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Mismatch between gallium-67 uptake and CT findings in a case of pulmonary alveolar proteinosis

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Gallium-67 citrate (^{67}Ga) scintigraphy has been used as an indicator of activity of diffuse interstitial lung diseases. However, little has been mentioned in pulmonary alveolar proteinosis (PAP). Here we present a 53-year-old man with PAP showing patchy ^{67}Ga uptake by single photon emission computed tomography (SPECT). Interestingly, the strong ^{67}Ga uptake was observed in areas where ground-glass opacities were faint on chest CT. The uptake persisted after whole-lung lavage while the ground-glass opacity improved markedly. Although the precise mechanism of ^{67}Ga uptake remains unclear, ^{67}Ga SPECT findings may reflect the different pathological condition of PAP than that shown by CT.

Key words: pulmonary alveolar proteinosis, gallium-67 citrate, SPECT

INTRODUCTION

PULMONARY ALVEOLAR PROTEINOSIS (PAP) is an uncommon disorder characterized by the accumulation of lipoproteinaceous materials within alveoli.[1–3] Although the chest radiographic features, especially high-resolution CT (HRCT) findings, of PAP are well characterized,[4] the findings of Gallium-67 citrate (^{67}Ga) scintigraphy have been reported in only a single case.[5] We report a case of PAP showing abnormal pulmonary uptake by ^{67}Ga single photon emission computed tomography (SPECT) before and after whole-lung lavage and discuss the significance of this observation.

CASE REPORT

A 53-year-old man consulted our hospital due to cough and progressive shortness of breath for 6 months. Chest auscultation on admission revealed coarse crackles in the lower lung field bilaterally. Arterial blood gas analysis revealed a pH of 7.44, $PaCO_2$ of 39.0 mmHg, and PaO_2 of 55.6 mmHg on room air. A chest radiograph showed diffuse alveolar infiltrates, predominantly in the lower lobes. A pulmonary function test demonstrated that total lung capacity (TLC) was 50.5%, and the diffusing capacity of the lung for carbon monoxide (DL_{CO}) was 16.7%, as predicted. HRCT showed diffuse ground-glass densities with thickened intralobular and interlobular septa (Fig. 1A and 1B, *left*). A patchy, strong ^{67}Ga accumulation was observed by SPECT examination (Fig. 1A and 1B, *right*). Comparison between SPECT and HRCT revealed that the areas of ^{67}Ga accumulation corresponded to the area where the opacities on HRCT were faint (Fig. 1A and 1B, *center*). The diagnosis of PAP was made after a lung biopsy from left S8 segment obtained by video-assisted thoracoscopic surgery.

The patient's respiratory status improved after a therapeutic whole-lung lavage was conducted in the operating room under general anesthesia. One week after the lavage, arterial blood gas analysis showed a pH of 7.39, a pCO_2 of 45.2 mmHg, and a pO_2 of 71.7 mmHg on room air. TLC and DL_{CO} were improved 66.6% and 31.8%, as predicted, respectively. Although lung was almost completely clear on HRCT, ^{67}Ga mild uptake persisted (Fig. 2A and 2B).

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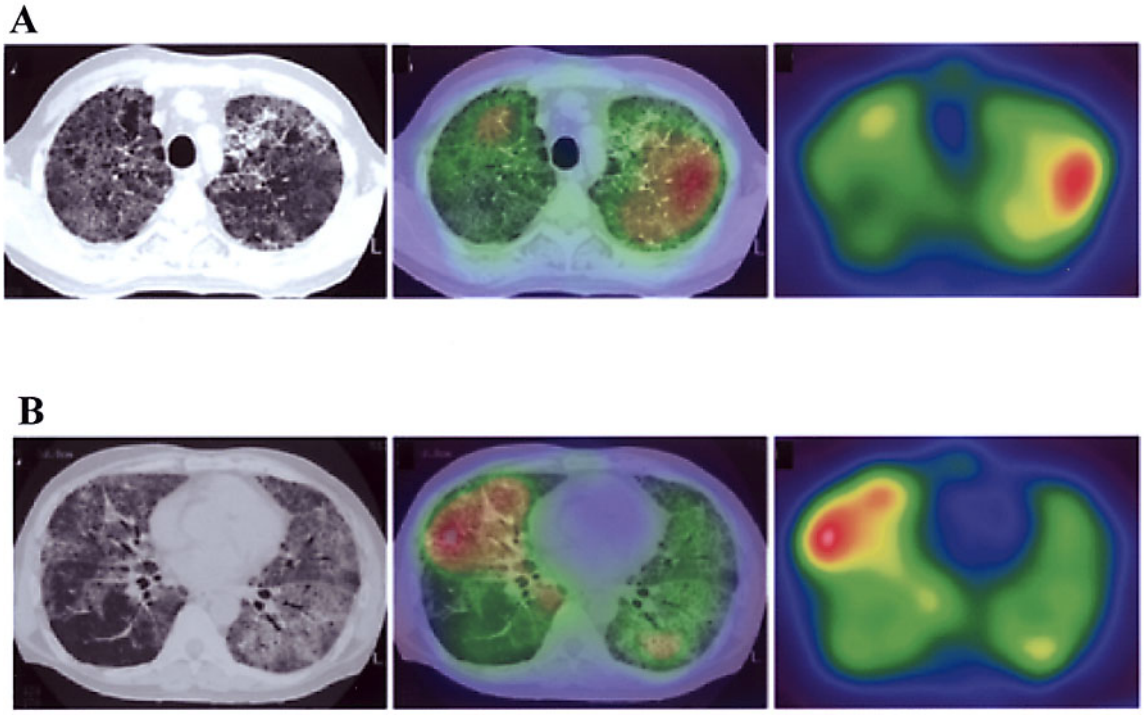

Fig. 1 HRCT scan (*left panels*), ^{67}Ga-SPECT (*right panels*), and their superimposed images (*center panels*) on admission in both upper (A) and lower (B) lung fields. HRCT shows a geographic distribution of ground-glass opacities with thickened interlobular septa, so called "crazy paving." The accumulation of ^{67}Ga is strong in red, yellow, and green order.

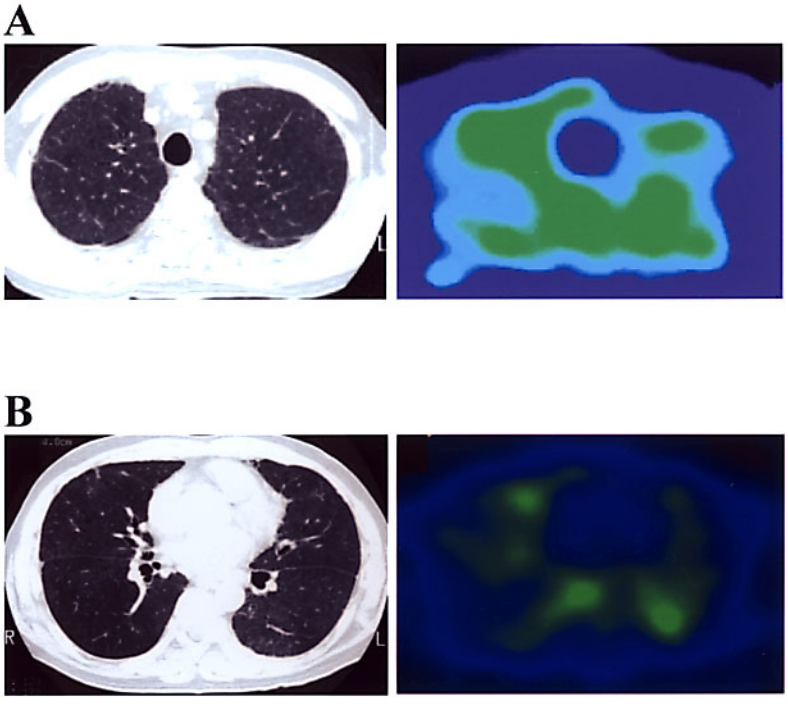

Fig. 2 HRCT scan (*left panels*) and ^{67}Ga-SPECT (*right panels*) in both upper (A) and lower (B) lung fields 1-month after whole-lung lavage. HRCT shows almost complete disappearance of ground-glass opacities whereas mild ^{67}Ga uptake is persisted.

DISCUSSION

PAP is a rare disorder and its clinical course is variable, ranging from respiratory failure to spontaneous resolution. Although lung biopsy is the gold standard for its diagnosis, it has recently been found that a diagnosis of PAP can be established in approximately 75% of clinically suspected cases by the finding of a "milky" effluent from bronchoalveolar lavage (BAL).[1,2] In the present case, however, lung biopsy was performed under video-assisted thoracoscopic surgery because of the difficulty of diagnosis by BAL and transbronchial lung biopsy. A lung specimen obtained from the left S8 segment showed proteinaceous material accumulating in alveolar spaces and intralobular septa this being a characteristic pathological finding of PAP.

Typical HRCT appearances of PAP include a geographic distribution of ground-glass opacity, and smooth thickening of interlobular septa.[4] The combination of these features results in a "crazy-paving" pattern. Ground-glass opacity reflects the filling of the phospholipid/proteinaceous materials within the alveoli. Septal thickening reflects septal edema and interstitial accumulation of the proteinaceous material. In the present case, consistently, the left S8 segment, where the characteristic pathological findings of PAP were observed by lung biopsy, showed typical crazy-paving (Fig. 1B).

Comparison between SPECT and HRCT findings indicates their mismatch. The distribution of ^{67}Ga uptake in SPECT was recognized in the area where crazy-paving was weak on HRCT. Moreover, ^{67}Ga uptake persisted even when the opacity on HRCT had improved.

Pulmonary accumulation of ^{67}Ga can be seen in a wide variety of diffuse pulmonary diseases, including pulmonary fibrosis and pulmonary infections, particularly *Pneumocystis carinii* infection.[6] Complications from these diseases must be excluded, because interstitial fibrosis and infection are frequently combined with PAP. However, the lung biopsy specimen revealed no interstitial fibrosis, distortion of alveolar architecture, or granulomas. Staining of microorganisms was negative. Microorganisms were also negative in cultures from therapeutic lavage fluid.

The mechanism of ^{67}Ga uptake in the lung is not fully understood. However, it has been hypothesized that ^{67}Ga citrate initially combines with transferrin in the blood, after which the complex is incorporated into the cells through transferrin receptors (TFRs). TFRs are expressed on the surface of alveolar macrophages in patients with interstitial lung disease such as idiopathic pulmonary fibrosis, pneumoconiosis, or sarcoidosis.[7] In a rat model of *Pneumocystis carinii* pneumonia, Stokes et al. demonstrated that ^{67}Ga uptake may reflect increased alveolar permeability and surfactant abnormalities.[8]

An important clue to the pathogenesis of PAP has come from the analysis of mice lacking granulocyte-macrophage colony-stimulating factor (GM-CSF); this lack causes an accumulation of lipoproteinaceous materials and foamy macrophages in the alveoli.[9] Analysis of mice lacking the βc chain of the GM-CSF receptor further revealed that alveolar macrophages but not type II alveolar epithelial cells are the principal target of GM-CSF in maintaining lung homeostasis.[10] It is therefore likely that some of the macrophage functions are damaged in patients with PAP. Although the precise mechanisms of abnormal ^{67}Ga uptake in PAP remain unclear, alveolar macrophages may be severely damaged in areas demonstrating the typical pathological changes of PAP, i.e., where crazy-paving is seen on HRCT. On the other hand, alveolar macrophages may be activated to uptake ^{67}Ga where the opacities are faint on HRCT. Unfortunately, however, regional analysis of lavage cells for the area of ^{67}Ga-uptake could not be performed in this case because the lung was not selectively lavaged.

Here we report a case of PAP showing abnormal pulmonary uptake by ^{67}Ga SPECT. Further study is required to determine whether the abnormal ^{67}Ga uptake observed in the present case is generally seen in patients with PAP. Although BAL and/or transbronchial lung biopsy are needed for the diagnosis of PAP, the unusual ^{67}Ga uptake observed in the present case might aid in the diagnosis of future case.

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