CLINICAL VIGNETTE

Chronic Beryllium Disease

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History of Present Illness

A 53-year-old male originally from El Salvador presented to pulmonary clinic for evaluation of dry cough. Patient first noted cough one year prior. It started intermittently and with exertion but progressed to be persistent. He also reported co-existing shortness of breath that was initially dyspnea with exertion but was now occurring even at rest. He was unable to exercise due to cough and shortness of breath. He denied hemoptysis, chest pain, sputum production, paroxysmal nocturnal dyspnea, rash, skin lesions, visual changes, headaches, and palpitations. He was otherwise healthy. He was born in El Salvador and moved to the United States in his 30s. He never smoked cigarettes. He was married with two children. He worked in a metal foundry for 6years. Subsequent to that he worked as a dental technician. At time of visit he owned a dental equipment processing business. Vital signs were remarkable for an oxygen saturation of 94%. Pulmonary exam revealed dry inspiratory crackles one quarter of the way up both lung fields posteriorly. Fingers showed clubbing. There was no cyanosis, cervical or supraclavicular lymphadenopathy, rashes, or skin lesions. Computer tomography showed bilateral diffuse subpleural and parenchymal interstitial pulmonary fibrosis predominantly involving upper lobes, with multiple calcified mediastinal and hilar adenopathy. Pulmonary function tests (PFTs) showed forced vital capacity of 2.30 liters (46 percent predicted), forced expiratory volume during the first second of 1.82 liters (50 percent predicted), total lung capacity of 3.80 liters (54 percent predicted), and diffusion capacity of carbon monoxide of 7.5 (28 percent predicted), consistent with a severe restrictive defect. He underwent surgical lung biopsy that showed extensive granulomatous inflammation with interstitial infiltrates. A peripheral beryllium lymphocyte proliferation test (BeLPT) was performed given his occupational history and histopathology findings, and was positive, consistent with the diagnosis of chronic beryllium disease (CBD).

Introduction

Beryllium is an alkaline earth metal that is lighter than aluminum and six times stronger than steel.[1,2] Exposure to beryllium occurs among workers in machine shops, electronics and defense industry, automotive and aerospace industry, dental alloy and appliance sector, and ceramic industry.[3] Chronic beryllium disease is a chronic allergic-type granulomatous disease in the lungs caused by exposure to beryllium. It shares many of the clinical and histopathological features of pulmonary sarcoidosis. The exposure-response relationship for the development of CBD is not clearly defined, with some studies suggesting that both the dose and duration of exposure are associated with increased risk of disease, while others show the development of clinically significant disease even at very low levels of exposure or after limited duration.[4] CBD has also been described in residents living in close proximity to beryllium manufacturing facilities,[5] and in family members of beryllium workers through second-hand exposure.[6] In certain heavy beryllium-using industries, the rate of disease has been quoted as high as 20 percent, with an overall prevalence of CBD among workers exposed to beryllium ranging from 1 to 5 percent.[7,8] The latency period between initial beryllium exposure and symptom onset varies from three months to 30 years.[9]

Pathophysiology

CBD may arise from the combination of an immunologic response to beryllium exposure, and an underlying genetic predisposition. Exposure to beryllium can lead to a cell-mediated or delayed hypersensitivity immune response where T cells become sensitized to beryllium. Each subsequent exposure leads to an immune response involving macrophages, CD4+ T-lymphocytes, proinflammatory cytokine production and release, and granulomatous proliferation.[10,11] Studies have shown that re-exposure to beryllium induces a beryllium-specific T cell proliferation response that is not induced by other metals.[12] These immune responses are strongest in the lungs as the lungs are the main avenue of beryllium entry. Studies have also revealed a genetic component to beryllium sensitivity. Specifically, beryllium-exposed workers with a mutation at the HLA-DPB1 Glu69 position have increased prevalence of beryllium sensitization and CBD.[13-16] HLA-DRB1 variants with glutamate at position 71 also have increased risk of CBD.[11]

Clinical Manifestations

Clinical manifestations of CBD are often nonspecific and include shortness of breath, cough, fever, chills, night sweats, weight loss, fatigue.[8,17] Physical examination may reveal bibasilar crackles, and signs of hypoxemia such as digital clubbing.

Differential Diagnosis

The differential diagnosis of CBD includes sarcoidosis, hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, and asthma.[18] Patients with CBD may be misdiagnosed with sarcoidosis given histopathological similarities, until a history of beryllium exposure is elicited and testing performed. It is estimated that up to 6 percent of patients diagnosed with sarcoidosis may actually have CBD, and in those in whom beryllium exposure can be confirmed, as many as 40 percent may have CBD.[19,20]

Diagnosis

Definitive diagnosis of CBD is based on history, documented sensitivity on beryllium lymphocyte proliferation test (BeLPT), and, noncaseating granulomatous inflammation on lung biopsy.[21] Diagnosis also can be based on a clinical history of beryllium exposure, a positive BeLPT test, and imaging showing radiographic characteristics of CBD such as hilar or mediastinal adenopathy, parenchymal nodules, ground glass opacities, or cystic cavitation.[22]

The BeLPT assay measures lymphocyte proliferation in beryllium exposed blood or bronchoalveolar lavage (BAL) mononuclear cells.[23] It has a sensitivity of 0.683 and a specificity of 0.96.[24] To improve its sensitivity, all borderline or negative tests are repeated.[23] The BeLPT test is standard industry surveillance tool for identifying workers sensitized to Beryllium, those with CBD, or those with ongoing exposure.

Treatment

The goals when treating berylliosis are to reduce symptoms and slow the progression of disease as no cure is available. The mainstay of treatment for CBD or beryllium sensitization is removal from further exposure to beryllium, and supportive care. Depending on the severity of CBD, rate of progression, and patient symptoms, therapy with corticosteroids or other immunomodulators may be warranted. Patients with beryllium sensitization do not warrant treatment but should be evaluated biennially for progression to CBD.[25]

Corticosteroids are the standard treatment for CBD. The efficacy of corticosteroids has not been evaluated in randomized controlled trials but has been documented in case reports, with the majority of patients experiencing improvement or stabilization of symptoms, imaging, and pulmonary function.[17,21,25,26] Corticosteroids should be initiated before fibrosis becomes established as this may improve efficacy. Therapy with Prednisone is usually initiated at 0.5 to 0.6mg/kg/day, with evaluation of symptoms, pulmonary function, and gas exchange, at three-month intervals. Once clinical response is noted, the dose of Prednisone should be tapered to the lowest effective dose to maintain disease improvement and stability.[17,27] Complete withdrawal can often result in recurrence of disease so patients may need to remain lifelong on a small dose of Prednisone.[25] Some patients fail to respond to corticosteroid therapy. This may be related to delay in initiation of treatment, delay in removal of exposure, or progression to fibrosis.[17,27] In non-responders after six months, therapy with another immunomodulator may be added or substituted. There is limited data on alternative immunosuppressive agents for corticosteroid non-responders, but Methotrexate or Azathioprine may be tried based on their therapeutic effect in sarcoidosis.

Prognosis

CBD has a variable course of progression with some patients remaining asymptomatic, but others remain permanently disabled from symptoms and progress to respiratory failure and death. The variability may depend on the type of industrial exposure, duration of beryllium exposure after the development of CBD, individual response to exposure and disease, and duration of clinical follow up.[28] Reported mortality rates range from 6 to 35%.[25,28]

Minimizing occupational exposure to beryllium is essential to prevent the development of this disease. Methods of minimizing exposure include decreasing the permissible limit for occupational exposure (PEL), using alternative safer materials, improving the ventilation system, and, providing personal protective equipment such as respirators when exposures cannot be adequately controlled.[29]

Outcome

Patient was treated with Prednisone 0.5mg/kg/day with a gradual taper over a twelve-month course. He derived minimal symptomatic response. His PFTs continued to decline. He was treated with a brief course of cyclophosphamide without disease improvement or stabilization. He subsequently underwent successful bilateral lung transplantation.

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