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A Case of a Mediastinal Mass in a Teenager Causing Chest Pain, Difficulty Breathing, and Emesis: A Rare Complication of a Relatively Common Disease

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Case Report

A 16-year-old female from Southeast Michigan with a history of Raynaud's disease presented with 2 weeks of cough, shortness of breath, fever, and right-sided chest pain. The chest pain was described as a constant, sharp pain radiating to the right axilla, worsening with cough and lying flat, and improving while standing. The cough was productive of white sputum without hemoptysis. She reported fatigue and night sweats, but no weight loss. The chest pain and fever acutely worsened 2 days prior to admission.

Physical examination was significant for right-sided crackles on auscultation. Significant laboratory findings included an elevated white blood cell count at 14 900/mm^3, with neutrophilic predominance (83%), and elevated erythrocyte sedimentation rate at 75 mm/h. Chest X-ray was unremarkable.

A computed tomography scan of the thorax was performed due to this subacute history of dyspnea, fever, and cough. It revealed a 4.6-cm calcified soft tissue mass in the right subcarinal region with bilateral hilar lymphadenopathy and mild compression of the right middle lobe bronchi and esophagus without complete obstruction. It also showed a 1.1-cm calcified soft tissue nodule in the left lower lobe (Figure 1). During the admission, the patient developed gastroesophageal reflux symptoms with intermittent emesis, which was attributed to the esophageal compression.

Evaluation for malignancy included lactate dehydrogenase, lactic acid, ferritin, and uric acid, which were within normal limits. Peripheral smear showed significant neutrophilia and flow cytometry showed no clonal population suggestive of leukemia. Due to the history of Raynaud's disease, tests for sarcoidosis, autoimmune, and connective tissue diseases were performed (ANA, dsDNA, ANCA, lysozyme, and angiotensin converting enzyme) and were all negative.

The clinical picture was suggestive of infectious etiology, specifically tuberculosis and fungal infection (histoplasmosis, blastomycosis, and coccidioidomycosis). Her mother was an intensive care unit nurse with previous tuberculosis exposure 3 years ago, but currently asymptomatic. Otherwise, she denied any other significant exposures. Respiratory culture was normal; PPD (purified protein derivative) skin test and acid-fast bacilli sputum stains were negative. Blood culture and β-D-glucan were negative. Blastomyces antigen and coccidioides antigen were both negative. Histoplasma urine antigen was negative and titers of histoplasma antibodies by complement fixation (CF) were 1:8, an inconclusive result. However, M and H bands were detected by immunodiffusion, conclusively diagnosing the patient with histoplasmosis. On further questioning, the patient recalled that she was managing large metal coils covered in bird feces with her father 2 months prior.

She was treated with 0.5 mg/kg prednisone daily for 7 days and itraconazole 200 mg 3 times a day for 3 days, followed by 200 mg twice a day for 12 weeks, based off of Infectious Diseases Society of America guidelines.[1] Immunoglobulin levels were normal, excluding immunodeficiency. Repeat computed tomography scan after treatment showed that the subcarinal mass decreased in size from 4.6 cm to 1.6 cm (Figure 2), along with the bilateral calcified hilar lymph nodes. This correlated with improvement in symptoms.

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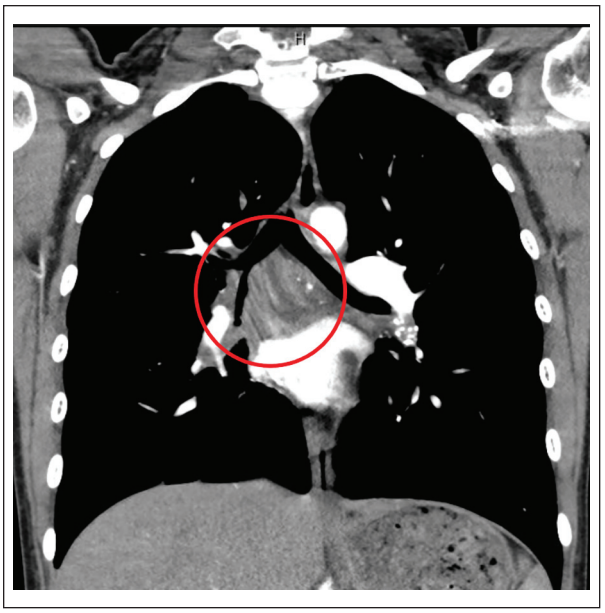

Figure 1. Coronal image of computed tomography scan of thorax with contrast showing a 4.6-cm calcified soft tissue mass and bilateral hilar lymphadenopathy causing mild compression of the right middle lobe bronchi.

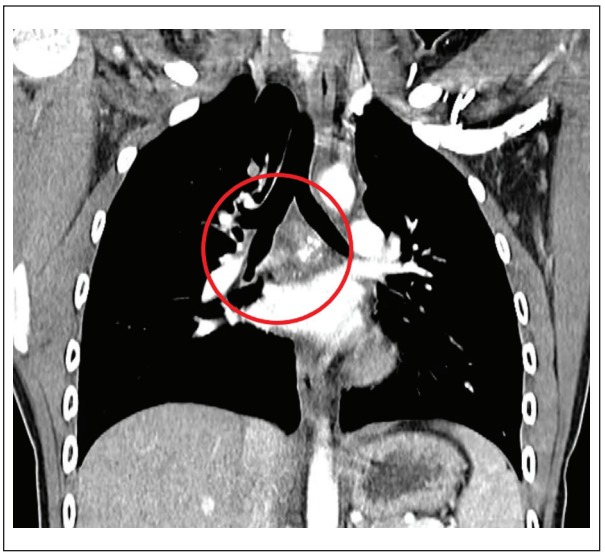

Figure 2. Coronal image of computed tomography scan of thorax after treatment with steroids and itraconazole showing an interval decrease in size of subcarinal soft tissue mass to 1.6-cm and hilar lymph nodes and improved patency of the right middle lobe bronchus.

Final Diagnosis

Pulmonary histoplasmosis with mediastinal granuloma causing compressive symptoms.

Discussion

Histoplasma capsulatum is a fungus that is endemic to the central and eastern United States, specifically the Mississippi and Ohio River valleys. It is typically found in soil contaminated by bird or bat excrement, barns, and caves.[2] After aerosolized conidia are inhaled, they germinate in the distal bronchioles and pulmonary alveoli, where they transition to their yeast phase, then proliferate within macrophages.[2,3] Immunocompetent people develop T-lymphocyte immunity after 1 month, and macrophages activate to kill the fungus and control the disease.[3]

Histoplasma capsulatum causes symptoms in <5% to 10% of infected people depending on age, immunocompetence, and size of inoculum.[3,4] Clinical manifestations are classified according to site (pulmonary or disseminated), duration (acute, subacute, or chronic), and pattern (primary or reactivation) of infection.[4] Most symptomatic patients develop acute pulmonary histoplasmosis, a brief, self-limited illness characterized by fever, chills, nonproductive cough, and malaise.[3] They then recover without treatment after 2 to 3 weeks. Disseminated disease and severe pulmonary histoplasmosis are usually only seen in immunocompromised patients. Radiography may show hilar or mediastinal adenopathy, or diffuse interstitial or reticulonodular pulmonary infiltrates.

As the presenting symptoms can be nonspecific, the initial differential will be wide and varied for a child presenting with a mediastinal mass. The differential diagnosis in the case presented above included lymphoma, leukemia, sarcoidosis, tuberculosis, blastomycosis, and coccidioidomycosis. Diagnostic laboratory tests to confirm histoplasmosis include serologic tests, antigen detection via quantitative enzyme immunoassay (EIA), culture, and tissue and body fluid examination.[3] Multiple positive results increase the positive predictive value of slightly positive serologic results. Rapid antigen EIA can be done on urine, serum, cerebrospinal fluid, and bronchoalveolar lavage fluid and is transiently positive. It is most sensitive for early active pulmonary infection and severe, disseminated infection.[2] CF and immunodiffusion assays detect antibodies toward *Histoplasma*. The CF test measures titers of antibody, is directly proportional to the severity of infection, and is more sensitive than the immunodiffusion test, although less specific. The immunodiffusion precipitin test looks for M and H bands; H bands are more suggestive of active infection. It is more specific than CF, with only 5% cross reaction, but less sensitive as H bands are only found in 23% of patients with acute pulmonary infection and M bands found in 76%.[3] Culture is the definitive

method of diagnosis. In some cases, all urine and serum tests may be negative, and it may require histologic examination of lung tissue to isolate *Histoplasma capsulatum*.[5] Identifying the typical intracellular yeast form by examination with Wright or Giemsa stains strongly supports the diagnosis.[2] Mediastinal granulomas tend to have negative EIA and cultures and can be "sometimes positive" for CF and immunodiffusion antibody, which was demonstrated by the patient described above, with an inconclusive CF titer but positive H and M bands but negative EIA and culture.[3]

Here we present a case of a rare complication of acute pulmonary histoplasmosis. Mediastinal granuloma causing compressive features is an uncommon, but well-documented complication of histoplasmosis, more commonly seen in children due to their greater airway pliability.[1] Mediastinal histoplasmosis can be divided into 3 syndromes: mediastinal adenitis, mediastinal granuloma, and fibrosing mediastinitis.[2,6] Mediastinal adenitis is mostly asymptomatic, but can cause severe chest pain and, rarely, compression of the hilar structures.[4,6] Lymph nodes in mediastinal adenitis are not calcified and usually subside.[6] Mediastinal granulomas are the result of chronic inflammation causing enlarged mediastinal lymph nodes to become necrotic and coalesce into a mediastinal mass. Similar to mediastinal adenitis, mediastinal granulomas are usually asymptomatic or minimally symptomatic, rarely presenting with compression of the airway, esophagus, pulmonary vessels, or superior vena cava. Fibrosing mediastinitis is a chronic disease characterized by excessive fibrosis surrounding the caseous nodes and invading into mediastinal structures, causing obstructive symptoms.[4,6]

In this case, that patient described developed chest pain, cough, and gastroesophageal reflux symptoms as a result of the compression of the right middle lobe bronchus and esophagus by the subcarinal soft tissue mass. Lack of pervasive fibrosis and presence of calcifications in the soft tissue mass suggest the diagnosis of a mediastinal granuloma.

A literature review performed using the PubMed database with the search term "mediastinal histoplasmosis" between 2000 and 2020 revealed 116 results. Case reports were then excluded based on disseminated disease, immunocompromised individuals, or a diagnosis of fibrosing mediastinitis. Between 2000 and 2020, there were 8 reported cases of pulmonary histoplasmosis causing mediastinal granulomas in immunocompetent individuals,[5,7-13] one of which did not cause obstructive symptoms.[7] Of the 7 patients who developed compression from mediastinal granulomas, 1 patient presented with a pulmonary arterial mass,[8] 2 patients with primarily esophageal involvement,[9,10] 3 patients with primarily bronchial obstruction,[5,11,12] and 1 patient with both esophageal and bronchial obstruction.[13] Although gastrointestinal histoplasmosis can occur as a consequence of disseminated disease, esophageal involvement associated with impingement from mediastinal histoplasmosis lymphadenopathy is only reported in 5% to 13% of cases.[9] Here we present what we believe to be the second reported case of both esophageal and bronchial obstruction by mediastinal granuloma from pulmonary histoplasmosis in the past 2 decades.

The recommended treatment for symptomatic mediastinal lymphadenitis and severe cases of obstruction is itraconazole 200 mg 3 times daily for 3 days and then 200 mg once or twice daily for 6 to 12 weeks plus prednisone 0.5 to 1.0 mg/kg daily in tapering doses for 1 to 2 weeks.[1] For symptomatic mediastinal granulomas, treatment is itraconazole 200 mg 3 times daily for 3 days and then 200 mg once or twice daily for 6 to 12 weeks, as was used in this case, along with corticosteroid treatment due to initial concern for mediastinal lymphadenitis. In this case, surgical intervention was unnecessary, as there was resolution of clinical symptoms and radiographic findings of compression with antifungal and corticosteroid treatment. However, surgical intervention is often necessary when there is compression of the pulmonary veins, pulmonary arteries, superior vena cava, or other mediastinal structures.

Conclusion

This case serves as a reminder that, with mediastinal masses, histoplasmosis must remain under clinical suspicion despite its rarity, as it is a mimicker of lymphoma, rheumatologic diseases, and tuberculosis. Diagnosis can be difficult and requires an understanding of the laboratory tests as, in this case, urine and serum antigens were negative, CF titers were inconclusive, but the M and H bands were positive and definitive diagnostic results. Clinicians must remember that even with all laboratory results being negative, diagnosis cannot be definitively excluded without lung tissue biopsy.

Author Contributions

TFC: Contributed to conception and design; contributed to acquisition, analysis, or interpretation of data; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

JYA: Contributed to conception and design; contributed to acquisition, analysis, or interpretation of data; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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