Primary Abdominal Disseminated Histoplasmosis Infection in a Patient on TNF-α Inhibitor Therapy Mimicking Intestinal Carcinoma

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Abstract

Histoplasmosis capsulatum is a dimorphic fungus often associated with opportunistic infections in immunocompromised patients. Many patients who take immunosuppressive medications for chronic inflammatory conditions are at increased susceptibility for Histoplasmosis infections. Pulmonary infection is the most common form of Histoplasmosis with risk for dissemination in immunocompromised populations. Other common clinical manifestations occur in the skin, adrenal glands, heart (endocarditis), or central nervous system.

This case involves a 68-year-old female from eastern Oklahoma with a fifteen year history of rheumatoid arthritis treated with infliximab and leflunomide who developed an atypical presentation of disseminated Histoplasmosis. Her initial symptoms of abdominal pain and weight loss were mimicked an abdominal malignancy. However, pathology revealed Histoplasmosis infection which responded to surgery and antifungal therapy for resolution of infection.

Introduction

Histoplasmosis capsulatum is the most prevalent endemic mycosis in the United States and is typically found in the Ohio River Valley region.[1,2] Asymptomatic or self-limited infection is common in immune competent individuals, but severe pulmonary infections or disseminated

disease can present as an opportunistic infection in immunocompromised patients. T cell immunity plays the predominant role in recovery from Histoplasmosis infection.[3] Once cellular immunity to Histoplasma develops, macrophage activation leads to interleukin (IL)-12 and interferon (IFN)-gamma activation and death of the invading organism.[3,4] Failure to activate macrophage fungicidal capacity appears to be the key defect in immunity to H. capsulatum in patients with progressive disseminated histoplasmosis. Risk factors for dissemination or reactivation of H. capsulatum include extremes of age, AIDS, hematologic malignancy, the use of prolonged corticosteroids, Tumor Necrosis Factor (TNF) antagonists, or other immunosuppressive agents.

In patients with inflammatory conditions like rheumatoid arthritis, TNF-α inhibitors halt disease progression but carry an inherent risk of lowering the immune system by decreasing macrophage activation and recruitment of neutrophils, macrophages, and impairment of granuloma formation. Leflunomide is also an immunosuppressant used to treat rheumatoid arthritis in the class of disease modifying antirheumatic drugs (DMARDS). This medication works uniquely by depleting intracellular pyrimidine, therefore reducing RNA synthesis.[5]

Case Report

A 68-year-old female from eastern Oklahoma presented to a community hospital with a three to four month history of weight loss (fifteen kilograms), nausea, vomiting, and abdominal pain. Her past medical history included a fifteen year history of rheumatoid arthritis which had been treated with infliximab infusion every eight weeks, leflunomide 10 mg daily, and intermittent oral corticosteroids for approximately ten of the fifteen years. The physical exam was significant for diffuse abdominal tenderness and synovitis of the proximal interphalangeal joints of her hands and feet. A CT scan of the abdomen and pelvis was performed which was interpreted as mesenteric panniculitis with moderate ascites without adenopathy. Because of worsening abdominal pain and vomiting, a follow up CT scan of the abdomen/pelvis was performed 48 hours later and showed findings consistent with omental carcinomatosis leading to an exploratory laparotomy. The surgeon identified intra-abdominal lesions with extensive small and large bowel involvement as well as omental adhesions. Biopsy showed fungal elements consistent with Histoplasmosis without evidence of malignancy. Blood cultures were positive for Candida albicans. A CT scan of her brain was unremarkable and a lumbar puncture was performed and was negative for fungal, bacterial, and viral cultures. She was found to have a positive urinary Histoplasma antigen as well as an elevated serum Histoplasma antigen. Testing for HIV was negative. Treatment with

intravenous amphotericin B lipid formulation was administered for fourteen days followed by a transition to oral itraconazole for a recommended total duration of one year.

Discussion

Histoplasmosis capsulatum is the most prevalent endemic mycosis in the United States and typically found in the Ohio River Valley, which includes the endemic region in which the patient presented.[1,2] Histoplasma capsulatum is acquired through inhalation of mycelial fragments and microconidia, typically from soil. Severe or disseminated Histoplasmosis often affects immunocompromised patients with pulmonary infections, but less common sites of infection include the skin, adrenal glands, heart (endocarditis), or central nervous system.[3-9] Immune competent patients often develop asymptomatic or self-limited diseases. Innate immunity is the primary defense mechanism with T cells playing the predominant role.[6,7] TNF-α is important for macrophage activation, phagosome activation, differentiation of monocytes into macrophages, recruitment of neutrophils and macrophages, granuloma formation, and maintenance of granuloma integrity.[7] The key defect in immunity leading to disseminated disease is failure of macrophage fungicidal ability to form granulomas.[9,10] Studies in animals have demonstrated the importance of TNF-α in protection against several pathogens including Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium bovis, Bacillus Calmette-Guérin (BCG), Aspergillus fumigatus, Histoplasma capsulatum, Toxoplasma gondii, Cryptococcus neoformans, and Candida albicans.[5,8,11]

TNF-α was discovered to be the driver of inflammatory cytokine production via monocytes/macrophages. This cytokine was initially studied for its apoptotic properties for anticancer therapy, but studies showed high toxicity in cancer treatment with longitudinal studies showing data for and against increased risk of malignancy. Further research elucidated its role in inflammatory conditions, leading to the approval of the first TNF-α inhibitor, etanercept, in 1998 for clinical use in rheumatoid arthritis.[12] In addition to increased infection risk, other side effects include injection site reactions, infusion reactions, neutropenia, demyelinating disease, heart failure, malignancy, or induction of autoimmunity.[3,13]

DMARDS are a class of drugs used to treat a variety of rheumatologic conditions with the goal to induce remission, reduce frequency of relapse, and allow tapering of steroids. These are typically used for treatment of rheumatoid arthritis before initiation of TNF-α therapy. Leflunomide is a DMARD that works uniquely by inhibiting synthesis of a pyrimidine known as ribonucleotide uridine monophosphate pyrimidine, therefore reducing RNA

synthesis.[14] Side effects include hepatotoxicity and infection risk, although this medication is typically not immunosuppressive enough to be associated with disseminated Histoplasmosis when used as monotherapy. In the largest single center series of patients with rheumatoid arthritis and histoplasmosis in the era of immunomodulatory therapy, most patients were on combination therapies: 58% were on anti-TNF agents, 58% on corticosteroids, and 81% on methotrexate. Leflunomide was involved with 19% of infections, but never as a solo treatment. [15]

A review of 240 cases reported to the FDA Adverse Event Reporting System of H. capsulatum infections associated with TNF-α inhibitor use was performed. The findings of the review yielded the following results: 90% of patients were treated with infliximab and 10% with etanercept; All patients were from endemic regions; In the cases associated with infliximab, symptoms of infection presented within one week to six months of the first dose; Typical presentation includes fever, malaise, cough, dyspnea, and interstitial pneumonitis.[10]

Another small case series of nineteen patients who presented to the Indiana University Medical Campus between 2000-2009 with histoplasmosis while receiving a TNF-α inhibitor revealed that progressive febrile illness was present in seventeen patients (89%). Fifteen patients (79%) had pulmonary involvement. Fifteen patients (79%) were hospitalized, and four (21%) developed respiratory failure and shock. All nineteen patients recovered.[16]

Colonic Histoplasmosis is a rare and difficult diagnosis. Colonic Histoplasmosis occurs in 3-12% of disseminated H. capsulatum cases, although gastrointestinal tract involvement is identified during autopsy in as many as 70-75% of cases. It can affect any portion of the GI tract with 120 case reviews of anatomic distribution during autopsies reporting tongue/buccal cavity involvement in fifteen patients, esophagus in two, stomach in three, small intestine in forty (three in the duodenum, four in the jejunum, and thirty-eight in the ileum), appendix in seven, and thirty-four in the colon. Granuloma formation occurred in 69% of cases. The cases all had vague symptoms at presentation of crampy abdominal pain followed by diarrhea. Typical pathologic findings showed mucosal ulceration, diffuse lymphohistiocytic infiltration of the bowel wall, submucosal nodules, polypoid lesions, and obstructing masses. Imaging findings included hepatosplenomegaly, generalized lymphadenopathy, diffuse interstitial pulmonary infiltrates. In most cases studied, the greatest incidence was in liver transplant patients.[17-19] Overall, there was a good prognosis if treated with antifungal therapy promptly.

This case presentation involves a 68-year-old female with rheumatoid

arthritis whose primary symptoms were weight loss, nausea, and vomiting. Her treatment history included more than ten years of TNF-α inhibitor therapy with infliximab in combination with leflunomide. Intra-abdominal (reactivation or subacute) H. capsulatum infection was histologically confirmed. She had confirmed infection with both H. capsulatum and C. albicans, although C. albicans was isolated from blood cultures. Initial imaging and exploratory laparotomy suggested a diagnosis of abdominal carcinomatosis. She had no initial presenting symptoms of cough, dyspnea, or pulmonary involvement.

This case helps to highlight the vigilance needed in suspecting disseminated Histoplasmosis cases involving the GI tract as well as other organ systems in all immunosuppressed patients, particularly in those living in endemic regions, even when primary pulmonary manifestations are not identified. Vigilance must be maintained even after years of being on immunosuppressant medications. Imaging, surgical, urine assay, and serum antibody titers all aid in the detection of this disease process. Outcomes are promising with prompt evaluation and treatment.

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