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An unanticipated pulmonary mass: Histoplasmoma mimicking malignancy

Yasir Ahmed, Mustafeez Ur Rehman, Sarah Hamid, Saadia Haleema, Nicholas Ludvik

ABSTRACT

Histoplasmoma is a rare form of chronic infection with *Histoplasma capsulatum* (HC) infection that is frequently misconstrued as malignancy. The diagnosis is invariably through histopathological studies and appropriate staining after surgical resection and carries an excellent prognosis even for lesions more than 3 cm.

We present a case of a young female whose clinical presentation and imaging studies were highly concerning for lung malignancy, such as non-Hodgkin's lymphoma (NHL) in controlled human immunodeficiency (HIV) infection and was resected accordingly. However, on histopathological examination, it was revealed to be a histoplasmoma. There were no signs of disseminated disease; hence antifungal therapy was not administered. The patient remained asymptomatic at outpatient follow-up after a year.

Infectious etiology should make the differential list when working up a pulmonary nodule or even a mass inappropriate setting, including well managed immunocompromised conditions. These are potentially treatable causes with an excellent prognosis. It is important to recall that such infections might have atypical presentations in immunocompromised patients, as highlighted in this case..

Keywords: Histoplasmoma, *Histoplasma capsulatum*, Pulmonary mass in HIV, Fungal mass

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INTRODUCTION

Pulmonary histoplasmosis represents a broad spectrum of clinical presentations, and histoplasmoma formation is one of the rare manifestations. These are typically asymptomatic and difficult to distinguish from malignancy or tuberculosis, especially in immunocompromised patients. Isolated pulmonary involvement without dissemination is even more occasional [1]. *Histoplasma capsulatum* is the most common endemic mycosis in HIV patients, although the risk has decreased since antiretroviral therapy. The disease is endemic to the areas surrounding the Mississippi and Ohio river valleys [2]. This case highlights the importance of consideration of such infections in appropriate patients, including those with controlled immunocompromising conditions. Awareness of the presence of such disorders has become particularly important to consider as more patients are being placed on biologic immunosuppression for autoimmune diseases.

CASE REPORT

A 33-year-old African-American female had a known medical history of chronic hepatitis B, asthma, polysubstance abuse, and HIV infection with a CD4 count of 553/mcL (normal 359–1519/mcL), on dolutegravir, emtricitabine, and tenofovir. She presented to the emergency department with acute onset shortness of breath associated with right-sided pleuritic chest pain that was worse with breathing. She had mild pain in the right chest for almost a month that worsened on the day of the presentation. She endorsed "B type symptoms," i.e., subjective fevers, night sweats, and unintentional weight loss for the same duration of time. The physical exam was unrevealing.

Initial lab workup, including complete blood count, renal function, electrolytes, prothrombin time, and urinalysis were completely within normal limit. A chest radiograph (CXR) demonstrated rounded opacity in the right mid-lung (Figure 1). Computed tomography (CT) of the chest was performed and revealed a 3.8 × 2.7 cm mass in the right lower lobe with surrounding ground-glass opacities and invasion of the intercostal muscles between ribs 6 and 7 rib along with associated subcarinal and right hilar lymphadenopathy highly suspicious of malignancy (Figure 2A and B). These imaging findings and the patient's clinical presentation were suggestive of a diagnosis of non-Hodgkin Lymphoma (NHL) in the setting of HIV infection. Pulmonary function tests showed the ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC) as 81%, and normal total lung capacity (TLC) and functional reserve capacity. Percutaneous biopsy was considered but was felt to represent unnecessarily high risk of pneumothorax, so the patient was taken to the operating room for a right thoracotomy with wedge resection of the right lower lobe and chest tube placement. The histopathologic analysis of the surgical specimen showed organizing and fibrinous pneumonia forming a mass lesion (3.2 cm), with micro-abscesses formation and scattered multinucleated giant cells on Hematoxylin and Eosin stain (H&E). Gomori-Grocott's methenamine silver stain (GMS) and Periodic Acid–Schiff (PAS) stains highlighted small, narrow-based budding yeasts, morphologically consistent with *Histoplasma* species (Figures 3 and 4).

Rest of the workup including three consecutive acid-fast bacillus (AFB) stains, serology including 1,3 Beta glucan and urine histoplasma antigens came back negative. Since the patient did not have evidence of disseminated infection, systemic antifungal therapy was not initiated. After routine post-surgical care and brief physical therapy, she was discharged home in a stable condition. Truvada and Tivicay were continued during the hospital stay and upon discharge as well. She is being followed outpatient and doing well with no signs of disseminated infection for over a year now.

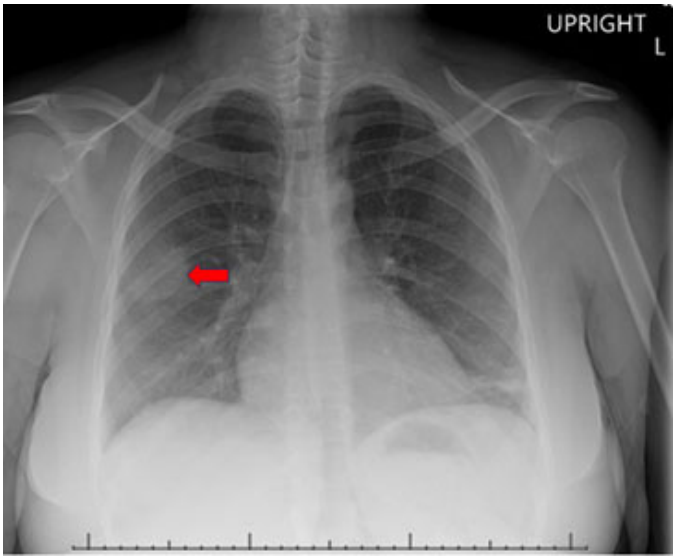

Figure 1: Rounded right mid-lung opacity (red arrow).

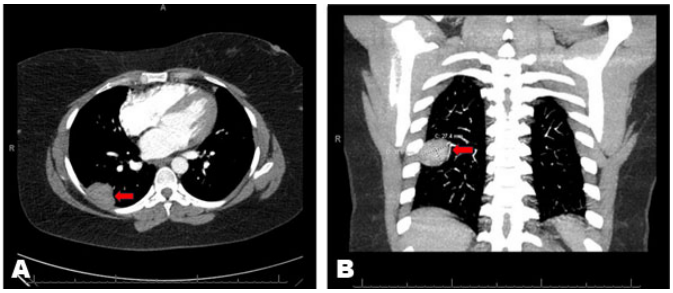

Figure 2: (A) (axial view) and (B) (coronal view): 3.8 × 2.7 cm area of soft tissue attenuation within the right lower lobe with invasion of intercostal muscle (red arrows) and associated subcarinal and right hilar lymphadenopathy. This should be considered malignancy until proven otherwise.

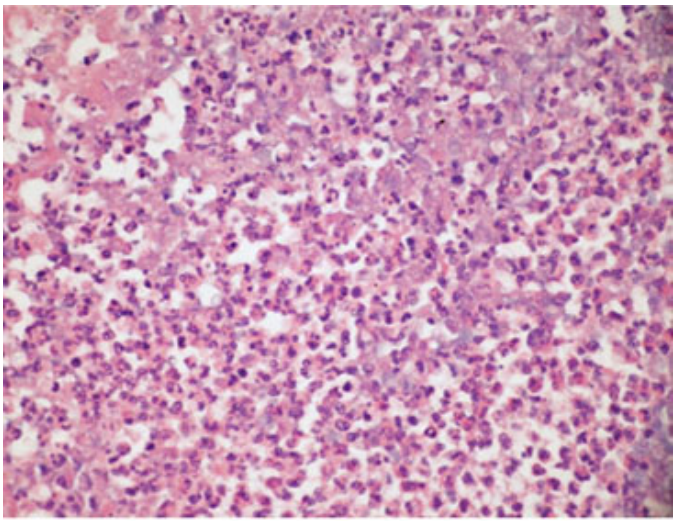

Figure 3: Hematoxylin and Eosin stain (H&E): Organizing and fibrinous pneumonia forming a mass lesion (3.2 cm), with microabscess formation and scattered multinucleated giant cells.

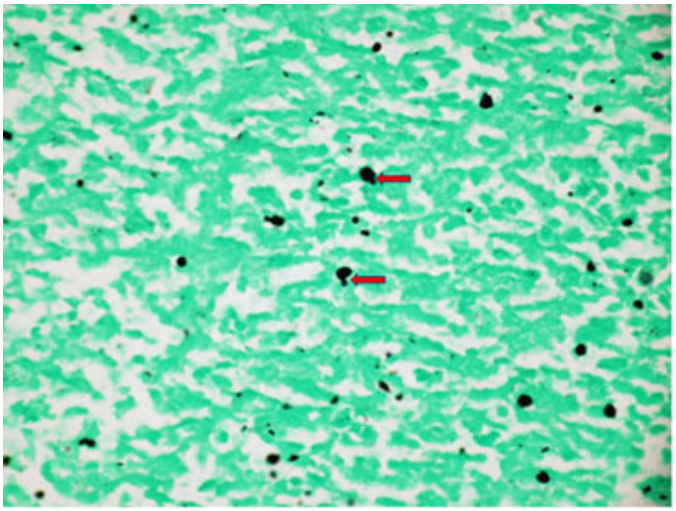

Figure 4: Grocott's methenamine silver stain (GMS): Highlights small, narrow-based budding yeasts, morphologically consistent with *Histoplasma* species (red arrows).

DISCUSSION

Histoplasma capsulatum (HC) is a ubiquitous, dimorphic fungus endemic to Central and Eastern United States and has a high seroprevalence in Ohio and Mississippi river valleys [2]. Infection occurs from inhalation of spores via dust or aerosols. Exposure to bats such as cave explorers is a well-known risk factor for histoplasmosis [1]. Historically when the intact tomb of 18th dynasty pharaoh, Tutankhamun, was discovered by a British explorer, Howard Carter, his benefactor Lord Carnarvon died of illness afterward, thus giving birth to the famous myth of "King Tut's Curse." He had arrived sick into the country and developed fever, swollen glands, pneumonia, and recent studies suggest that he might have had histoplasmosis [2–4].

The pulmonary *H. capsulatum* infection has four categories: (i) Acute infection; it occurs from high inoculum infection; (ii) Chronic infection; usually, the patient has underlying lung disease such as emphysema; (iii) Histoplasmoma; it is also a chronic infection, but rare; and (iv) disseminated histoplasmosis; which means extrapulmonary manifestations, usually seen in immune-compromised individuals. The presentation in any of these forms is determined by the number of inhaled spores, its duration, and the immune status of the host [5]. Histoplasmoma may be discovered even decades after the initial infection.

Half of the patients were asymptomatic in a case series of 58 patients, and cough (38%), chest pain (26%), and fever (17%) were the common symptoms in symptomatic patients, while weight loss, hemoptysis, and dyspnea were rarely reported [6]. Histoplasmoma forms due to excessive healing of the primary focus resulting in fibrosis, forming lesions 2–4 mm in size and rarely can progress up to 4 cm [6]. Since they are asymptomatic, remain small and stable in length, and enlarge slowly over time [7, 8]. They are discovered on routine screening, pre-operative, or pre-transplant workup [8]. Their typical size is <1 cm, and >3 cm histoplasmoma is rare [6]. The rate of their growth is variable and estimated at ~1.7 mm/year [8].

Histoplasmomas were frequently misdiagnosed as malignant tumors or tuberculomas before their description in 1953 by Pucket [9]. In our case, the patient had an exciting presentation in a sense that her chief complaint was right-sided chest pain and endorsed shortness of breath and night sweats that are less commonly observed. Computed tomography (CT) chest with contrast showed a mass of significant size and invasion of the intercostal muscles between ribs 6 and 7 rib, which is a unique finding, as described above in Figures 2A and B. The patient's overall presentation was highly concerning for malignancy, and infectious etiologies, including tuberculomas or fungal infection, were low on the differential. The patient was strictly compliant with antiretroviral therapy, and the CD4 count was within the normal range.

Imaging of the chest, though never diagnostic, may show calcification of the nodule; however, these calcifications may not be present in all cases, and their pattern does not necessarily rule out a malignancy. Therefore, the biopsy is pursued in most cases for definitive diagnosis. If present, the degree of calcification is considered to be more than their counterpart tuberculoma [2].

Definitive diagnosis is made by finding the fungus in histological sections that is facilitated by GMS and PAS staining, fungal growth on cultures, or positive serologic testing. The utility of diagnostic labs depends on the presentation of pulmonary histoplasmosis, with the sensitivity of the tests higher when they are performed in a patient with an acute presentation. For sensitivity and specificity of the antigen, antibody testing for diagnosing histoplasmosis is low in localized syndromes like mediastinal fibrosis and histoplasmosis, causing pulmonary nodule, which usually represents a healing process after an acute *Histoplasma* infection [10, 11]. Staining may be the only confirmatory test in the histological samples, which was the case in our patient. Cultures are mostly negative.

The prognosis is favorable for histoplasmoma after surgery, even for lesions greater than 3 cm [7, 12]. For asymptomatic patients with isolated histoplasmoma, antifungal treatment is not recommended by the infectious disease society of America Guidelines (an AIII recommendation) [3].

The diagnostic and therapeutic approach is determined by the size and location of the lesion and the level of suspicion for cancer [2]. For peripherally location lesions, transthoracic fine-needle aspiration or wedge resection is a suitable option [6, 13]. For focalized lesions, wedge resection is the surgery of choice, and the disease does not recur after the resection [6].

CONCLUSION

Fungal infections like histoplasmoma is a possible etiology for a pulmonary nodule or even a mass, particularly in immunocompromised patients. Its presentation can be atypical, but the recognition is important as the outcomes in these cases are more favorable compared to other etiologies.

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Yasir Ahmed – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree 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

Mustafeez Ur Rehman – Acquisition of data, Analysis of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree 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

Sarah Hamid – Acquisition of data, Analysis of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree 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

Saadia Haleema – Acquisition of data, Analysis of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree 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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Guarantor of Submission

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.