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Case Report

Colonic cryptococcosis presenting with chronic diarrhea in a person with advanced human immunodeficiency virus disease: a case report

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Abstract *Cryptococcus neoformans* infection usually occurs in patients with advanced human immunodeficiency virus (HIV) infection or with a CD4 T lymphocyte count of <100 cells/μL. Pulmonary and central nervous system infections are the most frequently encountered forms of cryptococcosis; however, colonic cryptococcosis is uncommon. We describe the case of a 41-year-old antiretroviral-naïve man with HIV infection diagnosed eight years prior and intermittent diarrhea for 4 months who presented to the emergency department with a 1-day history of low-grade fever and confusion. Brain magnetic resonance imaging and cerebrospinal fluid analysis revealed normal results; however, he was diagnosed with *Pneumocystis jirovecii* pneumonia based on chest computed tomography and bronchoalveolar lavage analysis. Trimethoprim-sulfamethoxazole administration was initiated followed by antiretroviral treatment. Although his condition gradually improved, he developed fever and abdominal discomfort, and the diarrhea worsened. Endoscopy revealed a small ulcer in the distal transverse colon. Histopathological examination of a colon tissue sample revealed cryptococcal infection. He improved substantially during liposomal amphotericin B and fluconazole treatment. We encountered a rare case of colonic cryptococcosis that caused chronic diarrhea in a patient with advanced HIV infection. Colonic cryptococcosis should be considered when patients with acquired immune deficiency syndrome present with gastrointestinal symptoms.

Key words: Cryptococcosis, Gastrointestinal tract, Diarrhea, HIV, Acquired immune deficiency syndrome

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INTRODUCTION

Diarrhea is a common comorbidity in patients with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). In addition to various common pathogens, opportunistic pathogens such as parasites or fungi can cause infectious diarrhea in immunocompromised hosts; however, colonic cryptococcal infection has rarely been reported.[1-3] Cryptococcal infection is one of the principal opportunistic infections

in immunocompromised patients, especially those living with HIV and in patients with other immunosuppressive conditions such as prolonged glucocorticoid or immunosuppressant use after organ transplantation. The incidence of cryptococcosis in AIDS patients has significantly decreased because of the early diagnosis of HIV infection and introduction of effective antiretroviral therapy (ART).[4,5] Although the lungs and central nervous system are most commonly affected, cryptococcal infections of the skin and musculoskeletal system are also frequently encountered; however, colonic cryptococcosis is extremely rare.[3,5] We recently encountered a rare case of colonic cryptococcosis that caused chronic diarrhea in a patient with AIDS.

CASE REPORT

A 41-year-old man presented to the emergency department with a 1-day history of low-grade fever and confusion. He had gradually lost 15 kg in weight and developed asthenia in the 6 months prior to presentation. Four months prior to presentation, he visited another hospital with recurrent abdominal discomfort and sporadic diarrhea, and planned to undergo further evaluation. He reported significant general debility and decreased appetite for several days. He had been diagnosed with HIV infection 8 years prior to visiting Jeju National University Hospital; nevertheless, he had never received medical treatment for HIV infection or undergone relevant laboratory tests. Physical examination revealed no neurological deficits but revealed difficulty in concentration.

His blood pressure was 131/86 mmHg, pulse rate was 113/min, respiration rate was 20 breaths/min, body temperature was 37.8°C, and oxygen saturation was 98% on room air. Laboratory studies revealed the following: white blood cell (WBC) count, 2,400/mm^3 (normal, 4,500-11,000/mm^3); segmented neutrophils, 78.9%; lymphocytes, 12%; C-reactive protein, 0.76 mg/dL (normal, 0-0.3 mg/dL); and erythrocyte sediment rate, 101 mm/hour (normal, 0-9 mm/hour). The HIV antigen/antibody test was positive, HIV-1 RNA level was 4,640,000 copies/mL, and CD4 T lymphocyte cell count was 62 cells/μL. Magnetic resonance imaging of the brain revealed nonspecific findings. A lumbar puncture was performed, and cerebrospinal fluid (CSF) analysis revealed the following normal findings: WBC count, 0/mm^3; protein, 78 mg/dL; and glucose, 53 mg/dL (serum glucose, 120 mg/dL). The Gram staining, India ink staining, and cryptococcal antigen test results were negative. Chest computed tomography (CT) revealed patchy ground-glass and mosaic attenuation in both lungs, suggesting atypical pneumonia, including *Pneumocystis jirovecii* pneumonia (PCP). On day 2, bronchoscopy and bronchial washing were performed. Polymerase chain reaction (PCR) of bronchoalveolar lavage (BAL) fluid was positive for *Pneumocystis jirovecii* but negative for *Mycobacterium tuberculosis* on PCR and acid-fast bacillus (AFB) smear (AFB culture was shown to be negative 2 months later). Treatment for PCP was initiated with trimethoprim-sulfamethoxazole, equivalent to trimethoprim 10 mg/kg/day. Highly active ART with bictegravir/emtricitabine/tenofovir alafenamide was initiated on day 5. Although his general condition gradually improved, his fever worsened, and he complained of abdominal discomfort and worsening

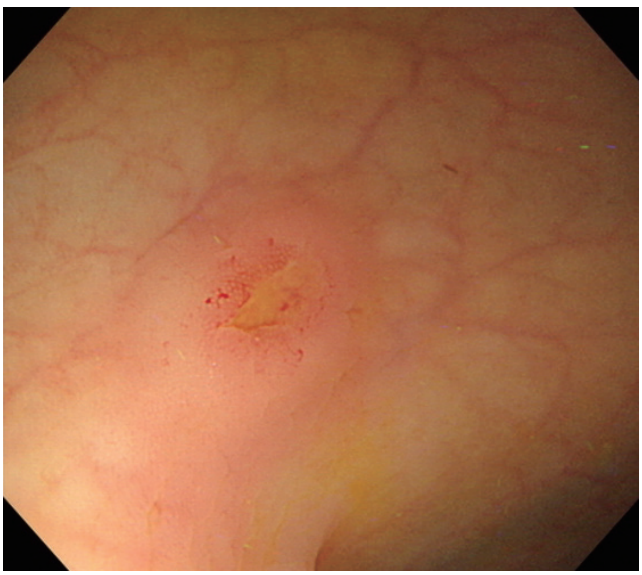

Figure 1. Endoscopic findings. A single small ulcer was observed in the distal transverse colon.

diarrhea. Abdominal CT revealed numerous enlarged lymph nodes, with some central necrotic lymph nodes in the mesenteric and aortocaval areas. Interferon-gamma release assay and cytomegalovirus PCR were performed, and anti-neutrophil cytoplasmic antibodies and anti-*Saccharomyces cerevisiae* antibodies in serum were tested; however, the results were all negative. Additional colonoscopy revealed a small ulcer in the distal transverse colon, and a biopsy of the ulcerative lesion was performed (Fig. 1). Histopathological examination of the colon tissue samples revealed focal active colitis with many histiocytic infiltrations and fungal spores. Grocott-Gomori's methenamine silver stain and periodic acid-Schiff stain results were compatible with cryptococcal infection, but the tissue was negative for *Mycobacterium tuberculosis* on PCR and AFB staining (Fig. 2). There was no evidence of cryptococcal involvement in other organs, including the lungs and central nervous system (CNS), on imaging studies, BAL fluid tests, CSF examination, and ophthalmological examination. Liposomal amphotericin B (6 mg/kg daily in combination with fluconazole 800 mg) was administered intravenously as induction treatment. Three days after initiating administration of the antifungal agents, the fever subsided, and during the 2 weeks of the induction phase, the patient achieved substantial clinical improvement. Two weeks after the induction therapy, the patient was discharged on oral fluconazole 400 mg daily as consolidation therapy. When the patient visited the outpatient clinic 1 month after discharge, he appeared well and reported improvement in his abdominal pain and diarrhea.

DISCUSSION

There are various causes of diarrhea in people infected with HIV. Organisms that cause infectious diarrhea vary based on the patient's geographic location and immune status.[1,2,6] Fungal opportunistic infections that can affect the gastrointestinal (GI) tract include histoplasmosis, cryptococcosis, and candidiasis.[2,6] This report describes a case of an antiretroviral-naïve patient with colonic cryptococcosis who had been suffering from chronic diarrhea. Most cryptococcal infections occur in patients with CD4 T lymphocyte counts <100 cells/mm^3. In many cases, the signs and symptoms of GI cryptococcosis are obscured by systemic presentations of pulmonary or central nervous system infections, and it is unusual for cryptococcosis to be localized specifically to the GI tract.[6] The clinical presentation of GI cryptococcosis varies from no symptoms to symptoms similar to those of other GI infections, such as abdominal pain, diarrhea, fever, and weight loss; the diagnosis of GI cryptococcosis is often incidental or in autopsies.[7-9] In a retrospective review of 23 autopsied patients with pulmonary or disseminated cryptococcosis, 8/24 patients (33%) had gastrointestinal tract cryptococcal infection, and among them, the colon was affected in some.[3] Thus, it can be surmised that there may be more cases of colonic cryptococcosis that were not diagnosed. Therefore, the diagnosis of colonic cryptococcosis requires high clinical suspicion on the part of the physician to order the relevant tests. Cryptococcosis is diagnosed by the isolation of *Cryptococcus*, direct

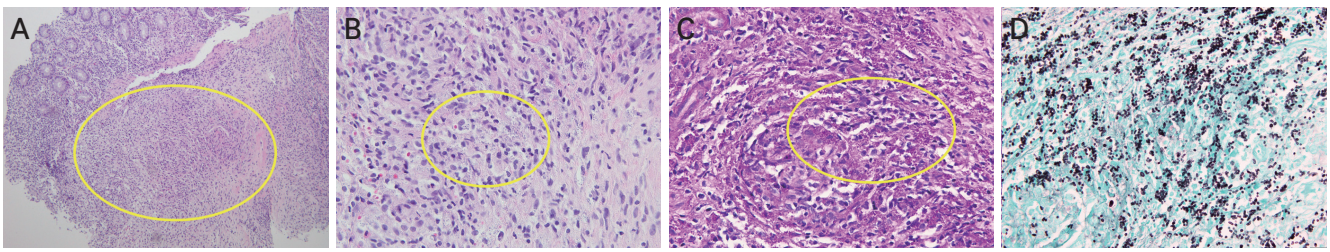

Figure 2. Histopathological findings of the endoscopic biopsy specimen from the distal transverse colon. Focal active colitis with many histiocytic infiltrations and fungal spores in the submucosa were visualized (in the yellow circles of A-C). (A) Hematoxylin and eosin (H&E) staining (×100). (B) H&E staining (×400). (C) Periodic acid-Schiff staining (×400). (D) Grocott-Gomori's methenamine silver staining (×400).

detection of the fungus by India ink staining of body fluids, histopathology, or molecular methods.[5,10] Endoscopic findings at the affected site vary, including erythema, erosion, ulcers, or masses.[7,9] The inflammatory reaction is variable and depends on the host's immune status, ranging from a suppurative necrotizing inflammatory reaction, often with granulomatous features, to virtually no reaction.[11] Treatment for non-meningeal extrapulmonary cryptococcosis is similar to that for CNS involvement: induction therapy using an amphotericin B formulation administered intravenously in combination with oral flucytosine for at least 2 weeks, consolidation therapy using fluconazole 400 mg daily for 8 weeks, and maintenance therapy for a minimum of 1 year using fluconazole 200 mg daily.[12] Although an amphotericin B formulation combined with oral flucytosine is recommended for induction therapy for cryptococcosis in patients with AIDS, flucytosine is not available in Jeju National University Hospital; therefore, fluconazole was administered instead.

In summary, we encountered a rare case of colonic cryptococcosis in a patient with AIDS who presented with chronic diarrhea. Although colonic cryptococcosis is rarely diagnosed, it should be considered in the differential diagnosis in patients with HIV/AIDS and diarrhea.

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