CASE REPORT

Pneumoconiosis Caused by Inhalation of Metallic Titanium Grindings

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Abstract:
A 61-year-old man was referred to our hospital with dyspnea and an abnormal lung shadow. His occupational history, pathological findings, and an elemental analysis led to a definitive diagnosis of pneumoconiosis induced by titanium grindings. The patient experienced gradual improvement solely by avoiding titanium grindings. Titanium-induced lung disease is very rare, and most of these cases are caused by inhalation of titanium dioxide (TiO₂), which is included in a wide range of commercially available products, such as paints, pigments, and cosmetics. However, industrial workers can also develop lung diseases due to the inhalation of metallic titanium materials during metal grinding.

Key words: pneumoconiosis, metallic titanium, titanium dioxide, elemental analysis, NSIP

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Introduction
Inhalation of metal dust and fumes can induce a wide variety of pulmonary diseases, including lung cancer, airway diseases, and pneumoconiosis (1-3). In cases of pneumoconiosis induced by metal inhalation, patients usually show yearly progression of disease, which results in pulmonary fibrosis. Various metals, including aluminum, iron, and hard metals, have been reported to cause pneumoconiosis (4-6); however, there are few reported cases of lung disease caused by titanium, with most such cases caused by titanium dioxide (TiO₂) or titanium dioxide nanoparticles (TNP) (2, 7-11). TiO₂ and TNP are usually included in paints, pigments, or cosmetics; however, titanium exposure can also occur in metal grinding. In general, titanium grindings are recognized as metal titanium and are distinguished from TiO₂ or TNP.

We herein present a case of subacute pneumoconiosis caused by the inhalation of metallic titanium grindings. The diagnosis was made based on a pathological examination and was confirmed by an elemental analysis. Lung infiltration gradually diminished without any medication after avoidance of titanium exposure.

Case Report
A 61-year-old man was referred to our hospital for the examination of an abnormal lung shadow. He had been engaged in the metalworking industry for 40 years. Four months prior to his admission, he had started a new task of cutting metal pipe and processing it into screws. Although the task involved heavy exposure to titanium grindings, he did not wear a dust protective mask during the work. Subsequently, he gradually developed a dry cough and dyspnea on exertion. One month prior to his admission, he went to a clinic because of these symptoms. Chest radiography showed consolidation on both sides of the upper lung fields. Despite treatment with antibiotics and diuretics, the lung consolidation gradually worsened. He was referred to our hospital for further investigation and treatment. His past medical history included chronic heart failure and paroxysmal atrial fibrillation. His medications included metildigoxin, candesartan cilexetil, carvedilol, and bepridil. He had a 20 pack/year smoking history but had stopped smoking for 20 years.

On examination, his vital signs were normal with a pe-
Peripheral oxygen saturation of 95%. Finger clubbing was observed and rhonchi were detected at the right middle lung field on auscultation. A laboratory analysis revealed elevated levels of Krebs von den Lungen-6 (KL-6; 1,910 U/mL) and surfactant protein D (SP-D; 340 ng/mL). A chest X-ray showed consolidation and reticular shadow on the right middle, right lower, left upper, and left lower lung fields. High-resolution CT (HRCT) showed ground-glass opacities with traction bronchiectasis, which was dominant in the upper lungs, where it showed a central distribution (Fig. 1). Bronchoalveolar lavage (BAL) indicated mild lymphocytosis with 33% lymphocytes and 66% macrophages. The ratio of CD4 to CD8 T lymphocytes in the BAL fluid was 0.61.

Video-assisted thoracoscopic biopsy (VATS) was performed to obtain specimens of the S1+2 and S6 lesions of the left lung for further investigation. Pathologically, mild infiltration of lymphocytes accompanied with alveolar collapse and fibrosis was observed with a centrilobular distribution, demonstrating a cellular to fibrotic nonspecific interstitial pneumonia (NSIP)-like pattern (Fig. 2). Giant cells were not detected. No obvious metal deposits were seen. Because of the distribution of the lesions, some type of inhalation was suspected as the etiology of the disease. An elemental analysis of the lung tissue was conducted by scanning electron microscopy, which indicated significant deposition of titanium in the lung (Fig. 3). Based on the results of the elemental analysis and the fact that the patient was involved in grinding titanium when the respiratory symptoms occurred, it was suspected that his pulmonary manifestation was caused by titanium exposure. We advised him to avoid exposure to titanium grindings. After the avoidance of titanium exposure, his symptoms and radiological abnormalities gradually diminished without any medication (Fig. 4).

**Discussion**

We presented a rare case of pneumoconiosis demonstrating an NSIP-like pattern induced by the inhalation of metallic titanium grindings. This case contains two interesting findings. First, metallic titanium grindings were identified as parallel.
Titanium is classified into metallic titanium and TiO₂. These products are refined from titanium ore (ilmenite and rutile) by different processes. Metallic titanium is used for various industrial applications, including applications in the aircraft industry, because of its low specific gravity. On the other hand, TiO₂ is used for wide range of commercially available products, such as paints, pigments, and cosmetics. Among TiO₂ materials, TNP has a minute particle size of <20 nm. More than 90% of the world’s titanium ore production is turned into TiO₂ or TNP, and approximately 5% is used for metallic titanium. Thus, most previous reports about lung toxicity have included cases caused by TiO₂ or TNP exposure. For example, Yamadori et al. reported a case of lung fibrosis and lung adenocarcinoma with TiO₂ deposition in the lung (2). In the case presentation, the patient had been engaged in TiO₂ packing for 13 years. Cheng et al. reported a case of bronchiolitis obliterans organizing pneumonia (BOOP) induced by exposure to TNP included in paints (7). Keller et al. also reported a case of titanium lung in a painter who developed pulmonary alveolar proteinosis (11). Titanium-induced lung diseases are rare and have tended to be reported in nonindustrial workers. Only one case of metallic titanium-associated lung disease has been reported. That report by Redline et al., described a case of granulomatous lung disease with titanium deposition due to daily exposure to various metallic fumes (12). In our case, which was caused by metallic titanium grindings, the pulmonary lesion did not demonstrate granulomas-instead we observed NSIP with peribronchial distribution. Thus, we should be aware that exposure to metallic titanium grindings in metal processing can also cause lung disease.

In the elemental analysis, deposition of aluminum and silicon was also observed. Based on the medical records provided by the patient, who was a reliable skilled worker, he was involved in grinding titanium. Thus, it can be stated that to some extent-titanium exposure directly or indirectly induced pneumoconiosis as the patient became subacutely symptomatic after he started performing metal titanium processing in the course of his daily work. It is also possible that aluminum and silicon had accumulated in the lung asymptomatically during metalworking processes that he was involved in before his work in titanium processing. It is un-

![Figure 3. Elemental analysis of the lung. In an elemental analysis by scanning electron microscopy (SEM), the X-rays provided by irradiation of an electron beam are counted along a red line in the specimen. As a result, significant deposition of titanium with aluminum, silicon, and oxygen was indicated.](image)

![Figure 4. The changes in the chest X-ray findings during the clinical course. (A) At the time of the diagnosis, bilateral consolidation, predominantly in the upper lung field, was indicated. (B) The consolidation gradually resolved after avoiding exposure to titanium for four years.](image)
clear whether titanium was the sole cause of pneumoconiosis or whether there was a synergistic effect between titanium and aluminum or silicon. Thus, there is a limitation in our ability to speculate on the etiology of this case.

Interestingly, the subacute progression of disease was seen in our case. This clinical course resembled that of the case reported by Cheng et al., in which the patient demonstrated BOOP after only 3 months of exposure to inhaled TNP in a paint factory (7). Other than these cases, a few cases of pulmonary silicosis and arc welder’s lung have been reported in which patients presented subacute progressive pneumoconiosis (13, 14). In general, however, pneumoconiosis has a chronic course, demonstrating centrilobular granular shadow and a slow progression of fibrosis. Pulmonary silicosis typically occurs after 10-20 years of work while the individuals usually remain asymptomatic (1). Moriyama et al. suggested that the exposure period of hard metal lung diseases was at least 2.5 years, and more than two-thirds of the patients in their study were exposed to hard metal for longer than 5 years (15). From this viewpoint, the clinical course of our case was quite different from a typical case of pneumoconiosis and may present an atypical etiology, such as metal fume fever or a hypersensitivity reaction. The size of the metal particles produced in the working process of metal grinding is between 4 μm and several 100 μm. Small amounts of fumes can also be produced. In this case, no obvious metal deposit was seen in the optical microscope analysis. Thus, we assume that small-sized particles and metal fumes are pathogenic.

In conclusion, we presented a case of pneumoconiosis induced by the inhalation of metallic titanium grindings. The clinical course showed subacute disease progression, indicating that the disease etiology was different from that of typical pneumoconiosis.

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

References

1. Cullinan P, Reid P. Pneumoconiosis. Prim Care Respir J 22: 249-252, 2013.
2. Yamadori I, Ohsumi S, Taguchi K. Titanium dioxide deposition and adenocarcinoma of the lung. Acta Pathol Jpn 36: 783-790, 1986.
3. Camus P, Nemery B. A novel cause for bronchiolitis obliterans organizing pneumonia: exposure to paint aerosols in textile workshops. Eur Respir J 11: 259-262, 1998.
4. Smolikova P, Nakladalova M. The etiology of occupational pulmonary aluminosis - the past and the present. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 158: 535-538, 2014.
5. Nemery B, Abraham JL. Hard metal lung disease: still hard to understand. Am J Respir Crit Care Med 176: 2-3, 2007.
6. Akira M. Uncommon pneumoconioses: CT and pathologic findings. Radiology 197: 403-409, 1995.
7. Cheng TH, Ko FC, Chang JL, et al. Bronchiolitis obliterans organizing pneumonia due to titanium nanoparticles in paint. Ann Thorac Surg 93: 666-669, 2012.
8. Warheit DB, Brock WJ, Lee KP, et al. Comparative pulmonary toxicity inhalation and instillation studies with different TiO1: particle formulations: impact of surface treatments on particle toxicity. Toxicol Sci 88: 514-524, 2005.
9. Park EJ, Yoon J, Choi K, et al. Induction of chronic inflammation in mice treated with titanium dioxide nanoparticles by intratracheal instillation. Toxicology 260: 37-46, 2009.
10. Lee KP, Trochimowicz HJ, Reinhardt CF. Pulmonary response of rats exposed to titanium dioxide (TiO2) by inhalation for two years. Toxicol Appl Pharmacol 79: 179-192, 1985.
11. Keller CA, Frost A, Cagle PT, et al. Pulmonary alveolar proteinosis in a painter with elevated pulmonary concentrations of titanium. Chest 108: 277-280, 1995.
12. Redline S, Barna BP, Tomaszewski JF Jr, Abraham JL. Granulomatous disease associated with pulmonary deposition of titanium. Br J Ind Med 43: 5, 1986.
13. Zimmerman PV, Sinclair RA. Rapidly progressive fatal silicosis in a young man. Med J Aust 19: 704-706, 1977.
14. Ishida Y, Sera K, Ohta K, Kageshita T. A case of rapid development of arc welder’s lung during the course of a year. Nihon Kokyuki Gakkai Zasshi 41: 351-355, 2003 (in Japanese, Abstract in English).
15. Moriyama H, Kobayashi M, Takada T, et al. Two-dimensional analysis of elements and mononuclear cells in hard metal lung disease. Am J Respir Crit Care Med 176: 70-77, 2007.