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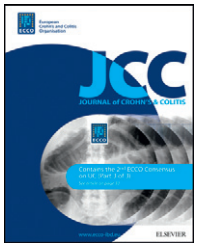

SHORT REPORT

Pulmonary cryptococcosis in a patient with Crohn's disease treated with prednisone, azathioprine and adalimumab: Exposure to chicken manure as a source of contamination

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Abstract

Background: Biotherapies targeting TNFα were proven to be effective in the most severe cases of Crohn's Disease, a chronic granulomatous inflammatory bowel disease that can involve any portion of the digestive tract. The tolerance of anti-TNFα therapy is usually good, although several infectious complications have been reported with these drugs.
Methods: We report a case of a Crohn's disease patient who developed pulmonary cryptococcosis following chicken manure exposition while he received adalimumab and azathioprine.
Case: A 54-year-old man, with history of severe Crohn's disease and ankylosing spondylitis, was admitted for diarrhea and abdominal pain under azathioprine treatment. In December 2010, he was treated with oral prednisone (1 mg/kg/day), but Crohn's disease relapsed when prednisone dose was lower than 30 mg/a day. The patient was then treated with adalimumab, but six weeks later he developed severe pulmonary cryptococcosis. The patient experienced a good outcome

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under antifungal therapy. We retrospectively found a high exposure to chicken manure in the last weeks.
Conclusion: Cryptococcosis is an opportunistic infection that can occur under anti-TNFα therapy. The environmental exposure to *Cryptococcus spp.* (in particular in chicken manure) is a source of contamination. Avoiding exposition to bird manure should be a recommendation for patients who are living in rural areas.

1. Introduction

Crohn's disease (CD) is a chronic granulomatous inflammatory bowel disease that can involve any portion of the digestive tract.[1] Therapeutic management depends on disease location, severity and presence of stenosing or penetrating complications. Biotherapies targeting TNFα were proven to be usefull in the most severe cases of CD, in particular in those refractory to steroids.[2] The tolerance of anti-TNFα therapy is usually good, although several infectious complications have been reported with these drugs.[3] Herein, we report a case of a CD patient who developed pulmonary cryptococcosis following chicken manure exposition while he received adalimumab and azathioprine. We discuss the characteristics of cryptococcosis in immunocompromised patients and the environmental exposure to *Cryptococcus spp.* (in particular to chicken manure) as a source of contamination.

2. Case report

In 1981, a 25-year-old man complained about inflammatory back pain and HLA-B27 positive ankylosing spondylitis was diagnosed. In 1985, ileal stenosis occurred leading to the histopathological diagnosis of CD. Between 1985 and 2005, the high activity of CD required the following therapeutic measures: four surgeries with ileocaecal, right colon and transverse colon resections; oral prednisone; infliximab therapy (5 infusions between September 2002 and April 2003 and 2 infusions in April 2005), which was discontinued because of anaphylactic shock following the 7th infusion; azathioprine (150 mg/day) as maintenance therapy since April 2005.

In November 2010, the patient presented anorexia, diarrhea and a 6 kg-weight loss in one month. Abdominal computed tomography (CT)–scan revealed a 20 cm length inflammatory bowel loop at 40 cm from the ileo-transverse anastomosis. Colonoscopy showed ulcerative and inflammatory lesions on the ileo-transverse anastomosis. All these findings were consistent with the diagnosis of active disease (Harvey-Bradshaw index = 11). The patient was treated with prednisone (1 mg/kg/a day) and exhibited a rapid resolution of his symptoms. Glaucoma and anxiety disorder appeared under steroids and a relapse occurred at corticosteroid tapering (prednisone 0.5 mg/kg/a day). Then, 160 mg adalimumab were subcutaneously administrated on February, the 23rd and followed by two additional injections (80 mg on March the 9th and 40 mg on March the 23rd), with a rapid resolution of the symptoms. Prednisone was stopped on March the 5th and azathioprine was continued at the dose of 100 mg/ a day.

It is noteworthy that the patient took care of a friend's chicken coop for two weeks in February 2011 and he was thus exposed to chicken manure in a confined space. On March the 15th, he presented with 38.5 °C fever, anorexia, cough, chest pain, dyspnea with minimal activity, arthralgia and myalgia. Physical examination disclosed bilateral crackles and SaO_2 was 88%. Cardiovascular, abdominal, neurological, joint and cutaneous examinations were normal. Laboratory findings were white blood cell count of 10.6×10^9/L with 9.6×10^9/L neutrophils, 0.98×10^9/L lymphocytes, 0.4×10^9/L eosinophils, and C-reactive protein (CRP) concentration 59 mg/L. HIV serology was negative and CD4 lymphocyte count was 697/mm3. Chest radiography demonstrated multiple bilateral nodular opacities (Fig. 1A). CT scan showed a 14 mm subcarinal lymphadenopathy and multiple bilateral nodular opacities, some of them being surrounded by ground glass opacities (Fig. 1B). The bronchoalveolar lavage (BAL) fluid contained 500 cells per mm^3 with 42% macrophages, 36% neutrophils, 16% lymphocytes and 16% bronchial cells. Grocott-Gomori staining demonstrated intra-macrophagic encapsulated yeasts whereas Ziehl-Neelsen staining was negative. BAL culture grew *Cryptococcus neoformans*. Cryptococcal polysaccharide antigens were detected in serum (1/128) but not in urine. The cerebrospinal fluid (CSF) protein level was 0.46 g/L, glycorrhachia was 3.6 mmol/L and CSF white cells were less than 3 per mm^3. Cryptococcal antigen was not detected in CSF. Echocardiogram was normal. A treatment by liposomal amphotericin B 3 mg/kg/a day and 5-fluorocytosine 100 mg/kg/a day was given. Azathioprine and adalimumab were stopped. Fever and chest pain disappeared within one week while cough and dyspnea decreased within three weeks. C reactive protein decreased to 1 mg/L within 2 weeks. Then a switch to oral fluconazole 200 mg/day was started after 10 weeks of intravenous therapy. After 4-month follow-up, the patient recovered completely from cryptococcosis. Prednisone (0.5 mg/kg/day) was reintroduced 7 months after its discontinuation, because of relapsing arthritis and was tapered rapidly. After 12 month follow-up, CD did not relapse and the patient is still receiving low dose prednisone (10 mg/day) and antifungal maintenance therapy with oral fluconazole (200 mg/day).

3. Discussion

The use of anti-TNFα therapy is associated with an increased risk of infections, which usually occurs within the first months of therapy.[3] While pyogenic infections and tuberculosis are the most commonly observed, opportunistic agents usually observed in severely immunocompromised patients have been reported: non tuberculous Mycobacteria, Nocardia,