Case Study

An advanced case of indium lung disease with progressive emphysema

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Abstract: Objectives: To report the occurrence of an advanced case of indium lung disease with severely progressive emphysema in an indium-exposed worker. **Case report:** A healthy 42-year-old male smoker was employed to primarily grind indium-tin oxide (ITO) target plates, exposing him to indium for 9 years (1998-2008). In 2004, an epidemiological study was conducted on indium-exposed workers at the factory in which he worked. The subject's serum indium concentration (In-S) was 99.7 µg/*l*, while his serum Krebs von den Lungen-6 level was 2,350 U/m*l*. Pulmonary function tests showed forced vital capacity (FVC) of 4.17 *l* (91.5% of the JRS predicted value), forced expiratory volume in 1 s (FEV$_1$) of 3.19 *l* (80.8% of predicted), and an FEV$_1$-to-FVC ratio of 76.5%. A high-resolution chest computed tomography (HRCT) scan showed mild interlobular septal thickening and mild emphysematous changes. In 2008, he was transferred from the ITO grinding workplace to an inspection work section, where indium concentrations in total dusts had a range of 0.001-0.002 mg/m^3. In 2009, the subject's In-S had increased to 132.1 µg/*l*, and pulmonary function tests revealed obstructive changes. In addition, HRCT scan showed clear evidence of progressive lung destruction with accompanying severe centrilobular emphysema and interlobular septal thickening in both lung fields. The subject's condition gradually worsened, and in 2015, he was registered with the Japan Organ Transplant Network for lung transplantation (LTx). **Conclusions:** Heavy indium exposure is a risk factor for emphysema, which can lead to a severity level that requires LTx as the final therapeutic option.
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Lung transplantation is an acceptable therapeutic option for patients with advanced pulmonary diseases. More than 45,000 lung transplantation operations have been performed worldwide till 2013[1], and 403 lung transplantation operations have been performed in Japan alone by the end of 2014[2]. Changes to the Organ Transplant Law in 2010 resulted in a relaxing of criteria for donors, and the number of lung transplantation operations has since been increasing in Japan.

Given its adverse pulmonary effects[3,4] and its potential as a lung carcinogen[5], indium was added to the list of substances regulated by the Ordinance on Prevention of Hazards due to Specified Chemical Substances (OPHSCS) in 2013. Indium is regulated by OPHSCS by checking levels of respirable indium dust in the workplace and by biological monitoring twice a year[6].

Indium lung disease[3,4,7] (interstitial pneumonia, emphysema, pneumothorax) is a recently described occupational lung disease that affects workers exposed to indium compounds, such as indium-tin oxide (ITO; used to manufacture electrodes to produce flat-panel displays) and indium oxide, indium hydroxide, and indium chloride, which are involved in the production or reclamation of ITO. Emphysematous change is listed as a long-term adverse ef-

fect on lungs resulting from exposure to indium[8]. However, no case reports focusing on emphysema as a component of indium lung disease have been published till date.

Here we report an advanced case of indium lung disease with severe emphysema in an indium-exposed worker who participated in our epidemiological study. This study was approved by the Ethics Committee of the School of Medicine, Keio University (approval number 20110268). Written informed consent was also obtained from the subject of this report.

Case History

In August 1998, a healthy 36-year-old male smoker began working at a job site where his main task was grinding ITO target plates, a role which he pursued for 9 years (1998-2008). In addition, the subject also experienced occupational exposure while grinding panels made of chromium, molybdenum, tantalum, and zinc oxide for the same period of time (9 years). Exposure to such metals has been suggested to be possibly related to emphysema[9]. The subject did not wear any respiratory protective device until 2003. The factory began measuring indium concentrations at worksites from 2005, and the indium concentration in total dust at his job site was found to range from 0.01 to 0.1 mg/m³. In 2008, the subject was transferred from the grinding job site to an inspection work section, where indium concentrations in total dust ranged from 0.001 to 0.002 mg/m³. Since December 2011, he has worked in an indium-free office.

In February 2004, we performed a baseline cross-sectional study to reveal the relationship between indium exposure and its effects on the lungs of workers, including our case subject, at his factory. He was 175.0 cm tall and weighed 51.0 kg, smoked 10 cigarettes/day for 22 years, was an occasional drinker, and had no significant medical history and no occupational history of dust exposure before working at the grinding job site.

In this baseline study, the subject reported having a cough for the previous 6 months, producing sputum for the past 7 years, and experiencing wheezing for the past 5 years, but had not visited a medical clinic or hospital to treat these symptoms. He did not have clubbed fingernails. His serum indium concentration (In-S) was 99.7 μg/l, serum Krebs von den Lungen-6 (KL-6) concentration was 2,350 U/ml (normal range, <500 U/ml), serum surfactant protein D (SP-D) concentration was 149 ng/ml (normal range, <110 ng/ml), and C-reactive protein (CRP) concentration was 0.03 mg/dL. Pulmonary function tests showed forced vital capacity (FVC) of 4.17 l [91.5% of the Japanese Respiratory Society (JRS) predicted value], forced expiratory volume in 1 s (FEV_1) of 3.19 l (80.8% of the JRS predicted value), and an FEV_1-to-FVC ratio of 76.5%. An HRCT scan revealed mild interlobular septal thickening and emphysematous change

in <10% of the upper, middle and lower lung fields, and no ground-glass opacities (Fig. 1). In February 2005, he was diagnosed with emphysema by a Japan Radiological Society-certified radiologist at a hospital and had follow-up HRCT scans once a year. He quit smoking in May 2007. His In-S (serum indium levels) measured by the factory were 90.3 μg/l (2005), 94.7 μg/l (2006), 124.8 μg/l (2007), and 116.5 μg/l (2008).

In September 2009, we performed our first follow-up study on baseline participants. The subject's In-S had significantly increased to 132.1 μg/l, while he had a KL-6 concentration of 1,830 U/ml, SP-D of 152 ng/ml, serum lactate dehydrogenase (LDH) of 287 U/l, aspartate transaminase (AST) of 33 U/l, and alanine aminotransferase (ALT) of 39 U/l. Pulmonary function tests showed a vital capacity (VC) of 3.95 l (87.1% of the JRS predicted value), FVC of 3.67 l (82.7% of the JRS predicted value), FEV_1 of 2.14 l (56.2% of the JRS predicted value), FEV_1-to-FVC ratio of 58.3%, and resting room air oxygen saturation (SpO_2) of 97%, suggesting obstructive changes. An HRCT scan showed clear evidence of progressive lung destruction and chest wall expansion with accompanying severe centrilobular emphysema in both lung fields, particularly the upper and middle levels, paraseptal emphysema in the periphery of both lung fields, and interlobular septal thickening in both lung fields (Fig. 1). Because the rapid progression of his emphysema as revealed by the HRCT scan could not be attributed entirely to smoking, an occupational physician from the factory recommended him to visit a JRS-certified pulmonologist. He was found to have a normal blood level of alpha-1 antitrypsin. The subject was diagnosed with emphysema, and he started taking tiotropium bromide hydrate and also took losartan potassium and amlodipine besylate for hypertension. In August 2014, he was admitted to the hospital for pneumonia, suffered dyspnea on exertion, and walked slower than people his age because of breathlessness (the Medical Research Council breathlessness scale of grade 3). He began home oxygen inhalation therapy (HOT) at 0.5-1.0 l/min. In November 2014, he claimed workers' compensation and was diagnosed with indium-induced lung disease.

The subject's condition gradually worsened despite treatment, and a JRS-certified physician judged that lung transplantation (LTx) was necessary. In April 2015, he was examined for adaptation of his condition to LTx at an LTx center in Fukuoka, Japan, approved by the Japanese Central Lung Transplant Adjustment Advisory Committee. He was registered with the Japan Organ Transplant Network and additionally diagnosed with pulmonary hypertension, for which he started a course of the medication sildenafil following examination.

In July 2015, we performed our second follow-up study on baseline participants at the factory. In our case subject, we recorded an In-S of 37.6 μg/l, KL-6 of 1,640 U/ml, SP-D of 222 ng/ml, LDH of 241 U/l, AST of 33 U/
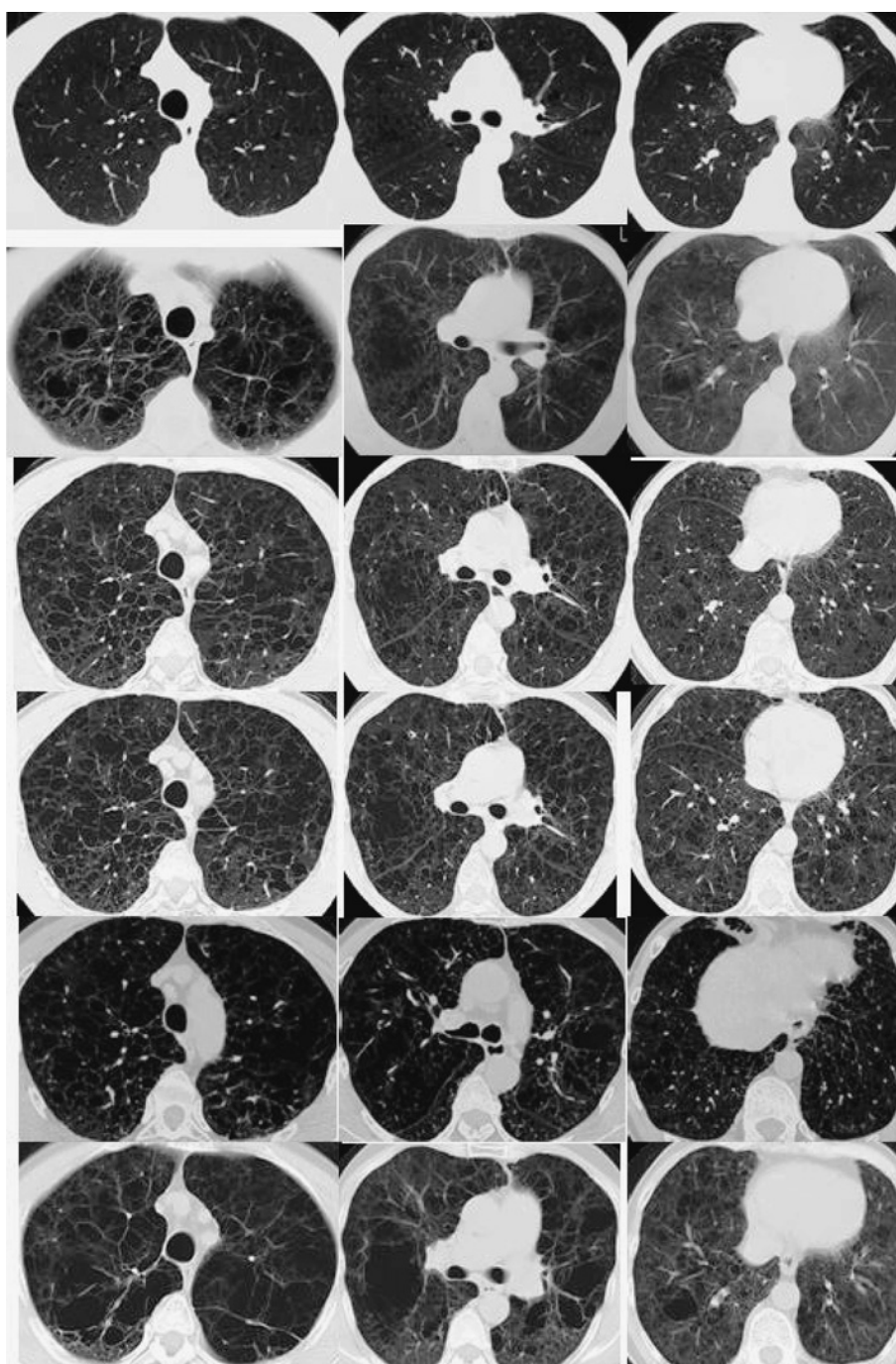
Fig. 1. HRCT scans from 2004, 2005, 2007, 2008, 2009, and 2015. HRCT scans in 2004 (top row), 2005 (2nd row), 2007 (3rd row), 2008 (4th row), 2009 (5th row), and 2015 (bottom row). Scans of upper, middle, and lower lung fields are shown from left to right. The HRCT scans were performed at the National Hospital Organization Omuta Hospital from 2005 to 2008.

l, ALT of 21 U/l, CRP of 0.10 mg/dl, a leukocyte count of 6,800 /μl, and hemoglobin of 17.3 g/dl. The subject's In-S had dramatically decreased since the first follow-up examination. Pulmonary function tests showed total lung capacity (TLC) of 5.14 l (82% of the National Health and Nutrition Examination Survey predicted value), VC of 3.77 l (87.8% of the JRS predicted value), FVC of 3.52 l (83.9% of the JRS predicted value), FEV_1 of 1.73 l (48.7% of the JRS predicted value), FEV_1-to-FVC ratio of 49.2%, residual volume (RV) of 1.48 l, %RV/TLC of 28.8%, a single-breath carbon monoxide diffusing capacity (D_{Lco}) of 4.2 ml/min/mmHg (15.2% of the value pre-

dicted using Nishida's equation for Japanese adult males[10]), and resting room air SpO_2 of 87%, suggesting severe emphysema. An HRCT scan showed evidence of lung destruction and accompanying severe emphysema in both lung fields, particularly the upper and middle levels and several large bullae (Fig. 1).

As of January 2016, the subject's HOT concentration is set at 0.5-1.0 *l*/min at rest and 3.0-4.0 *l*/min on exertion, and he works in an indium-free office.

Discussion

Among the indium-exposed workers we followed, the subject described here developed the most severe emphysema and was registered for an LTx via the Japan Organ Transplant Network in June 2015. Emphysematous changes have recently been highlighted as a long-term adverse effect on lungs in indium-exposed individuals with In-S ≥ 20 μg/*l* in our 5-year follow-up study[8] as well as a separate 8-year follow-up study[11], even after adjusting for age, duration since initial indium exposure, and smoking history[8]. Smoking is also an important risk factor for emphysema, and the subject had a Brinkman Index of 265; however, the rapid progression of his emphysema as revealed by the HRCT scan at the first follow-up study could not be attributed entirely to smoking. The mechanism of the progression of emphysema may have been that indium particles in the lungs perpetuated the phagocytosis and phagolysosomal acidifi cation[12] cycle performed by the alveolar macrophages. The proteases released by the macrophages and the cytotoxicity of indium may have promoted macrophage-mediated elastolysis, which is known to cause inflammation and destruction of the lung parenchyma[13], leading to emphysematous deterioration. Simultaneously, the high level of KL-6 has also been maintained. Although he has not had lung pathological examinations as of yet in 2016, indium lung disease is strongly suspected based on his occupational history of indium exposure, the results of medical examinations including In-S and KL-6, the observation of interstitial and emphysematous findings on HRCT scans, and the results of pulmonary function tests[4].

Though the subject started wearing a respiratory protective device in 2003 and transferred from the grinding job site in 2008, his In-S level had significantly increased in 2009. This may be because the clearance of indium in the lungs was slow. Also, the type of respiratory protective device that he wore used a filter that was at least 95% efficient in filtering airborne particles but was not sufficient to protect against the inhalation of indium dust. Thirdly, the subject was continuously exposed to indium, and the cumulative lung indium exposure concentration had reached a maximal level from 2006 to 2007, so the high value of In-S continued until 2009.

Given our observations in the present case study, we hypothesize that the subject may not have developed advanced indium lung disease had he been transferred to an indium-free workplace and quit smoking on showing mild symptoms and features of emphysema.

Conclusions

Heavy indium exposure is a risk factor for emphysema, which can lead to a severity level that requires LTx as the final therapeutic option.

Conflicts of interests: D.C. is an occupational physician of a surveyed company. None of the other authors have any conflicts of interest to disclose.

References

1) Yusen RD, Edwards LB, Kucheryavaya AY, et al ; International Society for Heart and Lung Transplantation. The registry of the International Society for Heart and Lung Transplantation : Thirty-first adult lung and heart-lung transplant report—2014 ; focus theme : retransplantation. J Heart Lung Transplant 2014 ; 33 : 1009-1024.

2) The Japanese Society of Lung and Heart-Lung Transplantation. Registry Report of Japanese Lung Transplantation-2015. Jpn J Transplant 2015 ; 50 : 175-178 (in Japanese).

3) Homma T, Ueno T, Sekizawa K, Tanaka A, Hirata M. Interstitial pneumonia developed in a worker dealing with particles containing indium-tin oxide. J Occup Health 2003 ; 45 : 137-139.

4) Omae K, Nakano M, Tanaka A, Hirata M, Hamaguchi T, Chonan T. Indium lung—case reports and epidemiology. Int Arch Occup Environ Health 2011 ; 84 : 471-477.

5) Nagano K, Nishizawa T, Umeda Y, et al. Inhalation carcinogenicity and chronic toxicity of indium-tin oxide in rats and mice. J Occup Health 2011 ; 53 : 175-187.

6) Ministry of Health, Labor, and Welfare. Amendment to Ordinance on Industrial Safety and Health Law and to Ordinance on Prevention of Hazards due to Specified Chemical Substances. Tokyo: Government of Japan. 2013. [cited 2016 Mar. 4]; Available from: URL: http://www.mhlw.go.jp/bunya/roud oukijun/anzeneisei48/dl/anzeneisei48-01.pdf (in Japnese).

7) Nakano M, Omae K, Tanaka A, et al. Causal relationship between indium compound inhalation and effects on the lungs. J

Occup Health 2009; 51: 513-521.

8) Nakano M, Omae K, Uchida K, et al. Five-year cohort study: emphysematous progression of indium-exposed workers. Chest 2014; 146: 1166-1175.

9) Nemery B. Metal toxicity and the respiratory tract. Eur Respir J 1990; 3: 202-219.

10) Nishida O. A clinical study of the carbon monoxide diffusing capacity. Med J Hiroshima Univ 1970; 18: 223-233 (in Japanese).

11) Amata A, Chonan T, Omae K, Nodera H, Terada J, Tatsumi K. High levels of indium exposure relate to progressive emphysematous changes: a 9-year longitudinal surveillance of indium workers. Thorax 2015; 70: 1040-1046.

12) Gwinn WM, Qu W, Shines CJ, et al. Macrophage solubilization and cytotoxicity of indium-containing particles in vitro. Toxicol Sci 2013; 135: 414-424.

13) Russell RE, Thorley A, Culpitt SV, et al. Alveolar macrophage-mediated elastolysis: Roles of matrix metalloproteinases, cysteine, and serine proteases. Am J Physiol Lung Cell Mol Physiol 2002; 283: 867-873.