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Disclaimer

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ABSTRACT

Objective: To study the prevalence of beryllium sensitization (BeS) and chronic beryllium disease (CBD) in a cohort of workers from a nuclear weapons research and development facility.

Methods: We evaluated 50 workers with BeS with medical and occupational histories, physical examination, chest imaging with HRCT (N=49), and pulmonary function testing. Forty of these workers also underwent bronchoscopy for bronchoalveolar lavage (BAL) and transbronchial biopsies.

Results: The mean duration of employment at the facility was 18 yrs and the mean latency (from first possible exposure) to time of evaluation was 32 yrs. Five of the workers had CBD at the time of evaluation (based on histology or HRCT); three others had evidence of probable CBD.

Conclusions: These workers with BeS, characterized by a long duration of potential Be exposure and a long latency, had a low prevalence of CBD.

INTRODUCTION

Chronic beryllium disease (CBD) is a granulomatous inflammatory disorder that is characterized by a specific cell-mediated immune response to beryllium and a clinical-pathological presentation similar to sarcoidosis.[1, 2] The diagnosis of CBD is usually made on the basis of confirmation of sensitization to beryllium through the use of the lymphocyte proliferation test (BeLPT) and histopathological evidence of epithelioid granulomas and/or mononuclear cell infiltrates on lung biopsy.[3, 4]

The exact exposure-response relationship for the development of sensitization and disease is unclear. Genetic susceptibility, dose and duration of beryllium exposure appear to be important risk factors for sensitization and disease. CBD has been viewed as a progressive disorder with a poor prognosis;[5, 6] however, there is evidence that some cases of CBD remain mild for a prolonged time.[7] In addition, there is evidence that some beryllium-sensitized individuals have not progressed to CBD over considerable follow up periods.[8]

Cross-sectional epidemiological studies using the BeLPT have been used to identify beryllium-sensitized individuals in settings with historically high occupational exposures to beryllium (e.g., beryllium machinists, ceramics workers, and nuclear weapons production workers). In this setting, it has been shown that a large proportion of sensitized workers will have CBD at the time of documentation of sensitization.[9-14] Recently, Newman and colleagues reported that in the longitudinal follow-up of beryllium-sensitized individuals without CBD at the time of identification, over 30 percent of such individuals progressed to CBD (based on lung histology) over a mean follow-up time of 3.8 yrs.[15] Interestingly, the severity of the CBD in this study

appeared to be mild, in contrast to historical cases from earlier decades prior to use of the BeLPT for case identification.[16] These findings have raised concerns that the widespread use of the BeLPT to screen populations of exposed workers may result in the identification of individuals with beryllium sensitization (BeS) who will never develop clinical disease.[16] In addition, it is unclear how often sensitization and disease occur in workers with lower levels of Be exposure.

We had the opportunity to evaluate currently employed or retired beryllium-sensitized workers from a nuclear weapons research and development facility where the occupational exposures were probably, in general, much lower than in production facilities. In this study we sought to determine the risk for development of CBD in these workers.

METHODS

Study Population

As part of a national U.S. Department of Energy (DOE)-sponsored medical surveillance program current or former employees of Lawrence Livermore National Laboratory (LLNL) were screened for beryllium sensitization based on at least two positive BeLPTs (i.e., beryllium-stimulated proliferation of lymphocytes from peripheral blood samples drawn on two separate occasions or on split samples tested in two different DOE-approved laboratories). Workers found to have positive BeLPTs were evaluated in the Occupational Medicine Clinic at San Francisco General Hospital between 1999 through 2005. Although the individuals were initially evaluated for clinical purposes, a protocol for aggregating the clinical data to prepare this report was approved by the Committee on Human Research of the University of California, San Francisco.

Clinical Evaluation

The standard clinical evaluation offered to these beryllium-sensitized individuals included a medical and occupational history, a routine physical examination, chest imaging [usually both plain chest radiographs and high-resolution computed tomographic (HRCT) scanning of the chest], pulmonary function testing (spirometry, lung volumes by plethysmography, and single-breath diffusing capacity), and fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsies.

Beryllium Exposure

Occupational medicine physicians obtained a lifetime work history that included information on dates and duration of employment at the nuclear weapons research facility and other jobs with

possible Be exposure. Historical information obtained from both the evaluated workers and occupational medicine physicians at the facility was used to generate a relative beryllium exposure index that had three categories of exposure: low (exposure to beryllium dust or fumes unlikely), moderate (occasional exposure to beryllium dust or fumes), and high (frequent exposure to beryllium dust or fumes). Each worker was assigned a level of beryllium exposure based on reported job title(s).

High Resolution Computed Tomography (HRCT)

HRCT scans were performed on a single-slice HighSpeed CT/i scanner (General Electric Medical Systems, Milwaukee, WI) using a standard interstitial lung disease (ILD) protocol.[17] Axial scans were obtained in full inspiration in both supine and prone positions at 2 cm intervals using 1 mm collimation employing standard thoracic CT settings (120 kVp, 200 - 350 mA). Expiratory imaging following a forced vital capacity maneuver was performed at three levels: the aortic arch, the tracheal carina, and above the diaphragm. Post-processing included reconstruction of the images using a high spatial frequency algorithm. HRCT images were viewed using hard copy format using image display parameters appropriate for lung (level = -700 HU, width = 1000 HU) and soft tissue (level = 40 HU, width = 400 HU) review. All scans were evaluated by a single chest radiologist experienced in ILD for findings consistent with CBD (e.g., perilymphatic nodules, thickened septal lines, ground glass opacification, and hilar adenopathy).[18]

Bronchoalveolar Lavage and Transbronchial Biopsy

Bronchoscopy was performed as follows. Intravenous access was established, supplemental O_2 was delivered, and the upper airways were anesthetized with topical lidocaine. Sedation with intravenous midazolam and fentanyl was used as needed for subject comfort. The bronchoscope was introduced through the mouth and vocal cords into the airways. The bronchoscope was then directed into the right middle lobe where bronchoalveolar lavage (BAL) was performed with four 60-ml aliquots of 0.9% saline warmed to 37°C (two aliquots to each of the medial and lateral segments). Immediately following BAL, an attempt was made to obtain eight transbronchial biopsies of peripheral lung tissue from the right lower lobe. After bronchoscopy, each subject was observed for an approximate 2-h recovery period.

Recovered lavage fluid was immediately put on ice. Total cells were counted on uncentrifuged aliquots of BAL using a hemocytometer. Differential cell counts were obtained from slides prepared using a cytocentrifuge, 25 g for 5 min, and stained with Diff-Quik (Dade Behring, Düdingen, Switzerland). BAL fluids were then centrifuged at 234 g for 10 min, and the cells were resuspended in 10 to 15 mL of RPMI-1640 media with 10% fetal calf serum and 0.5% penicillin and streptomycin to obtain a final concentration of about 5 to 10 million cells per mL. The cells were subsequently shipped to National Jewish Medical and Research Center in Denver, Colorado, at room temperature by overnight delivery for performance of BAL BeLPT.

Clinical-Radiographic-Pathological Review

A clinical-radiographic-pathological review of the data available for each of the evaluated individuals was done together by four of the authors (two pulmonologists -- JB, TK; a chest

radiologist -- MG; and a lung pathologist -- SN) to determine by consensus whether or not there was sufficient evidence to make a diagnosis of CBD. Chronic beryllium disease was defined as evidence of beryllium sensitization (all individuals evaluated) with epithelioid granulomas and/or mononuclear cell infiltrates in lung tissue. In these beryllium-sensitized individuals, the combination of a positive BAL BeLPT and HRCT findings consistent with CBD was also accepted as diagnostic of CBD. Probable CBD was defined as follows: 1) HRCT evidence of CBD without histological evidence of CBD or BAL lymphocytosis; 2) non-specific HRCT and histological evidence of fibrosis with BAL lymphocyosis; and 3) abnormal BAL BeLPT with BAL lymphocytosis. The differential cell count criterion for BAL lymphocytosis was set at 30% of total leukocytes (the criterion used by the ongoing DOE-sponsored, multi-center Beryllium Biorepository project).

Statistical Analysis

Statistical analysis was limited to descriptive parameters of the distributions of various characteristics of the population.

RESULTS

Beryllium Sensitization

Of the 1,875 current or former workers of Lawrence Livermore National Laboratory who underwent Be lymphocyte proliferation testing through 2005, 59 individuals had BeS based on the criterion described above, for a sensitization rate of 3.1%. Details of potential exposure to Be of the workers screened with Be lymphocyte proliferation testing are not known.

Chronic Beryllium Disease

Of these 59 individuals with BeS, nine refused any clinical evaluation for CBD and were not evaluated by us (Figure 1). The mean age of the 50 beryllium-sensitized individuals we evaluated was 63 years (range 39-81). Ten of the individuals were women. The mean duration of employment was 18 years (range 0.5-41). The mean potential latent period between start of employment and time of clinical evaluation was 32 years (range 12-48). Of the 50 individuals evaluated, 45 were no longer working at LLNL. None of the individuals who were still employed at the facility (n = 5) was currently being exposed to beryllium at the time of his/her clinical evaluation.

The classification of the likely beryllium exposure of the individuals is shown in Table 1. Most of the beryllium-sensitized individuals had low or moderate exposures. Average annual area monitoring data for beryllium at LLNL were available for the years 1962-1984 and 1992-1993. Area monitoring data for the Rocky Flats nuclear weapons production facility were reviewed for the years 1961-1988 (see online table A) as a comparison. The LLNL area beryllium levels are much lower than those at Rocky Flats for the years with available data (Figure 2).

Of the 50 individuals who did undergo clinical evaluation for CBD, 10 did not undergo bronchoscopy (seven refusals and three medical contraindications). Nine of the 10 individuals who did not undergo bronchoscopy had HRCT scans performed that showed no evidence of interstitial lung disease. One individual refused HRCT.

Of the 40 individuals who had bronchoscopy, five were diagnosed to have CBD through the clinical-radiographic-pathologic review described above. Four had epithelioid granulomas on transbronchial biopsy. The fifth individual was given the diagnosis of CBD despite the lack of granulomas or mononuclear cell infiltrates on transbronchial biopsies because she had BAL lymphocytosis, a positive BAL BeLPT, and HRCT evidence of pulmonary nodules in a pattern suggestive of sarcoidosis. All five were ex-smokers.

None of the five patients with diagnosis of CBD had severe disease based on their symptoms, pulmonary function test results, and HRCT findings (Tables 2 and 3), and thus none were treated with immunosuppressive therapy. An additional three individuals had HRCT and/or BAL abnormalities consistent with probable CBD, but did not meet our *a priori* criteria for a definitive diagnosis (Tables 2 and 3).

Thus, the CBD rate among sensitized individuals who underwent evaluation is either 5/40 (12.5%) or 5/49 (10.2%) depending on whether one requires pathological review of lung tissue or accepts HRCT as a surrogate. The CBD rate among the entire LLNL population tested for

BeS is 5/1,875 or 0.3%. If one includes the three individuals with some but not definitive evidence of CBD (see Table 3), the rate of CBD is (0.4%).

DISCUSSION

The primary finding of this descriptive study of beryllium-exposed workers from a research and development facility of the U.S. nuclear weapons industry is that the rate of beryllium sensitization is low (3%). In general, the workers screened for beryllium sensitization from this facility were exposed to only low levels of beryllium. The proportion with chronic beryllium disease among the sensitized individuals is also relatively low (10-12%) compared to workers in high-risk production operations such as beryllium machining or ceramics manufacturing. Furthermore, among the individuals with confirmed or probable CBD, there were no cases of disease severe enough to require immunosuppressive therapy.

Several other studies of U.S. workers in the nuclear weapons industry have reported low rates of beryllium sensitization (Table 4). A study by Welch et al. of 3,842 current and former construction workers at three DOE facilities (Hanford Nuclear Reservation, Oak Ridge Reservation, and the Savannah River Site) who participated in medical screening for beryllium sensitization showed that 53 (1.4%) of these workers had two positive BeLPTs; five workers were diagnosed to have CBD.[8] Stange et al. studied current and former workers at the Rocky Flats DOE facility, a nuclear weapons production plant with more workers potentially exposed to beryllium. Of the 5,173 individuals from Rocky Flats who had BeLPTs done, 154 (3%) were sensitized (based on two positive BeLPTs) and 81 (1.6%) were diagnosed to have CBD.[14] The highest prevalence of BeS was among machinists (11.4%), but other groups of workers thought to have lower exposures such as custodial workers also had some increase in risk (5.6% prevalence of BeS). We compared data on area concentrations of beryllium from Rocky Flats and LLNL as a rough guide to relative differences in potential exposures of workers to beryllium

between the two facilities (Figure 2 and online supplement). It is intriguing that while area concentrations at Rocky Flats were many times greater than at LLNL, the prevalence of beryllium sensitization is similar; however, the prevalence of CBD is approximately five times greater at Rocky Flats. Why a positive BeLPT has a lower positive predictive value for CBD at LLNL and Hanford than at Rocky Flats remains to be elucidated, but may be related to lower exposures to beryllium. Further investigation of the exposure-response relationships for both beryllium sensitization and CBD is needed.

A study of 2,221 workers involved in the cleanup of a former DOE nuclear weapons production facility that manufactured beryllium-containing weapon parts (presumably Rocky Flats) by Sackett et al. showed that 19 (0.8%) were beryllium-sensitized based on two or more abnormal BeLPTs.[19] These results taken together and extended by those we report here suggest that, in general, there is a relatively low risk of beryllium sensitization and CBD among workers in current or former nuclear weapons facilities and associated national weapons research laboratories, although some groups, such as production machinists, have much higher risk.

A diagnostic issue that our data touch on is the sensitivity of the BAL BeLPT, which has been suggested as being more sensitive than the peripheral blood BeLPT for predicting the presence of CBD.[3, 4] We report here that in three out of four cases of CBD for which a BAL BeLPT was performed, the test did not show abnormal lymphocyte proliferation to beryllium. In all three of the cases for which the BAL BeLPT was negative, two peripheral blood BeLPTs were positive. Although this sample of cases is too small to properly assess the sensitivity of the BAL BeLPT, our results do suggest that it might not be that sensitive for the diagnosis of CBD. The test can

be helpful in the diagnosis of CBD, however, if biopsied lung tissue shows no evidence of granulomatous inflammation and when combined with results of other tests (see Table 3).

Another clinical decision for which our data have relevance is when to perform bronchoscopy for the diagnosis of CBD. Because of the low prevalence of CBD among LLNL workers with beryllium sensitization as well as the lack of progression to clinically severe disease among those workers who have been diagnosed to have CBD, we have become more comfortable with annual medical follow-up of asymptomatic beryllium-sensitized workers with normal baseline pulmonary function tests and chest imaging instead of early bronchoscopy. It would be helpful if future research could provide more definitive evidence upon which to base the important decision for a beryllium-sensitized patient about whether or not bronchoscopy with transbronchial biopsies should be performed. Because the procedure is invasive and carries serious risk, the decision ought to be based on evidence.

In conclusion, aggressive evaluation of beryllium-sensitized workers using bronchoscopy for multiple transbronchial biopsies of lung tissue as soon as two BeLPTs are positive may be warranted in some cases. However, in populations that have low rates of CBD among the sensitized and lack of progression to severe disease among those with CBD, noninvasive longitudinal follow up may be preferable. With the current state of knowledge, bronchoscopy might best be reserved for individuals with progressive symptoms, decrements in pulmonary function, or chest imaging findings.

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FIGURE LEGEND

Figure 1

Flow chart of surveillance for beryllium sensitization (BeS) and chronic beryllium disease (CBD) among current and former workers from Lawrence Livermore National Laboratory.

Figure 2

Annual average beryllium area air sampling concentrations (in $\mu g/m^3$) from the Lawrence Livermore National Laboratory (LLNL) and Rocky Flats nuclear weapons production facility (RF) for the years 1962-1993 where available.

LLNL=♦; RF=■.