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DISSEMINATED CRYPTOCOCCOSIS: A DIAGNOSTIC CHALLENGE IN AN IMMUNOCOMPROMISED PATIENT

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ABSTRACT

Background: Cryptococcosis is an opportunistic fungal infection that causes disseminated disease in immunocompromised patients. Peritoneal involvement is rare and diagnostically challenging.

Case report: A 76-year-old man with Crohn's disease on infliximab and previously treated latent tuberculosis was admitted with constitutional symptoms and abdominal distention evolving over 5 months. Ultrasound revealed bilateral pleural effusion and ascites. Initial hypotheses—peritoneal carcinomatosis and tuberculosis—were excluded through computed tomography scan, laboratory tests, and exploratory laparoscopy with biopsy, which showed necrotizing granulomatous peritonitis. Disseminated cryptococcosis was confirmed by India ink staining, cultures from peritoneal and pleural fluids, and serum cryptococcal antigen. Cerebrospinal fluid analysis and ophthalmological evaluation excluded central nervous system and ocular involvement. Treatment with liposomal amphotericin B and flucytosine led to clinical improvement.

Conclusion: This case highlights the importance of considering cryptococcosis in the differential diagnosis of polyserositis in immunocompromised patients. Early diagnosis and antifungal therapy improve outcomes.

KEYWORDS

Disseminated cryptococcosis, Crohn's disease, immunocompromised patient, necrotizing granulomas, constitutional syndrome

LEARNING POINTS

- Disseminated cryptococcosis, although rare, should be considered in the differential diagnosis of polyserositis and necrotizing granulomatous peritonitis in immunocompromised patients.
- Cryptococcus can closely mimic tuberculosis or peritoneal carcinomatosis; negative mycobacterial studies should prompt fungal investigations, including cryptococcal antigen testing.
- Early diagnosis and timely initiation of antifungal therapy are crucial to reduce morbidity and mortality, with treatment tailored to comorbidities such as renal dysfunction.

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INTRODUCTION

Cryptococcosis is a fungal infection caused by *Cryptococcus neoformans* and *Cryptococcus gattii*[1]. *C. neoformans*, found worldwide in bird droppings, is transmitted by inhalation of spores[1,2], and disseminates hematogenously, leading to cryptococcosis, a condition frequently associated with immunocompromised individuals[3].

Patients with inflammatory bowel disease receiving corticosteroids, immunomodulators, and biological agents are considered immunocompromised and are at risk for opportunistic infections[4].

Approximately 1 million cases of cryptococcosis are reported each year, resulting in an estimated 625,000 deaths[5].

The most commonly affected sites in cryptococcal infections include the central nervous system (CNS), lungs, and skin, with rare involvement of the prostate, eyes, and gastrointestinal tract[3,6].

Among patients with human immunodeficiency virus (HIV), meningitis is the predominant clinical manifestation, whereas pulmonary or skin and soft tissue involvement is more frequent in immunocompromised individuals who do not have HIV[7]. Interestingly, patients without HIV tend to exhibit a slightly stronger inflammatory response, and consequently, they are more symptomatic[6].

In this context, we present a rare case of disseminated cryptococcosis in an immunocompromised patient with Crohn's disease receiving infliximab therapy.

Blood analysis	Value	Reference
Haemoglobin (g/dl)	11.2	13-18
White blood cells (×10⁹/l)	6.3	4.1-11.1
Neutrophil count (×10⁹/l)	4.3	2-7.5
Platelets (×10⁹/l)	299	150-500
Urea (mg/dl)	58	19-51
Creatinine (mg/dl)	2.09	0.7-1.3
N-terminal pro-brain natriuretic peptide (pg/ml)	3143	0-450
Creatine phosphokinase (U/l)	44	46-171
Myoglobin (ng/ml)	124	<110
Lactate dehydrogenase (U/l)	210	120-246
C-reactive protein (mg/l)	10.78	0-0.5
Procalcitonin (ng/ml)	0.17	<0.1
Albumin (g/dl)	3	3.4-4.8
Total protein (g/dl)	6.3	6.4-8.3

Abbreviations: NT-ProBNP, N-terminal pro-brain natriuretic peptide; CPK, creatine phosphokinase; LDH, lactate dehydrogenase.

Table 1. Blood analysis.

CASE DESCRIPTION

A 76-year-old man, independent in daily living, presented with 5 months of asthenia, anorexia, and 7 kg weight loss in the first 2 months. He also reported nocturnal sweating and a chronic, non-productive cough that occasionally precipitated episodes of tussive syncope. He denied fever, dyspnoea, chest pain, vomiting, nausea, changes in bowel habits, genitourinary complaints or skin changes.

The patient's medical history was notable for ileocolic and perianal Crohn's disease (Montreal classification A3L3B1p), treated with infliximab (5 mg/kg every 8 weeks), coronary artery disease with a prior stent placement, hypertension, atrial fibrillation, and stage G3a chronic kidney disease (baseline estimated glomerular filtration rate 54 ml/min/1.73 m^2), and treated latent tuberculosis.

His social history was significant for cohabitation with numerous domestic and wild birds (chickens, doves, a raven) and a dog, none of which were vaccinated. He denied recent travel, insect bites, or consumption of untreated water (drank only bottled water).

On admission, he appeared mildly pale and reported orthopnoea. Breath sounds were absent at the right lung base, with fine crackles over the left base. The abdomen was globular, soft, and non-tender, with a demonstrable fluid wave. Pitting oedema was noted up to the knees. No cutaneous lesions or lymph nodes were noted. Vital signs: blood pressure 82/65 mmHg, heart rate 99 bpm, respiratory rate 15 breaths/min, peripheral oxygen saturation 97% on room air, and a tympanic temperature of 37.6°C. Laboratory findings *(Table 1)* were significant for a normocytic anaemia, acute-on-chronic kidney injury, hypoalbuminemia, marked inflammation with normal procalcitonin and elevated N-terminal pro-brain natriuretic peptide. Urinalysis showed mild proteinuria.

Imaging studies included a chest X-ray, with a large right-sided pleural effusion and blunting of the left costophrenic angle. An abdominal ultrasound confirmed moderate ascites without focal liver lesions or portal vein thrombosis. A transthoracic echocardiogram showed preserved biventricular systolic function and no significant valvular disease, with the patient in atrial fibrillation.

During hospitalization, the patient remained intermittently febrile (38–38.3°C). Initial investigations focused on characterizing the polyserositis.

A diagnostic and therapeutic thoracentesis was performed, yielding pleural fluid with a total cell count of 1,508/µl: 13% neutrophils, 9% lymphocytes, 78% other cells. A diagnostic paracentesis drained serous-haemorrhagic ascitic fluid with a total nucleated cell count of 1,063/µl: 6% neutrophils, 25% lymphocytes, 69% other cells *(Table 2)*. Colonoscopy and computed tomography (CT) scan of the brain were unremarkable. A CT scan of the abdomen and pelvis showed a large right-sided pleural effusion with associated lower lobe collapse and a smaller effusion on the left and significant ascites, accompanied by densification of the mesenteric fat and peritoneal thickening, particularly in the pelvic region.

Parameter	Pleural Fluid	Ascitic Fluid
Appearance	Clear	Serohematic
Total cell count	1,508 ×10⁶/l	1,063 cells/µl
Differential cell count (%)	Neutrophils: 13 Lymphocytes: 9 Other: 78	Neutrophils: 6 Lymphocytes: 25 Eosinophils: 0 Other: 69
Total protein (g/dl)	4.8	5.6
Albumin (g/dl)	2.20	2.3
Lactate dehydrogenase (U/l)	238.76	-
Light's criteria classification	Exudate (all 3 criteria)	Not applicable
Serum-ascites albumin gradient	Not applicable	0.7 g/dl Non-portal hypertensive
Direct smear (Ziehl-Neelsen stain)	No acid-fast bacilli	No acid-fast bacilli
Culture for *M. tuberculosis* (Löwenstein-Jensen medium)	Negative	Negative
Polymerase chain reaction testing for *M. tuberculosis* by molecular biology	Negative	Negative

Abbreviations: LDH, lactate dehydrogenase; PCR, polymerase chain reaction.

Table 2. Summary of pleural and ascitic fluid analyses.

Reactive inguinal and left external iliac lymphadenopathy was noted.

Given the inconclusive initial findings and the high suspicion for peritoneal tuberculosis or carcinomatosis, the patient underwent an exploratory laparoscopy.

Intraoperatively, approximately 5 litres of brownish, serous ascitic fluid were aspirated. The surgical findings were not suggestive of peritoneal carcinomatosis. Instead, they revealed features of severe inflammatory peritonitis, including multiple fibrinous adhesions between bowel loops, a rough and friable peritoneum with small haemorrhagic suffusions, and sparse, punctate whitish infiltrates on the parietal peritoneum and hepatic surface. Multiple biopsies of the affected parietal peritoneum were taken.

The patient was discharged in a stable condition while awaiting the final histopathology and specialized microbiology results, with a close follow-up appointment scheduled.

The histopathological analysis of the peritoneal biopsies was pivotal, revealing granulomatous inflammation with focal necrosis *(Fig. 1)*. Cytology from the ascitic fluid showed reactive mesothelial cells and lymphocytes, consistent with a chronic inflammatory process, and was negative for malignancy. This finding narrowed the differential diagnosis to either infectious (notably tuberculosis or a systemic fungal infection) or inflammatory aetiologies (such as granulomatosis with polyangiitis or sarcoidosis). To further investigate, pending cultures from the initial admission were reviewed and additional tests were performed on stored and newly collected samples. Cytobacteriological analysis of the pleural fluid revealed the isolation of *C. neoformans*, which was susceptible to amphotericin B. Another diagnostic paracentesis was performed, revealing a positive antigen for *C. neoformans* in the ascitic fluid (also in blood cultures, with titres of 1:20 and 1:10, respectively). Furthermore, the India ink test yielded positive results in both peritoneal and pleural fluid.

Lumbar puncture excluded CNS involvement. Specific testing for cryptococcus and mycobacterial analysis in the cerebrospinal fluid were negative. Ophthalmology ruled out ocular fungal infection.

The diagnosis was necrotizing granulomatous peritonitis in the context of *C. neoformans* infection in an immunocompromised patient, along with disseminated infection.

The case was discussed with the Infectious Diseases Department that began treatment with a classic induction regimen with liposomal amphotericin B and flucytosine. However, after 10 days, acute kidney injury on chronic kidney disease was developed, with a peak creatinine level of 2.76 mg/dl (0.7-1.3), necessitating discontinuation of this regimen. Antifungal therapy was subsequently transitioned to intravenous fluconazole.

At the time of discharge, the patient was prescribed fluconazole at 200 mg/day (adjusted to kidney function). The patient reported no respiratory, gastrointestinal, or neurological complaints. Chest X-ray revealed significant improvement of bilateral pleural effusion, moderate in size, and abdominal ultrasound demonstrated a marked reduction in peritoneal effusion.

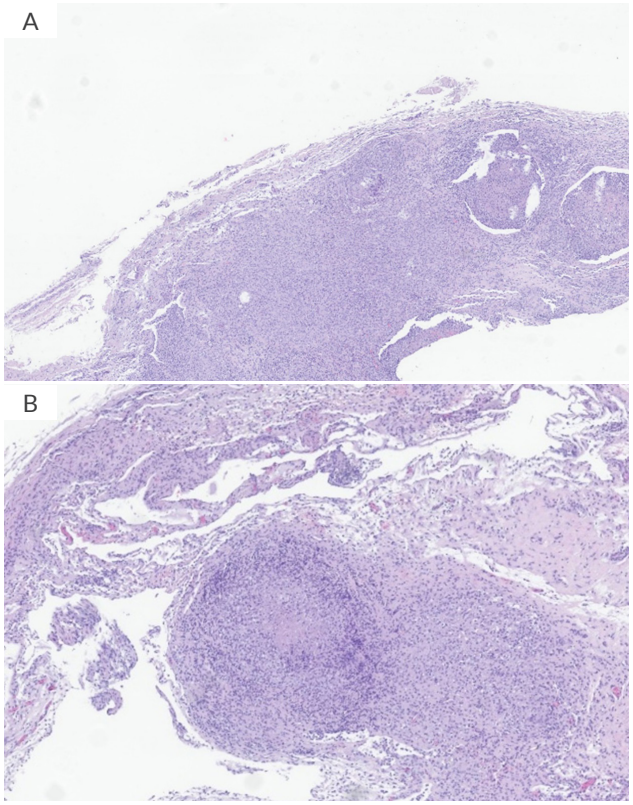


Figure 1. Histopathological analysis of the peritoneal biopsies showing A) granulomatous inflammation and B) granulomatous inflammation with focal necrosis.

Since the patient was discharged, he has been followed in infectiology and gastroenterology appointments. Treatment with infliximab has been discontinued, and Crohn's disease remained well-controlled, as indicated by normal calprotectin levels and unremarkable findings on colonoscopy, including biopsies showing no pathological changes. At this time, the patient is still on fluconazole, for at least 12 months.

DISCUSSION

Disseminated cryptococcosis represents a rare but important diagnostic challenge, particularly in immunocompromised patients[4]. Our patient's history of Crohn's disease treated with infliximab, and latent tuberculosis even though treated, placed him at an elevated risk for opportunistic infections, including cryptococcosis[3]. The case underscores the diagnostic complexity and the necessity of maintaining a broad differential diagnosis when managing immunosuppressed individuals with constitutional symptoms and polyserositis.

The diagnostic journey was particularly challenging, as the clinical presentation strongly mimicked more common conditions like peritoneal tuberculosis or carcinomatosis[4]. The patient's constitutional symptoms, combined with histopathological findings of necrotizing granulomas, initially steered the investigation towards tuberculosis, a known risk in patients on TNF-alpha inhibitors[8]. This diagnostic ambiguity underscores a crucial teaching point: in this patient population, cryptococcus can be a great mimicker of tuberculosis[3]. Therefore, when initial mycobacterial testing is negative, a thorough fungal investigation, including serum cryptococcal antigen testing and fungal cultures of relevant fluids, is mandatory[4].

Management was complicated by nephrotoxicity from amphotericin B, prompting a switch to fluconazole. The patient's subsequent clinical improvement highlights the efficacy of the treatment[9]. However, the absence of CNS involvement, as confirmed by cerebrospinal fluid analysis and brain CT-scan, was a key favourable prognostic factor that simplified the overall management strategy[10].

This case underscores the importance of early recognition and prompt antifungal therapy in cryptococcosis, as delays in diagnosis and treatment can result in significant morbidity and mortality[7].

From a broader perspective, this case emphasizes the critical role of multidisciplinary collaboration in managing complex infections in immunocompromised patients.

In conclusion, disseminated cryptococcosis should be considered in immunocompromised patients with unexplained polyserositis and systemic symptoms, emphasizing the importance of prompt diagnosis and individualized management to optimize outcomes.

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