Case Reports

Nonoccupational Beryllium Disease Masquerading as Sarcoidosis: Identification by Blood Lymphocyte Proliferative Response to Beryllium[1-3]

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SUMMARY Chronic granulomatous lung disease caused by industrial exposure to beryllium continues to occur, but no community cases have been reported in more than 30 yr. With the advent of a blood screening test that detects beryllium sensitization, physicians can discriminate chronic beryllium disease from sarcoidosis. A 56-yr-old woman in whom sarcoidosis was diagnosed had an unremarkable occupational history, but her husband was a beryllium production worker. Blood and bronchoalveolar lavage lymphocyte transformation tests, measuring the beryllium-specific cellular immune response, were abnormal, confirming a diagnosis of chronic beryllium disease. Chronic beryllium disease continues to occur in the nonoccupational setting and among bystanders in industry, masquerading as sarcoidosis. Because even transient or possibly low levels of exposure may cause disease, this case has important implications for how clinicians, industry, and government agencies define the populations at risk of chronic beryllium disease.

AM REV RESPIR DIS 1992; 145:1212-1214

Introduction

Chronic beryllium disease is an occupational granulomatous lung disorder. It afflicts the small percentage of beryllium-exposed workers who develop beryllium-specific, cell-mediated immunity (1-5). Interestingly, nonoccupational chronic beryllium disease has been described among residents living in the community surrounding a beryllium production plant (6, 7) and among family members of beryllium workers who were presumably exposed to beryllium-contaminated clothing (6-8). But no air pollution or household cases have been reported in more than 30 yr (9, 10). The disappearance of such cases has been attributed to improved control over air emissions and improved work practices such as mandatory work clothes exchange (8, 11). Alternatively, household and community cases of beryllium disease may still be occurring but are unrecognized or misdiagnosed. Because chronic beryllium disease is readily confused with sarcoidosis (12), persons in the community with this disorder may be misclassified as having granulomatous lung disease of unknown etiology.

With the advent of a specific and sensitive blood test of the cell-mediated immune response to beryllium, screening for the presence of beryllium sensitization and chronic beryllium disease among beryllium-exposed workers is possible (1, 13). This test, called the beryllium lymphocyte transformation test (BeLT), is the one reliable method of discriminating between beryllium disease and sarcoidosis (5). In fact, the BeLT has become a key diagnostic tool for chronic beryllium disease detection in some industries (1, 2, 14, 15). This test could also be used to identify and diagnose nonoccupational cases of chronic beryllium disease.

Case Report

A 56-yr-old Caucasian woman had been in her usual state of good health until approximately 1985 when she insidiously developed exertional dyspnea. She sought medical attention in November 1988, when she experienced more acute shortness of breath and right-sided pleuritic chest pain. Chest radiograph at that time demonstrated bilateral interstitial infiltrates and hilar lymphadenopathy. Despite two courses of intravenously administered antibiotics and supplemental oxygen, her symptoms worsened, and her chest radiograph showed increasing profusion of interstitial opacities over the next 2 months. In February 1989, open lung biopsy of the right middle lobe demonstrated noncaseating granulomas (figure 1), Schaumann bodies and cholesterol clefts, lymphocytic infiltration of lung parenchyma, and interstitial fibrosis. Peribronchial lymph nodes showed confluent noncaseating granulomas. Examination under polarized light showed birefringent material within granulomas. Special stains and cultures for acid-fast bacilli, bacteria, and fungi were negative. The patient was told she had sarcoidosis. Treatment with prednisone was initiated at 80 mg/d, tapered, and subsequently discontinued in June 1990. Prednisone was reinitiated 3 wk later because of worsening symptoms and radiographic progression.

The past medical history was free of any previous respiratory conditions, allergies, or known tuberculosis exposure. She was a lifelong nonsmoker who had always resided in Ohio. She had been self-employed, selling cosmetics and baby-sitting, raising her children, and, since 1973, doing stockroom work for a retailer.

Of note, her pulmonologist learned that the patient's husband worked from 1959 to the present at a beryllium production plant, with daily exposure to beryllium. The husband's principal beryllium exposure had been to beryllium oxides while operating furnaces and attrition mills, transferring beryllium oxide powder, machining, and metallizing beryllium ceramics. Throughout the entire time of his employment, his employer required work clothing exchange, and the husband showered at work before returning to his street clothes at the end of the shift. The family had always resided at least 28 miles from the two beryllium plants at which the husband had worked.

The patient had only been to the plant on two occasions. During one open house in the 1960s, she took a brief tour through the operating plant; once in the 1970s, she toured while it was not operating. She may have come in contact with beryllium at three other times. (*1*) For several months in 1976, her husband was an advisor to a new ceramics plant, where he did no hands-on work and wore street clothes, which his wife helped clean on several occasions. (*2*) In February 1979, a hydrogen furnace containing beryllium oxide exploded in her husband's face. He was rushed to the local emergency room, wearing contaminated work clothes. Upon his discharge from the emergency room, the patient was handed her husband's work clothes, which she placed in a plastic bag at home and returned to the plant guardhouse. Over the next several months, she scrubbed her husband's face several times a day with a motorized rotary brush, removing embedded metallic debris. (*3*) In September 1987, the patient's husband injured his ankle while on the job. When she retrieved her husband from the hospital, he was still wearing his work clothes. After riding home in her car, the husband carefully removed these dust-covered clothes and placed them in a plastic bag.

After eliciting this history in the summer of 1990, the treating physician sent a peripheral blood specimen by overnight courier to the National Jewish Center for Immunology and Respiratory Medicine for blood BeLT. The blood result demonstrated

(Received in original form August 8, 1991 and in revised form December 2, 1991)

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[2] Supported by Physician Scientist Award ES-00173 and Grant ES-04843 from U.S. Public Health Service, National Institutes of Health.

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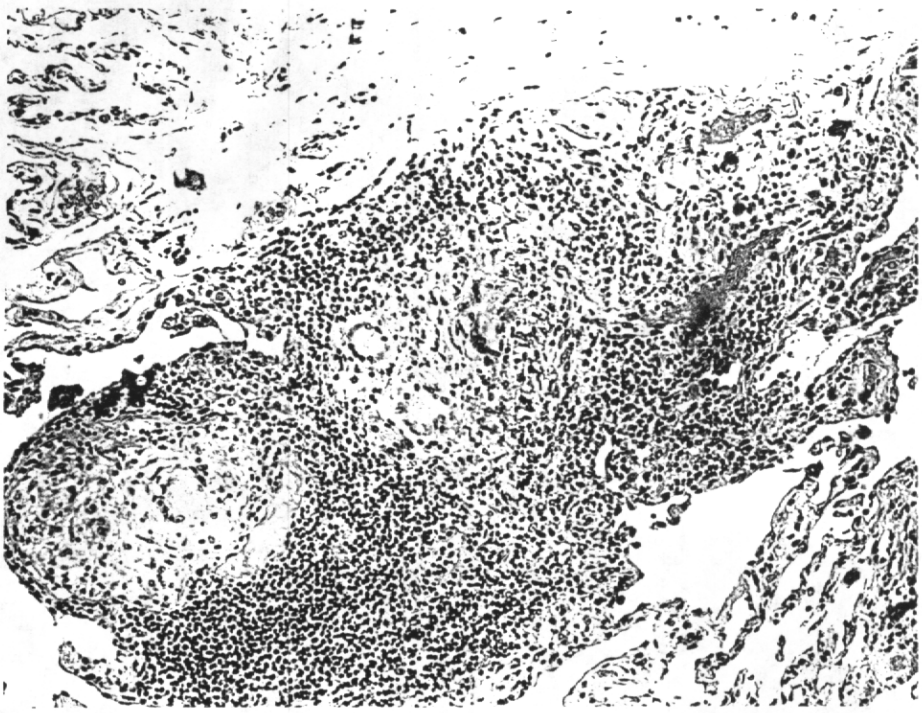

Fig. 1. Open lung biopsy from a patient with nonoccupational chronic beryllium disease demonstrates multiple noncaseating granulomas, multinucleated giant cells, mononuclear cell interstitial infiltrates, and interstitial fibrosis (hematoxylin-eosin stain; magnification: ×10).

beryllium sensitization, with an abnormal median peak stimulation index of 11.9 (normal < 1.4, based on mean of medians of three highest stimulation indices for 26 normal subjects + 2 SD) (13) leading to her referral to our institution for further evaluation in September 1990. Interestingly, the patient's husband's blood BeLT was normal, as is the case for most beryllium-exposed workers (1).

At the time of her evaluation, she reported exertional dyspnea and intermittent nonradiating right-sided chest pain. She denied cough, fever, night sweats, or weight loss. Medications included prednisone 40 mg every other day, verapamil hydrochloride 240 mg four times a day, furosemide 40 mg a day, and calcium and potassium supplements.

Physical examination abnormalities included a Cushingoid appearance, early bilateral cataract formation, bibasilar dry rales extending to the midlung fields, and trace pedal edema. Laboratory data were notable for elevated hematocrit (0.48) and hemoglobin (16.3 g/L). WBC count, differential, and biochemistry panel were normal. ANA was 1:80 (speckled pattern), with a negative rheumatoid factor and normal erythrocyte sedimentation rate. Serum angiotensin-converting enzyme activity was 25 U/L, (normal, 8 to 52 U/L). Chest radiograph was unchanged from the 1988 radiograph, but it showed interval improvement compared with a radiograph from June 1990 when the patient had deteriorated while not receiving corticosteroids.

Pulmonary function testing by body plethysmography showed restrictive physiology and normal airflow (FEV_1, 1.75 L [69% of predicted]; FVC, 2.03 L [62%]; total lung capacity, 3.22 L [75%]). Single-breath carbon monoxide diffusing capacity corrected for hemoglobin was low (10.78 ml/min/mm Hg [43%]) (16, 17). Resting room-air arterial blood gas measurements performed in Denver (5,280 ft) showed hypoxemia (pH, 7.40; P_{CO_2}, 37 mm Hg; P_{O_2}, 48 mm Hg). With the patient breathing supplemental oxygen (~29%), the arterial P_{O_2} fell from 102 mm Hg at rest to 61 mm Hg with maximal exercise, and the alveolar-arterial difference widened from 21 to 77 mm Hg. Electrocardiogram demonstrated normal sinus rhythm, zero-degree axis, and p pulmonale.

Bronchoalveolar lavage was performed and analyzed following standard protocols (18, 19). There were 62 × 10^4 white cells/ml lavage fluid (nonsmoking normal, 12.9 × 10^4 ± 2.0 SEM), with 41% lymphocytes (11.8 ± 1.1), 56% macrophages (85.2 ± 1.6), and 2% neutrophils (1.6 ± 0.07) (20). As illustrated in figure 2, the BeLT using bronchoalveolar lavage mononuclear cells was notably abnormal, with median peak stimulation index of 149.2 (normal < 3.8 based on mean median peak stimulation index + 2 SD for 17 patients with sarcoidosis), confirming the diagnosis of chronic beryllium disease (2, 5). Repeat of the blood BeLT yielded an elevated median peak stimulation index of 6.8. As further confirmation of exposure, the original biopsy specimen was submitted to Dr. W. Jones Williams for laser microprobe mass spectrometry by methods previously described (21, 22). This technique, which is capable of detecting beryllium in the range of 1 to 10 ppm on paraffin sections, found beryllium within this patient's granulomas and Schaumann bodies, as illustrated in figure 3.

Discussion

Chronic beryllium disease has generally been described among workers in whom a history of past beryllium exposure has been elicited. However, 65 nonoccupational cases were reported to the U.S. Beryllium Case Registry during the 1940s and 1950s, arising from a time when the beryllium industry did less to control environmental exposures. Twenty-three of these cases were attributed to household exposure to dust brought home on work clothes and 42 to air pollution (8). However, even with improvements in control of industrial exposure, occupationally related beryllium disease continues to occur in an unchanged small percentage of exposed workers. The actual number of current and former beryllium-exposed workers in the United States is unknown.

Because of the clinical availability of the blood BeLT, we have been able to confirm this as the first new case of nonoccupational chronic beryllium disease to be reported in 30 yr. This patient's symptoms, clinical course, and radiographic, physiologic, and pathologic derangements are all typical of advanced chronic beryllium disease (12). Her case meets current and past case definitions (2, 23), including those that require demonstration of an abnormal bronchoalveolar lavage BeLT (2, 5).

This is the first time that a nonoccupational case of chronic beryllium disease has been identified using a blood marker of beryllium-specific cellular immunity. This case suggests that a subset of sarcoid patients with negative occupational histories actually have beryllium disease, and that the blood BeLT can help in case ascertainment. Recent data suggest that the blood BeLT may be almost interchangeable with the more invasive bronchoalveolar lavage version of this test (13). In our hands, the blood BeLT is positive in 94% of cases of chronic beryllium disease in whom lavage BeLT is abnormal, and is negative in other granulomatous diseases (2, 13).

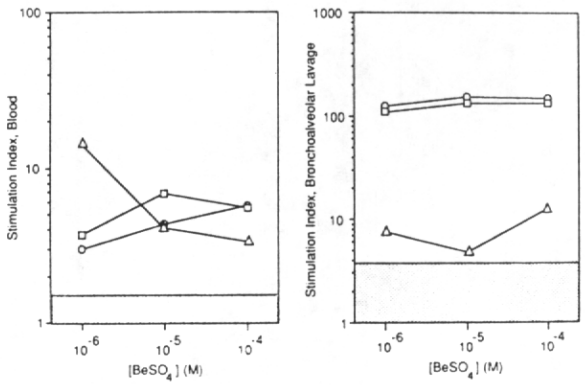

Fig. 2. Comparison of blood and bronchoalveolar lavage BeLT responses by beryllium sulfate concentration [$BeSO_4$] in a patient with nonoccupational chronic beryllium disease. Symbols represent stimulation indices for cells after 3 (*circles*), 5 (*squares*), and 7 (*triangles*) days in culture. Normal ranges for median peak stimulation index are shown in gray. For blood, counts per minute of tritiated thymidine uptake ranged from 374 ± 58 for unstimulated cells to 5,542 ± 1,420 for beryllium-sulfate-stimulated cells. For lavage, counts per minute of tritiated thymidine uptake ranged from 521 ± 70 for unstimulated cells to 89,619 ± 9,876 for beryllium-sulfate-stimulated cells.

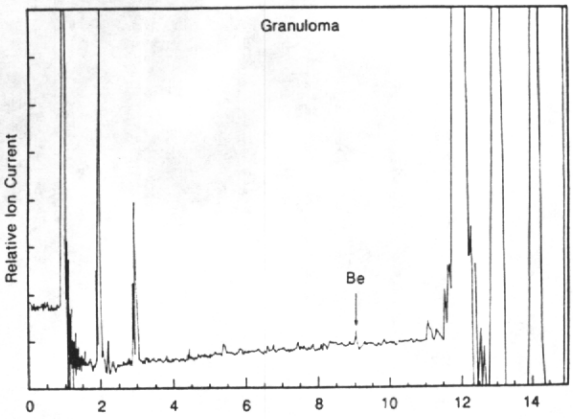

Fig. 3. Laser microprobe mass spectrometry demonstrates beryllium (Be) peak within the lung granuloma of this patient with nonoccupational beryllium disease. This analysis was performed by Professor W. Jones Williams (University of Wales College of Medicine).

However, not all laboratories performing the test have found such high correspondence between blood and lavage BeLTs (5).

This case has implications for how clinicians, industry, and government agencies define "beryllium exposure." Although it is impossible to know the dose of beryllium inhaled by our patient, her exposure would have been considered "trivial" by most physicians. For occupational air exposures, a permissible level of 2 $\mu g/m^3$ (8-h time-weighted average) with peak levels of less than 25 $\mu g/m^3$ is required. Previous research has suggested that beryllium exposures below existing regulatory standards may be sufficient to cause disease (6, 14, 24).

From a clinical standpoint, the correct diagnosis of chronic beryllium disease has implications both for patient prognosis and for prevention of disease in the community. Every patient with granulomatous lung disease should have a careful occupational and environmental history taken and if a history of direct or indirect contact with beryllium is elicited, additional testing be performed. This case suggests that until more is known, even persons with seemingly minor, incidental beryllium exposure should be considered to be at risk. As such, beryllium-using industries may need to include evaluation of passively exposed persons within the workplace when establishing beryllium surveillance programs and to notify employees of possible risk to their households. A much larger population may be at risk than is recognized.

Acknowledgment

The writers wish to thank David M. Atwell, M.D., and his patient for their contributions to this research. They also wish to thank Clara Wise, MT (ASCP), Jeri Teague, MT (ASCP), Ronald Harbeck, Ph.D., Beverly Schumacher, and Alma Kervitsky, CRTT, for their assistance in the laboratory, and Margaret Mroz, MSPH, for her assistance in data analysis.

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