Correspondence

Indium-Tin Oxide Does Not Induce GM-CSF Autoantibodies

To the Editor:

It has been reported that autoantibodies against granulocyte/macrophage colony-stimulating factor (GM-CSF autoantibodies) cause autoimmune pulmonary alveolar proteinosis (PAP), which accompanies increases in serum markers such as KL-6 and SP-D (1). In a previous issue, Cummings and coworkers (2) reported two cases of PAP that occurred in indium-tin oxide (ITO)-processing workers. Of these, one showed elevated serum GM-CSF autoantibody levels; in the other case, diagnosis was made post-mortem and serum was not available. Based on these findings, the authors suggested the possibility that inhaled ITO induces GM-CSF autoantibodies, and therefore PAP. This hypothesis is intriguing, because it is well known that rheumatoid arthritis, a typical autoimmune disease, is associated with occupational dust exposure (3). Because the production of ITO has increased markedly in recent years, due to its use in transparent conductive coatings for liquid-crystal and plasma display panels, it is necessary to examine this hypothesis in industrial medicine.

In Japan, pathologically proven cholesterol granuloma and pulmonary fibrosis with elevated serum KL-6 levels have been reported to occur in subjects exposed to ITO (4–7). Re-evaluation of lung specimens revealed that localized PAP-like findings characterized by accumulation of periodic acid-Schiff–positive materials in alveoli with cholesterol deposits were present in four of seven cases, but major pathological changes consisted of cholesterol crystal–laden macrophages and fibrosis in the interstitium. In contrast, amorphous materials diffusely occupied the alveoli in the cases reported by Cummings and colleagues. Chest high-resolution computed tomography (HRCT) features demonstrated that the Japanese cases had interlobular septal thickening in all seven cases, but not typical ground glass opacity. Lung biopsy was performed between1 and 2 years after the beginning of ITO exposure in the cases reported by Cummings and coworkers, whereas biopsy was performed 4 to 20 years after ITO exposure in the Japanese cases. We speculate that alveolar proteinosis represents a relatively acute phase response, particularly in cases of massive exposure, and it is replaced by cholesterol granuloma and fibrosis in the long term.

To clarify whether inhaled ITO induces GM-CSF autoantibodies, we measured serum GM-CSF antibodies in 17 current and former Japanese ITO workers at two factories, all of whom showed high levels of KL-6 (age, 41 ± 11 yr; mean ± SD). Of these 17 workers, nine had interstitial abnormalities on chest radiography and/or HRCT. Work duration, serum indium concentrations, serum KL-6, and SP-D levels of the subjects were 10.5 ± 1.2 years, 34 ± 6 ng/ml (normal range, 0.3 ± 2.6), 1,067 ± 185 U/ml (< 500), and 117 ± 20 ng/ml (< 110), respectively. Serum GM-CSF autoantibody levels were below the cut-off level in all subjects. This is consistent with our observation that serum GM-CSF autoantibodies were not induced in rats chronically exposed to ITO. Thus, our cases suggest that ITO inhalation does not induce GM-CSF autoantibodies.

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From the Authors:

As Omae and colleagues recently pointed out, it has been difficult to reconcile seven cases of interstitial pneumonia and three cases of pulmonary alveolar proteinosis among 10 published cases of lung disease in indium workers (1). Dr. Masuko and colleagues describe a re-evaluation of pathologic specimens from cases of interstitial pneumonia in Japanese indium workers that revealed the presence of periodic acid-Schiff–positive material not previously reported. We are pleased that the theory of disease evolution (from alveolar proteinosis to fibrosis and emphysema) initially proposed at a September 2010 workshop on indium-related lung disease sponsored by the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention has now been

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

accepted by workshop attendees who co-authored the letter. However, we object to the characterization of alveolar proteinosis as a response "particularly in cases of massive exposure," as exposure assessment has been lacking (1, 2) or limited (3, 4) and precludes comparative analysis among cases. Furthermore, this characterization is not supported by the development of alveolar proteinosis in animals exposed to indium-tin oxide in airborne concentrations as low as the NIOSH recommended exposure limit of 0.1 mg/m^3 (5).

We appreciate the information that Masuko and colleagues provide on the measurement of autoantibodies to granulocyte/macrophage colony-stimulating factor in 17 indium workers and in rats exposed to indium-tin oxide, which suggests that if autoimmunity played a role in indium toxicity in the second case we described (4), the mechanism of indium's toxicity is not exclusively autoimmune. Further investigation into the mechanism of indium toxicity is warranted, and may inform preventive efforts.

In describing the 17 indium workers, the authors note that the normal range of serum indium is 0.3 ± 2.6 ng/ml. While not a range *per se*, we wonder if these numbers are derived from analyses suggesting a serum indium greater than 2.9 ng/ml is associated with elevations in KL-6 in current indium workers (6). If so, we question the derivation of a normal range from an exposed population and encourage the use of norms derived from unexposed populations in the future. Whether office workers in indium facilities are truly unexposed—and without long-term risk of lung disease—remains to be determined from follow-up studies.

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Right Pulmonary Agenesis in a 12-Year-Old Girl

To the Editor:

Pulmonary agenesis, an uncommon congenital malformation, is usually unilateral, with male predominance (1). More than half of the patients also have cardiovascular, genitourinary, gastrointestinal, and skeletal malformations, and these contribute to the patient's mortality and prognosis (2–6). Thus, the assessments for these accompanying malformations are important after the diagnostic process of pulmonary agenesis. Recently, whole-body magnetic resonance imaging (WB-MRI) has come into

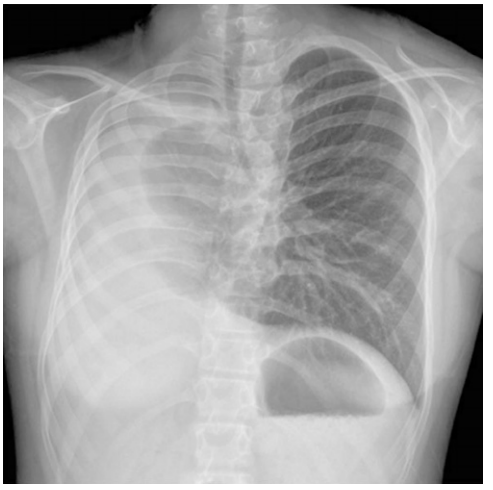

Figure 1. A chest radiograph showed complete opacification of right hemithorax, with hyperinflation of the left lung, and shifting of the mediastinum to the right side.

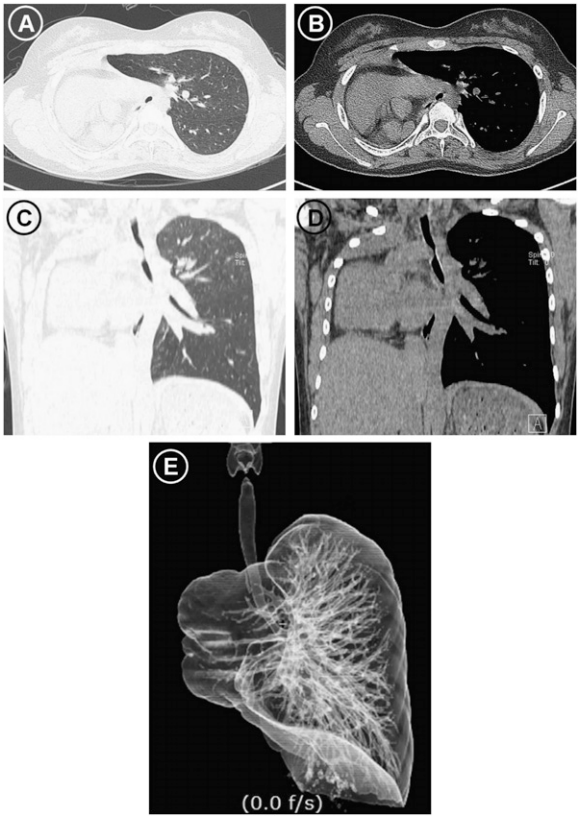

Figure 2. Chest computed tomography (CT) scan and three-dimensional CT bronchogram showed absence of the right main bronchus, right branch of the pulmonary artery, and right lung parenchyma, hyperinflated and enlarged left lung, and deviated heart and main vessels into right thoracic cavity (*A–D*: CT of chest, *E*: 3D CT bronchogram).