

PULMONARY ALVEOLAR PROTEINOSIS WITH PERIPHERAL ADENOCARCINOM

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ABSTRACT. *Background:* Pulmonary alveolar proteinosis (PAP) is a rare interstitial lung disease classified into congenital form, autoimmune form and secondary form. Secondary PAP is caused by underlying conditions including solid malignancies. Few cases reported PAP associated with lung cancers. *Objective:* To show the clinical features of PAP with adenocarcinoma, tried to seek for possible mechanism to explain whole clinical course. *Methods:* Reported a case of PAP associated with lung adenocarcinoma, and also reviewed the relevant literature on PAP. *Results:* The patient suffered from intermittent cough, fever, shortness of breath, thoracalgia or hemoptysis. Blood gas analysis showed hypoxemia. Spirometric abnormality is mildly restrictive defect. High-resolution computed tomography (HRCT) showed patchy, ground-glass opacities with interlobular septal thickening called as “crazy-paving” pattern. Positron emission tomography/computed tomography (PET/CT) revealed a nodule with characteristics of lobulation and spiculation in the right lung apex section and diffuse consolidation shadow spreading over rest of lung field. Bronchoalveolar lavage fluid (BALF) showed a large amount of amorphous red-dyed materials and a few alveolar macrophages scattered in endoalveolar space with PAS positive. Trans-bronchial lung biopsy found adenocarcinoma. Wedge resection with mediastinal lymphnode and then 2 cycles of postoperative chemotherapy was carried out. No ground-glass opacities were found in his chest CT pictures in the next nine months. This result may support the theory that lung cancer cells cause quantitative or functional damage to alveolar macrophages, which trend to secondary PAP. *Conclusions:* The patient had typical clinical features of PAP. PAP may be secondary to lung cancer. (*Sarcoidosis Vasc Diffuse Lung Dis* 2018; 35: 390-394)

KEY WORDS: pulmonary alveolar proteinosis, peripheral adenocarcinoma, lung cancer

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare interstitial lung disease, first described by Rosen et al in 1958 (1). Though without enough epidemiologi-

cal data to support the viewpoint yet, it seems that the incidence of PAP is increasing from 3.7 cases per million to 6.2 cases per million (2). Congenital PAP is caused by mutations in genes coding for surfactant protein and the GM-CSF receptor, while acquired type is caused by underlying conditions that reduce the number of or functionally impair alveolar macrophages. PAP is a progressive lung disease with varying degree of dyspnea, cough, fever, chest pain, hemoptysis, or even in absence of any symptoms. Bronchoalveolar lavage fluid (BALF) has an opaque, milky appearance and the most remarkable feature is enlarged foamy alveolar macrophages engorged with periodicacid-Schiff-positive (PAS+) intracel-

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lular inclusions. Typical performance of high-resolution computed tomography (HRCT) shows patchy, ground-glass opacities with interlobular septal thickening called as “crazy-paving” pattern. For all that, lung biopsy could always be the gold standard for diagnosis of PAP (2-4). Thus far, cases of PAP associated with primary lung cancer had been rarely reported and the relationship between these two diseases had not been clarified. Here we reported a case of PAP associated with lung adenocarcinoma. More importantly, PAP seemed to be healed after operative resection and chemotherapy for lung adenocarcinoma.

CASE REPORT

A 47-year-old male patient suffered from intermittent cough and fever for over 2 months, these symptoms aggravated for at last 20 days without sputum, shortness of breath, thoracalgia or hemoptysis. Initially, computed tomography (CT) scan of his chest showed a mass lesion in right upper lobe of his lung and partial of right pleural thickening, with diffuse consolidation and ground-glass opacity in bilateral pulmones (Figure 1). The doctors considered about interstitial pneumonia owing to infec-

tion. While after several days of antibiotic therapy (including sulbenicillin disodium and etimicin), his symptoms had not improved. So bronchoscopy was carried out. Atypical epithelial cells inclined to adenocarcinoma were found in transbronchial smear of cytology, while bronchial brushing and biopsy was negative. Unexpectedly the patient felt swollen of his neck just after bronchoscopy, so he underwent another CT at the same day. The CT scan showed bilateral pneumothorax and emphysema of mediastinum superius. Then he transferred to another hospital for symptomatic treatment 5 days later, positron emission tomography/computed tomography (PET/CT) revealed a nodule of about 2.7 cm of its long diameter with characteristics of lobulation and spiculation in the right lung apex section and diffuse consolidation shadow spreading over rest of lung field. The nodular lesion was deemed to be peripheral lung cancer, which average uptake value of (18)F-FDG was 4.3 and maximal uptake value was 5.7. Remaining consolidation was considered as diffuse lung cancer with mildly elevated uptake value of (18)F-FDG (Figure 2). Furthermore, lymph node metastasis of left hilar was likely to have arisen.

The patient came to our hospital for further diagnosis and therapy. After admission, the patient

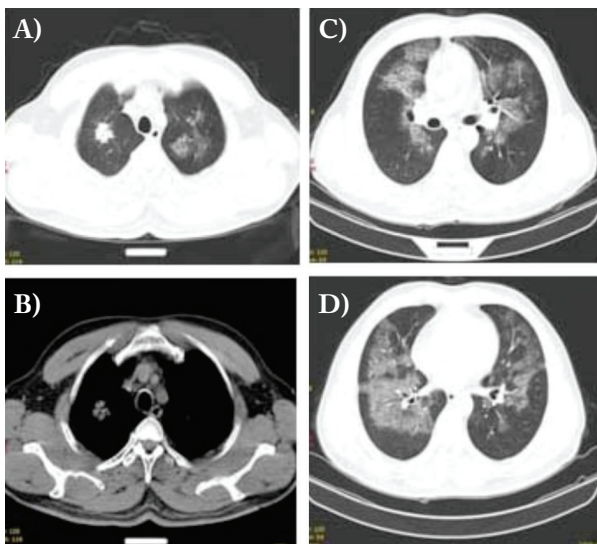


Fig. 1. Chest computerized tomography (CT) before any therapy. (A, B) CT slices showed a mass lesion in the upper lobe of right lung and partial of right pleural thickening. (C, D) CT slices showed diffuse ground-glass opacities with interlobular septal thickening called as “crazy-paving” pattern

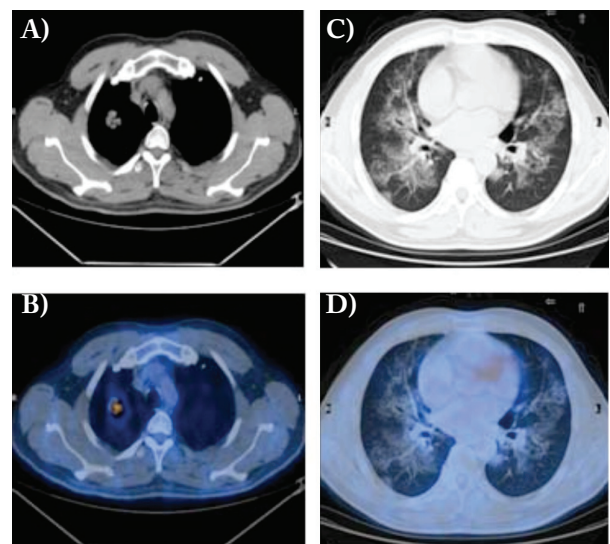


Fig. 2. PET/CT of pulmonary alveolar proteinosis complicating with lung adenocarcinoma. (A, B) A nodule showing an definite increase in glucose metabolism, with characteristics of lobulation and spiculation in the right lung apex section. (C, D) Diffuse consolidation shadow spreading over both of lungs, considered as diffuse lung cancer with mildly elevated uptake value of (18)F-FDG

never had a fever again and auscultation of lung was normal. His results of test for complete blood count, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), procalcitonin (PCT) and biochemical parameters (including lactate dehydrogenase, LDH) were normal. The patient's T cell subpopulations were normal and human immunodeficiency virus (HIV) antibody was negative. Serum tumor markers assay showed normal results as carcinoembryonic antigen (CEA): 3.4 ng/ml, section 19 of cytokeratin (CYR-FA21-1): 10.9 ng/ml, squamous cell carcinoma antigen (SCC): 0.8 ng/ml, and neuron specific enolase (NSE): 15.9 ng/ml. Blood gas analysis showed hypoxemia with partial pressure of oxygen (PaO_2) being 68 mmHg and peripheral blood saturation (SpO_2) being 93% on room air, while potential of hydrogen (PH) and partial pressure of carbon dioxide (PaCO_2) was normal. Spirometric abnormality is mildly restrictive defect manifested by decreased vital capacity (76.27% of predicted value) and mildly reduced diffusing capacity for carbon monoxide (73.28% of predicted value). Fiberoptic bronchoscopy was applied again for diagnosis. BALF showed a large amount of amorphous red-dyed materials and a few alveolar macrophages scattered in endoalveolar space with PAS positive (Figure 3). Transbronchial lung biopsy (TBLB) found great numbers of unstructured, red-dyed granules with PAS+ and adenocarcinoma with differentiated grade II with immunohistochemical analysis for ALK-D5F3(-), CEA(-), EGFR-E746(-), EGFR-L858(-), Ki-67(5%+), NapsinA(+), TTF-1(+), SPA(+), CD68(+) and CK(+) (Figure 4). Follow-up EGFR detection (ARMS used) showed mutations in exon 19 of the EGFR gene, while mutations were not detected in exon 18, 20 and 21.

We judged clinical stage IIB (cT1cN1M0) according to PET/CT, BALF and lung biopsy. Thoracic surgeons carried out wedge resection in VATS

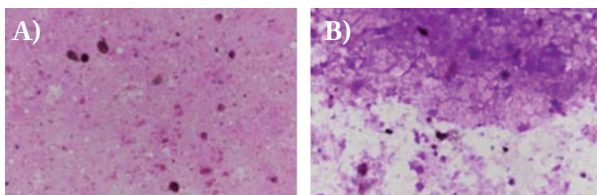


Fig. 3. BALF of right upper lung. (A) HE staining showed a large number of amorphous red-dyed materials, in which scattered in a small number of alveolar macrophages and inflammatory cells. (B) PAS staining showed PAS positive in cytoplasm of some alveolar cells

(video-assisted thoracoscopic surgery) with mediastinal lymphnode sampling (group 2,4). Pathological findings (in upper right lung) confirmed adenocarcinoma differentiated grade II~III, mainly presenting as acinar and solid type, rarely papillary type. Amorphous eosinophilic substance can be seen in the alveolar of pulmonary tissue around, which was consistent with PAP (Figure 5). In addition, bilateral lymph nodes of group 2 and 4 proved metastasis and carcinoma did not involve the visceral pleura. Then we revised as stage IIIIB (pT1cN3M0) and administered adjuvant chemotherapy (Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1, every 28 days for 4 cycles). Chest CT after 2 cycles of postoperative chemotherapy (Figure 6) showed no tumor recurrence and no patchy, ground-glass opacities. Chest CT of follow-up visits once every three months in local approved SD (stable disease). However ninth months after therapy, the patient felt pain on the left chest. CT showed multiple, subsolid nodules in both lungs and suspected metastasis in the left sixth rib

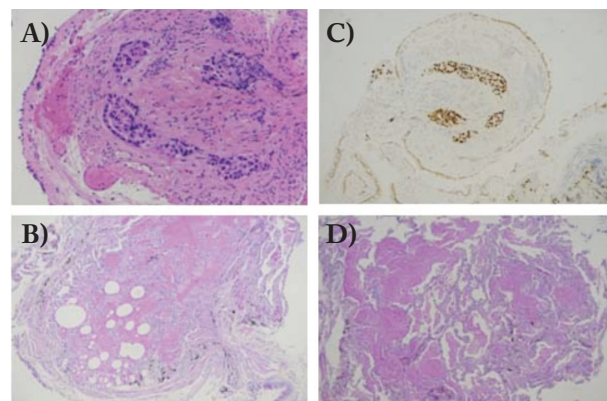


Fig. 4. Pathology of transbronchial lung biopsy. (A, B) A few cancer cells infiltrated in the right lung apex section. Immunohistochemistry showed TTF-1 (+). (C, D) Large amounts of amorphous red-dyed materials filled the alveolar space with PAS (+)

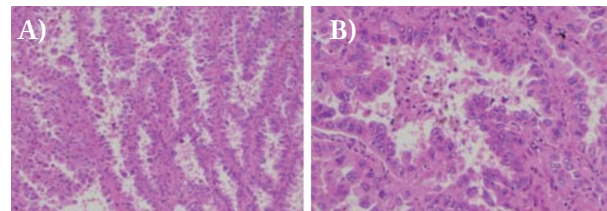


Fig. 5. The lesion of wedge resection in upper right lung. (A) Adenocarcinoma differentiated grade II~III, mainly presenting as acinar and solid type, rarely papillary type. (B) Little amorphous eosinophilic scattered over the alveolar space around

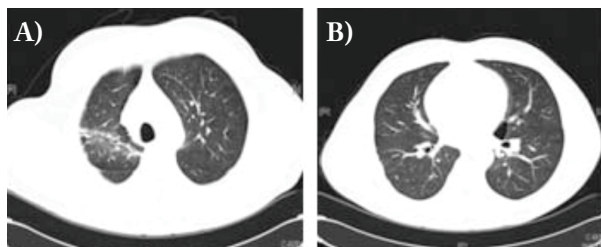


Fig. 6. Chest CT after 2 cycles of postoperative chemotherapy. (A) No tumor recurrence in right upper lobe of lung. (B) Diffuse consolidation and ground-glass opacity disappeared after therapy (wedge resection and 2 cycles of adjuvant chemotherapy)

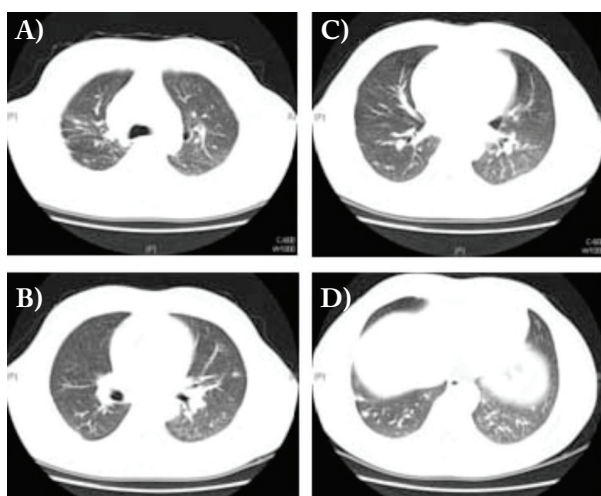


Fig. 7. Chest CT of ninth months after therapy. (A) A ground-glass nodule found in the superior segment of lower lobe. (B) A part-solid nodule found in the upper lobe of left lung. (C, D) Multiple subsolid nodules in lower lobe of both lungs

bone and T8 vertebral bone (Figure 7). SPECT/CT for whole body bone planar imaging showed multiple bone metastasis, considered the recurrence and metastasis of the adenocarcinoma. Then we reassessed as stage IVB (rT4N3M1c) and administered 2 cycles of primary chemotherapy (Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1, every 28 days for 4 cycles) up to now.

DISCUSSION

PAP is reported as a rare interstitial pulmonary disease all over the world. Reports revealed a prevalence of about 6.2 cases per million and a median age at diagnosis of PAP was 39 years old. And significant differences in gender with a male-to-female

ratio range of 2.1:1 to 2.7:1 and a later age of onset in the males (2). Even though there needs more epidemiological data still, it seems that PAP is a male-dominant disease and its prevalence trends to rise.

PAP is classified into congenital form, autoimmune form and secondary form, the latter two are also classified into acquired form. Congenital PAP is quite rare which caused by mutation in the SFTPB gene entailing a surfactant-protein- β deficiency, gene encoding for ABC transporter A3 and CSF2RB gene encoding GM-CSF receptor chain. Acquired forms are more common compared to congenital forms. Autoimmune PAP (primary or idiopathic PAP) constitutes more than 90% of all reported cases of PAP characterized by the presence of GM-CSF antibodies. Secondary PAP is caused by underlying conditions including hematologic or solid malignancies, inhalation of inorganic agents, chemotherapy treatment, opportunistic infections, and lysinuric protein intolerance that reduce the number of or functionally impair alveolar macrophages (2-3,5). We reported a case of PAP associated with adenocarcinoma which is seldom seen. Secondary PAP seemed to be established on the history of lung carcinoma. After resection and two cycles of chemotherapy, PAP seemed disappear. Earlier reports described PAP coexisted with primary lung cancer in some cases. Sulowska et al initially revealed the coexistence of PAP-like changes in the vicinity of non-small cell lung cancer (NSCLC) (6). Another three literatures reported respectively cases of extensively developed PAP associated with lung squamous carcinoma (7-9). Recently, Hiraki et al demonstrated the first case of PAP with small cell lung carcinoma (SCLC) (10).

Despite more research needed to illuminate specific and clear relationship between PAP and lung cancer, scientists have two kinds of possible theories. Friemann et al found that quartz-induced rats suffered alveolar proteinosis and a dose- and time-dependent increase of type II pneumocytes proliferation which increases risk of carcinogenesis in the process of frequent mitogenesis (5). Since our patient had no explicit history of dust exposure, this theory is hard to explain the clinical course. An alternative explanation supports that lung cancer cells exert a local inhibitory effect on macrophages through secretion of a chemical immune inhibitor, which trend to acquire PAP due to quantitatively or functionally impairing alveolar macrophages (6).

Dyspnea is the most common symptom of the patients with PAP. Cough isolated or in combination with white and gummy sputum production, fever and hemoptysis, more or less, are likely to occur in the whole course. There may be inspiratory crackles, clubbing, or cyanosis in physical examination. Approximately 10-30% of patients are asymptomatic at a certain time, while others may suffer with respiratory failure. The most common spirometric abnormality is restrictive defect, manifested by decreased vital capacity and lung volume, with or without a disproportionately reduced diffusing capacity for carbon monoxide. The characteristic performance helpful to diagnosis includes: on the one hand, BALF appears milky or opaque contains and contains phospholipids and surfactant proteins A, B, and D, and has relatively lower concentrations of phosphatidylcholine and phosphatidylglycerol with PAS positive. On the other hand, high-resolution CT shows smooth inter-lobular and intra-lobular septal thickening superimposed on a background of ground-glass opacities, which produces so-called "the crazy-paving" appearance (2,4). Our patient suffered from intermittent cough and fever without sputum, shortness of breath, thoracalgia or hemoptysis. Blood gas analysis showed hypoxemia. Spirometric abnormality is mildly restrictive defect manifested by decreased vital capacity and mildly reduced diffusing capacity for carbon monoxide. Chest CT shows "the crazy-paving". BALF showed a large amount of amorphous red-dyed materials and a few alveolar macrophages scattered in endoalveolar space with PAS positive.

Whole lung lavage is still the most widely accepted and effective therapy for PAP so far. For severe cases suffering from dyspnea, severe hypoxemia and hypercapnia, lung lavage is the only plausible treatment. Through the routine use of general anesthesia (GA), alternative options including larger lavage volume, lobar lavage, positional clearance and chest percussion can be performed. As for autoimmune pulmonary alveolar proteinosis (primary or idiopathic PAP), the GM-CSF substitution, biological treatment with monoclonal antibodies, plasmapheresis and hyperbaric oxygen therapy is deemed to an alternate to whole lung lavage. Anyhow the ultimate treatment for PAP is lung transplantation (2-3,11). Our patient accepted wedge resection in VATS

with mediastinal lymphnode sampling and adjuvant chemotherapy. We haven't administered any other therapy for PAP, while CT of the patient showed no tumor recurrence and patchy, no ground-glass opacities in the next nine months. The result may support above-mentioned theory that lung cancer cells cause quantitative or functional damage to alveolar macrophages, which trend to secondary PAP.

In conclusion, we reported a case of PAP with lung adenocarcinoma. Our discovery is still consistent with the earlier study and indicates PAP could occur associated with diverse of histopathology of lung cancer. Because it's not yet explicit that whether a causal relationship exists between PAP and lung cancer or whether they just are two independent diseases occurring by coincidence, more research needed to illuminate specific and clear relationship between PAP and lung cancer. We shouldn't emphasize the diagnosis of one and ignore another disease.

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