



WALID SABER, MD

Pulmonary and Critical Care Medicine,
Cleveland Clinic

RAED A. DWEIK, MD

Pulmonary and Critical Care Medicine,
Cleveland Clinic

A 65-year-old factory worker with dyspnea on exertion and a normal chest x-ray

A 65-YEAR-OLD MAN is referred for evaluation of dyspnea on exertion. He reports that he was well until 2 years ago, when he started noticing gradual dyspnea on exertion that progressed slowly and was associated with dry cough and fatigue.

The patient says he has had no fever, wheezing, hemoptysis, chest pain, cyanosis, lower-extremity edema, paroxysmal nocturnal dyspnea, or orthopnea. He has never smoked and has no history of lung disease, cardiac disease, or tuberculosis. He has had no exposure to pets and has not traveled outside of his home state of Ohio. He has worked in several manufacturing jobs, including an aluminum factory, a beryllium manufacturing facility, and a steel mill. He has no significant family history of lung disease. He is not taking any medications and has no known drug allergies.

Physical examination. The patient is afebrile and in no distress. Lung auscultation reveals dry crackles bilaterally. The rest of the physical examination is unremarkable.

Pulmonary function studies:

- Forced vital capacity (FVC)—3.3 L (70% of predicted)
- Forced expiratory volume in 1 second (FEV_1)—2.7 L (71% of predicted)
- Total lung capacity (TLC)—4 L (70% of predicted)
- Diffusing capacity for carbon monoxide (DLCO)—19.51 L (69% of predicted).

Arterial blood gas analysis (while breathing room air at rest):

- pH—7.42 (normal range 7.35–7.45)
- PaO_2 —78 mm Hg (normal range 85–95)

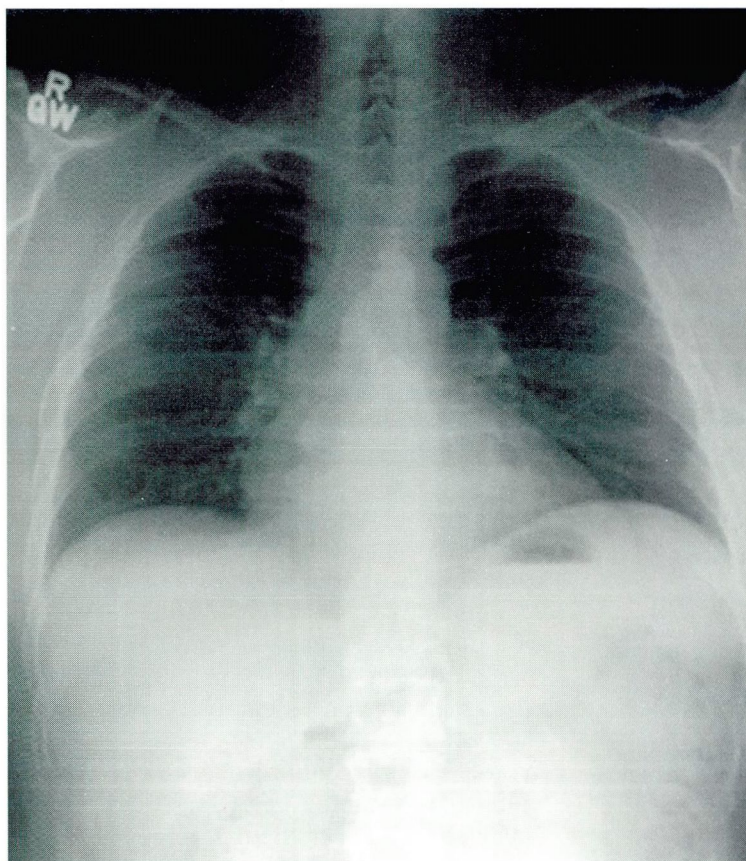


FIGURE 1. The patient's presenting posteroanterior chest radiograph, which is normal.

- PCO_2 —38 mm Hg (normal range 34–46).

Imaging studies. A chest radiograph is normal (FIGURE 1); however, a high-resolution computed tomographic (CT) scan of the chest reveals ground-glass opacification (FIGURE 2).

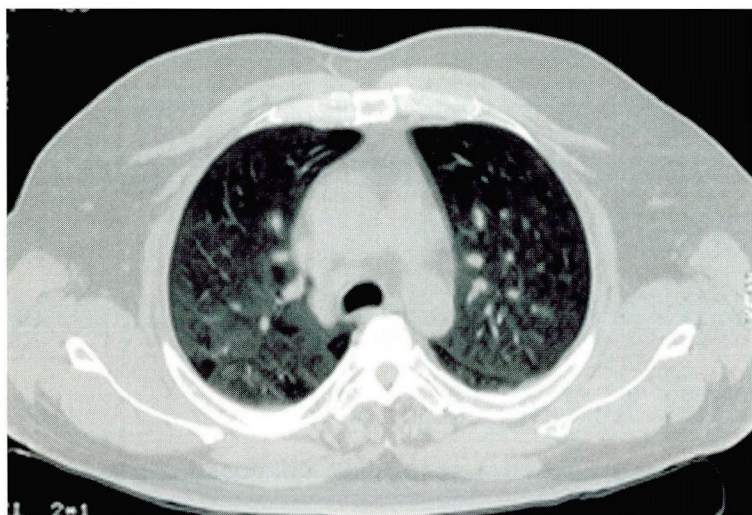


FIGURE 2. High-resolution computed tomographic scan of the patient's chest, showing ground-glass attenuation in the lower lung zones.

■ WHAT IS THE DIAGNOSIS?

1 What is your diagnosis?

- Hypersensitivity pneumonitis
- Idiopathic pulmonary fibrosis
- Sarcoidosis
- Tuberculosis
- Berylliosis

Industries with potential beryllium exposure: machining, nuclear power, aerospace, electronics

Although the radiographic presentation is not compatible with idiopathic pulmonary fibrosis or tuberculosis, ground-glass infiltrates can be seen in all the other three conditions. A history of exposure to beryllium, however, should raise the suspicion of chronic beryllium disease or berylliosis.^{1,2} Since chronic beryllium disease can arise clinically several years after the initial exposure to beryllium, and continuous exposure to beryllium is not necessary for the disease to develop, it should be suspected whenever someone with a history of exposure to beryllium presents with pulmonary symptoms.

Inhalation of beryllium dust can also lead to acute chemical pneumonitis, but this condition has nearly disappeared thanks to improved industrial hygiene. Chronic beryllium disease, however, continues to occur in industries in which beryllium is manufactured and processed.¹

Chronic beryllium disease

Chronic beryllium disease is a granulomatous lung disease similar to sarcoidosis. It is caused by a delayed-type hypersensitivity reaction, in which there is proliferation of beryllium-specific T cells. About 1% to 5% of exposed persons develop beryllium hypersensitivity, and about 2% develop chronic beryllium disease.³⁻⁵

The most significant exposure occurs in the occupational setting. Occupations with the highest potential for exposure are those involved with primary production, metal machining, and reclaiming scrap alloys. Other high-exposure areas are in the nuclear power, aerospace, and electronics industries.

In addition to environmental exposure, genetic predisposition seems to have a major role in the development of chronic beryllium disease. A variant of the human leukocyte antigen HLA-DPb1(Glu69) is found in 80% to 97% of patients with chronic beryllium disease but in only 30% of controls.⁶

The lung is the primary organ affected by chronic beryllium disease. Other organs that can be affected include the extrapulmonary lymph nodes, skin, salivary glands, liver, spleen, kidney, bone, myocardium, and skeletal muscle.

Symptoms are usually nonspecific and occur late in the course of the disease. Dyspnea is the most common symptom, but patients may also present with cough, chest pain, arthralgia, fatigue, and weight loss.

Physical signs, like symptoms, arise late in the course of the disease and include inspiratory crackles on pulmonary auscultation, lymphadenopathy, skin lesions, and hepatosplenomegaly.

Pulmonary function testing reveals an obstructive pattern in 39% of patients with chronic beryllium disease, and a restrictive pattern in 20%. The DLCO also declines over time in 36% of patients.⁷ However, the most sensitive test would be the finding of abnormalities in gas exchange (a widening alveolar-arterial oxygen gradient) during exercise.

The chest radiograph is normal in about half of patients with documented chronic beryllium disease. Abnormal findings in the other half include hilar adenopathy,

TABLE 1

Laboratories in the United States that perform the beryllium-specific lymphocyte proliferation test

Center for Epidemiologic Research

Oak Ridge Institute for Science and Education
Former Beryllium Worker Medical Surveillance Program
ORISE/CER, PO Box 117, Mail Stop 45
Oak Ridge, TN 27831-0117
(865) 241-6152

Performs testing for the United States Department of Energy (DOE) and DOE contractors only

Cleveland Clinic Foundation

Department of Clinical Pathology, L40
9500 Euclid Avenue
Cleveland, OH 44195
(216) 444-8844
(800) CCF-CARE (223-2273)
Extension 48844 or 55763

Hospital of the University of Pennsylvania

Pulmonary Immunology Laboratory
833 BRB II/III
421 Curie Boulevard
Philadelphia, PA 19104
(215) 573-9906

National Jewish Center for Immunology and Respiratory Medicine

Cellular Immunology Tests
Division of Environmental and Occupational Health Sciences
1400 Jackson Street
Denver, CO 80206
(303) 389-1723

Specialty Laboratories, Inc

2211 Michigan Avenue
Santa Monica, CA 90404-3900
(310) 828-6543
(800) 421-4449

increased interstitial markings, or both. High-resolution CT scanning of the chest is more sensitive than chest radiography.⁸ Typical findings on high-resolution CT are ground-glass opacification (FIGURE 2), parenchymal nodules, or septal lines. High-resolution CT, however, may be negative in up to 25% of patients with documented chronic beryllium disease.

■ CONFIRMATION IS NEEDED

2 How would you confirm the diagnosis of berylliosis in this patient?

- Blood beryllium-specific lymphocyte proliferation test
- Bronchoscopy, bronchoalveolar lavage, and transbronchial biopsy
- Open lung biopsy
- Cardiopulmonary exercise test
- Angiotensin-converting enzyme level

The diagnosis of chronic beryllium disease is based on:

- A history of beryllium exposure
- A positive beryllium-specific lymphocyte proliferation test performed on blood or bronchoalveolar lavage fluid
- Nonnecrotizing granulomas on lung biopsy.

Beryllium exposure. The current Occupational Safety and Health Administration (OSHA) standards for workplace air allow an 8-hour time-weighted average maximum permissible level of 2 $\mu\text{g}/\text{m}^3$ and a peak level of 25 $\mu\text{g}/\text{m}^3$. Some recent studies, however, suggest that the current 2- $\mu\text{g}/\text{m}^3$ limit may be too high and may not protect workers from developing chronic beryllium disease. Thus, any potential exposure to dusts or fumes of beryllium should be enough to raise the possibility of chronic beryllium disease.² Furthermore, the absence of an obvious history of exposure to beryllium would not exclude the diagnosis if the beryllium-specific lymphocyte proliferation test were positive and granulomas were present.

The blood beryllium-specific lymphocyte proliferation test is currently the screening test of choice to determine if a beryllium worker has become sensitized to beryllium or has developed chronic beryllium disease.^{9,10} The test involves exposing peripheral blood mononuclear cells to beryllium salts in vitro at varying concentration for variable times and looking for cell proliferation. Only a few laboratories in the United States perform this test, however (TABLE 1). The test can also be performed on mononuclear cells from bronchoalveolar lavage fluid, which is thought to be more sensitive than blood testing.

Bronchoscopy. To confirm a suspected diagnosis of chronic beryllium disease, one

usually needs to perform a flexible fiberoptic bronchoscopy with bronchoalveolar lavage and transbronchial biopsy. Bronchoscopy is also helpful in excluding other possible conditions with similar presentations, such as hypersensitivity pneumonitis or mycobacterial or fungal infection.

The hallmark of chronic beryllium disease on transbronchial biopsy is nonnecrotizing granulomas; this finding is diagnostic in the appropriate clinical and epidemiologic setting. However, the granulomas in chronic beryllium disease are indistinguishable from those in sarcoid granulomas. Therefore, an integral part of the diagnosis is to confirm exposure to beryllium by taking an occupational history, obtaining a beryllium-specific lymphocyte proliferation test, or finding beryllium in the lung tissue.

Patients with chronic beryllium disease usually have lymphocytosis in the bronchoalveolar lavage fluid (> 20% lymphocytes).

An open lung biopsy is rarely needed but could be resorted to if the transbronchial biopsy is negative and the suspicion for chronic beryllium disease remains high. Although the diagnostic yield is slightly higher than with transbronchial biopsy, the risk is also significantly higher.

The serum angiotensin-converting enzyme level has no diagnostic value. The serum ACE level may be high in chronic beryllium disease, as it is in other granulomatous diseases, but this finding has no diagnostic value.

Case continued:

Findings on bronchoalveolar lavage

The patient underwent flexible bronchoscopy with bronchoalveolar lavage and biopsy. The lavage fluid contained 45% lymphocytes and tested positive on the beryllium-specific lymphocyte proliferation test. Transbronchial biopsy revealed nonnecrotizing granulomas consistent with chronic beryllium disease (FIGURE 3). Special stains for acid-fast and fungal organisms were negative.

Chronic beryllium disease and sarcoidosis share many similarities (TABLE 2). Unless beryllium exposure is suspected, almost all cases of chronic beryllium disease will be misdiagnosed as sarcoidosis.

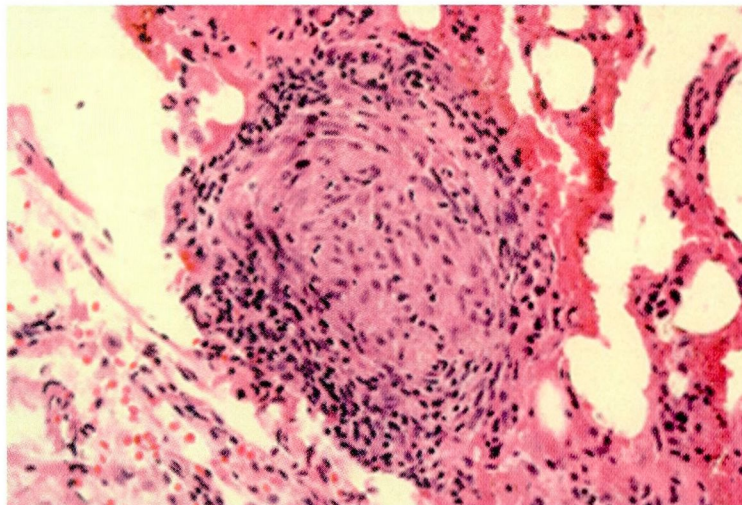


FIGURE 3. A histopathologic section of the lung, showing the typical nonnecrotizing granuloma, the hallmark of chronic beryllium disease.

MANAGEMENT

3 How would you manage this patient?

- Advise him to avoid any further beryllium exposure
- Start treatment with corticosteroids
- Start methotrexate therapy
- Avoid exposure and start corticosteroids
- No need for treatment

All patients with chronic beryllium disease should be advised to avoid any further beryllium exposure. Although there is no proof that stopping exposure to beryllium will improve the disease or halt its progression, it is prudent to avoid further exposure, in view of the immune-mediated nature of the disease.

There is currently no cure for chronic beryllium disease, and no controlled studies of chronic beryllium disease are available. However, on the basis of anecdotal reports, the immune-mediated pathogenesis of the disease, and the similarities with sarcoidosis (TABLE 2), chronic beryllium disease is treated with corticosteroids. Since corticosteroid therapy is not curative and has significant side effects, it is recommended only for patients who have symptoms or a decline in pulmonary function. This patient is symptomatic and has evidence of restriction on his pulmonary function testing, and he may benefit from therapy with corticosteroids.

OSHA standards for beryllium exposure may be too lax

TABLE 2

Features of chronic beryllium disease and sarcoidosis

FEATURE	CHRONIC BERYLLIUM DISEASE	SARCOIDOSIS
Occupational exposure	Yes	No
Onset	Acute or insidious	Acute or insidious
Respiratory symptoms	Predominant	Predominant
Erythema nodosum	No	Yes
Dermatitis	Yes	No
Cardiac involvement	Rare	Common
Pulmonary physiology	Gas exchange abnormalities common, obstruction early, mixed obstruction and restriction, or pure restriction late	Gas exchange abnormalities common, obstruction, or mixed pattern
Bilateral hilar adenopathy	Uncommon	Common
Infiltrates	Diffuse nodular or linear opacities, can be absent	Nodular and/or linear opacities, may be more focal than in chronic beryllium disease
Computed tomography	Small nodules, septal lines, ground glass appearance, adenopathy	Small nodules, septal lines, adenopathy
Beryllium lymphocyte proliferation test	Positive	Negative
Granulomas	Yes, nonnecrotizing	Yes, nonnecrotizing
Other histology	Diffuse mononuclear cell infiltrate common, bronchial submucosa involved occasionally	Diffuse mononuclear cell infiltrate common, bronchial submucosa involved occasionally
Beryllium in tissues	Yes	No
Skin tests		
Tuberculin	Negative	Negative
Kveim	Negative	Positive
Beryllium patch	Positive	Negative
Elevated angiotensin-converting enzyme	Uncommon	Common
Response to steroid treatment	Often stabilizes disease, may improve pulmonary physiology and symptoms, usually requires continuous therapy	Often stabilizes disease that has not spontaneously remitted, may require continuous therapy
Prognosis	Variable, cor pulmonale and progressive fibrosis in some patients, more benign in others	Good prognosis for approximately 80%, may progress to end-stage fibrosis and cor pulmonale

ADAPTED FROM WILLIAMS WJ. BERYLLIUM DISEASE. POSTGRAD MED J 1988, 64:511-516, AND NEWMAN LS. BERYLLIUM DISEASE AND SARCOIDOSIS: CLINICAL AND LABORATORY LINKS. SARCOIDOSIS 1995, 12:7-19.



Dear Doctor:

As editors, we'd like you to look into every issue, every page of the *Cleveland Clinic Journal of Medicine*. We'd like to know...

1 How many issues do you look into?

Here's our goal:

All Most Half Few

2 How do you read the average issue?

Here's our goal:

Cover-to-cover
 Most articles
 Selected articles

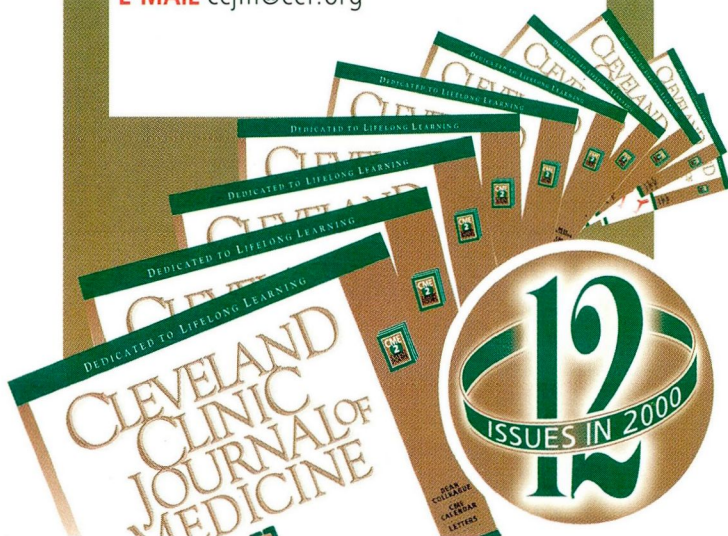
**We put it in writing...
 please put it in writing for us.**
 We want to hear from you.

CLEVELAND CLINIC JOURNAL OF MEDICINE
 The Cleveland Clinic Foundation
 9500 Euclid Avenue, NA32
 Cleveland, Ohio 44195

PHONE 216.444.2661

FAX 216.444.9385

E-MAIL ccjm@ccf.org



In patients for whom corticosteroids fail or who develop significant side effects, methotrexate may be considered. In end-stage cases, lung transplantation may be considered.

SUMMARY

Chronic beryllium disease is an occupationally acquired granulomatous lung disease similar to sarcoidosis. It is caused by exposure to beryllium in genetically susceptible persons. It should be suspected in patients with beryllium exposure who present with pulmonary symptoms or have a positive screening blood beryllium-specific lymphocyte proliferation test. The diagnosis is confirmed by the finding of granulomas on transbronchial biopsy in the appropriate clinical and epidemiologic setting. Although there is no cure, treatment with corticosteroids is usually beneficial. In view of the potential side effects, treatment is reserved for patients with symptoms or a decline in pulmonary function.

REFERENCES

- Meyer KC. Beryllium and lung disease. *Chest* 1994; 106:942-946.
- Dweik RA. Berylliosis. In: Plantz SH, Zevitz ME, editors. *eMedicine* (<http://www.emedicine.com/>). In press.
- Newman LS. Immunology, genetics, and epidemiology of beryllium disease. *Chest* 1996; 109:405-435.
- Newman LS, Kreiss K, King TE Jr. Pathologic and immunologic alterations in early stages of beryllium disease. Re-examination of disease definition and natural history. *Am Rev Respir Dis* 1989; 139:1479-1486.
- Saltini C, Winestock K, Kirby M. Maintenance of alveolitis in patients with chronic beryllium disease by beryllium-specific helper T cells. *N Engl J Med* 1989; 320:1103-1109.
- Richeldi L, Sorrentino R, Saltini C. HLA-DPB1 glutamate 69: a genetic marker of beryllium disease. *Science* 1993; 262:242-244.
- Pappas GP, Newman LS. Early pulmonary physiologic abnormalities in beryllium disease. *Am Rev Respir Dis* 1993; 148:661-666.
- Newman LS, Buschman DL, Newell JD Jr. Beryllium disease: assessment with CT. *Radiology* 1994; 190:835-840.
- Kreiss K, Newman LS, Mroz MM. Screening blood test identifies subclinical beryllium disease. *J Occup Med* 1989; 31:603-608.
- Stokes RF, Rossman MD. Blood cell proliferation response to beryllium: analysis by receiver-operating characteristics. *J Occup Med* 1991; 33:23-28.

ADDRESS: Raed A. Dweik, MD, Department of Pulmonary and Critical Care Medicine, Cleveland Clinic Foundation, A90, 9500 Euclid Avenue, Cleveland, OH 44195.



CME ANSWERS

Answers to the CREDIT TEST on page 863 of this issue

1 A 2 E 3 D 4 E 5 E 6 B 7 B 8 A 9 B 10 C
 11 D 12 E 13 D 14 C