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CASE FOR DIAGNOSIS

Severe breathlessness, mouth ulcers and skin blistering in a female

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Case history

A 63-yr-old housewife was referred in August 2001 with a 10-yr history of gradually worsening breathlessness on exertion, cough and repeated respiratory tract infections. She had never smoked. She had been diagnosed with follicular B-cell non-Hodgkin's lymphoma 10 yrs previously, which was treated with chemotherapy, including chlorambucil, vincristine and prednisolone, and subsequent radiotherapy for intra-abdominal recurrence. A year after the diagnosis of malignancy, she was seen in the local dermatology unit with a blistering eruption on her legs and oral mucosa, which was subsequently confirmed by skin biopsy and immunofluorescence studies to be bullous pemphigoid. She developed muscle weakness due to myasthenia gravis 2 yrs later. There was no evidence of an associated thymoma. Both her muscle and skin disease were controlled with oral corticosteroids and azathioprine, along with pyridostigmine, for nearly 10 yrs. In April 2001, her skin disease was further evaluated because of persistent oral ulceration; a diagnosis of paraneoplastic pemphigus (PNP) was confirmed by presence of circulating antibodies to a variety of intra- and extracellular epidermal antigens, including bullous pemphigoid antigen (230 kD), envoplakin (210 kD) and periplakin (190 kD).

Physical examination showed the presence of inspiratory crackles at lung bases; there was no cyanosis or clubbing. Serum autoantibodies were negative apart from those against skin. Her myasthenia gravis was under good control at the time of physical examination.

Pulmonary function test results are shown in table 1. High-resolution computed tomography (HRCT) scan of her chest is shown in figure 1, important findings of an open lung biopsy in figure 2 and direct immunofluorescence of a mucosal biopsy from the oral cavity in figure 3.

Table 1. – Pulmonary function test results

Parameter	Observed values (expected mean±SD)
FEV1 L	0.74 (2.15±0.63)
FVC L	2.10 (2.56±0.71)
FEV1/FVC %	35
FRC L	3.67 (2.65±0.82)
RV L	2.88 (1.90±0.58)
TLC L	4.93 (4.77±0.99)
CO transfer factor $mmol \cdot min^{-1} \cdot kPa^{-1}$	3.57 (7.26±1.92)

FEV1: forced expiratory volume in one second; FVC: forced vital capacity; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity; CO: carbon monoxide.

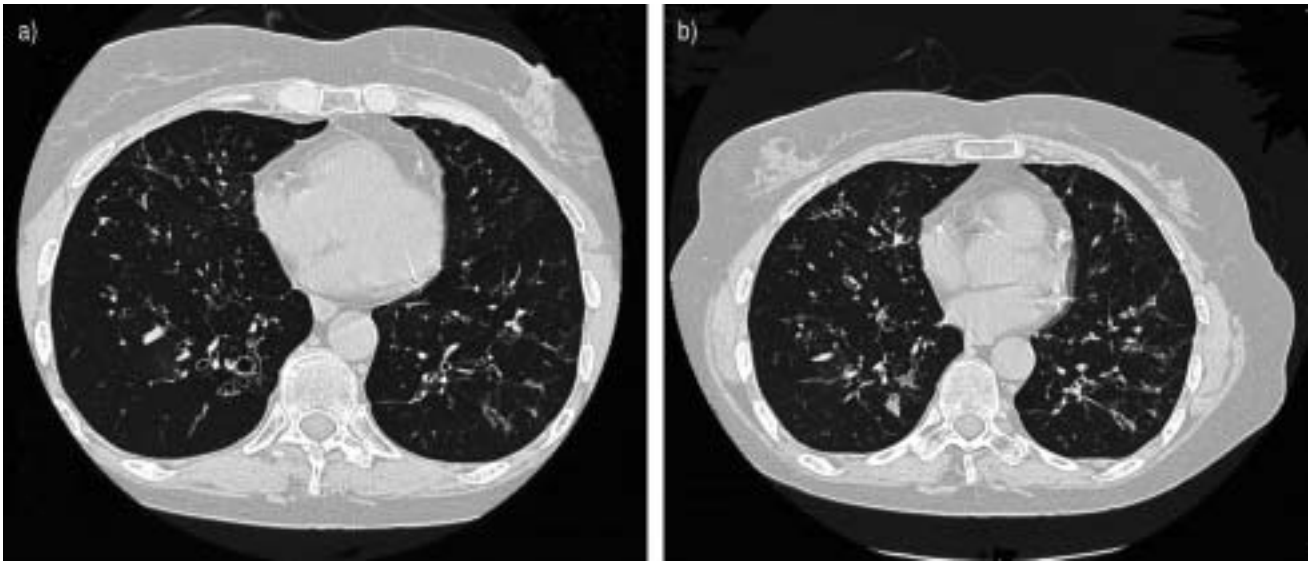

Fig. 1. – High-resolution computed tomography scan of chest performed at a) inspiration and b) expiration.

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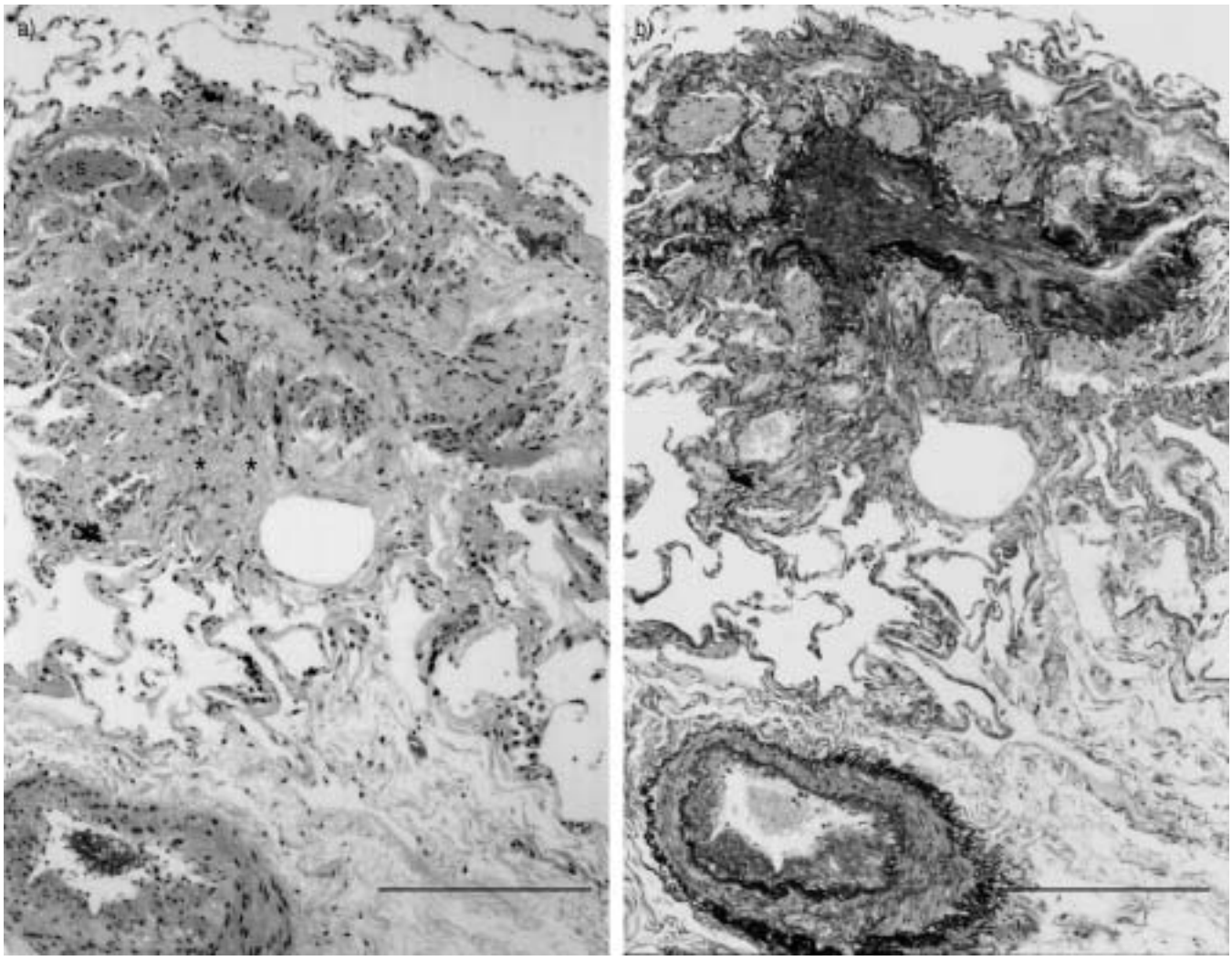

Fig. 2. – Photomicrographs of open lung biopsies stained with a) haematoxylin and eosin, and b) Van Gieson′s stain. Scale bars=500 μm.

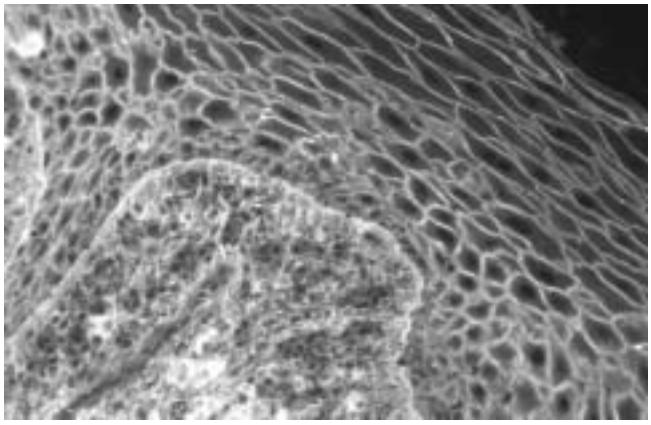

Fig. 3. – Immunofluorescence of a mucosal biopsy from the oral cavity.

BEFORE TURNING THE PAGE, INTERPRET THE ROENTGENOGRAMS, THE BIOPSIES AND THE PULMONARY FUNCTION DATA, AND SUGGEST A DIAGNOSIS.

Interpretation

Pulmonary function tests demonstrated severe airflow obstruction with gas trapping and impaired carbon monoxide gas transfer.

HRCT scan of chest performed in inspiration (fig. 1a) and expiration (fig. 1b) shows dilated thick-walled bronchi, most marked in the medial basal segment of right lower lobe. Expiratory films showed collapsing bronchi and evidence of mild air trapping, indicating that the bronchial dilatation was not fixed as seen in classical bronchiectasis.

Open lung biopsy (fig. 2a and b) shows marked narrowing and obliteration of the lumens of the bronchioles due to concentric fibrosis in the submucosa (*), which extends a limited distance (**) beyond the perimeter of residual smooth muscle bundles (S) of the airway wall without associated interstitial pneumonitis. Van Gieson′s stain in figure 2b demonstrates collagen deposited in the peribronchial region. Direct immunofluorescence of lung biopsy specimen in the current authors′ patient did not show any significant deposition of immunoglobulin (Ig) or complement.

Figure 3 shows a fluorescence microscopic photograph of oral mucosal biopsy showing typical findings of pemphigus with intercellular "chicken wire" deposition of IgG.

Diagnosis: Severe constrictive bronchiolitis obliterans associated with paraneoplastic pemphigus

Treatment and clinical course

The patient was treated with inhaled bronchodilators, increased doses of prednisolone and azathioprine. Unfortunately, there was progressive deterioration clinically, which was confirmed by deteriorating pulmonary function tests. She died within 6 months of diagnosis.

Discussion

Constrictive bronchiolitis obliterans (CBO) is characterised by inflammation and fibrosis occurring in the walls and contiguous tissues of membranous and respiratory bronchioles, resulting in narrowing of their lumens [1]. A spectrum of pathological changes can be seen, from bronchiolar inflammation with minimal scarring to severe submucosal fibrosis causing dramatic and irreversible reduction in the bronchiolar lumen [2].

CBO is most often found in the setting of lung transplantation; 63% of lung transplant recipients who survive 5 yrs may develop it [3]. Other known associations [4] with CBO include autoimmune diseases such as rheumatoid arthritis, Sjogren′s syndrome, scleroderma, polymyositis, systemic lupus erythematosus and cryoglobulinaemia. Bronchiolitis obliterans (BO) has also been described [4] in association with viral and mycoplasmal infections, such as *Mycoplasma pneumoniae*, adeno-, rhino-, corona and human immunodeficiency viruses. The inhalation of toxic fumes [4], such as nitrogen dioxide, chlorine and dimethyl disulphide, and the ingestion of drugs [4], such as penicillamine, gold, sulphasalazine and some cytotoxic agents, have also been linked with BO. In the current authors′ patient, there was no evidence of recent viral or *Mycoplasma* infection on serology.

The pathogenesis of CBO is unclear, but major histocompatibility complex class-II antigen expression on bronchial epithelium along with autoantigen presentation and subsequent T-cell activation and inflammation may play a role [5].

PNP [6] is a severe mucocutaneous blistering disease, characterised clinically by severe stomatitis and vesicobullous lesions on the skin and mucosae. PNP occurs in both adults and children [7]; it is most commonly associated with non-Hodgkin′s lymphoma in adults [8] and Castleman′s disease (angiofollicular lymph node hyperplasia) in children [7]. Other neoplasms [8] include chronic lymphatic leukaemia, retroperitoneal sarcomas, thymoma and Waldenström′s macroglobulinaemia. Characteristically, patients have circulating antibodies binding to murine bladder epithelium and antibodies binding to 210 kD (envoplakin) and 190 kD (periplakin) antigens in human epidermal extracts demonstrated by immunoblotting or immunoprecipitation [6].

The association of PNP and CBO has rarely been reported in respiratory journals [9]. PNP is associated with a mortality >90%, and >30% of patients develop progressive respiratory disease. The pathogenesis of respiratory complications of PNP is not clearly understood. Suppressor T-cells may have a role, as the majority of lymphocytes present in the bronchial wall in BO associated with PNP are of the CD8 phenotype [10]. NOUSARI *et al*. [11] have shown that sera of patients with PNP show the presence of antibodies against the plakin group of proteins present in extracts of normal human bronchial epithelial cells. This mixed antibody and cell-mediated immunological response against bronchial epithelial antigens could mediate the inflammatory response and result in fibrosis.

The cytotoxic agents (chlorambucil and vincristine) used in the treatment of this patient′s non-Hodgkin′s lymphoma have not been associated with BO. Fludarabine, another antimetabolite, has been implicated in a few patients [12], but PNP with constrictive bronchiolitis can occur in the absence of any drug ingestion in at least a third of patients. Current opinion is that drugs do not play a major role in the aetiology of PNP [13].

Therapy is difficult; despite immunosuppression, many patients continue to show deterioration of lung function. Lung transplantation should be considered, especially in children [14] or adults of the appropriate age. In other patients, management is generally supportive because most patients would have already reached the stage of irreversible fibrosis by the time they are diagnosed.

Paraneoplastic pemphigus-associated constrictive bronchiolitis obliterans should be considered in any patient exhibiting resistant mucosal ulceration and respiratory illness on a background of lymphoproliferative neoplasm.

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