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Fatal airway disease in an adult with chronic graft-versus-host disease

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Chronic graft-versus-host disease (GVHD) is a syndrome of disordered immunity in which a variety of opportunistic respiratory infections have been documented. Restrictive pulmonary disease without advanced fibrotic changes has been also known to occur; obstructive lower airways disease related to chronic GVHD has apparently not been referred to.[1 2] We report a patient with chronic GVHD and irreversible airways obstruction who died in respiratory failure caused by generalised bronchiolar damage progressing over a few months. Lung function studies showed severe airflow limitation and a leftward shift in the pressure-volume curve indicating a loss of elastic recoil pressure. Postmortem pulmonary lesions were consistent with a necrotising obliterative bronchiolitis. Our purpose is to describe this unusual complication not previously reported in chronic GVHD and discuss the pulmonary mechanics.

Case report

A 22-year-old white man received an allogeneic bone marrow graft for aplastic anaemia.The donor was an HLA-identical (MLC-negative) sibling. The evidence of a functioning allograft was confirmed by red cell antigens by day 80. In spite of prophylactic administration of methotrexate, the patient developed by day 36 a mild generalised maculo-erythematous rash, which disappeared spontaneously after a few days. By day 80, lichen planus-like lesions developed on face, hands, trunk, and extremities. Histopathological examination was consistent with chronic GVHD. The patient was treated orally with prednisone (25 mg on alternate days) and cyclophosphamide (50 mg daily). By day 140 the skin area previously involved appeared pigmented and slightly atrophic.

He had never smoked or been exposed to fumes. There was no history of respiratory infections, any previous lung disease, or occupational exposure. Pre-transplant alpha-l-antitrypsin blood levels and routine lung function data (table) were normal. Approximately nine months after transplantation he developed fever, cough, and mucopurulent sputum. After a short course of trimethoprim and erythromycin the fever disappeared but cough and mucopurulent sputum persisted, and a progressively severe breathlessness developed over a few months. On examination, he was short of breath at rest. The chest was distended with intercostal and neck muscle retraction. Vesicular sounds were markedly attenuated and moderate expiratory wheezing was present. Basal inspiratory crackles were repeatedly audible, but the loud pan-inspiratory squeak over the upper chest described in rheumatoid obliterative bronchiolitis[3] was not heard. Finger clubbing was not detected. Chest films showed hyperinflated lung fields but were otherwise normal. Lung function tests (table) revealed a severe obstructive ventilatory impairment, without bronchodilator response, and marked air trapping; static lung compliance (Cst) was increased and elastic recoil pressure (Pst) was reduced.

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Table *Lung function results*

Measurement	*Predicted values*	*Before transplant*	*Twelve months after transplant*	*One week before death*
FVC (l)	4610	80	39	48
FEV_1/FVC, %	84	95	34	25
MEF_{50}% (1 s^{-1})	5·38	87	5	4
MEF_{75}% (1 s^{-1})	2·87	115	6	5
Vtg (l)	3320	129	203	—
TLC (l)	6200	—	123	—
RV (l)	1590	—	376	—
sGaw (s^{-1}/cmH_2O)	0·131-0·36	0·164	0·009	—
Cst (l/cmH_2O)	0·234	—	0·490	—
Pst (cmH_2O) (at TLC)	45·5	—	6·5	—
DLCO (ml/min/mmHg)	35·6	75	32	32
DLCO/VA (min^{-1}/mmHg)	6·03	71	77	78
Pa_{O_2} (Torr)	90-105	—	55	54
Pa_{CO_2} (Torr)	38-42	—	38	46
pH	7·38-7·42	—	7·42	7·40

All the results are expressed in per cent of predicted values, except for Cst and Pst, and arterial blood gases. FEV_1/FVC, % and RV/TLC, % are expressed in actual per cent.

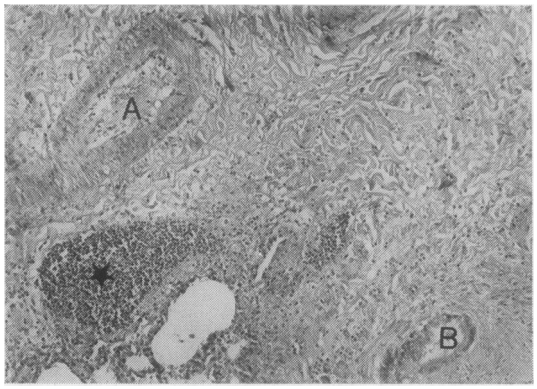

Figure *Partially obliterated bronchiole (B). Note small lumen compared to normal accompanying pulmonary artery (A). Accumulation of inflammatory cells, mostly neutrophils (*), and peribronchiolar fibrosis can be seen associated with other branches of small airways (H and E, original magnification × 140).*

Abnormal transfer factor (DLCO) but normal transfer coefficient KCO (DLCO/VA), hypoxemia at rest, and eventual hypercapnia were observed. In spite of treatment with steroids, bronchodilators and oxygen, the patient showed a progressive and rapid deterioration. Repeated serological testing and cultures from the respiratory tract for *Mycoplasma pneumoniae*, respiratory syncytial virus, adenoviruses, cytomegalovirus, and other respiratory viruses were negative. Five months after the beginning of his pulmonary disorder, the patient died from severe respiratory failure. Chest radiographs showed distended lungs with no other abnormalities. Necropsy was not permitted but several percutaneous postmortem lung biopsies from different locations were obtained. The pathological examination showed widespread obliteration of small airways. Additional abnormalities consistent with emphysema, chronic bronchitis, or interstitial pneunomia were not apparent. The narrowing of small airways was caused by peribronchiolar and mural infiltration by plasma cells and neutrophils (fig). Foci of bronchiolar necrosis were detected. Intraluminal polyps of granulation tissue were not observed; alveoli were not involved. Methenamine silver stain failed to demonstrate *Pneumocystis carinii* infestation. Bacterial, viral, and fungal cultures were not done on postmortem lung tissue.

Discussion

This patient, whose pulmonary problems started with an acute respiratory episode nine months after his bone marrow transplant, showed progressive clinical and functional deterioration over the next five months, and died in severe respiratory failure.

Functional studies showed irreversible airway obstruction and a loss of elastic recoil pressure without any accompanying evidence of pulmonary emphysema. It is generally accepted that both low elastic recoil pressure and increased static compliance are particularly related to morphological emphysema. However, several reports have shown similar changes in other clinical conditions such as acute exacerbations of asthma.[4] The mechanism responsible is not known. Different theories have been postulated—altered distribution of or changes in the amount of surfactant, changes in smooth muscle tone in peripheral airways, or reduction of tissue forces because of stress-relaxation. Airways changes such as those involved in the present case are more likely to be compatible with the former two theories. Whatever the mechanism responsible, this report illustrates another obstructive airway disease with evidence of loss of elastic recoil pressure.

The striking pathological finding of this case was generalised necrotising obliterative bronchiolitis. This disorder, uncommon in adults, has been described after the inhalation of irritant gases and as a consequence of respiratory tract infections.[5] Recently, it has also been reported in association with rheumatoid arthritis[3] and an immunological mechanism has been suggested. Although the pulmonary condition of this patient bore a strong clinical resemblance to that of those with rheumatoid disease, histologic examination showed some differences. Bronchiolar fibrosis in rheumatoid patients was mainly affecting the mucosa as well as the muscle coat and the peribronchiolar tissue.

The most probable aetiology of this patient's illness was either repeated respiratory tract infections by opportunistic agents in an immunosuppressed host or an immunological mechanism. Widespread airways obstruction was responsible for the rapid deterioration and death of this patient. Bronchiolitis should be included among the severe pulmonary complications of chronic GVHD.

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