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Pulmonary Fibrosis in a Steel Mill Worker

We report a case of pulmonary fibrosis in a 32-year-old man, who had worked at a steel mill and who died of respiratory failure due to interstitial fibrosis despite vigorous treatment. He showed SLE-associated symptoms, such as pleural effusion, malar rashes, discoid rashes, arthritis, leukopenia, and positive antinuclear antibody and anti-histone antibody. However, he did not present anti-DNA antibody. A thoracoscopic lung biopsy showed interstitial fibrosis, chronic inflammation and a small non-caseating granuloma in lung tissues, which could be induced by external agents such as metals. The manganese concentration in the lung tissue was 4.64 μg/g compared to 0.42-0.7 μg/g in the controls. The levels of other metals, such as iron, nickel, cobalt and zinc in patient's lung tissue were higher than those in the controls. The patient was probably exposed to Si and various metal dusts, and the lung fibrosis was related to these exposures. Exposure to Si and metal dusts should be sought in the history of any patient with SLE, especially in a male with pulmonary signs, and if present, exposure should be stopped. In the meantime, steps should be taken to ensure that workers exposure to Si and metal dusts in all environments have adequate protection.

Key Words: *Pulmonary Fibrosis; Silicon Dioxide; Manganese; Toxicity; Metals; Dust; Lupus Erythematosus, Systemic*

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INTRODUCTION

With growing interest in the field of environmental and occupational medicine, a high rate of underdiagnosed environmental and occupational diseases is being recognized (1-3). Pulmonary fibrosis is likely to become a sentinel event of an occupational disease, because it can be used as an index for occupational exposure. Also, growing evidence show the relationship between interstitial lung disease and occupational exposure (4-10). A population-based registry in the United States reported a interstitial lung disease incidence of 70 per 100,000 with over half occurring without any obvious cause (11). Two studies in the United Kingdom show that interstitial pulmonary fibrosis is associated with metal exposures and wood dusts (12, 13). Interstitial lung disease associated with Si or metal exposure has not been reported in Korea; we introduce the nation's first case of pulmonary fibrosis in a steel worker.

CASE REPORT

A 32-year-old man had a tingling sensation on lower extremities starting 1 year ago, and discoid ulcer and pus formation on the left arm and right thigh. Skin lesions were formed and remitted spontaneously to form crusts, but multiple joint pain and erythematous rash on the face and neck occurred starting 6 months ago. He was admitted to the hospital, diagnosed as SLE, and treated at the Department of Rheumatology at first. His skin lesions improved with steroid treatment. He was then discharged and followed up at the outpatient clinic. He revisited the hospital and was found to have pulmonary fibrosis on chest X-ray so he was readmitted for further evaluation and treatment in October 1998. He showed the symptoms of mild fever, weight loss, gait disturbance, arthralgia and discoid rashes. However, he did not show to have seizure, hematuria, frequency, edema, photosensitivity and anemia on the admission day.

We found that he worked at a steel factory from 1992 to 1999 and worked as a welder from 1987 to 1989. He had worked with a continuous casting machine at the steel mill (Fig. 1). Thus, the patient may have been exposed to manganese for nine years. His serum manganese level was 5.8 μg/dL, which was in the normal range (0.4-6.2 μg/dL); however, this reading was done with blood sampling three months after he was removed from

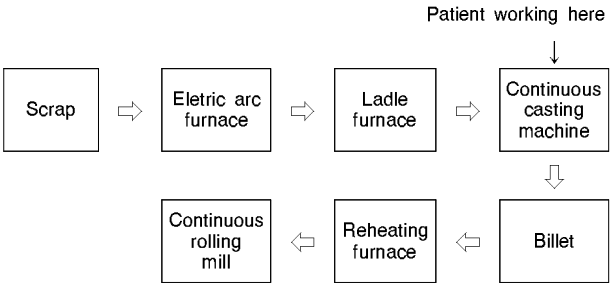

Fig. 1. Work procedure in the steel mill.

occupational exposure.

The evaluation results upon admission were as follows: hemoglobin was 12.1 g/dL; platelet count was 193,000/μL and white blood cell count was 4,500/μL, which was composed of 61.8% neutrophils, 24.8% lymphocytes, 1.2% eosinophils and 1.2% basophils. Biochemical data showed 47 U/L AST and 53 IU/L ALT; however, the levels of alkaline phosphatase, albumin, total bilirubin, γ-glutamyltranspeptidase (GGT), cholesterol, triglyceride, blood urea nitrogen and creatinine were normal. The results of urine analysis and 24 hr urine analysis were also normal. Rheumatoid factor, VDRL, and CRP were not reactive. T_3 was 41.9 ng/dL (normal value: 78.0-182.0 ng/dL); TSH was 2.29 mIU/L (normal value: 0.17-4.05 mIU/L) and FT_4 was 0.90 ng/dL (normal value: 0.80-2.00 ng/dL). ESR was slightly increased to 32 mm/hr. Antinuclear antibody was 1:40 homogenous, and anti-histone antibody also was moderately positive (1.9 U). Anti-DNA antibodies, anti-Ro (SS-A) and anti-Sm antibodies were negative. Abdominal ultrasonography revealed diffusely increased echogenicity in the liver, but there were no abnormal findings in the gall bladder, common bile duct, kidney, spleen, and pancreas. HBs Ag (hepatitis B antigen) and HCV were negative.

Although he complained of a tingling sensation in the lower extremities, there was no evidence of peripheral neuropathy on EMG. Blood culture, anti-*Mycoplasma* antibody, cold aggutinin and anti-*Legionella* antibody were negative.

Chest radiograph showed bilateral pleural thickening and a small effusion with increased interstitial markings on the adjacent lung (Fig. 2A). High resolution computerized tomography (HRCT) showed diffuse ground glass opacity and subpleural consolidation (Fig. 3A). To rule out vasculitis, a lung perfusion scan was performed. It revealed no abnormal findings. Bone scan also showed no abnormal findings of increased bone and joint uptake.

The laboratory follow-up evaluations showed decreased hemoglobin and platelet count in spite of intermittent transfusion. Follow-up chest PA showed progressive interstitial fibrosis on both lower lung fields (Fig. 2B). Follow-up HRCT showed aggravated reticulonodular opacities on posterior, basal segment of the lower lobes compared to the admission day (Fig. 3B, 3C). Pulmonary function test showed that FVC decreased from 3.13 L (70%) to 2.92 L (64%), FEV1 from 2.64 L (70%) to 2.45 L (65%), and DLCO% decreased from 78% to 41% on the 62nd day of admission.

He displayed SLE-associated symptoms, such as pleural

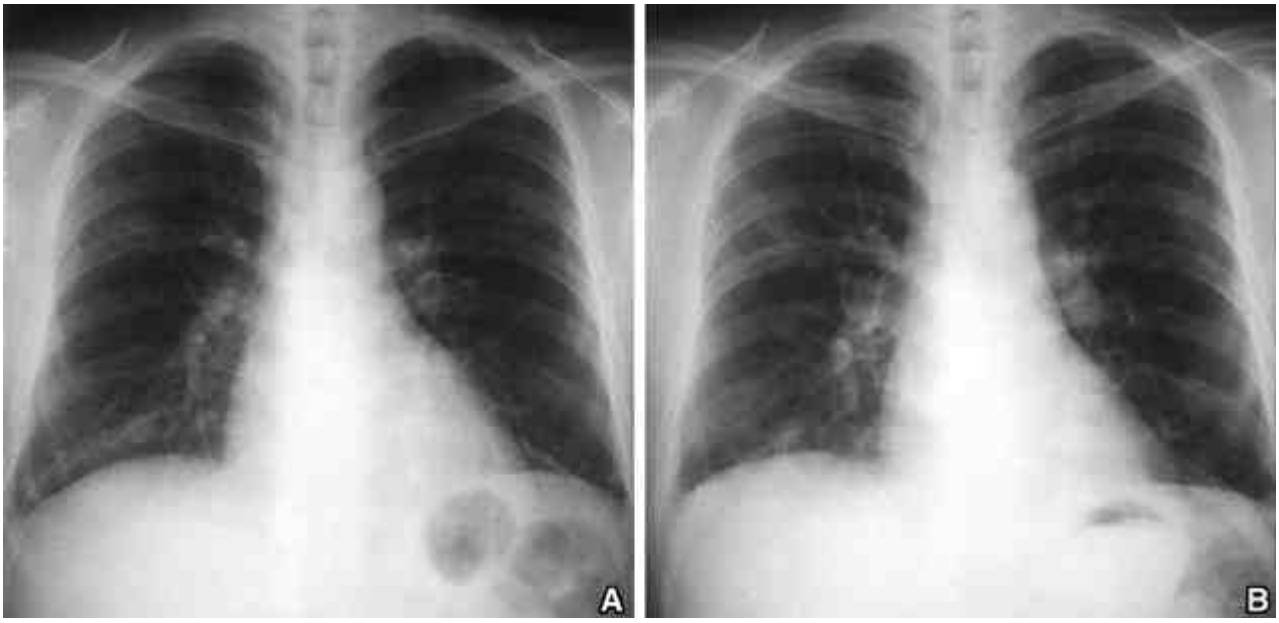

Fig. 2. A: Chest radiograph shows bilateral pleural thickening and a small effusion with increased interstitial markings on the adjacent lung. B: Follow-up chest radiograph shows progressive interstitial fibrosis on both the lower lung fields as compared to the admission day.

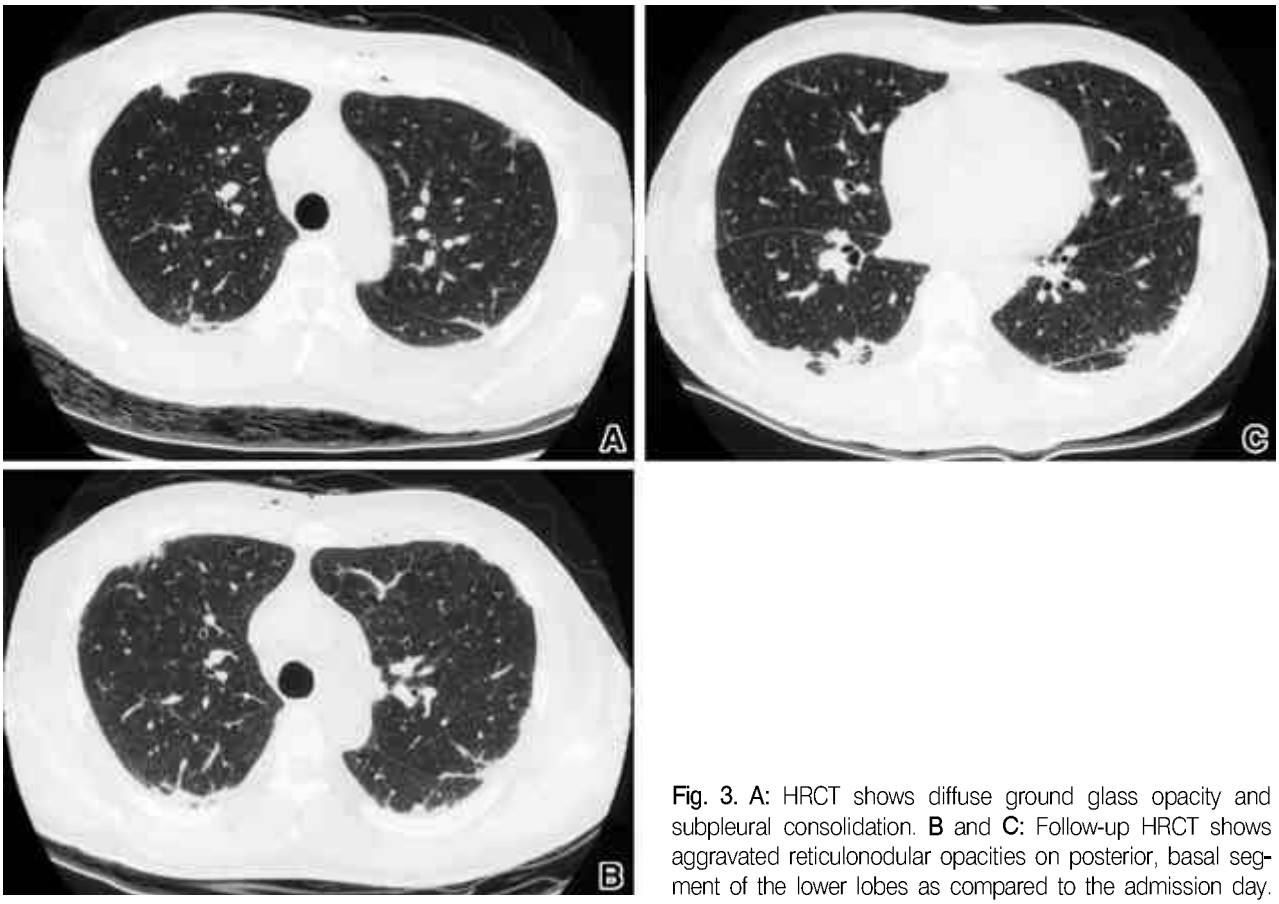

Fig. 3. A: HRCT shows diffuse ground glass opacity and subpleural consolidation. B and C: Follow-up HRCT shows aggravated reticulonodular opacities on posterior, basal segment of the lower lobes as compared to the admission day.

effusion, malar rashes, discoid rashes, arthritis, leukopenia and antinuclear antibodies. However, he had neither renal disorder nor anti-DNA antibodies. He was diagnosed as having SLE 3 months ago, and his symptoms slightly improved with early steroid treatment. But soon after anemia and thrombocytopenia, the impairment of airway diffusion capacity grew worse, and he died of respiratory failure due to interstitial fibrosis despite vigorous treatment.

A thoracoscopic lung biopsy was performed, and the involved area was sharply demarcated from the relatively intact adjacent parenchyma. The alveoli was thickened by the mixture of chronic inflammatory cells and collagen type fibrosis. Fibroblastic foci were frequently found in the interstitium and air spaces (Fig. 4A). The alveolar lining epithelium was hyperplastic, and the accumulation of pigmented, foamy macrophages was seen within the air spaces and interstitium. A small well-formed granuloma was found in the subpleural area (Fig. 4B). Fungus was not detected with periodic acid-Schiff reaction and Grocott's method. Tubercle bacilli were not confirmed with Ziehl-Neelsen staining and PCR. These findings suggested that the granuloma was caused by a inhaled foreign material, but no foreign material such as silica was identified with light microscope. Autopsy lung sample showed similar features to those of the previous lung biopsy. However, the fibroblastic foci disappeared, and progressed interstitial fibrosis was seen (Fig. 4C).

Environmental investigation of the workplace showed that particles containing ferrous oxide often exceeded the threshold limit (5.0 mg/m^3). Particles containing silicon dioxide more than 30 percent also often exceeded the threshold limit (2.0 mg/m^3). The level of manganese fumes was below the Korean occupational exposure limit (1.0 mg/m^3). The levels of iron oxide fume, inorganic lead particles and fumes were all below the occupational exposure limit (1.0 mg/m^3).

The manganese concentration in the lung tissues was 4.64 $\mu g/g$ and that of control lung tissues was 0.42-0.7 $\mu g/g$. The concentrations of other metals such as ferrous, nickel, cobalt and zinc of the patient were higher than those of the controls (Table 1). The lead and cadmium concentrations of lung tissue were 1.71 $\mu g/g$ and 2.31 $\mu g/g$, respectively, which were normal. The control measurements were made in five patients who had admitted to the hospital because of other respiratory diseases, such as pulmonary tuberculosis and lung cancer. In conclusion, the patient was probably exposed previously to various metal dusts, and these metal exposures were associated with pulmonary fibrosis.

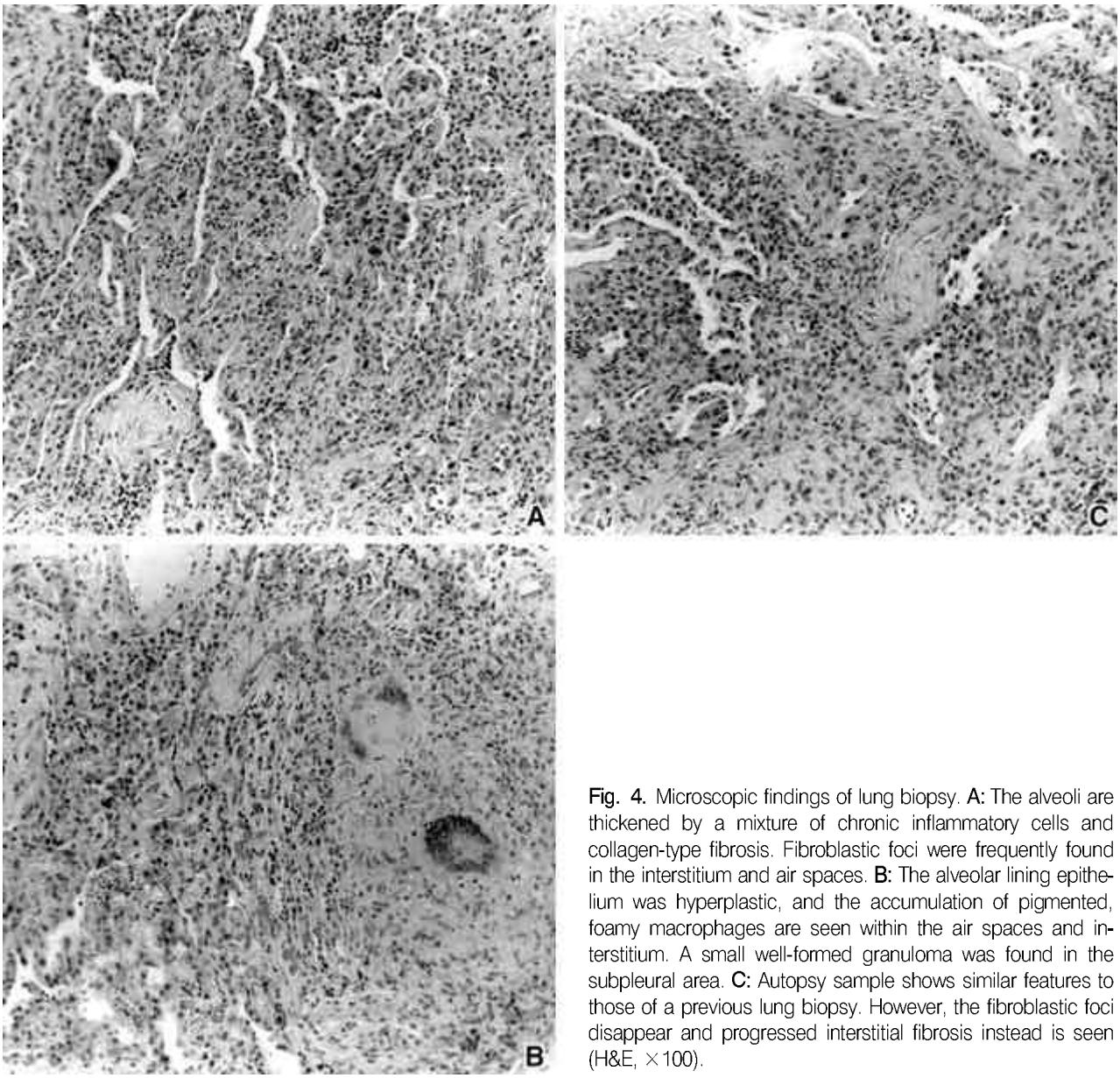

Fig. 4. Microscopic findings of lung biopsy. **A:** The alveoli are thickened by a mixture of chronic inflammatory cells and collagen-type fibrosis. Fibroblastic foci were frequently found in the interstitium and air spaces. **B:** The alveolar lining epithelium was hyperplastic, and the accumulation of pigmented, foamy macrophages are seen within the air spaces and interstitium. A small well-formed granuloma was found in the subpleural area. **C:** Autopsy sample shows similar features to those of a previous lung biopsy. However, the fibroblastic foci disappear and progressed interstitial fibrosis instead is seen (H&E, ×100).

Table 1. Comparison of metal concentrations in lung tissues between the present case and controls

	Manganese	Lead	Cadium	Fe	Zinc	Nickel	Cobalt
Control 1	0.79±0.23	0.34±0.06	4.20±0.33	612.9±99.7	335.1±22.8	1.00±0.99	0.45±0.13
Control 2	0.51±0.01	0.98±0.30	1.74±0.22	564.0±110.2	171.9±53.9	1.34±0.14	0.38±0.07
Control 3	0.7±0.05	1.91±0.22	1.32±0.07	1,372.0±119.0	320.9±48.7	0.72±0.25	0.17±0.04
Control 4	0.48±0.08	0.68±0.13	1.52±0.73	581.6±26.5	1,829.7±242.1	1.02±0.87	0.24±0.41
Control 5	0.42±0.09	0.88±0.06	1.66±0.41	502.1±139.8	515.2±47.1	1.38±0.79	0.07±0.17
The present case	4.64±0.03	1.71±0.92	2.31±0.63	2,152.7±46.6	1,634.1±15.9	4.28±0.09	1.07±0.04

unit: μg/g

DISCUSSION

There has been growing interest in the relationship between idiopathic fibrosis and the exposure to various metals, such as cobalt, aluminium, titanium, beryllium, and manganese. Metallic dusts deposited in the lung may give rise to more or less marked pulmonary fibrosis, depending on the intrinsic properties and amount of the inhaled agent, as well as hitherto poorly understood host factors. The fibrogenic potential of inhaled substances is

presumably determined by their ability to interfere with the pulmonary immuno-inflammatory system, either directly, e.g. via effects on alveolar macrophages, or indirectly, e.g. via injury to epithelial cells. In other words, as in other forms of interstitial lung disease, the fibrogenic process is probably dependent on the occurrence of alveolitis with abnormal release of mediators by some cells (4). The exposure to dust with a high content of silica may predispose to or initiate the development of SLE. Interstitial fibrosis often occur in SLE patients (14-18). The level of anti-histone antibody increases in patients with occupational exposures to metals. They meet the criteria of SLE or do not present these criteria. Upon removal from exposure, however, the level of anti-histone antibody drops to negative, and the patient becomes better. The current threshold limit value (TLV) of manganese as fume is 1.0 mg/m^3 in Korea (19), and that in the U.S.A. is 0.1 mg/m^3 from standards of American Conference of Governmental Industrial Hygienists (ACGIH) (20). It is likely that interstitial pulmonary fibrosis occurs due to occupational exposure below the current exposure limit.

Pulmonary fibrosis of the present case was probably work-related; he worked at a steel mill from 1992 to 1999 and worked as a welder from 1987 to 1989. His anti-histone antibody level was moderately positive (1.9 U). We do not know the exact pathogenic mechanism of metal induced pulmonary fibrosis, and further studies are needed on this subject. Exposure to Si and metal dusts should be sought in the history of any patient with SLE, especially in a male with pulmonary signs, and if present, the exposure should be stopped. In the meantime, steps should be taken to ensure that workers exposure to Si and metal dusts in all environments have adequate protection.

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