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Case report

Elemental analysis of occupational granulomatous lung disease by electron probe microanalyzer with wavelength dispersive spectrometer: Two case reports

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ABSTRACT

The parenchymal lung diseases caused by metal inhalation include interstitial fibrosis, giant cell interstitial pneumonitis, chemical pneumonitis, and granulomatous disease, among others. We reported two cases of granulomatous lung disease with occupational exposure to metal dusts other than beryllium. They had worked in the battery manufacturing industry for 7 years and in an aluminum-processing factory for 6 years, respectively. Chest high-resolution computed tomography showed diffuse micronodules, and histology of video-assisted lung biopsy specimens revealed granulomatous lesions in the pulmonary interstitium. Results of microscopic examination of the tissue with special stains for mycobacteria and fungi were negative. Analysis by an electron probe microanalyzer with a wavelength-dispersive spectrometer (EPMA-WDS) confirmed the presence of silicon, iron, aluminum, and titanium in the granulomas. In particular, aluminum was distributed in a relatively high concentration in the granulomatous lesions. Although chronic beryllium disease is well known as an occupational granulomatous lung disease, much less is known about the other metals that cause granulomatous reactions in humans. Our report pointed out manifestations similar to beryllium disease after other metal dust exposures, in particular aluminum exposure. To our knowledge, this is the first report showing two-dimensional images of elemental mapping in granulomatous lesions associated with metal inhalation using EPMA-WDS.

1. Introduction

Various metal dusts and fumes can induce a wide range of lung pathology, including not only parenchymal diseases but airway disorders and cancer as well [1]. The parenchymal lung diseases caused by metal inhalation include interstitial fibrosis, giant cell interstitial pneumonitis, chemical pneumonitis, and granulomatous disease, among others [1]. Most of the disorders arise from occupational exposures. A granulomatous disease caused by beryllium, known as chronic beryllium disease since its description by Hardy and Tabershaw [2], is a representative occupational granulomatous lung disease. Similar manifestations are occasionally reported from other metal dust exposures, such as to aluminum, zirconium, titanium, earth metals, and talc, the latter of which contains various amounts of aluminum and silica [3–11]. However, reports have been limited that describe the clinical, radiographic, and pathological findings of conditions other than the

Abbreviations: EPMA, electron probe microanalyzer; WDS, wavelength dispersive spectrometer; ACE, angiotensin converting enzyme; SP-D, surfactant protein D; PPD, purified protein derivative; VC, vital capacity; DLco, carbon monoxide diffusing capacity; HRCT, high-resolution CT; BAL, bronchoalveolar lavage.

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beryllium-induced granulomatous lung diseases as well as detailed information on mineralogical analyses of metal dusts.

An electron probe microanalyzer (EPMA) is an analytical tool used to non-destructively determine the chemical composition of small volumes of solid materials [12]. It irradiates specimens with a finely focused electron beam to obtain information about the elemental composition. Furthermore, EPMA with a wavelength-dispersive spectrometer (WDS) has higher sensitivity [13]. EPMA-WDS enables analysis of human lung tissue for deposits of elements by both qualitative and semi-quantitative methods [12]. We applied EPMA-WDS to biopsied lung tissue from patients presenting with granulomatous lung diseases with occupational exposure to metals other than beryllium to analyze the distribution of elements.

2. Case reports

2.1. Case 1

A 33-year-old man with a 12 pack-year history of cigarette smoking was referred to our hospital in 2006 because of exertional dyspnea. He had worked in the battery manufacturing industry for 7 years where he was exposed to cobalt, nickel, zinc, aluminum, and titanium. Beryllium was not used. He had begun working in that industry in 1998, and shortly thereafter developed skin eruptions with itching. In 2003, he was assigned by the company to a workplace dealing with cobalt hydroxide powder. There he developed an intense cough that was relieved after he left that workplace. He became aware of the onset of exertional dyspnea in 2004, and abnormal shadows on chest X-ray were detected at a health examination the next year. He left the industry and underwent examinations at a local hospital without a definite diagnosis. His past medical history included acute enteritis at the age of 30 years and depression at the age of 32 years. The patient's family history was unremarkable.

Physical examination revealed a well-developed, well-nourished man. On chest auscultation, fine crackles were heard subtly in both sides of the back and an abdominal examination revealed a smooth, non-tender liver edge 1 cm below the right costal margin. No evidence of uveitis, cervical or supraclavicular lymphadenopathy, arthralgia, skin eruptions, or muscle weakness was found.

Laboratory investigations showed the following values: WBC count 5900/mm^3 with 2.5% eosinophils, Hb 15.8 g/L, C-reactive protein 0.7 mg/dL, aspartate aminotransferase 74 U/L, alanine aminotransferase 101 U/L, lactate dehydrogenase 254 IU/L, ϒ-glutamyl transferase 417 U/L, creatinine 0.86 mg/dL, angiotensin converting enzyme (ACE) 24.0 U/L (normal range 6–21 U/L), serum KL-6 520 U/mL (normal range <500 U/mL), and surfactant protein D (SP-D) 30.5 ng/mL (normal range <110 ng/mL). Results of immunological tests were negative for autoimmune antibodies. Purified protein derivative (PPD) skin testing was positive at indurations of 15 mm × 15 mm. Arterial blood gas analysis while breathing room air revealed hypoxemia (PaO_2 60.2 Torr), with $PaCO_2$ 38.3 Torr and pH 7.432. Although vital capacity (VC) was within normal range at 3.69 L (89.1%), both total lung capacity and carbon monoxide diffusing capacity (DLco) were reduced to 4.33 L (69.4%) and 12.09 mL/min/Torr (40.8%), respectively.

Chest X-ray showed faint infiltrative shadows in the bilateral outside lung fields (Fig. 1A). Chest high-resolution CT (HRCT) revealed micronodules, most prominent in the upper and middle lung zones with mediastinal lymph node enlargement (Fig. 1B). Bronchoalveolar lavage (BAL) fluids obtained previously at another hospital had 8.4 × 10^5 cells per mL and 3.6% neutrophils, 0.8% eosinophils, and 21.4% lymphocytes. The ratio of CD4 to CD8 T lymphocytes was 0.38.

A video-assisted lung biopsy was performed and histological findings of tissue obtained from the left S^{1+2} region are shown in Fig. 2. Numerous epithelioid cell granulomas predominantly in the pulmonary interstitium and hyalinous elastolytic fibrosis predominantly in the bronchiolovascular sheath were observed. Epithelioid cell granulomas were also observed in visceral pleura (not shown). No giant cell interstitial pneumonia pattern was found. Results of microscopic examination of the tissue with special stains for mycobacteria and fungi were negative.

Because he had an occupational exposure to several kinds of metals, examination of tissue sections with an EPMA-WDS was performed according to procedures previously described [12,14]. Briefly, with this procedure lung tissues are inflated, fixed with

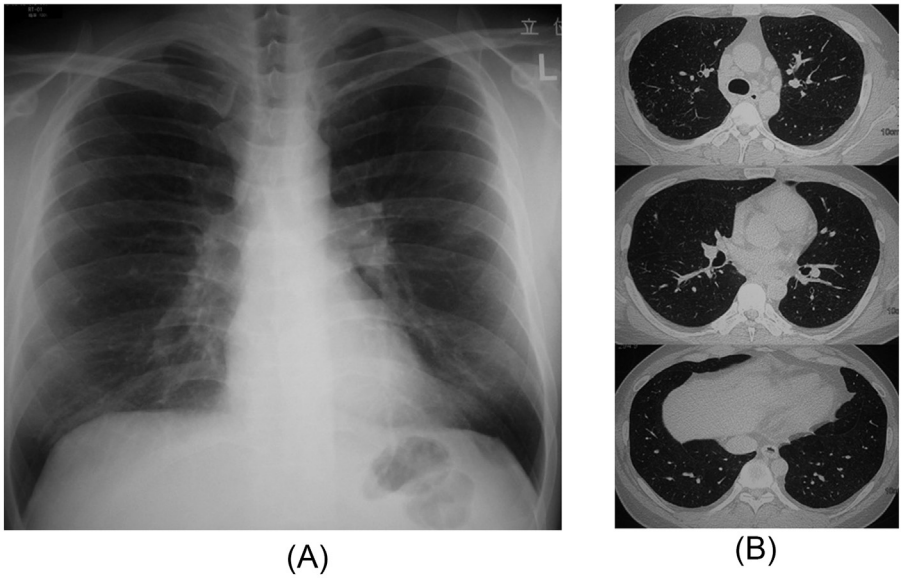

Fig. 1. Chest radiologic findings in Case 1. (A) Chest X-ray showed faint nodular shadows in the bilateral lung fields. (B) Chest high-resolution computed tomography shows diffuse fine nodular opacities that were distributed mainly in the upper and middle lung zones with mediastinal lymph node enlargement.