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PUBLISHED ABSTRACT

Disseminated Histoplasmosis with Liver Involvement in a Job's Syndrome Patient

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Introduction

Autosomal dominant hyper-IgE syndrome (AD-HIES), also known as Job's syndrome, is caused by dominant negative mutations in signal transducer and activator of transcription 3 (STAT3), the key transcriptional factor for many cytokines and growth factors that are essential for the homeostasis of immune and nonimmune systems. Patients with Job's syndrome have reduced Th17 cell numbers and functions, impaired neutrophil functions and adaptive immunity, which compromise their abilities to overcome fungal infections. While healthy individuals are asymptomatic with histoplasmosis, immunocompromised patients are susceptible to invasive histoplasmosis. We present the first case of disseminated histoplasmosis with liver involvement in a Job's syndrome patient.

Case presentation

In September 2019, a 22-year old male with Job's syndrome was presented to ED due to a 2-month history with an oral ulcer, shortness of breath, productive cough, chest pains and weight loss, with worsening symptoms and fever for 2 days. He has PMH of early onset severe atopic dermatitis, skin cold abscesses, recurrent sinopulmonary infections, Hodgkin's lymphoma, mucocutaneous candidiasis, a wrist facture a from minor trauma, and right pneumonectomy for a massive hemoptysis and pulmonary embolism resulting from lung aspergilloma. He was diagnosed with Job's syndrome at age 3, with the NIH diagnosis score of 44. There was no FHx of primary immunodeficiency. He has a hot spot STAT3 loss of function (LOF) mutation (c1144C>T, R382W) in the DNA-binding domain, and was usually treated with prophylactic bactrim DS, voriconazole and monthly intravenous immunoglobulin (IVIG), with lapses of noncompliance. On admission, the physical exam revealed Job's syndrome facies, retained primary teeth, mild tachypnea, left lower lobe crackles, hepatomegaly and mild scoliosis. Chest CT scan revealed bronchiectasis, multiple nodular and cavitary lesions in the left lung (**Figure 1**, Image on the left). Bronchial alveolar lavage cytopathology identified fungal filaments. Laboratory findings were essentially normal except for extremely elevated liver transaminases (alanine aminotransferase at 412, aspartate aminotransferase at 593, alkaline phosphatase at 2,476, Gamma-glutamyl transferase at 1,362). Subsequent liver ultrasound and MRCP (**Figure 1**, Image on the right) revealed liver cysts, biliary dilatation and mixed cholestasis. An extensive work up was performed, including blood, respiratory, urine and spinal fluid cultures, stool cultures with ova, parasites and Clostridium Difficile, and tests for cryptococcal antigen, HSV, CMV, HCV and HBV, and all tests were negative. Culture of the liver abscess drainage identified *Histoplasma capsulatum*. The initial serum histoplasma antigen was negative, though urine histoplasma antigen became positive 2 months later. The patient was treated with broad-spectrum IV antibiotics for pneumonia and a 7-day course of IV amphotericin B, followed by a short course of oral posaconazole; he was then transitioned to oral itraconazole. Immunoglobulin was infused as part of the immunotherapy. Subsequently, the patient's symptoms and liver enzymes slowly improved over months. His liver infection was complicated by biliary obstruction and common bile due stenosis, which were treated with endoscopic retrograde cholangio-pancreatography (ERCP) sphincterotomy, and stenting as well as oral ursodiol. He continues oral itraconazole therapy and receiving multispecialty cares as an outpatient.

Discussion

Histoplasmosis is quite uncommon in the New York State. Our patient, a New York resident, just had travel to the endemic area of City Caracas, Venezuela, 6 months prior to the presentation. To date, a total of 9 cases of histoplasmosis in Job's syndrome patients have been reported in the literature. Eight patients had localized infections in the tongue, larynx, lung, brain, and the gastrointestinal and genitourinary tracts, and one patient had a disseminated histoplasmosis. Our case is unique in its liver involvement.

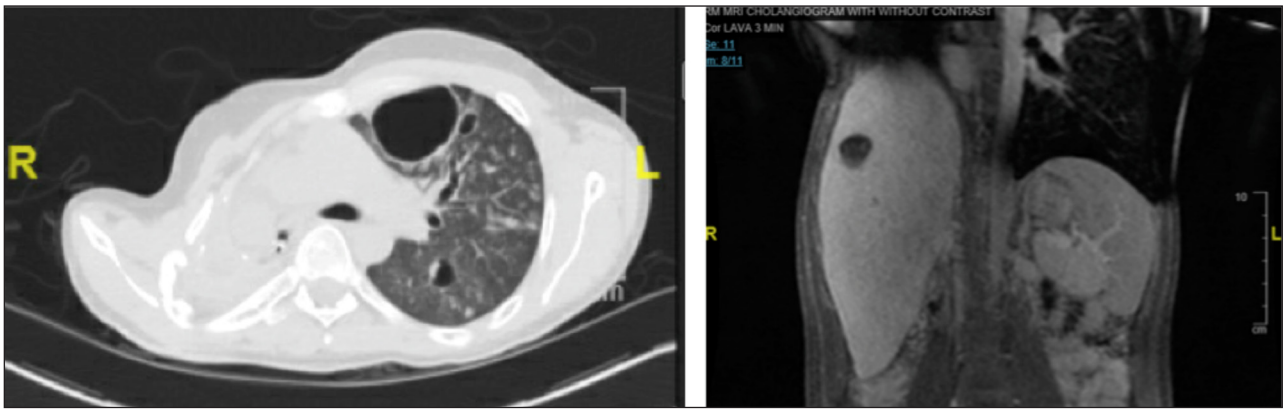

Figure 1: Left: Chest CT without contrast; Right: MRCP.

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