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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]



A Young Patient With a Minimal Smoking History Presents With Bullous Emphysema and Recurrent Pneumothorax*

Eduardo Mireles-Cabodevila, MD; Hina Sahi, MD; Carol Farver, MD; Tan-Lucien Mohammed, MD; and Daniel A. Culver, DO, FCCP

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A cute-onset dyspnea and substernal chest pain radiating to the back developed in a 46-year-old African-American woman while she was watching television. There was no cough, fever, or chills. She had been admitted to the hospital 3 months earlier with a similar presentation; a spontaneous, left basal pneumothorax was found and was treated with tube thoracostomy.

Six years before that, she had been first told she had emphysema and was treated with inhaled bronchodilators; she stopped smoking (smoking history, 13 pack-years). A review of prior chest radiographs demonstrated that emphysema involving predominantly the upper lobes had been present 13 years prior (smoking history at that time, 5 pack-years). Her medical history was remarkable for two episodes of suspected pneumonia in her early thirties, hypertension, hyperlipidemia, and diffuse idiopathic skeletal hyperostosis. She worked as a data processor in a health institution; had never been exposed to fumes, dusts, asbestos, or silica; denied any drug use; and had no family history of lung disease. A careful review of systems revealed occasional arthralgias,

mainly involving the hips, elbows, and the thoracic spine. There was no history of urticaria, ocular disease, or joint laxity.

Clinical Findings

Physical examination revealed a mesomorphic woman who was 166 cm tall, tachypneic (22 breaths/min), and hypoxemic (pulse oximetric saturation, 90% [while breathing room air]). The lung examination revealed decreased breath sounds bilaterally with hyperresonance at the left base. The cardiac examination findings were unremarkable. There were no skin lesions, clubbing, edema, synovitis, or joint deformities.

CBC count, comprehensive metabolic panel, α_1 -antitrypsin (A1AT) level (183 mg/dL), and angiotensin-converting enzyme level (30 U/L) were normal. The results of a tuberculin skin test were negative. Prior pulmonary function tests revealed an FVC of 3.60 L (99% predicted), an FEV₁ of 2.80 L (92% predicted), an FEV₁/FVC ratio of 77.8, and a moderate reduction in the diffusion of carbon monoxide (59% predicted). Plethysmography demonstrated normal total lung capacity (97% predicted) with mild hyperinflation (residual volume, 116% predicted).

Radiologic Findings

A chest CT scan performed 6 years prior showed extensive subpleural emphysema and no lymphadenopathy (Fig 1). Chest imaging performed at hospital admission demonstrated a left basal pneumothorax, bulky mediastinal and hilar lymphadenopathy, upper-lobe paraseptal emphysema, and large bullae (Fig 2).

Pathologic Findings

Because of recurrent pneumothorax, she was treated with bullectomy and pleurectomy. A pathologic exam-

*From the Departments of Pulmonary, Allergy and Critical Care Medicine (Drs. Mireles-Cabodevila, Sahi, and Culver), Diagnostic Radiology (Dr. Mohammed), and Anatomic Pathology (Dr. Farver), Cleveland Clinic, Cleveland, OH.

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Correspondence to: Daniel A. Culver, DO, FCCP, Department of Pulmonary, Allergy and Critical Care Medicine, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195; e-mail: culverd@ccf.org

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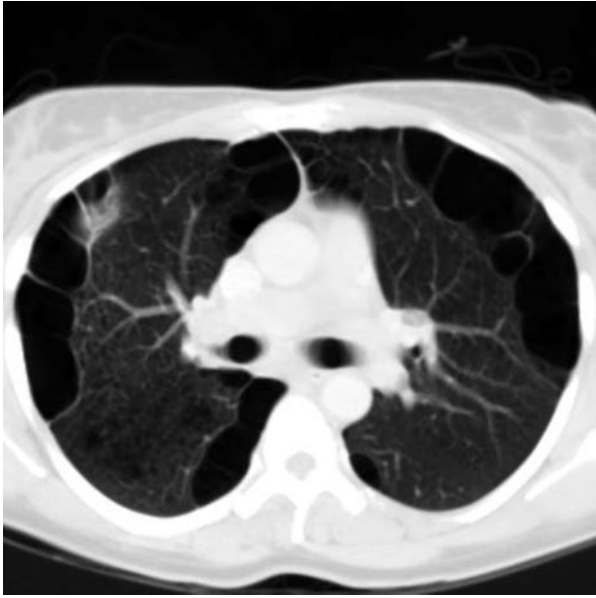


FIGURE 1. Axial CT scan image obtained 6 years prior to diagnosis. The image through the subcarina shows large paraseptal bullae. No nodules or masses are identified. Slice thickness, 5 mm.

ination demonstrated multiple nonnecrotizing granulomas in the subpleural region and in the walls of the bullae (Fig 3). No evidence of granulomas obstructing the airway was seen. Cultures and organismal stains were negative.



FIGURE 2. CT scan image obtained on hospital admission. This is a multiplanar coronal reconstructed image in the lung window demonstrating extensive bullous emphysema in a paraseptal distribution. The remainder of the pulmonary parenchyma is normal. The arrows indicate subcarinal and hilar adenopathy. The image was acquired with a pulmonary embolism protocol and a slice thickness of 5 mm.

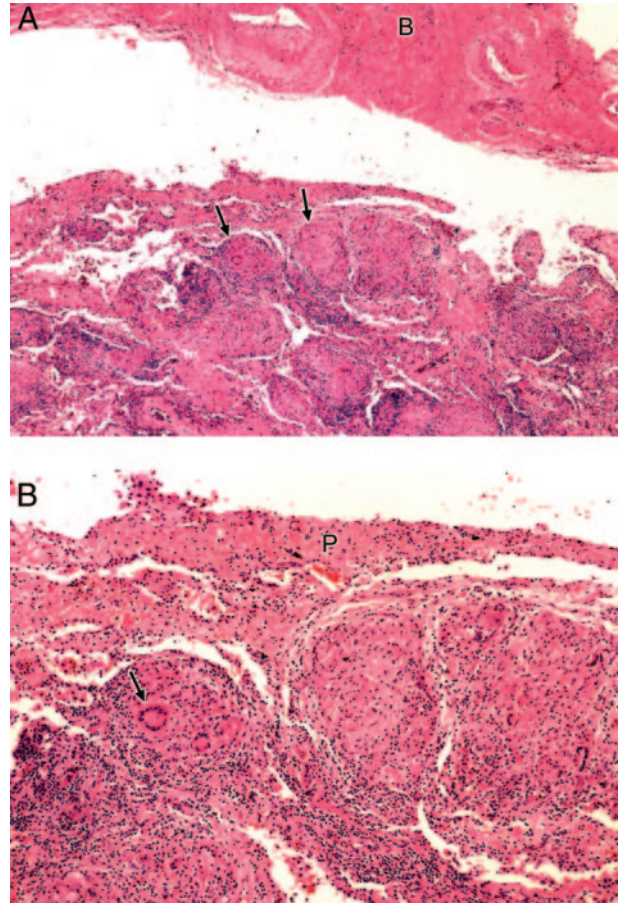


FIGURE 3. *Top, A:* fibrous wall of bulla (B) overlying areas of multiple nonnecrotizing granulomas (arrows) in subpleural areas (hematoxylin-and eosin, original $\times 1.25$). *Bottom, B:* multiple nonnecrotizing granulomas with overlying pleura (P). Giant cells (arrow) and epithelioid histiocytes are present in most granulomas. Tissue stains were negative for fungal and mycobacterial organisms (hematoxylin-eosin, original $\times 4$).

What is the diagnosis?

CLINICAL AND RADIOLOGIC DISCUSSION

Our patient presented with a disease that was characterized by upper lobe-predominant paraseptal emphysema with areas of bullous disease, spontaneous pneumothorax, mediastinal adenopathy, no airflow obstruction, and protracted time to diagnosis. The differential diagnosis for bullous lung disease is limited (Table 1).^{1,2} Secondary causes of emphysema may be overlooked in smokers, especially since their incidence is higher in the population of people who smoke.³ The diagnosis of the underlying etiology for bullous lung disease depends on recognizing that almost all of these conditions have systemic manifestations.

A1AT deficiency is an inherited disorder that predominantly affects white persons and is responsible for 1 to 4.5% of cases of COPD.⁴ Clues to this disorder include unexplained or early-onset emphysema, a family history of emphysema, bronchiectasis, liver dysfunction, necrotizing panniculitis, or Wegener granulomatosis.

HIV infection confers an increased risk for emphysema when compared to control subjects (15% vs 1%, respectively), apparently due to the accelerated progression to emphysema in smoking HIV-positive individuals.⁵ Besides tobacco, bullous lung disease has been associated with marijuana,⁶ cocaine,⁷ and IV drug use,^{8,9} with the latter being the strongest association.

Table 1—Differential Diagnosis of Bullous Lung Disease*

Bullous Lung Disease
Tobacco smoking
A1AT deficiency
HIV infection
IV drug use (<i>ie</i> , methylphenidate, heroin, cocaine, or talc)
Marijuana smoking
Cocaine smoking
Autoimmune diseases (<i>ie</i> , hypocomplementemic urticarial vasculitis syndrome, Sjögren disease, Wegener granulomatosis disease, and multisystem autoimmune dysfunction).
Connective tissue disorders (<i>ie</i> , cutis laxa, Ehlers-Danlos syndrome, and Marfan syndrome)
Bullous sarcoidosis
Idiopathic giant bullous emphysema
Birt-Hogg-Dubé syndrome
Neurofibromatosis
Placental transmogrification of the lung
Fabry disease
Salla disease

*Differential diagnosis based on cases of bullous emphysema and bullous lung disease reported in the literature.

Several autoimmune diseases have been implicated in bullous lung disease. The most common association is with hypocomplementemic urticarial vasculitis syndrome. It is an uncommon disorder of unknown etiology, which is characterized by persistent urticarial lesions, leukocytoclastic vasculitis, and decreased complement levels. Dyspnea, airflow obstruction, and emphysema are seen in half of cases, usually by the third decade of life.¹⁰ Case reports of bullous lung disease have also been reported with Sjögren disease,¹¹ lupus erythematosus,¹² multisystem autoimmune dysfunction,¹³ and Wegener granulomatosis disease (in the absence of A1AT deficiency).¹⁴

Marfan syndrome,¹⁵ Ehler-Danlos syndrome,¹⁶ and cutis laxa¹⁷ can present with early-onset emphysema and spontaneous pneumothorax. These disorders are the manifestations of defects in elastin and/or collagen. Systemic features include arachnodactyly, skin and joint laxity, ectopia lentis, aortic and valvular disease, and aneurysms. Idiopathic giant bullous emphysema is a rare syndrome of unknown etiology that affects young men, usually smokers, and is characterized by paraseptal emphysema and large bullae in the upper lobes.¹⁸

Birt-Hogg-Dubé syndrome is an autosomal-dominant genodermatosis that is characterized by multiple benign cutaneous neoplasms on the head, neck, and upper trunk during the third to fourth decades of life. The lung manifestations are subpleural cystic lesions and basal-predominant bullae. Spontaneous pneumothorax develops in up to 43% of patients.¹⁹ Neurofibromatosis has also been associated with bulla formation and pulmonary fibrosis in case reports. However, the largest and most recent series to date was unable to document a clear association.²⁰

Placental transmogrification or placentoid bullous lesion of the lung is an unusual condition in which the alveoli develop a villous configuration that resembles placental villi.²¹ The pathophysiology remains unknown.²² The characteristic presentation is a young patient with a giant bleb or cyst causing compression of a healthy lung.^{21,22}

Fabry disease is an inborn error of metabolism that results from the tissue deposition of ceramide trihexoside due to the deficiency of α -galactosidase. Airflow obstruction occurs in up to 36% of patients, and several case reports have described spontaneous pneumothorax and emphysema.²³ Salla disease is a very rare congenital disease that leads to the accumulation of sialic acid; reported only in Finland,²⁴ approximately 124 patients have been identified. One case of bullous emphysema has been described in the cohort.²⁴

Sarcoidosis affects the lungs in approximately 95% of patients,²⁵ but bullous sarcoidosis is a rare mani-

festation with an unknown incidence. A histopathologic review²⁶ of lung-volume-reduction surgery specimens at one center hinted that the diagnosis may be underrecognized, since 9 of 80 subjects (11%) had noncaseating granulomas. Unfortunately, the report²⁶ did not clearly correlate this finding with clinical or radiologic information, making the diagnosis tenuous in these individuals. Bullous sarcoid should be distinguished from cavitory or fibrocystic sarcoidosis, which may also lead to spontaneous pneumothorax.^{27–29} The paucity of fibrosis in the former contrasts with the well-established fibrosis that is typical in the latter conditions.

Bullous sarcoidosis was initially described in 1949, with a handful of subsequent case reports (Table 2).^{27,30–35} The reported cases describe predominantly young patients (mean age, 36 years). Most had obstructive physiology, leading to an initial diagnosis of emphysema or asthma, and resulting in a prolonged time to diagnosis. The absence of striking spirometric abnormalities, as in our patient, has been described in patients with paraseptal emphysema.^{36,37}

Although smoking may be associated with the development of bullous sarcoidosis, only approximately half of the available case reports specify the smoking history. Interestingly, smoking is thought to protect the patient from the development of sarcoidosis in general. In A Case Control Etiologic Study of Sarcoidosis,³⁸ the odds ratio for the development of

sarcoidosis among smokers was 0.62 (95% confidence interval, 0.50 to 0.77). However, a Japanese study³⁹ compared CT scan findings in 23 sarcoidosis patients with a modest smoking history (median smoking history, 12 pack-years) and 23 nonsmoking patients. Emphysema was the only statistically different finding between both groups (11 vs 1, respectively; $p < 0.002$), although the type of emphysema was not specified. Mediastinal adenopathy developed in our patient 6 years after she had stopped smoking. By then, evidence of emphysema had already been present for 9 years (she had accrued 5 pack-years of smoking at that time), raising the question of whether the delayed development of typical lymph node enlargement was a manifestation of the protective nature of tobacco in sarcoidosis or simply part of the natural history of the disease.

The evaluation of bullous lung disease begins with a detailed medical history, including the age of onset of the disease, and a physical examination, including determination of the presence of extrapulmonary symptoms or signs. Given the therapeutic and genetic implications, the measurement of A1AT level and the determination of phenotype are routinely warranted.⁴

If chest radiograph findings suggest an atypical distribution of bullae (*eg*, basal predominance) or lymphadenopathy, we suggest obtaining a high-resolution chest CT scan. Features that may heighten

Table 2—Reports of Bullous Sarcoidosis*

Study/Year	Age/Sex	Smoking History, pack-yr	Race	PFT Results	Radiologic Findings
Zimmerman and Mann ⁴³ /1949	21/M	NS	Black	Obstruction	Adenopathy, bilateral emphysema, concomitant tuberculosis
Harden and Barthakur ²⁸ /1959	41/M	NS	NS	Obstruction	Bilateral emphysema, lower lobe giant bullae
	30/F	NS	NS	Restrictive	Spontaneous pneumothorax, emphysema
Miller ³² /1981	31/F	NS	NS	NS	Fibrosis, bilateral bullae, cavitory lesion
	22/M	NS	White	NS	Adenopathy, coarse nodulation, apical bullae
	60/M	74	White	Obstruction	Diffuse bullous disease
Packe et al ³⁴ /1986	40/F	0	NS	Obstruction	Adenopathy, fine stippling, lower lobe bullae
	24/M	1†	NS	Obstruction	Extensive shadows then diffuse bullae
	28/M	1†	NS	Obstruction	Extensive shadows, adenopathy then diffuse bullae
Pena et al ³³ /1993	36/F	NS	Black	Restriction	Lower lobe bullae and interstitial infiltrates
Froudarakis et al ²⁷ /1997	33/M	NS	NS	Restriction	Adenopathy, diffuse bullous disease
Judson and Strange ³⁵ /1998	37/M	10	Black	Obstruction	Adenopathy, bilateral bullous disease
	40/M	< 10	White	Obstruction	Adenopathy, bilateral basal bullous disease
	48/F	0	Black	Obstruction	Adenopathy, bilateral bullous disease
Kumar and Epstein ³¹ /2001	57/M	15	NS	NS	Adenopathy, diffuse bullous disease
Mireles-Cabodevila et al (current study)	46/F	10	Black	Normal	Adenopathy, subpleural emphysema, and bilateral bullous disease

*M = male; F = female; NS = not specified; PFT = pulmonary function test.

†One pack per day, but no length established in years.

suspicion for sarcoidosis include lymph node enlargement, micronodules in a bronchovascular or subpleural location, or infiltrates not related to bullous compression of an adjacent lung. In our case, the absence of substantial airflow obstruction was an additional feature that is atypical for the common emphysema phenotype. The diagnosis of sarcoidosis-related bullous lung disease may be difficult due to the increased risk of complications from performing a biopsy. BAL may be useful to suggest the diagnosis, and transbronchial needle aspiration can be diagnostic. When pleurodesis is attempted for pneumothorax in patients with evidence of sarcoidosis, clinicians should consider surgical biopsy as well, since the management of progressing disease would be radically altered.

Pathology Discussion

The pathologic mechanism for bullous sarcoidosis is unknown. Packe et al³⁴ have suggested that an episode of diffuse parenchymal involvement, initial “extensive shadows” on the chest imaging, precedes the development of bullous lesions. Judson and Strange³⁵ have suggested the following three possible pathophysiologic explanations: endobronchial lesions causing obstruction; the retraction of surrounding fibrotic tissue; or inflammatory alveolitis leading to the destruction of lung tissue. As evidenced by the absence of significant spirometric or pathologic airways involvement and scant fibrosis in this case, we suspect that imbalanced protease-antiprotease manifestations of inflammation could be the culprit. Several matrix metalloproteinases have been implicated in smoking-related pulmonary emphysema,^{40,41} and their levels are also elevated in sarcoidosis patients.⁴²

CONCLUSION

The prognosis of bullous sarcoidosis is variable, with frequent recurrence of pneumothoraces and progression of physiologic derangements. Prolonged survival has been achieved after bullectomy, pleurodesis, or transplant.^{31,33,35} In our patient, 1 year after undergoing surgery, she has had no further pneumothoraces and no progression of her sarcoidosis.

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