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Successful treatment of meningeal involvement in Wegener's granulomatosis with infliximab

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Meningeal involvement in Wegener's granulomatosis (WG) is rare and only 32 cases have been reported by Reinhold-Keller and coworkers.[1 2] The outcome of the disease has improved with the institution of cytotoxic agents.[3] We report on a patient with WG and progressive pachymeningeosis despite treatment with cyclophosphamide (CyC) and glucocorticoids who responded well to infliximab treatment.

In December 2003 a 34 year old male chemist was diagnosed with localised WG, according to the American College of Rheumatology criteria and the Capel Hill Conference criteria, on the basis of granulomatous nasal inflammation, left-sided otitis media, and the detection of proteinase-3-antineutrophilic cytoplasmic antibodies (PR3-ANCA) >100 U/ml (normal <5 U/ml).[4 5] Because of progressive hearing loss oral prednisolone (1 mg/kg body wt) and intravenous CyC 0.8 g/m^2/month were started.

After 3 months when prednisolone was tapered to 15 mg/day the patient developed headache, bilateral paresis of the abducens nerve, and paresis of the left oculomotor nerve. Magnetic resonance imaging (MRI) disclosed dural thickening with enhanced gadolinium uptake across both cerebral hemispheres and the basal region (fig 1A), and another increase of PR3-ANCA (46 U/ml) supported the suspicion that WG had spread to the meninges and had become generalised. Methylprednisolone pulse therapy and oral CyC (2 mg/kg body wt) were successfully started.

After prednisolone was tapered to 50 mg/day the patient again complained of headache and incapacitating bilateral diplopia. MRI findings had remained virtually unchanged; the modified Birmingham Vasculitis Activity Score (BVAS/WG)[6] was 9 (BVAS1 = 4; BVAS2 = 5), and the PR3-ANCA level 18 U/ml.

Because oral CyC and prednisolone could not control the disease this led us to examine reports that infliximab might be effective in treating refractory WG.[7] After written informed consent was obtained and no signs of infection were found, infliximab (5 mg/kg body wt) at weeks 0, 2, and 6, and thereafter at 8-weekly intervals was started. After 2 weeks clinical symptoms of cerebral involvement had subsided, the BVAS/WG had fallen to 4, and the PR3-ANCA level was 10 U/ml. Oral CyC was reduced to 1 mg/kg body wt and prednisolone to 5 mg/day within 3 months. Over the following 12 months, the patient remained free of clinical symptoms and MRI findings improved impressively (fig 1B), indicating that infliximab was effective in controlling meningeal involvement.

Granuloma formation is a hallmark in localised WG. These granulomas consist predominantly of tumour necrosis factor α (TNFα) expressing T cells and macrophages, and different groups have shown that infliximab, a TNFα neutralising agent, was effective in refractory WG.[7 8] Our patient originally presented with localised WG that generalised and spread to the meninges despite immunosuppressive treatment. Infliximab induced and maintained remission in our patient with no side effects reported to date. This shows a difference between infliximab and etanercept, which could not prevent relapses in a recently published placebo-controlled trial.[9]

To our knowledge, ours is the first report demonstrating that infliximab may be a viable treatment option in generalised WG not responding to oral CyC and glucocorticoids.

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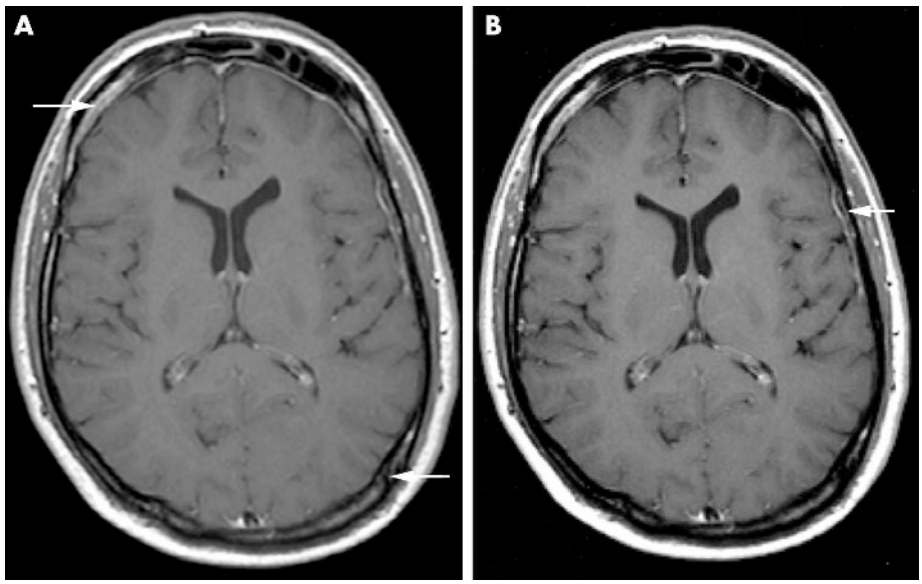

Figure 1 (A) T_1 weighted axial MR scan of a 43 year old male patient after contrast application shows meningeal inflammatory involvement with 3 mm thickening of the left hemispherical and right frontal meninges (arrows). (B) Six months after treatment with infliximab (5 mg/kg body wt) at weeks 0, 2, 6 and 8-weekly thereafter, meningeal contrast enhancement and thickening had clearly regressed.

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Bosentan may induce arthritis flare in patients with scleroderma concomitantly treated with methotrexate

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In recent years, endothelin receptor antagonism has emerged as an important therapeutic strategy for pulmonary arterial hypertension (PAH). Bosentan, an orally active endothelin receptor antagonist, has proved to be effective in primary PAH or PAH related to connective tissue diseases.[1–3]

Of 18 patients with PAH related to systemic sclerosis (SSc) treated with bosentan at our division of rheumatology during the past 2 years, two were also affected by rheumatoid-like arthritis before starting bosentan. We here report the clinical course of these two cases.

The first patient, a 55 year old woman, with SSc since 1988, developed a non-erosive polyarthritis affecting the hands, knees, and ankles, with positive rheumatoid factor (RF; 585 U/l) in March 2002. The second patient, a 57 year old woman, with SSc since 2001, showed a symmetric non-erosive arthritis of hands and wrists, with high RF (414 U/l) in January 2004. Both patients were treated with methotrexate (10 mg weekly) and low dose methylprednisolone (8 mg daily), with favourable effects. In August and October 2004, respectively, both patients observed the onset of effort dyspnoea. High resolution computed tomography of the lung did not show signs of pulmonary fibrosis, while a Doppler echocardiogram estimated a pulmonary artery mean pressure of 45 and 40 mm Hg, respectively.

Bosentan treatment for PAH was given orally at a dose of 62.5 mg twice daily for 1 month and then 125 mg twice daily, without modifying methotrexate and methylprednisolone dosages. One month later, the two patients had an evident flare of arthritis. An increase in erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) as well as