



Beryllium and other metal-induced lung disease

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Purpose of review

Metals can cause disease of the upper and lower respiratory tract that mirror disease due to other causes, such as asthma, rhinosinusitis, acute bronchitis, chronic bronchitis, acute pneumonitis, bronchogenic carcinoma, and interstitial lung disease. This article will describe some uncommon and unique lung diseases that can be induced by metals.

Recent findings

Our understanding of old occupational lung diseases, such as chronic beryllium disease, continues to increase. New exposures in the workplace, such as indium, have been identified as novel occupational hazards. New forms of exposure, such as titanium dioxide nanoparticles, create risk of lung disease that is not seen with larger particles.

Summary

Knowledge of several unusual and/or unique occupational lung diseases should prompt questioning about a patient's occupational history, which may uncover an occupational, rather than an idiopathic, lung disease.

Keywords

giant cell interstitial pneumonitis, granulomatous lung disease, occupational lung disease, organizing pneumonia, pulmonary alveolar proteinosis

INTRODUCTION

The key to identifying occupational lung disease is making the link between lung disease and occupational exposures. The best approach is to start with a detailed occupational and environmental history, which is the subject of another review in this issue. At minimum, the busy clinician should have knowledge of unusual lung diseases that should prompt a targeted occupational history. With the appropriate clinical picture, including signs and symptoms, physiologic, radiographic, and pathologic findings, and natural history including latency, eliciting a history of exposure to a relevant agent can establish the diagnosis of occupational lung disease. We will review several of these unusual and unique lung diseases caused by occupational exposure to certain metals, including granulomatous lung disease, giant cell interstitial pneumonitis, pulmonary alveolar proteinosis, 'benign' pneumoconiosis, and organizing pneumonia.

GRANULOMATOUS LUNG DISEASES

Several metals have been linked to granulomatous lung disease, namely beryllium, zirconium, titanium, aluminum, and copper sulfate. Of these, beryllium is the most common cause of granulomatous

lung disease, which can be indistinguishable from pulmonary sarcoidosis except for demonstration of beryllium-specific immune response. Links to zirconium, titanium, and aluminum are limited to case reports. Foreign body-type granulomas are reported among the forms of lung disease seen after exposure to copper sulfate-containing 'Bordeaux mixture' sprayed as an antimildew agent in vineyards. Granulomatous lung disease associated with barium and gold have not been reported in the occupational setting, but will be mentioned briefly here. Foreign body granulomas have been reported with aspiration of barium [1,2]. 'Gold lung' presents as hypersensitivity pneumonitis in rheumatoid arthritis patients treated with gold salts, with lymphocytic alveolitis, and occasional positive lymphocyte proliferation tests [3]. Foreign body granulomas have

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KEY POINTS

- Metals can cause a large variety disease of the upper and lower respiratory tract that mirror disease due to other causes and idiopathic disease.
- Diagnosis of granulomatous lung disease, pulmonary alveolar proteinosis, and organizing pneumonia should prompt a targeted occupational history before the disease is labeled idiopathic.
- Giant cell interstitial pneumonitis is pathognomonic for cobalt hard metal/substance disease.

been reported with hard metal/hard substance and indium lung disease described later in this article.

Beryllium

Beryllium is a light-weight element that is processed into beryllium copper alloy, pure beryllium metal, and ceramic for use in highly specialized applications, such as the defense, aerospace, and electronics industries. Most exposed workers do not develop beryllium sensitization (BeS) or chronic beryllium disease (CBD). Susceptible workers exposed to beryllium can develop a delayed-type hypersensitivity to beryllium, termed BeS. It is generally diagnosed based on the beryllium lymphocyte proliferation test (BeLPT), with demonstration of in-vitro proliferation of peripheral blood or bronchoalveolar lavage (BAL) cells following beryllium stimulation. Only some cases of BeS progress to CBD, with the development of lymphocytic alveolitis and epithelioid granulomata in the lung parenchyma. All patients diagnosed with pulmonary sarcoidosis should be asked about the current and past work in beryllium-using industries, as shown in Table 1 [4^{***}].

The risk of developing BeS/CBD depends on genetic factors, namely major histocompatibility complex human leukocyte antigen (HLA)-DPB1 Glu 69 (E69), with a glutamic acid substitution at position 69, and HLA-DRB1 Glu 71, with a glutamic acid substitution at position 71 [5,6^{***},7], and amount of beryllium exposure [5,6^{***}]. The prevalence of BeS among exposed workers ranges from less than 1% in aluminum smelters where exposure is low [8] to 20% in workers in highly exposed processes [9]. The proportion of workers with BeS that progress to CBD varies widely, ranging from 9 to 100% [10–22]. CBD develops approximately 10–20 years after first exposure, but has been reported up to 40 years after last exposure [23] and within months of first exposure [17]. The

longitudinal rate of progression from BeS to CBD has been estimated to occur at about 6–8% per year [24].

The acute manifestations of beryllium disease were the first form of beryllium disease identified [25,26]. It is still seen today in rare cases with very high levels of exposure [27,28]. The manifestations of acute beryllium disease include dry cough and progressive dyspnea on exertion, in addition to conjunctivitis, dermatitis, pharyngitis, and laryngotracheobronchitis [26,29]. Radiographic findings of diffuse bilateral alveolar infiltrates develop 1–3 weeks following onset of symptoms [30,31]. The clinical course can range from mild and self-limited to rapidly progressive [26], with death occurring in about 10% of cases [30]. Most who survive typically recover fully weeks to months later, but about 17% have disease that persists after 12 months [31,32].

The term chronic was ‘arbitrarily’ applied to beryllium disease lasting more than 1 year and is distinguished from acute beryllium disease by onset years after exposure. CBD presents with a dry cough, progressive dyspnea on exertion, fatigue, and night sweats [33]. The presentation and clinical course of CBD is highly variable, ranging from those who are asymptomatic, diagnosed based on medical surveillance with the BeLPT, to those with severe respiratory impairment and hypoxemia [34–36]. CBD today has a less fulminant course, with slow and insidious onset of symptoms, but severe impairment of lung function and hypoxemia can still be seen. CBD is typically progressive despite removal from exposure [31].

Pulmonary physiology is normal in BeS, as by definition, these individuals have no lung pathology, only an abnormal blood BeLPT. In early CBD, lung function is often normal. The most common physiologic abnormalities are mild airflow limitation [37] and slow decline in DLCO [35,36]. A restrictive pattern develops only in rare cases of advanced disease with fibrosis. Cardiopulmonary exercise testing can reveal abnormalities in early disease before routine changes in pulmonary function tests are detected [37,38].

Historically, micro-nodular, nodular, and linear radiographic patterns were described [33,39] that did not correlate well with physiology. In recent cohorts, radiographic findings are often normal in the earlier stages of disease. Computed tomography (CT) findings include small nodules, ground-glass opacification, mild hilar adenopathy and septal lines [40,41].

The clinical course of CBD is highly variable and occasionally fulminant. Patients may remain asymptomatic with normal radiographic and physiological

Table 1. Workplaces with potential sources of beryllium exposure

Industries and processes	Products	Comment
Fluorescent lamp manufacturing plants	Fluorescent lamps	Historical exposure, banned in 1949
Neon sign manufacturing (cottage industry)	Neon signs	Historical exposure, banned in 1949
Beryllium extraction plants	Beryllium metal, alloys, and ceramic for use in secondary industries	Historically extremely high exposures, with many cases of ABD and CBD. CBD was identified in residents living close to these plants and in household contact of workers. Exposures dramatically reduced, but still cases of CBD and BeS.
Foundries		Historically very high levels of exposure, and still occurs in some areas
Smelting and recycling		Potential very high level exposures. Still occurs when electronic parts are not screened before recycling
Radiographic equipment	X-ray transmission windows	Historically; current use not clear
Aerospace	High-speed structural components	Machining areas for engine parts, optical mirrors on telescopes at highest risk, but also risks for lower exposed workers, including maintenance and security personal.
	Essential guidance instruments	
	Missile and spacecraft parts	
	Airplane brake heat shields	
	Rocket nozzles	
	Gyroscope for aerospace guidance	
	Optical mirrors	
Automotive parts	Airbag release, electrical, windows, circuitry, electronic ignition	
Defense	Nuclear reactor components	Highest risk in machinists and areas of destructive testing.
	Nuclear warheads	
	Precision instruments	
	Nonsparking tools	
	Submarine cable housing	
	Instrumentation and control systems radar	
	Military vehicle armor	
Dental prosthesis manufacture		While banned by American Dental Association, still used in some parts of the United States and some overseas suppliers
Electronics	Audio components	Elevated risk from spot welding beryllium copper alloy electronic components
	Electrical contacts	
	Relays and switches	
	Integrated circuits	
	Insulators	
	Electric heat sinks	
	Wave and laser tubes	
	Sprinkler system couplings	
	Computer parts and circuits	
Telecommunications	Cable housing	
	Connectors for fiber optics	

Table 1 (Continued)

Industries and processes	Products	Comment
Tool and die	Nonsparking beryllium tools, other beryllium alloy castings	Risk from grinding nonsparking tools, cutting and annealing beryllium copper wire, not ordinary use.
High-end sporting equipment	Golf clubs Bicycles	

ABD, acute beryllium disease; BeS, beryllium sensitization; CBD, chronic beryllium disease. Reproduced with permission from [4^{***}].

parameters for years, although most experience gradual worsening, with increasing respiratory symptoms and physiologic decline [35]. A minority of patients experience significant physiologic impairment and radiographic progression of disease, especially in those who have had the highest exposure [42].

There are several skin manifestations, including contact dermatitis, beryllium ulcers, and dermal granulomas [26], which are not commonly seen today. A number of extra-pulmonary manifestations were reported in historic CBD cohorts [31], and this was more common in those with a fulminant course, but none of these manifestations are convincingly reported in more recent cohorts.

Beryllium sensitization is determined based on a history of beryllium exposure and abnormal BeLPT. BeS patients need to undergo work-up for potential CBD that includes pulmonary function tests, chest radiography, and, if deemed appropriate, a bronchoscopy with BAL and transbronchial biopsies. The current diagnostic criteria for CBD are: evidence of BeS and granulomatous inflammation, with or without abnormal BAL BeLPT and/or lymphocytosis, or CBD based on abnormal BAL BeLPT and lymphocytosis without granulomatous inflammation. The diagnosis of CBD can also be made on a medically probable basis, considering the patient's exposure history, clinical course, symptoms, physiologic findings, and radiographic imaging especially when bronchoscopy is not feasible.

Although there are no well controlled treatment trials in CBD, corticosteroids have comprised the mainstay of treatment. Early disease may be treated with inhaled corticosteroids, along with short-acting bronchodilator, if there is an airways component. Indications for systemic immunosuppressive therapy include significant physiologic impairment, especially with progressive decline. Whereas notable improvement with therapy can be noted, complete resolution is rare, and some cases of symptomatic and radiographic improvement are followed by progressive fibrosis even when immunosuppressive therapy is continued [33]. Systemic therapy is usually continued lifelong, because disease relapses were well

described historically and more recently [42,43]. Methotrexate and other immunosuppressive therapies have been used to reduce corticosteroid side effects [44^{***}]. In both BeS and CBD, minimizing further exposure to beryllium should be recommended.

Zirconium

Zirconium alloys are used in the nuclear and aerospace industries and used as a powder for polishing, foundry work, and in ceramics. Zirconium can cause granulomatous skin disease [45]. There have been report of granulomatous pulmonary hypersensitivity reactions [46,47] and allergic alveolitis granulomatous interstitial pneumonia in a ceramic tile glazer exposed to zirconium silicates [48]. A case of disease similar to sarcoidosis and beryllium disease was reported in a worker exposed to grinding particles and welding fumes in the nuclear industry [49]. Scanning electron microscopy confirmed the presence of zirconium particles and absence of beryllium within the granulomas.

Titanium

A furnace feeder in a titanium production plant developed granulomatous lung disease with titanium-specific lymphocyte proliferation testing, and titanium was found within the granulomas [50]. There was another report in the French literature of a worker exposed to titanium dioxide abrasive with granulomatous lung disease and titanium within the lesions [51].

Aluminum

A 31-year-old worker exposed to aluminum powder in the aircraft industry developed granulomatous lung disease, and electron microscopy confirmed the presence of aluminum [52]. A chemist who worked with aluminum powders developed granulomatous lung disease with a lymphocyte alveolitis [53]. Aluminum particles were identified in the

granulomas by mineralogic analyses, and peripheral blood cells showed abnormal lymphocyte proliferation in response to aluminum salts. A worker from a metal reclamation facility with exposure to aluminum dust as well as iron, copper, zinc, and nickel developed granulomatous lung disease, and aluminum was identified within the granulomas on scanning electron microscopy [54].

Copper sulfate

Vineyard sprayer's lung was identified several decades ago among Portuguese vineyard workers who sprayed 'Bordeaux mixture' to prevent grape vine mildew [55,56]. It continues to be used worldwide, although recent cases are not well described. Bordeaux mixture can cause several forms of lung disease, in which foreign body-type granulomas have been described.

GIANT CELL INTERSTITIAL PNEUMONIA

An extremely hard metal with qualities close to that of diamonds is produced when cobalt is sintered or cemented together with tungsten carbide. It is typically used for grinding other metals, such as metal tools. Exposure to the dust of this hard metal can cause a spectrum of lung diseases, collectively termed hard metal lung disease (HMLD). A similar disease is seen with dust from cobalt-diamond polishing [57], so we have included the term Hard Substance. Foreign body granulomas have been reported, but the classic pathology is giant cell interstitial pneumonitis (GIP), characterized by 'cannibalistic' multinucleated giant cells in the air spaces and interstitium that appear to be engulfing other cells, including macrophages and neutrophils. These cannibalistic cells may or may not be found on BAL, but when present, GIP is pathognomonic for hard metal/hard substance lung disease, and patients with this finding should be questioned about past grinding work. In addition to GIP, lymphoplasmacytic infiltration of the interstitium, type II pneumocytes, and occasionally features of desquamative interstitial pneumonia (DIP) and bronchiolitis obliterans organizing pneumonia can be seen [58].

Although cobalt does not cause epithelioid granulomas, there are several interesting similarities to CBD. There is no classic exposure-response relationship. HLA-DPB1 Glu 69 (E69) is associated with increased risk of disease [59], and there are both acute and chronic forms of disease. Radiographic features are variable, and include ground glass opacities, nonspecific interstitial pneumonia, usual interstitial pneumonia pattern, and cystic spaces [60]. As

opposed to CBD, removal from exposure in early disease can result in marked improvement of remission [58], although the fibrosis in later disease is not reversible. The mainstay of treatment is immunosuppressive therapy, which has resulted in clinical improvement radiographically [61].

PULMONARY ALVEOLAR PROTEINOSIS

Indium compounds are sintered alloys, and include indium tin oxide (ITO), indium oxide, and indium zinc oxide. They are relatively new and increasingly found in the occupational setting. They are used in transparent conductive film for flat panel displays on plasma TV and monitors. Workers involved in production, manufacturing, and reclamation can be exposed. Interstitial lung disease (ILD) due to ITO exposure was first described in Japan in 2003 [62]. Two cases of pulmonary alveolar proteinosis (PAP) were reported in the United States in 2010. Best evidence suggests that indium lung disease starts with PAP, which subsequently progresses to pulmonary fibrosis with or without emphysema [63], consistent with animal studies [64].

A detailed multidisciplinary review of 10 cases provided greater detail about this unique disease [63]. Onset of symptoms can begin a year after first exposure, with cough and dyspnea occurring in a nonwork-related pattern. Workers diagnosed after shorter disease latency had restrictive physiology with reduced diffusing capacity, along with the classic 'crazy paving pattern' of PAP, with ground glass opacities superimposed on interlobular septal thickening. Histology included intra-alveolar exudate typical of alveolar proteinosis, cholesterol clefts, and granulomas, along with some fibrosis. Workers diagnosed after longer latency had more classic features of ILD, with more modestly reduced diffusing capacity, and fibrotic changes on imaging and histology, with or without emphysema, and two developed pneumothoraces. Unfortunately, lung disease progressed despite removal from exposure, and there were two deaths due to the disease.

Subclinical disease has been found in workplace epidemiologic studies [65,66]. Subsequent screening in the workplace where the two sentinel cases of PAP were found revealed higher-than-expected spirometric abnormalities in other workers that had developed after hire [67]. Screening at an ITO facility in Korea revealed elevated serum biomarkers of ILD (Krebs von den Lungen-6 and surfactant protein D) without observed dose-response relationship, and a third of the workers studied were found to have intralobular interstitial thickening on chest CT [68]. The potential role of auto-antibodies against granulocyte macrophage colony-stimulating factor

(GM-CSF) in indium-induced PAP is controversial as one case report indicated the presence of anti-GM-CSF antibodies in the peripheral blood of a case of PAP with exposure to indium [69,70].

BENIGN PNEUMOCONIOSES

Certain radiodense metals can cause radiographic patterns consistent with ILD, but are termed 'benign' due to absence of associated signs or symptoms. This disconnect between radiographic signs of pneumoconiosis and the clinical picture strongly suggests a benign pneumoconiosis. These benign pneumoconioses are called stannosis in workers exposed to tin, siderosis in workers exposed to iron oxide, and baritosis in workers exposed to finely ground barium sulfate [71].

ORGANIZING PNEUMONIA

A case of bronchiolitis obliterans organizing pneumonia was reported in a 58-year-old worker after 3 months of exposure to a polyester powder paint [72]. Titanium dioxide nanoparticles (NP-TiO₂) were detected on mineralogical analysis of the paint and the patient's lung tissue. Severe inflammation followed by progressive epithelial and fibroproliferative changes were observed in rats following subchronic inhalation of NP-TiO₂ [73] and NP-TiO₂ has been found to cause osmotic and oxidative stress in microbial models [74]. Nanoparticles are defined by having at least one dimension smaller than 100 nm. They have the potential for enhanced toxicity, which is suggested in this case. Titanium dioxide is widely used in the paint industry, but report of organizing pneumonia is limited to NP-TiO₂. Patients with organizing pneumonia should be questioned about work with titanium dioxide nanoparticles.

CONCLUSION

There are a large number of metals that can cause occupational lung disease. While the best approach starts with a comprehensive occupational and environmental history, knowledge of several uncommon and unique lung diseases is another way to identify occupational lung disease. This is particularly important to consider before making the diagnosis of idiopathic lung disease, such as sarcoidosis, PAP, or organizing pneumonia. The identification of occupational lung disease is not only important for the patient, but also the patient's co-workers who may also be exposed and at similar risk for the development of disease unless exposure is reduced in the workplace. The patient may also be

eligible for compensation. With the advent of new technologies and industries, new exposures and novel forms of existing exposures such as nanoparticles are expected to increase the number of occupational lung diseases, such as in the case of NP-TiO₂, causing disease that is not reported with TiO₂ of large size.

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Conflicts of interest

None.

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