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Original Research

OCCUPATIONAL AND ENVIRONMENTAL LUNG DISEASES

Indium Lung Disease

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Background: **Reports of pulmonary fibrosis, emphysema, and, more recently, pulmonary alveolar proteinosis (PAP) in indium workers suggested that workplace exposure to indium compounds caused several different lung diseases.**

Methods: **To better understand the pathogenesis and natural history of indium lung disease, a detailed, systematic, multidisciplinary analysis of clinical, histopathologic, radiologic, and epidemiologic data for all reported cases and workplaces was undertaken.**

Results: **Ten men (median age, 35 years) who produced, used, or reclaimed indium compounds were diagnosed with interstitial lung disease 4-13 years after first exposure (n = 7) or PAP 1-2 years after first exposure (n = 3). Common pulmonary histopathologic features in these patients included intraalveolar exudate typical of alveolar proteinosis (n = 9), cholesterol clefts and granulomas (n = 10), and fibrosis (n = 9). Two patients with interstitial lung disease had pneumothoraces. Lung disease progressed following cessation of exposure in most patients and was fatal in two. Radiographic data revealed that two patients with PAP subsequently developed fibrosis and one also developed emphysematous changes. Epidemiologic investigations demonstrated the potential for exposure to respirable particles and an excess of lung abnormalities among coworkers.**

Conclusions: **Occupational exposure to indium compounds was associated with PAP, cholesterol ester crystals and granulomas, pulmonary fibrosis, emphysema, and pneumothoraces. The available evidence suggests exposure to indium compounds causes a novel lung disease that may begin with PAP and progress to include fibrosis and emphysema, and, in some cases, premature death. Prospective studies are needed to better define the natural history and prognosis of this emerging lung disease and identify effective prevention strategies.** ***CHEST 2012; 141(6):1512–1521***

Abbreviations: DLCO = diffusing capacity of lung for carbon monoxide; GM-CSF = granulocyte-macrophage colony stimulating factor; ILD = interstitial lung disease; ITO = indium-tin oxide; KL-6 = Krebs von den Lungen; LCD = liquid crystal display; PAP = pulmonary alveolar proteinosis

Indium is a relatively rare element that has had limited use for decades as a metal, in alloys, and for electronics applications. During the past 15 years, global demand for indium has increased several-fold, driven by the novel use of indium-tin oxide (ITO) thin films in the production of flat-panel displays (such as liquid crystal displays [LCDs]), touch screens, and other electronic devices.[1,2] ITO is a sintered ceramic material typically consisting of 90% indium oxide (In_2O_3) and 10% tin oxide (SnO_2). Exposures to indium metal and indium compounds (including indium hydroxide [$In(OH)_3$], indium oxide, and ITO) may occur during ITO production, ITO use for the creation of thin films, and reclamation. The bulk of the ITO industry is located in Japan, with some activity in the United States, China, Taiwan, and South Korea.[3]

As of May 2010, 10 clinical cases of lung disease in indium workers from three countries (Japan, United States, and China) had been reported.[2] Seven cases were described as interstitial lung disease (ILD) characterized by pulmonary fibrosis with or without emphysema. Three cases were described as pulmonary alveolar proteinosis (PAP). Individually, these 10 case reports left unclear why some workers developed ILD and others developed PAP, and the relationship, if any, between these distinct pulmonary disease processes.

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Materials and Methods

A multidisciplinary panel with knowledge of the previously published cases and workplaces was assembled for a workshop on indium lung disease. Authors provided additional clinical details and follow-up information for nine of the 10 reported cases[4-9]; the 10th case was included on the basis of the available published data.[10] A chest radiologist (R. J. T.) reviewed radiologic images (including at least one chest CT image per case) with attention to the findings of PAP, ILD, and emphysema. Three chest pathologists (R. A. H., V .L.R., and A. H.) evaluated pathologic materials using a modification of a standardized scoring sheet for idiopathic pulmonary fibrosis.[11] Due to logistical constraints, four cases were reviewed by two pathologists; all other cases were reviewed by three pathologists. A pulmonologist (B. C. T.) provided expertise on PAP. Epidemiologists and industrial hygienists reviewed findings of workplace investigations.

Results

Clinical Features

All cases occurred in men, with a median age at diagnosis of 35 years (Table 1). Case H, illustrative of the reviewed cases, is described in the e-Appendix.[7] The most common symptoms at diagnosis were cough, dyspnea, and sputum production (Table 1). In one case (G), the patient developed intermittent hemoptysis after diagnosis. In all cases, symptoms (other than those related to pneumothorax) were of insidious onset and lacked a work-related pattern. Latency from hire to symptom onset was 6-14 months for those initially diagnosed with PAP and 2-14 years for those initially diagnosed with ILD (overall median, 3 years). Latency from hire to diagnosis is shown in Table 1 (overall median, 6 years). Adventitious sounds on chest auscultation and digital clubbing occurred in a minority of cases (Table 1).

Laboratory Features

Laboratory studies were notable for normal WBC count in all but case D (13,000 cells/μL). Mild elevations of aspartate aminotransferase (maximum, 108 IU/L) and alanine aminotransferase (maximum, 96 IU/L) were seen in four of nine cases; liver biopsy was not conducted. C-reactive protein level was elevated in two of nine cases. Serum Krebs von den Lungen (KL-6), a high-molecular-weight glycoprotein expressed by alveolar type 2 epithelial cells that has been described as an ILD marker,[12,13] was elevated (median, 3,450 IU/L; range, 799-6,395 IU/L; normal < 500 IU/L) in all seven case patients initially diagnosed with ILD; it was not available in the other cases. In case B, autoantibodies to granulocyte-macrophage colony-stimulating factor (GM-CSF) were measured (by B. C. T.) and were elevated at 52.9 μg/mL (normal < 3 μg/L).

Pulmonary Function and Bronchoscopy Findings

Pulmonary function test results were variable (Table 1). Four case patients, including those initially diagnosed with PAP, had restriction and low diffusing capacity of lung for carbon monoxide (Dlco), while one case patient initially diagnosed with ILD had obstruction. In case B, serial spirometry revealed a fall in FEV_1 of 0.5 L in the first year of employment. BAL fluid analyses demonstrated overall increased cellularity (Table 1). Lymphocytes predominated in most cases, while there were increased macrophage counts in cases I and J.

Radiologic Features

Radiologic features at diagnosis are presented in Table 1; Figures 1A, 2A; and e-Figures 1B, 1C. In the three case patients initially diagnosed with PAP, a "crazy paving" pattern consisting of ground-glass opacities superimposed on interlobular septal thickening in a geographic distribution was noted. The patient in case C also had areas of ground-glass opacity nodules with a centrilobular distribution. The case D patient had nodules with a centrilobular distribution and the case E patient had nodules with a perilymphatic distribution.

Fibrotic changes were apparent in six case patients initially diagnosed with ILD and included traction

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Table 1—*Characteristics at Diagnosis of 10 Reported Cases of Lung Disease in Men Who Worked With Indium Compounds, in Order of Increasing Diagnostic Latency*

	Case Letter									
	A[8]	B[8]	C[9]	D[4]	E[6]	F[10]	G[5]	H[7]	I[5]	J[5]
Demographics										
Age, y	51	40	29	27	44	30	28	47	31	39
Smoke exposure, pk-y	0	<1	0	5	0	<1	0	10	0	18
Country	US	US	China	Japan	Japan	Japan	Japan	Japan	Japan	Japan
Indium exposure										
Year of hire	1999	2004	2005	1994	2000	1994	1992	1993	1990	1989
Job	R	TM	SB	G	IO	G	G	TM	G	G
Duration, y	1	2	2	3	4	4	8	10	12	12
Indium blood level, μg/L	NA	<5	152	290	65	51	99	92	40	127
Clinical features[a]										
Diagnostic latency, y	1	2	2	4	4	8	10	10	12	13
Cough	+	+	+	+	+	+	+	+	+	−
Dyspnea	+	+	+	+	+	+	−	−	−	−
Sputum production	−	−	+	−	+	−	+	−	+	−
Chest discomfort	+	+	+	−	−	−	−	−	−	−
Pneumothorax	−	−	−	+	−	−	+	−	−	−
Systemic symptoms	−	−	+	+	−	−	−	−	−	−
Chest exam findings	−	−	+	+	−	−	−	−	−	−
Digital clubbing	−	−	−	+	−	−	+	−	+	−
Pulmonary function										
FVC, % predicted	73	77	43	NA	74	93	95	89	92	79
FEV_1, % predicted	82	83	42	NA	72	73	52	89	82	76
FEV_1/FVC, %	90	87	98	NA	81	73	49	82	78	84
TLC, % predicted	75	66	NA	NA	75	109	117	NA	91	91
DLCO, % predicted	37	63	31	NA	39	89	78	NA	77	95
BAL										
Total cell count, $\times 10^5$/mL	9.8	NA	NA	NA	5.8	3.0	NA	1.2	6.7	5.9
Macrophages, %	59	NA	NA	NA	66	78	NA	54	97	84
Lymphocytes, %	39	NA	NA	NA	35	19	NA	44	3	9
Neutrophils, %	2	NA	NA	NA	0	2	NA	0	0	6
Eosinophils, %	0	NA	NA	NA	0	1	NA	0	0	1
Radiologic features[b]										
Ground glass opacity	+	+	+	−	−	−	+	+	+	+
Septal thickening	+	+	+	−	+	+	−	+	+	+
Fibrosis	−	−	−	+	+	−	+	+	+	+
Emphysema	−	−	−	−	−	+	+	+	−	+
Pathologic features[c]										
Biopsy type	S	S	TB, S	A	TB	S	S	TB, S	TB	TB
Indium present	+	+	+	+	+	+	NA	+	NA	NA
Foamy macrophages	+	+	+/++	+	+	±	−	+	+	−
Alveolar exudate	+++	+/++	++	+	±	−	+	+/++	±	+
Cholesterol clefts	+	+	++	+++	+	++	++	++	+	+
Granulomas	+	+	++	+++	+	++	++	++	+	+
Fibrosis	+	±	±	+++	−	+	++	+++	+	++

A = autopsy; DLCO = diffusing capacity of lung for carbon monoxide; G = wet surface grinder who machined sintered ITO tiles at an ITO production facility; IO = indium oxide maker who made indium oxide at a facility that was not known to produce or use ITO; ITO = indium-tin oxide; NA = not available; R = reclaimer who recovered indium metal from used ITO tiles and indium-containing production waste at an ITO production facility; S = surgical; SB = sandblaster who cleaned components of ITO thin-film production machinery by sandblasting with aluminum oxide at a facility manufacturing liquid crystal displays for mobile telephones; TB = transbronchial; TLC = total lung capacity; TM = tile maker who made sintered ITO tiles at an ITO production facility.

[a]Case D patient had pneumothorax at diagnosis and ultimately died of bilateral pneumothoraces. Case G patient had a history of right-sided pneumothorax and underwent surgical repair of left-sided pneumothorax after diagnosis. "Systemic symptoms" include fever, night sweats, anorexia, and weight loss.

[b]Findings from studies done as part of the initial diagnostic evaluation, corresponding to the histopathology, except in case D, in which reviewed histopathologic material was obtained at autopsy 3 years after diagnostic imaging. Severity was not systematically determined due to the limited number of images available in most cases.

[c]Pathologists reviewed original tissue specimens except in cases C (12 high quality digital images reviewed) and F (four published images reviewed). Severity reflects median score: − = negative; ± = minimal; + = mild; ++ = moderate; +++ = severe.

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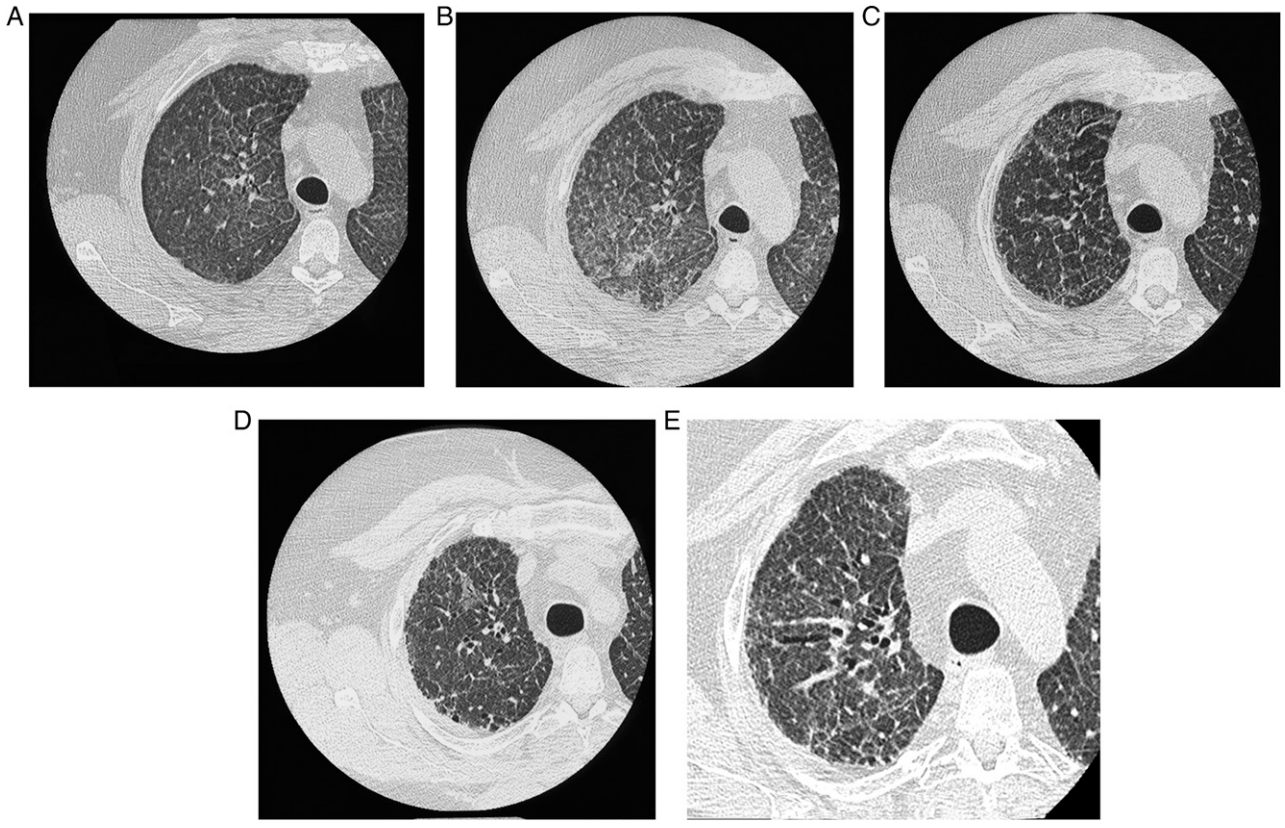

FIGURE 1. Case A: CT scans of the chest showing progression of disease over 5 years. A, In January 2001 at age 51 years, 3.5 months after leaving employment. In this area of the lung, the predominant finding is mild interlobular septal thickening. B, In July 2001 at age 51 years, 10 months after leaving employment. Increased septal thickening and the development of ground-glass opacities are seen. C, In February 2002 at age 52 years, 1.5 years after leaving employment and 6 months after whole-lung lavage. Fibrotic changes are now apparent, including subpleural septal thickening and traction bronchiectasis. D, In June 2005 at age 55 years, nearly 5 years after leaving employment. Early honeycombing changes are apparent posteriorly. E, In July 2006 at age 56 years, nearly 6 years after leaving employment. Further increases in septal thickening, traction bronchiectasis, and subpleural fibrosis have occurred.

bronchiectasis and/or bronchiolectasis in five cases, subpleural disease in four cases, hilar retraction in three cases, honeycombing in three cases, and evident volume loss in two cases. Case F was noted to have septal thickening, but otherwise, findings of fibrosis were not seen in the two available published images.[10]

Four case patients with 0-18 pack-year smoking histories had emphysema (Table 1), with a centrilobular pattern. In addition, although the single available CT image for case D did not demonstrate emphysema, the presence of pneumothorax, pneumomediastinum, and accompanying subcutaneous emphysema suggested emphysema may have been present on other images. Blebs were evident in cases G and J (the former patient having a history of pneumothorax).

Histopathologic Features

Histopathologic features at diagnosis or autopsy (case D) are presented in Figure 3, Table 1, and e-Figure 2. In all but case F, a granular, eosinophilic, intraalveolar exudate characteristic of alveolar proteinosis was noted by at least two pathologists. Cholesterol clefts (acicular spaces representing crystals of cholesterol esters[14] that have been dissolved by histologic processing[15]) were seen in all cases. Granulomas were observed in association with cholesterol clefts. Fibrosis was noted by at least two pathologists in all but case E. Fibrosis associated with cholesterol clefts was typically more common and more extensive than fibrosis not associated with cholesterol clefts. Honeycombing was noted in cases D and H. Emphysema was apparent histopathologically in case G, due to bullectomy.

In all cases, particles were noted in the lung tissue by light microscopy. Both for case patients initially diagnosed with PAP and case patients initially diagnosed with ILD, particle frequency ranged from occasional to abundant. Alveolar wall cellular infiltrate consisted primarily of occasional lymphocytes and macrophages. Alveolar wall metaplasia was uncommon. Airways mural fibrosis was universally absent.

Serial biopsy material was not available, with one limited exception. In case D, a published image from a surgical lung biopsy done 3 years before death of

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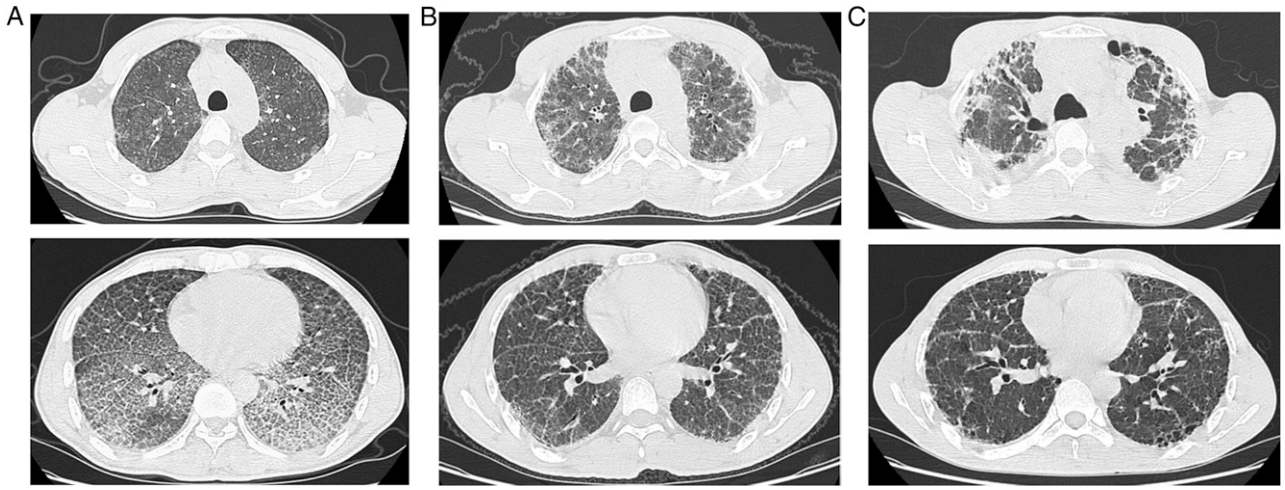

FIGURE 2. Case C: CT scans of the chest showing progression of disease over 3 years. A, In November 2007 at age 28 years, 4 months after leaving employment. The predominant findings are ground-glass opacities and interlobular septal thickening that in some areas give the appearance of crazy paving. B, In February 2009 at age 29 years, 1.5 years after leaving employment and 10 months after whole-lung lavage. Fibrosis is now apparent. C, In August 2010 at age 31 years, 3 years after leaving employment. Fibrosis has markedly increased. Prominent air spaces anteriorly may be a precursor to the emphysema seen in other cases.

the patient revealed abundant cholesterol clefts adjacent to apparently normal lung.[4] Fibrotic changes were not appreciated in the published images, in comparison with extensive fibrosis noted on autopsy.

Exposure to Indium Compounds

The case patients were employed in production, use, and reclamation jobs (Table 1) at five different facilities using indium compounds. Exposure assessments

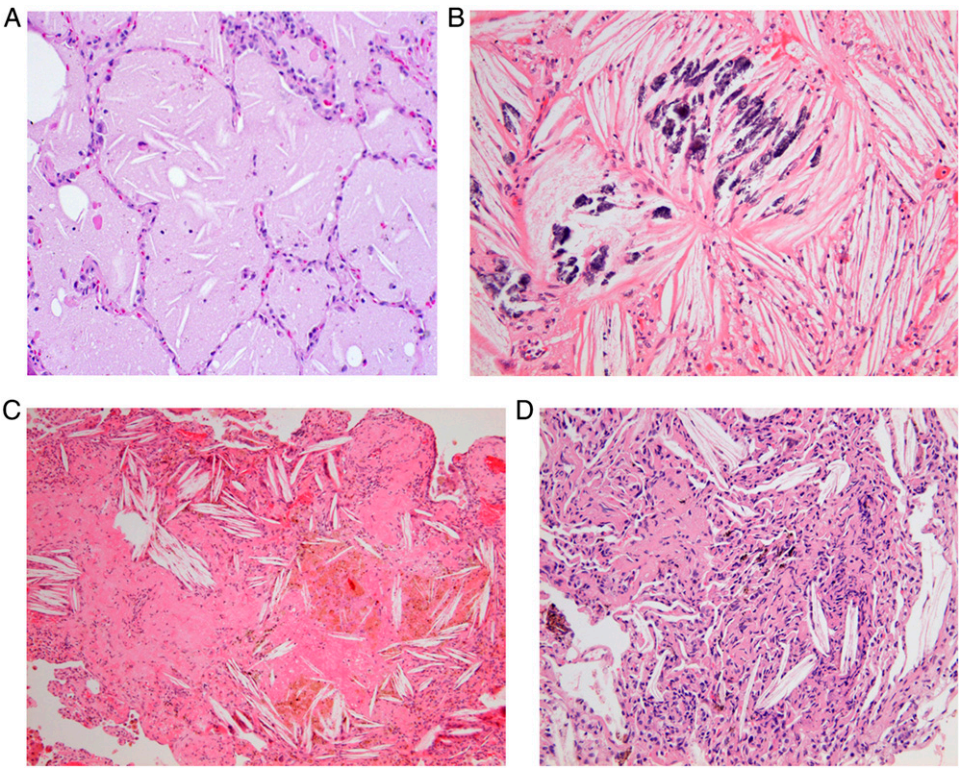

FIGURE 3. Spectrum of histopathologic features of indium lung disease (hematoxylin and eosin stains). A, Case B: intraalveolar exudate characteristic of alveolar proteinosis, with occasional cholesterol clefts (magnification ×200). B, Case D: innumerable cholesterol clefts (magnification ×200). C, Case G: intraalveolar exudate characteristic of alveolar proteinosis, cholesterol clefts, and fibrosis (magnification ×100). D, Case H: cholesterol clefts, associated multinucleated giant cells, interstitial fibrosis, and brown particles composed predominantly of indium (magnification ×200).

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at three of these facilities demonstrated the presence of particles in the respirable range (Table 2). Exposure assessment was not conducted at the third ITO production facility or at the indium oxide production facility. Respiratory protection either was not used (n = 3), or consisted of a disposable dust mask (n = 2) or half-face reusable respirator with filter cartridges (n = 5).

Blood indium concentration was evaluated in nine cases (Table 1). Among the eight cases with quantified serum indium, the median concentration was 96 μg/L (range, 40-290 μg/L; normal < 2.0 μg/L[16]). There was no relationship between serum indium and year of hire, duration of employment, facility type, job, or reported use of respiratory protection.

In six cases, the particles noted in lung tissue specimens were evaluated using techniques such as energy dispersive x-ray analysis, which confirmed the presence of indium. In case B, the patient's lung tissue was evaluated using inductively coupled plasma mass spectrometry, which demonstrated an indium concentration of 29.3 μg per gram of lung tissue (wet weight).

Natural History

Follow-up information was available through 2010 (or date of death) on all cases but case F, which was reported in 2005.[10] Exposure to indium compounds ceased prior to or at the time of diagnosis in all cases but case H, in which the patient continued to work with indium compounds through 2010. Two case patients experienced stabilization or some improvement in symptoms and objective abnormalities after diagnosis (Table 3). The patient in case B experienced some subjective and objective improvement after whole-lung lavage that was sustained over 5 years of follow-up. The patient in case F experienced symptom resolution and stabilization of objective abnormalities without specific treatment.

The remaining eight case patients worsened after diagnosis (Table 3). Serial radiologic studies demonstrated progression of disease over time (Figs 1, 2, e-Fig 1). Case A and C patients had some initial improvement after whole-lung lavage, followed by worsening, repeat whole-lung lavage, and subsequent progressive decline. Only the case G patient had an objective response to steroids, but it was unsustained. Two case patients ultimately died of their lung disease: case D at age 30 secondary to bilateral pneumothoraces 3 years after diagnosis, and case A at age 57 secondary to respiratory failure 6 years after diagnosis. Median blood indium concentration was 113 μg/L in cases that worsened and 40 μg/L in cases that stabilized or improved (Table 1). There was no relationship between clinical course and year of hire, duration of employment, facility type, reported use

Table 2—*Results of Exposure Assessments in Three Workplaces With Cases of Indium Lung Disease*

	Facility		
	ITO Production	LCD Production	ITO Production
Case information			
Case letter(s)	A, B[8]	C[9]	D, F, G, I, J[4,5,10]
Initial diagnosis	PAP	PAP	ILD
Fatal case occurred	Y	N	Y
Epidemiology			
No. of workers studied	57	15	108
Respiratory abnormalities	Abnormal PFTs	Symptoms (53%)	Interstitial changes (21%)
Exposure assessment			
Assessment year(s)	2004-2010	2007, 2009	2002
Air sampling			
Type	Personal	Area	Area
Location	Tile area, Reclaim area	Sandblasting room	Grinding room
Duration	Partial-shift, full-shift	Short (2007), full-shift (2009)	10-15 min
Dust,[a] mg/m^3	Tile: 0.24 (0.05-0.89) Reclaim: 1.2 (0.22-5.2)	Maximum: > 100 (2007) TWA: 3.27 (2009)	ND
Indium,[a] mg/m^3	Tile: 0.13 (0.03-0.59) Reclaim: 0.73 (0.06-4.0)	ND	0.05 (maximum: 0.24)
Particle size estimate			
Type	Dust, respirable fraction[b]	Indium oxide, diameter[c]	Dust, diameter[d]
Measurement	< 20%	0.1-6 μm	0.1-11 μm

ILD = interstitial lung disease; LCD = liquid crystal display; N = no; ND = not done; PAP = pulmonary alveolar proteinosis; PFT = pulmonary function test; TWA = time-weighted average; Y = yes. See Table 1 for expansion of other abbreviations.

[a]Values given are geometric mean (range) unless otherwise noted.

[b]The respirable fraction of dust in the air varied by location, but was < 20% by mass in four samples taken in locations throughout the facility.

[c]Determined from microanalyses of the sandblasting material.

[d]Determined by laser diffraction scattering method.

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Table 3—*Clinical Course Following Diagnosis of 10 Reported Cases of Lung Disease in Men Who Worked With Indium Compounds, in Order of Increasing Diagnostic Latency*

	Case Letter									
	A[8]	B[8]	C[9]	D[4]	E[6]	F[10]	G[5]	H[7]	I[5]	J[5]
Initial diagnosis										
Pulmonary alveolar proteinosis	+	+	+	−	−	−	−	−	−	−
Interstitial lung disease[a]	−	−	−	+	+	+	+	+	+	+
Follow-up period, y	6	5	3	4	5	3	8	7	8	8
Treatment										
Inhaled or oral steroids	+	+	+	+	+	−	+	+	−	−
Objective improvement	−	−	−	−	−	...	+	−	...	...
Sustained improvement	...	...	...	...	...	...	−	...	...	...
No. of whole-lung lavage	2	1	2	0	0	0	0	0	0	0
Objective improvement	+	+	+	...	...	...	...	...	...	...
Sustained improvement	−	+	−	...	...	...	...	...	...	...
Latest symptoms[b]										
Chest symptoms present	+	+	+	+	+	−	+	+	+	+
Progression since diagnosis	+	−	+	+	−	−	+	−	+	+
Latest pulmonary function										
FVC, % predicted	33	72	41	NA	NA	NA	89	NA	88	79
Change since diagnosis	↓	↓	↓				↓		↓	−
FEV_1, % predicted	37	73	35	NA	NA	NA	36	NA	75	77
Change since diagnosis	↓	↓	↓				↓		↓	↑
FEV_1/FVC, %	90	85	87	NA	NA	NA	35	NA	74	84
Change since diagnosis	−	↓	↓				↓		↓	−
TLC, % predicted	42	73	NA	NA	NA	NA	115	NA	91	74
Change since diagnosis	↓	↑					↓		−	↓
DLCO, % predicted	30	70	26	NA	NA	NA	54	NA	80	60
Change since diagnosis	↓	↑	↓				↓		↑	↓
Latest radiologic features[c]										
Fibrosis	+	−	+	NA	+	−	+	+	+	+
Emphysema	−	−	+	NA	+	+	+	+	+	+
Progression since diagnosis	+	−	+	NA	+	−	+	+	+	+
Status at end of follow-up[d]	↓ (D)	↑	↓	↓ (D)	↓	↑	↓	↓	↓	↓

(D) = died of lung disease. See Table 1 for expansion of other abbreviations.

[a]Interstitial lung disease diagnoses included interstitial pneumonia and pulmonary fibrosis with emphysema.

[b]Case B patient experienced some improvement in symptoms during follow-up. Case F patient experienced resolution of symptoms during follow-up. Case J patient was asymptomatic when identified through a workplace screening program. He later developed dyspnea, cough, and sputum production. Case I patient initially experienced resolution of symptoms, followed by recurrence and progression.

[c]In patients in cases A and C, fibrosis developed during follow-up. In patients in cases C, E, and I, cystic airspaces consistent with early emphysema developed during follow-up. For case F, follow-up imaging was not available for review, but was reportedly unchanged from reviewed imaging done at the time of diagnosis.

[d]↑ = improved compared with status at diagnosis; ↓ = worsened compared with status at diagnosis. Cases with symptom progression, pulmonary function decline, and/or radiographic progression were considered to have worsened since diagnosis.

of respiratory protection, symptom or diagnostic latency, diagnosis, or particle frequency on lung histopathology.

Epidemiologic Investigations

At the ITO production facility that employed the patients in cases D, F, G, I, and J, 108 current and former workers underwent chest CT scan; 23 (21%) had significant interstitial changes and 14 (13%) had significant emphysematous changes.[17] Chest CT scan abnormalities were more common in grinders and workers with higher serum indium concentration. In addition, percent-predicted values of total lung capacity and diffusing capacity decreased with increasing quartiles of serum indium. A subsequent multicenter study in Japan of nearly 600 indium workers (including those described by Chonan et al[17] and Hamaguchi et al[18]) found exposure-response relationships between serum indium and KL-6 at serum indium values exceeding 2.9 μg/L and between serum indium and surfactant proteins A and D at serum indium values exceeding 4.9 μg/L.[19] Spirometric abnormalities were more common at the highest serum indium concentrations.

At the ITO production facility that employed the patients in cases A and B, an unpublished evaluation of medical surveillance data on 57 production workers collected from 2002 to 2010 found that abnormalities on pulmonary function tests including spirometry and diffusing capacity were more common than

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expected. In addition, some workers were found to have developed radiographic abnormalities during employment. One-half of the workers tested after hire had blood indium concentrations above 5 μg/L.

At the facility manufacturing LCDs for mobile telephones that employed the case C patient, an unpublished evaluation revealed that 15 additional workers did the same job as the case during his employment. Eight (53%) left employment for health reasons: five noted being unable to tolerate the dust in the facility and three described cough and dyspnea.

Discussion

Ten young indium workers developed lung disease with relatively short latency from first exposure to indium compounds. Common clinical features at diagnosis included cough and dyspnea without a work-related pattern. Case patients initially diagnosed as PAP had restrictive physiology, markedly reduced diffusing capacity, crazy paving on chest CT scan, and prominent alveolar exudate on histopathology. With some exceptions, case patients initially diagnosed as ILD tended to have normal or obstructive physiology, preserved or more modestly reduced diffusing capacity, fibrosis and emphysema on chest CT scan, and prominent fibrosis on histopathology. In most cases, symptomatic, functional, and radiographic deterioration was observed over time regardless of initial diagnosis and despite therapy with whole-lung lavage and/or steroids. During a follow-up period that averaged <6 years, two deaths from lung disease occurred, including one case with fatal bilateral pneumothoraces. On initial evaluation, a broad differential diagnosis was considered in these cases, including infection, hypersensitivity pneumonitis, pneumoconioses, and idiopathic conditions such as PAP and idiopathic interstitial pneumonias. Further evaluation, including an occupational history and an examination of lung tissue that in most cases included analysis for indium, led the treating physicians in each case to suspect that exposure to indium compounds was responsible.

Our study provides multiple lines of evidence that occupational exposure to indium compounds including indium oxide and ITO causes a novel, potentially fatal lung disease that may progress from alveolar proteinosis, cholesterol ester crystals, and cholesterol granulomas to fibrosis, emphysema, and pneumothoraces. Cases with shorter diagnostic latency had findings more consistent with PAP, while cases with longer diagnostic latency had findings more consistent with ILD. Case patients initially diagnosed with ILD had histopathologic evidence of alveolar proteinosis. In case D, the limited comparison of a surgical biopsy image and subsequent autopsy specimens suggested histopathologic progression from cholesterol clefts to fibrosis. Patients in two cases (A and C) initially diagnosed with PAP had radiologic progression to fibrosis over several years. In three cases (C, E, and I), the appearance of cystic airspaces subsequent to fibrotic changes suggested developing emphysema.

Recent animal studies corroborate such an evolution. A study of the chronic pulmonary toxicity of indium compounds demonstrated initial exudation, subsequent appearance of cholesterol clefts and granulomas, and generally later emergence of fibrotic changes.[20] An inhalational study found alveolar proteinosis in rats after 2 and 13 weeks of ITO exposure; 26 weeks after the 13 weeks of ITO exposure, both alveolar proteinosis and fibrosis were apparent.[21]

The cases occurred throughout the ITO industry. They included case E, which occurred at an indium oxide production facility, where ITO exposure would not be expected. This observation is consistent with the results of animal studies that have demonstrated a spectrum of pulmonary lesions including alveolar proteinosis and interstitial fibrosis with exposures to indium oxide, indium phosphide, indium arsenide, and ITO.[20-25] Thus, it is clear that the respiratory hazard is not limited to ITO. Furthermore, case C, which occurred in an LCD production facility worker, demonstrates that risk is not limited to ITO production and reclamation operations.

The available environmental data confirmed the potential for exposure to respirable particles. They demonstrated a wide range of airborne dust and indium concentrations by facility and work area, with as much as a 1000-fold difference between minimum and maximum values. Although reduction of respirable indium exposure is prudent, a safe exposure level is not currently known. The Japanese Ministry of Health, Labor, and Welfare recently set a respirable indium concentration limit of 3×10^{-4} mg/m^3 on the basis of animal studies of indium toxicity.[26] Future workplace investigations may benefit from the use of novel exposure metrics such as the peak airborne concentrations of indium and from physicochemical characterization of indium-containing materials.

Workplace investigations demonstrated an excess burden of subclinical or undiagnosed lung disease among coworkers. Longitudinal evaluation is needed to determine the long-term consequences of occupational exposure to indium compounds, assess the impact of exposure reduction or cessation, and identify effective strategies for disease prevention. In the meantime, ongoing workforce medical monitoring is prudent. The Japanese Ministry of Health, Labor, and Welfare recently released recommendations on medical surveillance that include serum indium, KL-6, and chest CT scan.[26] Given that some case patients experienced disease onset within about a year of hire,

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more frequent noninvasive testing early in employment, such as with serial pulmonary function tests, may be useful. Robust prediction equations, population-based norms, and attention to declines within the normal range may increase the sensitivity of pulmonary function tests to detect subclinical disease.[27,28] Until more is known, exposure reduction or cessation for workers who develop abnormalities should be considered.

The pathogenesis of indium toxicity is not clear. One hypothesis is that indium compounds induce macrophage dysfunction, leading to accumulation of intraalveolar lipoproteinaceous material and development of cholesterol ester crystals. A "foreign body" reaction ensues against the crystals, with the formation of cholesterol granulomas and the eventual development of fibrosis and emphysema. The histopathological findings of granulomas and fibrosis in association with cholesterol clefts are supportive of this hypothesis. However, the observations of fibrotic foci in areas without cholesterol clefts and a distal, rather than diffuse, distribution of fibrosis suggest that fibrosis also may develop independent of such a pathway. In case B, autoantibodies to GM-CSF were found, raising the possibility of an autoimmune mechanism associated with exposure to indium compounds.[29] Other proposed explanations for this finding are that this case represents autoimmune PAP unrelated to indium compounds or exacerbated by exposure to indium compounds.[2,30] Japanese investigators have recently written that 17 indium workers with high serum KL-6 levels, and rats exposed to ITO, had no GM-CSF autoantibodies.[31] Further investigation is required to confirm the functionality of the detected autoantibodies and their possible role and persistence in indium lung disease.[32]

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Additional information: The e-Figures can be found in the "Supplemental Materials" area of the online article.

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