
Lung Disease and the Lightest of Metals

Now that they no longer put beryllium phosphors in fluorescent light bulbs, we no longer see a lot of beryllium-induced lung disease, or do we? It has been estimated that from 200,000 to 800,000 workers are exposed to beryllium in the United States.1 If one uses a conservative estimate that 2% of exposed workers will develop clinical disease, 2 4,000 to 16,000 individuals may have beryllium lung disease in this country. The apparent discrepancy between the clinical recognition of disease and the potential disease burden may be explained by the difficulty/failure to diagnose.3 In 2003, Fireman and coworkers found that 6% of patients in whom sarcoidosis was initially diagnosed actually had chronic beryllium disease (CBD). CBD is physiologically and histologically indistinguishable from sarcoidosis. Unless one identifies and confirms an exposure to beryllium, sarcoidosis may, in fact, be a correct diagnosis. Along those lines, an especially interesting article has explored the question “is chronic beryllium disease sarcoidosis of known etiology?”.

Beryllium is a rare but naturally occurring metal that is found in bertrandite and beryl rock. It is the lightest of metals, with an atomic weight of 4 and a molecular weight of 9. This element has some very special properties that make it especially useful in many applications. Exposure to the metal occurs in such industries as ceramics, aerospace, nuclear energy, automotive, electronics, and telecommunications. Beryllium is often used as an alloy along with copper, nickel, aluminum, and magnesium. The recycling of scrap alloy material, for example, in the recovery of metal from electronic and computer parts, is a less obvious cause of exposure but is becoming more common.

Lung disease associated with exposure to beryllium was first described in 1933 by Weber and Engelhardt,6 and later in 1943 in the United States by Van Ordstrand et al.7 Both groups reported cases of what is now called acute berylliosis. CBD was first described in 1946 by Hardy and Tabershaw8 in a report on 17 fluorescent light workers who presented with an insidious and debilitating granulomatous lung disease that had occurred after long and variable periods of exposure to beryllium salts. Advances in the knowledge of the pathogenesis of beryllium-induced lung disease has resulted in the current classification that divides beryllium-associated disease into acute berylliosis, beryllium sensitization, subclinical disease, and CBD.

Patients with acute berylliosis develop cough and dyspnea after an identifiable exposure event. The nasopharynx, trachea, bronchi, and the lung parenchyma may be affected by the irritative/toxic effects of exposure to beryllium, usually inhaled in the form of a soluble salt. If the exposure is sufficient, a chemical pneumonitis may result and may be fatal. If the patient survives the exposure, complete recovery is the rule. Acute berylliosis is primarily a disease of historical importance only. With improved workplace controls, this form of the disease is rarely encountered today, except for the rare accidental or unexpected exposure.

Unlike the acute form of berylliosis, CBD continues to occur in exposed and susceptible individuals. This form of beryllium-associated disease is virtually indistinguishable from sarcoidosis, both clinically and pathologically. Patients with CBD complain of insidious and progressive shortness of breath along with night sweats, cough, chest pain, anorexia, weight loss, and fatigue. Chest roentgenogram findings may be normal, or may reveal reticulonodular opacities or ground-glass opacifications, along with enlarged hilar and mediastinal nodes. High-resolution CT scanning is more sensitive, but findings may be normal in up to 25% of cases.9 Although this chronic disease may take > 30 years to develop, sensitization to beryllium can occur within 2 months and the disease can occur within 3 months of the initial exposure.

Because CBD is associated with a delayed skin test reaction to beryllium, which occurred in only 1 to 5% of exposed individuals, was not associated with a clear-cut dose-response curve, and was associated
with a granulomatous reaction, hypersensitivity to beryllium has long been suspected as the cause.\textsuperscript{10} This hypothesis was confirmed when an analysis of BAL fluid obtained from patients with confirmed CBD, as opposed to control subjects, yielded CD4+ T lymphocytes that proliferated on \textit{in vitro} exposure to beryllium salts.\textsuperscript{11} Furthermore, \textit{in vivo}, beryllium-specific, effecter-memory CD4+ T cells were found to accumulate at the site of active lung disease.

The pathogenesis of CBD is thought to be initiated by the inhalation of beryllium into the lung, where, acting as a hapten, the metal binds to proteins in the lung and elicits a proliferation of CD4+ lymphocytes. These sensitized lymphocytes, in turn, secrete a variety of cytokines (\textit{eg}, interleukin-2, tumor necrosis factor-\textalpha, and \textgamma-interferon) that recruit and activate macrophages, which mature into epithelioid cells. Epithelioid cell granulomas develop, which leads to fibrosis with subsequent destruction of the lung parenchyma.\textsuperscript{11}

It is now clear from numerous studies that genetic susceptibility affects the risk of beryllium-related health effects. Some genes, such as \textit{Glu69}, are important in the development of an antigen-specific, cell-mediated immune response to beryllium (\textit{ie}, sensitization), and others may be important in the development of a beryllium-specific granulomatous inflammation (\textit{ie}, disease). It is likely that sensitization and disease are multigenetic processes, and that these genes interact with exposure to determine the risk of disease.\textsuperscript{12}

A beryllium lymphocyte proliferation test performed on cells from peripheral blood or BAL fluid can identify sensitized individuals.\textsuperscript{13} This test also has been used as a surveillance tool for workers in affected industries. Any patient with sarcoidosis who has worked around metal dust or fumes should be offered a beryllium lymphocyte proliferation test (a list of referral laboratories can be found at www dimensional.com/~mhj/medical_testing.html). Recently, a lymphocyte proliferation test using flow cytometry has been reported.\textsuperscript{14}

Using clinical and laboratory information, one may classify beryllium-exposed workers as follows: (1) as being sensitized but with no evidence of disease; (2) as having subclinical disease wherein the patient has evidence of sensitization and biopsy evidence of noncaseating granulomas but no symptoms or physiologic evidence of respiratory impairment; and (3) as having CBD.

Because CBD is uncommon and is less often diagnosed, the appropriate management of patients has not been extensively studied. The available information on the subject either is derived from expert opinion or is based on anecdotal experience. It is unlikely that a randomized controlled trial of treatment will ever be undertaken.

The weight of the published literature suggests that patients who are sensitized but do not yet have CBD do not need active treatment. They must be removed from all further exposure and should be placed under continual surveillance. Patients with subclinical disease probably do not require treatment but, once again, should be closely monitored. Most published reports and reviews advocate active treatment of clinically evident CBD with systemic corticosteroids. Dosages and regimens vary, but common recommendations suggest therapy with oral prednisone, from 20 to 40 mg/d (or every other day). Generally, patients are treated for 3 to 6 months followed by a gradual taper to the lowest effective dose. Although the disease may undergo remission or stabilize after the cessation of exposure, CBD is typically a progressive disease that often requires treatment for life.

The article in this issue of \textit{CHEST} (see page 2000) by Sood et al adds to the anecdotal information available. The authors report the course of six patients with documented CBD who were treated with corticosteroids. Two patients showed no improvement while receiving corticosteroids, and four showed an initial improvement that was not sustained. Five of six patients showed improvement on the cessation of exposure. While providing no definitive conclusions, this report provides evidence that therapy with corticosteroids may be beneficial in selected patients but that the response is variable. It also confirms the obvious fact that patients with CBD should be removed from further exposure.

Prevention is, of course, the key to controlling beryllium-induced disease, but it is not easy. The current permissible exposure limit for beryllium, which has been in effect since 1949, is 2 \textmu g/m\textsuperscript{3} as an 8-h time-weighted average. In addition, a ceiling limit of 5 \textmu g/m\textsuperscript{3}, not to be exceeded for > 30 min, and a maximum peak limit of 25 \textmu g/m\textsuperscript{3}, never to be exceeded, have been established. This level of exposure, however, does not protect those who are susceptible to sensitization from becoming sensitized. As a result, a considerable effort is currently underway to identify new standards. It is also important to recognize that beryllium has been categorized by the International Agency for Research on Cancer\textsuperscript{15} as a human carcinogen.

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