LETTERS TO THE EDITOR

Autologous haemopoietic stem cell transplantation in a patient with severe pulmonary hypertension complicating connective tissue disease

Bone marrow transplantation, especially with autologous bone stem cells, is increasingly being discussed as a treatment for severe lung or organ threatening autoimmune diseases. In this context we describe a case so treated.

A 47-year-old woman was referred to our hospital for assessment of increasing chronic cough over three years, associated with NYHA (New York Heart Association) grade II dyspnoea and Raynaud syndrome. She complained of symptoms compatible with reflex oesophagitis but no true dysphagia. Barium swallow was normal. There were no skin changes proximal to the fingers and no telangectasia. Capillary microscopy showed changes seen with systemic sclerosis. Antinuclear antibodies were positive at 1:640 with a centromere pattern, and the antititre antibody was also positive by elisa to a titre of 1/10 240. Other autoantibodies, including anticardiolipin, were negative, as was the lupus inhibitor test. The hepatitis enzymes were raised less than threefold of normal. Tests for antibodies to hepatitis A, B, and C, and smooth muscle and mitochondrial antibodies were negative.

Pulmonary assessment showed a normal x-ray and high resolution computerised tomography scan of the lungs, normal lung volumes, and a slightly reduced diffusion capacity (69% of predicted). Bronchoalveolar lavage revealed normal total cell count but lymphocytosis of 32% (CD4/CD8 3.5). Maximum oxygen uptake was reduced to 72% predicted values (VO₂ max 20.6 ml kg⁻¹ min⁻¹) on exercise testing. Doppler echo showed estimated systolic pulmonary artery pressure (mPAP) of 28 mm Hg, suggesting pulmonary hypertension. Treatment with 0.5 mg kg⁻¹ prednisolone was given over eight weeks with some improvement of cough and exercise induced hypoxaemia, but it was withdrawn because of side effects. Further management consisted of felodipine (5-10 mg) and omeprazole 20 mg twice daily with reasonable control for the next nine months, when a recurring cough and increasing dyspnoea (NYHA grade III) prompted re-evaluation. At this time pulmonary hypertension, with estimated systolic pulmonary artery pressure (PAP) 60 mm Hg and signs of tricuspid incompetence, was observed. VO₂ max had fallen to 31% predicted (8.9 ml min⁻¹ kg⁻¹).

Otherwise the clinical and laboratory observations were unchanged. Prednisone 40 mg was resumed with the addition of anticoagulants, digitalis, and diuretics without significant improvement. Therefore three pulses of 750 mg cyclophosphamide intrave-}

ously were given at monthly intervals. Because of the unchanged clinical condition vasodilator treatment was evaluated. A Swan-Ganz catheter showed mean PAP of 45 to 50 mm Hg, with an improvement of more than 20% in PAP and pulmonary vascular resistance with a prostacyclin infusion. Oral administration of nifedipine retard 120 mg daily produced similar results. Prednisone was reduced to 10 mg/d and vasodilator treatment with nifedipine continued. After eight weeks of subjective improvement the patient deteriorated further with signs of right heart failure (anaemia, and electrocardiographic evidence of right heart strain. In addition, an exudative pleural effusion and polypyrhsalaemia developed. Despite short term symptomatic improvement with nifedipine, the administration of 2 x 40 mg, and increased diuretics, the situation was considered critical and lung transplantation was discussed. On the grounds of the systemic disease this approach was refused, but in collaboration with autologous stem cell rescue was undertaken after ethics committee approval and informed consent.

Primarily we proceeded with 2 x 3300 mg of cyclophosphamide followed by granulocyte colony stimulating factor (G-CSF, 600 µg daily subcutaneously). Haemopoietic stem cells were harvested from the peripheral blood 12 days later. There was no blood to be given because of anaemia. Labial herpes simplex infection was treated with acyclovir. Anticoagulation with dicumarol was replaced by heparin injection. The harvested total nucleated cell count was 34 x 10⁹ consisting of 10.4% CD 34 positive cells. After positive selection for CD34 (Cephar) the cell count was 1.8 x 10⁹. T and B cell depletion was achieved with combined anti-CD2/CD3 (Daclizumab, Xoma) and anti-CD19/CD20 (Baxter) antibodies using a Maxsep selection device yielding an end product of 11.5 x 10⁹ kg⁻¹ body weight and a total of 10.1 x 10⁹ kg⁻¹ body weight of CD34 cells. Ten days later conditioning was performed with 50 mg kg⁻¹ cyclophosphamide given each day for four days followed by infusion of 10.1 x 10⁹ kg⁻¹ T and B cell purged autologous stem cells. GCSF (four daily doses of 300 µg, five doses of 480 µg) was administered for a total of nine days to shorten the duration of a aplasia, such that the leucocyte count increased above 1 x 10⁹ litre⁻¹ 19 days after stem cell transplantation and was normal one day later. Complications included a hypotonic collapse on day 6, cholecytitis on day 9, and right side pleural effusion on day 14. Antibiotics (amikacin, ceftazidime) were given on day 5 because of low grade fever during aplasia. Because the systemic blood pressure was lower than usual, nifedipine was stopped for one day, during which time she suffered a cardiovascular collapse (day 6). Mean PAP was 55 mm Hg (diastolic 30 mm Hg, diastolic 41 mm Hg), pulmonary vascular resistance 1046 dyn s cm⁻⁵ (normal 200), and the cardiac index 1.92 litres min⁻¹ m⁻². With readministration of nifedipine and 500 ml 0.9% NaCl, mPAP and resistance dropped by 15-25%, suggesting that a reversible component of pulmonary hypertension was still present. On day 15 urgent cholecystectomy was performed because of cholecystitis associated with abdominal pain and markedly raised liver enzymes not resolving with conservative treatment. The postoperative course was uneventful apart from aspiration of 1200 ml of pleural effusion and the need for increased doses of diuretics. The patient was discharged from the transplant unit 22 days following stem cell transplantation and eight days after cholecystectomy.

There have been several reports of patients with autoimmune disease who underwent allogenic and autologous bone marrow transplantation, for concomitant haematological disease. Immunoablation and rescue allows more intensive immunosuppression and is therefore being discussed as a treatment strategy for severe autoimmune diseases which do not respond to conventional treatment. This is the first case of a CREST-like syndrome undergoing such treatment due to otherwise uncontrollable pulmonary hypertension. Harvesting of stem cells was uncomplicated. A study showed eight patients of CD34-positive cells despite previous treatment with cyclophosphamide. T and B cell purging was performed because an altered immune mechanism and the possibility of a more severe immunological disease. Immunoablation was well tolerated by the patient. Management of fluid balance and vasodilators was difficult because of severe pulmonary hypertension. It is of note that the infection complicated agranulocytosis. However, the patient recovered uneventfully.

Although, it is too early to determine if there will be long term benefit from this treatment, the patient is now free of symptoms, and has subjective improvement of effort tolerance in the first two months after bone marrow transplantation and the angina disappeared. In the eighth post-transplant week a viral respiratory infection (cytomegalovirus negative) developed, with high fever (39.5°C) which resolved without antibiotics. One week later the patient suffered a pulmonary embolus with dyspnoea grade 4 and hypoxemia. Echo Doppler study was performed and the right ventricular thrombi and estimated indirect pulmonary artery pressure of 120 mm Hg systolic. Such thrombi had never previously been demonstrated, and the anticardiolipin antibodies remained negative. With heparin therapy and increase in oral anticoagulation the clinical signs slowly improved and the indirect pulmonary arterial pressure fell to 90 mm Hg. The anti-centromere and, labial herpes simplex infection complicated agranulocytosis. However, the patient recovered uneventfully.
The association between fibromyalgia and carpal tunnel syndrome in the general population

Fibromyalgia and carpal tunnel syndrome are common diseases in adult women. Their prevalences in the whole population are 2%1 and 9.2%2, respectively. Recently, a study performed in northern Spain has suggested that the two conditions are often associated, with higher prevalences in women showing evidence of carpal tunnel syndrome.3 This 16% prevalence for the association is higher than that observed for carpal tunnel syndrome alone and suggests that common underlying mechanisms are at work. However, the study was done on patients referred to the clinic for fibromyalgia and no data are known about the occurrence of the association in the general population. During a survey on the prevalence of peripheral pain in an Italian population sample, we came across several patients with fibromyalgia or carpal tunnel syndrome and have studied the occurrence of the association between the two conditions.

A postal questionnaire4 was sent to 4456 subjects living in Chiavari, northern Italy, to investigate the presence of articular signs and symptoms. Subjects were asked to report if they had any joint pain or swelling for more than four continuous weeks and if they currently had joint pain or swelling, by indicating the relevant sites on a mannequin. In addition, they were asked to report the presence of morning stiffness lasting more than 30 minutes. This set of questions was originally developed by the ARCo Epidemiology Unit in Manchester, United Kingdom1 and its primary goal was to detect prevalent cases of rheumatoid arthritis.

The diagnosis of fibromyalgia was based on the criteria suggested in 1990 by the American College of Rheumatology5 that is, widespread pain and the presence of tenderness in at least 11 of 18 sites (tender points).

The diagnosis of carpal tunnel syndrome was made on clinical grounds. It included (a) history of numbness, paraesthesia, and/or pain in the fingers innervated by the median nerve, and (b) positive Tinel sign or positive Phalen sign. Invasive tests, such as nerve conduction studies, were not performed in view of the epidemiological nature of the research. After two mailings, 2440 out of 4456 subjects (54.8%) returned the questionnaire. Of these, 182 (7.5%) had joint pain and swelling in at least two joints. This group of patients was offered a clinical examination; 93 (51.1%) agreed to be visited. Fibromyalgia was present in 21 (22.6%) of these patients and carpal tunnel syndrome in 26 (28%). Both conditions occurred simultaneously in nine patients (9.7%) (table). The odds ratio for patients with any one of the conditions of showing the other one was 2.4 (95% confidence interval 0.9 to 6.8). These fibromyalgia-carpal tunnel syndrome patients were 23.5 years old, whereas patients with carpal tunnel syndrome were male. What is more, if only women with carpal tunnel syndrome or fibromyalgia are considered, nearly half of them also had the other disease. The mean number of tender points was obviously higher in patients with fibromyalgia than in those with carpal tunnel syndrome alone (13.2 ± 3.8; P < 0.001). Self-reported joint swelling and early morning stiffness were more, similarly distributed in the three groups of patients.

Our data show that responders who reported a history of joint pain and swelling of peripheral joints were often affected by fibromyalgia or carpal tunnel syndrome. This study does not disclose the absolute prevalence of fibromyalgia and carpal tunnel syndrome because the questionnaire was intended for screening patients with possible rheumatological conditions among those with fibromyalgia or carpal tunnel syndrome. However, in a pilot study, most of the outpatients with these conditions attending a rheumatological clinic answered positively to the questionnaire. We believe that patients with fibromyalgia reported articular involvement on the mannequin because they were unable to differentiate articular from extra-articular pain. In addition, they frequently over-reported swelling. Patients with carpal tunnel syndrome as a rule complain of pain and numbness associated with a subjective sensation of swelling in the hands, especially in the morning. Both fibromyalgia and carpal tunnel syndrome are characterised by morning stiffness.

In addition, there is the possibility of a selection bias due to over-representation of patients with more severe disease, since this subgroup is more likely to respond to questionnaires. A further limitation of this study was that the same observer performed the Tinel and Phalen tests and pressed tender points. Therefore, information bias cannot be excluded. Both biases would increase the strength of this association. Nevertheless we feel that the magnitude of the association between fibromyalgia and carpal tunnel syndrome is the general population showed by our study should prompt further investigation on possible similarities in the aetiopathogenic mechanisms at work in these conditions.
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