Non-smoker with pulmonary nodules

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PATIENT HISTORY

A 57-year-old man was admitted to the hospital in May because of fever, night sweats, cough, dyspnea, and multiple pulmonary nodules.

He had non-insulin dependent diabetes and had been in his usual state of health until three months before admission, when he was successfully treated with a six-week course of antibiotics for right foot osteomyelitis. One month before admission, he was treated for a dry cough and dyspnea, attributed to worsening congestive heart failure. Five days before admission, he developed fever, night sweats, dry cough, pleuritic chest pain, but no hemoptysis. Over the past six months, he had lost 30 pounds. He was admitted for workup. Antibiotics were not started.

The patient was a married, black, retired handyman/doorman with a past history of diabetic retinopathy, CHF, mitral regurgitation, remote CVA with residual left facial droop. There was no history of recurrent sinusitis. His medications included furosemide, captopril, digoxin, glyburide, lovastatin, ranitidine, and oxycodone. He was born in New York City and had spent most of his life in New York, except 20 years ago, when he lived in Western Texas for three to four months. He had not traveled outside of North America. There was no history of tobacco use, drug use, alcohol abuse, HIV risk factors, asbestos exposure, or undercooked seafood ingestion. He did not have pets or unusual bird exposure.

On examination, the temperature was 100.6°F, blood pressure 150/80 mmHg, pulse 92/min, and respiratory rate 20/min. Fundoscopic examination revealed diabetic retinopathy, but no evidence of endophthalmitis. No adenopathy was found. Jugular venous distention was elevated at 10 cm. There were bibasilar crackles and pedal edema. Oxygen saturation was 96% on room air. No clubbing was noted. There were no murmurs, Osler nodes, Janeway lesions, splinter hemorrhages, subconjunctival hemorrhages, or Roth spots. There was no hepatosplenomegaly. Prostate was normal. Stool was negative for occult blood. There were no skin lesions, including at the previous foot infection site. Neurologic examination was unremarkable, except for a mild residual left facial droop.

The white blood count was \(8.3 \times 10^9/L\), with 73% neutrophils, 15% lymphocytes, 11% monocytes, and 1% eosinophils. The hematocrit had dropped from 39 to 28% three months prior to admission, but had been stable since then. The platelet count was 428 x 10^9/L (ref: 150-450 x 10^9/L). ESR was elevated at 98. Electrolytes were normal. BUN was 17 mg/dL and creatinine was 1.3 mg/dL. Calcium was normal. Transaminases, bilirubin, and alkaline phosphatase were normal. LDH was normal at 228 U/L. Urinanalysis was positive for protein, 3–5 WBC/HF, and 11–20 RBC/HF. Seven sets of blood cultures were negative for bacteria and fungi. Urine culture was negative. Sputum culture was positive for Candida albicans and Penicillium spp., but negative for Legionella. Urine Legionella antigen was negative.

Three sputum smears were negative for acid-fast bacilli and malignancies. PPD was negative with positive controls. HIV serology was negative. Aspergillus, coccidioides and histoplasma antibodies were negative. Serum cryptococcal antigen was negative. Tests for rheumatoid factor, ANA, and ANCA were negative. ACE level was normal. Esophagogastroduodenoscopy and colonoscopy tests were negative.

CXR (Figure 1) revealed multiple ill-defined pulmonary nodules bilaterally, with confluent opacities in the right lower lobe. There were bilateral pleural effusions, those in the right being greater than in the left. These nodular densities were not present one month before admission. A CT of the chest, obtained without contrast, showed multiple non-calcified nodules in all lobes, from <0.5 to 8 cm in diameter. Many were surrounded by a halo of ground-glass haziness. There were no cavitary lesions. The right hilum was enlarged. This was interpreted by the radiologist to be either adenopathy or contiguous parenchymal nodules. Pleural effusions were present bilaterally. The transesophageal echocardiogram revealed no vegetations.

The patient underwent bronchoscopy. Smears and cultures from bronchial washings and transbronchial biopsies were negative for bacteria (including mycobacteria), fungus, and malignancies. Likewise, bone marrow was negative for all microbiologic studies, with normal cellularity and no malignant infiltrates.
Figure 1. CXR on admission revealed multiple new ill-defined pulmonary nodules bilaterally, with confluent opacities in the right lower lobe. There were bilateral pleural effusions, greater in the right than in the left.

The differential diagnosis of pulmonary nodules is summarized in Table 1. In this case, our differential diagnosis included the following:

**Table 1. Differential diagnosis of multiple pulmonary nodules**

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Non-infectious</th>
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<tbody>
<tr>
<td><strong>Bacterial</strong></td>
<td>Lung metastasis</td>
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<tr>
<td>Mycobacterium tuberculosis</td>
<td>Lymphoma</td>
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<tr>
<td>Non-tuberculous mycobacteria</td>
<td>Sarcoïdosis</td>
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<td>Staphylococcus aureus</td>
<td>Amyloidosis</td>
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<td>Legionella spp.</td>
<td>Rheumatoid nodules</td>
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<td><strong>Bacterial endocarditis</strong></td>
<td>Wegener's granulomatosis</td>
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<tr>
<td>Melioidosis</td>
<td>Goodpasture's syndrome</td>
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<td>Nocardiosis</td>
<td>Pulmonary A-V malformation</td>
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<td>Rhodococcus equi</td>
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<td><strong>Fungi</strong></td>
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<td>Invasive pulmonary aspergillosis</td>
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<tr>
<td>Mucormycosis</td>
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<tr>
<td>Coccidioidomycosis</td>
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<td>Paracoccidioidomycosis</td>
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<td>Cryptococcosis</td>
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<td>Histoplasmosis</td>
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<td>Blastomycesis</td>
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<td>Penicilliosis</td>
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<td><strong>Parasites</strong></td>
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<td>Paragonimiasis</td>
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**Tuberculosis**

Tuberculosis should be considered in this patient. Smears and cultures of multiple sputum specimens, bronchial washings, and transbronchial and thorascopic-lung biopsies were negative for acid-fast bacilli despite the presence of cough and pulmonary nodules. PPD was negative and the patient was not anergic or HIV positive. PPD non-reactivity can occur during active tuberculosis in 20% of patients. False negative tests are associated with improper technique, HIV, corticosteroids or other immunosuppressive agents, protein malnutrition, sarcoidosis, viral infections, live viral vaccines, and reticuloendothelial diseases. The rapidity in development of nodules argues against tuberculosis except for miliary TB. However, we have no other evidence of miliary TB. The negative smears and cultures for acid-fast organisms also allow us to exclude infection by non-tuberculous mycobacteria, nocardia, and rhodococcus.

**Bacterial endocarditis**

*Staphylococcus aureus* pneumonia can result in multinodular lung infiltrates in the setting of antecedent influenza infection or right-sided *S. aureus* endocarditis. It was the wrong time of the year for influenza.

Septic emboli can present with pulmonary nodules like the ones seen in this patient. However, this patient had no history of intravenous drug use, no indwelling intravenous lines, no history of endocarditis or rheumatic fever, and multiple blood cultures remained negative. In addition, TEE did not show evidence of endocarditis.

**Coccidioidomycosis**

Environmentally-derived fungi, such as *Coccidioides immitis*, usually cause a rather self-limited or asymptomatic infection in normal hosts, but can produce disseminated disease in immunocompromised patients. Coccidioidomycosis (San Joaquin Valley Fever) is endemic in the semiarid southwestern United States (including western Texas, southern California, and Arizona). Infection is by inhalation of arthrospores dislodged from the soil. It can be acquired even after a brief exposure, like driving through an endemic area with car windows down. Increased risk of exposure occurs with earthquakes, excavations, duststorms, or droughts followed by heavy rains. Even though this patient had lived in an endemic area in the remote past, he has not been exposed recently. Symptoms usually occur within a month after exposure. The fact that he had negative serology and no pulmonary nodules even as recently as one month prior to admission argues against chronic coccidioidomycosis. The diagnosis, like that of most deep fungal infections, depends on the identification of *C. immitis* in body tissues or fluids, optimally not only by culture, but also histopathologically. Paracoccidioidomycosis is acquired almost
exclusively in Central and South America, but our patient had not traveled there.\textsuperscript{10}

**Histoplasmosis**

The geographic distribution of histoplasmosis is along the Mississippi and Ohio river valleys, the Caribbean, and Central America.\textsuperscript{6,11} In New York, most cases occur in immigrants from Puerto Rico and the Dominican Republic.\textsuperscript{12,13} In endemic areas, increased risk of infection is associated with excavation, chicken coops, bird and bat droppings.\textsuperscript{14-17} Radiographic findings can mimic malignancies or TB showing solitary or multiple nodular densities, with predilection for the upper lobes. Unlike TB, hilar adenopathy is uncommon, whereas mediastinal fibrosis is a hallmark of histoplasmosis. The patient's lack of risk factors and negative serology make this diagnosis unlikely.

**Invasive pulmonary aspergillosis**

Invasive pulmonary aspergillosis occurs most commonly in patients on corticosteroids or who are neutropenic and receiving broad-spectrum antibiotics.\textsuperscript{18} Additionally, pulmonary cavities in patients with pre-existing destructive lung processes, such as sarcoidosis, pneumoconiosis, and tuberculosis, many become colonized with *Aspergillus*. The most serious complication is massive hemoptysis. Chest CT sometimes shows a characteristic lung mass with surrounding low attenuation halo or air crescent formation.\textsuperscript{19} Definitive diagnosis of invasive *Aspergillus* pneumonia requires tissue diagnosis of pulmonary invasion.\textsuperscript{20} This entity is unlikely since he was not neutropenic, did not receive antibiotics, and all his cultures (including lung biopsy) were negative for aspergillus.

**Candida pneumonia**

Although *Candida* species are frequently detected in sputum, *Candida* pneumonia is uncommon. When it occurs, it usually results from hematogenous dissemination or aspiration in immunocompromised patients.\textsuperscript{21} Definitive diagnosis requires tissue diagnosis of pulmonary invasion.\textsuperscript{20} This entity is unlikely since he was not neutropenic, did not receive antibiotics, and his biopsy was negative for *Candida*.

**Penicilliosis**

Clinical manifestations of *Penicillium marneffei* include fever, lymphadenopathy, hepatosplenomegaly, molluscum-like umbilicated skin lesions, interstitial or reticulonodular changes on CXR, anemia, leukopenia, and thrombocytopenia. Acquisition of this organism is restricted to Southeast Asia.\textsuperscript{22,23} Penicilliosis has been rare until recently when HIV-infected individuals in Thailand started acquiring the disease. It has become the third most common opportunistic infection in HIV patients in northern Thailand.\textsuperscript{24} Other non-marneffei bronchopulmonary penicillioses are even rarer\textsuperscript{25} The identification of *Penicillium* from a single sputum specimen, but not from tissue samples, was not likely to be significant.

**Cryptococcosis**

*Cryptococcus neoformans* can present with multiple nodules, but this usually occurs with underlying disease (particularly lymphoma, HIV, or sarcoid), or after corticosteroid therapy. Certainly cryptococcus alone would not explain the six-month history of weight loss or the anemia. The patient had not received steroid therapy, and did not have HIV or sarcoid. This could be cryptoccocosis complicating lymphoma. The negative cryptococcal antigen in the presence of such extensive pulmonary lesions is strongly against the diagnosis but does not rule it out.

**Wegener's granulomatosis**

Based on the information we have, we can confidently rule out the possibility of Wegener's granulomatosis. In addition to hemoptysis, the nasopharynx and kidneys are often involved. This patient did not have hemoptysis, red cell casts, or nasopharyngeal findings, and ANCA was negative. Likewise, the rare entity, Goodpasture's syndrome, usually occurs in young men with hemoptysis, hematuria, and rapidly progressive glomerulonephritis.

**Lymphoma**

This seemed a very good possibility given the long course, the weight loss and anemia, and the plethora of negative smears, cultures and serologies.

**COURSE**

Despite a non-toxic appearance, daily low grade fevers continued. In view of the inability to reach a diagnosis, a thorascopic lung biopsy was performed. No granulomas were seen. Stains and cultures were negative for bacteria (including mycobacteria), fungi, and viruses. Histopathology and immunostains revealed diffuse large cell non-Hodgkin B cell lymphoma. He was started on combination chemotherapy. Two months later, CXR showed marked shrinkage of the pulmonary nodules.

**DISCUSSION**

Less than 1\% of lung malignancies are primary lymphomas. These can be either Hodgkin's disease or non-Hodgkin's lymphomas. The latter, while rare, account for the vast majority of these lymphomas. They can be
further subdivided into: low grade, small B-cell lymphomas; b. high grade, large B-cell lymphomas; and c. angiocentric lymphomas.

**Low grade, small B-cell lymphoma**

Most primary pulmonary non-Hodgkin’s lymphomas (60–90%) are low grade, small B-cell lymphomas arising from bronchus-associated lymphoid tissues (BALT), 26 5–10% of cases are associated with autoimmune diseases, such as Sjögren’s syndrome, or SLE.

Peak incidence is in the sixth decade of life, with no gender difference. 27–29 The disease is often discovered incidentally on a routine CXR, as half of the patients are asymptomatic. For those who are symptomatic, their presentations include fever, weight loss, night sweats, cough, hemoptysis, and dyspnea. Monoclonal gammopathy, most often IgM type, is found in 25% of cases. Radiographic lesions are non-specific. They can be nodular or reticulonodular, unilateral or bilateral, single or multiple. Cavitation and hilar adenopathy are usually absent. 30,31

The vast majority of these lymphomas are slow-growing localized tumors that can be cured by resection alone. Prognosis is excellent, with a 10-year survival of up to 80%. 29,33 Close follow up is necessary to monitor for local recurrences, distant MALT (mucosa-associated lymphoid tissue) lymphomas, and the development of aggressive high-grade large B-cell lymphomas. 28,29,32

**High grade large B-cell lymphoma**

About 10% of primary pulmonary non-Hodgkin’s lymphomas are the large B-cell type. Unlike patients with the small cell type, these patients usually present with respiratory and constitutional symptoms. The pulmonary nodules or infiltrates may develop rapidly, as in this patient, mimicking an infectious process. 33,34

Cavitations are frequently seen. Even with aggressive chemotherapy, these tumors are prone to recur locally or disseminate. Prognosis is less favorable, with a 5-year survival of 50%. 27

**Angiocentric lymphoma**

This aggressive lymphoma is characterized by atypical neoplastic lymphoid vascular invasion and necrosis. Recent evidence suggests a possible role of Epstein–Barr virus in its pathogenesis. 35,36 There is a male preponderance. Respiratory and constitutional symptoms are common. Radiographic findings are similar to those of the large cell type. Dissemination is common, often to skin, kidneys, CNS, or peripheral nerves. Prognosis is determined by the degree of pulmonary/extra pulmonary involvement and the number of atypical lymphocytes within the lymphoma.

**REFERENCES**

22. Deng Z, Ribas JL, Gibson DW, Connor DH. Infections caused by *Penicillium marneffei* in China and Southeast
Non-smoker with pulmonary nodules


*Editor-in-Chief Note:* This case brings to an end the series of case reports from the Intercity Rounds.