

## Brief Report

## THE MECHANISM OF RESPIRATORY FAILURE IN PARANEOPLASTIC PEMPHIGUS

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**P**ARANEOPLASTIC pemphigus<sup>1</sup> is an autoimmune disease that accompanies an overt or occult neoplasm and causes blisters. It is characterized by the presence of IgG autoantibodies that react against desmosomal and hemidesmosomal plakin proteins,<sup>2-5</sup> desmosomal transmembrane proteins (desmogleins),<sup>6</sup> and an unidentified 170-kd antigen. Blistering of stratified squamous epithelium results from acantholysis, the loss of cell-cell adhesion, induced by pathogenic antibodies against the desmogleins.<sup>6</sup> The most commonly associated neoplasms are, in decreasing order of frequency, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, Castleman's disease, thymoma, retroperitoneal sarcomas, and Waldenström's macroglobulinemia.

Progressive respiratory failure with clinical features of bronchiolitis obliterans is frequently the cause of death among patients with paraneoplastic pemphigus. Possible causes of the respiratory failure include infection, toxic effects induced by chemotherapy, neoplasia, and autoantibody-mediated pulmonary injury.<sup>7-16</sup> Deposits of IgG in the bronchial epithelium, which have sometimes been observed,<sup>17</sup> suggest that autoantibody-mediated injury has a role in this process.

To define the mechanisms of the pulmonary injury further, we studied two patients with paraneoplastic pemphigus and progressive respiratory failure. We found that autoantibodies directed against plakin proteins may cause acantholytic changes in the respiratory epithelium, leading to respiratory failure and death.

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## CASE REPORTS

### Patient 1

In 1995, Patient 1, a previously healthy 13-year-old boy, presented with painful ulcerations of the tongue and buccal mucosa that were refractory to topical and systemic treatment for presumed herpetic infection. The mucosal lesions affected most of the oropharynx, and severe pain necessitated the use of a gastrostomy tube for feeding. Subsequently, cutaneous blisters and erosions appeared on the genitals, trunk, and extremities. A skin-biopsy specimen showed acantholysis with deposition of IgG and complement on the surfaces of keratinocytes and along the basement-membrane zone. Serum autoantibodies characteristic of paraneoplastic pemphigus were detected at a titer of 10,000; their antigenic specificity was confirmed by immunoprecipitation. Evaluation for occult neoplasm revealed a mediastinal mass. This mass was excised and found to be a manifestation of Castleman's disease of the hyaline vascular type. Castleman's disease is a rare lymphoproliferative disorder that is often associated with autoimmune phenomena and that occurs in two variants: a benign, localized, hyaline vascular type and an aggressive multicentric plasma-cell type.

Computed tomography (CT) of the lungs showed no abnormalities. Treatment with 5 mg of cyclosporine per kilogram of body weight per day, 1.5 mg of prednisone per kilogram per day, and plasmapheresis produced little clinical improvement. Residual tumor tissue was detected and resected, with marked improvement of the skin and mucosal lesions. One month after surgery, dyspnea and cough developed, but chest radiographs were unremarkable and sputum and blood cultures were negative. Despite treatment for presumed pneumonia, the dyspnea progressed and was followed by increasing cough, which was productive of white sputum. Skin and mucosal lesions remained in clinical remission. Serum autoantibodies characteristic of paraneoplastic pemphigus remained present at a titer of 250.

CT scanning showed no residual tumor in the chest, abdomen, or retroperitoneum but revealed changes indicative of diffuse bronchiectasis and areas of hypodensity in the lung. Hyperinflation without infiltrates was visible on chest radiographs. Arterial-blood gas analysis revealed severe hypoxemia, and spirometry revealed severe obstructive lung disease (Table 1). The pulmonary parenchyma appeared normal on thorascopic lung biopsy, with delicate alveolar septa and a striking quantity of mucus in the bronchioles, but no fibrotic changes. Bronchial-lavage fluid was highly cellular, with 81 percent neutrophils, 11 percent band forms, and 8 percent mononuclear cells. Cultures of bronchoalveolar-lavage fluid and lung tissue were negative. Bronchoscopy showed diffuse central-airway erythema, striking amounts of mucus, and areas of epithelial sloughing. An endobronchial-biopsy specimen was obtained from the right mainstem bronchus and submitted for histologic and immunopathological examination.

Treatment continued with prednisone, cyclosporine, prophylactic trimethoprim-sulfamethoxazole, and respiratory therapy. The patient was placed on a waiting list for lung transplantation. Pulmonary-function tests showed that obstruction was increasing, resulting in partial pressures of carbon dioxide of 80 to 100 mm Hg and necessitating nasal ventilation. The patient died suddenly, approximately two and a half years after the initial presentation with mucosal lesions and one year after the onset of pulmonary symptoms. Autopsy revealed bronchiolitis obliterans, including marked pulmonary overinflation and patchy broncholar obliteration with fibrosis. There was extensive squamous metaplasia of the proximal airways associated with patchy areas of acantholytic epithelial detachment, basement-membrane thickening, and abundant mucus in the airways. No residual Castleman's disease and no evidence of infection were found.

### Patient 2

Patient 2 was a 39-year-old man who received chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone for low-grade B-cell non-Hodgkin's lymphoma in 1993. The lym-

phoma recurred after three years and was treated with interferon alfa and tumor necrosis factor  $\alpha$ . One year later, in 1997, erosive lesions of the oral, ocular, nasal, and genital mucosa developed along with lichenoid and erosive skin lesions and onychodystrophy. Skin-biopsy specimens showed changes resembling lichen planus and necrosis of the keratinocytes. Direct immunofluorescence showed deposition of IgG and complement on the keratinocyte surfaces and deposition of complement along the basement-membrane zone. Serum autoantibodies associated with paraneoplastic pemphigus were present at a titer of 1280; their antigenic specificity was confirmed by immunoprecipitation. The mucocutaneous lesions resolved slowly with the administration of 1.0 mg of prednisolone per kilogram per day.

Five months later, rapidly progressive dyspnea developed. No abnormalities were seen on chest radiography. CT scanning showed areas of slight ground-glass attenuation in the lungs. Arterial-blood gas analysis showed severe hypoxemia, and spirometry revealed severe airflow limitation (Table 1). Sputum cultures were negative for *Mycobacterium tuberculosis* and other bacteria. Bronchoscopy showed erythema and edema of the respiratory epithelial mucosa with no evidence of neoplasm or infection. An endobronchial-biopsy specimen was obtained from the right mainstem bronchus. Despite treatment with 4 mg of cyclosporine per kilogram per day and prednisolone, progressive pulmonary compromise developed. The patient died approximately one year after the mucocutaneous lesions appeared. When he died, paraneoplastic pemphigus autoantibodies were still present in the serum, at a titer of 640. An autopsy was not performed.

## METHODS

Endobronchial-biopsy specimens were processed with hematoxylin and eosin, Brown-Brenn, periodic acid-Schiff, Giemsa, Fite, and pentachrome stains. Frozen sections were probed with fluoresceinated antibodies specific for IgG, IgA, IgM, complement, and fibrin.<sup>18</sup> Written informed consent was obtained from both patients for the investigations, which were part of their clinical evaluation for respiratory failure of unknown cause.

Serum samples from both patients were tested by indirect immunofluorescence with the use of monkey esophagus and murine bladder, heart, and liver as substrates. Serum from these patients, from a control patient with lymphoma-associated paraneoplastic pemphigus, and from a patient with pemphigus vulgaris was tested by immunoprecipitation of extracts of radiolabeled keratinocytes, as previously described.<sup>19</sup> Additional radiolabeled extracts were prepared in an identical fashion from human respiratory epithelial cells (Clonetics, San Diego, Calif.) that were grown in bronchial-epithelial-cell growth medium (Clonetics).

Fusion proteins of the homologous tail region of plectin, bullous pemphigoid antigen 1, desmoplakin I and II, envoplakin, and periplakin were cloned from a human matchmaker complementary DNA library (Clontech, Palo Alto, Calif.) by the polymerase chain reaction with the use of primers according to published techniques.<sup>5</sup> Reactivity of serum to the fusion proteins was tested by immunoblotting.

For passive transfer of IgG into mice, IgG was purified from specimens from Patient 1<sup>1,20</sup> and injected into neonatal mice at a dose of 10 mg per gram of body weight. Neonatal mice are the animals of choice for such passive-transfer studies because their small size allows reproduction of circulating IgG levels similar to those in the human disease and because their hairless skin facilitates the induction and observation of cutaneous blistering. After 12 hours, when cutaneous blisters were present, the mice were killed and coronal sections were obtained. All epithelial surfaces were examined for signs of acantholysis and deposition of human IgG.

## RESULTS

Endobronchial-biopsy specimens from both patients showed acantholysis of differentiated ciliary epithelial cells from the underlying basilar cells. Basilar

**TABLE 1. RESULTS OF PULMONARY-FUNCTION TESTS AND ARTERIAL-BLOOD GAS ANALYSES IN THE TWO PATIENTS.\***

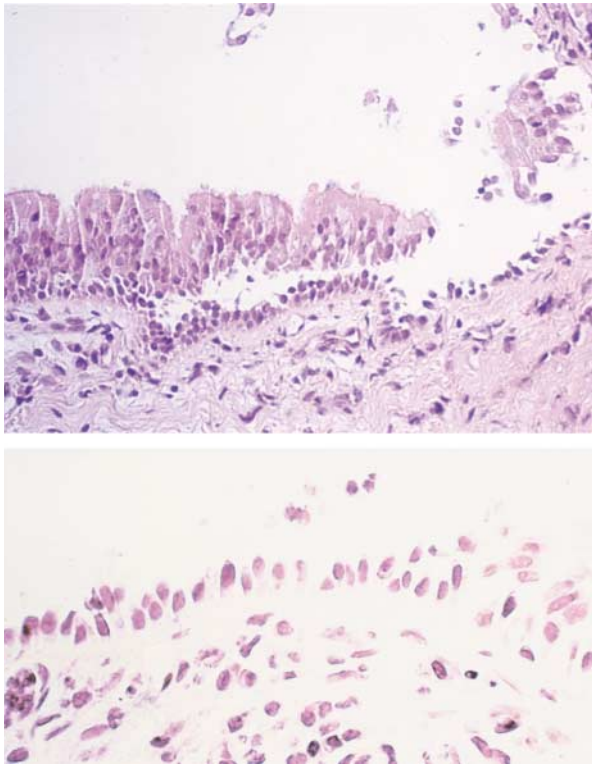
VARIABLE	PATIENT 1		PATIENT 2	
	ACTUAL VALUE	PERCENT OF PREDICTED VALUE	ACTUAL VALUE	PERCENT OF PREDICTED VALUE
FVC (liters)	1.54	35	2.27	58
FEV <sub>1</sub> (liters)	0.51	13	0.72	21
FEV <sub>1</sub> :FVC	0.33		0.31	
FEF <sub>25-75%</sub> (liters/sec)	0.23	6	0.32	15
Total lung capacity (liters)	5.83	117	4.70	80
Residual volume (liters)	3.97	370	2.40	110
pH	7.38		7.47	
Arterial partial pressure (mm Hg)				
Carbon dioxide	45		44	
Oxygen	50		54	
Bicarbonate (mmol/liter)	27		30	
Oxygen saturation (%)†	83		89	

\*FVC denotes forced vital capacity, FEV<sub>1</sub> forced expiratory volume in one second, and FEF<sub>25-75%</sub> forced expiratory flow at 25 to 75 percent vital capacity.

†Oxygen saturation was measured while the patients were breathing room air at 1620 m above sea level.

cells showed no detachment from the underlying lamina propria but did detach from adjacent cells on their apical and lateral surfaces, producing a histologic change resembling a row of tombstones (Fig. 1). A mixed inflammatory infiltrate consisting of lymphocytes, neutrophils, eosinophils, and plasma cells was present in the submucosa. Staining with specialized reagents did not reveal bacteria, fungi, mycobacteria, or *Pneumocystis carinii*. Pentachrome staining, which can reveal changes in elastic fiber and collagen indicative of early fibrosis, was negative. There was no cytologic evidence of cytomegalovirus infection or cancer. Evaluation of frozen tissue showed deposition of IgG and complement in a linear manner on the respiratory-epithelial-cell surfaces and in a linear and granular manner along the lamina propria (Fig. 2).

Both patients' serum samples contained IgG autoantibodies that reacted to the epithelial surfaces and basement membrane of monkey esophagus as well as to murine urinary-bladder epithelial cells, intercalated disks of myocardium, and hepatocyte desmosomes. Serum from both patients also contained antigens of 250, 230, 210 (a doublet), and 190 kd, representing desmoplakin I, bullous pemphigoid antigen 1, desmoplakin II and envoplakin (migrating as the doublet), and periplakin, respectively. These antigens were detected in both the keratinocyte extracts and the respiratory epithelial extracts (Fig. 3). The 170-kd antigen was detected in the keratinocyte extracts but not in the respiratory epithelial extracts. The control serum from the patient with pemphigus vulgaris did not detect expression of the 130-kd pem-



**Figure 1.** Micrographs of the Endobronchial-Biopsy Specimen from Patient 1.

Ciliated respiratory epithelial cells are detached from the adherent, nonciliated epithelial cells beneath them (upper panel; hematoxylin and eosin,  $\times 100$ ). At a higher magnification (lower panel), the adherent, nonciliated respiratory epithelial cells can be seen to be detached from each other at their apical and lateral surfaces, but still normally adherent to the underlying lamina propria. This condition produces a histologic "row of tombstones" characteristic of the loss of cell-cell attachment (acantholysis) mediated by the pemphigus antibody (hematoxylin and eosin,  $\times 400$ ).

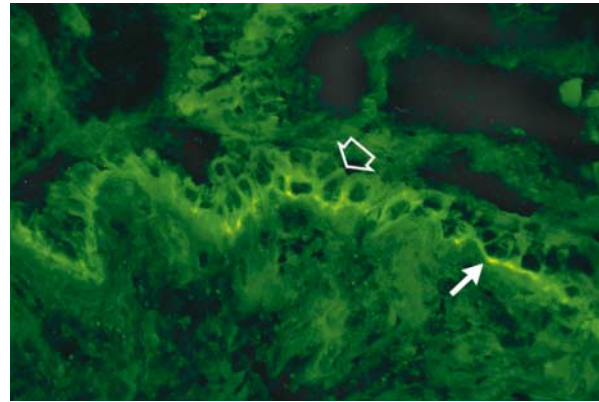
phigus vulgaris antigen<sup>21</sup> by the respiratory epithelial cells, but it strongly detected the pemphigus vulgaris antigen in epidermal-cell extracts by immunoprecipitation (data not shown).

The serum samples reacted strongly to fusion proteins from the homologous tail region of envoplakin, reacted with moderate intensity to periplakin and plectin, and reacted weakly to desmoplakin I and the bullous pemphigoid antigen 1.

Histologic examination of tissue from neonatal mice showed cutaneous acantholytic blistering. We detected neither acantholysis nor specific deposition of human IgG in the bronchial epithelium, despite the presence of human pemphigus autoantibodies in the serum at a titer of 1280.

#### DISCUSSION

Pemphigus diseases of the skin are characterized by acantholytic blistering caused by the reaction of IgG



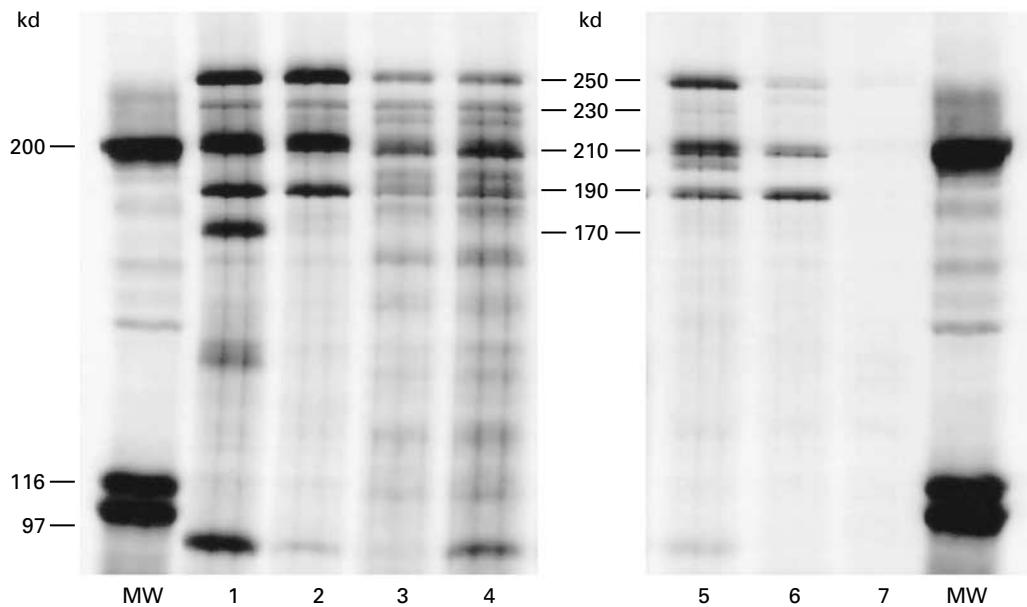
**Figure 2.** Direct Immunofluorescence of the Endobronchial-Biopsy Specimen from Patient 1.

Linear deposition of IgG is visible on the surfaces of the respiratory epithelial cells (open arrow) as well as along the basement-membrane zone (solid arrow). This pattern of autoantibody deposition is identical to that seen in the epidermis of patients with paraneoplastic pemphigus (antihuman IgG,  $\times 400$ ).

autoantibodies against desmogleins. In pemphigus foliaceus, blisters are superficial; mucous membranes are never involved. Antibodies against desmoglein 1 are responsible for this limited form of the disease. In pemphigus vulgaris, patients also produce antibodies against desmoglein 3, and blisters form on both the skin and the mucous membranes. However, because the expression of desmoglein 3 is limited, the lesions are restricted to tissues covered by stratified squamous epithelium.<sup>22</sup>

In patients with paraneoplastic pemphigus, pathogenic autoantibodies react against the desmogleins, but the antibodies are present at a low titer and can be detected only by a sensitive enzyme-linked immunosorbent assay.<sup>6,23,24</sup> Such patients also have high titers of autoantibodies against plaklin proteins.<sup>4</sup> The plaklins are a group of sequence-related proteins that form the intracellular plaques of desmosomes and hemidesmosomes and that mediate attachment of the cytoskeletal intermediate filaments to transmembrane adhesion molecules, such as desmogleins. These plaklin proteins are found in numerous tissues,<sup>25,26</sup> including all epithelium (e.g., respiratory, intestinal, urinary, and transitional), intercalated disks of myocardium, and nonepithelial desmosomes (e.g., hepatocytes). Because these autoantibodies have such broad reactivity, we suspected that the lesions in paraneoplastic pemphigus may not be restricted to organs covered by stratified squamous epithelium. To date there is evidence only that the autoantibodies to plaklin proteins cause pulmonary injury.

In our experience with 84 patients with paraneoplastic pemphigus, the mortality rate is more than 90 percent. Deaths have been attributed to compli-



**Figure 3.** Reactivity of Paraneoplastic Pemphigus Autoantibodies with Respiratory Epithelial Antigens.

Immunoprecipitation was performed on metabolically labeled keratinocytes and normal human bronchial epithelial cells. Molecular-weight (MW) markers are shown at 200, 116, and 97 kd. Lanes 1 and 2 show control serum from a patient with paraneoplastic pemphigus. Serum from epidermal cells (lane 1) contains autoantibodies that recognize the paraneoplastic pemphigus antigen complex, with bands detected at 250, 230, 210, 190, and 170 kd. Serum from respiratory epithelial cells (lane 2) immunoprecipitates protein bands at 250, 230, 210 and 190 kd, showing that these cells also express the plakin antigens. Lanes 3 and 4 (Patient 1) and lanes 5 and 6 (Patient 2) show antigens recognized by serum from patients with paraneoplastic pemphigus and pulmonary involvement. Serum from both patients reacts with plakin antigens expressed by both keratinocytes (lanes 4 and 5) and respiratory epithelial cells (lanes 3 and 6). Lane 7 shows results with respiratory epithelial cells from a patient with pemphigus vulgaris; this control serum fails to immunoprecipitate any of the antigens of the paraneoplastic pemphigus complex. This finding confirms that the pemphigus vulgaris antigen is not expressed by respiratory epithelial cells, as expected. This control serum also shows that the 170-kd antigen is expressed in epidermal cells, but not in respiratory epithelial cells, in paraneoplastic pemphigus.

cations associated with immunosuppressive therapy, such as sepsis and multiorgan failure. A recently recognized complication in about 30 percent of patients is respiratory failure with features of bronchiolitis obliterans (unpublished data).

The two patients we describe had respiratory symptoms characteristic of paraneoplastic pemphigus. Progressive dyspnea was associated initially with an absence of findings on chest radiography. Despite immunosuppressive therapy and apparent resolution of the skin and mucosal lesions, symptoms progressed to tracheal and bronchial inflammation, gradual deterioration of pulmonary function, and hypoxia, and death followed. Both patients had severe airflow obstruction that affected the large and small airways. The large airways appeared to be involved early in the course of the disease, and biopsy of endobronchial epithelium at that time revealed the key immunopathological features of pemphigus, acantholysis and autoantibody deposition. In Patient 1 thoracoscopic lung-biopsy specimens obtained early in the course of the pulmonary disease showed only accumulated mucus in the small airways. Later involvement of the small airways produced radiologic, histologic, and

functional changes characteristic of bronchiolitis obliterans<sup>27</sup> and led to respiratory failure.

Bronchial epithelial tissue from these patients showed acantholysis and deposition of IgG autoantibodies on the cell surfaces. There is no evidence that antibodies against desmogleins play any part in the induction of respiratory lesions. In patients with pemphigus vulgaris or pemphigus foliaceus, the lungs are exposed to autoantibodies against desmoglein 3 and desmoglein 1 for years or decades, and respiratory involvement has not been observed. Our labeling studies confirmed that desmogleins 3 and 1 are not expressed in respiratory epithelium.<sup>28</sup> Respiratory epithelial cells do, however, express all the plakin antigens recognized by paraneoplastic pemphigus autoantibodies.

We focused on antiplakin antibodies because desmogleins are evidently not involved in pulmonary injury and because our labeling studies showed that the only other candidate antigen, the 170-kd antigen, is also apparently not expressed in respiratory epithelium. The nature of the 170-kd antigen is not known; there is no monospecific probe for it, and the gene that encodes it has not been identified.

The detection of autoantibodies that react to antigens in respiratory epithelium and the concomitant presence of acantholysis suggest a causal relation, but causation has not yet been proved. Pulmonary epithelial lesions were not induced in mice either by infusion of pemphigus vulgaris IgG (with antibodies specific for desmoglein 3)<sup>20</sup> or by IgG with antibodies against plakin proteins from patients with paraneoplastic pemphigus. However, there are potential explanations for these negative results.

First, plakin proteins are entirely intracellular. Although there is evidence that autoantibodies may enter living cells and interact with cytoplasmic or nuclear antigens,<sup>29</sup> the mechanisms by which this process might occur are poorly understood. Second, in passive-transfer studies in neonatal mice, the duration of exposure to the human autoantibodies is generally less than 48 hours. This is due to the behavior of the mothers: if a newborn mouse appears to be diseased or otherwise not thriving, it may be starved or eaten by the mother within 72 hours. Short-term exposure to transfused antibodies may not be sufficient to cause respiratory acantholysis. Third, in humans, pulmonary involvement in paraneoplastic pemphigus is usually a late complication. It may be that additional inflammatory events occur to allow these antibodies to bind within the desmosomal plaque of respiratory epithelium. The immaturity of neonatal bronchial epithelium and variations in the epitope structures of murine antigens may also be factors. Finally, cell-mediated cytotoxic mechanisms may be important, and such mechanisms cannot be reproduced by passive transfer of IgG alone into the mice.

Evidence to date indicates that in paraneoplastic pemphigus, autoantibodies directed against plakin proteins may be responsible for acantholytic changes in the respiratory epithelium. Our study establishes that pulmonary epithelial injury with progressive respiratory failure is a characteristic feature of paraneoplastic pemphigus.

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