CHRONIC BERYLLIUM DISEASE: AN UNEXPECTED OCCUPATIONAL HAZARD FOR A JEWELLER

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ABSTRACT

Beryllium is used widely in industry due to its favourable elemental properties. Its extraction and subsequent incorporation into alloys and composites generate hazardous fumes and dust. Chronic beryllium disease (CBD) is an occupational interstitial lung disease that clinically resembles sarcoidosis. We present a case of a 33-year-old jeweller who developed CBD from exposure to dust while grinding unfinished gemstones. While workplace protection exists for beryllium workers, the health risks in artisans are unrecognised. Most cases are diagnosed in industries primarily involved in the use of beryllium (Table I); however, in our case the exposure to beryllium was unexpected. Lymphocyte proliferation testing for beryllium is a key investigation in patients with suspected CBD. To our knowledge, this is the first reported case of CBD diagnosed in a jeweller in South Africa.

Keywords: beryllium, chronic beryllium disease, occupational health, interstitial lung disease, lymphocyte proliferation test

INTRODUCTION

Beryllium is widely used in many industries due to its favourable elemental properties (see Table I). While it is inert in solid metal form, its chemical extraction and subsequent incorporation into metal alloys and composite materials generate hazardous vapours and dust. The United States produces 60% of the world's beryllium and the protection of beryllium workers is well established under the Occupational Health and Safety Administration (OHSA).[1] However, the health risks may be unrecognised in novel or artisanal industries where beryllium exposure may be either new or unexpected.

CASE DESCRIPTION

A 33-year-old man presented with a history of progressive shortness of breath, dry cough and weight loss over the past 12 months. He was a smoker with prior diagnoses of asthma and inhalant allergy. His airway symptoms failed to improve with standard asthma therapy.

Coughing episodes were sometimes accompanied by fever, chills and myalgia. On enquiry into his occupational history, the patient revealed that he had been working as a jeweller for the past 14 years. The work entailed cutting, grinding, faceting and polishing gemstones. The patient reported that he noticed that his nose would be filled with dust when he blew his nose. The patient did not use any personal protective equipment (PPE) or a mask during his work. He also melts and casts various metal alloys while crafting jewellery. The patient lives in a suburban neighbourhood in Cape Town and does not keep animals.

TABLE I: INDUSTRIES USING BERYLLIUM IN THE WORKPLACE

1.	Primary beryllium and alloy production
2.	Aircraft and aerospace manufacturing
3.	Automotive manufacturing
4.	Mining
5.	Nuclear energy
6.	Nuclear weapons development
7.	Computer components manufacturing
8.	Telecommunications
9.	Abrasive blasting
10.	Electronic recycling and refurbishment

Adapted from: MacMurdo MG, Mroz MM, Culver DA, Dweik RA, Maier LA. Chronic beryllium disease: update on a moving target. Chest. 2020;158(6):2458–2466.

On physical examination, no digital clubbing, pallor, lymphadenopathy, jaundice or peripheral oedema was present. The respiratory examination was unremarkable.

Chest radiography revealed bilateral diffuse infiltrates and nodules (Figure 1). Spirometry indicated a mixed pattern of airway disease with a severely reduced FEV1 and FVC (36% and 46% of predicted respectively) and a normal FEV1/

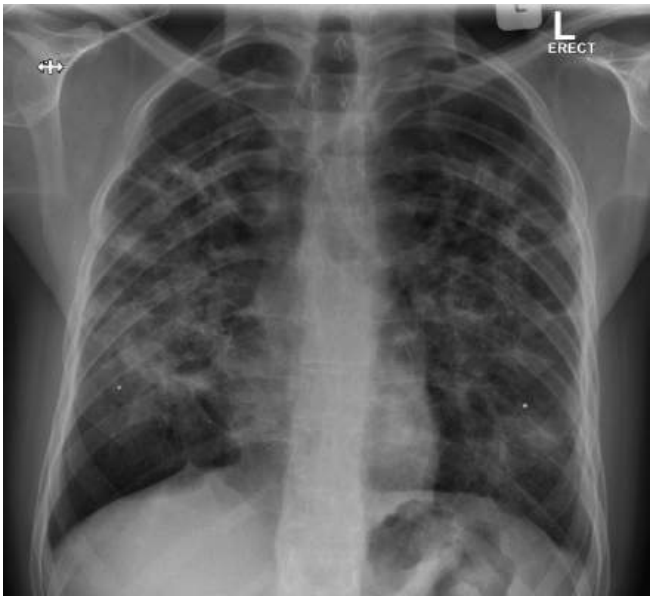

Figure 1: Erect postero–anterior chest X-ray: in keeping with bilateral interstitial lung disease

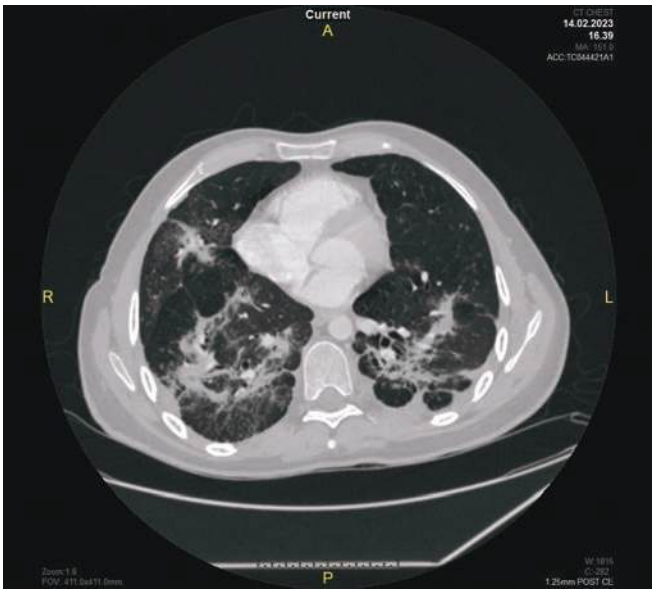

Figure 2: High-resolution chest CT scan: asymmetric bilateral parahilar irregular speculated airspace infiltrates which extend to involve all the lung zones. A background of extensive asymmetric micronodularity noted throughout the lung parenchyma with scattered interlobular septal thickening and septal lines

FVC ratio of 78%. The bronchodilator challenge showed no reversibility. The diffusion capacity was 43% of what is predicted, indicating a significant impairment of gaseous exchange. High-resolution computed tomography (HRCT) revealed asymmetric bilateral parahilar irregular speculated airspace infiltrates, which extended to involve all the lung zones. A background of extensive asymmetric micronodularity was noted throughout the lung parenchyma, with scattered interlobular septal thickening and septal lines. There were scattered subcentimetre hilar and mediastinal lymph nodes (Figure 2). The full blood count, inflammatory markers, serum total IgE, autoimmune screen and serum angiotensin-converting enzyme (SACE) levels were within normal limits. The patient tested negative for human immunodeficiency virus (HIV). Bronchoalveolar lavage fluid (BALF) analysis showed increased lymphocytes (10%) and neutrophils (19%) with no eosinophils. Tests for tuberculosis and fungal infections were negative. A transbronchial biopsy revealed non-caseating granulomas.

DIAGNOSIS AND MANAGEMENT

The patient's peripheral blood mononuclear cells (PBMC) were isolated and exposed to beryllium sulphate tetrahydrate ($BeSO_4$ $4H_20$) in cell culture. Lymphocyte proliferation was assessed after six days using Ki-67 staining and flow cytometry on a BD FACS Canto flow cytometer. Lymphocyte proliferation is reported as a stimulation index (SI) that is calculated as the ratio between the mean fluorescence intensity (MFI) of the stimulated lymphocytes and the negative control lymphocytes. An SI of 4–9 is considered positive and ≥ 10 strongly positive. A strongly positive SI of 22 was observed, confirming that the patient is sensitised to beryllium (Figure 3). Chronic beryllium disease (CBD) was diagnosed based on the finding of non-caseating granulomas and beryllium sensitisation (BeS).

The patient was prescribed prednisone 40 mg daily to control the granulomatous inflammation and a personalised protection plan was negotiated with the patient's employer. The patient was provided with PPE and a respirator that is to be used when cutting or grinding gemstones. The case was reported to the South African Department of Labour in terms of the Compensation of Occupational Injuries and Diseases Act (COIDA) of 1993 (amended in 1997) and compensation was granted. The patient is financially dependent on his income and decided to continue working, opting to limit his exposure through the use of PPE.

DISCUSSION

Gemstone cutting and grinding generate dust that may contain beryllium. Metal ions are potent haptens and a population of metal-specific memory T-lymphocytes may establish itself in the body following exposure in predisposed individuals.[2] Re-exposure activates the resident metal-specific memory T-cells to induce lymphocyte proliferation.[3] Lymphocyte proliferation in the presence of beryllium is a useful test for CBD and for this reason a beryllium lymphocyte proliferation test (BeLPT) was ordered to screen for BeS.

Beryllium exposure is an occupational hazard. It causes CBD in susceptible individuals after the inhalation of beryllium dust or fumes.[1,4] Most cases are diagnosed in workers who are employed in the beryllium extraction and composite material production industries. Other high-risk industries include metal working (aerospace, weapons, shipbuilding, automobile manufacturing), nuclear-power generation, mining, construction, consumer electronics and dental-product manufacturing.[4,5]

The beryls are a group of minerals that includes emeralds, aquamarines, beryls and bertrandites and grinding these minerals aerosolises beryllium dust. Gemstone cutters may also

TABLE II: DIFFERENTIAL DIAGNOSIS OF BALF CELL COUNTS		
LYMPHOCYTIC PATTERN (> 15% LYMPHOCYTES)	EOSINOPHILIC PATTERN (> 1% EOSINOPHILS)	NEUTROPHILIC PATTERN (> 3% NEUTROPHILS)
Sarcoidosis	Eosinophilic pneumonias	Collagen vascular disease
Chronic beryllium disease	Hypersensitivity pneumonitis	Idiopathic pulmonary fibrosis
Hypersensitivity pneumonitis	Asthma, bronchitis	Aspiration pneumonia
Drug-induced pneumonitis	Bone marrow transplant	Bacterial and fungal infections
Radiation pneumonitis	Churg-Strauss syndrome	Bronchitis
Collagen vascular diseases	Allergic bronchopulmonary aspergillosis	Asbestosis
Cryptogenic organising pneumonia or non-specific interstitial pneumonia	Bacteria, fungal, helminthic and pneumocystis infections	Acute respiratory distress syndrome (ARDS)
Lymphoproliferative disorders	Hodgkin's disease	Diffuse alveolar damage (DAD)

Adapted from: Meyer KC, Raghu G, Baughman RP, et al. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. Am J Resp Crit Care Med. 2012;185(9):1004–1014.[10]

be exposed to nickel, aluminium, silica, chromium and lead that are present in minerals and grinding discs. A Sri Lankan study conducted in 2013 documented the adverse respiratory effects in gemstone cutters due to gemstone dust and the authors recommended changes in the workplace to prevent ongoing exposure.[6] Assessing this occupational risk is challenging, since jewellers work with a variety of precious minerals and metals and respiratory exposures are often mixed.

Beryllium is poorly soluble and accumulates in the tissues. Attempts at chelation have been unsuccessful.[4] Acute pneumonitis occurs at high exposures, but CBD is not clearly dose-dependent.[4,5] BeS is a key first step in CBD pathogenesis and can be screened for in peripheral blood with a BeLPT.[1,4] The BeLPT can also be performed on lymphocytes from bronchoalveolar lavage fluid with enhanced specificity.[8] CBD results from a chronic Type-IV hypersensitivity reaction in the pulmonary interstitium. Beryllium ions are presented by antigen-presenting cells to naive CD4+ T-cells, triggering immune activation, cytokine release, inflammation and the formation of beryllium-specific memory T-cells.[4,9] Re-exposure induces lymphocytic alveolitis that progresses to granuloma formation.[9] HLA-DBP1 E69 has been associated with a higher risk of BeS and CBD.[1] Beryllium also enhances the innate immune response by inducing the activation and maturation of macrophages and dendritic cells, which augments antigen presentation, cell differentiation, cytokine secretion and T-cell responses.[9] Disease latency from exposure to symptom onset is variable and symptoms are mostly respiratory. A mortality rate of 30% has been reported and is mainly due to chronic respiratory failure.[1,4]

Spirometry may show restrictive, obstructive or mixed patterns, but may also be normal in early disease. Impaired gas exchange during cardiopulmonary exercise testing is an early finding.[1,4] Chest radiography findings resemble those of pulmonary sarcoidosis but perihilar and mediastinal lymphadenopathy are less frequent.[4,8] Lung nodules are the most common finding on HRCT, together with ground-glass infiltrates and thickening of the bronchial walls and/or the interlobular septae. Honeycombing, subpleural cysts and calcifications may be seen in advanced cases of the disease.

The hallmark histological finding in both CBD and sarcoidosis is non-caseating granulomas.[4] Bronchoalveolar lavage and transbronchial biopsy provide essential confirmatory evidence. A differential cell count on BALF includes counting macrophages, lymphocytes, neutrophils and eosinophils. A differential diagnosis of abnormal BALF cell counts is presented in Table II. Lymphocyte counts > 25% are highly suggestive of CBD. Lymphocyte subset analysis is not routinely recommended.[10]

Epithelioid granulomatous reactions may be seen in sarcoidosis, fungal pneumonia, pulmonary tuberculosis, atypical mycobacterial pneumonia and pneumoconiosis caused by beryllium, aluminium, nickel, titanium, chromium, palladium, silica, mercury and zirconium dusts. Non-caseating granulomas consist of aggregated epithelioid histiocytes with a collar of mostly CD4+ T-cells.[4,11] CBD patients are often misdiagnosed with pulmonary sarcoidosis due to the clinical similarity and therefore a detailed occupational history and metal LPT testing are required to make the distinction. Table III demonstrates the clinical differences between CBD and sarcoidosis.

Beryllium particles are present in granulomas in CBD patients and can be identified using mass spectroscopy or electron probe X-ray microanalysis (EPMA), but this is no longer routinely required. The current diagnostic criteria for CBD are summarised in Table IV. BeLPT testing has a high variability and tests should be repeated for confirmation, especially if borderline or negative. A single BeLPT detects BeS with 68% sensitivity and 96.6% specificity. Repeat testing improves the sensitivity to 88%. Beryllium skin-patch testing is no longer recommended since it may induce BeS.[4]

Management includes avoiding further beryllium exposure and suppressing the ongoing immune response to beryllium.[4] Lifelong therapy is required and systemic corticosteroids

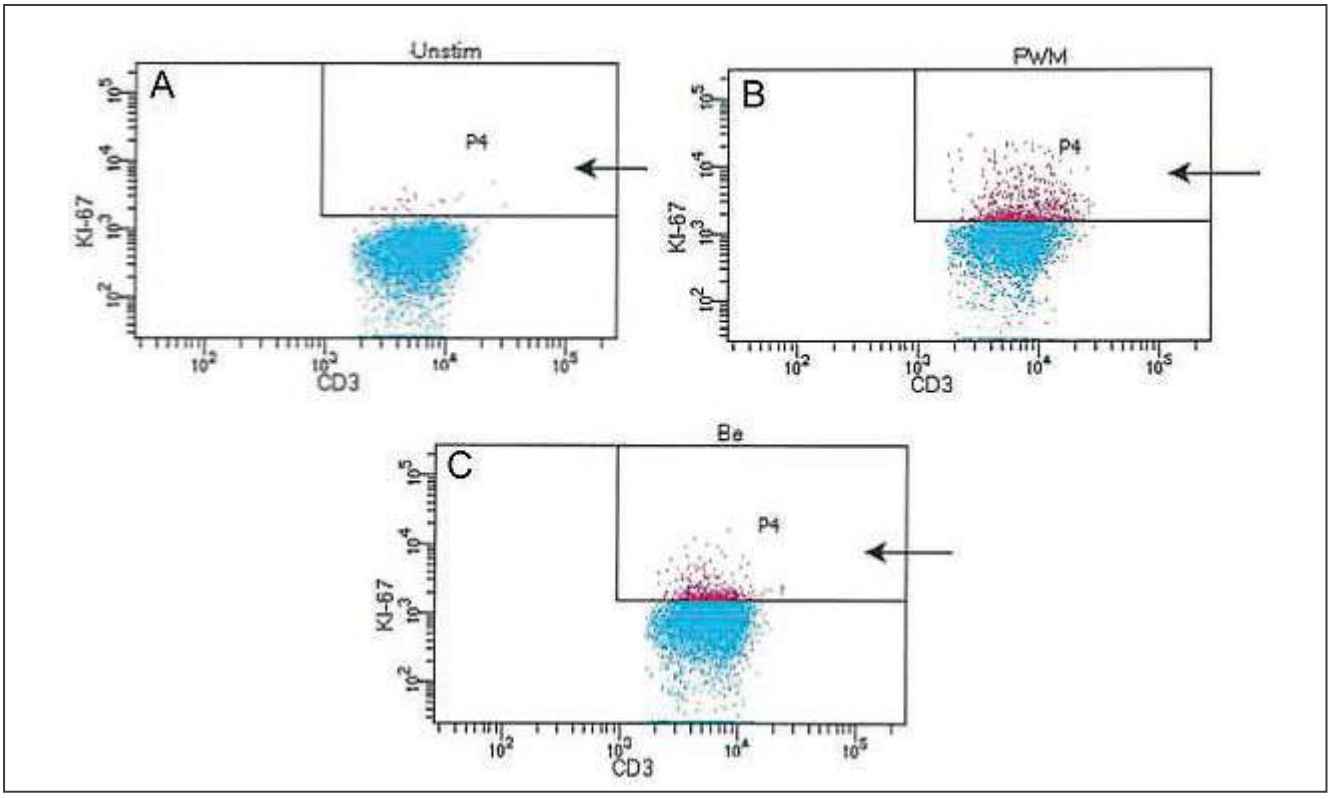

Figure 3: (A) BeLPT negative control (unstimulated), gated to show resting CD3+ lymphocytes at baseline (blue)
(B) BeLPT positive control (stimulated with Pokeweed Mitogen/PWM), gated to show CD3+ lymphocytes proliferating in response to PWM in the P4 window
(C) BeLPT patient test (stimulated with beryllium), gated to show proliferation of CD3+ lymphocytes in response to beryllium in the P4 window

are considered to be the first-line treatment for patients with significant symptoms of pulmonary functional decline. Steroid-sparing agents such as infliximab, cyclophosphamide, methotrexate, azathioprine and mycophenolate mofetil can also be used based on treatment approaches for sarcoidosis.[1,4] Patients with severely impaired gaseous exchange may benefit from infliximab, use of which has shown improved lung function and quality of life in CBD patients.[1]

OCCUPATIONAL REGULATION OF BERYLLIUM EXPOSURE

Berylliosis was first described as an occupational lung disease in 1943, when the United States became inundated with cases of interstisial lung disease linked to rapid industrialization. Disease registries were established, and a link to beryllium exposure was established over time. The first regulations on allowable beryllium exposure were promulgated in 1949, and officially adopted by OHSA in 1971.[1] The original regulations limited beryllium exposure per eight-hour shift to ≤ 2.0 ug/m^3.[1,3,4] Ambient air emissions were also restricted to ≤ 0.01 mg/m^3.[3,4] Evidence of 'safe' levels of exposure was still lacking at the time, but the regulations did curb rates of acute beryllium pneumonitis, which is a dose-dependent disease. However, cases of CBD continued to occur in facilities that were compliant with the regulations of the time.[1,4] The allowable exposure per eight-hour shift was finally reduced to ≤ 0.2 ug/m^3 in 1999, as evidence increasingly revealed inadequate protection of workers.[4]

The South African Compensation for Occupational Injuries and Diseases Act (COIDA) of 1993 (amended 1997) lists those diseases caused by beryllium and its compounds as an occupational health disease. Workers who develop CBD are eligible for compensation under COIDA.[12] COIDA does not specify occupational exposure levels (OELs) for beryllium in South Africa.

Beryllium-working industries should implement a risk management plan to minimise inhalational and cutaneous exposure. This includes raising awareness and training workers to use appropriate PPE. PPE should be supplied to frontline workers, and include a filtering full face mask or negative pressure respirator, gloves, coveralls and overshoes. Production processes should be streamlined and access-controlled, to prevent non-essential exposure of administration, cleaning and security staff.[4] Frontline workers should undergo annual medical surveillance and BeLPT testing, with further evaluation for CBD if the BeLPT results are positive. Rigorous workplace control and compliance with housekeeping rules have been shown to reduce the rates of BeS.[1,4] OSHA recommends the avoidance of further exposure in patients with BeS or established CBD, but, unfortunately, this will not necessarily halt progression.[1]

OTHER HAZARDOUS OCCUPATIONAL EXPOSURES TO MINERALS AND METALS IN GEMSTONE WORKERS

The complexity of materials used in industry can render it difficult to identify a single causative agent because

TABLE III: CLINICAL DIFFERENCES BETWEEN CHRONIC BERYLLIUM DISEASE AND SARCOIDOSIS		
	CBD	SARCOIDOSIS
Beryllium lymphocyte proliferation testing	Abnormal	Normal
Exposure history	History of work/environment exposure to beryllium	Unknown
Ophthalmological involvement	Conjunctivitis only	Uveitis, conjunctivitis and retinal involvement
Erythema nodosum	No	Yes
Lupus pernio	No	Yes
Onset	Insidious	Acute or insidious
Neurological involvement	None	May involve central or peripheral nervous system
Cardiac involvement	Rare	Occasional
Hepatic involvement	Occasional	Common
Isolated hilar adenopathy	Very rare	Common
Extrapulmonary manifestations without pulmonary involvement	No	Yes

Adapted from Balmes JR, Abraham JL, Dweik RA, et al. An official American Thoracic Society statement: diagnosis and management of beryllium sensitivity and chronic beryllium disease. Am J Resp Crit Care Med. 2014;190(10):34–59.[4]

occupational exposure often involves multiple substances that may cause disease through different mechanisms. In addition to beryllium, gemstones may also contain silicate, aluminium, nickel, chromium and cobalt, which may contribute to disease pathogenesis.[7]

Silicosis is a progressive interstitial lung disease (ILD) that is linked to the inhalation of silica dust. Silica is toxic to macrophages and induces macrophage apoptosis with the release of inflammatory mediators in the lung parenchyma. This inflammatory reaction recruits fibroblasts, which ultimately cause fibrosis.[5] Precious gemstones such as quartz contain mainly silicate.[7] A 2017 small-case series in Brazil reported that 57/118 (48.3%) of precious gemstone cutters were diagnosed radiologically with silicosis.[13] The authors highlighted the fact that the workers in this industry often have poor working conditions.[13] A 1991 South African study also reported six cases of silicosis in gemstone workers.[14] These small studies highlight the need for regular preventative measures to be implemented in workplaces and regular surveillance of such artisans.[13,14]

Aluminosis is an occupational ILD that may affect gemstone cutters, aluminium shavers and polishers who inhale aluminium dust.[5,7,15] Gemstone cutters working specifically with corundums such as rubies and sapphires may have a higher risk due to the aluminium content in these gemstones.[7] Lung histology and an aluminium LPT (Al-LPT) are useful in making the diagnosis. Mineralogical analysis of BALF or lung biopsy tissue may also show high levels of aluminium.[15]

Nickel exposure may cause interstitial fibrosis, COPD or asthma. Nickel has also been associated with lung and nasal cancers. Exposure to it induces inflammation and epithelial–mesenchymal transition (EMT), a process during which epithelial cells lose cell-to-cell adhesions and acquire mesenchymal properties. Aberrant EMT may lead to fibrosis, tissue destruction and malignant transformation.[16]

Hard-metal lung disease (HMLD) results from the inhalation of tungsten carbide and cobalt dust. These two metals are usually heated together and compacted to form a durable heat- and stress-resistant alloy that is used to sharpen drills, polish gemstones and manufacture dental prostheses.[17] Chromium is also used to create durable alloys and is sometimes combined with tungsten and cobalt in the manufacture of abrasives and grinding discs.[7] Cobalt is widely regarded as the primary cause, but tungsten carbide and cobalt may also have synergistic effects. Cobalt acts as a hapten to induce an IgE-mediated response. HMLD presents with occupational asthma, acute allergic alveolitis or fibrotic ILD.[17] Chromium and nickel have also been linked to occupational asthma and lung cancer.[7,18]

Zirconium has also been implicated in ILD, but it is difficult to prove a definite link because most respiratory exposures are mixed. A case was reported of a patient with occupational exposure over a period of 15 years who presented with pneumoconiosis. Lung histology demonstrated birefringent particles that were identified as zirconium compounds.[19]

CONCLUSION

We reported a case of CBD in a jeweller who was exposed to beryllium through grinding and polishing beryl gemstones. While inhalational exposures in gemstone cutters are often mixed, the positive BeLPT in this patient confirmed CBD as the most likely diagnosis. Avoidance is often not possible in essential first-line workers, but exposure can be managed through PPE and workplace screening programmes. Workplace prevention strategies that limit exposure prevent BeS effectively if they are adhered to. Metals are strong haptens, and lymphocyte

TABLE IV: DIAGNOSTIC CRITERIA FOR CHRONIC BERYLLIUM DISEASE

DEFINITE	PROBABLE
Suggestive occupational history	*Suggestive occupational history*
Evidence of BeS which may include: • Two positive BeLPTs ***or*** • 1 positive BeLPT plus 1 borderline BeLPT ***or*** • 3 borderline BeLPTs ***or*** • 1 positive BeLPT in BALF	Evidence of BeS which may include: • Two positive BeLPTs ***or*** • 1 positive BeLPT plus 1 borderline BeLPT ***or*** • 3 borderline BeLPTs ***or*** • 1 positive BeLPT in BALF
Compatible imaging findings	Compatible imaging findings ***or*** BALF lymphocytosis > 15%
BALF lymphocytosis > 15%	
Non-caseating granulomas	

Adapted from Balmes JR, Abraham JL, Dweik RA, et al. An official American Thoracic Society statement: diagnosis and management of beryllium sensitivity and chronic beryllium disease. Am J Resp Crit Care Med. 2014;190(10):34–59.[4]

proliferation testing plays an important role in detecting metal sensitisation in patients who are exposed while pursuing their occupation. Workers who become sensitised during their careers are likely to experience progression despite the prevention of further exposure. Lifelong medical surveillance is accordingly required, even after they have left the workplace.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL

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