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Commentary

Paraseptal Emphysema in Indium Lung: Tracing the Pathological Footprints of Chronic Exposure

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Indium lung is an occupational lung disease caused by exposure to indium-tin-oxide (ITO) dust. Compared to other occupational lung diseases, indium lung has a shorter latency period and the respiratory status continues to worsen even after exposure to the work environment improves. Paraseptal emphysema which affects mainly the subpleural area is seen on chest images obtained via computed tomography (CT), regardless of the smoking history. However, the pathogenesis of emphysema in indium lung is still unclear. Therefore, we re-evaluated the pathology of three previously reported cases of indium lung. Paraseptal emphysema was observed in both smokers and nonsmokers. Obstructive respiratory impairment worsened over time in the cases with paraseptal emphysema. Many alveolar walls were destroyed independent of the presence or absence of emphysetamous changes or fibrosis. Moreover, bronchiolitis was found to be less common in indium lung than in asbestosis (the most common occupational lung disease) or common cases of chronic obstructive pulmonary disease caused by smoking. It has been shown that ITO causes protease anti-protease imbalance, oxidant-antioxidant imbalance, and continuous, abnormal inflammation (the three major causes of emphysema). In addition, nano-sized ITO is less likely to be trapped in the upper airways and may easily reach the subpleural alveoli. Furthermore, ITO may continue to cause sustained tissue injury at the alveolar level potentially resulting in emphysema. Further studies are needed to elucidate the detailed pathogenesis of indium lung by comparing it with other occupational lung diseases.

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Commentary

Indium lung is an occupational lung disease that develops after months or years of inhalation of poorly soluble indium compounds such as indium-tin-oxide (ITO) dust. ITO is generally used as transparent electrodes in flat panel displays. Pathologically, indium lung is characterized by emphysema and interstitial pneumonia, accompanied by numerous cholesterol granulomas with brownish fine particles engulfed by alveolar macrophages and giant cells. In addition, some patients have varying degrees of pulmonary alveolar proteinosis (PAP)-like histology that alveoli contain amorphous, eosinophilic, and Periodic acid-Schiff stain-positive material, although anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) antibodies are exclusively negative in Japanese ITO workers.

The latency period of indium lung is shorter than that of the other occupational lung diseases such as asbestosis. After quitting the job or with the improvement in the work environment, interstitial changes regressed partially as seen on high-resolution computed tomography (HRCT), however in workers with higher serum indium levels the emphysematous changes have progressed. Moreover, the progression of respiratory dysfunction was not statistically related to the smoking history (Amata et al. 2015). It is possible that the inhaled indium compounds may strongly

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influence the development of emphysema, especially of paraseptal type. Paraseptal emphysema is a type of emphysema accompanied by the destruction of distal mainly subpleural alveolar ducts and sacs. Yet, the pathogenesis underlying indium lung development remains unclear. Therefore, we aimed to re-evaluate the histopathology of the indium lung cases, especially focusing on emphysema.

A total of three indium lung cases with or without a history of smoking were evaluated. All three cases have been previously reported elsewhere: Case 1 was reported by Yabuuchi et al. (2023), Case 2 by Amata et al. (2019); Case 3 by Chonan et al. (2019) and Inoue et al. (2023). Case 1 was an ex-smoker, and Cases 2 and 3 were never-smokers.

Case 1 was a 64-year-old man, who underwent video-assisted thoracic surgery (VATS) of the middle and lower lobes to examine the cause underlying the progression of emphysema 10 years after stopping indium exposure. Clinically, the obstructive respiratory disorder was progressed, and the predicted forced expiratory volume in one second (%FEV1.0) decreased from 91% to 63% over the 10 years. Histological examination of the specimens indicated paraseptal emphysema and honeycombing. Generally, in paraseptal emphysema, there is no fibrosis, whereas in honeycombing there is a complete loss of acinar architecture and there are numerous cystic airspaces with thick fibrous walls which represent the late stages of various lung diseases. In this case, many alveolar walls were ruptured and destructed in the areas with or without paraseptal emphysema (Fig. 1a). Hyperplasia of alveolar type II epithelium was focally observed. Bronchiolitis was mild (Fig. 1b), but infiltration of lymphocytes was occasionally observed in the pleura.

Case 2 was a 46-year-old man who underwent VATS of left S9 for treatment and examination of the metastatic site of a lung adenocarcinoma which primarily arose in the left S1+2 after 12 years of stopping exposure to indium. Respiratory function did not change significantly and %FEV1 was approximately 80% in 12 years. Histologically, the lung tissue adjacent to the metastatic tumor showed fibrosis and smooth muscle hyperplasia along with architectural remodeling in the subpleural lung. Numerous macrophages and cholesterol granulomas were seen in the alveoli. These histological findings aligned with that of usual interstitial pneumonia (UIP) and secondary changes related to pulmonary alveolar proteinosis. No emphysema was noted in this area.

Case 3 was a 47-year-old man, who underwent VATS for the treatment of pneumothorax two times in the same year and four years after exposure to indium ceased. The %FEV1 significantly decreased from 52% to 19% in 18 years. This case underwent lung transplantation for respiratory failure after 20 years after exposure to indium ceased. Paraseptal emphysema was predominantly observed in VATS specimens (Fig. 1c). Many alveolar walls were destructed in the areas with or without paraseptal emphysema (similar to Case 1). The right lung specimen obtained during transplantation showed various degrees of paraseptal emphysema and fibrosis. Honeycombing and UIP-like patterns were partially observed. Specimens obtained from the second VATS and transplantation showed hemosiderosis indicating previous hemorrhage caused by the destruction of the lung tissue.

The pathological findings that were common to all the three included cases can be summarized as varying degrees of alveolar wall destruction and fibrosis, irrespective of the smoking history. Moreover, brown particles of ITO contained in the macrophage and multinuclear cells were identified in the stroma where lymphocytes infiltrated (Fig. 1d). The lung parenchyma, including the alveolar walls, pleura, and bronchioles as seldom infiltrated with lymphocytes. The CD4 : CD8 was 2-3 : 1, a non-specific pattern. Infiltration with neutrophils and eosinophils was rarely observed. Emphysema was seen in two of the three cases, in particular paraseptal emphysema was observed instead of centrilobular. Based on these findings it was hypothesized that after reaching the alveoli, ITO might damage and destruct the alveolar walls, and could move into the lymphatic vessels or stay in the stromal area. Respiratory function in Case 2 was stable, but Cases 1 and 3, who had prominent alveolar wall destruction and paraseptal emphysema had declining %FEV1 function suggesting that the presence of ITO in the lung tissues of these cases might

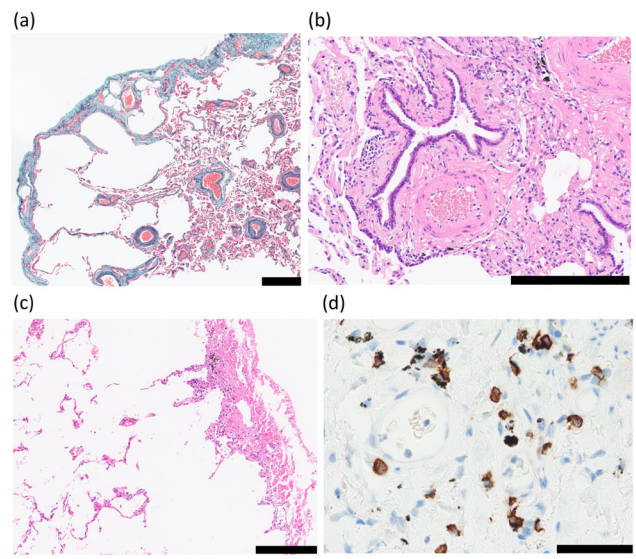

Fig. 1. Pathological features of indium lung cases.
Alveolar walls were destructed predominantly in the subpleural area in the lung of the patients with or without a history of smoking in Case 1 (a, b) and Case 3 (c, d). (a) The sample of paraseptal emphysema in Case 1. Elastica Masson staining, bar = 500 μm. (b) Mild bronchiolitis with infiltration of lymphocytes in Case 1, bar = 250 m. (c) The sample of paraseptal emphysema in Case 3. A specimen of the first video-assisted thoracic surgery (VATS) by hematoxylin eosin staining, bar = 250 μm. (d) CD8 positive lymphocytes (stained in brown) infiltrated around the depositions of brown to black particles of ITO in Case 3, bar =50 μm.

have caused progressive tissue injury over 10 years.

The main mechanisms of emphysema pathogenesis are disturbed protease-anti-protease balance, oxidant-antioxidant balance, and chronic inflammation (Hasleton and Flieder 2013). ITO has been shown to cause these three recognized factors increasing free radicals, proteases, and many cytokines which cause persistent inflammation (Badding et al. 2014; Jiang et al. 2017; Wang et al. 2021; Liu et al. 2022). In the subpleural area, elastic fibers are known to be more fragile compared to other areas (Travis et al. 2002). In our cases, ITO particles were widely distributed in the pleura and other interstitial regions. Many alveolar macrophages that engulfed ITO particles were accumulated in alveoli including the subpleural area. Inflammation and fibrosis at bronchioles were milder in indium lung disease than in other inhalational lung diseases. The inhaled material could reach the alveoli if it is small and not trapped and removed by the upper airways, as well as gases in smoking smoke or ultrafine and ultrashort asbestos fibers. Experimental models using artificial fluids have shown that the concentrations of ^{115}In and ^{118}Sn were higher in the lower airways than in the upper airways in contact with ITO powder despite the very low solubility of ITO (Andersen et al. 2017). Nano-sized ITOs were expelled more slowly in an animal model of indium lung (Qu et al. 2021). Endocytosis of ITO by macrophages resulted in production of cytokines and pyroptosis or apoptosis of macrophages (Badding et al. 2014; Naji et al. 2016), other macrophages may engulf apoptotic cells or ITO released from dead cells, and ITO could remain in lung tissue (Fig. 2). These findings suggest that smaller-sized ITO could easily pass through the bronchus and bronchiole to the alveoli and interstitium in the subpleural area, which is the most distal area of the airway. In addition, ITO might pass the alveolar barrier and reach lung interstitium via osmotic and hydraulic pressure gradient, as demonstrated in asbestosis (Miserocchi et al. 2008). ITO might damage alveolar walls by increasing free radicals, proteases, and cytokines in subpleural area (Fig. 2) causing paraseptal emphysema.

In conclusion, indium might have a strong influence (equivalent to or stronger than smoking) on development of emphysema, especially the paraseptal type. In addition to detailed clinical and histological observations, to elucidate pathogenesis of indium lung, comprehensive studies are needed to compare the differences in cytokines in bronchoalveolar lavage fluid or single-cell RNA sequencing of macrophages and lymphocytes in indium lung and other respiratory diseases.

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Conflict of Interest

The authors declare no conflict of interest.

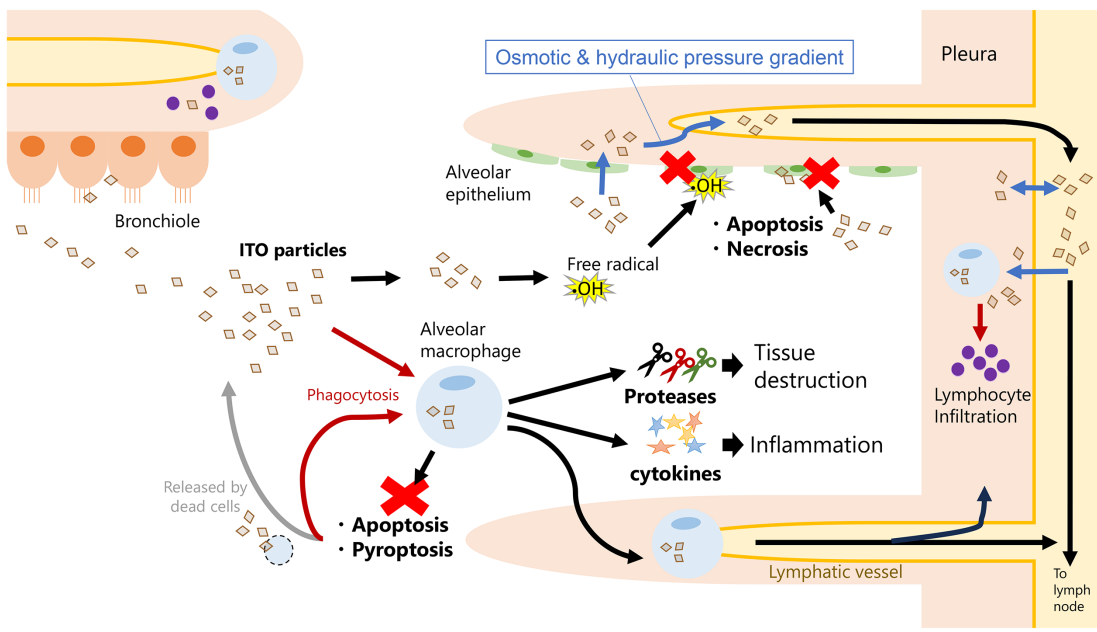

Fig. 2. Schema of possible mechanisms of tissue damage caused by indium-tin-oxide (ITO) which results in paraseptal emphysema.
Nano to micro-sized ITO might reach subpleural alveoli without being trapped. ITO could injure the alveolar epithelium by increasing free radicals. Macrophage which engulfs ITO may produce a variety of cytokines and proteases, and/or result in cell death. ITO might remain in alveoli due to the cell death of macrophages. A combination of these factors may work together to cause paraseptal emphysema.

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