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Progression of Smoking-Induced Emphysema in a Case with Indium Lung

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Recently, it has become clear that inhaled indium-tin oxide causes emphysematous as well as interstitial changes in the lung. Here, we present a 59-year-old male ex-smoker, quitting smoking at the age of 55. He had been engaged in indium-tin oxide processing from 27 to 37 years of age, with 22 years having passed since the final exposure to indium. He was found to have a high serum indium concentration and Krebs von den Lungen-6 (KL-6). Furthermore, bilateral centrilobular emphysema was recognized in high-resolution computed tomography (HRCT). After transferring jobs to a non-indium-tin oxide section, KL-6 returned to a normal level within 4 years, whereas neither serum indium concentration nor emphysema had decreased to normal despite 22 years having passed since the exposure ended. At the age of 59, a thoracoscopic lung biopsy was performed to assess the contribution of smoking and that of indium to the lung destruction. The pathological findings demonstrated cholesterol granulomas with the accumulation of macrophages and multinucleated giant cells that had phagocytosed particles. Together with the typical findings of indium lung, fibrotic and emphysematous changes were observed. The elemental analysis of the biopsied specimens revealed excessive deposition of indium throughout the airways, interstitial spaces and alveoli. The pathological findings of this case may be the result of two kinds of pulmonary damage, i.e., smoking and indium. This report indicates that occupationally-inhaled indium could remain in the lung for as long as 22 years and continue to insult the lung tissue with inflammation caused by smoking.

Keywords: cholesterol granuloma; elemental analysis; indium-tin oxide; lung fibrosis; pneumoconiosis
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Introduction

Indium is mainly used as indium-tin oxide, which contains 90% indium oxide and 10% tin oxide; its production has been increased to make thin-film liquid crystal displays (Cummings et al. 2012; Chonan et al. 2019). However, it has been reported that inhaled indium dust could cause a new type of pneumoconiosis, comprised of histopathological findings such as cholesterol granulomas, pulmonary fibrosis, pulmonary emphysema and alveolar proteinosis (Cummings et al. 2012; Chonan et al. 2019). Recently, we encountered a case of indium lung with smoking-induced emphysema, who underwent surgical lung biopsy 22 years after the discontinuation of exposure. There have been no reports of indium lung in which surgical lung biopsy was performed long after the cessation of exposure. Together with our previous reports, it is hypothesized that the heavy inhalation of indium compounds could promote progressive

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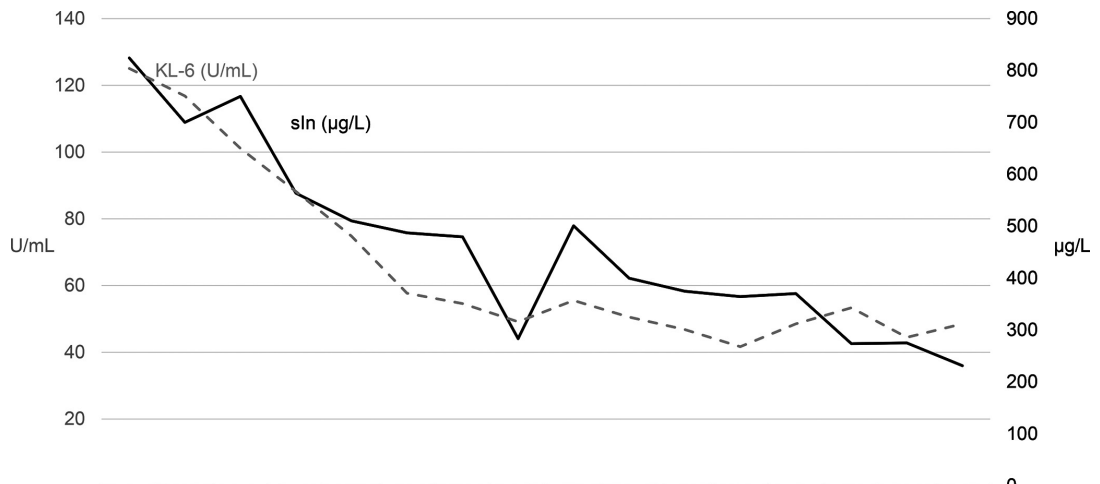
emphysema, even induced by smoke, in the lung.

Case Presentation

The patient is a 59-year-old male ex-smoker. He quit smoking at the age of 55 and his total smoking index was 15 pack-years. He has hyperuricemia and takes a xanthine oxidase inhibitor. He had been mainly engaged in the surface grinding of indium-tin oxide targets for 10 years from the age of 27 to 37, while wearing a dust respirator with a 99.9% trap rate at work; however, he sometimes removed the dust respirator when he felt uncomfortable. The available data of environmental indium concentrations in his workplace ranged from 0.01 to 0.15 mg/m^3 at that time. At the age of 42, he was found to have high levels of serum indium (sIn) at 128.9 μg/L (reference range 0.06 ± 0.03 μg/L) and his level of Krebs von den Lungen-6 (KL-6) was 806 U/mL (reference range < 500 U/mL). Moreover, pulmonary emphysematous lesions were recognized in many areas of the whole lung. Following a job transfer, the level of KL-6 decreased steadily (Fig. 1). However, dyspnea upon exertion increased gradually. At the age of 59, he was admitted to our hospital for a precise pulmonary diagnosis and management respiratory distress.

On presentation, he was fully conscious, with a height of 178 cm, body weight of 100.5 kg, body temperature of 35.8°C and percutaneous oxygen saturation (SpO_2) of 97% on room air. Physical examination revealed bilateral clubbed fingers. There were no abnormal laboratory findings. The levels of sIn and KL-6 are shown in Fig. 1. Chest X ray showed progression of hyperinflation the lungs gradually (Fig. 2). High-resolution computed tomography (HRCT) mainly indicated centrilobular emphysema in the bilateral upper lobes, whereas ground glass opacities were observed predominantly on the lower lobes. After quitting smoking, from the age of 55 years, emphysematous lesions continued to increase (Fig. 3). The results of the pulmonary function test are shown in Table 1. The helium dilution technique was applied for the measurement of lung volume. The values of forced expiratory volume in 1.0 s (FEV_1), FEV_1/forced vital capacity (FVC) and diffusing capacity of



Age	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57
—sIn	128.2	108.9	116.7	87.7	79.4	75.8	74.6	44.1	77.9	62.2	58.3	56.7	57.6	42.6	42.8	36
– –KL-6	804	751	650	567	481	371	351	316	357	325	301	268	312	343	286	312

Fig. 1. The time course of serum indium concentration (sIn; continuous line) and Krebs von den Lungen-6 (KL-6; dotted line).
From the age of 42, after a job transfer, both serum markers decreased, although the reduction in serum indium concentration was much slower.

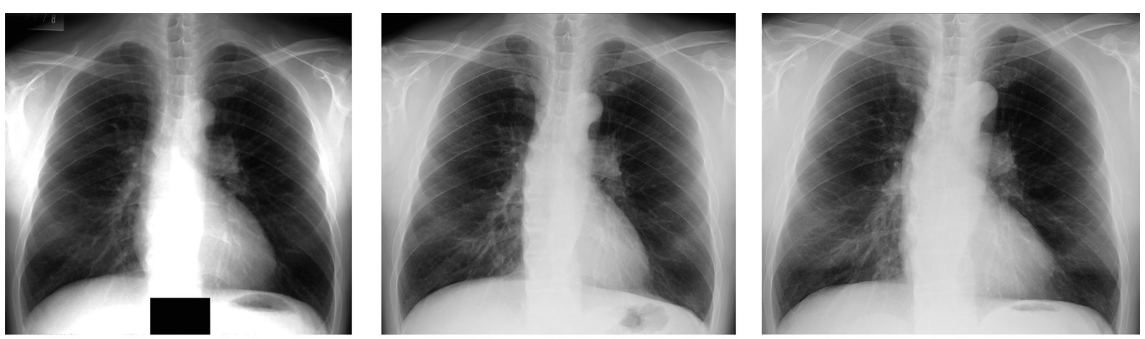


Fig. 2. Images of the chest X ray showing no overt change of the lungs from the ages of 42-59 years.

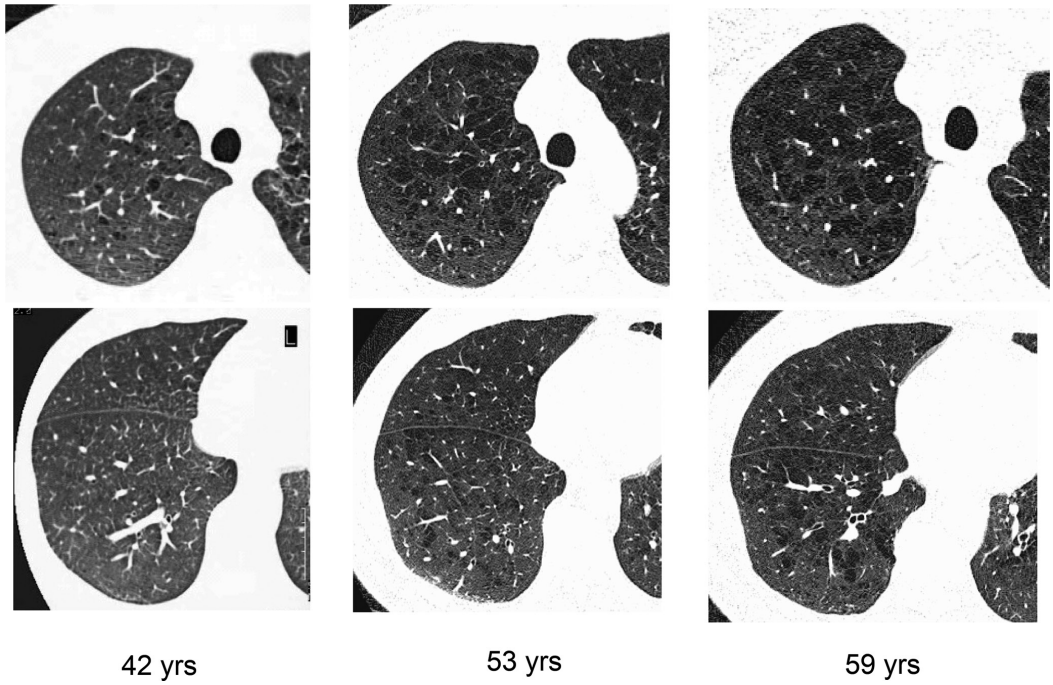


Fig. 3. Images of the high-resolution chest computed tomography (HRCT) presenting the progression of centrilobular emphysema from the ages of 42-59 years.
Although the patient quit smoking at 55 years, the progression of emphysematous changes continued from the upper to the lower lobe.

the lung for carbon monoxide (DL_{CO}) had decreased remarkably. However, total lung capacity (TLC) and residual volume (RV) had increased (Table 1). Emphysema and decreased pulmonary function could be induced by both indium inhalation and smoking; therefore, at 59 years old, a surgical lung biopsy was performed in the right middle and lower lobes. Histologically, the specimen from the middle lobe showed moderate fibrotic and emphysematous changes in separate areas (Fig. 4a, b). Furthermore, it was observed that giant cells and macrophages had phagocytosed black particles and giant cells had phagocytosed cholesterol crystals, forming cholesterol granulomas (Fig. 4c). One slide of the lower lobe also showed a variety of pathological changes, including emphysema and fibrosis, as in the middle lobe, with the accumulation of surfactants being observed in the air spaces (Fig. 4d, e). Elemental analysis of the biopsied specimens (the bronchioles and the surrounding lung, Fig. 5a-i) indicated the existence of a high amount of indium in the interstitium, confirmed by elemental mapping images (Fig. 5b-i). The macrophages and one cholesterol granuloma also contained a high amount of indium and tin (Sn) (Fig. 5a-ii b-ii, c-i, c-ii). It appeared that the distributions of indium and tin were not matched in elemental mapping (Fig. 5b-i, b-ii, c-i, c-ii). This might have been caused by differences in the composition of indium-tin oxide, i.e., 90% indium oxide and 10% tin oxide (Chonan et al. 2019). These findings are compatible with previous reports on indium lung (Cummings et al. 2012; Chonan et al. 2019).

This study was approved by the Nikko Memorial Hospital ethical committee. Written informed consent was obtained from the patient and patient's family for publication of this case report and the accompanying images.

Discussion

We present a plausible case of smoking-induced emphysema that progressed rapidly under the background of indium lung and a case of indium lung which progressed rapidly with smoking. As far as we are aware, there have been no reports on indium lung that have been pathologically diagnosed and observed for 22 years after the exposure to indium was stopped. The findings of this study are consistent with previous observations over a period of 5 to 9 years (Nakano et al. 2014; Amata et al. 2015) and suggest that heavy occupational indium exposure could evoke the progression of emphysematous changes of the lung, especially in smokers. It is also suggested that inhaled indium could stay in the lung for as long as 22 years. This patient presented here is an ex-smoker; therefore, it is suggested that smoking is one of the factors of emphysematous change.

It has been reported that indium lung demonstrates various radiological and pathological features (Cummings et al. 2012; Nakano et al. 2014; Chonan et al. 2019). On HRCT, indium lung showed interstitial lung disease ranging from fibrosis, traction bronchiectasis and/or bronchiolectasis, loss of volume and honeycombing (Cummings et al. 2012; Chonan et al. 2019). Various types of emphysematous changes in the lung have also been reported in indium lung (Table 2): "paracicatricial emphysema" showing

Table 1. Chronological changes in pulmonary function and diffusing capacity.

Age	VC [L] (% Pred)	FVC [L] (% Pred)	FEV_1 [L] (% Pred)	FEV_1/FVC [%]	FRC [%] (% Pred)	TLC [L] (% Pred)	RV [L] (% Pred)	DL_{CO} [mL/min/mmHg] (% Pred)
42	6.44 (135.3)	6.14 (126.1)	3.88 (91.6)	60.2	4.78 (142.1)	8.23 (137.4)	1.96 (118.2)	26.6 (94.1)
43	6.09 (118.2)	6.00 (120.2)	3.50 (87.4)	58.3	4.60 (130.7)	8.59 (143.0)	2.46 (148.1)	26.3 (93.5)
44	6.07 (118.0)	6.00 (121.1)	3.40 (85.6)	56.7	4.72 (142.4)	7.95 (133.2)	1.66 (99.8)	24.1 (84.0)
45	6.47 (137.6)	6.35 (133.1)	3.33 (85.2)	52.0	4.76 (146.1)	8.07 (135.1)	1.82 (108.4)	27.3 (99.1)
46	NA	NA	NA	NA	NA	NA	NA	NA
47	6.39 (132.8)	5.65 (110.0)	2.93 (78.3)	52.0	4.90 (162.5)	8.41 (142.2)	1.87 (110.1)	21.5 (78.7)
48	6.11 (130.0)	5.95 (114.3)	2.85 (75.9)	48.1	4.78 (159.2)	8.49 (143.7)	2.33 (136.6)	25.9 (82.1)
49	6.11 (130.1)	5.95 (114.3)	2.63 (68.9)	44.3	5.22 (175.3)	8.26 (139.8)	2.34 (135.4)	22.7 (81.5)
50	6.15 (130.8)	5.45 (118.1)	2.57 (68.5)	47.1	4.89 (150.2)	8.27 (140.5)	2.28 (133.1)	23.9 (82.0)
51	5.85 (129.6)	5.68 (122.6)	2.55 (68.4)	45.2	5.03 (172.0)	8.37 (143.0)	2.45 (142.6)	23.2 (81.4)
52	5.57 (123.7)	5.31 (117.4)	2.35 (63.6)	44.1	4.90 (168.7)	8.17 (139.8)	2.62 (150.1)	20.9 (77.7)
53	5.46 (121.8)	4.73 (111.6)	2.35 (63.4)	50.3	5.42 (180.6)	8.72 (151.1)	3.04 (172.0)	20.6 (76.9)
54	5.40 (121.1)	4.83 (111.3)	2.31 (63.1)	48.0	4.88 (173.2)	8.57 (147.0)	3.12 (177.3)	19.7 (73.9)
55	5.29 (119.7)	4.06 (94.2)	2.26 (62.3)	56.1	5.22 (186.3)	8.78 (151.1)	3.33 (188.1)	16.8 (63.6)
56	5.42 (123.7)	4.78 (112.2)	2.22 (62.0)	46.0	5.13 (196.2)	8.61 (148.7)	2.82 (159.3)	19.4 (72.6)
57	5.25 (120.1)	4.54 (106.6)	2.12 (59.4)	47.2	4.97 (190.5)	8.67 (149.7)	2.78 (155.3)	16.6 (62.1)
58	5.10 (117.5)	4.42 (104.7)	2.12 (60.1)	48.4	4.75 (190.8)	8.85 (153.4)	3.49 (193.9)	18.8 (70.8)
59	4.48 (103.5)	4.06 (96.4)	1.78 (50.6)	43.8	4.90 (192.9)	7.94 (137.8)	3.13 (174.9)	15.0 (55.9)

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1.0 s; FRC, functional residual capacity; TLC, total lung capacity; RV, residual volume; DL_{CO}, diffusing capacity of the lung for carbon monoxide; Pred, predicted; NA, not available.

around a scar, usually caused secondary to airspace distortion by pneumoconiosis (Foster et al. 1993; Homma et al. 2005; Chonan et al. 2007; Pipavath et al. 2009); "paraseptal emphysema", showing rectangular cysts sharing a subpleural wall commonly in the upper lobe (Homma et al. 2003; Pipavath et al. 2009; Tsao et al. 2021); and "centrilobular emphysema", most commonly caused by smoking, showing centrilobular hypoattenuation with upper lobe predominance, which has been reported in indium lung (Pipavath et al. 2009; Nakano et al. 2016). As far as we are aware, there have been 7 reported cases of indium lung which had emphysema in HRCT (Table 2): 5 cases were the paraseptal type, the most common pattern among 7 cases (Homma et al. 2003; Homma et al. 2005; Cummings et al. 2012; Chonan et al. 2019). Paracicatricial type was confirmed in one case who had never smoked (Chonan et al. 2007). Centrilobular type was reported in one case, who had a smoking history of 11 pack-years, which progressed more severely than in our case (Nakano et al. 2016).

From these perspectives, it is more likely that centrilobular emphysema in this case was evoked by smoking; moreover, indium compounds also played a key role in the pathogenesis and enhancement of emphysema. The pathological features of indium lung have been reported as alveolar proteinosis, cholesterol granulomas, particles engulfed by macrophages, pulmonary fibrosis including honeycombing and emphysematous changes (Homma et al. 2005; Cummings et al. 2012; Chonan et al. 2019). In our case, the histopathological findings of the obtained specimens were compatible with previously reported indium lung (Fig. 4a-e). Furthermore, elemental analysis of the obtained specimen revealed that particles in the fibrotic interstitium

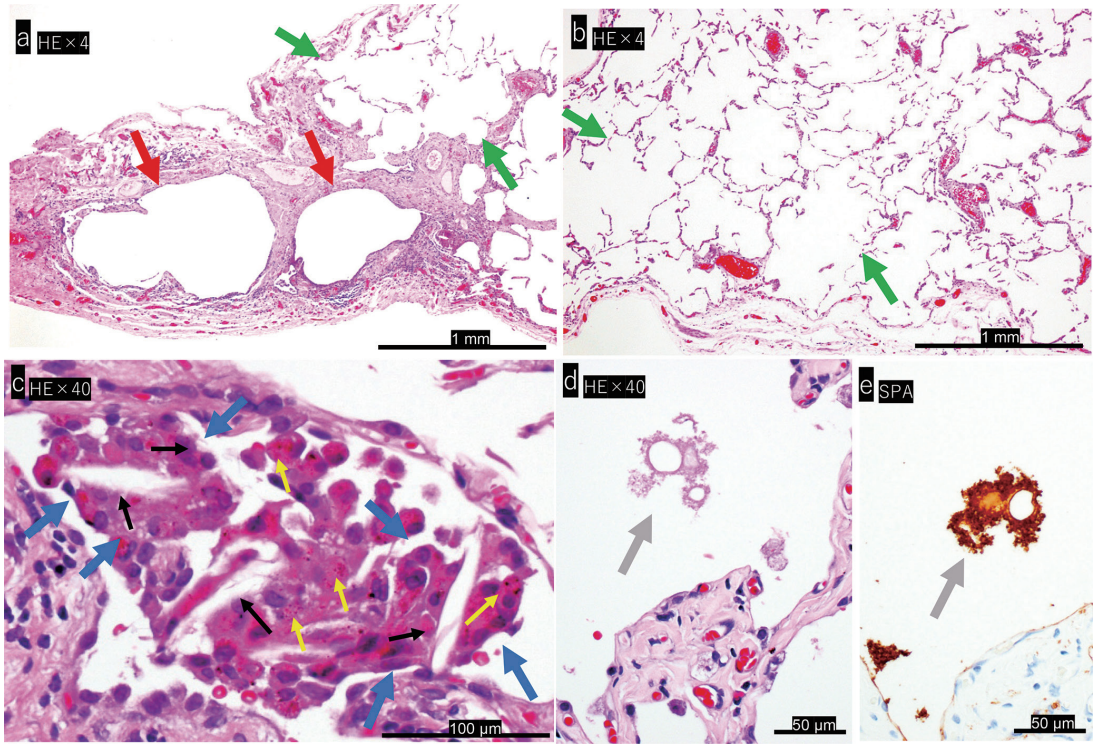


Fig. 4. Pathological findings of biopsied specimen in right middle and lower lobes.
(a) A biopsied specimen of the right middle lobe, which presents both honeycombing (indicated by red arrows) and emphysematous changes (shown as green arrows). (b) A biopsied specimen of the right lower lobe, in which emphysematous changes are presented (shown as green arrows). (c) Accumulation of giant cells and macrophages which have phagocyted particles (denoted by yellow arrows) and cholesterol crystals (shown as black arrows), forming a cholesterol granuloma (the range indicated by blue arrows). (d) Surfactant in the alveolar air space (denoted by gray arrows). (e) Surfactant protein A (SPA) staining (denoted by gray arrows).
HE, hematoxylin and eosin (HE) staining.

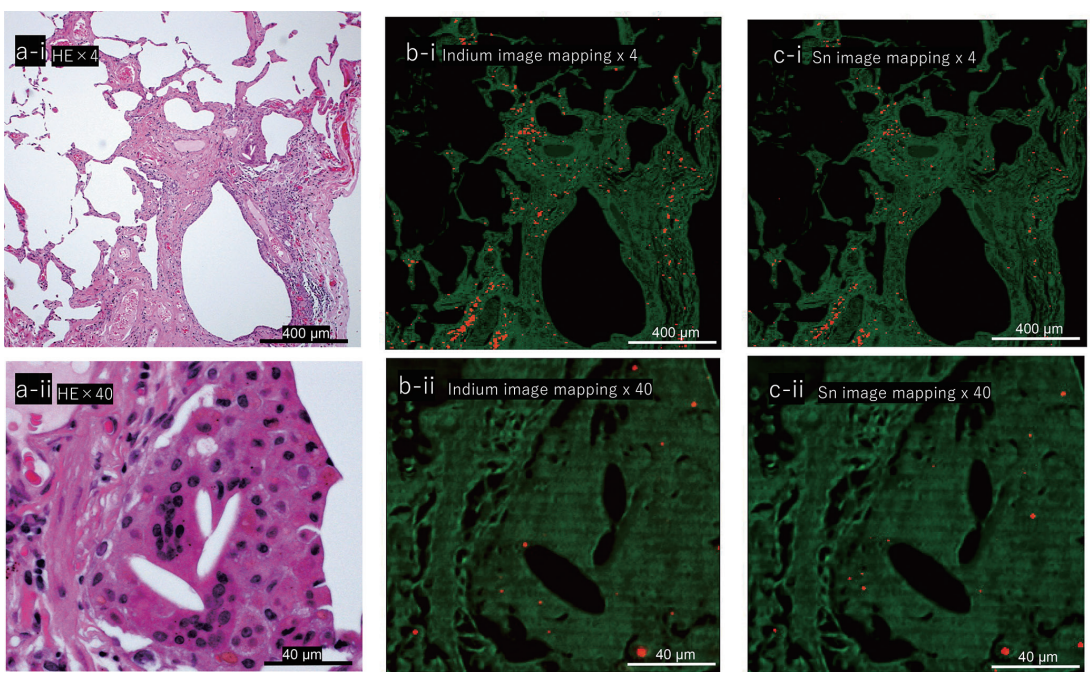


Fig. 5. Elemental analysis images of biopsied specimen in right lower lobe.
(a-i and a-ii) Biopsied specimens stained with hematoxylin and eosin (HE). (b-i and b-ii) Mapping image for indium in the elemental analysis. The deposition of the elements in the specimen is indicated in red to yellow; green indicates the deposition of nitrogen, used as a control. (c-i and c-ii) Mapping images for Sn.

Table 2. Clinical characteristics of previous indium lung cases.

Authors and publication year	Sex /Age	Smoking history (pack years)	sIn (μg/L)	Type of emphysema in HRCT	Other findings in HRCT	Interval between SLB and the end of exposure (years)
Homma et al. 2003	M/27	5	290	Paraceptal	Honeycomb, GGO	1
Homma et al. 2005	M/30	0.45	51	Paraceptal	Centrilobular fine nodular density, GGO	4
Chonan et al. 2007	M/28	Never	99	Paracicatricial	Fine reticulonodular shadows, GGO	NA
Cummings et al. 2012	M/29	5	152	Paraceptal	Interlobular septal thickening, GGO, subpleural fibrosis	NA
Cummings et al. 2012	M/51	Never	NA	Paraceptal	Interlobular septal thickening, GGO, traction bronchiectasis, subpleural fibrosis	NA
Nakano et al. 2016	M/36	11	99.7	Severe centrilobular	Interlobular septal thickening	10
Chonan et al. 2019	M/39	18	127	Paraceptal	Fine reticulonodular shadows	NA
Our case	M/59	15	128.9	Centrilobular	GGO	22

sIn, serum indium; HRCT, high-resolution computed tomography; SLB, surgical lung biopsy; M, male; GGO, ground grass opacity; NA, not available.

and giant cells resulted from the accumulation of macrophages containing the element indium (Fig. 5b-ii).

Although the mechanism of pulmonary parenchyma destruction by indium particles has not been determined, it has been reported that macrophages become dysfunctional after phagocytosing indium particles, resulting in fibrosis and emphysema (Cummings et al. 2012; Nakano et al. 2016).

In conclusion, this case report describes the progression of indium lung, especially the emphysematous changes of indium lung for 22 years after the end of exposure. It is suggested that indium-tin oxide particles deposited in the lung could persist and continue to damage pulmonary alveoli over a long period of time. The relative contribution of indium and smoking in the pathophysiology of indium lung remains to be explored.

Author Contributions

Y.Y., T.C. and A.A. treated the patient. A.A. supervised the bronchoscopy and subsequent treatment. H.I. performed the operation. Y.K. made the pathological diagnosis. H.M. and T.K. performed the elemental analysis. Y.Y. drafted the initial manuscript and submitted the final manuscript. T.C., N.H. and Y.K. revised the manuscript. T.N. and A.A. critically reviewed the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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