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 marrow stem cells, is increasingly being discussed as a treatment for severe life 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 consistent with systemic sclerosis. Antinuclear antibodies were positive at 1:640 with a centromere pattern, and the antitcentromere antibody was also positive by ELISA to a titre of 1/10 240. Other autoantibodies, including antitcentriopulin, were negative, as was the lupus inhibitor test. The heparin enzymes were raised less than threefold of normal. Tests for antibodies to hepatitis A, B, and C, and anti-smooth muscle and mitochondrial antibodies were negative.

Pulmonary assessment showed a normal x-ray and high resolution computed 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 (VO2max 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kg-1 prednisolone was given over eight weeks with some improvement of cough and exercise induced hypoxaemia, but it was withdrawn because of side effects.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 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. VO2max 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 triple pulses of 750 mg cyclophosphamide intra-
nously 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 led to 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 (rheumatic pericarditis, and electrocardiographic evidence of right heart strain. In addition, an exudative pleural effusion and polyarthralgia developed. Despite short term symptomatic improvement with nifedipine and increased nitrates (2 x 40 mg), and increased diuresis, the situation was considered critical and lung transplantation discussed. On the grounds of the systemic disease this approach was refused. The patient with autologous stem cell rescue was undertaken after ethics committee approval and informed consent.

Primarily was preceded 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. G-CSF of 300 µg/kg had to be given because of anaemia. Labial herpetic simplex infection was treated with acyclovir. Anticoagulation with dicumarol was replaced by heparin injection. The harvested total nucleated cell count was 34 x 10^6 consisting of 10.4% CD34 positive cells. After positive selection for CD34 (Cepare) the cell count was 1.8 x 10^6. T and B cell depletion was achieved with combined anti-CD2/CD3 (OKT3) and anti-CD19/CD20 (Baxter) antibodies using a Maxsep selection device yielding an end product of 11.5 x 10^5 kg-1 body weight and a total of 10.1 x 10^6 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 10^6 kg-1 T and B cell purged autologous stem cells. GCSF (four doses of 300 µg, five doses of 480 µg) was administered for a total of nine days to shorten the duration of aplasia, such that the leucocyte count increased above 1 x 10^9 litres-1 19 days after stem cell transplantation and was normal one day later. Complications included a hypertonic collapse on day 6, cholecytitis on day 9, and right side pleural effusion on day 14. Antibiotics (amikacin, ceftazidime) were given on day 9 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 26 mm Hg, systolic 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 cholecytitis associated with abdominal pain and markedly raised liver enzymes not resolving with conservative treatment. The postoperative course was uneventful. With readministration 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. Besides this patient, engraftment and reduction of immunosuppressive treatment or 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 single lung transplantation, was performed for CD34-positive cells despite previous treatment with cyclophosphamide. T and B cell purging was performed because an altered immune mechanism, and the anti-CD2/CD3 (OKT3) antibody was deleted. The patient was weaned off immunosuppressive treatment and the cell depleted blood transfusion stopped. The postoperative course was uneventful. The patient recovered uneventfully.

Although, it is too early to determine if there will be long term benefit from this treatment, the patient's overall condition, and the 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) was diagnosed, which resolved without antibiotics. One week later the patient suffered a pulmonary embolus with dyspnoea grade 4 and hypoxemia. Echo Doppler testing revealed right ventricular thrombi and estimated indirect pulmonary artery pressure of 120 mm Hg systolic. Such thrombi had never previously been demonstrated, and the anticoagulants and antibiotics 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-CD2/CD3 (OKT3) antibody was also deleted. The postoperative course showed a trend downwards from 1:10 240 (1992), 1:2560 (12/1995; after priming with cyclophosphamide), to 1:640 10 weeks and six months after bone marrow transplantation. Formal right heart catheter studies were performed six months after bone marrow transplantation, showing a mean pulmonary artery pressure of 44 mm Hg and pulmonary vascular resistance (PVR) of 1000 dyn s cm-5. Mean PAP could be reduced by 10% and PVR by 16% using inhaled nitric oxide as a vasodilator in addition to the oral calcium antagonists. Re-evaluation will be performed at 12 and 24 months to determine the long term results.

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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%, respectively. Recently, a study performed in northern Spain has suggested that the two conditions are often associated, with a prevalence of fibromyalgia showing evidence of carpal tunnel syndrome. 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 questionnaire was sent to 4456 subjects living in Chiavari, northern Italy, to investigate the presence of articular signs and symptoms and questions 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 ARC Epidemiology Unit in Manchester, United Kingdom 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 Rheumatology. a diagnosis of 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 found to have 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. While 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 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 rheumatoid arthritis. The questionnaire was 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, we 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 pathology, 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 in the general population showed by our study should prompt further investigation on possible similarities in the aetiopathogenic mechanisms at work in these conditions.

Demographic and clinical characteristics of the patients, expressed as means and 95% confidence intervals (CI)

<table>
<thead>
<tr>
<th>Fibromyalgia</th>
<th>Carpal tunnel syndrome</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Men/women</td>
<td>1/11</td>
<td>4/13</td>
</tr>
<tr>
<td>Mean age (years (SD))</td>
<td>58.7 (15.5)</td>
<td>51.8 (14.6)</td>
</tr>
<tr>
<td>Mean number of tender points</td>
<td>13.4 (11.5-15.5)</td>
<td>13.8 (9.5-17.4)</td>
</tr>
<tr>
<td>Mean duration of morning stiffness (min)</td>
<td>65.7 (23.2-108.2)</td>
<td>44.5 (25.7-63.3)</td>
</tr>
<tr>
<td>Mean number of joints reported as swollen</td>
<td>5.8 (3.5-8.1)</td>
<td>3.8 (2.9-4.7)</td>
</tr>
</tbody>
</table>
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