SHORT REPORT

Disseminated Cryptococcus neoformans infection and Crohn's disease in an immunocompetent patient

Guido Sciaudone a, Gianluca Pellino a, Ilaria Guadagni a, Anna Somma b, Francesco P. D'Armiento b, Francesco Selvaggi a,⁎

a I Division of General Surgery, Second University of Naples, Italy
b Department of Pathology, University "Federico II", Naples, Italy

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Abstract

Cryptococcus neoformans is a human pathogen ubiquitously present in the environment. It primarily affects immunocompromised patients, but individuals with no underlying disease or immunodeficiency can also be affected.

We herein describe the case of a patient found to have Crohn's disease and disseminated cryptococcosis simultaneously. She had no predisposing underlying cause for impaired immunity.

Our patient showed signs that would have made it hard to discriminate between an inflammatory bowel disease and an infection if bowel only would have been involved. The patient underwent surgical intervention; medical therapy was effective against Cryptococcus. She is at now being followed-up for Crohn's disease.

When dealing with patient affected with inflammatory bowel diseases, careful history taking, objective and instrumental examination are demandable in order not to overlook associated conditions or infectious diseases.

Diagnosis and therapy of cryptococcosis infection in patient with Crohn's disease are herein discussed.

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1. Introduction

Cryptococcus neoformans is a human pathogen ubiquitously present in the environment. It primarily affects immunocompromised patients, but it is estimated that 45–50% of HIV-negative patient with cryptococcosis have no underlying disease or immunodeficiency.1,2 HIV-seronegative patients are often diagnosed with disseminated cryptococcosis, occurring in more than 60% of patients.2 Gastrointestinal tract involvement probably occurs frequently in disseminated

Abbreviations: CD, Crohn's disease; EGDS, esofago-gastro-duodenoscopy; PCS, pancolonoscopy; SUV, standardized uptake value; BAL, bronchoalveolar lavage; BAS, bronchoaspiration; sCRAG, serum Cryptococcus antigen.

⁎ Corresponding author. via Francesco Giordani, 42, 80122 Naples, Italy. Tel.: +39 3358419132; fax: +39 0815666722.
E-mail address: fselvaggi@hotmail.com (F. Selvaggi).
disease\textsuperscript{3}. Despite the recent increase in the incidence of this disease, due to growing AIDS pandemic, especially in sub-Saharan Africa, the evidence of symptomatic gastrointestinal infection reported in the literature still remains rare. We herein report an inflammatory bowel disease happening with disseminated cryptococcosis in an immunocompent patient. At our knowledge, no cases of Crohn’s disease (CD) occurring with disseminated cryptococcosis has been described.

2. Case report

A 26-year-old nun from Indonesia was admitted to our institution after several episodes of diarrhoea with melena, abdominal pain, weight-loss, and headache. She had a history of erosive gastritis causing melena, treated with omeprazole 40 mg twice daily 2 years before. She denied NSAIDs use. She had never smoked and she was abstemious. At clinical examination, she had no neurological symptoms, body temperature was 38 °C. A mild monolateral laterocervical lymphadenopathy (left-sided) was present. The patient presented dry-cough. Cardiac examination was negative. Abdominal tenderness was present, more evident in the right iliac fossa.

Laboratory values showed: CRP of 10.1 mg/dl (normal value <1 mg/dl), ESR 110 mm/h, WBC count 7.780/mm\(^3\) with 70.9\% neutrophils and 17.4\% lymphocytes, haemoglobin 10.2 g/dl. Urinalysis was negative and stool exam revealed melena, while blood cultures were negative. The patient refused lumbar puncture.

The patient underwent esofago-gastro-duodenoscopy (EGDS) and pancolonoscopy (PCS): the antro-pyloric mucosa was hyperaemic; an ulceration was seen in the sigma; several raised, patchy lesions interspersed with ulcerations were present in the transverse colon and caecum. Biopsies were taken. Gastric biopsies showed mononuclear cells (CD68\textsuperscript{+}) and granulocytes; \textit{Helicobacter pylori} was not found.

A CT-scan showed an area (max diameter 2 cm) of parenchymal thickening in the apical segment of the left lung inferior lobe, with eccentric calcification, hilar nodular lymph node enlagement with microcalcifications bilaterally (Fig. 1). The left lobe of the liver was hypertrophic. The last ileal loop presented a concentric parietal thickening, involving the caecum, with contrastographic enhancement; a similar finding was evident in the proximal transverse colon. These areas were surrounded by peri-lesional and mesenteric root lymphoadenopathies.

A FDG-PET-CT examination, performed to evaluate the described areas, showed intense captation: in the rinopharynx posterior wall (SUV max 8); in the left laterocervical (SUV max 7), paratracheal (SUV max 2.4) and hilar (SUV max 3) lymph node stations; in the area of the left lung with parenchymal thickening (SUV max 5); in the parietal thickened areas of terminal ileum (SUV max 12) and ascending colon (SUV max 10).

The general status of the patient suddenly worsened in a few days. She complained of severe abdominal pain and abdominal defence was present in right iliac fossa. Abdominal ultrasound examination confirmed the thickness of the terminal ileum, and reported deep ulcerations.

The patient underwent surgical intervention. The last loop and another tract of the ileum and the caecum were thickened, and also fissures were found; these tracts were resected. A biopsy of the left laterocervical lymph node was performed too. To open, colonic mucosa was scalloped and ileum showed an ulcerated area of 5×2.5 cm (Fig. 2). Both ileal and colonic mucosa showed multiple ulcerated areas, with fistulas, glandular distortion, crptic injury and abscesses, gastric metaplasia in small intestine mucosa and intense active chronic inflammatory infiltrate affecting the
entire wall; many giant cell granulomas involving perivisceral and laterocervical lymph nodes were observed. The lesion also involved the appendix.

After the intervention, the general status of the patient slowly improved and she underwent fibrobroncoscopy with bronchoalveolar lavage (BAL) and bronchoaspiration (BAS). A sub-mucosal capillaritis was found; the fluid was sent to microscope and culture examination.

The pathological examination of the resected specimens revealed CD (CD68+) and cryptococcus-like aspects. Histochemical examination with Grocott (fungi) and Ziehl–Nielsen (acid-resistant bacteria) resulted negative; immunohistochemical investigation performed with PAS showed oval or round yeasts forms. PAS-positivity leaned towards cryptococcosis. In a resected ileal tract CD and cryptococcoid aspect were simultaneously present. The biopsies performed during EGDS and PCS confirmed CD; the biopsy taken from the left laterocervical lymph node revealed the same cryptococcid findings (Fig 3).

ELISA test for HIV 1 and 2 antibodies were negative, and a lymphocyte subsets analysis revealed no alterations of CD4+ and CD8+ count.

Endobronchial aspirate fungal culture grew *C. neoformans* var *neoformans*. Serum cryptococcal antigen (sCRAG) titer was 1:256. The patient was administered mesalazine (800 mg daily) to control gut disease. After administration of liposomal Amphotericin B the patient had cutaneous rash, abdominal pain with AST and ALT increase, requiring immediate drug withdrawal. After recovering, she was tested with fluconazole (400 mg daily for the first week, then 200 mg for 5 weeks), which resulted well tolerated and effective against yeast infection.

The patient was discharged after 10 days in good health status. Two weeks after fluconazole suspension blood cultures and a CT-scan were negative. sCRAG titre is actually negative; the patient is being followed-up for CD.

**3. Discussion**

*C. neoformans* is an ubiquitous yeast which is usually found in soil rich in avian droppings or in association with eucalyptus trees. Cell-mediated immunity is responsible for natural defence against this pathogen, CD4+ lymphocytes playing a central role. AIDS patients are consequently at higher risk of being infected, but several conditions can predispose patients to cryptococcosis, such as immunosuppressive, biological or corticosteroid drugs, diabetes, cirrhosis, chronic leukemia and lymphoma.1,4,5 The infection has also been reported in association with Job’s syndrome and primary immunodeficiencies.6 Infection is thought to begin with inhalation of the pathogen in the lungs, spreading hematogenously to other organs. The central nervous system is the most frequently involved. The aspect of lung involvement typically consists of granulomatous reactions, and infiltrates, like our patients showed.7 Other sites where the pathogen can rarely cause disease are reported to be the peritoneum,1 bones8 and gastrointestinal tract.1,9 Gastrointestinal involvement is very rare, and it can mimic other processes, whether by mass or signs of inflammation.2 Our patient showed signs that would have make it hard to discriminate between an inflammatory bowel disease and an infection if only bowel would have been involved. Diagnosis of cryptococcosis infection is based on cultural examination of blood, cerebrospinal fluid, direct microscopic observation of the pathogen and PAS stain positivity on hystochemical analysis.9 We found PAS useful in distinguishing damages due to cryptococci from CD ones; while cultural blood examination was negative, it’s remarkable that BAL and BAS were able to get fluid which grew *C. neoformans*. Therapy consists of anti-fungal drugs such as Amphotericin B +/- flucytosin or Fluconazole; nervous system involvement requires high drug dosage.10

CD is an inflammatory bowel disease which can affect the entire bowel, usually diagnosed in patient between 15 and

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**Figure 3**

A) Intestinal mucosa with ulceration, intense chronic inflammation, histiocytic activation and granulomas. B) Lymph node showing epithelioid granulomas, with giant cells (hematoxylin eosin stain). C) PAS reaction: spheroidal PAS-positive forms inside a giant cell. The arrow indicates a PAS-positive body with flare effect. D-E-F) PAS reaction: intra- and extra-citoplasmatic spheroidal PAS-positive bodies.
30 years old. A recent European Crohn’s and Colitis Organization evidence based Consensus on diagnosis and management of CD highlighted the importance of evaluating clinical, histological and endoscopic features to make diagnosis.\textsuperscript{11} In our patient, Cryptococcosis did not justify all the lesions found at surgery and after histological examination. At macroscopic observation, discriminating features for ileal CD consisted of fat wrapping and thickening of the bowel wall; microscopic discriminating features were sarcoid granuloma and sub-mucosal nerve fiber hyperplasia and ganglionitis. Moreover, the patient also underwent EGDS with biopsies, finding focal active gastritis with infiltrate composed of mononuclear cells (CD68+) and granulocytes, without \textit{H. pylori}. Even if not exclusive to CD, focal gastritis can help establishing CD,\textsuperscript{11} CD can be often characterized by heterogeneous extraintestinal manifestations.\textsuperscript{12,13} Although pulmonary findings are often overlooked, lung manifestations of CD have been well described.\textsuperscript{13} Parenchymal pulmonary involvement is relatively infrequent, heterogeneous and often disguised by manifestations due to inflammatory bowel diseases specific drugs; it is more frequently observed in ulcerative colitis.\textsuperscript{14} Our patient did not show usual patterns of pulmonary primitive CD involvement, moreover positivity of cultural examination and responsiveness to therapy (hardly obtained in CD lung involvement)\textsuperscript{14} excluded this eventuality.

In our patient no predisposing underlying cause for impaired immunity was identified. Her CD4$^+$ count was in the normal range, and should have not predisposed patient to cryptococcal infection; moreover recent researches suggest that inflammatory bowel diseases result from a complex interplay of genetic, environmental, and immunologic factors, and an inappropriate mucosal immune response to normal intestinal constituents is a key feature, leading to an imbalance in local pro- and anti-inflammatory cytokines.\textsuperscript{15} In CD this leads to high level of pro-inflammatory substances, like TNF-\(\alpha\), a cytokine which is normally produced in response to inflammation by CD4$^+$ lymphocyte. Cases of opportunistic infection in CD are reported in literature, but patients were taking immunosuppressive, corticosteroid or biological drugs at the time of infection.\textsuperscript{5}

The case that we describe is unique in literature. The possibility that CD may be active despite a profound immune deficiency has been described.\textsuperscript{16} Our patient was not immunocompromised, but our report could further challenge the significance of CD4$^+$ cell behaviour in CD.

When dealing with inflammatory bowel disease patients, following Occam’s razor (entities must not be multiplied beyond necessity) is almost always the best way to proceed in decision-making; however we should bear in our mind the eventuality that more than one disease can overlap even in such individuals.

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AS, FPDA carried out the histological examination and literature review.

FS conceived of the report, and participated in its design and coordination and helped to draft the manuscript.

All authors read and approved the final revised manuscript.

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