CASE REPORT

Histoplasma meets Crohn's disease: a rare case of new-onset ascites

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SUMMARY

A 53-year-old man with Crohn's disease treated with adalimumab was hospitalised with abdominal pain, fatigue, fever and chills. CT scan of the abdomen showed chronic thickening of the terminal ileum and cecum and new-onset ascites. Further studies revealed weakly positive urine and serum histoplasma antigen. Laparoscopy revealed metastatic caking of the omentum and abdominal wall; peritoneal biopsy demonstrated organisms morphologically consistent with *Histoplasma capsulatum*. No dissemination outside of the peritoneal cavity was evident. The patient completed 2 weeks of liposomal amphotericin B followed by oral itraconazole for 1 year. Adalimumab therapy was held for 10 weeks, then restarted. Presenting symptoms resolved following initiation of antifungal therapy. Follow-up MRI of his abdomen demonstrated resolution of ascites. To our knowledge, this is the first reported case of histoplasmosis presenting as peritonitis in a patient with Crohn's disease receiving antitumour necrosis factor- α (TNF- α) therapy. Many clinicians are aware that patients receiving anti-TNF- α therapy are at increased risk for histoplasmosis, but may fail to consider the diagnosis in the absence of lung involvement.

BACKGROUND

Infectious complications related to Crohn's disease and immunosuppressive therapy are well known, and are the most reported serious adverse events associated with antitumour necrosis factor- α (TNF- α) therapy.¹ There have been multiple documented cases of histoplasmosis in association with anti-TNF- α therapy in Crohn's disease. *Histoplasma capsulatum* is acquired through inhalation of spores from environmental sources, often following exposure to disturbed soil contaminated with bird or bat droppings. The fungus primarily affects the lungs but dissemination to multiple other organs can occur, particularly in patients with impaired cell-mediated immunity.² Treatment guidelines for management of histoplasmosis in the setting of Crohn's disease are not well established with regard to duration of antifungal treatment or management of immunosuppression. In most instances, immunosuppression is discontinued, and at times, antifungal therapy may be lifelong. However, new evidence suggests that antifungal therapy can be discontinued after 12 months if there has been a favourable clinical response.³ Additionally, some experts suggest that it may be safe to resume anti-TNF- α therapy while treating histoplasmosis, if the

patient is closely monitored.³ We present a unique case of peritonitis caused by *H. capsulatum* in a patient with Crohn's disease treated with adalimumab and prednisone. This case highlights the challenging aspects of managing antifungal therapy and immunosuppressive therapy in the setting of histoplasmosis.

CASE PRESENTATION

A 53-year-old man with a 16-year history of Crohn's ileocolitis presented to the emergency department with complaints of abdominal pain and fatigue of 1-month duration. He had associated fever, chills and weight loss. He denied any nausea, vomiting, constipation or diarrhoea. His Crohn's disease maintenance therapy was adalimumab 40 mg every 2 weeks, starting 8 months prior to presentation. He had received multiple courses of corticosteroid therapy prior to initiation of adalimumab, but had not been on corticosteroids subsequently. Medical history was otherwise notable only for gastro-oesophageal reflux disease. He worked as a utility pole installer throughout the Southeastern USA. Initial vital signs were normal, and he remained afebrile throughout hospitalisation. Physical examination was significant for right lower quadrant abdominal pain on palpation. A colonoscopy had been performed 8 months prior to his presentation, which revealed a deformed ileocecal valve with chronic inflammation and fibrosis. Terminal ileum biopsies showed focal minimal acute ileitis.

INVESTIGATIONS

Chest X-ray was unremarkable. Laboratory investigation was significant for white cell count $8.8 \times 10^9/L$, erythrocyte sedimentation rate 39 mm/hour, C reactive protein 13 mg/dL and albumin 2.7 g/dL. A CT scan of the abdomen (figure 1) demonstrated chronic wall thickening of the terminal ileum and cecum and new moderate volume abdominal ascites. A paracentesis revealed yellow, hazy fluid with 6287 nucleated cells (7% neutrophils, 38% monocytes, 55% lymphocytes), total protein 4.5 g/dL, albumin 2.2 g/dL and glucose 89 mg/dL. His serum-ascites albumin gradient (SAAG) was 0.5. Ascitic fluid bacterial culture, acid-fast bacillus smear and cytology were negative. HIV-1 and HIV-2 antibodies were negative; CD4 count was 732 cells/ μL . Urine histoplasma antigen assay was positive, but the level was below the limit of quantification. Serum histoplasma antigen was weakly positive at 2.4 U/mL. Diagnostic laparoscopy for

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Figure 1 CT of the abdomen and pelvis with contrast.

peritoneal biopsy showed metastatic caking of the omentum and abdominal wall. Peritoneal biopsies (figures 2–4) revealed small Grocott's Methenamine Silver (GMS)-positive yeast-like forms that were morphologically consistent with *H. capsulatum*. CT of the chest, MRI of the brain and lumbar puncture provided no evidence of further dissemination. Terminal ileum biopsies from the previous colonoscopy were rereviewed by pathology and showed no evidence of *H. capsulatum*.

Figure 2 Peritoneal biopsy, low power field showing granulomatous reaction in the peritoneal fat.

Figure 3 Peritoneal biopsy, high power field showing granulomatous inflammation (numerous histiocytes with a few intermingling chronic inflammatory cells).

DIFFERENTIAL DIAGNOSIS

Ascites is a pathological condition where fluid accumulates in the peritoneal cavity. While the vast majority of ascites is caused by cirrhosis of the liver (~75%), the differential diagnosis is broad. SAAG is the most important diagnostic parameter to determine ascites aetiology. A SAAG that is greater than 1.1 g/dL is typically related to portal hypertension, whereas a SAAG less than 1.1 g/dL suggests the cause is not related to portal hypertension. In non-portal hypertension ascites, peritoneal malignancy, chronic peritoneal infections and nephrotic syndrome are the most common causes. Fungal, parasite, chlamydia, spontaneous bacterial peritonitis and tuberculosis are potential infectious causes of ascites with SAAG <1.1 g/dL.⁴

TREATMENT

The patient completed 2 weeks of intravenous liposomal amphotericin B at a dose of 3 mg/kg every 24 hours. He was then transitioned to oral itraconazole, 200 mg three times a day for 3 days. Long-term treatment consisted of itraconazole 200 mg two times

Figure 4 Peritoneal biopsy, high power Grocott's Methenamine Silver-stained slides showing the small yeast forms within histiocytes/macrophages.

Figure 5 MRI of the abdomen with and without contrast.

per day for 1 year. Adalimumab was initially stopped at hospital admission.

OUTCOME AND FOLLOW-UP

Following discharge, the patient had monthly follow-up visits with an inflammatory bowel disease specialist and an infectious diseases specialist. He noted improvement of abdominal pain and fatigue and resolution of fevers and chills. Following discussion between the gastroenterology and infectious diseases consultants, adalimumab was restarted 10 weeks after the initiation of antifungal therapy. Given the documented efficacy of adalimumab in the treatment of Crohn's disease, we felt that the resumption of adalimumab was important in minimising Crohn's related symptoms and complications.⁵⁻⁷ Although there are few published data to guide the timing of the reintroduction of adalimumab, an effort was made to weigh the risk of exacerbating infection versus the need to control the patient's Crohn's disease. A follow-up MRI of the abdomen (figure 5) was performed 7 months after diagnosis and revealed no evidence of ascites. After 12 months of therapy with itraconazole, the histoplasma urine antigen was not detectable, and antifungal therapy was discontinued. After 2 years, the patient has had no evidence of recurrence of histoplasmosis.

DISCUSSION

Patients with Crohn's disease treated with immunosuppressive therapy are at increased risk for infection, including opportunistic infections. A recent analysis of over 23 000 patients exposed to adalimumab revealed serious infection as the most reported serious adverse event.¹ Reports of anti-TNF- α therapy-associated histoplasmosis in inflammatory bowel disease patients have been well documented. In a recent review of 98 cases of histoplasmosis diagnosed in patients on anti-TNF therapy, 38.1% had inflammatory bowel disease.³ Another retrospective study revealed histoplasmosis as the most frequent invasive fungal infection in patients receiving anti-TNF- α therapy.⁸ In the majority of histoplasmosis cases associated with anti-TNF therapy, pneumonia is the primary presenting syndrome.⁹ The US Food and Drug Administration has recommended that clinicians be cognisant of the risk of histoplasmosis in patients

treated with anti-TNF- α therapy due to increased morbidity and even death.¹⁰

Ileocolonic histoplasmosis has been shown to occur in Crohn's disease, both as a primary site of infection, and as a part of disseminated histoplasmosis. However, ileocolonic histoplasmosis typically presents with significant bowel thickening and prominent mesenteric lymphadenopathy.^{11 12} Our patients CT showed chronic wall thickening of the terminal ileum and colon (which was unchanged from previous imaging) without any significant mesenteric lymphadenopathy. Furthermore, biopsies from the patient's colonoscopy 8 months prior to presentation did not show evidence of *H. capsulatum*.

Histoplasmosis is acquired by inhalation of microconidia, usually from a soil source. Within the alveoli, organisms transform from conidia to the yeast phase, and are ingested by phagocytic cells. Immune responses (both innate and cell-mediated) are initiated and begin to limit replication of the fungus. In immunocompetent individuals, primary pulmonary histoplasmosis is typically asymptomatic, although a flu-like syndrome (that may be severe) can occur following inhalation of a heavy inoculum. Yeast are able to disseminate widely (to liver, spleen, gastrointestinal tract, etc), through trafficking of macrophages, but symptomatic disseminated infection virtually never occurs in an immunocompetent patient. These organisms may persist in granulomas for life in many healthy individuals. If an infected person subsequently develops depressed cell-mediated immune responses, reactivation may occur, resulting in non-pulmonary histoplasmosis, which may explain the absence of pulmonary involvement in our patient.¹³ However, the relative contribution of latency with reactivation versus reinfection remains a subject for further investigation.

This is the first reported case of peritonitis caused by *H. capsulatum* in a patient with Crohn's disease on immunosuppressive therapy. Additionally, this is the only reported case, to our knowledge, of histoplasma peritonitis presenting without clinically apparent involvement of any other organ system. This presentation is uncommon; the spectrum of disease with anti-TNF- α therapy-associated histoplasmosis most frequently features pulmonary involvement, which was absent in our patient.⁸ Tuberculous peritonitis can present in a similar fashion in patients with Crohn's disease on anti-TNF- α therapy, and it was included in our differential diagnosis.¹⁴ The patient's initial diagnosis of histoplasmosis was suspected, but not confirmed by the weakly positive histoplasma antigen studies (which can sometimes present a false-positive result from other fungal infections including blastomycosis and coccidioidomycosis) and non-specific ascitic fluid studies. Based on these results, a decision was made to pursue laparoscopic biopsy that confirmed the diagnosis of histoplasma peritonitis.

Therapy for Crohn's disease can be challenging in the setting of opportunistic fungal infections. Questions remain as to both the duration of antifungal therapy and the safety of immunosuppressive therapy. The role of extended antifungal therapy to prevent relapse is not known, and the Infectious Diseases Society of America has no specific recommendations on chronic suppressive therapy for histoplasmosis in this setting. Based on a recent multicentre retrospective review of histoplasmosis associated with anti-TNF- α therapy, 12 months may be an appropriate duration of antifungal therapy if a favourable clinical response is achieved.³ There is no clear guidance from the literature recommending when it is safe to resume immunosuppressive therapy after diagnosis of histoplasmosis. Although the duration for which anti-TNF- α therapy should be held is uncertain, a recent

retrospective study suggests that resumption of anti-TNF- α therapy during the course of antifungal therapy appears safe.³ With close monitoring, we treated our patient with a 12-month course of antifungal therapy and resumed adalimumab after a 10-week hiatus in therapy. He has not exhibited evidence of relapse or recurrence of his histoplasmosis. During 24 months of follow-up, the patient demonstrated good control of his Crohn's disease without evidence of relapsing histoplasmosis.

Learning points

- ▶ Patients with Crohn's disease receiving immunosuppressive therapy (including antitumour necrosis factor- α inhibitors and corticosteroids) are immunocompromised and therefore at increased risk for opportunistic infection.
- ▶ This is the first reported case of isolated histoplasma peritonitis in a patient with Crohn's disease on immunosuppressive therapy.
- ▶ While no consensus guidelines are available, immunosuppressive therapy can be safely resumed in some cases if the patient has shown good response to antifungal therapy and can be monitored closely.

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