The role of Bronchoalveolar Lavage (BAL) in the diagnosis of Chronic Beryllium Disease (CBD)

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Occupational exposure to beryllium and proliferation of industrial uses of beryllium is resulting in an unrecognized epidemic of chronic beryllium disease (CBD) in the United States and abroad as evidenced by many epidemiological studies over the past decade. Beryllium was first used in industrial applications in the 193Os in Europe, Russia and soon thereafter in the United States (US). Subsequently, reports of lung and skin disease surfaced along with identification of cases of acute and chronic beryllium disease. The exact number of workers exposed to beryllium currently or previously in the US and internationally is unknown. Estimates have ranged from 135,000 current workers to 800,000 current and former workers in the U.S. Furthermore, this is not a problem limited to the US as beryllium exposure and cases of CBD have been reported in Canada, UK, Germany, Poland, Israel and Japan. The estimates of workers exposed in other countries are quite limited; thus the global impact of beryllium exposure is unknown. Once largely confined to exposure in the primary manufacture of beryllium products and in the nuclear weapons industry, exposure to beryllium is now being discovered in downstream industries as diverse as metal machine shops, defense, electronics, aerospace, aircraft manufacture, aluminum, cop-
per and magnesium alloy manufacturing, dental laboratories, jewelry making, and metal recycling. As a result of ongoing industrial use of beryllium internationally, cases of chronic beryllium disease (CBD) and its precursor, beryllium sensitization, continue to occur throughout the world in numerous industries.

Based on the demonstration of immunologic response to beryllium, the blood lymphocyte proliferation test (BeLPT), performed on bronchoalveolar lavage cells, was the first diagnostic method able to distinguish CBD from sarcoidosis. Extended for use with blood cells in the late 1980s, the BeLPT became a valuable screening tool, able to identify beryllium sensitization (BeS), an immune response to beryllium and a precursor to the lung disease along with the scarring lung disease CBD.

As was hypothesized by Sterner and Eisenbud, CBD is an immune-mediated hypersensitivity lung disease. CD4+ T cells play a critical role in the immunopathogenesis of CBD. The diagnostic test for CBD, the beryllium lymphocyte proliferation test (BeLPT), detects the ability of blood and/or BAL T cells to proliferate in the presence of beryllium sulfate (BeSO/O) in culture. This beryllium-induced proliferative response is specific for CBD as neither blood nor BAL T cells from sarcoidosis subjects proliferate in the presence of beryllium.

Inhalation of beryllium (Be) has been associated with two pulmonary syndromes: an acute chemical pneumonitis and a granulomatous lung disease known as chronic beryllium disease (CBD), or berylliosis.

- **Chronic beryllium disease (CBD)** – Based on our current understanding of the pathophysiology of CBD as delayed-type hypersensitivity, the immune response to beryllium is an integral aspect to establishing the diagnosis which is based on the presence of all of the following:

  1. Evidence of an immune response to beryllium by shown as a positive blood or bronchoalveolar lavage beryllium-specific lymphocyte proliferation test (BeLPT) or a positive skin patch test.
  2. The presence of non-necrotizing granuloma on lung biopsy

- **Beryllium sensitization (BeS):** The currently accepted definition requires: 2 abnormal blood/BAL BeLPT, or BAL BeLPT, with no lung pathology. The lung is the primary organ affected by CBD. Other organs can also be affected including the extrapulmonary lymph nodes, skin, salivary glands, liver, spleen, kidney, bone, myocardium, and skeletal muscle.

The main differential diagnosis of CBD is sarcoidosis. CBD shares many clinical and histopathological features with pulmonary sarcoidosis, and it is estimated that up to 6 percent of all patients diagnosed with sarcoidosis actually have CBD. The diagnosis of CBD and BeS requires a high degree of clinical suspicion with the occupational history being crucial to the diagnostic evaluation. Symptoms are nonspecific and include both respiratory and constitutional complaints most commonly cough, dyspnea, wheezing and fatigue and may have been present for a number of years before patients seek medical attention. Therefore, further evaluation is required, beginning with the beryllium lymphocyte proliferation test.
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In the late 1980s the laboratory assay was adapted for use with peripheral blood cells and since that time the blood and BAL BeLPT have become the cornerstone in the diagnosis of CBD, allowing practitioners to detect disease before clinical abnormalities occur. The most recent and most thorough estimate of sensitivity and specificity was published by Stange et al. based on 19,396 BeLPT results. The group determined that the BeLPT has sensitivity for CBD of 68.3% and a specificity of 96.9%. Once a patient is determined to be sensitized by the BeLPT the clinician still needs to determine whether or not CBD is present. The main test used for this purpose is bronchoscopy to obtain lung biopsy. Pulmonary function testing is non-specific featuring a range of abnormalities including obstruction, restriction, a mixed process, and/or a reduced DLCO, with obstruction being the most common abnormality. Normal pulmonary function testing is also common especially in early disease. Likewise, radiologic testing including chest x-ray and high resolution CT will miss a significant number of cases of beryllium disease. It was shown that the sensitivity of the chest radiograph for biopsy-proven chronic beryllium disease was about 45%, compared with about 89% for HRCT. As sensitivity and specificity of both radiologic and physiologic studies is less than that of bronchoscopy for the detection of chronic beryllium disease one should consider performing a bronchoscopy on sensitized individuals who do not have contraindications for the procedure in order to definitively define their disease status and guide subsequent management. The bronchoscopy should include both bronchoalveolar lavage and transbronchial biopsy when possible. The biopsies are performed to establish the presence of granulomas and/or mononuclear interstitial infiltrates consistent with chronic beryllium. A BAL is also obtained to determine if a lymphocytic alveolitis is present and whether lung cells respond to beryllium in a BAL BeLPT. When sensitized patients cannot undergo a bronchoscopy a probable diagnosis of CBD may still be reached if a high resolution CT shows typical abnormalities. Preliminary results with adding neopterin measurements to the peripheral blood BeLPT show an improved ability to differentiate CBD from BeS. ELISPOT analysis demonstrate that patients with CBD have a significantly elevated number of IFN-γ-producing and IL-2-producing beryllium-specific CD4+ T cells in blood compared with both BeS and normal control subjects. Analysis of induced sputum for lymphocyte percentage and CD4:CD8 ratio correlates well to those recovered by BAL and can effectively and non-invasively identify CD4+ inflammation in order to distinguish between sarcoidosis and other non-granulomatous interstitial lung diseases.

In conclusion BAL is a well-defined tool in the Diagnostic Algorithm for CBD and research of immunopathogenesis of disease.

References
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