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Angiotropic large cell lymphoma presenting as interstitial lung disease

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ABSTRACT A case of angiotropic large cell lymphoma is reported in which the patient presented with only pulmonary symptoms. It suggests that this rare and highly malignant lymphoma should be considered in the differential diagnosis of interstitial lung disease, and shows the value of open lung biopsy in unexplained interstitial lung disease. This patient responded well to treatment with cyclophosphamide, doxorubicin, vincristine, and prednisone.

Angiotropic large cell lymphoma is a rare disease characterised histologically by proliferating mononuclear cells within the lumen of capillaries, venules, arterioles, and small arteries.[1-3] Originally described in cutaneous small vessels,[4] later reports have shown that various organs may be affected, especially the nervous system and adrenal glands.[5]

Previously angiotropic large cell lymphoma was known as "malignant angioendotheliomatosis" presuming an endothelial origin of the tumour cells; but recent studies using cell surface markers suggest a lymphoid origin,[2 3 6] and the terms angiotropic large cell lymphoma[3] and malignant intravascular immunoblastic lymphoma[7] have been suggested. We report a case presenting with pulmonary symptoms.

Case report

A 56 year old woman, an insulin dependent diabetic, was admitted to hospital because of persistent fever over the preceding week, progressive exertional dyspnoea, a non-productive cough, and malaise. Two years earlier she had had pancreatitis during a period of alcohol abuse, but she had since abstained from alcohol. Until the onset of fever she had been well. There were no complaints of weight loss, skin lesions, disorientation, arthralgia, pruritis, or nocturnal sweats. Ske kept a parakeet and a cat and had no known allergies. Her only treatment was insulin.

Physical examination showed that she had a fever of 39°C and bilateral fine inspiratory rales at the bases of both lungs. No lymphadenopathy or hepatosplenomegaly was detected.

The erythrocyte sedimentation rate was 45 mm in the first hour and the white blood cell count $4{\cdot}8 \times 10^9$/l, with 57% segmented neutrophils, 17% band neutrophils, 18% lymphocytes, 3% monocytes, 1% myelocytes, 2% eosinophils, and 1% basophils. Arterial blood gas analysis showed the following: pH 7·39, oxygen tension (Po_2) 7·9 kPa, carbon dioxide tension (Pco_2) 4·5 kPa, bicarbonate 19 mmol/l, and base excess 4. A bone marrow aspirate showed no abnormalities. Cultures of sputum, blood, and urine were sterile. Serological tests for viruses, chlamydia, *Treponema pallidum*, brucella, and legionella gave negative results, as did tests for rheumatoid factor and antinuclear factor. Precipitating antibodies against parakeet proteins were absent. A chest radiograph showed interstitial changes in both lungs but no hilar lesions (fig 1). Pulmonary function tests showed a restrictive pattern with a vital capacity (VC) of 1500 (predicted 3550) ml, a one second forced expiratory volume (FEV_1) of 950 ml (63% of VC), a one second forced inspiratory volume (FIV_1) of 1350 ml (90% of VC), and carbon monoxide transfer factor (T_{LCO}) of 0·54 ml/kPa/min (30%).

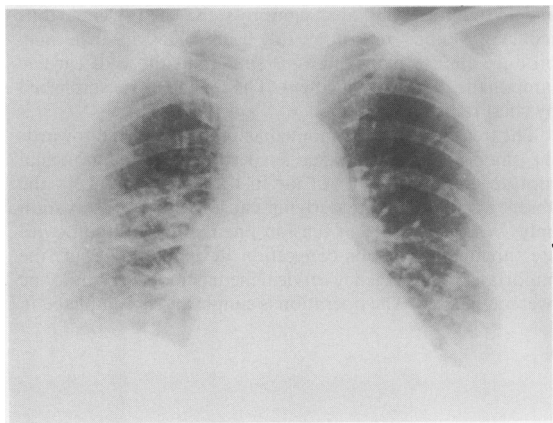

Fig 1 *Diffuse interstitial lung disease without hilar enlargement.*

Biopsies of skin muscle and temporal artery showed no vasculitis. At bronchoscopy no abnormalities were found and lavage fluid contained no tumour cells. At thoracoscopy the lung appeared normal and peripheral biopsy specimens showed slight pleural fibrosis without interstitial inflammation or other lesions. An open lung biopsy was performed. Part of the material was quick frozen in liquid nitrogen and the remainder underwent routine processing and staining. Examination of the slides produced by the latter process showed areas of lung with many vascular lumina and capillaries filled with non-adhesive aggregates of round or oval shaped cells with large nuclei and one or more prominent nucleoli (fig 2). The anatomy was partly abnormal

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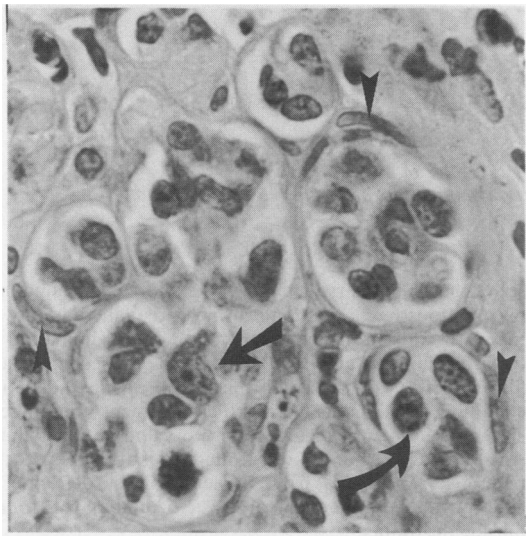

Fig 2 *Endothelium lined vascular lumina (arrow heads) filled with non-Hodgkin's lymphoma cells (arrows). In this area the normal anatomy has been disturbed by thrombosis with recanalisation.*

owing to thrombosis and recanalisation. Staining of the frozen sections with the monoclonal antibodies DLC (leucocyte common antigen), Leu-14 (anti-B cell), and Leu-4 (anti-T cell) showed cell membrane staining only with DLC and Leu-14, consistent with B cells. Immunofluorescence studies for IgG, IgA, and IgM heavy chain and kappa and lambda light chains showed only membrane staining for IgM heavy chain and kappa light chain. Additional immunostaining with PAL-E antibody[8] (monoclonal antibody against endothelium) showed strong staining of the endothelial cells surrounding non-staining intravascular tumour cell aggregates.

The histology of the lung tissue and the immunohistological types were consistent with the diagnosis of angiotropic large cell lymphoma of B cell origin.

The patient remained free of fever after the open lung biopsy. Treatment was started with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), which resulted in a rapid recovery. After the first course of CHOP the results of pulmonary function tests improved: VC 2000 (predicted 3500) ml, FEV_1 1125 ml (56% of VC), FIV_1 1700 ml (85% of VC), and TLCO 0·70 ml/kPa/min (39%). The radiographic appearance of the lung became normal. After the second course of CHOP the patient developed polyneuropathy in both legs, which was attributed to vincristine. Vincristine was replaced by VP-16 100 mg/m^2. Eight courses were given. Follow up after six months disclosed no recurrence of tumour activity. Pulmonary function test results were further improved: VC 1950 ml, FEV_1 1450 ml, FIV_1 1850 ml and TLCO 1·01 ml/kPa/min. Arterial blood gas analysis showed: pH 7·47, Po_2 9·7 kPa, Pco_2 4·5 kPa, bicarbonate 25 mmol/l, and base excess 2·3. The chest radiograph was unremarkable. Our patient has now survived 10 months from diagnosis.

Discussion

Angiotropic large cell lymphoma is a rare disease in which mononuclear cells (B cell lymphocytes) proliferate within vessels. The reason for this predilection is unknown. Angiotropic large cell lymphoma is generally considered to be a highly malignant lymphoma, associated with a grave prognosis. In a review of 73 cases[5] the overall mortality is over 80%, with a survival time ranging from two to 48 months after diagnosis (median six months, mean 10 months).

Regarding angiotropic large cell lymphoma as a B cell lymphoma with vascular predilection, we considered this case to be a non-Hodgkin's lymphoma and decided on treatment with CHOP. In general, this lymphoma responds poorly to chemotherapy and radiotherapy,[1 2 9] but in some cases a favourable response has been achieved.[3 5 9 10] Our patient responded well to chemotherapy, which resulted in the disappearance of objecive pulmonary disease.

Our patient presented only with pulmonary symptoms. We would suggest that angiotropic large cell lymphoma should be included in the differential diagnosis of interstitial lung disease and that the value of open lung biopsy in unexplained interstitial lung disease should be emphasised.

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