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Treatment of ankylosing spondylitis with infliximab

In January 2000 a 35 year old man presented with severe ankylosing spondylitis (AS), diagnosed in 1981. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was 6.0, the Bath Ankylosing Spondylitis Functional Index (BASFI) was 3.0, and on a 1–10 visual analogue scale (VAS) for pain in the previous two months he had a score of 6.

Schober's test was 0 cm (normal 4 cm), Ott's test 1 cm (normal 2 cm), finger-floor distance 16 cm, lateral flexion 3 cm, tragus-wall distance 21 cm, cervical rotation 30°.

C reactive protein (CRP) was 41 mg/l (normal <5), erythrocyte sedimentation rate (ESR) was 25 mm/1st h (normal <15), and HLA-B27 genotype was positive.

Conventional radiography showed typical signs of AS. Magnetic resonance imaging (MRI) detected inflammatory activity in the ileosacral joints[1] by contrast enhancement after gadolinium application in the apical portion of the right ileosacral joint in T_1 weighted sequences (fig 1).

We started treatment with infliximab,[2] a monoclonal antibody (IgG1) directed against tumour necrosis factor α (TNFα), at a dose of 5 mg/kg body weight. Intravenous infusions were given in weeks 0, 2, 6, and then continued at six weekly intervals for one year without any additional disease modifying drug.

Pain improved within 24 hours of the first infusion. Within six weeks the patient required no ibuprofen and CRP, ESR, BASDAI, BASFI, and VAS improved dramatically (fig 2). With the exception of CRP and ESR, all variables remain normal up to now. CRP and ESR increased mildly at week 12 owing to a mild upper respiratory tract infection. There were no other adverse events. Two mobility variables (cervical rotation and tragus-wall distance) had improved at the end of one year's treatment.

MRI of the ileosacral joints showed no contrast enhancement at weeks 14 and 41 of treatment (fig 1).

The patient denied any loss of effect at the end of the six weekly infusion intervals or after one year of treatment. Except for the mild upper respiratory tract infection, which abated after two weeks without specific treatment, there were no adverse events.

This case report documents the first long term application of infliximab in a patient with AS. Two previous studies reported effective treatment of a total of 22 patients with AS with three infusions of infliximab at a dose of 5 mg/kg body weight.[3 4]

The pharmacological basis for TNFα inhibitory treatment in AS is the detection of TNFα-mRNA and TNFα protein in biopsy specimens of ileosacral joints of patients with active AS.[5] In rheumatoid arthritis (RA) and Crohn's disease (CD), several TNFα inhibitors seem to be successful in significantly reducing inflammatory activity.[6 7]

Theoretically, up regulation of the TNFα receptors and subsequent tachyphylaxis might be expected upon constant blockade of the agonist. This has not been noted in studies on infliximab, etanercept, and D2E7 in RA, CD, and psoriatic arthritis (PA) during long term treatment, even when constant therapeutic plasma levels are maintained.[7–9] This case report suggests this is true also for patients with AS.

In summary, we present the case of a patient with AS effectively and safely treated with infliximab over a period of more than one year. This indicates that treatment of AS with TNFα inhibiting substances may have equal long term safety and long term benefits on peripheral and spinal joint function as does treatment of RA, CD, and PA. Randomised controlled double blind studies are needed to investigate this in further detail.

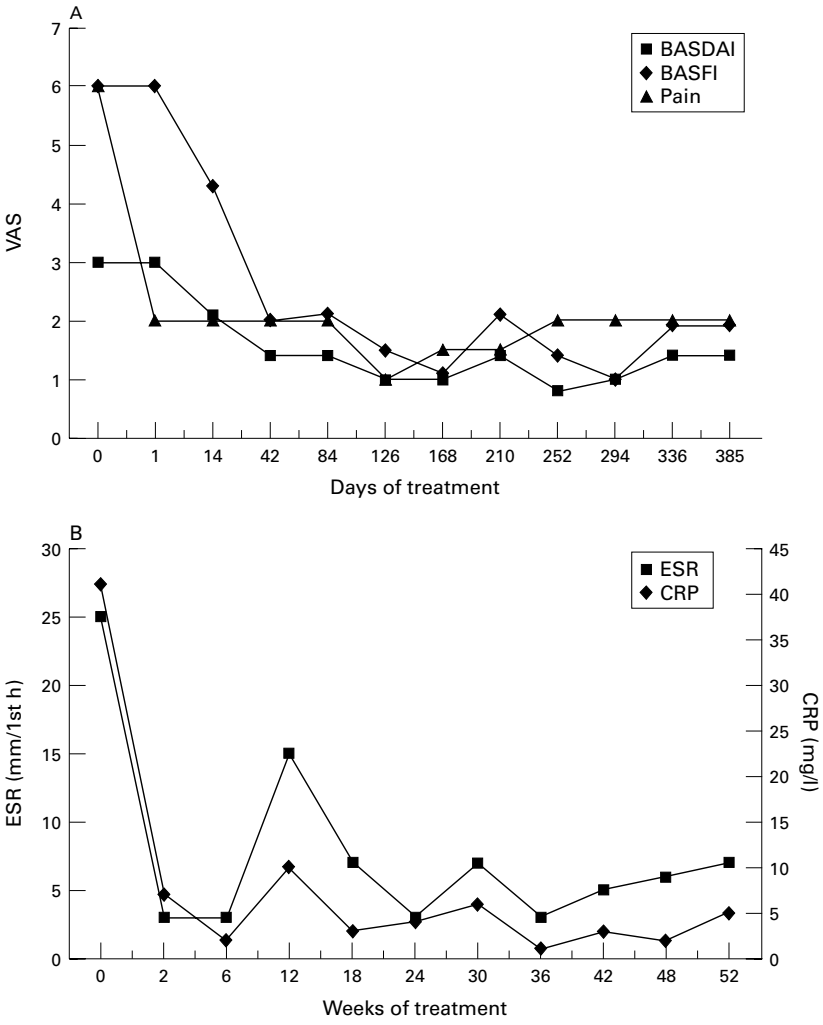

Figure 2 Self assessment of pain on a 1–10 visual analogue scale (A) and CRP and ESR (B).

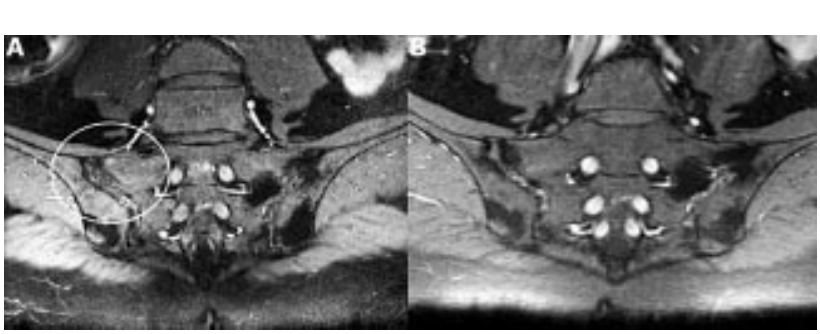

Figure 1 Gadolinium contrast enhanced T_1 weighted magnetic resonance imaging before treatment with infliximab (A) showing contrast enhancement in the right ileosacral joint, and (B) in week 41 of treatment showing no contrast agent uptake.

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Retrocalcaneal bursitis in polymyalgia rheumatica

Polymyalgia rheumatica (PMR) is a relatively common disease of the elderly affecting the synovial membrane.[1]

Recent studies have emphasised the prominent involvement of the extra-articular synovial structures in both proximal and distal regions of both the arms and legs.[1–7] In the distal part of the arms tenosynovial membrane inflammation is responsible for carpal tunnel syndrome, distal swelling of hands and feet with or without pitting oedema, and localised episodes of distal tenosynovitis.[4–7]

We recently observed the case of a patient with PMR showing retrocalcaneal bursitis, which we describe briefly here.

A 68 year old woman was referred to us for evaluation of a three month history of marked aching and morning stiffness in her neck, shoulder, and hip girdles associated with low grade fever. Her medical history was otherwise unremarkable except for a hereditary cerebellar cortical degeneration. Her family history was negative for rheumatic diseases, including spondarthritis.

Physical examination showed tenderness and limitation of cervical and shoulder movement. The typical gait and abnormal stance of cerebellar ataxia were also present.

Laboratory evaluation disclosed an erythrocyte sedimentation rate (ESR) of 72 mm/1st h (Westergren) and a C reactive protein (CRP) concentration of 80 mg/l (normal <5). Tests for rheumatoid factor, antinuclear antibodies, and serum tumour markers were negative, and HLA typing did not show the B27 antigen.

Methylprednisolone at a dose of 16 mg/day was started and symptoms rapidly disappeared. ESR and CRP were normal after one month of treatment.

Nine months after starting treatment, when the dose of methylprednisolone was 6 mg/day, the patient experienced pain in her shoulder girdle and right foot. Physical examination showed an enlarged and painful right retrocalcaneal bursa. There was no pain and swelling along her right Achilles tendon and at its calcaneal insertion. Magnetic resonance imaging (MRI) showed an enlarged retrocalcaneal bursa without any sign of Achilles tendonitis or enthesitis (fig 1). An anteroposterior view of her pelvis showed normal sacroiliac joints. Both shoulder girdle symptoms and retrocalcaneal bursitis disappeared promptly when the dose of methylprednisolone was increased and have not reappeared so far, 12 months after discontinuation of treatment.

Our patient had PMR and showed retrocalcaneal bursitis as a distal manifestation of the disease.

The prominent involvement of the extra-articular synovial structures in both the peripheral and distal inflammatory processes of PMR has only recently been demonstrated.[2–7] The distal manifestations of PMR include tenosynovitis in addition to joint synovitis.[1 4–7] Extensor tenosynovial sheath involvement, which may give swelling with pitting oedema over the dorsum of the hands and feet, is common and has been recorded by MRI.[4–7] Tenosynovitis under the transverse carpal ligament may cause carpal tunnel syndrome.[7] The involvement of hand flexor, posterior tibial and peroneal tendons may occur and has been documented with MRI.[1 4 5 7]

To the best of our knowledge retrocalcaneal bursitis has never been reported in patients with PMR. Chuang *et al* found "bursitis-tendinitis" in 48/96 (50%) patients with PMR.[8] Although they considered these as part of the disease, no mention of the affected bursae was made in their article. Possibly, some of the 48 patients developed retrocalcaneal bursitis. The retrocalcaneal bursa differs from other deep bursae, such as the subacromial and subdeltoid bursa and the gastrocnemius-semimembranous bursa.[9] The synovial membrane is present only at its roof while its anterior wall is fibrocartilage layered onto the calcaneus and its posterior wall sesamoid fibrocartilage differentiated in the Achilles tendon. This anatomical arrangement makes the bursa an integral part of the Achilles enthesis. In spondarthritis, which is a disease of the entheses, retrocalcaneal bursitis often occurs in association with Achilles enthesitis.[10] In contrast, retrocalcaneal bursitis tends to occur in isolation in rheumatoid arthritis, suggesting that the synovial membrane at the top is the primary site of inflammation.[9] The same may be valid for PMR. Our patient had no clinical sign of Achilles tendon involvement and MRI showed no sign of enthesitis, that is to say, tendon swelling and bone oedema.

In conclusion our report suggests that the synovial membrane of distal bursae may also be affected in PMR.

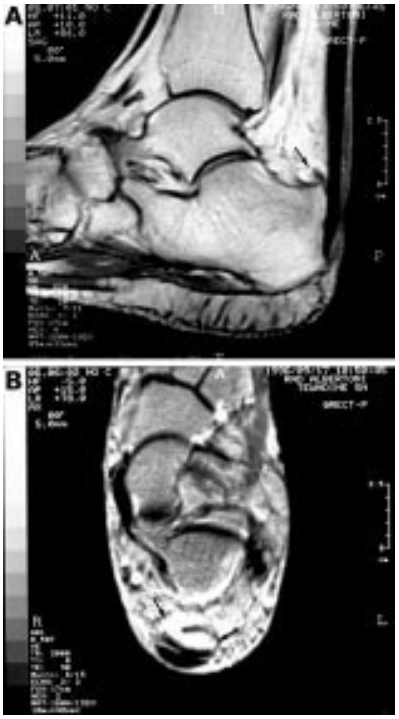

Figure 1 Sagittal T_1 (A) and axial T_2 (B) weighted images of the left Achilles tendon showing the distension of the retrocalcaneal bursa by fluid collection (arrows) together with normal Achilles tendon and enthesis.

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