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Histoplasmosis Related to Immunosuppression in a Patient with Crohn's Disease: A Diagnostic Challenge

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Patient: Male, 39-year-old
Final Diagnosis: Disseminated histoplasmosis
Symptoms: Fever • profuse sweating • splenomegaly • abdominal pain
Medication: —
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology

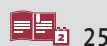
Objective: Unusual clinical course
Background: Infliximab, a monoclonal antibody against tumor necrosis factor (TNF) alpha with proven efficacy and known safety profile, is currently widely used in the treatment of inflammatory bowel diseases. Increased risk for serious infections and malignant neoplasms secondary to immunosuppression is a major concern during therapy with this medication. Histoplasmosis is a granulomatous disease caused by the fungus *Histoplasma capsulatum*. Disseminated forms of the disease have immunodepression as a major risk factor.

Case Report: A 39-year-old man had been followed with refractory fistulizing ileocolonic Crohn's disease using combination therapy (infliximab plus azathioprine) and also receiving short courses of steroids. After 2 years of this immunosuppressive therapy, the patient presented with high fever (39.5°C) for 5 days, associated with profuse sweating, and moderate pain in the left hypochondrium. The patient was hospitalized. Diagnoses of tuberculosis, malignancy, autoimmune diseases, and bacterial and viral infections were rapidly discarded after investigation. Clinical, laboratory, and image signs of liver involvement prompted a guided percutaneous biopsy, which revealed granulomatous hepatitis, with the presence of fungal structures suggestive of *Histoplasma capsulatum*. Upon treatment with liposomal amphotericin followed by itraconazole, the patient showed an impressively positive clinical response.

Conclusions: TNF blockers, particularly when associated with other immunosuppressors, are a serious risk factor for opportunistic infections. This unusual case of disseminated histoplasmosis in a patient with Crohn's disease using infliximab in combination with azathioprine and steroids emphasizes the need for surveillance of this uncommon but potentially lethal complication before starting TNF blockers therapy.

Keywords: Crohn Disease • Histoplasmosis • Tumor Necrosis Factor-alpha

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/925345>



Background

During the last 2 decades, a new paradigm emerged in the treatment of inflammatory bowel diseases (IBD), leading to the increased use of antibodies against tumor necrosis factor alpha (anti-TNF- α) (infliximab, adalimumab, certolizumab pegol, and golimumab) [1]. They were originally used for the treatment of moderate to severe active Crohn's disease (CD), but recently were approved for more severe forms of severe ulcerative colitis (UC) [2-5].

Histoplasmosis is a systemic granulomatous disease acquired by inhalation of microconidia from the fungus *Histoplasma capsulatum*, which is found in soil and in the droppings of birds and bats and is endemic in several regions in Brazil [6,7].

The disease's clinical presentation may vary according to the patient's immunity, and immunodepression is a major risk factor for the development of more severe forms of the disease, such as disseminated histoplasmosis. This may manifest with a variety of symptoms, including fever (91%), cough (65%), hepatosplenomegaly or lymphadenopathy (52%), weight loss (48%), and anemia (39%). Usually, the primary infection in an immunocompetent host is generally asymptomatic or presents as a self-limiting flu-like illness [8].

Among the most worrisome adverse effects of anti-TNF- α are the increased risk of developing serious infections, such as tuberculosis (TB), other opportunistic bacterial infections, systemic mycoses, such as histoplasmosis, which may appear in the disseminated form, and reactivation of latent viral infections, as well as malignancies. Thus, surveillance before starting TNF blockers therapy and close monitoring of patients afterwards are needed to increase patient safety [9,10].

We herein report an unusual case of disseminated histoplasmosis in a patient with Crohn's disease using anti-TNF- α (infliximab) in combination with azathioprine and corticosteroids.

Case Report

A 39-year-old white man in outpatient follow-up due to ileocolonic CD presented with fever in a routine outpatient visit. CD had been diagnosed 11 years before, after a segmental small bowel resection due to enteric-enteric fistulas. For over 3 years, the patient had been receiving immunosuppressive therapy with azathioprine 150 mg daily (2.0 mg/kg) and infliximab (IFX) maintenance therapy (5 mg/kg every 8 weeks). During follow-up, despite receiving this combo therapy, he had presented a few episodes of disease activity, requiring courses of steroids. He also reported frequent trips to the interior of the Brazilian states of Minas Gerais and Goiás, besides

contact with birds and poultry in his residence. In a routine visit, he was found to be in clinical and endoscopic remission of CD but presented with high fever (39.5°C) for 5 days, with profuse sweating and moderate pain in the left hypochondrium. He denied urinary and respiratory symptoms and reported passing well-formed stools once a day. Physical examination revealed a bulky splenomegaly. The patient was then hospitalized for investigation, and the treatment for IBD was entirely suspended on this occasion. Laboratory data on admission revealed an increase of aspartate amino transferase (AST) of 291 U/L (reference value: 41 U/L), alanine amino transferase (ALT) of 119 U/L (reference value: 38 U/L), normal canalicular enzymes, and slightly elevated C-reactive protein of 3.1 mg/dL and bilirubin (total bilirubin of 1.7 mg/dL, indirect bilirubin of 1.1 mg/dL). Screening by bacterial cultures, tuberculosis (tuberculin test, polymerase chain reaction and culture), serological tests for viral hepatitis, HIV, syphilis, antigenemia, and polymerase chain reaction (PCR) for cytomegalovirus (CMV) and Epstein-Barr virus were negative. Plain chest radiographs did not show any abnormality. Further evaluation included computed tomography (CT) scans of the thorax and abdomen. The chest CT scan evidenced a pulmonary nodule on the right lung with a halo in "frosted glass", suggesting an infectious process, and right and mediastinal hilar lymph node enlargement. The abdominal CT scan showed hepatosplenomegaly, periaortic abdominal lymph node enlargement, hepatic steatosis, and bilateral renal lithiasis.

The patient evolved with maintenance of fever and gradual clinical worsening, with onset of mild dyspnea, dry cough, and jaundice with a total bilirubin peak of 23.22 mg/dl (17.13 mg/dl of direct bilirubin), in addition to elevation of aminotransferases (AST of 336 U/L and ALT of 191 U/L), pancytopenia, and acute renal failure (creatinine of 5.66 mg/dL and urea of 126 mg/dL), which prompted referral to hemodialysis. A bone marrow needle aspiration revealed cytoplasmic inclusion in macrophages, suggesting an infectious process. Further tests included enzyme immunoassay (ELISA) for leptospirosis, serology for toxoplasmosis, and Wright's reaction, which were all negative. Counterimmunoelectrophoresis (CIE) for fungi was then found positive for *Histoplasma* until dilution 1: 8. It was then decided to perform a guided needle liver biopsy, which revealed granulomatous hepatitis, with presence of fungal structures suggestive of *Histoplasma capsulatum* (Figure 1). Therapy with liposomal amphotericin (1.0 mg/kg body weight) was then initiated, with gradual improvement of symptoms and recovery of renal function, as well as resolution of jaundice. After 6 weeks of treatment, the patient was discharged from the hospital and switched to oral itraconazole.

On 6-month follow-up, the patient was still using oral itraconazole, and the CIE for histoplasmosis was still positive, but only until the 1: 2 dilution. A new chest tomography performed 6

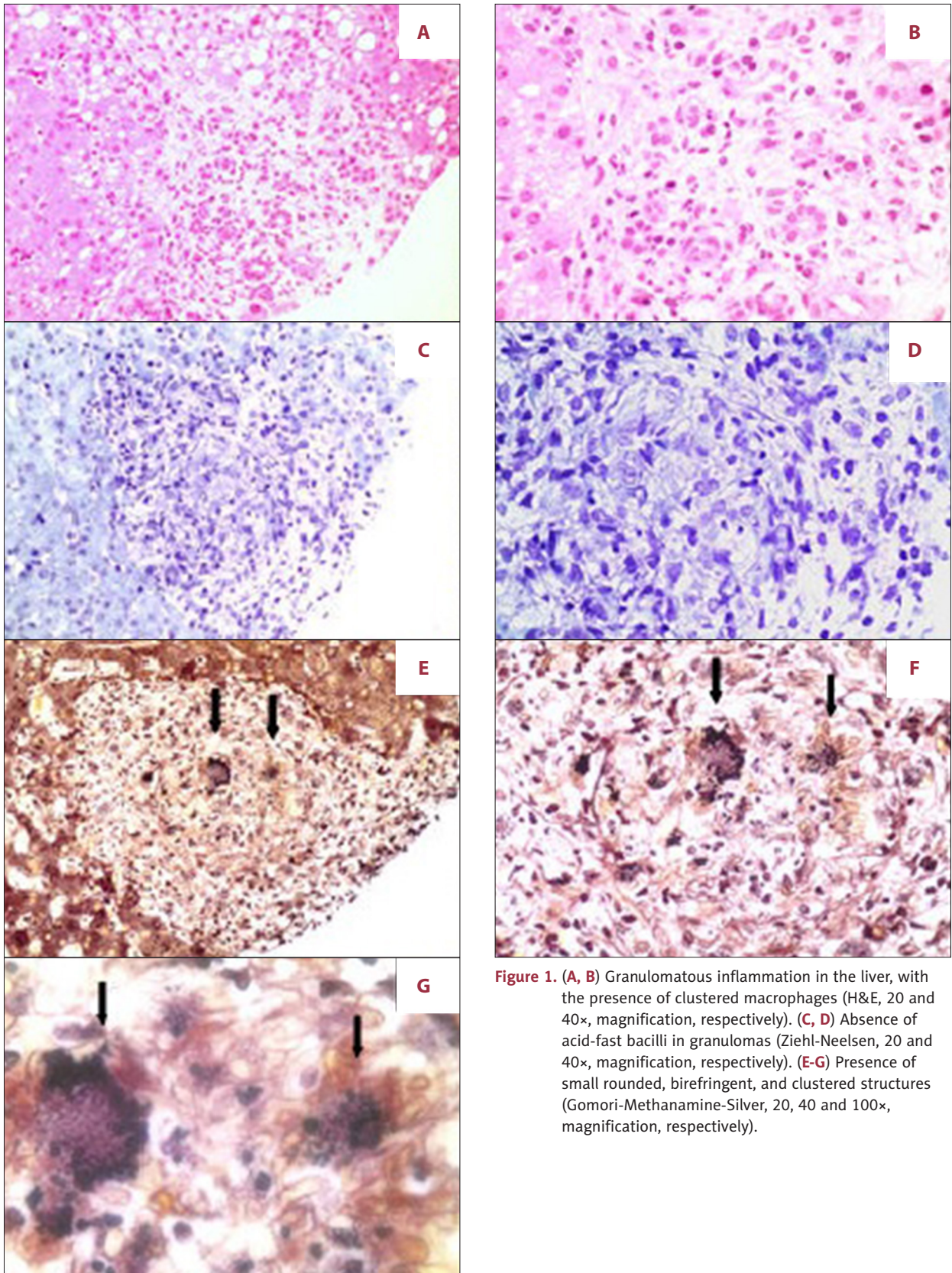


Figure 1. (A, B) Granulomatous inflammation in the liver, with the presence of clustered macrophages (H&E, 20 and 40 \times , magnification, respectively). (C, D) Absence of acid-fast bacilli in granulomas (Ziehl-Neelsen, 20 and 40 \times , magnification, respectively). (E-G) Presence of small rounded, birefringent, and clustered structures (Gomori-Methanamine-Silver, 20, 40 and 100 \times , magnification, respectively).

months after starting anti-fungal specific treatment showed complete resolution of the pulmonary nodule located in the right lung. At this time, treatment for CD was resumed with the reintroduction of azathioprine alone. Itraconazole was suspended after 12 months of uninterrupted use, after a new CIE for fungi tested negative.

Discussion

TNF- α is a proinflammatory cytokine produced by macrophages in response to stimuli such as oxidative stress or endotoxins. This agent has a key function in the immune system, since it stimulates the differentiation of monocytes into macrophages, the recruitment of neutrophils, and the formation of granulomas, thus playing an important role in the host defense system against infectious diseases [11]. Furthermore, TNF- α stimulates the production of interferon, which is crucial for both phagocytosis and fungicidal activity [12]. Inhibition of this cytokine by anti-TNF- α in the context of treatment of IBD may potentially reduce the efficacy of host immune function in defense against infectious organisms, thus leading to an increased risk of infections, including serious infections [13]. In general, the use of anti-TNF- α agents as a treatment option for IBD increases the odds of opportunistic infection by a factor of 3, and with the combination of 2 or 3 drugs, such as immune suppressors or corticosteroids, the odds ratio is increased to 14 [14].

Disseminated histoplasmosis represents a serious clinical condition, associated with dysfunctions of the host immune system and, more specifically, to impairment of cellular immunity that affects the T cells, thus allowing spread of the disease. However, only a small proportion of exposed individuals (<0.1%) actually develop disseminated disease [15].

Other cases of disseminated histoplasmosis associated with the use of infliximab in patients with Crohn's disease have been reported [10,16-18] in addition to a case of fatal *Histoplasma pneumoniae* in a patient with ulcerative colitis treated with IFX [19]. In a recent review based on medical reports from an area with moderate endemicity for histoplasmosis, a total of 357 cases of disseminated histoplasmosis were identified, 8 (2.2%) of whom were receiving TNF- α inhibitor therapy at the time of diagnosis. Five patients were receiving infliximab and 3 were receiving adalimumab [20]. Therefore, the risk of disseminated histoplasmosis in patients receiving anti-TNF- α is now widely recognized [17]. In these reports, similarly to ours, all patients had received immunosuppressive drugs concomitant with anti-TNF- α agents. A previous review of 19 patients diagnosed throughout a decade in a single academic center [18] showed that symptoms and signs of pulmonary involvement were present in 70-80% of cases. Although hepatic enzyme

elevation may occur in dissemination, an overt hepatitis-like presentation is uncommon [18,19]. In the case herein presented, despite the finding of a suspect pulmonary nodule, respiratory clinical manifestations were less impressive and there was overt jaundice. A granulomatous hepatitis, with presence of fungal structures suggestive of *Histoplasma capsulatum* in the liver tissue, was clearly demonstrated and provided the basis for the etiologic diagnosis and prompted anti-fungal therapy initiation.

On the other hand, common features between our case and other reports of disseminated histoplasmosis concern the diagnostic difficulty and a complete response to anti-fungal treatment, most likely helped by the cessation of the inciting TNF- α inhibitor [10,15].

Usually, the endogenous reactivation of old, mainly pulmonary, foci during a state of immunosuppression works as a trigger of the disseminated form of histoplasmosis. TNF- α blockade is nonetheless associated with an increase in the risk of infection by intracellular, granuloma-forming pathogens, such as *Histoplasma capsulatum* [11]. In the present case, the underlying immunosuppressive therapy of our patient (azathioprine and IFX, in addition to courses of corticosteroids) due to the character of Crohn's disease, in an individual with a history of contacts with birds and travel to areas endemic for histoplasmosis (mold sporulation can be accelerated by bat and bird feces), might have been a risk factor for reactivation of latent disease focus and evolution to disseminated form.

The diagnosis of disseminated histoplasmosis often presents a great challenge, considering that it can affect any organ, and this circumstance can contribute to a "chameleon-like" clinical image and diagnostic errors. Although with some limitations, such as false-positive reactions that can occur during the course of other fungal infections (eg, blastomycosis and paracoccidioidomycosis) and in the presence of malignant tumors, serological tests are useful adjuncts in the diagnosis of histoplasmosis, especially in the forms where positive cultures are rarely obtained. The complement fixation test (CF) or the immunodiffusion assay (ID) [21], followed by counterimmunoelectrophoresis (CIE), are the most commonly used tests for diagnosing systemic fungal infections, including histoplasmosis. The *Histoplasma* antigen can be detected in urine, serum, cerebrospinal fluid, or bronchoalveolar lavage [22-24]. Antigen sensitivity is 90% in urine and 80% in serum [21,23].

In our case, the diagnosis of disseminated histoplasmosis was made by combining results from CIE (1: 8 after dilution) with findings from histopathology after percutaneous liver biopsy that demonstrated granulomatous hepatitis, with the presence of fungal structures suggestive of *Histoplasma capsulatum*. We opted for CIE because it is more rapidly performed

(approximately 90 min) than the ID or the CF test (both taking at least 24 hours) [22] and it is the most frequently used method in our service for the diagnosis of systemic fungal infections.

Currently, there are no formal guidelines or absolute recommendations regarding the use of anti-TNF- α agents in patients at risk for systemic fungal infections, such as histoplasmosis [25]. Considering the small number of cases of histoplasmosis reported in association with the use of anti-TNF- α agents in patients with IBD, a routine screening proposal to reliably identify patients at increased risk of reactivation of histoplasmosis has not been so far recommended [14]. Likewise, anti-fungal prophylaxis in this situation is thought to be unnecessary [14].

On the other hand, patients with active fungal infection should not start treatment with anti-TNF- α agents, and interruption of treatment with anti-TNF- α and immunosuppressive agents is indicated for the established infection, together with the appropriate targeted anti-fungal therapy [25]. In our case, we opted for suspending both infliximab and azathioprine and immediately initiated anti-fungal therapy with amphotericin B after the diagnosis was confirmed. It is difficult to decide to reintroduce anti-TNF therapy in patients previously diagnosed with disseminated histoplasmosis, as the duration of the high-risk period after the end of TNF- α block (weeks or months) is uncertain, even when the infection responds to treatment. Regarding immune suppressors, which would remain as the sole option to control IBD, reintroduction after the infection responds to treatment should be coupled with secondary prophylaxis, as well as with other measures eventually advised by an infectious disease expert [25]. In our case, after the response to anti-fungal treatment was assessed by the decrease of fungal antigens levels, as measured by CEI tests at 2 months, and then approximately every 3 months during therapy and for at least 6 months after treatment is stopped, we opted for the reintroduction of an azathioprine monotherapy regimen, as a specific treatment of inflammatory bowel disease.

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Thus, it is essential that disseminated histoplasmosis be remembered as a possible diagnosis in patients using immunosuppressive therapies. Current guidelines support screening for bacterial and viral infections, such as tuberculosis, hepatitis B, and varicella zoster, before the onset of anti-TNF- α agents, and this makes screening for fungal infection tempting as well. However, this may not be effective because the reactivation of fungal disease is rare. Our suggestion is that, in view of the seriousness of cases, all patients prior to the use of anti-TNF- α agents should be informed of the risk for acquiring systemic mycoses, such as histoplasmosis, paracoccidioidomycosis, and cryptococcosis, as well as of the type of environment likely to be contaminated, activities to avoid, and symptoms for which they should seek medical attention, especially in endemic areas.

Conclusions

This report calls attention to an unusual case of disseminated histoplasmosis, which is a serious clinical condition, most likely arising from an adverse effect of combined immunosuppression with IFX, azathioprine, and courses of corticosteroids in a patient with Crohn's disease.

In this condition, all efforts should be made to recognize this serious infectious complication in patients treated with anti-TNF- α agents, and the specific treatment should be instituted as soon as possible. Diagnosis requires a high degree of suspicion, recognition of the most common forms of disease presentation, and familiarity with the use of specific diagnostic tests.

Conflicts of Interest

None declared.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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