Lung Squamous Cell Carcinoma in Pulmonary Alveolar Proteinosis

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Pulmonary alveolar proteinosis (PAP) is a rare pulmonary disease characterized by alveolar accumulation of surfactant. There are only four sporadic PAP case reports associated with lung cancers. These case reports describe only that lung cancer might develop subsequently or coincidently with PAP. Here, we report a case of PAP associated with lung squamous cell carcinoma. This patient with PAP was a 57-year-old man, who had smoked one and a half pack of cigarettes per day for 30 years. In this case, PAP increased with lung cancer developing and disappeared after lung cancer resection. PAP may be the result of the lung squamous cell carcinoma developing in this case.

Keywords: pulmonary alveolar proteinosis, radiology diagnosis, lung cancer

Introduction

Pulmonary alveolar proteinosis (PAP) is a rare pulmonary disease characterized by alveolar accumulation of surfactant. There are only a few published case reports of PAP occurring in association with solid cancers.1–3) We herein, report a case of PAP associated with lung squamous cell carcinoma.

Case Report

In February 2009, a 57-year-old man presented with a cough and white sputum for 6 months. Physical examination was generally normal. There was no clubbing or cyanosis. This patient had smoked one and a half pack of cigarettes per day for 30 years. His past history and family history were not special. Laboratory examinations showed that lactate dehydrogenase (LDH) level was 158 U/L. Oxygen saturation was normal. Tuberculin purified protein derivative (PPD) and acid-fast Bacilli (AFB) smear were negative. HIV serology was negative. Auto-antibody and vasculitis screens were not significant. Viral nasopharyngeal swab and sputum culture for bacteria, fungi, and mycobacteria were all negative. Pulmonary function test revealed normal lung volumes and diffusing capacity. Serum carcinoembryonic antigen (CEA) was 4 ng/l (reference range 0–6 ng/l). The granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibody was negative.

Chest computed tomography (CT) revealed a bilateral symmetrical, diffuse ground-glass density with a patchy, geographic pattern, mainly in the lower lung fields (Fig. 1A). This patient then underwent diagnostic bronchoalveolar lavage (BAL), and the retrieved BAL fluid (BALF) was mildly opalescent, viscous, and grossly milk-like. Histology and cytology were reported to show no evidence of AFB, atypia or malignancy. Periodic acid-Schiff (PAS) stain was positive after BALF was centrifuged. Ultrastructural analysis of BALF showed numerous lamellar bodies (Fig. 2A). As a result, this patient was diagnosed with PAP.

The patient was followed-up during the period after diagnosis, and underwent a CT scan in March 2011.
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because of increased cough for 1 month. Chest CT scan showed ground-glass opacities (GGO) and crazy-paving appearance increased more obviously than before. There was a 22-mm nodule in the basal segment of the right lower lobe (Fig. 1B), which was not observed in the previous CT scan. Physical examination was generally normal. Serum CEA was detected high this time (25.3 ng/l). Bronchoscopy was performed on the basal segment of the right lower lobe, on which bronchial mucosal erosion and purulent secretions on the surface could be detected. Squamous cell carcinoma in the right lower lobe was diagnosed by bronchoscopic biopsy and the preoperative stage was cT1N0M0-IA based on TNM staging (version 7). He stopped smoking 2 weeks before operation. Subsequently, the patient underwent right lower lobe lobectomy and mediastinal lymph nodes dissection in April 2011. The postoperative stage was pT1N0M0-IA and the postoperative pathology was well-differentiated squamous cell carcinoma (Fig. 2B). Pericarcinomatous tissue showed alveolar filling by granular eosinophilic (Fig. 2C) and digested PAS-positive material typical of PAP (Fig. 2D).

One month after surgery, this patient felt shortness of breath. A chest CT scan was performed again and it showed that GGO and crazy-paving appearance were bigger than earlier (Fig. 1C). Physical examination revealed unilateral coarse crackles concentrated in the right lung. This patient had no treatment but follow-up after surgery. However, his symptom gradually improved and coarse crackles in his right lung disappeared in the next 6 months after surgery. A plain CT scan was interpreted as showing almost minimal residual interstitial infiltrates in October 2011 (Fig. 1D). He performed CT scan which showed PAP did not recur in October 2012.

Discussion

PAP is a rare disease characterized by alveolar accumulation of surfactant composed of proteins and lipids due to defective surfactant clearance by alveolar macrophages. GM-CSF is a key cytokine in PAP development. Sakagami and his colleagues reported GM-CSF autoantibodies reproduce the pathologic manifestations of idiopathic pulmonary alveolar proteinosis in healthy macaques.4)

PAP is classically divided into three subgroups based on the etiology: congenital, acquired, and secondary.5) Congenital PAP is seen especially in children, and radio-clinical presentation depends on the mutated gene. Acquired (or autoimmune) PAP represents most PAP cases, which is caused by neutralizing antibodies against GM-CSF. Secondary PAP has been described in association with congenital disorders, immunodeficiency states, hematologic malignancies, myelodysplastic syndrome,
infection with Pneumocystis carinii, and inorganic dust exposure. Detection of anti-GM-CSF antibodies may be the best tools to identify the idiopathic form because the antibodies were not discovered in congenital and secondary forms. This case is best categorized as secondary PAP because of negative anti-GM-CSF antibodies.

There have been only four sporadic case reports associated with lung cancers, including two primary squamous cell carcinoma of the lung in males,\(^1,2\) and two primary adenocarcinoma cell carcinoma of the lung in females.\(^3\) These case reports described only that lung cancer might develop subsequently or coincidently with PAP, and its association could be a coincidence in view of the frequency of lung cancer. This case showed that lung cancer occurred in the basal segment of the right lower lobe, which is surrounded by accumulation of PAP, which increased as lung cancer developed and disappeared after lung cancer resection. Thus, lung cancer may be a crucial factor during PAP development in this patient. PAP in this case may be developed as a result of the initially unidentified lung squamous cell carcinoma.

The association of PAP and hematological disorders is well established, mostly, myelodysplastic syndromes and acute myeloid leukaemia. In hematological diseases, alveolar macrophages could be numerically or functionally unable to clear the surfactant.\(^6\) Hematological therapy, chemotherapy, and/or bone-marrow transplantation can cure PAP, particularly in cases of acute leukaemia. It was also reported that patients with primary lung cancer had an increase in the number of macrophages that were functionally incompetent.\(^7\) Sulkowska demonstrated the coexistence of PAP-like changes in the vicinity of non-small cell lung cancer.\(^8\) These morphological changes were partly attributed to the increase in desquamation and disintegration of type II pneumocytes, which were subjected to damage.\(^9\) In this case, PAP increased with lung cancer developing. This suggested that the existence of some chemical immune inhibitors secreted from the lung cancer cells causing a local inhibitory effect on macrophages, which probably induced PAP. The PAP got worse after the lung cancer was resected may be on account of these inhibitors increasingly released during
the operation. Spontaneous clinical resolution of PAP clearly occurred 6 months post lung cancer resection, which could explain this mechanism.

In conclusion, we have described a case of PAP associated with lung squamous cell carcinoma which may secrete some chemical immune inhibitors that induced PAP. PAP may be associated with the lung squamous cell carcinoma developing in this case.

Disclosure Statement

None declared.

References