Pulmonary Small Lymphocytic Lymphoma (Mucosa-Associated Lymphoid Tissue Type) Associated With Pulmonary Hyalinizing Granuloma*

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A case of pulmonary hyalinizing granuloma (PHG) and concomitant low-grade, small lymphocytic lymphoma of the lung is presented. This is the first occurrence of pulmonary lymphoma in patients with PHG ever reported. The infiltrates around a left lower lobe nodule with left pleural effusion and thickening seen on chest CT were histologically proven to be lymphomatous infiltrates of the lung, pleura, and chest wall muscle. We believe that the lymphoma developed around the nodule and spread to the pleura and muscle in our patient. When infiltrates around the nodules, pleural effusion, or adenopathy are developed in a patient with proven PHG, close follow-up, biopsy, or careful cytology should be seriously considered to rule out a developing lymphoma.

Key words: mucosa-associated lymphoid tissue lymphoma; non-Hodgkin's lymphoma; pulmonary hyalinizing granuloma; pulmonary lymphoma; small lymphocytic lymphoma

Abbreviation: PHG = pulmonary hyalinizing granuloma

Pulmonary hyalinizing granuloma (PHG) is a rare etiology of lung nodules. Since the first report by Engleman et al1 in 1977, to the best of our knowledge, 61 cases of PHG have been reported in the English-language literature.2–7 The nodules are typically benign in histology and clinical course, but slowly grow in size and number. Because of their behavior and to rule out a malignancy, biopsy is required to establish the primary diagnosis of PHG. The occurrence of small cell-type malignant disease, specifically lymphoma in this condition, has long been postulated, but only one case with PHG associated with stage IV diffuse lymphocytic lymphoma of the abdomen has been reported.8 We present the first case of PHG and concomitant low-grade small lymphocytic B lymphoma of the lung.

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Figure 1. Top: Initial CT scan at the lower-thoracic level demonstrated four nodules, three in the right lung and one in the left lung. The largest nodule in the right lower lobe measured 5.0 × 3.5 cm and showed irregular, central calcification. The left lower lobe nodule (arrow) measured 1.8 × 1.6 cm. Bottom: Follow-up CT scan prior to surgery at the same level demonstrated that the left lower lobe nodule increased in size to 3.1 × 2.0 cm. Note the infiltrate around the left lower lobe nodule extending to the pleura laterally (arrow) with parietal pleural thickening (curved arrow) and effusion.
At presentation to our institution, the patient was without shortness of breath, cough, sputum production, or hemoptysis, and he denied chest pain, weight loss, fever, or chills. He was born in Syria but had lived most of his adult life in the United States. He had not received Bacille Calmette-Guérin vaccination and had no known drug allergies. His medical history was noncontributory. He did not have any occupational exposures that would place him at risk for pulmonary complications.

On physical examination, the lungs were symmetrical in movement, slightly dull to percussion in the left lower lung, and clear to auscultation with no egophony. Findings of heart and abdominal examination were normal. Pulmonary function tests performed at our institution revealed FVC of 3.27 L (73% predicted), FEV1 of 2.34 L (64% predicted), and FEV1/FVC ratio of 72% (81% predicted).

A chest CT was repeated in September of 1997, which showed enlarging bilateral multiple nodules of variable sizes ranging from 0.6 to 3 cm with irregular borders and interval small pleural effusion compared to the previous CT study (March 1997). His follow-up chest CT in December of 1997 showed the nodules were more spiculated with an irregular border and slight increase in size from the initial study. The left lower lobe nodule showed an interval increase up to 3.1 cm with an infiltrate extending to the pleura peripherally (Fig 1, bottom). There was interval progression in the thickening of the parietal pleura. It was suggested that the findings may represent an active phase of PHG or associated with another etiology, such as an infectious or a malignant process. Cytologic examination of the left pleural effusion fluid showed marked lymphocytosis with small atypical lymphocytes. Flow-cytometric analysis of the left pleural fluid was of limited value due to poor cell viability. A diagnosis of lymphoproliferative disorder was proposed. Accordingly, video-assisted thoracoscopic lung and pleural biopsies were performed. Intraoperative findings showed the left lower lobe nodule was firm and the surrounding parietal pleura was thickened. The resected lung nodule measured 2.5 × 1.8 × 1.7 cm, and was microscopically similar to the previous material and consistent with PHG. Repeat fungal, acid-fast, and Congo red stain findings were negative. All culture findings were negative. The adjoining lung tissue showed multiple nodules of monotonous-appearing small atypical lymphocytes most consistent with low-grade small lymphocytic lymphoma of the mucosa-associated lymphoid tissue type (Fig 3). Likewise, the left parietal pleura and chest wall in the region of lung biopsy were heavily infiltrated by lymphoma cells (Fig 2, top right, B and bottom left, C). Immunohistochemical studies confirmed the diagnosis with the lymphoma cells staining positively for CD20 (L26, pan B marker) and CD43 (Leu 22, pan B marker), and negative for CD3 (pan T marker). The postoperative course was uneventful. The patient was discharged 6 days after surgery. The patient was closely followed up for 2 years with minor deterioration of his symptoms until September 2000, when chemotherapy was initiated in Ann Arbor, MI. He received cyclophosphamide, vincristine, and prednisone, and reported improvement in his symptoms as well as a reduction of his PHGs by 50% of their original size.

**DISCUSSION**

PHG is a rare entity that is considered to be a benign process. It is usually diagnosed in the workup of a single or multiple nodules on chest radiography. There are only 61 reported cases in the English-language literature. Clinically, the majority of patients presented with symptoms including cough, dyspnea, and pleuritic pain. The remaining patients were asymptomatic and in whom the lesions were seen on routine health-screening examinations. Our patient was slightly older than the average age of 42 years.
The sex distribution is approximately equal with no racial predominance.

The primary diagnosis of PHG cannot be made solely from the radiologic features. The chest radiographs show either single, or more often multiple, unilateral or bilateral nodules ranging from 0.2 to 15 cm in size with an average size of 2.0 cm. As seen on CT in our patient, they are randomly distributed in one or both lungs with no specific predilection. The nodules characteristically show spiculated, ill-defined borders with or without calcification or necrosis within them, and with slow interval growth in many cases. The doubling time was reported as 1 year in one case. It has been suggested that when the nodules are located near the hilum or mediastinum, fibrosing mediastinitis may be prone to develop. This is the most common complication that developed in patients with PHG. The nodule in the left lower lobe in our patient showed more irregular infiltrative changes around it with associated pleural effusion and thickening. These were histologically proved to be due to lymphomatous involvement. The radiologic differential diagnoses included primary or metastatic neoplasms, sarcoid and rheumatoid nodules, amyloidosis, Wegener’s granulomas, and granulomas from tuberculosis or fungal infections.

The histopathologic findings and pathologic differential diagnosis of PHG have been well described by many researchers. The lesions characteristically consist of central concentric or haphazard hyaline lamellae, and as peripheral rim of plasma cells and lymphocytic infiltrate with occasional lymphoid follicles. In early active lesions, the cellular components predominate, while the collagenous lamellar bands are more prominent in old chronic lesions. The increase of plasma cells, lymphocytes, and other inflammatory cells corresponds with the spiculated, ill-defined border and progressive growth of the nodules seen on chest radiograph and CT. The stimulus triggering these progressive changes is unknown, and the pathogenesis of PHG has not been well understood as well. Since sclerosing mediastinitis, retroperitoneal fibrosis, rheumatoid arthritis, uveitis, and ocular papillitis have been frequently associated with PHG, it has been hypothesized that all of these conditions may present essentially the same reactive response of an immunologic mechanism triggered by histoplasma organisms, tuberculosis bacilli, or other infectious agents. Neoplastic disease associated with PHG has rarely been reported. These include abdominal lymphoma, multiple myeloma, Paget’s disease of the breast, and astrocytoma of the brain. The case with lymphoma was that of a female patient who presented with abdominal mass and multiple pulmonary nodules. A stage IV diffuse lymphocytic lymphoma was diagnosed with a laparotomy, and the lung nodules were presumed to be metastasis without biopsy. Nine years later, the patient developed proven plasmacytoma of the rib and abnormal bone marrow with 25% plasma cells and many atypical forms and areas of marrow replacement by plasma cells in sheets. She died 2 years later, and the postmortem studies showed multiple PHG, amyloid deposits in multiple organs, but no evidence of lymphoma in the lungs or elsewhere. It was concluded that the occurrence of two different small cell neoplasms and PHG may be a coincidence, but raised the possibility of transformation from one B-cell neoplasm to another. The low-grade lymphocytic lymphoma in our patient may be a coincidental occurrence with PHG. However, one can postulate that a transformation from lymphocytes or lymphoid follicles around the nodule to lymphocytic lymphoma is possible on the basis of the histopathologic changes. Further investigation and future reports of similar cases are desirable to support our proposal. As seen in our patient, associated findings such as pleural changes, infiltrates around the nodule, or hilar or mediastinal
adenopathy may be the signs suggesting a developing malignant disease, specifically small cell type neoplasm, and more careful evaluation may be warranted in the patients with proven PHG. Close follow-up, biopsy, and careful cytology of the aspirated pleural effusion should be considered in these instances.

REFERENCES


Donor-Acquired Small Cell Lung Cancer Following Pulmonary Transplantation*

Anthony G. De Soyza, MRCP; John H. Dark, FRCP; Dinah V. Parums, FRCPath; Ann Curtis, PhD; and Paul A. Corris, MRCP

We describe a case of donor-acquired small cell lung cancer after pulmonary transplantation for cystic fibrosis. The recipient was an ex-smoker with a 10-pack-year history who had abstained for 20 years prior to suffering a catastrophic subarachnoid hemorrhage. The recipient’s posttransplant progress was straightforward, although a Pseudomonas empyema required drainage and IV antibiotics. Immunosuppression was conventional, with cyclosporine, azathioprine, and steroids following a 3-day course of induction antithymocyte globulin, as is routine at our center. Results of a CT scan of his chest performed at 4 months in order to investigate retrosternal pain were unremarkable. Surveillance bronchoscopy and transbronchial biopsy were carried out at 1 week, 3 months, 6 months, and 9 months. There was never any evidence of rejection on these biopsies (International Society for Heart-Lung Transplantation grade A1 or less), and no other endobronchial or histologic abnormalities were seen.

The patient presented 13 months after transplant with severe back pain after no obvious injury. Physical examination revealed local tenderness over the lumbosacral spine and right sacroiliac joint but no evidence of lymphadenopathy. Neurologic examination findings of the lower limbs were normal, as was sphincter control.

Investigations

Routine biochemistry revealed hyponatremia of 130 mmol/L, with a grossly elevated alkaline phosphatase (1,212 IU/L; normal range, 5 to 115 IU/L). Bilirubin and alanine transaminase levels were normal. Total and ionized calcium levels were raised. Results of thyroid function tests and prostate specific antigen were normal. C-reactive protein was elevated at 304 mg/L (normal range, 0 to 4 mg/L). Serum immunoelectrophoresis detected no paraproteins, and no Bence-Jones proteins were detected in the urine. The whole-blood cyclosporine level on hospital admission was 232 ng/mL.

Plain radiography confirmed a sclerotic lesion of the right scapula and also of the right sacral alae. Radiosotope bone scanning revealed numerous “hot spots” consistent with metastatic disease. CT of the abdomen revealed intraperitoneal masses, and a CT-guided liver biopsy was performed. Histology revealed metastatic small cell carcinoma.

Progress

The patient was fully informed of his diagnosis. His cyclosporine dose was reduced to attain a level of 100 to 150 ng/mL. Demebulcycline was used to control hyponatremia. Rescue analgesia was commenced IV with ketamine and morphine and converted to oral when satisfactory analgesia was obtained. A

genetic techniques revealed that the primary tumor and metastases were different to recipient tissues, confirming the donor origin.

(CHEST 2001; 120:1030–1031)

Key words: bronchial neoplasm; lung transplantation; postoperative complications

We describe a case of donor-acquired small cell lung cancer after pulmonary transplantation for cystic fibrosis. Donor-acquired small cell lung carcinoma has never been described as a consequence of pulmonary transplantation, reflecting the careful examination and selection of potential donor tissue, prior to grafting, by transplant surgeons.

CASE REPORT

A 25-year-old man underwent bilateral lung transplantation for end-stage cystic fibrosis. His donor was a 50-year-old man, an ex-smoker with a 10-pack-year history who had abstained for 20 years prior to suffering a catastrophic subarachnoid hemorrhage. The recipient’s posttransplant progress was straightforward, although a Pseudomonas empyema required drainage and IV antibiotics. Immunosuppression was conventional, with cyclosporine, azathioprine, and steroids following a 3-day course of induction antithymocyte globulin, as is routine at our center. Results of a CT scan of his chest performed at 4 months in order to investigate retrosternal pain were unremarkable. Surveillance bronchoscopy and transbronchial biopsy were carried out at 1 week, 3 months, 6 months, and 9 months. There was never any evidence of rejection on these biopsies (International Society for Heart-Lung Transplantation grade A1 or less), and no other endobronchial or histologic abnormalities were seen.

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