Anti-tumour necrosis factor α monoclonal antibody therapy for recalcitrant cerebral vasculitis in a patient with Behçet's syndrome

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Behçet's disease (BD) is a relapsing systemic vasculitis of unknown definite cause, mainly characterised by recurrent oral and genital ulceration, uveitis, skin lesions, and arthritis. It is also one of the best recognised condition known to cause vasculitis in the central nervous system (CNS), presenting as one of the most devastating manifestations of the disease.

Corticosteroids and immunosuppressive agents are the preferred drugs in the treatment of both primary and secondary CNS vasculitis. Immunosuppressive agents (for example, azathioprine, cyclosporin, cyclophosphamide, and chlorambucil), however, given alone or in different combinations, have not been shown to prevent the development of neurological complications of the disease, to reduce its exacerbations, or stop its progression.

The aetiopathogenesis of BD has not yet been fully elucidated; however, increased concentrations of tumour necrosis factor α (TNFα) and soluble TNF receptors have been found in the serum of patients with active disease.[1]

Therapeutic TNF blockade has been successfully used for treating various conditions in which TNF seems to be of importance in mediating inflammation (for example, Crohn's disease, rheumatoid arthritis).[2] We and others have also presented data on the efficacy of anti-TNF therapy for severe recalcitrant manifestations of BD.[3–5] In this report we describe the use of the anti-TNFα chimeric monoclonal antibody, infliximab (Remicade, Centocor Inc, Malvern, PA, Schering Plough SpA, Italy), in a patient with BD who had severe CNS disease refractory to standard treatment.

CASE REPORT

A 59 year old woman with a history of recurrent oral aphthous ulcers, chronic erythema nodosum, superficial thrombophlebitis, and arthritis was admitted in October 2001 for a sudden occurrence of CNS disease. She presented findings of pyramidal involvement and hemiplegia. Results of a chest *x* ray examination and urine analysis were normal, blood pH and Po_2 were in the normal range. White blood cell count was 5.6×10^9/l, erythrocyte sedimentation rate (ESR) 104 mm/1st h, and C reactive protein (CRP) 54 mg/l. Antinuclear, anti-dsDNA, antineutrophil cytoplasmic, and anticardiolipin antibodies and lupus anticoagulant were negative. Cerebral magnetic resonance imaging (MRI) showed two (cortical-subcortical and para-sagittal) high signal intensity lesions in the frontal lobe and another (cortical-subcortical) lesion in the temporal lobe (figs 1A and B). Intravenous methylprednisolone (1 g/day for three days) and cyclophosphamide (1 g/m^2) was started, followed by oral prednisone (50 mg/day). After four weeks intravenous methylprednisolone and cyclophosphamide were repeated as previously.

In December 2001 she was readmitted for the occurrence of severe CNS manifestations. She was lethargic. Although a partial resolution of the previous lesions was present at MRI, new cortical-subcortical lesions in parietal lobes and cortical-subcortical lesions in the frontal lobe were seen (figs 1C and D). An infusion protocol with infliximab was designed and approved by the Department of Medicine Institutional Board and informed consent was obtained from the patient. The patient was infused with infliximab 5 mg/kg at weeks 0, 2, and 6. Infliximab was administered by two-hour infusion and the patient observed for a further two hours; no adverse effect was seen. An improvement in symptoms was noticed within 24 hours after receiving the first infusion and remained stable throughout the observation period. In particular, her well-being improved markedly. Cerebral MRI performed a week after the infusion showed a complete resolution of signal

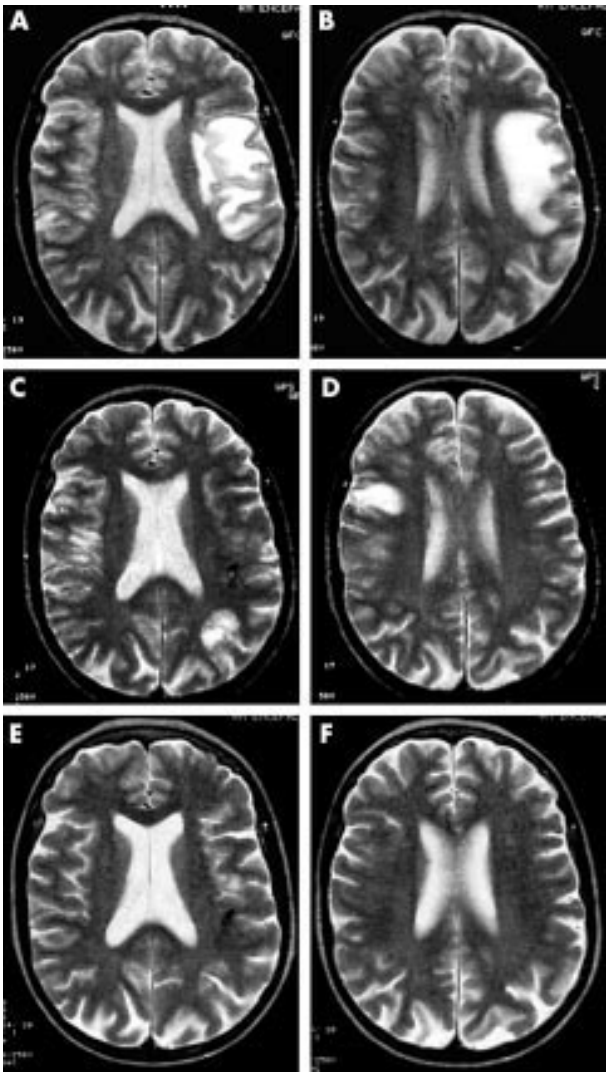

Figure 1 Axial T_2 weighed sequence MRI (0.5 T; TR (repetition time) 2500 ms; TE (echo time) 25 ms) at admission (A, B), after intravenous methylprednisolone and cyclophosphamide (C, D), and after anti-TNF therapy (E, F).

abnormalities (figs 1E and F). After the second infusion she had a complete remission of all signs and symptoms of neurological involvement. No changes (either clinical or instrumental) were present after one month's observation (not shown). The ESR was 15 mm/1st h and CRP 3.8 mg/l and they have remained normal until now.

DISCUSSION

This is the first report, to our knowledge, of the treatment of cerebral vasculitis in BD with anticytokine-specific treatment. Indeed, anti-TNF therapy has been successfully used in other forms of vasculitis.[6 7] Treatment with infliximab led to a complete remission of all disease manifestations in our patient and there was no recurrence for up to eight weeks after the last infusion. This effect appears to be remarkable as standard treatment had failed in our patient. No side effects were seen in this short term observation period. Our results may indicate also a possible role for anti-TNF therapy in primary cerebral vasculitis or in CNS involvement in the course of other immunological conditions in which TNFα is considered to play a part.

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Tubulointerstitial nephritis and uveitis syndrome: a diagnosis that should be considered by rheumatologists

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Tubulointerstitial nephritis and uveitis (TINU) syndrome is an entity known mainly to the nephrologists. It has similar features to some of the rheumatic diseases, especially Sjögren's syndrome and lupus. However, many rheumatologists are not familiar with this entity. TINU syndrome should be considered in the differential diagnosis in patients with renal and/or ocular involvement.

CASE REPORT

A 56 year old woman was referred to the rheumatologist for the evaluation of musculoskeletal pain, positive antinuclear antibody (ANA), and renal failure. She reported diffuse musculoskeletal pain for the past two months, with worsening of these symptoms during the past week. She denied morning stiffness or swelling of the joints. One month ago she also had sore eyes with some redness and was evaluated by an ophthalmologist, who prescribed "eye drops" with good results. She also had dry cough during the past month. Otherwise she had no chronic health problems. She denied dry mouth, photosensitivity, alopecia, oral or genital ulcers, Raynaud's phenomenon, or swallowing problems. For the musculoskeletal pain she took simple analgesics only. A physical examination showed blood pressure 110/70 mm Hg, and diffuse trigger points without joint swelling. There was no organomegaly or lymphadenopathy. Skin was normal. Sclera and conjunctiva looked normal. Lungs were clear.

Laboratory studies showed a white cell count of 8.7×10^9/l, haemoglobin 103 g/l, packed cell volume 0.33, platelets 224×10^9/l, neutrophils 0.66, lymphocytes 0.22, urea 8.3 mmol/l (normal 2.5–6.0), serum creatinine 140 μmol/l (serum creatinine was normal one year ago), sodium 134 mmol/l, potassium 3.8 mmol/l, calcium 2.3 mmol/l, phosphorus 1.00 mmol/l, total protein 77 g/l, globulins 37 g/l, uric acid 150 μmol/l (normal 140–340), glucose 4.8 mmol/l. Liver function tests, prothrombin time, partial thromboplastin time, and fibrinogen were normal. A Coombs test was negative. Erythrocyte sedimentation rate (ESR) (Westergren) was 85 mm/1st h, C reactive protein 570 mg/l (normal 0–50), ANA positive, antibodies to DNA, SS-A, SS-B, RNP, Sm, Jo-1, Scl70, HIV, HCV, glomerular basement membrane, and cardiolipin were all negative. Antibodies to brucella, chlamydia, Epstein-Barr virus, cytomegalovirus, and toxoplasma were negative for acute infection. Rheumatoid factor (RF), hepatitis B surface antigen, and antineutrophil cytoplasmic antibodies (ANCA) were negative also. C3 was 1.4 g/l (normal 0.9–1.8), C4 0.4 g/l (normal 0.1–0.4), antistreptolysin O antibody titre 98 IU/ml (normal 0–200), serum IgG 20.7 g/l (normal 7.00–15.00), IgA 3.47 g/l (normal 1.30–4.00), IgM 3.34 g/l (normal 0.50–2.00). Immunoelectrophoresis was normal. Angiotensin converting enzyme (ACE) level was normal. Urine analysis showed glucose 5.6 mmol/l, protein 250 mg/l, pH 7.0, specific gravity 1.01, erythrocytes 4–6/high power field (hpf), leucocytes 1–3/hpf, granular casts 2–4/hpf, and few epithelial casts. Twenty four hour urine protein was 1.39 g/day, creatinine clearance 0.52 ml/s, Schirmer test 5 mm (during five minutes). Rose bengal staining was negative. Chest radiographs and electrocardiograms were normal.