Reactivation Histoplasmosis Manifested by Lymphocutaneous Fistula with Cervical Drainage of Stones

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Abstract: Histoplasmosis, the most common endemic fungal infection in the United States, is usually self-limiting but can cause a myriad of unusual manifestations, including lithiasis. Despite more than a century of clinical experience with the disease, controversy persists regarding the potential for latent infection with subsequent reactivation. We report a case of an apparently immunocompetent young woman who developed recurrent histoplasmosis after eight years. The presumed secondary reactivation was complicated by a lymphocutaneous fistula with the drainage of stones from her neck after the initiation of antifungal therapy. This case supports the concept of reactivation histoplasmosis. Patients with histoplasmosis are at risk for paradoxical transiently worsening local inflammation while receiving effective antifungal therapy.

Keywords: Histoplasmosis; Lithiasis; Lymphocutaneous fistula

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Case Presentation

A 22-year-old female from the midwestern U.S. presented for the assessment of a tender neck lesion. Eight years earlier, she underwent a biopsy of a mass in the same location; the culture grew *Histoplasma capsulatum*. The patients prior physicians felt that the infection was likely to be self-limiting and did not prescribe antimicrobial therapy. The mass resolved spontaneously.

In February 2020, she developed progressively worsening pain, erythema, and swelling over a period of several weeks at the site of the prior neck mass (Figure 1). She did not have fever, weight loss, night sweats, or dysphagia. Otherwise, her past medical history was unremarkable, and there was no apparent evidence of immunosuppression. Physical examination revealed a 4 $\times$ 3 cm firm, tender, erythematous non-fluctuant mass in the left lower anterior cervical area. No lymphadenopathy was noted elsewhere. Her lungs were clear. The cardiac and abdominal examinations were normal. No skin lesions were observed.

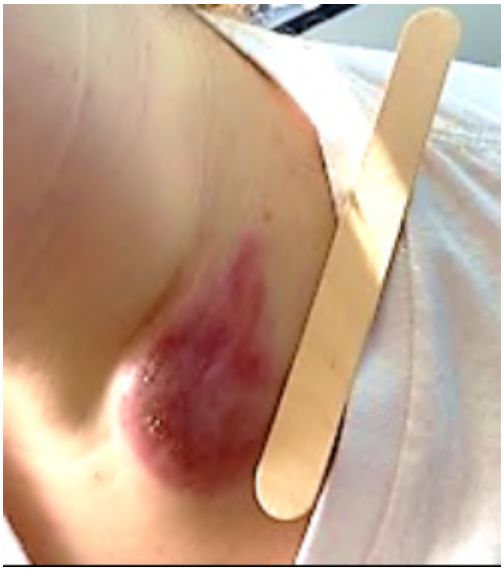

Figure 1: Left Neck Mass.

The chemistry panel and complete blood count were normal; C-reactive protein was 18.3. The neck ultrasound revealed two avascular neck soft tissue lesions, measuring 1.6 $\times$ 3.0 $\times$ 1.6 cm and 4.3 $\times$ 4.3 $\times$ 2.1 cm, respectively. Numerous tiny bright echoes, presumed to represent calcifications, were seen in both lesions (Figure 2). On the cine images, there appeared to be movement within the central portion of the lesions, suggesting a complex cystic component. Chest imaging studies were not conducted. The Histoplasma yeast complement fixation titer was 1:32, and m-band immunodiffusion was positive; the urine Histoplasma antigen (tested at Quest Laboratory ®) was negative. The HIV antibody was negative.

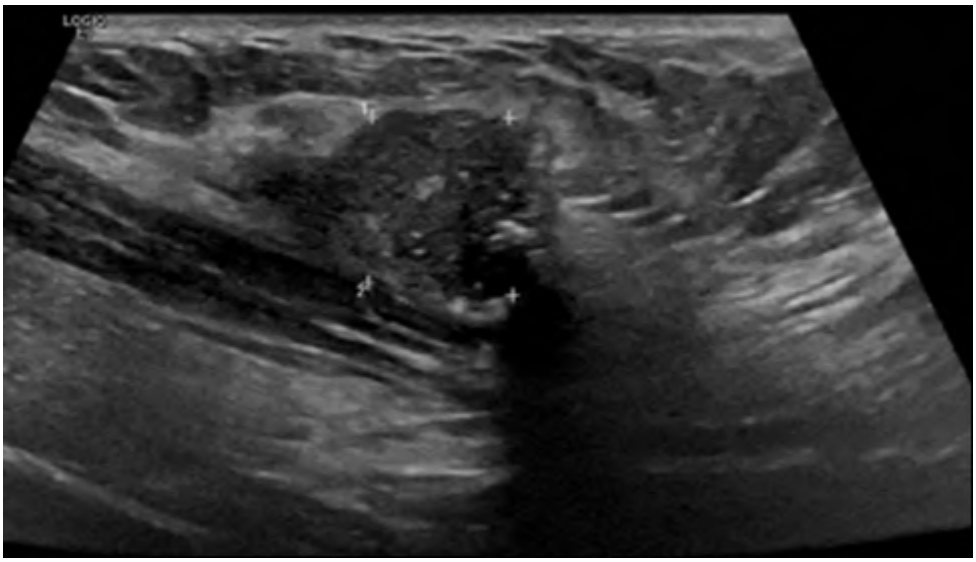

Figure 2: Ultrasound of left anterior cervical region.

The patient received a loading dose of itraconazole, 200 mg tid for 3 days, and then was treated with 200 mg bid for 6 months. Eight days after the initiation of treatment, she returned to clinic when she noted spontaneous copious thick yellow neck drainage (Figure 3), which contained multiple 1–2 mm gravel-like stones (Figure 4). A fungal culture was not completed. The drainage abated within a few days without intervention, and her neck mass resolved within 3 months.

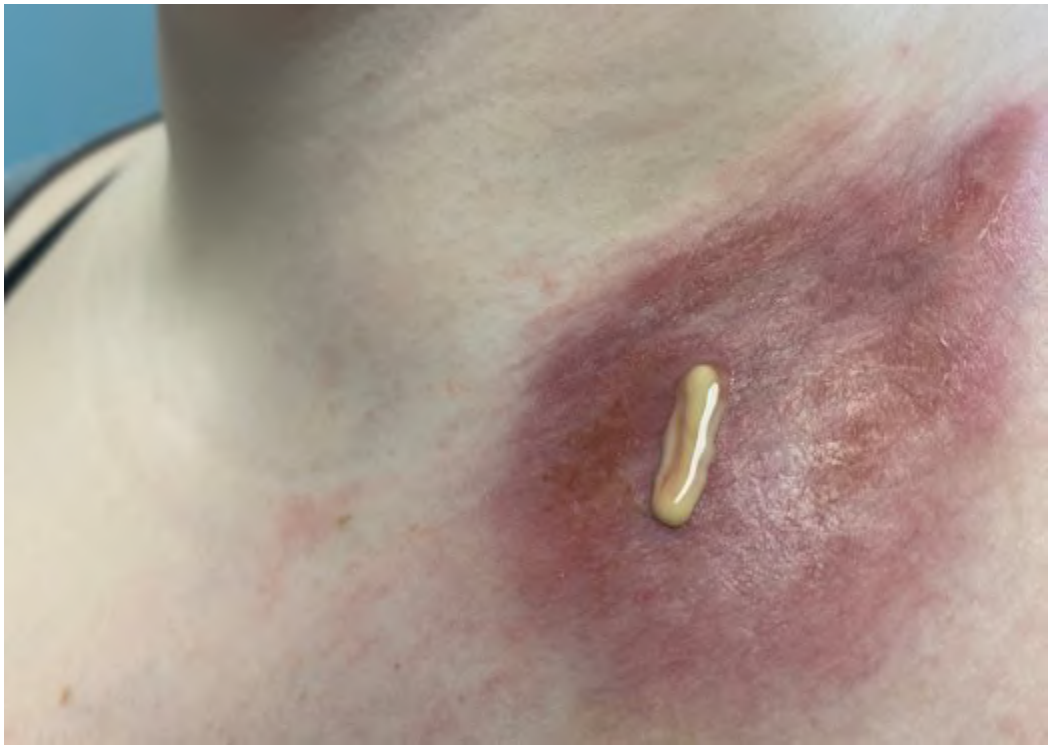

Figure 3: Caseous drainage from neck mass.

Figure 4: Photo courtesy of Brett Pruett.

Discussion

Histoplasma capsulatum is the most common endemic mycosis in the United States [1]. Although most cases are asymptomatic, disseminated infection involving the reticuloendothelial system occurs in approximately 1 in 2000 infected individuals [2]. Disseminated histoplasmosis is much more common among patients with impaired cellular immunity, in whom the infection is progressive and life-threatening, but cases also occur in persons with no known immunosuppressing conditions [2]. In immunocompetent persons, disseminated histoplasmosis can pursue an indolent course [3]. The detection of Histoplasma antigenuria is the most sensitive diagnostic test [4]. However, false negative urine Histoplasma antigen results have been reported in patients with documented disseminated infection [5].

A unique manifestation of this case was the spontaneous drainage from the neck of a large volume of caseous material containing calcified stones. This process was analogous to lithoptysis, a well-known manifestation of either pulmonary histoplasmosis or tuberculosis that occurs when calcified mediastinal lymph nodes erode into the airway [6,7]. Rarely, mediastinal nodes can rupture and fistulize to the neck [8]. The calcification of healed granulomas is a hallmark of healed histoplasmosis [9]. Our patient likely had disseminated histoplasmosis years prior to her presentation in 2020, involving neck lymph nodes which then became effaced by calcified granulomas, later rupturing and causing a lymphocutaneous fistula. There was no apparent evidence of tuberculosis, and the response to antifungal therapy provided strong support for the diagnosis of histoplasmosis.

The issue of whether *H. capsulatum* organisms can remain viable within calcified lymph nodes for prolonged periods, and then reactivate years later in a manner akin to *Mycobacterium tuberculosis* infection, has been debated and remains unsettled [10–13]. In our patient, it seems likely that fungi persisted within granulomas for a period of 8 years prior to causing progressively worsening symptomatic infection. No fungal cultures were conducted in 2020 after the infection recurred, but

the strongly positive complement fixation and immunodiffusion serologies, in conjunction with clinical signs of worsening disease, were consistent with active rather than remote infection.

The timing of the onset of the copious drainage of caseous material, 8 days after the initiation of itraconazole, suggested an inflammatory response to lysed *H. capsulatum* organisms. Post-Infectious Inflammatory Response Syndrome (PIIRS), a recognized manifestation of tuberculosis [14] and cryptococcosis [15], has been reported in a single patient with central nervous system histoplasmosis (Histo-PIIRIS) [15]. The proposed criteria for Histo-PIIRIS include worsening clinical status despite appropriate antifungal therapy; improving laboratory parameters (serology or antigen); and laboratory evidence of cerebrospinal fluid immune activation [16]. Our patient did not have antigenuria, and serology studies were not repeated. Thus, she did not fulfill criteria for Histo-PIIRS; however, the exacerbation of her illness after the initiation of antifungal therapy raises the possibility that PIIRIS could occur outside the central nervous system.

Conclusions

Histoplasmosis-induced lithiasis is not limited to the respiratory tract. The reactivation of latent infection appears plausible. Patients with histoplasmosis are at risk for paradoxical transiently worsening local inflammation, either in the central nervous system or elsewhere, while receiving ultimately effective antifungal therapy.

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