

## Beryllium Disease: First Case Reported in Israel

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Beryllium disease is a multisystem entity caused by dust, fumes or mists of beryllium metal or its salts. Since the primary and most common entrance into the body is the respiratory tract, the effects of this pathology are predominantly pulmonary. The disease has two forms: acute berylliosis – a non-specific, chemical tracheobronchopneumonia; and chronic beryllium disease – an epithelioid, granulomatous disorder that results in diffuse fibrosis capable of causing severe respiratory disability. Although a pathology not commonly seen in daily clinical practice, this entity is of medical importance in light of the increasing use of beryllium in a variety of industries and products (metal working and extraction, ceramics, electronics, space and atomic engineering, laboratories, dental alloys, fluorescent lamps). Today the diagnosis is made according to generally agreed upon criteria [1]. These include: a) a history of exposure, b) the presence of granuloma in affected tissues, c) the detection of beryllium in tissue, particularly in granulomas, d) evidence of hypersensitivity (yielded by the beryllium lymphocyte transformation test, e) consistent clinical, radiographic and physiological features, and f) the exclusion of other granulomatous diseases.

### Patient Description

We report a 27 year old white female non-smoker whose medical history was unremarkable for serious illness. After 3 years of employment as a dental techni-

cian, she was referred to the emergency room because of shortness of breath, weakness, nausea, vomiting, diarrhea, and weight loss (12 kg). The chest X-rays were normal. She was referred to a psychiatrist and was treated by Prozac.

Because of the considerable deterioration in her condition she was again referred to the emergency room 6 months later. Her chest X-rays and computed tomography scan now showed an increased interstitial pattern with hilar lymphadenopathy. Echocardiography revealed severe pulmonary hypertension (90 mmHg) with marked tricuspid insufficiency and an enlarged right atrium and ventricle. The liver enzymes were all elevated. Blood gases showed a pCO<sub>2</sub> of 38.9 mmHg, a pO<sub>2</sub> of 67.0 mmHg, and a pH of 7.358. Serological and immunological parameters (human immunodeficiency virus, hepatitis C virus, hepatitis B surface antigen) as well as the purified protein derivative were negative. Pulmonary function tests showed a severe restrictive pattern with a marked decrease in the diffusing capacity of the lung for CO (FVC 44% predicted, FEV<sub>1</sub> 48% predicted, FEV<sub>1</sub>/FVC 95, total lung capacity 53% predicted, DLCO 24% predicted, DLCO/vacuum aspiration 46% predicted). The patient's condition continued to deteriorate, necessitating high oxygen flow. Since her respiratory failure precluded

transbronchial biopsy, open lung biopsy was performed. Histological analysis showed abundant non-caseating granulomas. The diagnosis at this point was thought to be sarcoidosis, and treatment with intravenous hydrocortisone and later prednisone (Meticorten 60 mg daily) was initiated. The perfusion lung scan was normal and ruled out the presence of pulmonary emboli. Her condition improved slowly, both in arterial oxygenation and in the reduction of pulmonary pressures. It was presumed that the high pulmonary pressure was related to the severe lymphadenopathy compressing on the major pulmonary arteries as well as to the severe interstitial lung disease. This was further supported by an improvement in her pulmonary pressure when the mediastinal lymphadenopathy had resolved.

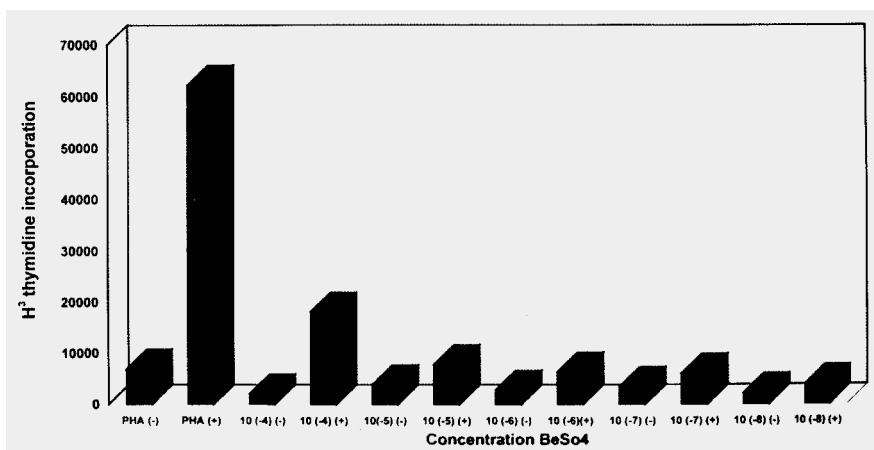
In light of her occupational history, she was referred to our clinic for chemical analysis of induced sputum and the BeLTT to rule out a possible misdiagnosis of silicosis/berylliosis. Analysis of sputum by a scanning electron microscope and by petrographic microscopy showed abundant particles (1.6–2.5 μm) of clay minerals [AlSiFe, AlSiCa, Al<sub>2</sub>Si<sub>4</sub>(OH)<sub>2</sub>, quartz (SiO<sub>2</sub>), and barite (BaSO<sub>4</sub>). The BeLTT revealed values of 5.90 and 2.54 on the stimulation index at 10<sup>-4</sup>M and 10<sup>-5</sup>M of BeSO<sub>4</sub>, respectively (normal values SI < 1.7) [Figure].

FEV<sub>1</sub> = forced expiratory pressure in 1 sec

FVC = forced vital capacity

DLCO = diffusing capacity of the lung for CO

BeLTT = beryllium lymphocyte transformation test  
SI = stimulation index



Beryllium lymphocyte transformation test (BeLTT).

$10^6$  of the mononuclear cells that had been isolated by Ficoll-Paque (Pharmacia, Piscataway, NJ, USA) were incubated for 6 days with  $10^{-4}$ M,  $10^{-5}$ M,  $10^{-6}$ M,  $10^{-7}$  M and  $10^{-8}$ M Be SO<sub>4</sub>. Proliferation of the lymphocytes was tested by <sup>3</sup>H thymidine incorporation. The BeLTT was considered to be abnormal if there were two or more elevated values on the stimulation index (SI) at any concentration. The upper limit of the normal range is laboratory dependent and based upon mean peak SI plus 2 SD for unexposed subjects.

SI = counts/minute of cells cultured in Be<sub>2</sub> SO<sub>4</sub> divided by counts/minute of cells without Be<sub>2</sub> SO<sub>4</sub>, Y axis = counts/minute (cpm), X axis = concentrations Be<sub>2</sub> SO<sub>4</sub>.

Genetic studies showed that the patient was homozygous for HLA DPB1Glu 69 (02012 and 1001, both of which code for glutamine at position 69), confirming the diagnosis of beryllium disease. The patient is currently being followed. Her condition is significantly improved, and she has only minimal dyspnea upon exertion. Her lung function has improved (FEV<sub>1</sub>, FVC and TLC by 15%), as has the DLCO although it is still very low (40% of predicted). A repeat echocardiography showed normal pulmonary pressure. An attempt to discontinue the use of corticosteroids failed because her dyspnea and cough worsened, and prednisone treatment (20 mg daily) was reinstated. Today, more than a year later, she is still taking prednisone.

## Comment

Chronic beryllium disease is a twentieth century man-made disorder that occurs among people employed in diverse industries. It is considered to be a chronic systemic disease that develops insi-

diously (from 1 month to 5 years). The most common symptom is dyspnea upon exertion, followed by a usually unproductive cough. There is progressive weight loss, malaise, lassitude, anorexia, and arthralgia in the advanced form of the disease. Clinicians have long noted the strong clinical and pathologic similarities between CBD and sarcoidosis [2]. Thus, differentiating between them has typically involved relying on the presence of epidemiological evidence of beryllium exposure or the demonstration of immunological reactivity for beryllium.

The BeLTT is capable of diagnosing patients with beryllium disease at a very early stage. Several studies have shown that the BeLTT values are elevated in patients with CBD but not in normal subjects, beryllium-exposed normal subjects, or patients without beryllium exposure but who have other granulomatous diseases such as sarcoidosis and hypersensitivity pneumonitis [3]. Interestingly, not every individual with an abnormal blood BeLTT has CBD, but it was demonstrated that one-half of the

sensitized workers who showed an abnormal BeLTT did progress to develop granulomas within the lung [4]. Moreover, it was shown that not only exposure but also the genetic constitution of the individual is an important factor in the development of the disease. Finally, HLA-DPB1-Glu<sup>69</sup> (glutamine at position 69) may be a genetic marker for CBD and may play a direct role in triggering antigenic recognition to beryllium [5]

In conclusion, while the condition is well described worldwide this is the first documented case of beryllium disease in Israel. In spite of the fact that beryllium has been and continues to be used in various industries in Israel, we believe that CBD may not have been diagnosed before due to a lack of awareness of the disease and to the methods of diagnosis. We suspect that many such patients may have been diagnosed as having sarcoidosis. This case report emphasizes the extreme importance of including an occupational history in the anamnesis of patients suspected of having sarcoidosis. We strongly urge the implementation of industrial screening programs among workers exposed to beryllium.

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TLC = total lung capacity

CBD = chronic beryllium disease