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Melphalan-Induced Pulmonary Fibrosis in Osteosclerotic Myeloma

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To the Editors,

Patients with multiple myeloma and osteosclerotic bony lesions on presentation have been described although the occurrence is rare and the pathogenesis is unknown [1]. In this report we document a patient with osteosclerotic myeloma and a very high alkaline phosphatase (AP) on presentation who developed pulmonary fibrosis following treatment with mel-phalan.

A 57-year-old retired dress machinist presented with a 3-month history of tiredness. On examination abnormal findings were pallor and 2 cm hepatomegaly. Investigations revealed Hb 8.7 g/dl, WBC $13 \times 10^9/l$, platelets $140 \times 10^9/l$, ESR 84 mm in the first hour. Blood film showed neutrophils 34%, lymphocytes 54%, monocytes 9%, eosinophils 3%, 9 nucleated red cells/100 WBC. Liver function tests showed bilirubin $9 \mu\text{mol/l}$ (NR < 17), AST 24 IU/l (NR < 18), LDH 237 IU/l (NR 30-90), AP 1,580 IU/l (NR 20-90), 5-nucleotidase 10 IU/l (NR 1-15), total protein 71 g/l (NR 60-80), albumin 25 g/l (NR 35-47). Immunoglobins were IgG 30 g/l (NR 7.2-18), IgA 0.2 g/l (NR 1.0-3.6), IgM 0.2 g/l (NR 1.2-2.5), IgG kappa monoclonal band was detected on immunoelectrophoresis. Urinary protein excretion was 0.6 g in 24 h and concentrated urine electro-phoresis showed free K light chains. Appearances of the bone marrow trephine biopsy, skeletal survey and ^{99}Tc bone scan were consistent with the diagnosis of osteosclerotic myeloma. Serum calcium, phosphate and urate were normal. Chest X-ray was reported and has since been reviewed as normal.

She was commenced on 6-weekly courses of mel-phalan and prednisolone. After two courses of treatment and despite a satisfactory blood count, she complained of breathlessness. There was little abnormal on physical examination. Chest X-rays revealed reticular shadowing at the bases. Lung function studies showed a marked diffusion defect. The transfer factor was reduced at 10 ml/min/mm Hg (predicted 21.5) and respiratory function tests were consistent with restrictive lung disease. After six courses of chemotherapy she was breathless on moderate exertion. However, her Hb stabilised without further transfusions at 14 g/dl, the platelet count rose to $168 \times 10^9/l$, ESR fell to 15 mm in the first hour. The AP fell to 293 IU/l, IgG to 20.6 g/l, LDH to 90 IU/l and AST to 10

IU/1. Albumin rose to 39 g/l. Chest X-rays showed steadily increasing reticular shadowing.

She relapsed on chemotherapy 30 months after presentation. Treatment was changed to cyclophosphamide, vindesine and prednisolone and she has received three courses of this. She is now severely disabled by her breathlessness and is tachypnoeic at rest. Chest X-ray shows increased coarse reticular shadowing at both mid and lower zones. Her lung function has deteriorated – FEV₁ has fallen to 0.8 litres (predicted 2.2) and the transfer factor to 5.5 (predicted 21) ml/min/mm Hg.

The pulmonary fibrosis in our patient was associated with the treatment rather than the disease. She had not received any other drugs except melphalan and prednisolone prior to the development of signs of pulmonary fibrosis; therefore, it is quite likely that this was induced by melphalan. The association between melphalan and pulmonary fibrosis, although rare, has been reported increasingly in the past few years [2,3] and histologically consists of interstitial fibrosis and atypical alveolar hyperplasia [3]. The pathogenesis of melphalan-induced pulmonary fibrosis is unknown but we feel this has important clinical implications as illustrated by this patient.

Serum AP is rarely raised in classical myeloma even in the face of extensive bone damage and this is taken as evidence of a lack of osteoblastic activity. Paradoxically, osteosclerotic myeloma is no more frequently characterised by a raised serum AP [1] and our patient is unusual in this respect.

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Acute Hepatitis and Selective Erythroblastopenia

Transient pure red blood cell aplasia has been observed following viral infections, treatment with several drugs, acute renal failure, kwashiorkor, deficit of vitamin B₁₂, riboflavin and folate, and associated with immunological disorders and carcinoma. Only in two reports it has been described in association with viral hepatitis. We are reporting a new case of this association.

A 26-year-old male patient was admitted to our hospital in March 1979 due to an acute hepatocellular insufficiency. A diagnosis of acute HBsAg-negative hepatitis was made at that time. On March 26, 1979, the blood tests showed: hemoglobin 6.2 g/dl; hematocrit 18%; reticulocytes 0.2%; WBC $6.1 \times 10^3/\mu\text{l}$; platelets $240 \times 10^3/\mu\text{l}$; direct and indirect Coombs tests were negative. Bone marrow aspirate revealed a complete depletion of erythroblastic cells with normal granulocytic and megakaryocytic lines. The clinical picture was interpreted as a severe acute hepatitis, possibly of viral origin with pure red blood cell aplasia. Several transfusions of concentrated red cells were

performed. On April 26, 1979, the patient presented an obvious improvement in peripheral blood findings: hemoglobin 13 g/dl; hematocrit 40%; and reticulocytes 9%. A new bone marrow aspirate showed a recovery of the erythroblastic cell population. A liver biopsy revealed a histologic picture compatible with an acute hepatitis. The patient was

discharged on May 6, 1979. The patient has been feeling well until the present time, and all biochemical parameters have been normalized. A new liver biopsy, on October 15, 1979, showed a persistent chronic hepatitis.

After the initial description, by Sears et al. [1], of an association of acute viral hepatitis with a pure red cell aplasia in 2 brothers, an additional case has been reported by Wilson et al. [2]. A positive HBsAg was found in only 1 of these 3 patients.

In several aspects, our case is similar to those previously reported. As the other 3 patients, ours had severe acute hepatitis, and several weeks later developed a sudden anemia, without signs of bleeding or hemolysis. The bone marrow aspirate showed a complete depletion of erythroblastic cells. Sears et al. described the first 2 cases in 2 brothers, both of whom developed, within a 4-year period, hepatitis associated with selective erythroblastopenia, suggesting a possible genetic link. A brother of our patient had hepatitis 8 years ago, but it was not studied serologically. It seems that he never developed a simultaneous anemia. In 2 of the 3 reported cases the patient developed chronic hepatitis. Our patient also has persistent chronic hepatitis. The immunological studies were completely negative in 3 of the 4 cases studied, including the one described here. Only in 1 case a positive LE cell phenomenon and the presence of