Infliximab-induced lupus-like reaction in a patient with psoriatic arthritis

SIR, Infliximab is a chimeric monoclonal antibody that binds to transmembrane-bound and soluble TNF-α; this drug is currently used in the treatment of several inflammatory diseases, including psoriatic arthritis [1, 2]. Some of the adverse effects linked to its use, although rare, are described as lupus-like syndromes that generally appear in patients with rheumatoid arthritis (RA) [3–5].

We report the case of a 50-yr-old woman with a 20-yr history of psoriasis vulgaris and a subsequent 1-yr history of articular involvement with spondylitis and peripheral asymmetrical oligoarthritis. Previous treatments performed by dermatologists had included cyclosporin, PUVA (psoralen plus ultraviolet light) and methotrexate but they had very little effect on the disease. No significant clinical or laboratory abnormalities were present, except for a positive antinuclear antibody (ANA) test (1:80) with a homogeneous pattern, and no history of clinical features suggestive of lupus was noticed. She was then treated with intravenous infliximab (400 mg at weeks 0, 2, 6 and 14). The patient experienced a rapid improvement of both cutaneous and articular manifestations.

After the third infusion, she developed a high fever and acute thoracic pain due to pleural effusion. She was given prednisolone 25 mg/day for 7 days and ciprofloxacin 1000 mg/day of for 10 days, which resulted in a temporary improvement. When the patient came to our hospital after the fourth infliximab infusion she had hypophonia of the right hemithorax. Cardiology was normal but a chest X-ray revealed a right pleural effusion. Laboratory tests showed an erythrocyte sedimentation rate (ESR) of 53 mm/h, C-reactive protein (CRP) 11.5 mg/l, fibrinogen 361 mg/dl; platelets 588 000/μl; positive ANA with titre 1/2560 and a homogeneous pattern, single-stranded DNA (ssDNA) 40.6 U/ml and anti-histone antibodies 285 U/ml; anti-extractable nuclear antigens (ENA) and native DNA (nDNA) antibodies were within the normal range. A drug-induced lupus-like syndrome was diagnosed and therapy with 12.5 mg/day prednisolone, 200 mg/day hydroxychloroquine and 10 mg/week methotrexate was started.

Three weeks after discharge, she was readmitted for acute dyspnoea, chest pain, high fever, asthenia and widespread arthralgias consistent with symmetrical polyarticular arthritis. The laboratory tests showed lymphocytosis of 15 540/μl with relative lymphopenia, thrombocytosis (696 000/μl), high ESR (112 mm/h), fibrinogen 809 mg/dl, CRP 192 mg/l, mild proteinuria and haematuria, and an increase in blood sugar levels. A CT chest scan showed a bilateral pleural effusion and an echocardiograph revealed a pericardial effusion. Immunology showed a positive ANA with titre 1/2560 and a homogeneous pattern, and anti-histone antibodies 302 U/ml, but negative anti-centromere, nDNA and ENA antibodies. A bacterial cultural of the pleural effusion, including a check for mycobacteria, was negative and biochemistry showed a clear transudate with mononuclear cells, mainly lymphocytes. Therapy with methylprednisolone 60 mg/day in gradually decreasing doses and methotrexate 15 mg/week was given. Within a few months, a gradual reduction of the clinical symptoms was seen, the ANA titre decreased to 1/160 and anti-histone and anti-ssDNA antibodies disappeared. A year later the patient is being treated with methotrexate 15 mg/week for an acute phase of psoriatic arthropathy.

TNF-α is a cytokine that is mainly secreted by monocytes and macrophages. It is known to play a pivotal role in the regulation of inflammatory and immune functions [1]. It also has an important role in the pathogenesis of psoriasis, since it increases the synthesis of proinflammatory cytokines such as IL-1, IL-6 and IL-8, it promotes the migration of leucocytes into the skin by induction of vascular endothelial growth factor (VEGF), it induces adhesion molecule synthesis on keratinocytes and endothelial cells, and it enhances keratinocyte proliferation [3, 6].

Infliximab is used in the treatment of many inflammatory diseases, such as RA, ankylosing spondylitis, Behcet’s disease and Crohn’s disease [1, 2]. It has also been used successfully to treat several cutaneous diseases. Many studies have shown its efficacy in the treatment of cutaneous and articular psoriasis. The drug quickly improves the skin condition through a reduction in epidermal thickness, the number of epidermal T-cells and the normalization of expression of K16 cyto keratin and intercellular adhesion molecule 1 (ICAM-1) [1].

Infliximab is generally well tolerated, with rare adverse events [1, 2]. The production of autoantibodies is known and well documented. In a study of 62 patients affected by RA, 32 were positive for ANA autoantibodies before treatment and 51 after treatment, whereas seven ANA-negative patients affected by ankylosing spondylitis became positive after therapy [4]. Another report showed the development of ANA, anti-dsDNA (both IgM and IgG) and anti-nucleosome antibodies in a significant number of the 53 patients treated with infliximab for RA [7]. However, the rate of drug-induced lupus is only 0.22% of the patients treated with anti-TNF-α and two important studies describe a lupus-like syndrome only in 5/2292 treated and 6/1372 cases, respectively [5, 7, 8].

We found no evidence in the literature of lupus-like syndrome induced by anti-TNF-α therapy in subjects affected with cutaneous or articular psoriasis.

In conclusion, when considering which psoriatic patients to treat with infliximab, we think it is essential to carry out adequate serum autoimmunity monitoring both before and during therapy and to pay particular attention to any new signs and symptoms that may appear during the course of treatment.

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Lower limb hypertrophic osteoarthropathy can reveal aortic graft infection in Behçet syndrome

Sir, Pierre–Marie–Bamberger syndrome [1], or secondary hypertrophic osteoarthropathy (HOA), is characterized by clubbing of digits, periostal new bone formation and synovial effusion. Secondary HOA accompanies a variety of disorders, thoracic affections in particular, and may precede clinical features of the disease. Forms of HOA localized to one or two limbs occur as the result of an endothelial injury, such as an infection of arterial aneurysms or vascular grafts [2]. We report the case of a 44-yr-old woman with Behçet disease (BD) with predominantly unilateral lower limb HOA revealing an aortic graft infection.

The patient was diagnosed with BD because of recurrent episodes of oral and genital ulcers and pseudofoliculitis [3]. A pathergy test was negative. She also suffered from arthritis, three relapses of deep vein thrombosis despite continuous anticoagulation, and a history of an abdominal aortic aneurysm discovered at age 30. An aorto-biiliac graft and left femoral grafts had been inserted.

She was hospitalized for fever, arthralgia and deep pain in the left leg. On examination, her temperature was 38°C and she had arthritis of the ankles and knees, and bilateral femoral murmurs. Eye and skin examinations were normal and there were no oral or genital ulcers. Biological tests failed to evidence infection. The level of C-reactive protein (CRP) in the blood was 40 mg/l. An abdominal computed tomography (CT) scan showed a 3-cm large right iliac aneurysm facing the proximal anastomosis of the left aorto-iliaco-femoral graft. Bone X-rays revealed subperiostal new bone formation with corresponding hyperfixation on a bone 99Tc scintiscan (Fig. 1a and b). Treatment with corticosteroids, azathioprine and colchicine was rapidly efficient on general status, fever and arthralgia.

Two months later, she was readmitted for excruciating pain in the left lower limb associated with fever and severe anaemia. Blood cultures were positive for group D Streptococcus spp. and Escherichia coli. Scintigraphy with 67Ga-labelled leucocytes was highly positive on the vascular graft (Fig. 1c). Abdominal CT scan suggested a fistula between the aorta and the digestive tract (Fig. 1d). Surgery revealed a fistula between the D3 portion of the duodenum and the vascular graft close to the prosthetic fork. A bilateral axillo-femoral bypass graft was placed. Antibiotic treatment and surgery led to prolonged remission and improvement of the fixations on the bone 99Tc scintiscan.

Since aortic graft infection has been described as a cause of secondary lower limb HOA, a growing number of cases of localized HOA revealing early cases of vascular graft infections have been reported [4]. In a review of 115 cases of HOA, deep infection was responsible for 2.6% of cases of periostitis. Patients usually suffer from progressive pain and swelling of one or both extremities, associated with radiographic periostosis; clubbing of the toes is rare [5, 6]. The pathogenesis of digital clubbing and HOA remains largely unknown. Current thinking suggests that localized activation of endothelial cells by an abnormal platelet population, with the ensuing release of fibroblast growth factors, plays a central role [2]. In the case of HOA associated with vascular infection, the substance that causes HOA could either be produced by vascular tissue or be a precursor activated by contact with abnormal vascular tissue. This theory is supported by the localization of HOA in the limb vascularized by the infected graft and clinical improvement after its removal [4, 5]. Diagnosis of HOA is made using physical examination and imaging studies, finding periostitis and ruling out osteonecrosis, although no international criteria exist [2]. Bone scintigraphy showing localized hyperfixation can help confirm the diagnosis.

BD is characterized by recurrent oral and/or genital ulcers, uveitis, skin and joint involvement. Vascular manifestations appear in 9–38% of patients, mostly as vein thrombophlebitis. Arterial involvement including thrombosis, stenosis and/or aneurysms is less frequent (10–15% of vascular involvement) [7]. Aneurysms, sometimes described as arterial aphthae, may be multifocal and involve mostly the abdominal aorta and the pulmonary arteries. Vascular surgery entails a specific risk of recurrent aneurysm on the anastomosis, aorto–intestinal fistulas, graft infection and thrombosis. A combination of corticosteroids with immunosuppressive therapy is necessary to prevent relapse and appears to be more effective than corticosteroids alone [8].

In our patient, scintigraphy with radiolabelled leucocytes helped localize aorta infection, as in other cases [9]. The diagnostic yield of scintigraphy with radiolabelled leucocytes for aortic graft infections may not be as specific in BD as in other settings because specific vascular inflammation may occur without infection and thus enhance vascular fixation.

Interestingly, high-dose steroids and azathioprine treatment did not appear to abate the HOA clinical features in our patient. The regression of HOA after treatment for graft infection is in favour of a causal link between vascular graft rejection and HOA, ruling out BD as a cause of HOA.

Our observation points out the importance of early diagnosis of BD, even if it affects the lower limbs or if digital clubbing is lacking, as it can permit early diagnosis of life-threatening vascular graft infection. Particular attention should be paid to patients with BD as they are prone to infectious complications, because of both arterial Behçet-specific inflammation and a long course of immunosuppressive therapy.

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