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Haematopoietic stem cell transplantation for refractory Takayasu’s arteritis

Sir, Takayasu’s arteritis is a rare large-vessel vasculitis with a variable natural history. Manifestations range from asymptomatic disease to catastrophic neurological impairment and 5-yr survival is 60–70% in up to 25% of patients with progressive disease. Fifty per cent of patients respond to steroids and 30–50% of non-responders benefit from other forms of immunosuppression [1].

Eleven cases of small- or medium-vessel vasculitis submitted to autologous haematopoietic stem cell transplantation (HSCT) have been reported worldwide [2, 3] and a further two in Brazil [4, 5]. Outcome is variable: 1/1 complete remission (CR) in polyanarteritis nodosa, 1/3 CR in Wegener’s granulomatosis, 1/3 CR and 1/3 partial remission (PR) in Behçet’s disease, 2/3 CR in cryoglobulinaemia and 1/1 PR in an undifferentiated vasculitis. To the best of our knowledge, this is the first case of HSCT for large-vessel arteritis reported in the literature; it was briefly presented at an international meeting [6].

Takayasu’s arteritis was diagnosed in June 1990 in a 41-yr-old Brazilian woman presenting with upper and lower limb claudication, dizziness, headache, polyarthries, malaise, myalgia and occasional fever. There was no kidney or heart involvement. Doppler ultrasound (US) showed biphasic or monophasic pulse waves with slow speed in the abdominal aorta (41 cm/s) and in the upper and lower limbs. The arteriography showed irregularities and stenosis of the abdominal aorta, of both carotid and iliac arteries and of the left subclavian artery. The patient was treated with various immunosuppressive agents, such as steroids (two pulses of 6-methylprednisolone 1 g × 3, and up to 80 mg prednisone per day since diagnosis), oral cyclophosphamide (50 mg/day for 30 days), mycophenolate mofetil (MMF; 2 g/day for 11 months), methotrexate (25 mg/week for 6 months) and chlorambucil (6 mg/day for 3 months), but none of those therapies stopped disease progression. In October 2002, while on MMF and steroids, a magnetic resonance angiogram (MRA) showed narrowing and irregularities in both carotid and subclavian arteries and in the brachiocephalic artery (Fig. 1A). This result was associated with worsening of clinical symptoms and prompted the patient and her physician to choose our experimental protocol of autologous HSCT for refractory autoimmune diseases [4, 5] which was approved by the Committee of Ethics in Research of the University Hospital of the School of Medicine of Ribeirão Preto. An informed consent according to the Declaration of Helsinki was signed. In December 2002 fibromyalgia was also diagnosed.

In March 2003 haematopoietic stem cells were mobilized from the bone marrow with cyclophosphamide (2 g/m²) and granulocyte colony-stimulating factor (G-CSF) (10 µg/kg/day), collected by leucapheresis (two sessions) and frozen in liquid N². In April 2003 the patient was conditioned with cyclophosphamide (50 mg/kg/day × 4) plus rabbit anti-thymocyte globulin (ATG; Tecelec, Biotest, Germany; 4.5 mg/kg divided in five doses and preceded by 125 mg of hydrocortisone), followed by stem cell infusion (3.9 × 10⁷/kg CD34+ cells). Complications during the neutropenic phase included fever of unknown origin, hyperglycaemia, subconjunctival haematomata and emotional liability. Cefepime and teicoplanin were used as empirical treatment for neutropenic fever, acyclovir for prophylaxis of herpes infection and trimethoprim/sulphamethoxazole for prophylaxis of Pneumocystis carinii infection. G-CSF (5 µg/kg/day) was used from day 5 through to neutrophil engraftment which was observed on day 9. On day 14 the patient presented with a skin rash and on day 16 she was discharged from the hospital. Amenorrhea developed in the pre-transplant period after use of leuprolide and persisted after transplantation. The clinical condition improved rapidly; there was complete resolution of headache, dizziness and malaise while limb claudication was significantly reduced. After transplantation (day 320), arterial pulses of the left lower limbs and of the carotid arteries showed normal shape and speed by Doppler US and the wave speed of abdominal aorta increased to 73 cm/s. There were still stenotic areas in the arteries of the upper limbs and a low-speed biphasic pattern in the wave speed of the right lower limb. In the last clinical follow-up on day 270 the patient presented manifestations only of fibromyalgia and hand paraesthesia. C-reactive protein was 2.4 mg/dl pre-transplant and 0.8 mg/dl on day 147 and day 183. The erythrocyte sedimentation rate was 84 mm/1st h (Westergren method) pre-transplant, and 34 mm/1st h on day 350. Immunophenotyping of peripheral blood lymphocytes showed inversion of the CD4/CD8 ratio, and reduction of CD4 memory cells at day 210 post-transplantation. Pre- and post-transplantation immunoglobulin...
levels were respectively: IgG 750 and 924 mg/dl, IgA 395 and 110, IgM 426 and 144. In the evaluation of day 60 the MRA of the aortic arch branches showed recovery of the previous brachiocephalic artery stenosis and great improvement in the irregularities of the left carotid artery and the left subclavian artery (Fig. 1B). The patient was off any immunosuppression on day 400.

Haematopoietic stem cell transplantation has been employed since 1996 for isolated refractory autoimmune diseases; more than 500 autologous transplants have been registered at the EBMT/EULAR data base in Basel [7] and about 150 have been performed in North and South America [8, 9]. Neurological diseases such as multiple sclerosis, and rheumatic diseases such as systemic lupus erythematosus, systemic sclerosis and adult and juvenile rheumatoid arthritis are currently the main indications for HSCT. Many other autoimmune diseases, including small- and medium-vessel arteritis [2, 3], have been successfully treated with autologous HSCT, but this is the first case of a large-vessel arteritis submitted to this treatment.

The mechanisms of therapeutic benefit of HSCT in autoimmune disease are currently under investigation and may include immunosuppression induced by high-dose chemotherapy and immunotherapy, tolerance induced by autologous stem cells or tissue repair mediated by transdifferentiated stem cells [9]. In the present case, inhibition of inflammatory activity is likely to be a consequence of immunosuppression by cyclophosphamide and ATG, but the surprisingly fast improvement in artery structure and function might be due to angiogenic properties of HSC, as hypothesized in HSCT for systemic sclerosis [10].

Although our patient still has a short follow-up and some arterial abnormalities, the encouraging results suggest that high-dose chemo/immunotherapy associated with HSCT can modify the clinical course of severe and refractory large-vessel vasculitis.

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Rheumatology

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<td>Autologous haematopoietic stem cell transplantation may remit Takayasu’s arteritis.</td>
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**Normalization of anticardiolipin antibodies following rituximab therapy for marginal zone lymphoma in a patient with Sjögren’s syndrome**

Sir, Sjögren’s syndrome (SS) is associated with the development of lymphoma, most commonly marginal zone lymphoma (MZL), and antiphospholipid antibodies (aPL). While a diagnosis of SS places a patient at 44-fold increased risk of developing lymphoma, the association of SS with aPL is less often described [1, 2]. However, the occurrence of secondary antiphospholipid syndrome (APS) in patients with SS has been reported [3]. Few cases in the literature report the occurrence of both aPL and APS in non-SS patients with various forms of lymphoma [4–8].

Rituximab, a chimeric monoclonal CD20 antibody, has been used successfully to treat non-Hodgkin’s lymphoma and several autoimmune disorders, including systemic lupus erythematosus (SLE), rheumatoid arthritis, autoimmune thrombocytopenia and autoimmune haemolytic anaemia [9]. In addition, rituximab has recently been shown to improve lymphoma associated with SS, as well as the symptoms of SS itself [10].

We describe a case of normalization of anticardiolipin antibodies (aCL) in a patient with SS and secondary APS treated with rituximab for MZL. We feel that this report is of interest as it may relate to future uses of rituximab to treat APS, in particular the catastrophic APS. The patient is a 46-year-old female who was diagnosed with SS in 1984. At that time, she had typical sicca symptoms, a positive minor salivary gland biopsy and an antibody...