More Is Less

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This icon represents the patient's case. Each paragraph that follows represents the discussant's thoughts.

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A 64-year-old man presented with a 2-month history of a nonproductive cough, weight loss, and subjective fevers. He had no chest pain, hemoptysis, or shortness of breath. He also described worsening anorexia and a 15-pound weight loss over the previous 3 months. He had no arthralgias, myalgias, abdominal pain, nausea, emesis, or diarrhea.

Two weeks prior to his presentation, he was diagnosed with pneumonia and given a 5-day course of azithromycin. His symptoms did not improve, so he presented to the emergency room.

He had not been seen regularly by a physician in decades and had no known medical conditions. He did not take any medications. He immigrated from China 3 years prior and lived with his wife in California. He had a 30 pack-year smoking history. He drank a shot glass of liquor daily and denied any drug use.

Weight loss might result from inflammatory disorders like cancer or noninflammatory causes such as decreased oral intake (eg, diminished appetite) or malabsorption (eg, celiac disease). However, his fevers suggest inflammation, which usually reflects an underlying infection, cancer, or autoimmune process. While chronic cough typically results from upper airway cough syndrome (allergic or nonallergic rhinitis), gastroesophageal reflux disease, or asthma, it can also point to pathology of the lung, which may be intrinsic (bronchiectasis) or extrinsic (mediastinal mass). The duration of 2 months makes a typical infectious process like pneumococcal pneumonia unlikely. Atypical infections such as tuberculosis, melioidosis, and talaromycosis are possible given his immigration from East Asia, and coccidioidomycosis given his residence in California. He might have undiagnosed medical conditions, such as diabetes, that could be relevant to his current presentation and classify him as immunocompromised. His smoking history prompts consideration of lung cancer.

His temperature was 36.5 °C, heart rate 70 beats per minute, blood pressure 118/66 mm Hg, respiratory rate 16 breaths per minute, oxygen saturation 98% on room air, and body mass index 23 kg/m^2. He was in no acute distress. The findings from the cardiac, lung, abdominal, and neurologic exams were normal.

Skin exam found a fixed, symmetric, 5-cm, firm nodule at the top of his sternum (Figure 1A). Also, he had two 1-cm, mobile, firm, subcutaneous nodules, one on his anterior left chest and another underneath his right axilla. He also had two 2-cm, erythematous, tender nodules on his left anterior forearm and a 1-cm nodule with a central black plug on the dorsal surface of his right hand (Figure 1B). He did not have any edema.

The white blood cell count was 10,500/mm^3 (42% neutrophils, 37% lymphocytes, 16.4% monocytes, and 2.9% eosinophils), hemoglobin was 12.2 g/dL with a mean corpuscular volume of 91 fL, and the platelet count was 441,000/mm^3. Basic metabolic panel, aminotransferase, bilirubin, and alkaline phosphatase were within reference ranges. Serum albumin was 3.1 g/dL. Serum total protein was elevated at 8.8 g/dL. Serum calcium was 9.0 mg/dL. Urinalysis results were normal.

The slightly low albumin, mildly elevated platelet count, monocytosis, and normocytic anemia suggest inflammation, although monocytosis might represent a hematologic malignancy like chronic myelomonocytic leukemia (CMML). His subjective fevers and weight loss further corroborate underlying inflammation. What is driving the inflammation? There are two localizing findings: cough and nodular skin lesions.

His lack of dyspnea and normal oxygen saturation, respiratory rate, and lung exam make an extrapulmonary cause

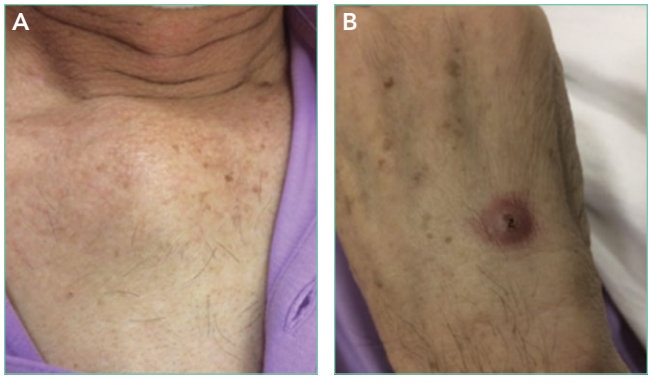

FIG 1. Cutaneous Findings Discovered on Physical Exam. (A) A 5-cm fixed, symmetric, nonmobile, firm nodule at top of sternum. (B) A 1-cm firm nodule with a central black plug on the dorsal surface of the right hand.

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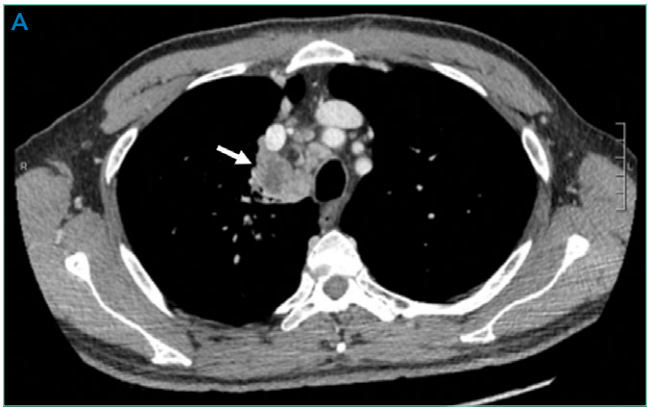

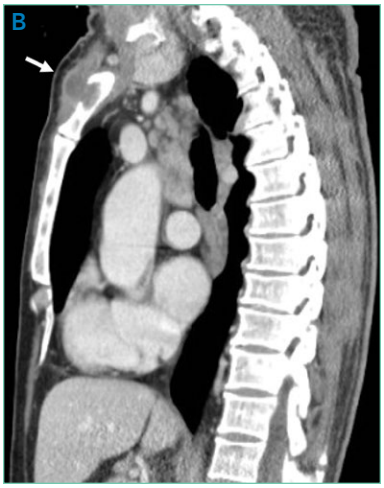

FIG 2. Computed Tomography of the Chest With Intravenous Contrast. (A) A 3.8 x 2.1-cm centrally necrotic soft tissue mass in the right hilum. (B) A 2.6 x 4.7-cm necrotic mass in the anterior chest wall with erosion into the manubrium.

of cough such as lymphadenopathy or mediastinal infection possible. The number of nodular skin lesions, widespread distribution, and appearance (eg, erythematous, tender) point to either a primary cutaneous disease with systemic manifestations (eg, cutaneous lymphoma) or a systemic disease with cutaneous features (eg, sarcoidosis).

Three categories—inflammatory, infectious, and neoplastic—account for most nodular skin lesions. Usually microscopic evaluation is necessary for definitive diagnosis, though epidemiology, associated symptoms, and characteristics of the nodules help prioritize the differential diagnosis. Tender nodules might reflect a panniculitis; erythema nodosum is the most common type, and while this classically develops on the anterior shins, it may also occur on the forearm. His immigration from China prompts consideration of tuberculosis and cutaneous leishmaniasis. Coccidioidomycosis can lead to inflammation and nodular skin lesions. Other infections such as nontuberculous mycobacteria, nocardiosis, and cryptococcosis may cause disseminated infection with pulmonary and skin manifestations. His smoking puts him at risk for lung cancer, which rarely results in metastatic subcutaneous infiltrates.

A chest radiograph demonstrated a prominent density in the right paratracheal region of the mediastinum with adjacent streaky opacities. A computed tomography scan of the chest with intravenous contrast demonstrated centrilobular emphysematous changes and revealed a 2.6 × 4.7-cm necrotic mass in the anterior chest wall with erosion into the manubrium, a 3.8 × 2.1-cm centrally necrotic soft-tissue mass in the right hilum, a 5-mm left upper-lobe noncalcified solid pulmonary nodule, and prominent subcarinal, paratracheal, hilar, and bilateral supraclavicular lymphadenopathy (Figure 2).

Flow cytometry of the peripheral blood did not demonstrate a lymphoproliferative disorder. Blood smear demonstrated normal red blood cell, white blood cell, and platelet morphology. HIV antibody was negative. Hemoglobin A1c was 6.1%. Smear microscopy for acid-fast bacilli (AFB) was negative and sputum AFB samples were sent for culture. Bacterial, fungal, and AFB blood cultures were collected and pending.

Causes of necrotizing pneumonia include liquid (eg, lymphoma) and solid (eg, squamous cell carcinoma) cancers, infections, and noninfectious inflammatory processes such as granulomatosis with polyangiitis (GPA). Given his subacute presentation and extrapulmonary cutaneous manifestations, consideration of mycobacteria, fungi (eg, *Coccidioides*, *Aspergillus*, and *Cryptococcus*), and filamentous bacteria (eg, *Nocardia* and *Actinomyces*) is prioritized among the myriad infections that can cause a lung cavity. His smoking history and centrilobular emphysematous changes are highly suggestive of chronic obstructive pulmonary disease, which puts him at increased risk of bacterial colonization and recurrent pulmonary infections. Tuberculosis is still possible despite three negative AFB-sputa smears since the sensitivity of smear microscopy (with three specimens) is roughly 70% in an immunocompetent host.

The lymphadenopathy likely reflects spread from the necrotic lung mass. The frequency of non-Hodgkin lymphoma increases with age. The results of the peripheral flow cytometry do not exclude the possibility of an aggressive lymphoma with pulmonary and cutaneous manifestations.

The erosive property of the chest wall mass makes an autoimmune process like GPA unlikely. An aggressive and disseminated infection or cancer is most likely. A pathologic process that originated in the lung and then spread to the lymph nodes and skin is more likely than a disorder which started in the skin. It would be unlikely for a primary cutaneous disorder to cause such a well-defined necrotic lung mass. Lung cancer rarely metastasizes to the skin and, instead, preferentially involves the chest. Ultimately, ascertaining what the patient experienced first (ie, respiratory or cutaneous symptoms) will determine where the pathology originated.

Computed tomography scan of the abdomen and pelvis with intravenous contrast demonstrated multiple ill-defined lytic lesions in the pelvis, including a 12-mm lesion of the left sacral ala and multiple subcentimeter lesions in the medial left iliac bone and superior right acetabulum. In addition, there were two 1-cm, rim-enhancing, hypodense nodules in the subcutaneous fat of the right flank at the level of L5 and the left lower quadrant, respectively. There was also a 2.2 × 1.9-cm faintly rim-enhancing hypodensity within the left iliopsoas muscle belly.

These imaging findings further corroborate a widely metastatic process probably originating in the lung and spreading to

the lymph nodes, skin, muscles, and bones. The characterization of lesions as lytic as opposed to blastic is less helpful because many diseases can cause both. It does prompt consideration of multiple myeloma; however, multiple myeloma less commonly manifests with extramedullary plasmacytomas and is less likely given his normal renal function and calcium level. Bone lesions lessen the likelihood of GPA, and his necrotic lung mass makes sarcoidosis unlikely. Atypical infections and cancers are the prime suspect of his multisystemic disease.

There are no data yet to suggest a weakened immune system, which would increase his risk for atypical infections. His chronic lung disease, identified on imaging, is a risk factor for nocardiosis. This gram-positive, weakly acid-fast bacterium can involve any organ, although lung, brain, and skin are most commonly involved. Disseminated nocardiosis can result from a pulmonary or cutaneous site of origin. Mycobacteria; *Actinomyces*; dimorphic fungi like *Histoplasma, Coccidioides,* and *Blastomyces*; and molds such as *Aspergillus* can also cause disseminated disease with pulmonary, cutaneous, and musculoskeletal manifestations.

While metastases to muscle itself are rare, they can occur with primary lung cancers. Primary lung cancer with extrapulmonary features is feasible. Squamous cell lung cancer is the most likely to cavitate, although it rarely spreads to the skin. An aggressive lymphoma like diffuse large B-cell lymphoma or cutaneous T-cell lymphoma (higher occurrence in Asians) might also explain his constellation of findings. If culture data remain negative, then biopsy of the chest wall mass might be the safest and highest-yield target.

On hospital day 2, the patient developed new-onset severe neck pain. Magnetic resonance imaging of the cervical, thoracic, and lumbar spine revealed multilevel, bony, lytic lesions with notable cortical breakthrough of the C2 and C3 vertebrae into the prevertebral space, as well as epidural extension and paraspinal soft-tissue extension of the thoracic and lumbar vertebral lesions (Figure 3).

On hospital day 3, the patient reported increased tenderness in his skin nodules with one on his left forearm spontaneously draining purulent fluid. Repeat complete blood count demonstrated a white blood cell count of 12,600/mm^3 (45% neutrophils, 43% lymphocytes, 8.4% monocytes, and 4.3% eosinophils), hemoglobin of 16 g/dL, and platelet count of 355,000/mm^3.

The erosion into the manubrium and cortical destruction of the cervical spine attests to the aggressiveness of the underlying disease process. Noncutaneous lymphoma and lung cancer are unlikely to have such prominent skin findings; the visceral pathology, necrotizing lung mass, and bone lesions make cutaneous lymphoma less likely. At this point, a disseminated infectious process is most likely. Leading considerations based on his emigration from China and residence in California are tuberculosis and coccidioidomycosis, respectively. Tuberculous spondylitis most commonly involves the lower thoracic and upper lumbar region, and less commonly the cervical

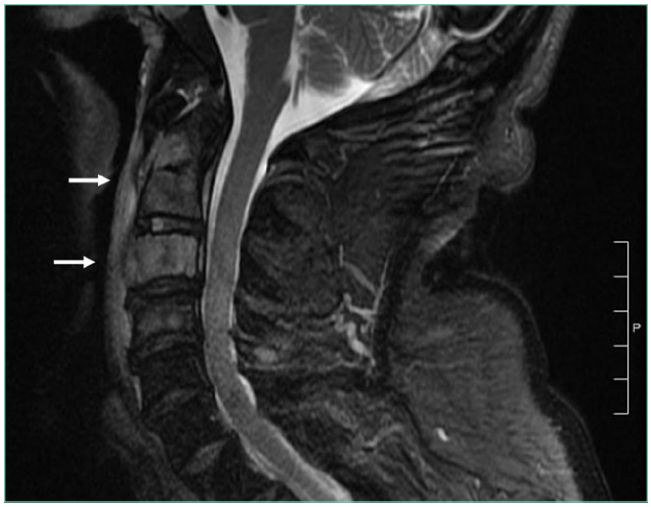

FIG 3. Magnetic Resonance Imaging of the Cervical Spine. Imaging reveals bony lytic lesions with notable cortical breakthrough of the C2 and C3 vertebrae into the prevertebral space (arrows).

spine. His three negative AFB sputa samples further reduce its posttest probability. Ultimately microbiologic data are needed to distinguish between a disseminated fungal process, like coccidioidomycosis, or tuberculosis.

Given the concern for malignancy, a fine needle aspiration of the left supraclavicular lymph node was pursued. This revealed fungal microorganisms morphologically compatible with *Coccidioides* species, with a background of necrotizing granulomas and acute inflammation. Fungal blood cultures grew *Coccidioides immitis.* AFB blood cultures were discontinued due to overgrowth of mold. The *Coccidioides immitis* antibody immunodiffusion titer was positive at 1:256.

During the remainder of the hospitalization, the patient was treated with oral fluconazole 800 mg daily. The patient underwent surgical debridement of the manubrium. In addition, given the concern for cervical spine instability, neurosurgery recommended follow-up with interval imaging. Since his discharge from the hospital, the patient continues to take oral fluconazole with resolution of his cutaneous lesions and respiratory symptoms. His titers have incrementally decreased from 1:256 to 1:16 after 8 months of treatment.

COMMENTARY

This elderly gentleman from China presented with subacute symptoms and was found to have numerous cutaneous nodules, lymphadenopathy, and diffuse osseous lesions. This multisystem illness posed a diagnostic challenge, forcing our discussant to search for a disease process that could lead to such varied findings. Ultimately, epidemiologic and clinical clues suggested a diagnosis of disseminated coccidioidomycosis, which was later confirmed on lymph node biopsy.

Coccidioides species are important fungal pathogens in the Western Hemisphere. This organism exhibits dimorphism, existing as mycelia (with arthroconidia) in soil and spherules in tissues. *Coccidioides* species are endemic to the Southwestern

United States, particularly California's central valley and parts of Arizona; it additionally remains an important pathogen in Mexico, Central America, and South America.[1] Newer epidemiologic studies have raised concerns that the incidence of coccidioidomycosis is increasing and that its geographic range may be more extensive than previously appreciated, with it now being found as far north as Washington state.[2]

Coccidioidal infection can take several forms. One-half to two-thirds of infections may be asymptomatic.[3] Clinically significant infections can include an acute self-limiting respiratory illness, pulmonary nodules and cavities, chronic fibrocavitary pneumonia, and infections with extrapulmonary dissemination. Early respiratory infection is often indistinguishable from typical community-acquired pneumonia (10%-15% of pneumonia in endemic areas) but can be associated with certain suggestive features, such as erythema nodosum, erythema multiforme, prominent arthralgias (ie, "desert rheumatism"), and a peripheral eosinophilia.[4,5]

Extrapulmonary dissemination is rare and most commonly associated with immunocompromising states.[6] However, individuals of African or Filipino ancestry also appear to be at increased risk for disseminated disease, which led to a California court decision that excluded African American inmates from state prisons located in *Coccidioides* endemic areas.[7] The most common sites of extrapulmonary dissemination include the skin and soft tissues, bones and joints, and the central nervous system (CNS).[6] CNS disease has a predilection to manifest as a chronic basilar meningitis, most often complicated by hydrocephalus, vasculitic infarction, and spinal arachnoiditis.[8]

Cutaneous manifestations of coccidioidomycosis can occur as immunologic phenomenon associated with pulmonary disease or represent skin and soft tissue foci of disseminated infection.[9] In primary pulmonary infection, skin findings can range from a nonspecific exanthem to erythema nodosum and erythema multiforme, which are thought to represent hypersensitivity responses. In contrast, *Coccidioides* species can infect the skin either through direct inoculation (as in primary cutaneous coccidioidomycosis) or via hematogenous dissemination.[9,10] A variety of lesions have been described, with painless nodules being the most frequently encountered morphotype in one study.[11,12] On histopathologic examination, these lesions often have features of granulomatous dermatitis, eosinophilic infiltration, gummatous necrosis, microabscesses, or perivascular inflammation.[13]

Another common and highly morbid site of extrapulmonary dissemination is the musculoskeletal system. Bone and joint coccidioidomycosis most frequently affect the axial skeleton, although peripheral skeletal structures and joints can also be involved.[6,12] Vertebral coccidioidomycosis is associated with significant morbidity. A study describing the magnetic resonance imaging findings of patients with vertebral coccidioidomycosis found that *Coccidioides* species appeared to have a predilection for the thoracic vertebrae (in up to 80% of the study's cohort).[14] Skip lesions with noncontiguously involved vertebrae occurred in roughly half of patients, highlighting the usefulness of imaging the total spine in suspected cases.

The diagnosis of coccidioidomycosis is often established through serologic testing or by isolation of *Coccidioides* species on histopathology or culture. Obtaining sputum or tissue may be difficult, so clinicians often rely on noninvasive diagnostic tests such as coccidioidal antigen and serologies by enzyme immunoassays, immunodiffusion, and complement fixation. Enzyme immunoassays IgM and IgG results are positive early in the disease process and need to be confirmed with immunodiffusion or complement fixation testing. Complement fixation IgG is additionally useful to monitor disease activity over time and can help inform risk of disseminated disease.[15] The gold standard of diagnosis of disseminated coccidioidomycosis infection remains histopathologic confirmation either by direct visualization of a spherule or growth in fungal cultures.[16] Polymerase chain reaction testing of sputum samples is an emerging diagnostic technique that has been found to have similar sensitivity rates to fungal culture.[17]

Treatment decisions in coccidioidomycosis are complex and vary by site of infection, immune status of the host, and extent of disease.[16] While uncomplicated primary pulmonary infections can often be managed with observation alone, prolonged medical therapy with azole antifungals is often recommended for complicated pulmonary infections, symptomatic cavitary disease, and virtually all forms of extrapulmonary disease. Intravenous liposomal amphotericin is often used as initial therapy in immunosuppressed individuals, pregnant women, and those with extensive disease. CNS disease represents a particularly challenging treatment scenario and requires lifelong azole therapy.[8,16]

The patient in this case initially presented with vague inflammatory symptoms, with each aliquot revealing further evidence of a metastatic disease process. Such multisystem presentations are diagnostically challenging and force clinicians to reach for some feature around which to build their differential diagnosis. It is with this in mind that we are often taught to "localize the lesion" in order to focus our search for a unifying diagnosis. Yet, in this case, the sheer number of disease foci ultimately helped the discussant to narrow the range of diagnostic possibilities because only a limited number of conditions could present with such widespread, multisystem manifestations. Therefore, this case serves as a reminder that, sometimes in clinical reasoning, "more is less."

KEY TEACHING POINTS

- Coccidioidomycosis is a fungal infection that can present with pulmonary or extrapulmonary disease. Risk of extrapulmonary dissemination is greatest among immunocompromised individuals and those of African or Filipino ancestry.[3,7]
- The most common sites of extrapulmonary dissemination include the skin and soft tissues, bones and joints, and the CNS.[6]
- While serologic testing can be diagnostically useful, the gold standard for diagnosis of disseminated coccidioidomycosis infection remains histopathologic confirmation with direct visualization of a spherule or growth in fungal cultures.[16]

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