Eur Respir J 1999; 13: 934–937
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European Respiratory Journal
ISSN 0903-1936

CASE STUDY

Constrictive bronchiolitis obliterans and paraneoplastic pemphigus

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Constrictive bronchiolitis obliterans and paraneoplastic pemphigus. Y. Hasegawa, K. Shimokata, S. Ichiyama, H. Saito. ©ERS Journals Ltd 1999.

ABSTRACT: Constrictive bronchiolitis obliterans is rare, and the pathogenesis of the disease often remains unknown. This study reports on the case of a 38 yr-old female with constrictive bronchiolitis obliterans and paraneoplastic pemphigus associated with malignant lymphoma. The patient developed progressive obstructive lung disease. The chest radiograph showed almost normal lungs. Paraneoplastic pemphigus is a newly described syndrome in which patients have autoantibodies binding to some epithelia, including in the respiratory tract. The disease develops in association with non-Hodgkin's lymphomas or other malignant neoplasms. The case presented here suggests that constrictive bronchiolitis obliterans associated with paraneoplastic pemphigus may be one of the facets of autoimmune responses in this context.

Eur Respir J 1999; 13: 934–937.

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Keywords: Autoimmune disease
bronchiolitis obliterans (constrictive)
chronic obstructive airways disease
non-Hodgkin's lymphoma
paraneoplastic pemphigus

Received: March 23 1998
Accepted after revision October 10 1998

Constrictive bronchiolitis obliterans (BO) is a relatively rare disease which has been described in allograft recipients such as bone marrow and heart/lung transplants, in patients with collagen vascular disease such as rheumatoid arthritis (with or without penicillamine treatment), systemic lupus erythematosus, in patients with Stevens–Johnson syndrome, primary biliary cirrhosis and following exposure to fumes of tobacco or toxic agents [1–7]. Some of these reports have suggested that an immunological response may play a role in the pathogenesis of constrictive BO [5–7].

Paraneoplastic pemphigus is a newly described syndrome, in which patients have a severe mucocutaneous eruption with clinical features reminiscent of both erythema multiforme major and pemphigus vulgaris. Paraneoplastic pemphigus occurs in association with non-Hodgkin's lymphoma and other malignant neoplasms [8, 9]. Patients with paraneoplastic pemphigus have been reported to have a unique set of autoantibodies that bind to the epithelium of the urinary bladder and the respiratory tract, as well as the skin [9]. Immunoglobulin (Ig) G deposition has been shown within the bronchial epithelium [9]. These findings suggest that the lung may be a target organ for these autoantibodies. This study reports on the case of a patient with constrictive BO and paraneoplastic pemphigus associated with non-Hodgkin's lymphoma.

Case report

A 38-yr-old female with no significant medical history presented with complaints of repeated bouts of stomatitis and an abdominal tumour in November 1992. An abdominal computed tomography (CT) scan revealed a large (11.5×13 cm dimensions) retroperitoneal tumour adjacent to the abdominal aorta at the level of L2–L3. At first, there was a suggestion of sarcoma based on the results of a CT-guided needle biopsy, and oral tegaful-uracil (UFT; 400 mg·day^{-1}) was given on an outpatient basis. After 2 months of oral UFT, the patient was admitted to hospital in January 1993, because of severe painful mucosal ulceration, (especially in the oral cavity) and polymorphous skin lesions (bullae and erosions) of her whole body in spite of the rapid regression of the abdominal tumour. She also complained of increasing dyspnoea on exertion. A skin biopsy was performed and pathological findings showed intraepidermal acantholytic blister and spongiosis (fig. 1). Direct immunofluorescence microscopy of lesional skin showed deposits of IgG in the intercellular spaces and on the surface of keratinocytes. These findings were compatible with pemphigus. CT-guided needle biopsy specimens of the abdominal tumour were re-evaluated and combined with immunohistochemical staining by CD45 (leukocyte common antigen), CD45RO (memory T-cells) and CD20 (marker for B-lineage cells) monoclonal antibodies. The final pathological diagnosis of the tumour was non-Hodgkin's lymphoma (T-cell lymphoma, diffuse small cleaved cell type; CD45-positive, CD45RO-dominant rather than CD20). From these results, she was diagnosed as having paraneoplastic pemphigus associated with non-Hodgkin's lymphoma.

Thereafter, the patient received five courses of cyclophosphamide, doxorubicine, vincristine and prednisone

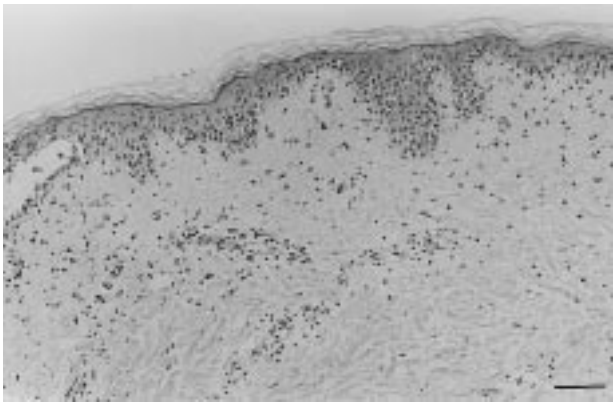

Fig. 1. – Histological specimen of skin biopsy from the trunk. The biopsy specimen showed intraepidermal acantholytic blisters, spongiosis and mononuclear cell infiltration. (Haematoxylin & eosin; internal scale bar = 250 μm.)

with or without etoposide (VP-16). The skin lesions vanished gradually, although painful mucosal ulceration in oral cavity persisted until death. During the second course of chemotherapy, she complained of progressive dyspnoea at rest. Physical examination revealed decreased breath sounds in both lungs with scattered wheezes. The chest radiograph and CT-scan showed normal or slightly hyperinflated lung (fig. 2). Pulmonary function tests showed an obstructive pattern with a forced vital capacity (FVC) of 55% predicted and forced expiratory volume in one second (FEV_1) of 47% pred. A lung perfusion scan with technetium-99m-labelled macroaggregates of human albumin and a ventilation scan using krypton-81m showed multiple matched defects. An arterial blood gas sample (room air) showed an arterial oxygen tension (P_{a,O_2}) of 8.7 kPa (65 mmHg) with oxygen saturation of 93%, an arterial carbon dioxide tension P_{a,CO_2} of 5.5 kPa (41 mmHg) and an alveolar–arterial oxygen gradient of 4.5 kPa (34 mmHg). Although the patient received bronchodilators (β_2-agonists, theophylline and prednisone) in an attempt to reverse dyspnoea, respiratory failure developed and the blood gases while breathing 50% O_2 were P_{a,O_2} 10.0 kPa (75 mmHg) and P_{a,CO_2} 7.9 kPa (59 mmHg). She was admitted to the intensive care unit, and mechanically ventilated. The chest radiography and CT-scan still revealed normal or slightly hyperinflated lung. A pulmonary angiography suggested tapered or occlusive small arterioles of the lung, but no thrombi were visible. Examination with a flexible bronchoscope showed no specific findings. In July 1993, an open lung biopsy was performed and specimens were obtained from the left upper lobe (superior lingular segment).

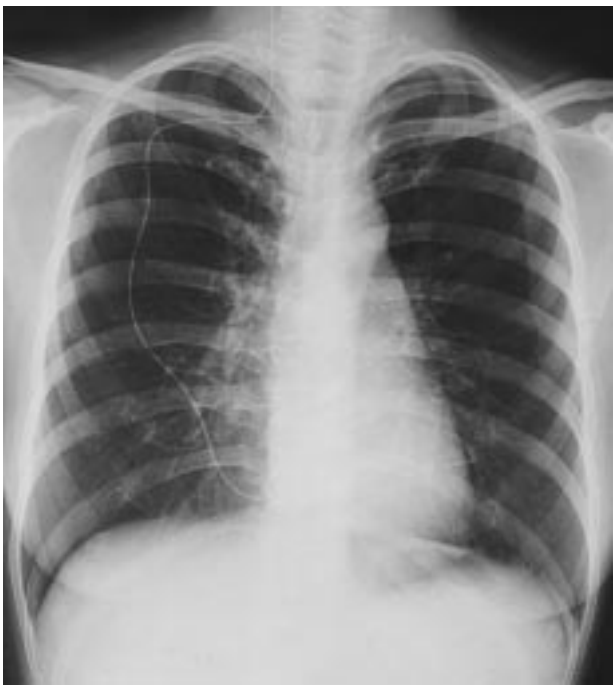

Fig. 2. – Chest radiograph showing slightly hyperinflated lungs.

Histological examination of the biopsy specimens showed normal alveolar walls, slightly dilated blood vessels and air-space hyperinflation. Although she was initially controlled under mechanical ventilation *via* a tracheostomy, her respiratory status worsened, with a P_{a,O_2} of 16.4 kPa (123 mmHg) (inspiratory oxygen fraction. (F_{I,O_2} 0.5)) and a P_{a,CO_2} of 14.8 kPa (111 mmHg). The P_{a,CO_2} rose progressively to 16.3 kPa (122 mmHg) and then 21.7 kPa (163 mmHg) in February 1996. She died from cardiac arrest in July 1996 after 3 yrs of continuous mechanical ventilation.

At autopsy, microscopical examination of the lung revealed submucosal and peribronchiolar fibrosis, with obliteration of the bronchiolar lumens (fig. 3). As the small airways were extensively involved with chronic inflammation, bronchiolar scarring, fibrous obliteration and dilatation, a histological diagnosis of constrictive BO was established (fig. 3). The mucosa and submucosa of the large airway showed nonspecific chronic inflammatory changes caused by long-term mechanical ventilation and iterative episodes of bacterial infection. At the site of the retroperitoneal tumour, there was only residual fibrous tissue with no evidence of malignant cells.

Discussion

The term BO was first introduced by Lange in 1901 and the histological concept of BO was investigated later [10, 11]. It was recognized histologically as the presence of: 1)

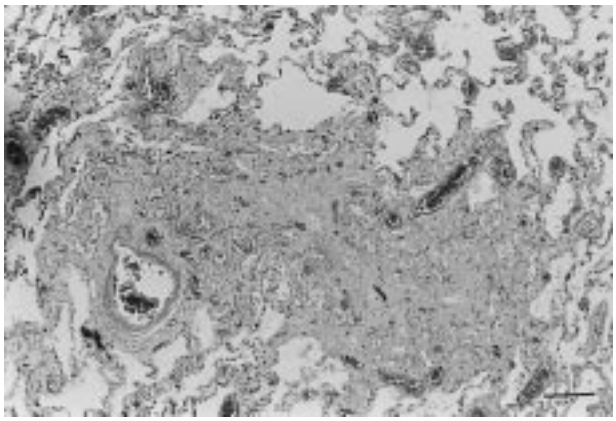

Fig. 3. – Microscopical examination of the lung at autopsy. The specimen showed chronic inflammation of small airways, bronchiolar scarring and fibrous obliteration of bronchiolar lumens. (Elastica Masson stain; internal scale bar = 250 μm.)

plugs of granulation tissue within the lumen of small airway, and 2) destruction of small airways with obliterative scarring. If granulation tissue within small airways extends into the alveoli, the disease is called bronchiolitis obliterans organizing pneumonia (BOOP) [12]. Thereafter, the specific histological form of BO, which is characterized by extrinsic narrowing and obliteration of bronchiolar lumen caused by submucosal and peribronchiolar fibrosis and scarring, distinguished the disease from classic BO with intraluminal polyps and the term constrictive bronchiolitis was used by GOSINK *et al.* [13] and WRIGHT *et al.* [1]. The intraluminal polyp is usually not a component of constrictive bronchiolitis. The terms obliterative bronchiolitis, pure BO, constrictive bronchiolitis and constrictive BO have been used interchangeably for this entity [13–15].

The causes and aetiological contexts for constrictive BO are manifold and include exposure to toxic fumes, infections, drugs and connective tissue diseases [1–5, 16, 17]. Constrictive BO may also associate with a proliferation of pulmonary neuroendocrine cells or the intake of the vegetable *Sauropus androgynus* [18, 19]. Sometimes, no cause is found and the disease is deemed idiopathic [20]. Many cases of constrictive BO have been reported in patients with bone marrow [5] or heart/lung transplantation [21] and in patients with rheumatoid arthritis with or without penicillamine treatment [22]. The case reported here did not have any underlying collagen vascular diseases, such as rheumatoid arthritis, systemic lupus erythematosus or scleroderma, according to clinical, serological and autopsy findings. Since the symptom of dyspnoea on exertion was present before chemotherapy it is unlikely that any drug used for chemotherapy of the non-Hodgkin′s lymphoma was responsible for inducing BO.

The pathological diagnosis of BO was not determined at the time of open lung biopsy. Although the biopsy specimens revealed several terminal and respiratory bronchioles, peribronchiolar fibrosis or inflammation and obliteration of bronchiolar lumens were not detected in the specimens stained with haematoxylin and eosin. In this connection, HASLETON *et al.* [14] pointed out that the changes of constrictive BO may be patchy and the diagnosis may be missed if the lung is inadequately sampled, even at *post mortem*. Further, as bronchiolar lumens are reduced to slit-like spaces and are eventually totally obliterated, an elastic tissue stain may be helpful in identifying obliterated bronchioles [14].

Paraneoplastic pemphigus is a newly described syndrome and ANHALT *et al.* [8] proposed five criteria to define the disease, as follows: 1) painful mucosal erosions and a polymorphous skin eruption; 2) cutaneous histological changes (intraepidermal acantholysis, keratinocyte necrosis and vacuolar-interface dermatitis); 3) deposition of IgG and complement in the epidermal intercellular spaces; 4) serum autoantibodies that bind the cell surface of skin and mucosae; and 5) a complex of four proteins immunoprecipitated from keratinocytes by these autoantibodies. Although no attempt was made to detect the serum autoantibodies in this case, the histological changes and immunofluorescence testing of the skin biopsy specimens were compatible with paraneoplastic pemphigus. FULLERTON *et al.* [9] also described the remarkable features of this disease, one of which was the absence of detectable tumour at the time of onset of the syndrome. They concluded that an associated malignant neoplasm need not be still active or detectable and can even be cured when the syndrome develops. In the present patient, polymorphous skin lesions, but not mucosal ulcerations in the oral cavity improved during the course of chemotherapy for non-Hodgkin′s lymphoma.

Interestingly, the malignant lymphoma was inactive when BO and attendant respiratory failure developed. FULLERTON *et al.* [9] described immune deposits within the bronchial epithelium, associated with erosions and respiratory compromise [8, 9]. This suggests that autoimmune responses may play an important role in the pathogenesis of constrictive BO.

In summary, this study has reported on a case of constrictive bronchiolitis obliterans and paraneoplastic pemphigus, which may be facets of autoimmune responses associated with malignant lymphomas.

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