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Infliximab treatment efficacy in lymphoedema associated with ankylosing spondylitis

Sir, Lymphoedema is an extra-articular manifestation rarely found in rheumatoid arthritis (RA) and juvenile idiopathic arthritis, and is quite rare in psoriatic arthritis (PsA) [1–4]. Literature research shows few published cases of lymphoedema: 30 cases in patients with RA and only eight cases in PsA [5–7]. The aetiology is unknown. Several hypotheses have been advanced on its pathogenesis in patients with RA, such as lymphangitis, lymphatic obstruction, capillary permeability increase, abnormal fibrinolysis and other disorders related to lymphatic function and structure [4]. The diagnosis ‘under suspicion’ is clinical, as one or more limbs have been observed to undergo painless swelling. Scintigraphy demonstrates existing lymphatic disorders [8]. Treatment for lymphoedema is inefficient and is usually limited to symptomatic treatment. In most cases of RA or PsA, introduction of disease-modifying drugs does not improve the oedema [3, 5, 9–11]. With regard to anti-TNF-α therapy, infliximab, recently approved for treatment of ankylosing spondylitis (AS), has been found to be efficient on peripheral articular manifestations and on the axial skeleton. However, there is little information available on its efficacy for extra-articular manifestations. We describe the first case of a patient diagnosed with AS complicated with right upper limb lymphoedema who, after receiving treatment with infliximab, showed complete disappearance of the lymphoedema.

The patient was a 58-yr-old male with a background of gastric ulcer, venous thrombosis in the central nervous system and secondary osteoporosis. From the age of 15 he had presented a clinical picture compatible with AS, but this was not diagnosed until the age of 51. Initially, the patient was treated with non-steroid anti-inflammatory drugs (NSAIDs) and corticosteroids. In 1998, he developed a painless oedema in the right upper limb. Lymphatic scintigraphy showed findings compatible with lymphoedema. In May 1999, treatment with sulphasalazine was begun and articular clinical results improved, but lymphoedema persisted and acute-phase reactants increased. In September 2000, methotrexate was added at a dose of 10 mg/week without improvement. In March 2001, previous therapies were discontinued and treatment with infliximab was begun at the dose of 5 mg/kg, repeating the dose at 2, 4 and 8 weeks. At 2 weeks, the patient experienced clinical improvement and acute-phase reactants had stabilized. At 12 weeks, the lymphoedema had disappeared completely. Treatment with infliximab was continued for 1 yr, after which it was discontinued when the patient was found to be asymptomatic. In September 2003, treatment was reinitiated due to symptomatic worsening of the axial skeleton.

Our patient is the first reported case presenting lymphoedema associated with AS in whom the lymphoedema disappeared completely after 3 months of treatment with infliximab. The way in which infliximab acts on lymphoedema is not known, but the drug is believed to act on the inflammatory response of the lymphatic vessels. Therefore, anti-TNF therapy can be considered for the treatment of extra-articular manifestations in AS, such as lymphoedema. Further experience is necessary to confirm the beneficial effect of infliximab and to learn how it acts on other extra-articular manifestations.

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Juvenile onset spondylodiscitis: magnetic resonance imaging changes with infliximab

Sir, Spondylodiscitis is an uncommon presentation of ankylosing spondylitis (AS). TNF-α blockade has previously been shown to
be markedly effective in controlling the clinical manifestations of AS with improvement in enthesis and osteitis, as demonstrated by magnetic resonance imaging (MRI) [1]. We report dramatic improvement, both clinically and radiologically, in an adolescent with unusually florid signs of spondylodiscitis as the initial manifestation of AS, following treatment with infliximab.

A 14-yr-old male presented to his general practitioner with a 4-week history of severe back pain and stiffness in 1999. Clinical examination revealed scoliosis concave to the left. Plain thoracolumbar spine radiographs showed endplate irregularity and early sclerosis at D7/8; the sacroiliac joints were normal. An orthopaedic opinion was requested. MRI of the thoracolumbar spine showed loss of height of the D10/11 disc (disc space narrowing) and sclerosis of the vertebral endplates at several levels, with focal endplate collapse consistent with Scheuermann’s disease. He was referred to physiotherapy and advised to use NSAIDs as required; nevertheless his symptoms persisted.

Three years later, he represented to rheumatology with constant spinal pain, prolonged early morning stiffness, intermittent retrosternal chest pain and kyphosis. He was struggling to remain in full-time employment. Blood investigations revealed haemoglobin 11.9 g/dl (range 13.5–18 g/dl), platelets 450 × 10^9/litre (range 150–450 × 10^9/litre), ESR 31 mm/h (range 1–10 mm/h), C-reactive protein (CRP) 28 mg/l (normal range 0–10 mg/l) and serum albumin 37 (range 35–50 g/l). HLA B 27 tissue typing was positive. There was no history of psoriasis, enthesopathy or acute uveitis. MRI showed unusually florid multilevel inflammatory endplate changes that were most pronounced at T11/12, manifest as oedema, endplate irregularity and disc space narrowing (Fig. 1A). A diagnosis of inflammatory spondyloarthropathy was raised, particularly as there was also focal oedema at a number of the vertebral entheses. Radiographic evidence of bilateral sacroiliitis (grade 3) supported this diagnosis. Refractory spinal pain improved with phenylbutazone 100 mg three times a day. One year later, he developed an irritable left hip. Ultrasound demonstrated synovitis with an effusion which responded well to an intra-articular injection of 80 mg methylprednisolone and 1 ml of bupivacaine.

Due to unrelenting axial symptoms, hip involvement, persistent anaemia with raised inflammatory markers, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 6.03, Bath Ankylosing Spondylitis Functional Index (BASFI) 6.46 and Bath Ankylosing Spondylitis Metrology Index (BASMI) 5.4, a request was submitted to the local drugs and therapeutics committee for infliximab. Methotrexate and sulphasalazine were not considered as his disease was entirely axial.

While awaiting approval, he was admitted with severe diarrhoea. Blood investigations showed haemoglobin 11.6 g/dl, platelets 574 × 10^9/litre, ESR 41 mm/h and CRP 101 mg/l. Colonoscopy and barium follow-through confirmed Crohn’s disease, which improved on steroids (40 mg prednisolone daily tapering regime over 7 weeks) and mesalazine (800 mg three times a day). Spinal symptoms were unchanged: ESR 50 mm/h, CRP 94 mg/l.

Infliximab (3 g/kg) was commenced at a 0-, 2- and 6-week loading regime and maintained 6-weekly thereafter. By 2 weeks, AS disease activity and Crohn’s disease had improved significantly (ESR 15 mm/h, CRP <7 mg/l, BASDAI 2.56, BASFI 3.28, BASMI 4.7). MRI evaluation following the fifth infusion of infliximab showed considerable resolution of the endplate and enthesal oedema with residual inflammatory change confined to the L3/4 disc level (Fig. 1B).

The estimated incidence of juvenile-onset spondyloarthropathy (SpA) is between 1.44 and 2.10 per 100 000 children in Canada [2] and 2.0 per 100 000 children in the USA [3]. The diagnosis fulfils European Spondyloarthropathy Study Group (ESSG) criteria, which have been validated in children [4]. Enthesitis-related arthritis (ERA) is the International League of Associations for Rheumatology (ILAR) classification equivalent for juvenile idiopathic arthritis [5]. Psoriasis and the presence of systemic arthritis (as defined in the criteria) are exclusions, as are reactive arthritis and inflammatory bowel disease arthropathy. Extra-articular manifestations of ERA are enthesitis and acute uveitis. These children usually present with oligoarthritis of the lower extremities and enthesopathy. Spinal and sacroiliac joint involvement develops most frequently between 5 and 10 yr of disease.

Spondylodiscitis, although an uncommon manifestation of AS [6, 7], is usually asymptomatic unless it affects the lumbar or lower thoracic spine. Previously thought to be a late manifestation of AS [8]; it may be an early, and even the first, radiological sign of AS. Radiographic characteristics include proliferative enthesial erosions and sclerosis of the vertebral endplate adjacent to the
Disc with eventual progression to ankylosis of the spine. Early inflammatory lesions are common at the vertebral entheses, notably at the junction of the annulus fibrosus with the periosteum of the vertebra. Although not usually visualized on radiographs, these early changes are identifiable on MRI as focal areas of bone oedema.

Spondylodiscitis associated with Crohn’s disease has been reported twice [9, 10]. The association of juvenile-onset SpA with Crohn’s disease may only emerge later in the course of the disease [11]. Spondylodiscitis can be the initial manifestation of AS and lead to diagnostic confusion. This case illustrates the dramatic MRI changes in the presence of minor plain radiographic features at initial diagnosis and the prompt clinical, laboratory and MRI improvement following infliximab therapy.

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<th>Rheumatology</th>
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<td>• Spondylodiscitis can be the initial manifestation of AS and is responsive to anti-TNF-α therapy.</td>
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SIR, A 24-yr-old man was followed for 13 yr for Cushing’s syndrome. He had two hypophysecomies (the first was partial and the second complete). Histological examination did not confirm an adenoma and the surgery did not bring about a decrease of secretion of adrenocorticotropic hormone (ACTH). The outcome extension was negative. Bilateral adrenal gland surgery did not improve the Cushing’s syndrome nor the ACTH secretion.

In 2002, after a small trauma, the patient presented with violent pain in the right leg, mainly in the ankle. On examination he was found to have oedema of the right calf. The remainder of the physical examination was normal except for the Cushing’s syndrome which was already known. Right ankle radiographs showed a radiolucent area with a well-defined rim of bone. Magnetic resonance imaging (Fig. 1) showed multiple areas of bone involvement with increased intensity on T2-weighted images; there were the same lesions in muscle. Biopsies of the bone and muscle lesions confirmed the diagnosis of epithelioid haemangioendothelioma (HE), characterized by the presence of epithelioid and histolytic endothelial cells with primitive vascular differentiation. The tumor was surgically removed and the patient treated with radiation therapy. Excision of the tumour mass permitted prompt biochemical remission of hypercortisolism and normalization of ACTH secretion for the first time for more than 13 yr. The clinical presentation and biological evolution favoured a diagnosis of paraneoplastic Cushing’s syndrome.

HE is a rare malignant vascular neoplasm described in soft tissue and bone. It seems to have a predilection for males and to affect all age groups, but mainly patients in the second and third decade. The most frequent symptoms are pain and fracture. Multicentric involvement has been reported in 22 to 64% of patients.

Paraneoplastic Cushing’s syndrome is also a rare entity; it results from ectopic corticoliptropin secretion. In some cases the primary tumour presents late. Some studies have demonstrated the synthesis of corticotrophin-releasing factor in non-neuroendocrine tissues.

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**Epithelioid haemangioendothelioma and paraneoplastic hypercorticism**

Fig. 1. Ankle RMN: multiple areas of bone involvement.