

## CLINICAL PROBLEM-SOLVING

## A Crazy Cause of Dyspnea

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*In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.*

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N Engl J Med 2011;364:72-7.

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**An 18-year-old black woman with a history of asthma presented with fever, ear pain, and dull discomfort on the right side of her chest that was unchanged with movement or inspiration. She had no other symptoms and had been well until the morning of presentation. On examination, her temperature was 38.8°C, and her right tympanic membrane was inflamed. Although the lungs were clear on auscultation, radiography revealed air-space opacities in both lower lobes. Azithromycin was prescribed. Her symptoms resolved within 24 hours, and repeat radiography performed 1 week later showed that the opacities, although still present, had diminished.**

In a healthy young adult presenting with acute fever and otitis media, it is most likely that the observed pulmonary opacities are infectious in origin. Infection with *Streptococcal pneumoniae* or *Chlamydia pneumoniae* is a common cause of both otitis media and pneumonia. Incomplete radiographic resolution 1 week after presentation is not surprising, since the radiographic features of pneumonia may take weeks to fully resolve. In the absence of continued or recurrent symptoms, no additional imaging would be necessary.



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Several months later, the patient returned, reporting a nonproductive cough and dyspnea on exertion. Frequent coughing spells had forced her to discontinue participation in competitive soccer and dance. Initially, the dyspnea occurred only with coughing, but it slowly progressed to the point of limiting her functional capacity, despite the use of inhaled albuterol. She had no fevers, chills, or night sweats, and her weight was stable. The results of a physical examination were unremarkable. The patient was referred for asthma education, through which potential home triggers (a cat and wall-to-wall carpeting) were identified and poor inhaler technique was noted. It was not possible to complete pulmonary-function testing because of the patient's cough. She was given a spacer and peak-flow meter, began using a fluticasone-salmeterol inhaler (delivering 250 µg of fluticasone and 50 µg of salmeterol per puff), and was given a prescription for loratadine in addition to the albuterol.

A logical question at this point is whether the patient's current symptoms are related to her initial presentation. Has the initial, presumably infectious process failed to resolve? Is her current illness the result of her initial illness (e.g., postinfectious bronchiolitis obliterans with organizing pneumonia)? A chest radiograph would have been useful to see whether there are persistent or recurrent opacities. Alternatively, her cough and shortness of breath may reflect progression of her asthma;

more information is needed on her asthma history. Although a course of relentless and progressive asthma symptoms is somewhat atypical at her age, an “asthma-plus” syndrome, such as the Churg–Strauss syndrome, chronic eosinophilic pneumonia, parasitic infection, or allergic bronchopulmonary aspergillosis, is possible. An acquired or congenital immunologic defect should be considered as a cause of possible recurrent infection, including a humoral defect (e.g., hypogammaglobulinemia or hyper-IgM or hyper-IgE syndrome), a phagocytic defect (e.g., chronic granulomatous disease), or a defect in cellular immunity (e.g., infection with the human immunodeficiency virus [HIV]). Alternatively, her asthma could be a misdiagnosis of symptoms caused by an underlying lung disease that has predisposed her to infection (e.g., cystic fibrosis — unlikely, given her race — or congenital bronchiectasis).

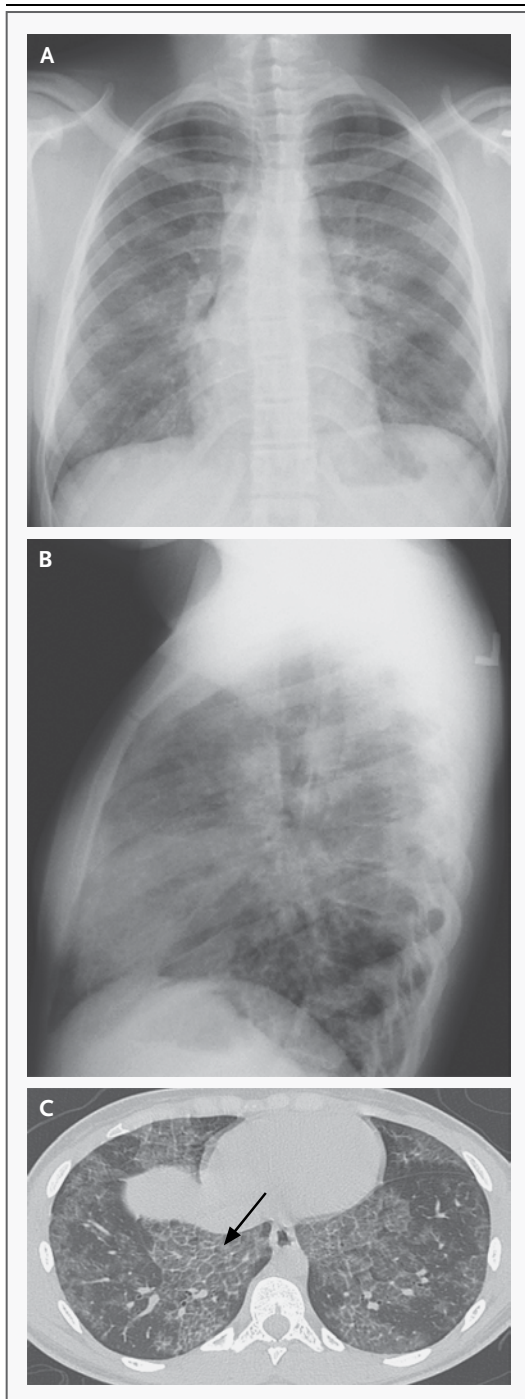
**The patient’s asthma had previously occurred only with exercise and had been well controlled when she used albuterol before beginning activities; she had never required glucocorticoids or hospitalization. Her medical history also included seasonal allergic rhinitis, an allergy to bee stings, eczema, and pneumothorax at birth. Her medications included albuterol, loratadine, and fluticasone–salmeterol. She had no known drug allergies. Her family history was notable for an aunt with sarcoidosis and multiple family members with allergies and asthma. The patient was a high-school student and lived with her mother. She had no history of alcohol, tobacco, or illicit drug use and had not traveled recently.**

Although sarcoidosis is less likely to be familial in blacks than in whites, the patient’s family history raises the possibility of a diagnosis of sarcoidosis. Eczema and allergic rhinitis are commonly associated with asthma and support a diagnosis of asthma or an asthma-plus syndrome as the cause of her symptoms. Exercise-induced dyspnea and cough are common in patients with asthma and thus are not helpful in narrowing the differential diagnosis. The absence of recurrent spontaneous pneumothorax makes it likely that the cause of neonatal pneumothorax was isolated, perhaps owing to a birth-related trauma or positive-pressure ventilation in the newborn period; it is unlikely to be related to the current presentation.

**Over the next 2 months, symptoms progressed to the extent that the patient noted considerable dyspnea while walking and occasional dyspnea while talking. She continued to have episodes of non-productive cough, although they were infrequent. She had occasional night sweats but no fevers or chills. She reported having dry eyes and dry skin but no pain or discomfort in her joints. Despite having a normal appetite, the patient had lost about 1.5 kg since her initial presentation. On repeat physical examination, she did not appear ill. Her temperature was 36.7°C, heart rate 86 beats per minute, blood pressure 98/60 mm Hg, and oxygen saturation 96% while she was breathing ambient air. The conjunctivae were clear, and funduscopic examination was normal. The tympanic membranes were normal, and the mucous membranes were moist. The neck was supple, without thyromegaly, and there was no lymphadenopathy. The jugular venous pressure was not elevated. The lungs were clear on auscultation. Cardiac examination revealed a regular rate and rhythm, with no murmurs, rubs, or gallops. The abdomen was soft and nontender. The extremities were warm and well perfused. The neurologic examination was unremarkable.**

The patient’s clinical status has worsened substantially, with progressive dyspnea, functional limitation, and extrapulmonary symptoms, including symptoms consistent with a sicca-type syndrome, weight loss, and some night sweats. Pertinent negative results on physical examination include the normal jugular venous pressure and normal cardiac and lung findings. The absence of wheezing, however, does not rule out obstructive lung disease — a chest radiograph should be obtained. Ambulatory oxygen saturation should also be assessed, since patients with gas-exchange abnormalities resulting from lung disease may have desaturation with exercise, and such testing provides information on the patient’s functional capacity. In addition, the nature of changes in the heart rate in response to exercise can be informative, since a rapid increase in the rate may indicate poor cardiac function or arrhythmia.

**A complete blood count (with a differential count) and the results of serum chemical tests (including tests of liver function and renal function) were within normal limits. A chest radiograph revealed**



**Figure 1. Imaging Studies of the Chest.**

Radiographs of the chest (posteroanterior view in Panel A and lateral view in Panel B) show bilateral, predominantly perihilar, hazy air-space opacities. The pulmonary vasculature appears normal. A computed tomographic scan of the chest (Panel C) shows patchy ground-glass opacities with associated intralobular septal thickening (“crazy paving,” arrow), without involvement of the interlobular septa.

the presence of extensive pulmonary opacities, with the most severe in the left perihilar region, and diffuse bilateral involvement sparing the apices (Fig. 1A and 1B). A 5-day course of azithromycin was prescribed, with no radiographic or symptomatic improvement.

Given the diffuse parenchymal radiographic abnormalities, a repeat course of antibiotics is appropriate. The persistence of symptoms after multiple courses of antibiotics suggests a cause other than community-acquired pneumonia and demands a broadened differential diagnosis and more aggressive evaluation. The laboratory data and physical examination do not provide evidence of extrapulmonary or systemic disease. The absence of an eosinophilia reduces the likelihood of an asthma-plus syndrome.

Sputum smears should be obtained for Gram’s staining, staining for acid-fast bacilli, and fungal culture. An assessment of immune status is also warranted and should include an HIV test and measurement of antinuclear antibodies and serum immunoglobulin levels. Tests for hypersensitivity pneumonitis and for sensitivities to mold mixes and bird-feather antigens should be performed, as well as a test for antineutrophil cytoplasmic antibodies (ANCA). In addition, pulmonary-function tests and a computed tomographic (CT) scan of the chest are needed for a more complete characterization of the patient’s diffuse parenchymal lung disease.

A sputum culture grew oral flora. Pulmonary-function testing showed a forced vital capacity (FVC) of 1.85 liters (58% of the predicted value), a forced expiratory volume in 1 second ( $FEV_1$ ) of 1.8 liters (64% of the predicted value), and a ratio of  $FEV_1$  to FVC of 97%. Total lung capacity was 1.82 liters (41% of the predicted value), and residual volume was 0.46 liters (41% of the predicted value). The corrected carbon monoxide diffusing capacity was 36% of the predicted value. Treadmill testing showed a baseline oxygen saturation of 97%, with desaturation to 85% while the patient was walking.

The pulmonary-function tests point to a restrictive ventilatory defect, a finding that is consistent with the diffuse air-space disease observed on radiography. Measurements of lung volume are also important for the assessment of airflow obstruction. In patients with restriction, a low-value

FVC can mask the presence of an obstruction on spirometry by bringing the ratio of FEV<sub>1</sub> to FVC into the normal range. On lung-volume testing, however, airflow obstruction and the resulting trapped gas may be evident when there is a relative or absolute elevation of the residual volume. The observation of a low residual volume in this case makes asthma or an asthma-plus syndrome unlikely. The low saturation of ambulatory oxygen reflects compromised gas exchange.

**The serum level of angiotensin-converting enzyme was 23 U per liter (normal range, 9 to 67), and the lactate dehydrogenase level was 153 U per liter (normal range, 100 to 250). An antinuclear-antibody screen was negative, as was the result of a tuberculin skin test. A CT scan of the chest revealed extensive bilateral ground-glass opacities and septal thickening without apparent hilar adenopathy (Fig. 1C).**

Although an elevated level of angiotensin-converting enzyme is present in the majority of patients with sarcoidosis, the test's sensitivity and specificity are insufficient to warrant its inclusion in this diagnostic workup. Similarly, measurement of the level of lactate dehydrogenase does not help to refine the differential diagnosis. The bilateral ground-glass opacities seen on the chest CT scan represent alveolar filling, which points to a differential diagnosis that includes diffuse alveolar hemorrhage, infection, edema, cancer (e.g., bronchoalveolar carcinoma or primary pulmonary lymphoma), and interstitial lung disease, a category encompassing diffuse parenchymal lung processes that often involve both the interstitium and the alveolar space. In this case, hemorrhage, edema, and infection are unlikely, although we cannot rule out atypical chronic infections, such as tuberculosis or pneumocystis pneumonia. A tumor would also be unlikely, given the patient's age and the clinical progression.

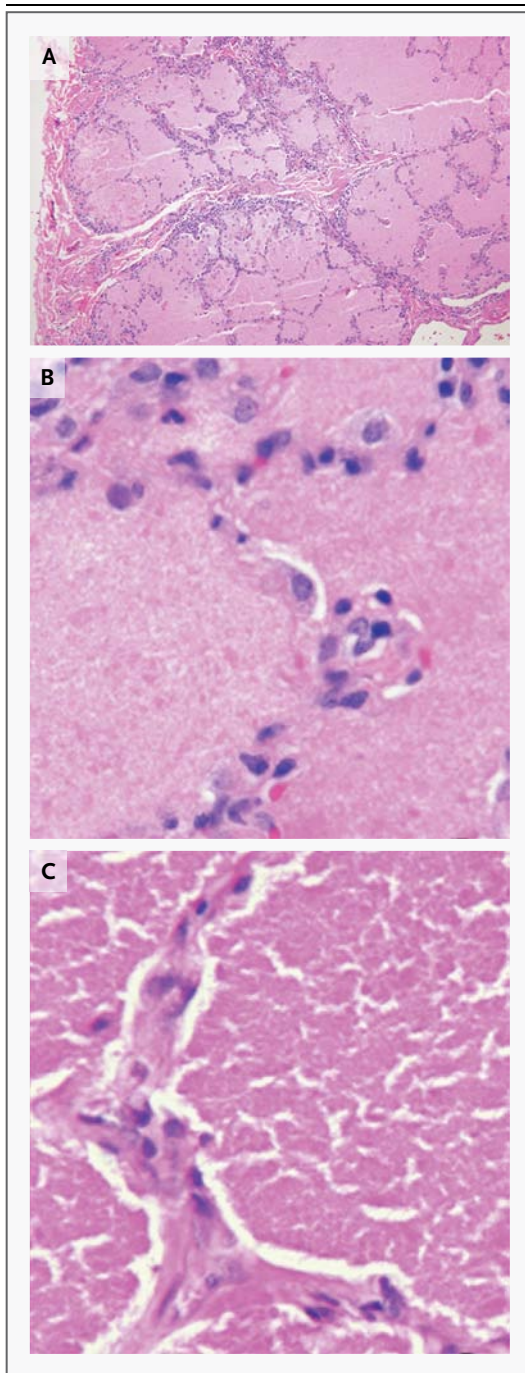
Interstitial lung diseases include conditions resulting from occupational or environmental exposures (e.g., hypersensitivity pneumonitis), drug-induced lung injury, pneumonitis associated with collagen vascular disease, inherited processes (e.g., tuberous sclerosis), and other specific syndromes, such as sarcoidosis, alveolar proteinosis, the Churg–Strauss syndrome, and chronic eosinophilic pneumonia. Finally, there are the remaining idiopathic interstitial pneumonias, which infrequently have pathognomonic

radiographic or clinical findings. Our patient is a nonsmoker who has not had obvious environmental or toxic exposures likely to cause hypersensitivity pneumonitis or lung injury, although some exposures can be difficult to identify. The possibility of sicca-type symptoms notwithstanding, there is no evidence of a collagen vascular disease, and a test for antinuclear antibodies was negative.

In addition to showing ground-glass opacities, the CT images reveal extensive lobular septal thickening, a diagnostic turning point in this case. Although septal thickening often represents nonspecific accumulation of interstitial fluid — most commonly, pulmonary edema — the combination of septal thickening and variable alveolar filling can be manifested as a “crazy paving” radiographic pattern. Crazy paving is highly characteristic of pulmonary alveolar proteinosis, although it can also be observed in other diseases (e.g., alveolar sarcoidosis, lipoid pneumonia, and mucinous bronchoalveolar carcinoma). The pathophysiological basis of pulmonary alveolar proteinosis is primary macrophage dysfunction, which allows surfactant and lipid-laden macrophages to accumulate in the intraalveolar and interstitial spaces. The CT scan should be reviewed with a chest radiologist to determine whether the noted septal thickening is consistent with crazy paving.

**A review of the chest CT showed that the septal thickening had a pattern consistent with crazy paving, predominately in the lower lobes and perihilar regions. This regional distribution is frequently observed in pulmonary alveolar proteinosis.**

Bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy constitute the preferred diagnostic procedure for pulmonary alveolar proteinosis, but a surgical lung biopsy is also reasonable. If this diagnosis is confirmed by histologic analysis, the level of granulocyte-macrophage colony-stimulating factor (GM-CSF) antibodies should be measured to determine whether this is a case of autoimmune pulmonary alveolar proteinosis. Treatment of autoimmune pulmonary alveolar proteinosis focuses on symptom management. Treatment options include whole-lung lavage, GM-CSF administration, immunosuppression (with rituximab or mycophenolate mofetil), or a combination of these treatments. In contrast, other cases of pulmonary alveolar pro-



**Figure 2. Lingular-Biopsy Specimens.**

The lingular-biopsy tissue shows proteinaceous material filling alveoli (Panel A, hematoxylin and eosin), a finding that is characteristic of pulmonary alveolar phospholipoproteinosis; prominent lobular septa correlate with the crazy paving seen on radiography. The intraalveolar material is pale eosinophilic, granular, and largely acellular (Panel B, hematoxylin and eosin). Periodic acid–Schiff staining (Panel C) reflects a composition that is rich in pulmonary surfactant (deep magenta).

teinosis (those in which GM-CSF antibodies are undetectable) are considered to be a result of other disease processes that impair the function of alveolar macrophages (e.g., hematologic cancer, immunosuppression, or toxic inhalation), and treatment of these cases is directed at the underlying condition or cause.

A wedge-biopsy specimen of the left upper lobe, obtained by means of video-assisted thoracoscopic surgery, revealed alveolar phospholipoproteinosis (Fig. 2). The level of anti-GM-CSF antibodies was elevated, at a titer of 1:12,800. Multiple lung lavages were performed and provided some symptomatic improvement, but the treatment had to be repeated up to four times a year for symptom control. Subsequent trials of rituximab and mycophenolate mofetil were without benefit. For the past 3 years, the patient has been treated with inhaled GM-CSF twice daily. She has had a good clinical response and has not required whole-lung lavage since beginning this medication. She is able to do office work and exercises at low intensity on a regular basis.

#### COMMENTARY

The patient's symptoms — cough and shortness of breath — are seen often in primary care. In the majority of cases, the underlying process is benign. How, then, do physicians discriminate between patients requiring an aggressive and expensive evaluation and those whose care can be managed conservatively?

In adults, the differential diagnosis of and clinical approach to cough are guided by the duration of symptoms, from acute (less than 3 weeks) to subacute (3 to 8 weeks) to chronic (more than 8 weeks).<sup>1</sup> This patient presented with a history of cough and shortness of breath. Although chronic cough is most often caused by postnasal drip, gastroesophageal reflux, or asthma, the progression of symptoms and the lack of response to empirical asthma therapy in this case pointed to causes that are less common and more ominous.

The shortness of breath, in particular, warranted an aggressive diagnostic evaluation, including ambulatory oximetry and radiographic assessment. Measurement of ambulatory oxygen saturation at the patient's second presentation would probably have facilitated an earlier diag-

nosis. Instead, trials of empirical therapy were selected to address common causes of cough that did not readily explain her associated (and progressive) shortness of breath. The patient's history of asthma probably gave her physicians a false sense of assurance that asthma was the cause of her symptoms, when in fact her presentation and course were atypical for asthma.

Pulmonary alveolar proteinosis is a rare disease, with a reported incidence of 1 case per 300,000 persons in the United States.<sup>2,3</sup> The disease is more common in men than in women (occurring at a ratio of approximately 4 to 1), and the median age at diagnosis is 39 years.<sup>2-4</sup> Therefore, this case reflects a somewhat atypical presentation of a rare disease that was nonetheless suspected once the characteristic crazy-paving pattern<sup>5</sup> was noted on imaging. Pulmonary alveolar proteinosis often presents initially as an apparent bilateral, community-acquired pneumonia, which then fails to resolve despite multiple courses of appropriate antibiotics. Radiographic findings are often more impressive than reported symptoms, a clinical discordance that can help direct the diagnostic evaluation. The disease can be congenital but is more commonly acquired.<sup>2-4</sup> Congenital pulmonary-surfactant derangements are caused by mutations in surfactant protein genes or GM-CSF-receptor genes<sup>6</sup>; these derangements vary in clinical severity and are increasingly recognized as a cause of adult interstitial lung disease with a radiographic pattern similar to that of pulmonary alveolar proteinosis. Acquired pulmonary alveolar proteinosis can result when alveolar macrophage function is

impaired or reduced because of inhalational exposures (e.g., exposure to silica or insecticides), hematologic cancers, or immunosuppression (e.g., as a result of HIV infection or immunosuppressive medications); symptoms generally resolve with treatment of the underlying cause. However, the majority of acquired cases (approximately 90%) result from an autoimmune process with neutralizing anti-GM-CSF antibodies (with evidence of causality in a mouse model<sup>7</sup>), not a GM-CSF deficiency.

In case series, GM-CSF administration has been associated with improvement in oxygenation and quality of life in about 50% of acquired cases<sup>8</sup>; randomized trials are needed to further assess the efficacy of this therapy. In a retrospective analysis, the 10-year rate of survival from pulmonary alveolar proteinosis increased from 85% among patients who were not treated with lavage to 95% in patients who were treated with lavage, with up to 85% of patients having immediate improvement in symptoms, oxygenation, or radiographic signs of disease.<sup>4</sup> At present, whole-lung lavage remains the treatment of choice. Patients requiring repeated alveolar lavages have a poorer prognosis and greater rate of progression to fibrosis. Lung transplantation is a therapeutic option for refractory pulmonary alveolar proteinosis, but its long-term benefit is not well characterized; the disease can recur in the lung allograft.<sup>9</sup>

Financial and other disclosures provided by the authors are available with the full text of this article at NEJM.org.

We thank Sara Vargas for her assistance with the histopathological analysis and Susan Vignolo-Collazzo for assistance with preparation of an earlier version of this article.

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