

Pulmonary veno-occlusive disease after bone marrow transplantation

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Pulmonary veno-occlusive disease is a very rare pulmonary vascular disease and has not previously been described after bone marrow transplantation. We report the case of a 12 year old boy who developed pulmonary veno-occlusive disease after bone marrow transplantation for acute lymphoblastic leukaemia.

Case report

A 7 year old white boy who had previously been healthy was admitted to hospital in 1978 with acute lymphoblastic leukaemia. Complete remission was obtained with vincristine (2 mg), cyclophosphamide (600 mg), daunorubicin (35 mg daily on days 1, 2, and 3) and cytarabine (70 mg daily on days 1, 2, and 3). Maintenance treatment was continued.

Five years later (1983) he suffered a relapse: a second complete remission was obtained with four injections of vincristine (2.5 mg) and prednisone. Appreciable hypercalcaemia of 4.6 mmol/l (180 mg/l) was observed; it was reduced with mithramycin, and disappeared during remission.

Five months later a second relapse occurred, also associated with hypercalcaemia of 3.5 mmol/l (140 mg/l). A course of chemotherapy with vincristine (2.5 mg), prednisone, cyclophosphamide (700 mg), and daunorubicin (40 mg) was started. Complete remission could not be achieved, and it was decided to perform a marrow transplant, although 15% blast cells were observed in the bone marrow. The hypercalcaemia was again reduced with mithramycin. Until this time there had been no signs of respiratory disease and the chest radiographs had been normal throughout.

An allograft was performed with engraftment from his sister, who had homologous leucocytic antibodies, after conventional preparation with combination of cyclophosphamide (60 mg/kg on days 5 and 4) and total body irradiation of 10 Gy (1000 rad) with pulmonary shielding above 8 Gy (800 rad). Methotrexate was given on days 1 (20 mg), 3 (13 mg), and 6 (13 mg) as prophylaxis against graft versus host disease but prednisone (1 mg/kg) was required on day 18 for grade 1 graft versus host disease.

The transplanted marrow engrafted on day 22. Bacterial pneumonia (*Pseudomonas aeruginosa*) developed in the left lower lobe on day 32 and resolved incompletely with cefsulodin (3 g daily for 10 days).

On day 40 he complained of abdominal pain and examination showed peripheral oedema, ascites, and hepatosplenomegaly. The conjugated bilirubin concentration was 76 (normal <8) $\mu\text{mol/l}$ (444 (normal <46.8) mg/100 ml), alkaline phosphatase activity 158 (normal <200) IU/l, serum aspartate aminotransferase activity 64 (normal <18) IU/l, and serum glutamic pyruvate transaminase activity 120 (normal <25) IU/l.

On day 44 interstitial pneumonitis, predominantly affecting the right lung, developed. No cardiac abnormalities were observed on the chest radiograph or electrocardiogram. Bronchoalveolar lavage performed in the right pyramidal segment showed numerous siderophages. His respiratory state grew worse, and he died from respiratory failure despite ventilatory help. A postmortem "biopsy" of the right lower lobe was performed within an hour after death. A full necropsy was not possible, and the heart and liver could not be examined.

Histological sections were stained with haematoxylin-eosin, orcein, Masson's trichrome, Perl's and von Kossa's stains. The most striking lesion was eccentric intimal fibrosis of most of the pulmonary veins observed. The small intralobular veins were regularly narrowed. The interlobular veins were also narrowed (fig 1) and some were totally occluded by the intimal fibrosis (fig 2). No intraluminal thrombi were observed. The intimal fibrosis was composed of loose myxoid, finely fibrillar, tissue containing few cells; in particular, no inflammatory cells were observed. No hypertrophy or arterialisation of the media was observed in medium sized pulmonary veins. Elastic fibres of the media were enlarged, fragmented, and encrusted with calcium without iron. Medial hypertrophy was seen in some muscular pulmonary arteries, and a few recent thrombi were also observed, but no major arterial changes were present.

Discussion

Although the clinical signs and the electrocardiographic pattern were not suggestive of pulmonary hypertension, the presence of numerous siderophages in the bronchoalveolar lavage and the histological findings confirm the diagnosis of pulmonary veno-occlusive disease. Pulmonary

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Accepted 10 August 1984

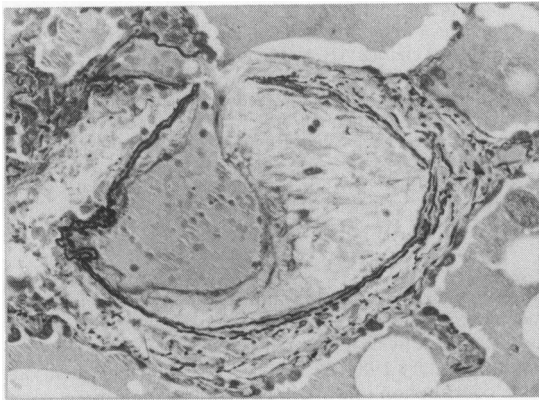


Fig 1 Interlobular pulmonary vein narrowed by eccentric intimal fibrosis. (Orcein, $\times 320$.)

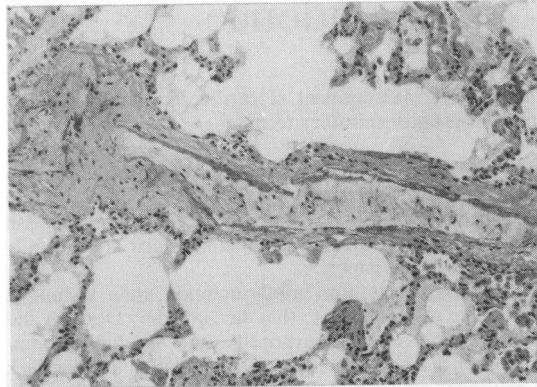


Fig 2 Interlobular pulmonary vein almost completely occluded by finely fibrillar tissue. ($\times 125$, Iron haematoxylin and eosin stain.)

veno-occlusive disease has rarely been described, and its pathogenesis remains unknown. Infectious agents,¹⁻³ familial factors,⁴ and deposition of immune complexes⁵ have been implicated. Recently, a case of pulmonary veno-occlusive disease occurring after chemotherapy (bleomycin, mitomycin, cisplatin) was reported.⁶ Pulmonary veno-occlusive disease has not previously been reported after marrow transplantation, but hepatic veno-occlusive disease is well recognised in this situation,^{7,8} and there may be a common pathogenesis. Although histological examination of the liver was not possible in our patient, liver function was appreciably abnormal.

Possible aetiological factors in the present case included irradiation, multiple chemotherapy, and acute graft versus host disease. The intrapulmonary calcification was probably a result of the hypercalcaemia observed during the course of leukaemia.

We thank N Relin, S Daude, and S Mousky for their technical help.

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