Sustained response to infliximab in a patient with relapsing polychondritis with aortic involvement

Sir, Relapsing polychondritis (RP) is a systemic disorder, which is characterized by recurrent inflammation and destruction of cartilage structure [1]. Auricular, nasal, ocular, tracheobronchial and articular impairment are well-recognized manifestations of RP [1]. Aortic involvement is considered to be rare, and usually occurs during the course of the disease [2–3]. We recently observed a new case, which is of particular interest as the patient developed aortic involvement, revealing a recurrence of refractory RP, with favourable outcome after initiation of infliximab.

A 38-year-old woman presented in July 2005 with a 2-month history of asthenia and abdominal pain. She was diagnosed as having RP in March 2004 because of the following manifestations: bilateral auricle chondritis, nasal chondritis, hoarseness of the voice and ocular inflammation. The patient was given prednisone (at an initial dose of 1 mg/kg daily), resulting in improvement of clinical symptoms of RP. In May 2004, the patient received MTX (20 mg weekly); she developed hepatic cytolysis, resulting in MTX discontinuation. In June 2004, the patient further received AZA (150 mg daily). When steroid regimen was reduced (7.5 mg/day), the patient relapsed in July 2005. Indeed, she experienced bilateral auricle chondritis, nasal chondritis, hoarseness of the voice and ocular inflammation; she also complained concomitantly of abdominal pain. At admission, the patient had no fever; physical examination also revealed tender abdomen on palpation. Laboratory studies disclosed the following: ESR: 86 mm/h, CRP: 130 mg/l, haemoglobin: 11.5 g/dl, white blood cell count: 8.1×10^9/l, platelet count: 401×10^9/l; findings of renal and liver tests as well as blood electrophoresis were normal. CT scan of both lungs and abdomen showed circumferential thickening of the abdominal aortic wall. Blood cultures and bacterial serologies (especially Treponema pallidum) were negative; autoantibody screening was also negative for RFs, ANAs and anti-cytoplasmic antibodies. The diagnosis of RP aortic involvement was conducted. The patient was given combined therapy of prednisone (1 mg/kg daily) and pulses of cyclophosphamide (0.7 g/m^2, monthly). Four months later, the patient still exhibited severe ocular inflammation and abdominal pain. CT scan demonstrated aortic aneurysm located on the abdominal aorta and circumferential thickening of the abdominal aortic wall (Figs 1 and 2). Because RP was refractory to steroid/immunosuppressive therapy, the patient was given anti-TNF-α: infliximab (5 mg/kg) at weeks 0, 2, 6 and then 8 weekly. Infliximab therapy resulted in resolution of ocular inflammation; repeated CT scan showed improvement of aortic impairment. At 3-year follow-up, the patient is symptom free, receiving prednisone (3 mg daily) and infliximab (5 mg/kg, every 2 months); repeated CT scan showed no deterioration of aortic localizations.

Aortic involvement is rare in RP, being encountered in 4–9% of the patients [2–3]. Aortic impairment may lead to life-threatening complications in patients with RP, such as severe aortic insufficiency, active aortitis and aortic aneurysm [2–3]. Optimal therapy for management of patients with RP remains unclear; steroids and immunosuppressive drugs (AZA, MTX and cyclophosphamide) can decrease the frequency, duration and severity of recurrences, although they might not be able to stop disease progression [2–3]. Recently, few investigators have also suggested that other immunosuppressive agents may be an effective therapy for RP, i.e. LEF (by controlling T lymphocyte-mediated autoimmunity) [4] and IL-1 receptor antagonist anakinra [5, 6], although no definite conclusion can be drawn from these latter data.

After several immunosuppressive drugs had failed to control RP-related aortic involvement in our patient, infliximab was used, although anti-TNF-α agents have not yet been licensed for the therapy of RP; however, because TNF-α has a potential pathological role in RP, anti-TNF-α agents may, in fact, be of therapeutic benefits in patients with RP refractory to conventional drugs. Indeed, RP bears many of the hallmarks of a
TNF-α-mediated disease; i.e.: (i) T-cell clones reactive to type II collagen have been identified in RP, suggesting a Th 1-type autoimmune disease producing TNF-α; and (ii) TNF-α has been found in vitro to induce increased synthesis of matrix-degrading proteases from chondrocytes, resulting in damage in RP [7]. Few reports have, in fact, described previously improvement of auricular, nasal, ocular and joint complications in patients, who were unresponsive to cytotoxic drugs, after the initiation of infliximab [8, 9]. Moreover, Mpofu et al. [7] and Subrahmanyam et al. [10] have also reported a patient with recalcitrant respiratory tract localizations, in whom infliximab led to resolution of active disease. Our case is also original in that our patient with refractory RP-related aortic involvement (aneurysm of the abdominal aorta and active abdominal aortitis) was successfully given infliximab. We therefore suggest that infliximab may be an effective therapy for RP-related aortic involvement that is unresponsive to conventional therapy. In fact, at 3-year follow-up, our patient was symptom free and CT scan revealed no deterioration of aortic involvement. In 2006, the patient recovered clinically and the CD4+ T-cell counts improved without reaching the normal range.

IHL is a rare immunodeficiency syndrome affecting 0.0002% of the adults. It is defined by a CD4+ T-cell count <300/μl or a percentage of <20% CD4+ T cells of total T cells on at least two occasions. For diagnosis, HIV infection as well as any other defined immunodeficiency or cytotoxic drug therapy associated T-cell lymphopenia has to be excluded [1].

The differential diagnosis of CD4+ lymphocytopenia in adults includes infections, malignancies, autoimmune diseases, drugs and primary immunodeficiency syndromes. Often, IHL becomes apparent through manifestation of opportunistic infections (OIs)—mainly, cryptococcosis, followed by mycobacteriosis, human papilloma virus and herpes zoster [2, 3]. The manifestation of OI cells for evaluation of the cellular immune system and especially for CD4+ lymphocytopenia. The most important differential diagnosis is HIV infection. Since 1992, the US Center of Disease Control and Prevention (CDC) has identified a group of HIV-negative patients with CD4+ lymphocytopenia has previously been associated with extra-pulmonary tuberculosis. A retrospective study in West Africa [4] and a prospective study in Dakar observed CD4+ T-cell counts <300 cells/μl in 9.6 and 14.4% of the 115 and 430 HIV seronegative patients with tuberculosis, respectively [5].

In general, IHL is associated with more severe mycobacterial infections, but patients with disseminated mycobacterial infection demonstrated significant improvement of CD4+ T-cell counts after 4–8 weeks of anti-tuberculous therapy [6].

In the present case, no complete normalization of CD4+ T-cell count was observed after successful anti-tuberculous therapy within 5 years, suggesting that CD4+ lymphocytopenia was rather a pre-existing condition than the result of mycobacterial infection. In most patients with IHL, immunologic phenotyping reveals a concomitant, less pronounced decrease of CD8+ T cells, a slightly decreased CD4:CD8 ratio and normal B-cell numbers. Naïve CD45RA+ T cells are more severely diminished than the CD45RO+ cells [3, 7, 8].

This case presented initially with panlymphopenia of 139 cells/μl (23.7%) CD4+ T cells and 219/μl (37.5%) CD8+ T cells resulting in a decreased CD4:CD8 ratio of 0.63. Among CD4+ T cells, naive CD45RA+ T cells were severely reduced to 29 cells/μl (21%). Also the B-cell count was diminished to 87 cells/μl (14.9%). Thus, the patient fulfilled the CDC criteria for IHL, presenting with a characteristic immunologic phenotype.

Functional T-cell evaluation revealed lymphoproliferation to mitogens and antigens in the lower normal range (data not shown). Cytokine production (IL-2, -10, IFN-γ and TNF-α) was virtually normal after stimulation with Staphylococcal enterotoxin B (SEB) and soluble anti-CD3, but deficient after stimulation with PHA or anti-CD3/anti-CD28 coupled to beads (Table 1). This was not only due to the reduced total count of CD4+ T cells, since T-cell activation via anti-CD3/anti-CD28 also caused a reduced up-regulation of CD69 and CD25 (data not shown). Pre-activated CD4+ T cells of IHL patients express higher levels of Fas and Fas ligand that is associated with an increased apoptosis of these cells in vitro, particularly when stimulated with PHA or anti-CD3 [9, 10]. This increased apoptosis after stimulation causes reduced proliferation and possibly the alteration of cytokine production after certain stimulating mitogens. IFN-γ receptor expression and function and IL-12 production were normal (data not shown) excluding other