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【 CASE REPORT 】

Occupational Lung Disease Caused by Exposure to Polytetrafluoroethylene

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Abstract:
We herein report a 45-year-old-man with multiple foreign body granulomas in the lungs caused by polytetrafluoroethylene (PTFE). A mass in the right lower lobe of the lung and bilateral centrilobular lung nodules were found unexpectedly during the patient's visit to a hospital for a respiratory infection. The patient's occupation for 26 years involved spraying PTFE. A lung biopsy using bronchoscopy revealed granulomatous lesions and giant cells. The presence of fluorine in the granulomatous lesions was confirmed using an electron probe microanalyzer with wavelength dispersive spectrometer. Fluorine is a component of PTFE and is not found in normal lung tissue.

Key words: polytetrafluoroethylene, granuloma, electron probe microanalyzer with wavelength dispersive spectrometer

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Introduction

Interpreting computed tomography (CT) imaging patterns and findings is critical for diagnosing diffuse lung diseases. Centrilobular nodules are found in a wide variety of lung pathologies, including bronchiolitis, infectious pneumonia, aspiration pneumonia, hypersensitivity pneumonia, interstitial pneumonia, pneumoconiosis, and granulomas with foreign bodies in the lung.

Granulomas are a focal collection of inflammatory cells, including activated macrophages and epithelioid cells. Granulomas in the lung can be caused by mycobacterial or fungal infections, sarcoidosis, granulomatosis with angiitis, and exposure to a variety of antigens, such as fungi, mycobacteria, animal/plant proteins, and hard metals. It is often difficult to identify the causative agent of foreign bodies. In our previous study, we used an electron probe microanalyzer with wavelength dispersive spectrometer (EPMA-WDS) to analyze the inhaled particles in lung specimens with occupational and environmental lung diseases (1). An EPMA-WDS is used to perform non-destructive chemical composition analyses of human lung tissue in order to identify deposits of elements by both qualitative and semi-quantitative methods (2).

We herein report a rare case involving multiple centrilobular nodules and a mass in the lung due to foreign body granulomas caused by prolonged exposure to polytetrafluoroethylene (PTFE).

Case Report

A 45-year-old Japanese man presented with a history of anorexia and productive cough for a duration of 2 months.

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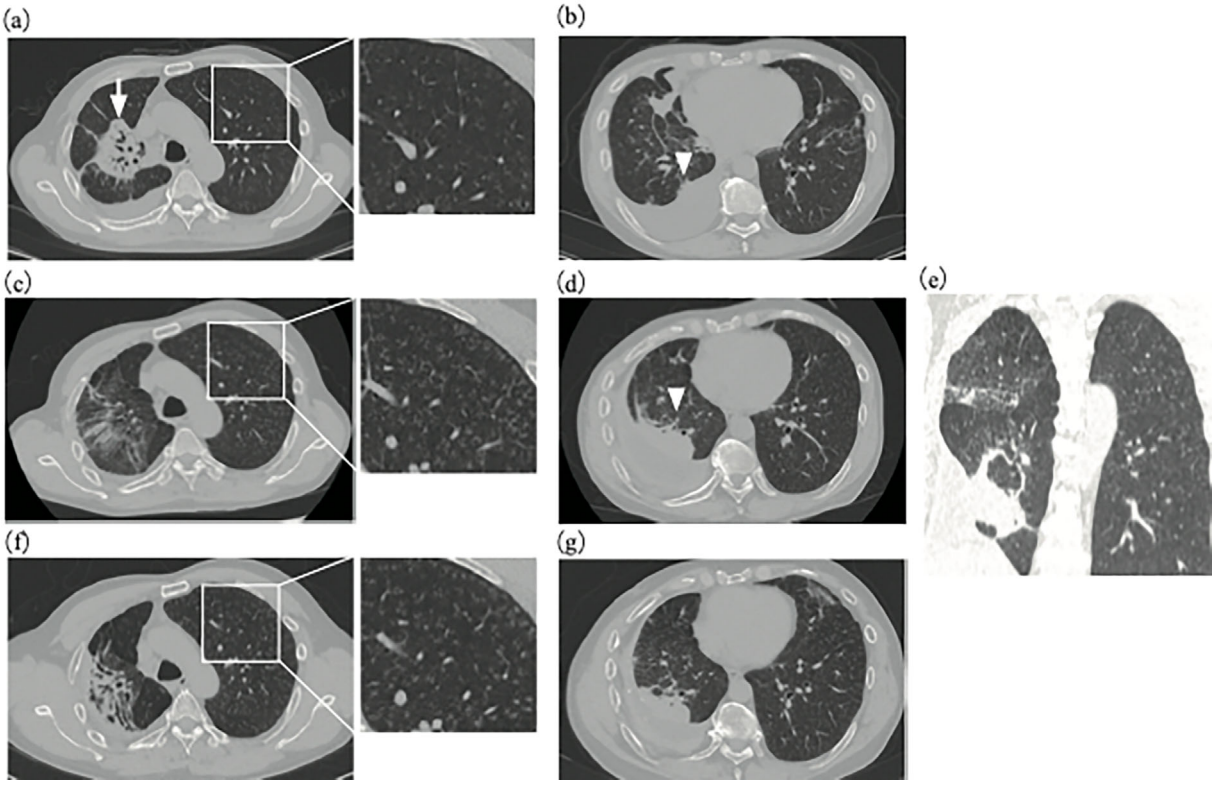

Figure 1. Computed tomography (CT) findings of the patient's lungs. Axial CT scans of the upper lobe (a, c, f) and the lower lobe (b, d, g). The insert shows higher-magnification views of the indicated squares. Coronal CT findings on admission (e). CT scans of the patient recovering from invasive pneumococcal disease two years before presentation. Organization of the right upper lobe (arrow), residual right pleural effusion, and a small lesion adjacent to the pleura (arrowhead) are observed. Multiple centrilobular nodules were not obvious in either lung but were present (a, b). CT on admission shows a mass in the right lower lobe (arrowhead), right pleural effusion, and bilateral centrilobular nodules (c, d). A round lesion with the comet tail sign adjacent to the pleura in the lower right lobe is observed. These features are typical of round atelectasis (e). Four years after admission, the CT scans had not changed (f, g).

The patient was a current smoker with a smoking history of 22 pack-years. His primary job for 26 years had been to spray PTFE onto pans, until 1 year ago. The patient had worked in a small factory that processed only PTFE. All procedures of PTFE, including spray coating at room temperature, drying at 200°C, and heating at 400°C, were performed near each other. There were ventilation duct systems in place, but the patient rarely wore face masks.

The patient had a history of invasive pneumococcal disease two years prior. After the resolution of the infection, the patient had developed secondary organizing pneumonia and had been treated with prednisolone for four months. However, mild pleural effusion persisted (Fig. 1a, b). In addition, the patient also had a history of idiopathic osteonecrosis two years ago, for which he had undergone right bipolar hip arthroplasty.

The patient first visited another hospital because of the prolonged anorexia and cough. His white blood cell count was 13,900/μL (reference range, 3,000-9,000), and C-reactive protein levels were 9.72 mg/dL (reference range, 0-0.3). CT of the chest showed a mass in the right lower lobe of the lung, right-sided pleural effusion, and bilateral centrilobular lung nodules. Antibacterial therapy improved his symptoms and blood inflammatory marker levels; however, the CT findings were unchanged. Therefore, he was referred to our hospital approximately one month after his first hospital visit.

CT on admission revealed a mass in the right lower lobe of the lung, right-sided pleural effusion, and bilateral centrilobular lung nodules (Fig. 1c, d). The patient had an oxygen saturation of 98% while breathing ambient air and body temperature of 36.5°C. On an examination, diminished lung sounds were noted on the right lateral side of the lung, with no crackles. The white blood cell count was normal at 7,440/μL, but the C-reactive protein level was still elevated at 2.68 mg/dL. Pleural fluid cultures showed the presence of *Propionibacterium*, and the pleural effusion met the criteria for an exudate; cytology showed no evidence of malignant cells. The results suggested that the patient had right chronic bacterial pleurisy, likely from secondary infection of the residual pleural fluid from the previous pneumococcal infection.

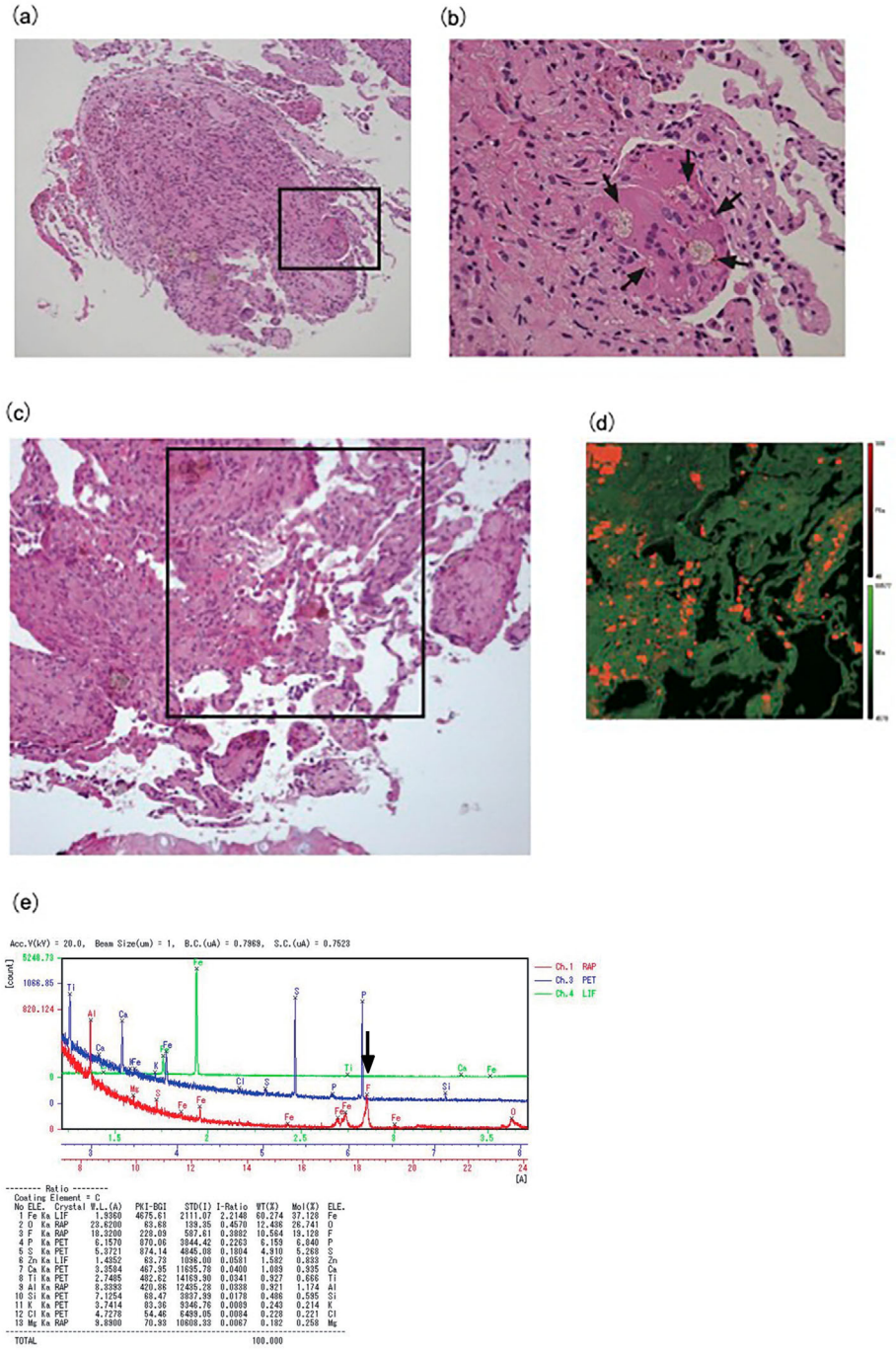

Figure 2. Histologic features of pulmonary granulomatous lesions obtained from the mass in the right lower lobe and an image of an electron probe microanalyzer with wavelength dispersive spectrometer (EPMA-WDS). Many granulomatous lesions are seen on Hematoxylin and Eosin (H&E) staining (×100 magnification) (a). The higher-magnification image shows multinucleated giant cells with amorphous transparent particles (arrow) (×400) (b). Granulomatous lung lesions with H&E staining (×100) (c). Element distribution of EPMA images. A qualitative colored image of fluorine distribution (colored red) is superimposed on the lung tissue image with amino nitrogen (colored green). The distribution of fluorine (F) is wide (d). A one-dimensional analysis yielded peaks of elements on the curves as detected with WDS crystals: rubidium-acid-phthalate (RAP, green), pentaerythritol (PET, blue), and lithium fluorine (LiF, red). The arrow shows the peak of F (e).

Pulmonary function tests showed the following results: a vital capacity (VC) of 2.59 L (67.8% of predicted value), a forced vital capacity (FVC) of 2.52 L (66.8% of predicted value), a forced expiratory volume in 1 second (FEV_1) of 1.80 L, FEV_1/FVC of 74.8%, $\%FEV_1$ of 58.0%, and a diffusing capacity for carbon monoxide per alveolar ventilation volume (DLco'/VA) of 64.6%. The results revealed restrictive ventilatory impairment and a decrease in diffusing ca-

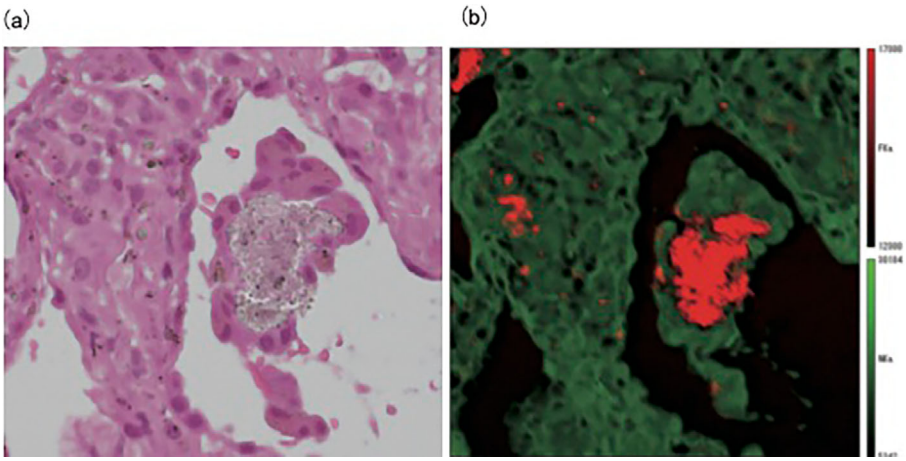

Figure 3. **EPMA-WDS image of a peripheral lung specimen presenting with airway-centered nodules. On Hematoxylin and Eosin staining, granulomatous lesions are observed with amorphous transparent particles (×400) (a). Two-dimensional EPMA image of element mapping, showing F distribution (colored red) in the lung tissue (b).**

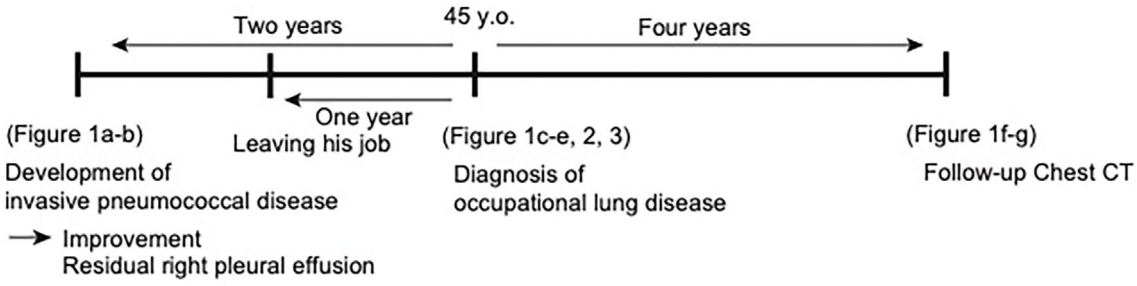

Figure 4. **The time course of this case.**

pacity. The mass was suspected to be malignancy or round atelectasis based on the CT findings (Fig. 1d). Coronal CT findings of the mass showed comet tail sign adjacent to the pleura, which suggested round atelectasis (Fig. 1e).

To examine the lung lesions, we performed bronchoalveolar lavage (BAL), a lung biopsy using endobronchial ultrasonography with a guide sheath (EBUS-GS) from the mass in the right lower lobe of the lung, and a transbronchial lung biopsy (TBLB) of the peripheral regions in left B8a and B9b. BAL fluid from left B5 contained 1.6×10^5 cells/mL with 89% macrophages, 9.5% lymphocytes, 1.0% neutrophils, and 0.5% eosinophils; foreign body material was identified in the macrophages. Regarding histology, both biopsies showed non-necrotizing granulomas with multinucleated giant cells and amorphous transparent material (Fig. 2a, b, 3a). No vasculitis was seen. No bacteria, mycobacteria, or fungi were identified on Gram, Ziehl-Neelsen, or Grocott staining. Next, to confirm the identity of the foreign body components, we performed an elemental analysis using an EPMA-WDS with the specimens obtained from the mass and peripheral lung region. Notably, an EPMA-WDS analysis revealed fluorine deposition in the granulomatous lesions from both biopsy specimens (Fig. 2c-e, 3a, b). Fluorine, which is a component of PTFE, is not found in normal lung tissue.

The multiple centrilobular nodules were notably more distinct than they has been in the CT images obtained two years earlier (Fig. 1a, c). The patient's exposure to PTFE had decreased after leaving his job one year earlier. The findings thus suggested that the granulomatous lesions were chronic, and it was concluded that long-term exposure to PTFE had caused pulmonary granulomatosis. The patient had already quit his work associated with PTFE. A follow-up examination was performed four years after the initial diagnosis of occupational lung disease, and the chest CT findings of the patient revealed no further changes (Fig. 1c, d, f, g). A timecourse of the main events is shown in Fig. 4.

Discussion

In this report, we presented a case of centrilobular granulomatous lesions associated with occupational exposure to PTFE. PTFE, known colloquially as Teflon™, is a synthetic fluoropolymer of tetrafluoroethylene. Strong fluorine-carbon bonding gives PTFE powerful resistance to high temperatures, high pressures, and most chemicals. Therefore, there are numerous applications for PTFE coating, including to pans and other cookware and in hair curling irons, hoses, and machine parts. Most reports of PTFE-related pulmonary

diseases thus far have featured noncardiogenic pulmonary edema due to inflammation of the airways and alveoli caused by inhalation of fumes generated during high-temperature heating of PTFE (3, 4). The toxicity of the fumes is due not to the gaseous phase but to the size of the aggregated pyrolytic products, as the median diameter of the ultrafine particles is reported to be approximately 18 nm (5). Polymer fume fever results from acute lung injury; in contrast, our case showed chronic manifestation of PTFE-induced injury in the form of foreign body granulomatous lesions.

In this case, we identified the causative agent using EPMA. Elements such as Al, Si, Ti, and Fe are naturally found in environmental dust; therefore, they are found in control subjects as well. Fluorine, however, is not a normal component found in the healthy lung tissue (1). As the distribution of fluorine was found widely in this case, we considered chronic exposure to PTFE to have caused the granulomatous lesions. Recent reports from Korea have described several cases of chronic granulomatous pulmonary lesions related to PTFE inhalation, similar to our case (6, 7). Lee et al. reported the size of PTFE particles (1-22 μm) from air sampling of the work environment, which corresponded to the PTFE particle size used in the spraying process (6). The size of the pyrolyzed particles during the coating process is smaller than PTFE particles during the spraying process; they therefore concluded that the lung lesions had been caused by the PTFE spraying procedure. In the present patient, the exposure opportunity was the inhalation of aerosolized PTFE particles during the spraying process.

CT images of this case showed a variety of findings, including a mass lesion suggestive of round atelectasis, which made the diagnosis difficult. The main finding of round atelectasis is marked pleural fibrosis with foci of thickened pleura invaginated into the subjacent lung parenchyma (8). Therefore, observation of the pleura is necessary for the pathological diagnosis of round atelectasis. In the present case, the alveolar region around the granuloma showed fibrous thickening of the alveolar wall, suggesting that atelectasis or the alveolar space may have been reduced. However, it was impossible to histologically prove that the mass lesion was a round atelectasis, since a biopsy using EBUS-GS cannot reach the pleura. Round atelectasis is known to result from any type of pleural inflammatory reaction with resultant fibrosis (8). In the present case, the right lung mass lesion gradually increased in size as the pleural effusion persisted due to an infection that had started two years earlier, and the lesions other than the mass lesion showed small granular shadows, similar to previous reports (6, 7). These observations suggest that the mass lesion in the right lung was not due to granulomatous inflammation alone. We therefore speculated that the mass lesion might be a mixture of round atelectasis and granulomas.

We found that chronic inhalation exposure to PTFE caused foreign body granulomatous lesions in the lung, which mainly presented as a mass and centrilobular distribution on CT imaging. It is important to inquire about occupational exposure and the history of inhalation when noting a centrilobular distribution pattern in the lungs.

The authors state that they have no Conflict of Interest (COI).

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