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MORNING REPORT

A 35-Year-Old Man with Chronic Cough and Worsening Dyspnea

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Abstract

Morning Report is a time-honored tradition where physicians-in-training present cases to their colleagues and clinical experts to collaboratively examine an interesting patient presentation. The Morning Report section seeks to carry on this tradition by presenting a patient's chief concern and story, inviting the reader to develop a differential diagnosis and discover the diagnosis alongside the authors of the case.

This report examines the case of a 35-year-old man who presented to the emergency department with cough and dyspnea on exertion. The cough began 2 years prior and has persisted despite multiple treatment courses of antibiotics. He began to feel dyspneic 1 year ago; it has progressively worsened, and he now has difficulty climbing up a flight of stairs. Using questions, physical examination, and testing, an illness script for the presentation emerges. As the clinical course progresses, the differential is refined until a diagnosis is made.

Pierre O. Ankomah, M.D., Ph.D., Editor

Reason for presentation: cough

Part 1: The Patient's Story

History of Present Illness: A 35-year-old man presented to the emergency department with cough and shortness of breath. The cough began 2 years prior; it was dry and intermittent. Over the past year, he had become short of breath. He initially noticed it only on maximal exertion, but recently, he needed to use a slow walking pace for any distance longer than a few blocks. Since his symptoms began, he had received treatment with antibiotics multiple times for presumed bacterial pneumonia, but the symptoms persisted. He lost 15 pounds over 2 years but had not changed his diet or levels of activity. He had no hemoptysis, fevers, chills, or chest pain. He sought emergency department evaluation because of increasing frequency of coughing episodes and inability to walk up a flight of stairs without feeling short of breath.

Drs. Afif and Fazio contributed equally to this article.

Additional information about the patient is shown in Box 1.

Box 1: Medical and Surgical History, Medications, Allergies, and Social History

Medical and Surgical History

No history of childhood asthma, atopy, or allergic rhinitis

Medications

No medications

Allergies or Adverse Reactions

No known drug allergies

Social History

The patient moved from Mexico to Los Angeles, California, 9 years ago with his family. He has worked in the construction industry since moving to the United States. He does not smoke cigarettes. He does not drink alcohol or use any other drugs.

The data thus far define the problem as a chronic progressive cough and shortness of breath with associated unexplained weight loss in a person who immigrated from Mexico. We can refine the problem representation and generate a differential diagnosis by asking additional questions.

WHAT ADDITIONAL QUESTIONS WOULD HELP FORMULATE A PROBLEM REPRESENTATION AND GENERATE AN INITIAL DIFFERENTIAL DIAGNOSIS?

Q1: Does the patient have any risk factors for tuberculosis (TB)?

Rationale for question: Chronic cough and weight loss should prompt consideration for active pulmonary TB. People who have immigrated from regions of the world where TB is endemic, such as this patient, account for the majority of TB cases in the United States.[1]

Answer: He has not had close contact with individuals infected with TB before or after immigration, and he has never been homeless or incarcerated.

Q2: Did anything exacerbate or improve the patient's symptoms?

Rationale for question: Identifying triggers for the cough and shortness of breath may help refine the differential diagnosis. For example, asthma is a common cause of cough and shortness of breath in younger individuals and is caused by reversible bronchoconstriction often provoked by exercise, aspirin, allergens, or occupational exposures. If his symptoms had improved with an inhaled short-acting bronchodilator, a diagnosis of asthma would be likely.

Answer: The patient's symptoms were exacerbated by inhalation of large amounts of dust, which occurred when he manufactured kitchen countertops at work. Nothing seemed to make his symptoms better.

Q3: Did the patient have any vision changes, dry eyes, rashes, joint pains, myalgias, or family history of rheumatologic disease or interstitial lung disease (ILD)?

Rationale for question: When evaluating a young patient with chronic dry cough and progressive shortness of breath, it is essential to consider ILDs as part of the differential diagnosis. The queried symptoms can signal underlying connective tissue diseases, which are possible causes of ILDs.

Answer: The patient has not had sicca symptoms, rashes, joint pains, or myalgias. He is unaware of any family history of rheumatologic diseases or ILDs.

PHYSICAL EXAMINATION

Box 2: Vital Signs

Temperature (oral): 36.4°C; heart rate: 118 beats per minute; blood pressure: 131/88 mm Hg; respiratory rate: 18 breaths per minute; and O_2 saturation: 91% breathing ambient air

The patient's vital signs are shown in Box 2. He appeared comfortable and was able to speak in complete sentences. Cardiovascular examination demonstrated normal jugular venous pressure; tachycardia; regular rhythm; and no murmurs, gallops, or rubs. Pulmonary examination revealed diffuse crackles predominantly at the lung bases. There was no wheezing, pursed lip breathing, tripoding, or use of accessory muscles. The abdomen was soft, nontender, and nondistended. His extremities were without edema, with normal pulses bilaterally in the lower extremities, and there was no evidence of joint swelling, tenderness, or deformity. His hands demonstrated callouses without deformity to joints or nails, and there were no rashes on his skin.

Part 2: Formulating the Problem Representation and Building the Differential Diagnosis

When evaluating the etiology of cough, tachycardia, and shortness of breath in the emergency department, patient stability should be established first. It is important to expeditiously diagnose conditions that require emergent intervention, such as pneumothorax, pulmonary embolism (PE), asthma exacerbation, or sepsis from pulmonary infection. The differential diagnosis can separately consider pulmonary and cardiovascular causes as summarized in Box 3; however, chronic persistent cough is more typical of pulmonary etiology from infections, underlying lung disease, or malignancy.

Box 3: Framework for Building the Differential Diagnosis for Chronic Cough and Shortness of Breath

Pulmonary Disease

Pneumothorax

Pulmonary embolism

Infections

- Active pulmonary TB, nontuberculous mycobacteria infection
- Bacterial or viral pneumonia
- Fungal infection (e.g., coccidioidomycosis, paracoccidioidomycosis, cryptococcosis, aspergillosis)

Underlying lung disease

- Reactive airway diseases
  - Asthma
  - Occupational airway diseases (e.g., asthma-like syndromes due to plicatic acid or pine wood components)
- Interstitial lung diseases
  - Sarcoidosis
  - Cryptogenic organizing pneumonia
  - Connective tissue disease–associated lung diseases

(continued)

(Box 3 continued)

  - Pneumoconioses of multiple potential etiologies
  - Hypersensitivity pneumonitis
  - Idiopathic pulmonary fibrosis

Malignancy

- Lung cancer
- Metastatic cancer to lungs (e.g., germ-cell tumors, lymphomas)

Cardiovascular Disease

Acute coronary syndrome

Congestive heart failure

Valvular dysfunction

Indolent fungal infections like coccidioidomycosis, which is endemic in the southwestern United States and northern Mexico, and paracoccidioidomycosis, which is endemic in Central America and South America, often cause chronic cough and dyspnea. Active pulmonary TB remains a consideration given his unintentional weight loss, chronicity of respiratory symptoms, and immigration from a TB-endemic region. Community-acquired pneumonia from bacteria or viruses is unlikely to be the primary cause of his symptoms but could be superimposed on underlying lung disease, causing acute worsening.

The absence of wheezing on physical examination makes a diagnosis of asthma less likely. The patient's mild hypoxemia and tachycardia prompt consideration of PE or pneumothorax; however, bilateral crackles on examination signal a possible abnormality of the lung parenchyma. The insidious nature of the worsening dry cough, exertional dyspnea, and eventual weight loss over months to years is typical of ILDs. ILD can often be the first presenting symptom of a rheumatologic disorder; therefore, connective tissue disease–associated ILD remains on the differential despite the absence of joint, skin, and ophthalmologic signs and symptoms. Construction work can be associated with the generation of respirable crystalline silica, which is implicated in the development of silicosis and autoimmune diseases, such as rheumatoid pneumoconiosis.[2] Exposure to fungi that colonize wood products used for construction can lead to hypersensitivity pneumonitis. Other ILD subtypes, such as idiopathic pulmonary fibrosis or cryptogenic organizing pneumonia, should also be considered.

The patient's weight loss should prompt consideration for malignancy; as a young nonsmoker, a primary lung malignancy would be unlikely, although metastatic disease in the lungs is possible. Congestive heart failure and cardiac valvular dysfunction, such as mitral valvular regurgitation, can cause chronic cough and dyspnea; however, the absence of elevated jugular venous pressure, extra heart sounds, or peripheral edema lowers the likelihood of a cardiovascular etiology.

WHAT ADDITIONAL INVESTIGATIONS WOULD BE HELPFUL?

A chest radiograph is a practical initial evaluation for suspected pneumothorax, pulmonary infections, and ILDs; high-resolution computed tomography (CT) imaging may be needed depending on the results. Blood cell counts with differential may be informative; leukocytosis or neutrophilia can suggest possible bacterial pneumonia, whereas eosinophilia would increase the likelihood of a fungal or atopic etiology such as allergic bronchopulmonary aspergillosis. Testing for circulating respiratory viruses and procalcitonin could be reasonable in evaluating the etiology of the patient's acute worsening but would not explain the chronic respiratory symptoms. A brain natriuretic peptide (BNP) and troponin will assist with evaluating for decompensated congestive heart failure or myocardial infarction.

SHOULD EMPIRICAL TREATMENTS BE STARTED?

The patient is not distressed on examination and does not require any emergent intervention.

Part 3: Refining the Differential Diagnosis

RESULTS

The results of initial laboratory studies are shown in Figure 1. Chest radiograph results are shown in Figure 2.

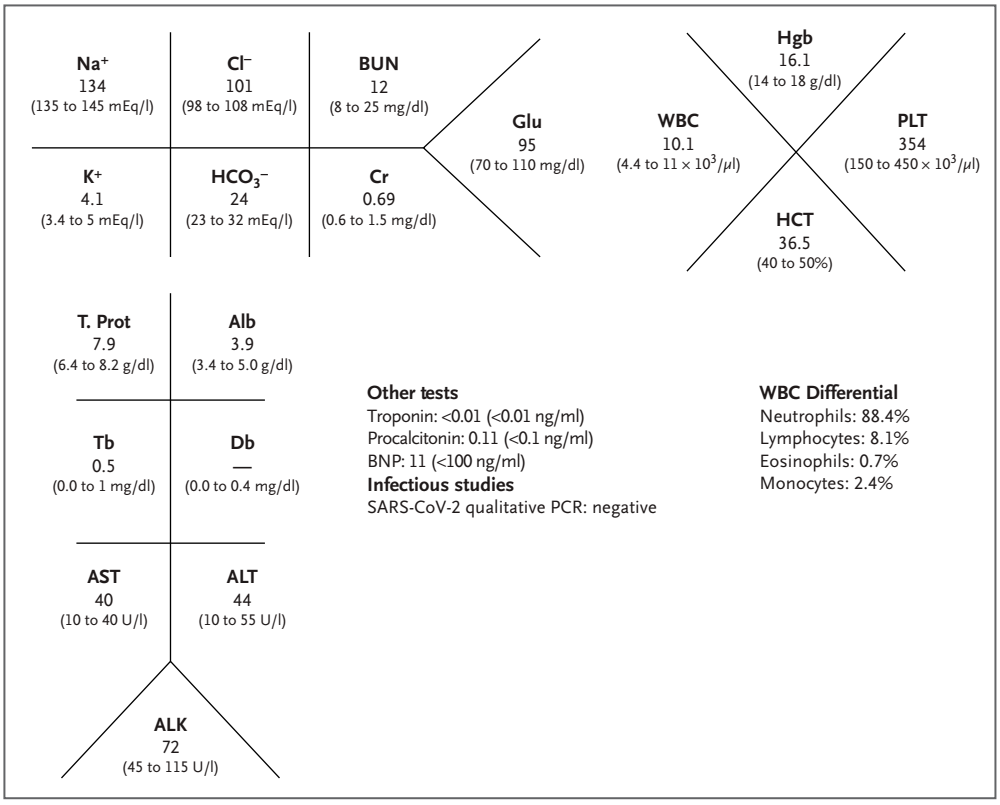

Figure 1. The Patient's Initial Laboratory Values.

Reference ranges are in parentheses. Alb denotes albumin; ALK, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; Cl^-, chloride; Cr, creatinine; Db, direct bilirubin; Glu, glucose; HCO_3^-, bicarbonate; HCT, hematocrit; Hgb, hemoglobin; K^+, potassium; Na^+, sodium; PCR, polymerase chain reaction; PLT, platelet; Tb, total bilirubin; T. Prot, total protein; and WBC, white blood cell.

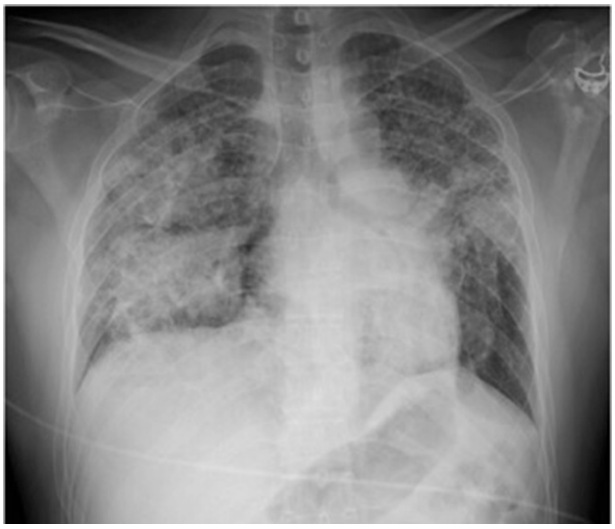

Figure 2. The Patient's Chest Radiograph.

WHAT DO WE LEARN FROM THIS ADDITIONAL INFORMATION?

The chest radiograph demonstrated multifocal consolidation and reticulonodular confluent opacities with associated volume loss most prominent in the mid- and upper zones and obliteration of the paratracheal stripes, suggesting mediastinal lymphadenopathy. No pleural effusions were present. These findings are consistent with a pulmonary parenchymal process, effectively excluding pneumothorax and making asthma and PE less likely. Pneumonia caused by atypical bacteria and respiratory viruses can present with bilateral and multifocal consolidations; however, the pretest probability for these infections is low, and the normal procalcitonin and white blood cell count further discount these infections. Although chest radiography has limited resolution for identifying pulmonary masses or cavities, no obvious mass or cavitary disease suggestive of TB, fungal infections, or large tumor was seen. The cardiac silhouette of normal size and the absence of pulmonary vascular congestion or pleural effusion, along with normal BNP and troponin, exclude decompensated heart failure. The revised differential diagnosis is shown in Box 4.

Box 4: Revised Differential Diagnosis

Pulmonary Disease

~~Pneumothorax~~

~~Pulmonary embolism~~

(continued)

(Box 4 continued)

Infections

- Active pulmonary TB, nontuberculous mycobacteria infection
- ~~Acute bacterial or viral pneumonia~~
- Fungal infection (e.g., coccidioidomycosis, paracoccidioidomycosis, cryptococcosis, aspergillosis)

Underlying lung disease

- ~~Reactive airway diseases~~
  - ~~Asthma~~
  - ~~Occupational airway diseases (e.g., asthma-like syndromes due to plicatic acid or pine wood components)~~
- Interstitial lung diseases
  - Sarcoidosis
  - Cryptogenic organizing pneumonia
  - Connective tissue disease–associated lung diseases
  - Pneumoconioses of multiple potential etiologies
  - Hypersensitivity pneumonitis
  - Idiopathic pulmonary fibrosis

Malignancy

- Lung cancer
- Metastatic cancer to lungs (e.g., germ-cell tumors, lymphomas)

Cardiovascular Disease

~~Acute coronary syndrome~~

~~Congestive heart failure~~

~~Valvular dysfunction~~

WHAT ARE THE NEXT STEPS IN THE WORKUP?

To distinguish between the remaining potential diagnoses, higher-resolution CT imaging of the chest may be helpful. Testing for *Mycobacterium tuberculosis* and coccidioides, which are the two most likely infectious etiologies based on his exposure history, should be prioritized. Autoimmune markers, such as antinuclear antibodies (ANAs), aldolase, and

rheumatoid factor, are useful adjunct tests when investigating a possible ILD diagnosis. An elevated ANA in the absence of systemic symptoms or specific antibodies is nonspecific, but it is often positive in patients with ILD who do not have connective tissue diseases and in patients with pneumoconiosis.[3,4] Although angiotensin-converting enzyme (ACE) levels are not sensitive for sarcoidosis, elevated ACE levels with mediastinal lymphadenopathy or pulmonary fibrosis on CT could support the diagnosis. Aldolase can be an early biomarker of ILD-associated diseases such as polymyositis or other rare amyopathic connective tissue diseases where overt symptoms of myopathy are absent initially, such as antimelanoma differentiation-associated gene 5–associated ILD.[5] Serodiagnosis including a panel for hypersensitivity and and an extended myositis is useful for excluding this family of diseases.[6]

CLINICAL COURSE 1

A CT scan of the chest without intravenous contrast demonstrated a diffuse bilateral micronodular pattern, with areas of peribronchovascular consolidation with calcification and surrounding ground glass, along with mediastinal and hilar adenopathy (Fig. 3). ANAs were detected in serum at 1:80 in a speckled pattern, an aldolase level was slightly elevated at 9.9 U/l (reference range, <8.1 U/l), and an ACE level was in the normal range. Serologic tests for coccidioides, three serially induced sputa acid-fast bacillus smears and cultures, and an *M. tuberculosis* DNA polymerase chain reaction from a sputum sample were negative.

HOW DO THESE RESULTS AFFECT YOUR DIFFERENTIAL DIAGNOSIS?

The micronodular imaging pattern is more commonly associated with miliary TB, sarcoidosis, and pneumoconioses than with connective tissue disease–associated ILD or cryptogenic organizing pneumonia. Connective tissue disease–associated ILDs typically demonstrate a usual interstitial pattern (UIP) characterized by reticulations and honeycombing at the lung bases or a nonspecific interstitial pattern characterized by diffuse ground glass opacities and absence of UIP findings. Cryptogenic organizing pneumonia causes patchy consolidations similar to multifocal pneumonia. CT images did not demonstrate cavitating nodules typical of coccidioidomycosis or TB, nor did they

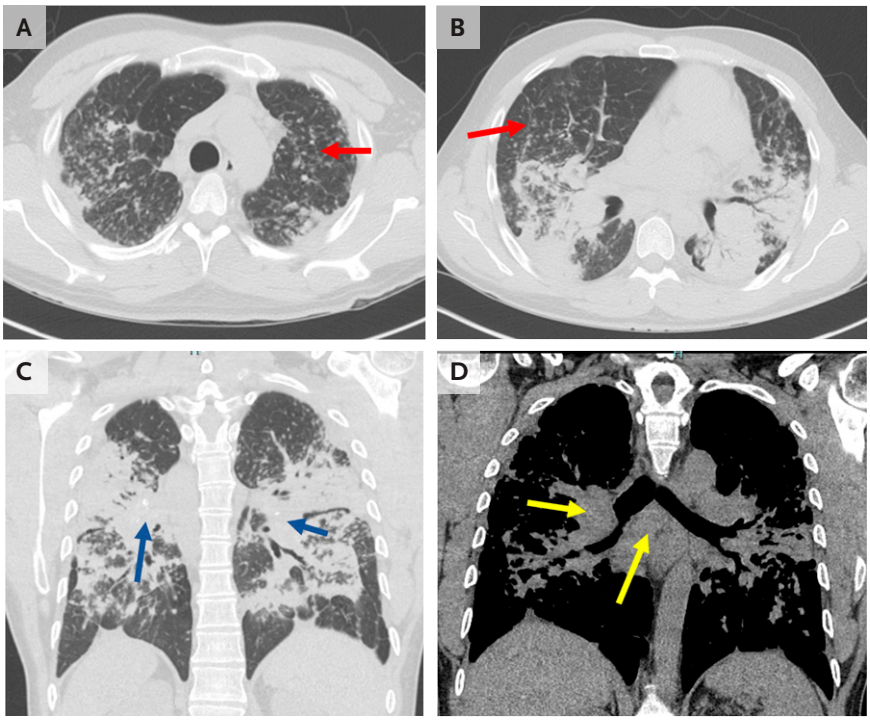

Figure 3. CT Imaging of the Chest without Intravenous Contrast.

Panels A and B show axial views of (Panel A) lung apices and (Panel B) inferior sections demonstrating bilateral perilymphatic micronodules (red arrows). Panels C and D show coronal views that demonstrate (Panel C) large areas of micronodular conglomeration into masslike densities with calcification (blue arrows) and (Panel D) prominent mediastinal and hilar lymphadenopathy (yellow arrows). CT denotes computed tomography.

demonstrate small airway impaction, which is often associated with nontuberculous mycobacterial infection. However, multiple coexisting diagnoses can be present, as some ILDs can increase the risk of mycobacterial or fungal infections. No solitary pulmonary masses were seen, making malignancy highly unlikely in this patient at low risk.

CLINICAL COURSE 2

Despite the negative microbiologic sputum and serologic tests, mycobacterial and fungal infections and hypersensitivity pneumonitis could not be excluded completely given the imperfect sensitivity of these tests.[7] Bronchoscopy with bronchoalveolar lavage (BAL) was performed to obtain samples for additional microbiologic testing. Transbronchial and mediastinal lymph node biopsy specimens were also obtained. No organisms were identified on bacterial, fungal, and mycobacterial stains and cultures from BAL. Lymph node biopsy specimens demonstrated polarizable crystalline silica particles (Fig. 4A) and noncaseating granulomas (Fig. 4B), consistent with pneumoconioses.

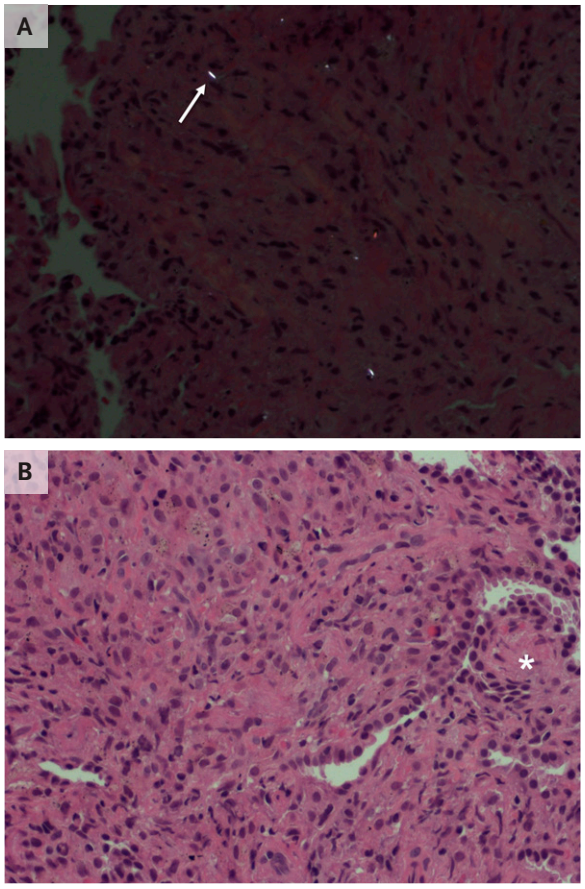

Figure 4. Transbronchial Lymph Node Biopsy.
Panel A shows microscopic examination with polarized light. Crystalline silica particles are shown at 200× magnification (arrow). Panel B shows loosely formed noncaseating granulomas (asterisk; hematoxylin and eosin, 200× magnification).

Part 4: Making the Diagnosis

Pneumoconioses are occupational lung diseases that develop from the inhalation of inorganic particles and mineral dust. The most common types are coal workers' pneumoconiosis, silicosis, and asbestosis. Distinguishing among these conditions requires a thorough occupational and environmental history to investigate exposures. Further history obtained from the patient revealed that for the past 9 years, his job involved using marble, granite, and quartz/engineered stone to manufacture kitchen countertops. He had previously worn masks infrequently, but as his respiratory symptoms worsened, he started wearing a disposable N95 mask at work. The history of silica exposure and findings from imaging and pathology specimens are consistent with a diagnosis of pulmonary silicosis.[8] The patient underwent pulmonary function testing (Fig. 5), which demonstrated a mixed obstructive and restrictive ventilatory defect with a severe reduction in diffusing capacity of the lungs for carbon monoxide (DLCO) at 35% predicted, typical of advanced-stage silicosis.

FINAL DIAGNOSIS AND WRAP-UP

The final diagnosis was pulmonary silicosis with progressive massive fibrosis, the advanced form of the disease. The patient likely developed severe disease because of daily high-level exposure to respirable crystalline silica from cutting engineered stone countertops, which, compared with natural stones like marble or granite, contains a much higher silica content of approximately 90%.[9] Further history revealed that the patient's work environment did not have silica dust engineering control measures, such as water suppression, exhaust ventilation, or dust collection systems, to reduce aerosolized silica particles. He reported not having access to adequate personal protective equipment, which should include a full-face mask with bilateral dust-specific filters. The patient quit his job immediately after the diagnosis, partly because of the functional inability to continue working. The state Occupational Safety and Health Association was alerted; per a report, an investigation at the workplace demonstrated silica dust levels violating the permissible exposure limit of 50 $\mu g/m^3$ averaged over an 8-hour period.[10]

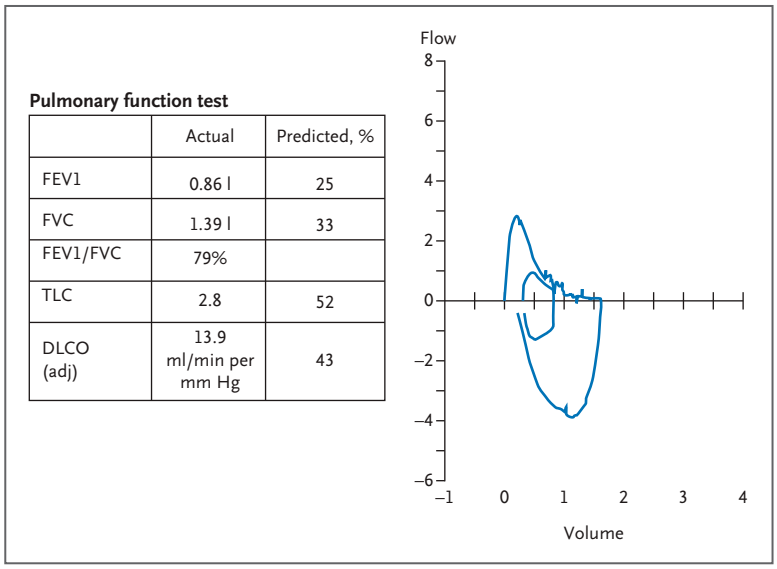

Figure 5. The Patient's Pulmonary Function Tests.

FEV1/FVC less than 70 and low TLC are consistent with a mixed obstructive and restrictive defect. DLCO is moderately reduced. The flow-volume loop (right panel) shows a "witch's hat" configuration consistent with restrictive disease and also shows "scooping" of the expiratory limb, consistent with an obstructive ventilatory defect. FEV1 denotes forced expiratory volume in 1 second; FVC, forced expiratory volume; TLC, total lung capacity; and DLCO, diffusing capacity of the lung for carbon monoxide.

Silicosis is a chronic and progressive occupational pneumoconiosis, which historically required decades of exposure to develop. However, with the growing popularity of high silica–containing countertops, there has been increasing global recognition of an accelerated form of pulmonary silicosis.[11-13]

There is no effective treatment for pulmonary silicosis; however, clinicians can urge prevention of further exposure, monitor progression with serial pulmonary function testing and imaging, update vaccinations to prevent superimposed infections, and facilitate timely evaluation for lung transplantation, which is the only therapeutic option for severe disease. This patient has developed severe functional debilitation and hypoxemia at rest; he is currently undergoing evaluation for lung transplantation.

Take-Home Points

- The differential diagnosis for chronic cough and dyspnea includes indolent infections, ILDs, malignancy, and cardiovascular causes.
- Evaluation for ILDs should include a detailed occupational history that includes the patient's industry, specific job tasks, possible exposures, place of current or former work, and duration in relation to symptom onset.
- After an occupational-related diagnosis such as silicosis has been determined, coordination with public health authorities for enforcement of occupational safety is essential to prevent further exposure to other workers.

Disclosures

Author disclosures are available at evidence.nejm.org.

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