Necrotizing Tracheobronchitis With Progressive Airflow Obstruction Associated With Paraneoplastic Pemphigus*

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Paraneoplastic pemphigus (PNP) is an autoimmune disease associated with leukemia and non-Hodgkin’s lymphoma. A patient with stage IVB poorly differentiated lymphocytic lymphoma developed characteristic upper and lower airway involvement with profound mucocutaneous erosion and tracheobronchial epithelial desquamation. Immunofluorescence testing confirmed autoantibody deposition along the basement membrane of bronchial epithelium. Disruption of the cellular adhesion mechanisms, including desmosomes, hemidesmosomes, and possibly the integrin subunits, is presumed to have led to disruption and desquamation of the tracheobronchial epithelial barrier, severe obstruction of the airways and hypoxia, and possibly bacterial superinfection. As far as can be determined, the feature of airflow obstruction occurring in association with PNP has not been described. Physicians should be aware that these complications of PNP may rapidly lead to hypoxic respiratory failure and death.

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Key words: airway obstruction; autoantibody; desmosome; hemidesmosome; necrotizing tracheobronchitis; non-Hodgkin’s lymphoma; paraneoplastic pemphigus

Abbreviations: IIF=indirect immunofluorescence; PNP=paraneoplastic pemphigus

Paraneoplastic pemphigus (PNP) is an autoimmune disease which occurs in association with leukemia, malignant lymphomas, and other neoplasms.1-4 Wide-

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spread inflammatory vesiculobullous lesions involving the skin and the oral and conjunctival mucosae are characteristic.1,3,5 Polyclonal IgG autoantibodies that bind to epidermal proteins of desmosome and hemidesmosome origin have been identified by immunoprecipitation techniques.1,5-7 These proteins have been implicated as a cause of the blistering and erosive mucocutaneous lesions found in PNP.1,5,7,8

Although pulmonary involvement leading to respiratory compromise in patients with PNP has been previously reported, the information about this association is limited. A man with non-Hodgkin’s lymphoma developed PNP and a necrotizing tracheobronchitis associated with severe airflow obstruction and hypoxia. This case report will help further define the pulmonary manifestations of this increasingly recognized but uncommon paraneoplastic process.

REPORT OF A CASE

A 57-year-old man who had never smoked had stage IVB nodular poorly differentiated lymphocytic lymphoma and was treated with cyclophosphamide, doxorubicin, vincristine, and prednisone combination therapy in 1990. From 1991 through 1992, several chemotherapeutic regimens were administered because of persistent lymphomatous infiltration of the bone marrow, eventually with successful control of the disease.

In October 1993, vesiculobullous lesions developed over his trunk, upper extremities, lips, oral mucosa, and conjunctivae. A skin biopsy specimen failed to reveal evidence of acantholysis or deposition of IgG, IgM, IgA, and complement. A presumptive diagnosis of bullous pemphigoid was made, and treatment with dapsone and prednisone was instituted. Four months later, he presented with progressive dyspnea, wheeze, and cough. He described two-pillow orthopnea and rare episodes of paroxysmal nocturnal dyspnea and denied fever, diaphoresis, or chest pain. Initial examination revealed a respiratory rate of 18 breaths per minute, a clear chest examination, and normal heart sounds. A maculopapular rash was present over the trunk and extremities and pustular vesiculobullous lesions were found to cover the buccal mucosae, the gums, the soft palate, the lips, and the nasal and conjunctival mucosae.

Laboratory examination revealed a WBC count of 5,100/mm³. The chest radiograph showed a diffuse, faint reticulon pattern. With the patient breathing room air, arterial blood gas values were as follow: pH, 7.46; Pco2, 44 mm Hg; and Po2, 55 mm Hg.

A high resolution chest CT scan revealed normal pulmonary parenchyma and pleura and nonpathologic mediastinal lymphadenopathy. Pulmonary function testing revealed moderate obstruction with air-trapping and a significant reduction in the diffusing capacity (Table 1, examination 1).

Another skin biopsy was done, and it demonstrated suprabasal acantholysis and focal erosion. Indirect immunofluorescence (IIF) studies confirmed linear deposition of IgG along the basement membrane zone and on the surface of keratinocytes in the lower portion of the dermis. These findings supported a diagnosis of PNP. A bronchoscopy performed to exclude the possibility of an opportunistic infection disclosed postural, vesiculobullous lesions which covered the nasal, nasopharyngeal, and laryngeal mucosae. Copious mucopurulent secretions filled the tracheobronchial lumina. The airways were edematous and erythematous and exhibited white, plaquelike lesions which were adherent to the bronchial mucosa throughout the tracheobronchial tree.

Cytopathologic examination was negative for lymphomatous...
cells. No viral inclusions were seen. Additional studies for mycobacteria species, fungi, Legionella species, and *Pneumocystis carinii* were negative. The protected specimen brush catheter grew 7,000 colony-forming units (CFU)/mL of α-hemolytic streptococci and 300 CFU/mL of Neisseria species.

Antibiotics were administered, which resulted in a mild improvement in the patient’s symptoms. Within 10 days, however, disabling dyspnea and cough had returned. A chest x-ray film revealed infiltrates of the lower lobe of the right lung and lingula; pulmonary function tests revealed worsened airflow obstruction (Table 1, examination 2).

A second bronchoscopic examination was performed to obtain bronchial biopsy specimens. Histologically, these specimens of respiratory epithelial showed evidence of acute and chronic inflammation (Fig 1). The epithelium contained a few dark, dense scattered intraepithelial bodies, suggesting an apoptic change, and were consistent with individual cell death. Occasional squamous cells were found to have hydric change. Squamous metaplasia and reactive atypia without blistering effect also were present.

Direct immunofluorescence of bronchial epithelium found linear IgG (Fig 2) and C3 immunofluorescence along the basement membranes. Deposition of IgG and C3 within intercellular spaces was not seen. Immunofluorescence staining for IgA was negative. An indirect immunofluorescence study using fluorescein-tagged antihuman IgG, the patient’s serum, and rodent tracheobronchial, alveolar, and esophageal epithelia showed weak immunofluorescence along the basement membrane in the tracheobronchial epithelium. Tiny intraepithelial deposits in the squamous epithelium and in the intercellular junctions of squamous epithelium of the esophagus were seen as well. The alveolar epithelium was nonfluorescent. These immunohistologic findings supported tracheobronchial involvement by PNP.

**Discussion**

PNP is an autoimmune disease clinically and immunologically distinct from pemphigus vulgaris and pemphigus foliaceus. PNP has been found to occur most commonly in association with non-Hodgkin’s lymphomas but is also known to occur in association with chronic lymphocytic leukemia, thymoma, bronchogenic squamous cell carcinoma, poorly differentiated spindle cell sarcoma, Castleman’s disease, and Waldenström’s macroglobulinemia.1,4,5,7

Little has been written about the pulmonary manifestations of PNP since the index case reported by Anhalt and colleagues.1 Subsequent case reports have helped further define the pulmonary manifestations of PNP.3,4,9,10,12 Dyspnea out of proportion to roentgenographic abnormalities or oxygenation status has been described.3 The chest radiographic findings have included hyperinflation with flattening of the diaphragms, pleural thickening, and parenchymal infiltrates.1,13 Hypoxia and respiratory compromise leading to death appears to be a frequent occurrence.1,3,9,10

Diffuse upper and lower airway mucosal erythema, denuded mucosal epithelium, pemphiguslike lesions throughout the trachea, and obstruction of distal bronchi by necrotic debris have all been described following bronchoscopic examination.3,4 Biopsy specimens of bronchial mucosa prepared using direct immunofluorescence techniques have demonstrated C3 and IgG deposition within intercellular spaces of the respiratory epithelium similar to those seen in skin.3,9 In the case reported here, we observed linear deposition of both C3 and IgG along
the basement membrane but did not identify deposition of the C3 or IgG within intracellular spaces. However, IIF showed tiny intraepithelial deposits of IgG in rodent esophageal squamous epithelium, which has been reported in IIF examination of monkey esophagus and human and mouse skin reacted with sera from patients with PNP.1

The results of pulmonary function testing in patients with PNP have not been published, and as best as can be determined, this is the first case to measure airflow obstruction in PNP. The presence of an obstructive airway process in this nonasthmatic subject who never smoked is considered to have been due to occlusion of the intermediate and small airways by denuded and necrotic tracheobronchial epithelium. Air trapping without hyperinflation was most certainly due to airway obstruction by the inflammatory exudate. Though the decreased FEV1/FVC ratio indicates airflow obstruction, a decrease in the vital capacity may in part be explained by weakness in a critically ill patient. The mechanism of the moderate hypoxemia manifested by this patient may have been similar to the resting hypoxemia commonly found in adult patients with small airway disease,11 and its presence is not surprising given the marked bronchial and bronchiolar obstruction. Impaired gas exchange due to ventilation-perfusion inequality resulted as a consequence of the obstruction of small airways by necrotic debris.

This patient’s illness was characterized by an exudative tracheobronchitis which led to progressive airflow obstruction. Obstruction may have been the direct result of the desquamative effects of the epidermal proteins found deposited along the tracheobronchial epithelium10 or the result of a secondary infectious process or of both. A necrotizing tracheobronchitis leading to airway obstruction has been described in patients with infection due to invasive aspergillosis,12 influenza,13 and herpetic tracheobronchitis.14 No evidence of either fungal or viral infection was documented in this patient.

The integrity of the tracheobronchial epithelial surfaces is maintained by several adhesive mechanisms which include both structural (desmosome and hemidesmosome) and molecular (integrin) cellular adhesive components. Desmosomes are symmetrical structures found along the lateral edges of suprabasal cells and at the interface between suprabasal cells and the cells of the basal layer (Fig 3). Hemidesmosomes link basal epithelial cells to the underlying basement membrane to provide a stable connection between these two surfaces. Hemidesmosomes of respiratory epithelia contain the bullous pemphigoid protein.15,16 Integrins, located in the subbasal portion of the hemidesmosome, are adhesion molecules present in bronchial epithelium which help to maintain the integrity of the airway and may be responsible for adhesion of the endothelial and basal epithelial cells to the basement membrane.16,17

In contrast to both pemphigus vulgaris and pemphigus foliaceus, the autoantibodies found in PNP have been shown to bind not only to stratified squamous epithelium but also to the cell surfaces of simple, columnar and transitional epithelia.7 These serum autoantibodies, by binding to respiratory epithelium, may in fact disrupt the cellular adhesive mechanisms and thereby lead to cell necrosis and sloughing of the epithelium.

The formal criteria used to define PNP are as follows: (1) painful mucosal erosions and a polymorphous skin eruption, with papular lesions progressing to blisters and erosive lesions affecting the trunk, extremities, and palms and soles, in the context of an occult or confirmed neoplasm; (2) cutaneous histologic changes—intraepidermal acantholysis, keratinocyte necrosis, and vacuolar-interface dermatitis; (3) deposition of IgG and complement in the epidermal intercellular spaces along the epidermal basement membrane zone on direct immunofluorescence testing; (4) serum autoantibodies that bind the cell surface of skin and mucosae in a pattern typical of pemphigus but in addition bind to simple, columnar, and

![Schematic diagram of the bronchial epithelium](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21755/ on 04/02/2017)

**Figure 3.** Schematic diagram of the bronchial epithelium which shows the relationship of the columnar cells (CE), reserve cells (RC), and basement membrane (BM) to the principal structural cellular adhesive components.
transitional epithelia; and (5) a complex of four proteins immunoprecipitated from keratinocytes by these autoantibodies.

This patient met four of the five criteria necessary to confirm the diagnosis of PNP. Immunoprecipitation studies on sera from this patient were not performed. As has been shown, indirect immunofluorescence testing has demonstrated both IgG and complement deposition in a linear pattern along the basement membrane zone and/or in the intercellular spaces of affected epithelial surfaces.1,5,6

IF techniques using sera from patients with PNP will identify polyclonal autoantibodies that bind to the cell surfaces of various tissues, including monkey esophagus, human epidermis, and mouse skin and bladder.1,6,8 IIF techniques have the advantage of being reproducible, inexpensive, and easy to perform,9 and in the appropriate clinical setting, the diagnosis of PNP may be made with histologic findings and serum IIF studies.9 IIF testing of serum using transitional epithelium of the rodent bladder may be used in place of immunoprecipitation studies.5,8

In summary, for the first time severe airflow obstruction associated with PNP has been described. This seems to be the result of disruption of the cellular adhesion mechanisms caused by autoantibody deposition within the tracheobronchial epithelium. The hypothesis is that autoantibody deposition subsequently led to desquamation of the tracheobronchial epithelial barrier, severe obstruction of the distal airways, hypoxia, and possibly bacterial superinfection. As PNP is becoming increasingly recognized, physicians should be aware of its effects on the respiratory system and the risk for respiratory death.

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Antiphospholipid Antibody Syndrome Presenting as a Refractory Noninflammatory Pulmonary Vasculopathy*

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The clinical manifestations of antiphospholipid antibody syndrome (APLAS) are protean. Pulmonary manifestations are often thromboembolic in origin; ARDS and pulmonary hypertension have been reported as features of a widespread vasculopathy associated with systemic lupus or Sjögren’s syndrome. This is the report of a woman with primary APLAS who died of a noninflammatory pulmonary vasculopathy. The case is unusual in its pulmonary manifestations, its initial response to corticosteroids and antithrombotic medications, its failure to stabilize with high-intensity warfarin sodium and aspirin treatment, and finally its fulminant progression despite multiple interventions.

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Key words: antiphospholipid antibodies; case report; corticosteroids; pulmonary manifestations

Abbreviations: APLAS=antiphospholipid antibody syndrome; aCL=anticardiolipin; INR=international normalized ratio; SLE=systemic lupus erythematosus

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