Clinical Conundrums

Meant to Be

Brenna Lilley, MD[1], Shilpa Vasishta, MD[2], Satya Patel, MD[1,3]

[1] Department of Medicine, UCLA Health,
[2] Department of Infectious Disease, Montefiore Medical Center,
[3] Department of Medicine, VA Greater Los Angeles Healthcare System

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Abstract

We describe an elderly patient who presented with progressively worsening weakness, significant subacute constitutional symptoms associated with pulmonary nodules and lymphadenopathy.

A 79-year-old man with a history of benign prostatic hypertrophy, hyperlipidemia, and hypertension presented to the emergency department for two months of progressive generalized weakness, rendering him unable to perform activities of daily living from a prior baseline of walking several miles daily. He also endorsed progressively worsening dyspnea on exertion, fevers and chills, decreased appetite, and an unintentional 20-lbs weight loss over this time period.

He was born in Iran and immigrated to the Southwest United States 40 years ago. He had not traveled for the past several years. He had a 25-pack year smoking history but stopped smoking several decades ago. He has had no sick contacts. He hiked locally. Family history was notable for lung cancer in his mother. His prescribed medications included amlodipine-olmesartan, aspirin, rosuvastatin, tamsulosin, mirabegron, folic acid, ascorbic acid, ferrous sulfate, and cholecalciferol.

At the onset of his symptoms two months ago, he took multiple COVID-19 tests that were negative. Six weeks ago, he developed left leg swelling and erythema. Ultrasound of the lower extremities did not show evidence of deep venous thrombosis (DVT). He was diagnosed with cellulitis and treated with cephalexin. He was referred to cardiology to evaluate his dyspnea and had a normal echocardiogram and cardiac stress test. Four weeks ago, he developed a non-productive cough; computed tomography (CT) angiography of the chest was negative for a pulmonary embolus (PE) but showed diffuse random pulmonary nodules, mediastinal lymphadenopathy, and additional findings as described in Figure 1.

This patient presents with significant subacute constitutional symptoms associated with pulmonary nodules and lymphadenopathy. Malignancy rises in the differential based on his age and tobacco use history, as does infection coming from a tuberculosis (TB)-endemic region and with unknown HIV status. At this time, it is unclear if the unilateral leg swelling is at all related to the underlying syndrome or is simply due to an additional process.

One week ago, he presented to an outside hospital for worsening of his symptoms and was admitted for hyponatremia with serum sodium 121 mmol/L that was thought to be due to hypovolemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH). He was treated with intravenous fluids and salt tabs. He was noted to have low-grade fevers throughout this hospitalization. Workup was notable for a positive TB interferon gamma release assay (IGRA), however there were two negative induced sputum *Mycobacterium tuberculosis* complex PCRs (MTB-PCR) and three negative induced sputum acid-fast bacilli (AFB) stains and cultures. Coccidioides serologies were negative. He was discharged with a plan for outpatient bronchoscopy and endobronchial ultrasound-guided lymph node biopsy. After leaving the hospital, his symptoms worsened and he returned to the emergency department with his current presentation.

This patient's age and co-morbidities place him at risk for TB reactivation, even in the absence of significant immunosuppression. The sensitivity of any single AFB smear for pulmonary TB is limited; AFB cultures are more sensitive but remain contingent on adequate sampling. Coccidiomycosis is a compelling consideration

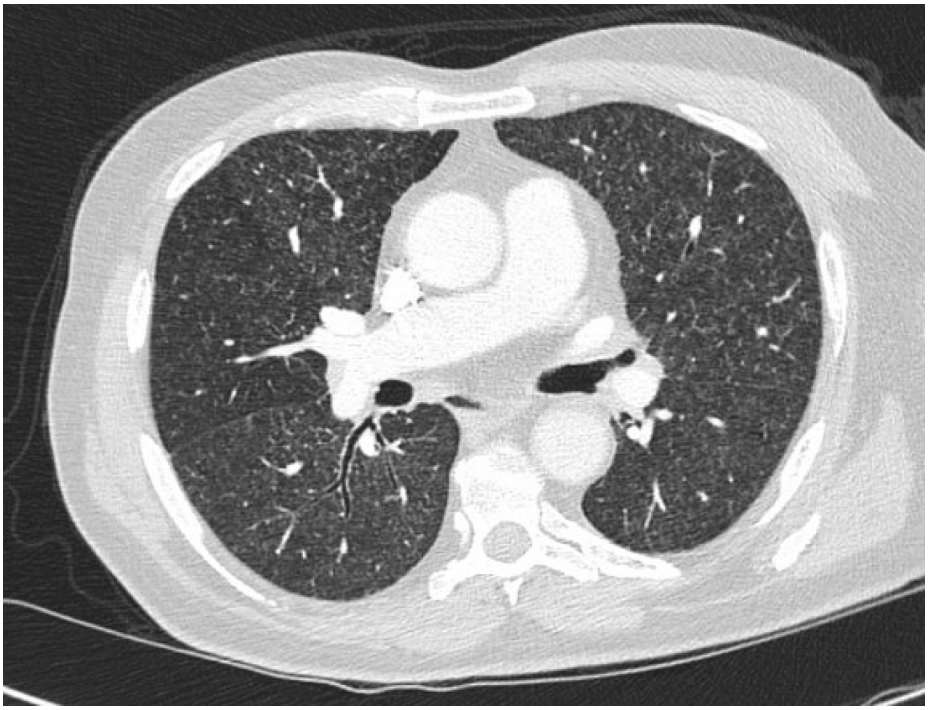

Figure 1. CT angiography of the chest showing diffuse random pulmonary nodules without lobar predominance on a background of faint ground glass opacity as well as bilateral peribronchial and peribronchiolar wall thickening.

given the patient's location, as are other fungal entities with a ubiquitous geographic distribution such as pulmonary aspergillosis and cryptococcosis (particularly *Cryptococcus gattii* for an individual on the United States west coast with extensive outdoor exposure). Classic endemic fungal maps are becoming increasingly blurred in association with climate change, therefore with a fitting clinical presentation it may also be useful to consider entities not traditionally associated with this region, such as histoplasmosis. Endocarditis with septic pulmonary emboli is another potential source of multifocal lung nodules which may be missed on transthoracic echocardiography.

Vital signs on presentation were a temperature of 101.3°F, heart rate 117 beats per minute, blood pressure 134/85 mmHg, respiratory rate 20 breaths per minute, and oxygen saturation 95% on room air. He was alert and oriented to name, place, date, and situation. Cardiovascular exam was notable for tachycardia and lung exam demonstrated diffuse inspiratory crackles in bilateral lung fields. Dermatologic exam did not reveal any skin lesions. Cranial nerves II-XII were intact, normal reflexes and intact strength in the upper and lower extremities.

The patient's physical exam, including tachypnea, relative hypoxia, and abnormal lung auscultation, further raises suspicion for a primary pulmonary process. While additional findings such as rashes or enlarged lymph nodes might have been helpful in identifying a disseminated process, their absence does not rule out this possibility.

Labs revealed a white blood cell count of 9,800/μL with a decreased absolute lymphocyte count of 590/μL, hemoglobin 11.9 g/dL, and platelet count 249,000/μL. Basic metabolic panel was normal except for blood urea nitrogen (BUN) 29 mg/dL, serum creatinine 1.5 mg/dL (baseline 1.1-1.2 mg/dL), and serum calcium 12.1 mg/dL. Liver function tests were normal except for alkaline phosphatase 132 IU/L and serum albumin 3.4 g/dL. Other labs included B-type natriuretic protein 52 pg/mL (normal: <100 pg/mL), procalcitonin 0.8 μg/L (normal: <0.10 μg/L), and serum lactic acid 20 mg/dL (normal: 5-18 mg/dL). Urinalysis showed trace protein. COVID-19 PCR was negative. Chest X-ray showed diffuse bronchial wall thickening and peribronchial cuffing.

This patient's constellation of lymphopenia, anemia, and hypoalbuminemia further support a subacute inflammatory process. The presence of metabolic abnormalities including hypercalcemia, elevated alkaline phosphatase, renal insufficiency, and proteinuria raise particular consideration of multiple myeloma or other malignancies with bone involvement. Hypercalcemia could reflect a non-malignant granulomatous process such as tuberculosis, sarcoidosis, or chronic fungal infection; alternatively, a neoplasm productive of parathyroid hormone-related protein (such as squamous cell carcinoma of the lung) or of calcitriol (such as lymphoma).

He was admitted to the hospital for further workup and treatment. His hypercalcemia was treated with intravenous fluids. Additional lab testing revealed parathyroid hormone 6 pg/mL (normal: 11-51 pg/mL), parathyroid-related hormone peptide 2.1 pmol/L (normal: 0.0-2.3 pmol/L), 25-hydroxy vitamin D 65 ng/mL (normal: 20-65 ng/mL), 1,25-dihydroxy vitamin D (calcitriol) 140 pg/mL (normal: 19.9-79.3 pg/mL), and angiotensin converting enzyme (ACE) 78 U/L (normal: 16-85 U/L). Microbiology testing included negative bacterial blood cultures, negative nares respiratory viral PCR panel, negative sputum *Mycoplasma pneumoniae* PCR, negative sputum *Chlamydia pneumoniae* PCR, negative urine Legionella antigen, two negative induced sputum MTB-PCRs, three negative induced sputum AFB stains and cultures, negative urine AFB stain and culture, negative blood AFB stain and culture, negative serum Coccidioides IgG/IgM, negative serum Aspergillus antigen, negative serum Cryptococcal antigen, negative urine Histoplasma antigen, negative serum (1,3)-beta-D-glucan, and negative HIV testing. Repeat TB IGRA was positive. The patient underwent a bronchoscopy with bronchoalveolar lavage (BAL) and endobronchial ultrasound-guided lymph node and lung biopsies. Coccidioides antigen and Aspergillus antigen from the BAL fluid were negative. There were two negative MTB-PCRs and three negative AFB stains from the BAL fluid. Two AFB cultures from the BAL fluid were negative but one culture grew *Mycobacterium gordonae*. Two AFB stains and cultures from lung tissue were negative. Bacterial and fungal stains and cultures of the BAL fluid and lung tissue were negative. Pathology of the lung biopsies showed non-necrotizing granulomas and pathology of the lymph node biopsies showed lymphoid tissue with anthracosis and histiocytosis as well as focal non-necrotizing granulomas. AFB and Grocott Methenamine Silver stains were negative on three different lung biopsies. Elastic trichrome stain showed collagen deposition.

This patient's labs suggest primary calcitriol overproduction as would be expected from the granulomatous process demonstrated on pathology. The finding of non-necrotizing granulomas raises suspicion for sarcoidosis, which could align with features of this patient's subacute cough, fevers, and intrathoracic lymphadenopathy. The normal ACE level does not exclude sarcoidosis, as serum ACE level has limited sensitivity (41.4%) and specificity (89.9%) for identification of sarcoidosis.[1] The absence of necrosis is not entirely specific, particularly in situations of compromised immune status. Within the infectious differential for necrotizing granulomatous disease, tuberculosis is an important consideration that has now been rigorously evaluated with sputum, BAL fluid, lung tissue, and lymph node tissue with consistently negative AFB smears and cultures. Pathogenic nontuberculous mycobacteria such as *Mycobacterium avium* complex or *Mycobacterium kansasii* may also be associated with chronic respiratory symptoms and nodular lung disease and may have similar histologic findings. *Mycobacterium abscessus*, a rapidly growing mycobacterium, is becoming a more common respiratory pathogen. The significance of *Mycobacterium gordonae* in this patient's cultures is less clear, as this organism is typically considered nonpathogenic and would generally require repeated isolation over time, with elimination of other causes, to be considered a culprit for this presentation. Dimorphic fungi such as Coccidioides may produce granulomatous changes and would typically be associated with positive serologies 2-3 months into symptoms, though these could potentially be missed on serologic testing in an individual with impaired antibody response. Cryptococcus and Aspergillus may also be missed on serum antigen testing when disease is isolated to the lungs; moreover, both of these have been associated with sarcoidosis and other inflammatory lung diseases (even in the absence of immunosuppressive therapy) so it would be important to consider as co-occurring processes.

After discussion between the rheumatology, infectious disease, and pulmonology teams, preliminary diagnoses of pulmonary sarcoidosis and latent TB infection were made. The patient's hypercalcemia was attributed to granulomatous disease. The patient was started on prednisone with a plan to start treatment for latent TB once the AFB cultures finalized. He was discharged and began to improve overall, including ambulating without assistive devices, increased appetite, and resolution of his dyspnea and cough, however, he continued to have intermittent fevers. A few days after discharge, he established care with an outpatient pulmonologist, who was skeptical about the diagnosis of sarcoidosis explaining his illness since he had no prior diagnosis of sarcoidosis or history of sarcoid flares. The decision was made to taper off the steroids and consider positron emission tomography-CT to further evaluate for malignancy if a repeat CT scan of his chest appeared worse. At this time, he also established care with outpatient infectious disease, who were considering starting empiric TB treatment depending on repeat imaging and finalized cultures due to ongoing concern for miliary TB. Two weeks after the patient's bronchoscopy, a send-out broad-range MTB-PCR testing on lung tissue came back positive for *Mycoplasma tuberculosis*. The patient was then diagnosed with miliary TB based on the miliary pattern of the pulmonary nodules on radiography and the new molecular evidence; at the

time he had no other evidence of disseminated disease. He was started on rifampin, isoniazid, pyrazinamide, and ethambutol. Serial CT scans of the chest showed interval improvement in the diffuse pulmonary nodules and his fevers resolved. However, there was a persistent 1.5 cm pulmonary nodule concerning for possible adenocarcinoma. He underwent a lung biopsy, showing atypical pneumocytes in a background of fibrosis and chronic inflammation, which could represent inflammatory changes from TB or adenocarcinoma. After discussion, the patient elected for close surveillance imaging, which is ongoing, and consideration of surgical resection if the pulmonary nodule increases in size.

Two months after starting treatment, he developed balance issues and encephalopathy. On magnetic resonance imaging (MRI) of the brain, there were numerous enhancing supratentorial and infratentorial lesions with associated edema, which could represent intracranial TB versus malignancy. He was evaluated by neurosurgery one week later, who recommended a brain biopsy for a definitive diagnosis. Due to significant improvement in his neurologic symptoms by that time, the patient elected to pursue repeat MRI of the brain instead. On imaging one month later, the brain lesions had improved with continuation of TB treatment alone, thus the lesions were thought to represent intracranial TB and the onset of neurologic symptoms was felt to be due to treatment-related paradoxical inflammation. Since the symptoms had resolved and there was radiographic improvement in disease, adjunctive steroids and invasive diagnostics such as brain biopsy or lumbar puncture were deferred.

DISCUSSION

Miliary TB is caused by lymphohematogenous dissemination of *Mycobacterium tuberculosis*. It is uniformly fatal if left untreated, and the mortality rate among adults treated remains high at 25-30% due to delays in diagnosis and treatment.[2] Miliary TB was predominantly a disease in infants and children before the 1980s. However, the incidence has increased in adults since then, primarily due to immunodeficiency from HIV/AIDS and increasing use of immunosuppressive therapies for rheumatologic, gastrointestinal, renal, and neurologic autoimmune or inflammatory diseases.[2] It is more common in males across all age groups.[2] Overall, miliary TB constitutes only 2% of cases of TB and 20% of cases of extrapulmonary TB.[2] Miliary TB can occur as a primary infection, reactivation, or reinfection of TB. Predisposing factors include a history of tobacco smoking and malignancy, both of which were noted or suspected in this patient.[2]

The disease often presents with non-specific and indolent symptoms. Patients typically experience weeks to months of weight loss, weakness, and cough; symptoms of fevers, chills, night sweats, and dyspnea may or may not be present.[2] Due to the non-localizing nature of these symptoms, the diagnosis may be delayed or confused for other inflammatory processes such as autoimmune disease, malignancy, or other infections. In this case, the patient presented with symptoms that could suggest any such inflammatory process. His course involved both related pathologies (hyponatremia due to SIADH from affected lung tissue and hypercalcemia from granulomatous disease) and unrelated issues (the left lower extremity cellulitis initially concerning for DVT/PE), resulting in a broad workup and significant amount of data to synthesize. Throughout the process, it was essential to remain mindful that he was from a TB-endemic region, to obtain sampling from multiple sources for workup ultimately, and not to exclude miliary TB even after the AFB stains and cultures were negative.

The diagnosis of miliary TB is made from clinical symptoms, radiographic evidence of miliary pattern in the lungs, and microbiological, histopathological, or molecular evidence.[2] In patients with miliary TB, the relative diagnostic yield from various microbiological and histopathological methods are as follows: sputum AFB stain and culture is 41.4%, bronchoscopy including BAL and lung biopsy is 46.8%, and lymph node biopsy is 90.9%.[2] The microbiological yield is low due to the lymphohematogenous nature of the disease – the bacteria are involved in the alveolar walls, not the alveolar space, causing interstitial lung disease.[3] On histopathologic exam, caseating granulomas suggest a diagnosis; however positive microbiological or molecular testing is necessary to make the diagnosis.[4] In this patient, none of the AFB stains or cultures from sputum, BAL fluid, or lung tissue were positive for *Mycoplasma tuberculosis,* and the pathology showed non-caseating granulomas, which contributed to the initial misdiagnosis of sarcoidosis. However, it is important to note that non-caseating granulomas are nonspecific for sarcoidosis, and other causes of granulomatous disease should be ruled out.[5] Additionally, granulomas of sarcoidosis may contain minimal, focal areas of necrosis, and TB can feature non-caseating granulomas, further complicating the diagnosis.[5,6]

Aside from pulmonary involvement, the more commonly affected organ systems include the skin, central nervous system (TB meningitis occurs in 10-30% of patients and can occur with or without intracranial tuberculoma), and adrenal glands (presenting as adrenal insufficiency).[2] When a diagnosis of miliary TB is not possible through a pulmonary source but the clinical suspicion remains high, it is important to consider further invasive diagnostic procedures if there is evidence of extrapul-

monary disease. Such diagnostics include bone marrow biopsy, extra-thoracic lymph node biopsy, liver biopsy, lumbar puncture, and pleural or ascitic fluid sampling.[4]

In this case, when the patient was discharged, a diagnosis of miliary TB was not made due to a lack of microbiologic, histopathologic, and molecular evidence. However, due to the high mortality associated with miliary TB, it remained on the differential until it could be definitively excluded. It was when the broad-range MTB-PCR resulted positive for *Mycoplasma tuberculosis* that a correct diagnosis of miliary TB was made. Broad-range PCR may be performed on tissues when standard culture-based diagnostics are unrevealing but there remains high suspicion for infection, including entities that may be difficult to isolate through traditional methods. A limited number of studies have shown that broad-range PCR can increase the detection rate of pathogens.[7] Broad-range PCR may be a tool clinicians can consider on a case-by-case basis when suspicion for infection is high and culture-based studies have not yielded a diagnosis. PCR-based studies importantly do not provide susceptibility data, which poses a significant limitation in ensuring optimal therapy for complex infections, including multidrug-resistant TB.

Miliary TB is treated with RIPE (rifapentine, isoniazid, pyrazinamide, and ethambutol) therapy, or as dictated by susceptibility data. Without meningeal involvement, six months of treatment is recommended for new diagnoses with no prior TB treatment history. With meningeal involvement, a more prolonged course of 9-12 months of treatment is recommended, and there is limited evidence suggesting adjunctive steroids may be beneficial. The treatment course includes two months of an intensive phase with RIPE therapy followed by a continuation phase with rifampin and isoniazid alone.[2] Clinical monitoring for treatment response (including symptomatic improvement and microbiologic clearance), paradoxical reactions, and treatment adherence and toxicities is warranted throughout therapy.

It is important to consider a diagnosis of miliary TB when an individual presents with indolent, constitutional symptoms and risk factors for TB exposure, such as this patient from a TB-endemic region. It is a can't-miss diagnosis due to its potential high mortality but is highly treatable if diagnosed without significant delay. Furthermore, this case is a stark example of how TB can remain latent and reactive decades later, underscoring the importance of treating latent TB infection to prevent significant morbidity or mortality in the future.

Author Contributions

All authors have reviewed the final manuscript prior to submission. All the authors have contributed significantly to the manuscript, per the International Committee of Medical Journal Editors criteria of authorship.

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Corresponding Author

Brenna Lilley, MD
Resident Physician, UCLA Health Internal Medicine Residency Program
Mailing Address: 757 Westwood Plaza Suite 7236
Los Angeles, CA 90095-7417
Telephone: 310-948-4042
Email address: brenna.lilley@gmail.com

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