 (a) and follow-up in November 2018 (b).

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).
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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.

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References