Worsening of osteomalacia in a patient successfully treated for neuro-Behçet's disease with infliximab

Sirs,

There is little available data on the effectiveness of the anti-TNF monoclonal antibody infliximab in the treatment of neuro-Behçet's disease (NBD) refractory to high-dose steroids and cyclophosphomide (1-4). Several reports of adverse events with infliximab have been published, but information regarding its effect on the action of alfacalcidol is lacking. We describe the successful treatment of refractory NBD with infliximab, but clinical and biochemical worsening of coexisting osteomalcia.

A 49-year-old female patient presented with a history of recurrent orogenital ulcers, erythema nodosum, superficial thrombophlebitis and arthritis since 1990. Treatment with azathioprine 2.5 mg/kg for 4 years failed, while cyclosporine 3 mg/kg induced remission. The patient was not keen to receive corticosteroids.

In 2002 she complained of fatigue and chest pain on the right side that increased with breathing. Physical examination disclosed severe tenderness at the level of the right medial and lower ribs. X-rays of the chest and right ribs were normal. A bone scan showed multiple focal and diffuse areas of abnormal increase tracer uptake. Tests showed alkaline phosphatase (ALP) 6.4 ukat/L (NV 1.67-4.84), calcium 2.38 mmol/L (NV 2.12-2.55) phosphorous 0.52 mmol/L (NV 0.8-1.6), PTH 9.96 pmol/L (NV 1.6-6.9) compatible with osteomalacia, which was controlled with calcium 1 gm and alfacalcidol 1.25 mcg/day.

Seven months after beginning cyclosporine the patient presented with headache, dizziness, reduced concentration, diplopia, hypersomnolence and frequent yawning. A brain MRI showed patchy, small hyperintense lesions in the brain stem (Fig. 1, a-1 and a-2). Intravenous (IV) methylprednisolone (CS) for 3 days and cyclophosphomide 750 mg monthly were administered. Two months after receiving the 6th dose the patient relapsed. Repeat brain MRI showed persistence of the abnormal findings (Fig. 1, b-1 and b-2). CBC, ESR, kidney and liver tests, ALP and PTH were normal, CRP 5.9 mg/L (NV < 5). CSF showed glucose 44, protein 146, IgG index 0.79 (NV <0.7), WBC 210, N 90%, L 10%, culture negative. IVCS 500 mg for 3 days and infliximab 5 mg/kg were given at weeks 0, 2, 6 and then every 8 weeks up to the present, plus methotrexate 10 mg/week. Complete remission including CNS manifestations was observed within one week. A brain MRI performed in March 2006 was normal (Fig. 1, c-1 and c-2). However, the patient complained again of bone pain, weakness, and developed a new rib fracture. PTH was 11.27 pmol/L and a rise in ALP followed each infliximab infusion (6.1, 9.03, 11.04, 11.64, and 12.09). Potential causes of osteomalacia were excluded. Substitution of alfacalcidol by calcitriol led to clinical and biochemical improvement of osteomalacia. Methotrexate was replaced by AZA 100 mg/day.

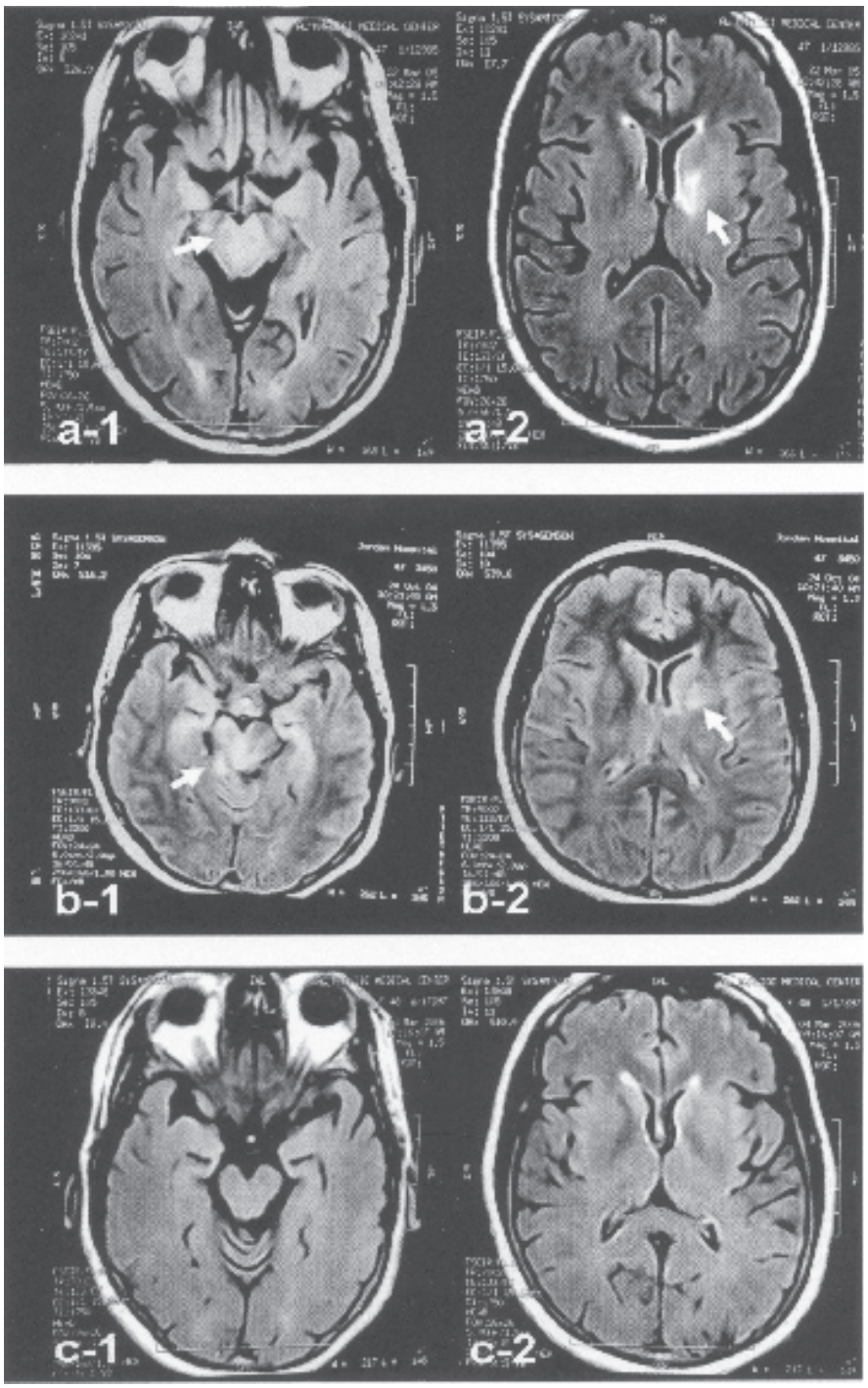

Fig. 1. (**a-1, a-2**) Brain MRI 2004: patchy small hyper-intense lesions seen in the brain stem, mainly at the lower mid-brain, right thalamus and left basal ganglia. (**b-1, b-2**) Brain MRI 2005: evidence of abnormal signal lesions seen in the brain stem and left deep parietal and peri-ventricular regions. (**c-1, c-2**) Brain MRI 2006: hyperintensity of the deep peri-ventricular white matter only, seen adjacent to the frontal horns of both lateral ventricles; other brain tissue and structures normal; no contrast uptake by brain tissue could be depicted.

TNF plays a central role in the pathogenesis of BD; this is supported by reports of the efficacy of anti-TNFα agents in the treatment of various manifestations of BD (5). A few reports of the successful treatment of NBD with infliximab have been reported (1- 4), 3 cases of which were refractory to traditional treatment (1, 2, 4). Different doses were used (3 or 5 mg/kg) with similar results and no side effects were observed. Infliximab seems

to have a suppressive effect only; one patient took infliximab for one year, but then relapsed 7 months after interrupting this treatment (2). Clinical trials are clearly needed to determine the optimal dose and duration.

Our patient also was refractory to immunosuppressive therapy, but infliximab led to the complete remission of all disease manifestations, including radiological signs of NBD. As the osteomalacia was controlled before infliximab with alfacalcidol and calcium, we strongly suspect that infliximab was involved in the worsening of this condition in our patient, particularly with its effect on alfacalcidol. Alfacalcidol is hydroxylated in the 25 position by the hepatic microsomal system to form 1.25-(OH)2D3. Infliximab could inhibit this mechanism, as replacing alfacalcidol by the readily active Vit-D metabolite calcitriol led to improvement of the osteomalcia.

Development of secondary osteomalacia has been reported in a rheumatoid arthritis patient treated with etanercept (6).

Although no definitive conclusions can be reached on the basis of case reports, our case strongly supports the beneficial effect of infliximab in the treatment of refractory NBD. However, caution should be exercised in patients receiving alfacalcidol during treatment with infliximab. To our knowledge this is the first report on the interaction between infliximab and alfacalcidol.

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