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CASE STUDY

Suspected Case of Histoplasmosis-Related Immune Reconstitution Inflammatory Syndrome Manifesting as Unilateral Pleural Effusion

Van Anh Do[1], Raihaan Khattak[2], Jacqueline Kropf[3], Patricia Couto[2], and Steve J. Carlan[4,*]

ABSTRACT

Background: **Histoplasmosis is a prevalent endemic mycosis that frequently causes opportunistic infections among individuals living with HIV (human immunodeficiency virus), and acquired immunodeficiency syndrome (AIDS). The initiation of antiretroviral therapy (ART) can result in a rare histoplasma-associated immune reconstitution inflammatory syndrome (IRIS) that may be difficult to distinguish between active progressive disease and inflammatory reaction to the medication.**

Case report: **A 35-year-old male with newly diagnosed HIV and cervical biopsy-confirmed histoplasmosis was admitted from the emergency department with disseminated histoplasmosis for HIV antiretroviral treatment and antifungal treatment. Discharged after a 2-week inpatient treatment the patient returned 1 week later with a large left pleural effusion. Two liters of serosanguinous fluid were removed and all fluid cultures and cytology were negative. An extensive work-up remained negative, and given the timeline of presentation in relation to the initiation of ART, it was felt that this isolated left-sided pleural effusion was a manifestation of IRIS. Eventually, corticosteroids were given for IRIS and the patient improved and was discharged on long-term treatment.**

Conclusions: **Immunocompromised subjects are at serious risk for a virulent, aggressive, rapidly advancing histoplasma infection and should be counselled accordingly. Any clinical signs or symptoms of organ system deterioration or compromise should be reported to the provider and a workup for histoplasmosis considered. In patients treated with antiretrovirals, IRIS is particularly confounding since it is difficult to differentiate from active disease. Using corticosteroids in already immunocompromised patients with an established fungal infection requires caution. Compliance with treatment is one of the most important components of care, especially considering the months of protocol.**

Keywords: Antiretroviral therapy (ART), Histoplasmosis, human immunodeficiency virus (HIV) infection, immune reconstitution inflammatory syndrome (IRIS).

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[1] Department of Internal Medicine, Orlando Regional Medical Center Orlando, USA.
[2] Department of Infectious Disease, Orlando Regional Medical Center Orlando, USA.
[3] Department of Hematology and Oncology, Orlando Regional Medical Center Orlando, USA.
[4] Division of Academic Affairs and Research, Orlando Regional Medical Center Orlando, USA.

**Corresponding Author:*
e-mail: stevecarlan@gmail.com

1. Background

Histoplasma capsulatum is a dimorphic fungus endemic to certain regions of the world, especially the Mississippi and Ohio River valleys in the United States [1]. It frequently causes opportunistic infections among individuals living with HIV (human immunodeficiency virus), and acquired immunodeficiency syndrome (AIDS). Histoplasmosis typically clinically presents as primary lung pathology but also is known to disseminate to other parts of the body [2]. The initiation of antiretroviral therapy (ART) is typically advisable for those with acute histoplasmosis and human immunodeficiency virus (HIV) infection [3]. However, a small subset of patients can develop histoplasma-associated immune reconstitution inflammatory syndrome (IRIS) when treatment with ART is initiated. IRIS is uncommon but can manifest in a

variety of disease presentations. The condition generates significant morbidity and the constellation of symptoms poses a difficulty for clinicians because they must discriminate between inadequately treated infection, new infection, or exaggerated host response, among other things [4]. We present a 35-year-old male with newly diagnosed HIV who developed IRIS associated with histoplasmosis which manifested as an isolated pleural effusion.

2. Case Report

We present the case of a 35-year-old male who initially presented to our emergency department complaining of severe abdominal pain. The patient moved from Ecuador 1 year ago and had been in good health until 2 months prior when he developed tender cervical lymphadenopathy. He saw an ear, nose, and throat (ENT) physician who ordered a computed tomographic (CT) soft tissue neck that showed prominent cystic or necrotic bilateral cervical lymphadenopathy (Fig. 1). A core biopsy of right neck lymphadenopathy showed a yeast fungal organism with features suggestive of histoplasmosis without malignancy. The patient left to visit Ecuador and was informed of his diagnosis while he was there. He saw a physician overseas and was prescribed itraconazole; however, the patient discontinued the medication after five days due to side effects.

In the emergency department, the patient was febrile, and tachycardic, and exhibited jaundice, bilateral icterus, and exquisitely tender hepatosplenomegaly. He also had generalized lymphadenopathy with tender swelling of the right neck on physical examination. Initial laboratory analysis revealed a white blood cell count of 8.2 g/uL, hemoglobin of 8.7 g/dL, platelet count of 57 k, creatinine of 2.22 mg/dL, blood urea nitrogen (BUN) of 4.7 mg/dL, aspartate aminotransferase (AST) of 200 U/L, alanine aminotransferase (ALT) of 77 U/L, alkaline phosphatase of 500 U/L, and total bilirubin of 2.8 mg/dL. His HIV screening was positive, and he denied any prior knowledge of HIV infection. He was found to have a CD4+ count of 9.4 cells/mL3 and a plasma HIV RNA viral load of 47,300 copies/ml. Initial imaging included a CT scan of the chest that showed small bilateral pleural effusions, and a magnetic resonance imaging (MRI) of the abdomen and pelvis revealed, hepatosplenomegaly, with possible splenic infarcts, pericholecystic fluid, and gallbladder wall thickening (Fig. 2).

A cell-free microbial DNA next-generation sequencing test was positive for Histoplasma capsulatum, and Kaposi Sarcoma-associated herpesvirus. The patient subsequently underwent a repeat right cervical lymph node excision that showed a lymph node with necrotizing granulomatous inflammation, positive for histoplasmosis by Periodic acid-Schiff stain-green and Grocott's methenamine silver stains. No acid-fast microorganisms were identified by acid-fast bacillus (AFB) stain and were negative for lymphoma or Kaposi Sarcoma.

Based on the previous biopsy results, the decision was made to start treatment with liposomal amphotericin B 3 mg/kg daily for 14 days for disseminated histoplasmosis. The patient also started Antiretroviral therapy (ART) with Bictegravir, emtricitabine, and tenofovir alafenamide (Biktarvy). Shortly after beginning treatment, the patient developed worsening anemia with a hemoglobin of 5.6 g/dL, platelet count of 32 g/uL, and white blood cell count of 8.7 g/uL. A bone marrow biopsy was performed to help rule out other possible infectious causes and further work up his anemia. The bone marrow aspirate smear revealed numerous yeast cells consistent with extracellular and intracellular yeast forms of Histoplasma capsulatum (Fig. 3). He completed the 14-day course of liposomal amphotericin and started on oral Itraconazole. After a 2-week hospitalization, his symptoms had significantly improved, and he was eventually discharged on Biktarvy, Itraconazole, and trimethoprim/sulfamethoxazole for Pneumocystis jirovecii pneumonia prophylaxis.

The patient returned to the Emergency Department about 1 week later with complaints of severe shortness of breath and left-sided chest discomfort. A chest x-ray and Computerized Tomography (CT) of the chest revealed a near complete left-sided pleural effusion that required chest tube placement (Fig. 4). Two liters of serosanguinous fluid were removed. Fluid studies revealed 869 WBCs, 189,000 RBCs, 53% lymphocytes, 20% neutrophils, glucose

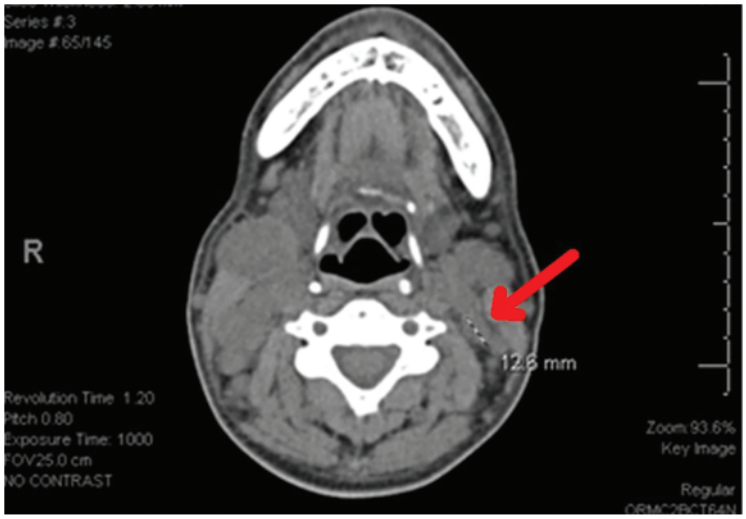

Fig. 1. CT soft tissue of the neck shows cervical lymphadenopathy (red arrow).

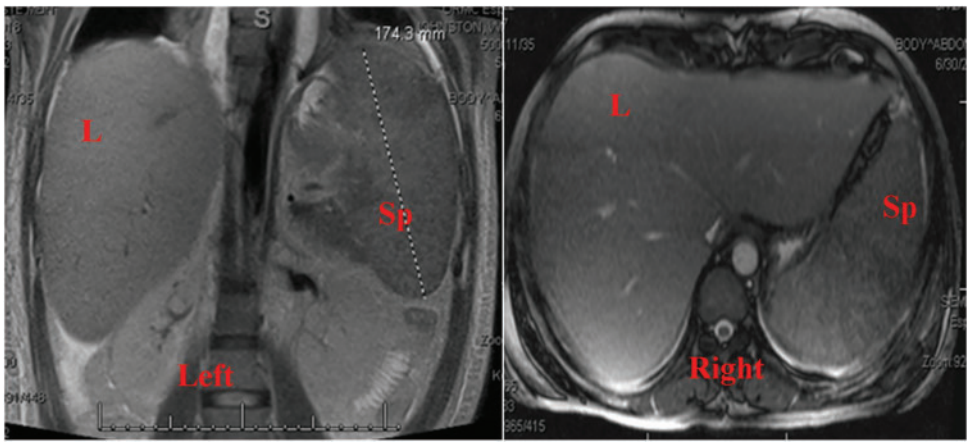

Fig. 2. Coronal (left) and transverse (right) MRI of the abdomen and pelvis revealed hepatosplenomegaly, moderate splenomegaly with possible splenic infarcts, general pericholecystic fluid, and gallbladder wall thickening. L: liver, Sp: spleenç.

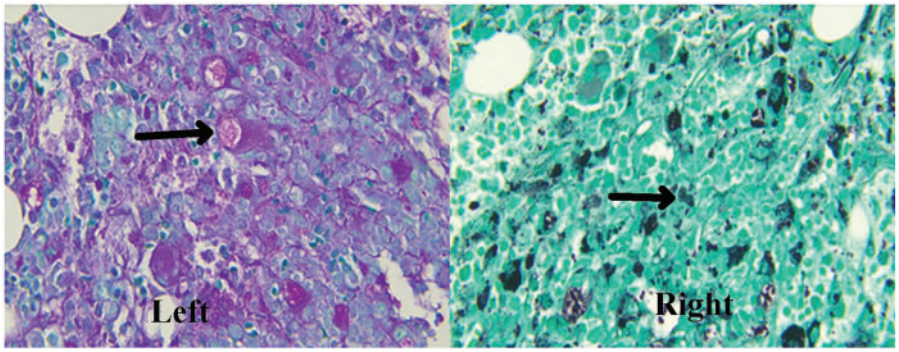

Fig. 3. Bone marrow core reveals the presence of multiple small narrow-based budding yeast within the cytoplasm of numerous macrophages on both Hematoxylin and Eosin (left) and Grocott's methenamine silver stain (right).

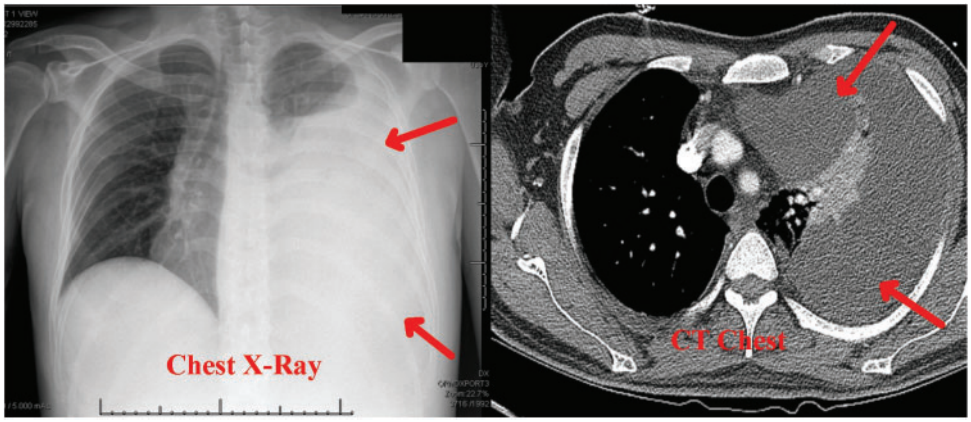

Fig. 4. Chest x-ray and computerized tomography (CT) performed during admission showed near complete left-sided pleural effusion (arrows) with atelectatic changes.

89, lactic dehydrogenase (LDH) 95, protein 4.6, and pH 7.75. Aerobic, anaerobic, fungal, and AFB cultures were all negative. Cytology was negative for malignancy.

Our initial differential was broad and included parapneumonic effusion or empyema, Human herpes virus-8 (HHV-8)-associated primary effusion lymphoma, tuberculosis, or nontuberculous mycobacteria infection, and even autoimmune diseases such as Castleman's and Kikuchi's disease. However, our extensive work-up remained negative, and given the timeline of presentation in relation to initiation of ART, it was felt that this isolated left-sided pleural effusion was a manifestation of IRIS.

He was started on steroids and experienced rapid improvement in his symptoms. He had the chest tube removed after 1 week and was discharged in stable condition. He had monthly follow-up visits with the Infectious Disease clinic and has recovered back to normal health.

3. Discussion

Histoplasmosis is a fungal infection commonly found in individuals with HIV, especially in regions where the disease is endemic. The incidence of histoplasmosis in HIV-infected individuals is much higher than that of the general population, and the risk increases as CD4 count

declines [1]. The primary mode of transmission is through inhalation of fragments of contaminated soil [2]. Most individuals with histoplasmosis are asymptomatic or have mild symptoms that resolve without treatment. However, in individuals with weakened immune systems, especially those with advanced HIV infection, the disease can disseminate and cause significant morbidity and mortality [2].

The exact mechanism of the pathogenesis of histoplasmosis is not well understood, but it is believed to involve the release of fungal antigens and the activation of the host immune response. The fungus grows as a yeast in tissues and can spread to other parts of the body, including the liver, spleen, and lymph nodes [3]. The immune response to the fungal antigens results in the formation of granulomas and tissue damage [1], [3]. The severity of the disease is determined by the balance between the host's immune response and the fungal burden.

IRIS is a well-known condition in the context of opportunistic infections, including histoplasmosis. It is a phenomenon where patients develop new or worsening symptoms after the initiation of ART in individuals with HIV infection [4]. IRIS occurs as a result of the improvement of the immune system in response to ART, leading to an increased ability to mount an immune response against previously controlled infections [4]. The paradoxical immune reaction results in increased inflammation and tissue damage.

The exact mechanism of IRIS is not well understood, but it is believed to be related to the release of cytokines and other immune mediators in response to dying fungal cells. The incidence of IRIS varies depending on the specific opportunistic infection, with higher rates reported for mycobacterial infections [1], [4].

IRIS in the context of histoplasmosis is a rare but crucial phenomenon. There have been several reported cases of pleural effusion as a manifestation of the initial primary infection with the organism, however, we could not find any cases of IRIS-associated pleural effusion. No report has been published, to our knowledge, of a case of an HIV-positive individual with disseminated histoplasmosis infection. The diagnosis of IRIS is typically made based on the presence of new or worsening symptoms after ART initiation in the context of a positive histoplasmosis diagnosis [5]. The clinical presentation of IRIS can vary, but common symptoms include fever, night sweats, and increased respiratory symptoms such as cough, shortness of breath, and in our case an isolated pleural effusion [4], [5].

The treatment of disseminated histoplasmosis and IRIS typically involves antifungal therapy and management of inflammation [4]. Amphotericin B is the most commonly used antifungal medication for disseminated histoplasmosis and depending on the severity of the disease is generally followed by a course of oral Itraconazole for up to 1 year [3]–[5]. In cases of IRIS, antifungal therapy is continued, and corticosteroids may be added to reduce inflammation and control symptoms. The duration and dose of corticosteroids depend on the severity of symptoms and the individual patient's response.

4. Conclusions

Our case highlights a rare and unusual presentation of histoplasmosis associated with IRIS and reminds us of the importance of close monitoring of patients in the weeks immediately following the initiation of ART. Further studies are necessary to better characterize and understand the findings and risk factors associated with IRIS.

Data Availability

All data underlying the results are available as part of the article and no additional source data are required.

Conflict of Interest

Authors declare that they do not have any conflict of interest.

Abbreviations

HIV: human immunodeficiency virus
ART: antiretroviral therapy
IRIS: immune reconstitution inflammatory syndrome
AIDS: Acquired immunodeficiency syndrome
ENT: ear, nose, and throat
CT: computed tomographic
BUN: blood urea nitrogen
AST: aspartate aminotransferase
ALT: alanine aminotransferase
AFB: Acid-Fast Bacillus
LDH: lactic dehydrogenase
HHV-8: Human herpes virus-8

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