

### Successful treatment of leg ulcers in Behçet's disease using adalimumab plus methotrexate after the failure of infliximab

Sirs,

Various types of skin lesions have been reported in Behçet's disease (BD) (1), but leg ulcers are rare and may be associated with vasculitis or deep venous thrombosis (2). The vasculitic type has a chronic recurrent course and is refractory to conventional treatment. We have successfully treated a patient with vasculitic leg ulcers using adalimumab plus methotrexate (MTX).

This 33-year-old man was admitted to our Rheumatology Unit because of the onset of right knee arthritis in early 1989 and, after a few months, erythema nodosum like-lesions and papulopustular eruption appeared on his legs. By 1990, he had developed oral aphthosis, genital ulcers and recurrent epididymitis, and a diagnosis of BD was made. He required oral prednisone and cyclosporine at a dose of 200 mg/day as maintenance therapy, which led to partial improvement of the mucocutaneous symptoms and signs. In 2002, he developed multiple painful and destructive leg ulcers which, despite treatment with high doses of prednisone and cyclosporine, continued to recur for four years.

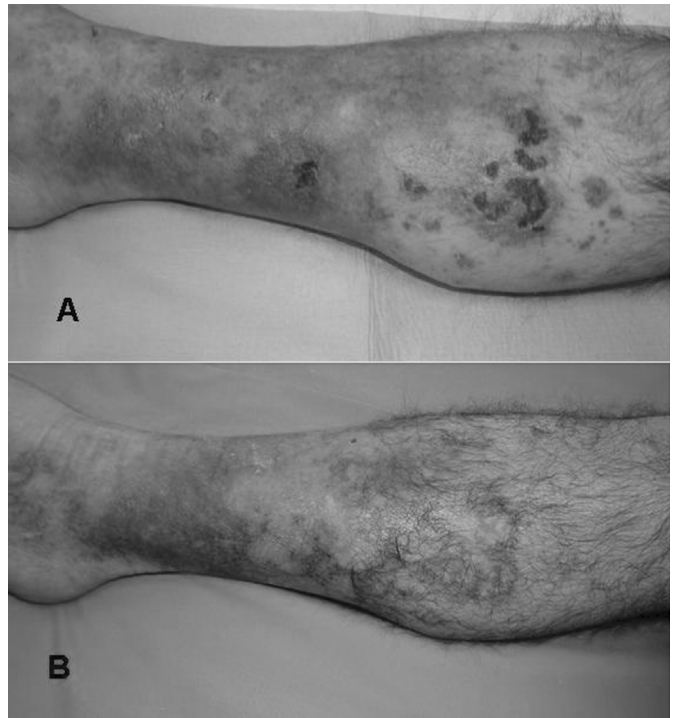
Physical examination revealed widespread papulopustular lesions, diffuse swelling of the right leg with multiple scars due to the previous ulcers, and no active lesions. The results of slit-lamp and fundus examinations were normal. A pathology test was negative. The serological and immunological work-up including rheumatoid factor, antinuclear antibodies, anti-double stranded DNA c and p-antineutrophil cytoplasmic antibodies (ANCA) antibodies were negative. Hepatitis B and C were negative. Anticardiolipin antibodies and lupus anticoagulant were negative. HLA-B51 was absent.

The results of Doppler ultrasound were normal, and the work-up for a hypercoagulable state (functional activities of protein C, protein S, and anti-thrombin III, Factor-V-Leiden mutation) did not reveal any abnormality.

In May 2007, the cutaneous ulceration worsened, with the appearance of multiple 1–3 cm lesions on the right leg with well-demarcated margins and a ragged overhanging edge; a biopsy revealed leukocytoclastic vasculitis. We stopped cyclosporine and began infliximab at a dose of 5 mg/kg at weeks 0, 2 and 6, and subsequently every two months. The symptoms and signs of the ulcers rapidly improved, and disappeared after the third infusion.

In March 2008, an ulcer on the right leg recurred, and so the infusion was brought forward by one month but had no effect. In June, we switched to subcutaneous adalimu-

**Fig. 1.** Leg ulcers after the last injection of adalimumab monotherapy (A) and after four weeks of combination treatment with methotrexate (B).



ma 40 mg every other week, and the ulcer disappeared after the fourth injection. However, despite this treatment, a further small ulcer appeared at the end of August so we decided to use adalimumab 40 mg s.c. every week. Four weeks later, the ulcerous lesions had improved but the patient was not yet in remission. Weekly i.m. metho-trexate (10 mg) was added and the ulcers disappeared within a few weeks. Now, 10 months after the combined treatment, the patient is still ulcer free (Fig. 1).

Our case suggests that anti-TNF agents (3–9) may also be useful for vasculitic leg ulcers, and that the failure of one TNF inhibitor does not preclude the success of another (8). Switching between different anti-TNF-alpha agents is a common treatment strategy in patients with rheumatoid arthritis and spondyloarthritis failing a first treatment course for inefficacy or adverse events and it could be a useful opportunity in patients with BD. Combining anti-TNF agents and MTX is unusual in BD, but knowledge that the lack of a response may be due to innate neutralising anti-TNF antibodies (9) that are inhibited by MTX provides a rationale for our therapeutic strategy (10).

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