Cryptoccocal menigitis as a primary manifestation in a patient with intestinal lymphangictasia

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Abstract

Opportunistic infections usually occur in patients with an immunocompromised state, and can be severe. Cryptoccocal meningitis is a fatal condition if left untreated, and is usually found in such patients. We report the case of an adult patient with cryptoccocal meningitis secondary to intestinal lymphangiectasia. A 30-year-old female was admitted to our hospital for meningitis. Biochemical and radiological investigations were performed. A cerebrospinal fluid latex agglutination test showed positive cryptoccocal antigen. In addition, there were features of humoral and cell-mediated immunity deficiency (lymphopenia, hypoalbuminemia, hypogammaglobulinemia), with a negative human immunodeficiency virus (HIV) test by enzyme-linked immunosorbent assay and polymerase chain reaction. An upper gastroduodenoscopy was performed, which showed multiple lymphangiectasias, and a biopsy confirmed the diagnosis of primary intestinal lymphangiectasia (PIL). The patient was treated with intravenous amphotericin B and oral flucytosine, and the meningitis resolved. PIL should be suspected in patients with cryptoccocal meningitis, combined with humoral and cell-mediated immunity with a negative HIV test. The management issues, in addition to antifungal therapy, include nutritional supplements for the protein losing enteropathy.

Key Words

Cryptoccocal meningitis, cellular and humoral immunity, intestinal lymphangiectasia

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Introduction

Primary intestinal lymphangiectasia (PIL) is a rare disorder characterized by dilated intestinal lacteals, resulting in lymph leakage into the lumen of the small bowel, and is responsible for protein-losing enteropathy, leading to lymphopenia, hypoalbuminemia and hypogammaglobulinemia.[1] Although PIL patients have moderate to severe hypogammaglobulinemia and lymphopenia, their risk of contracting a pyogenic bacterial infection is not significantly elevated, and opportunistic infections are uncommon. Only one case of a severe infection with group G streptococcal empyema was reported,[2] and another had cryptococcal meningitis.[3] In this report, we describe the occurrence of cryptoccocal meningitis in an adult as the primary manifestation of PIL.

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Case Report

A 30-year-old woman (weight 46 kg) presented to our department with severe headache since the last 7 months. Her past history was unremarkable. On general physical examination, there was moderate pallor with mild pedal edema. Neurological examination revealed bilateral papilledema. There were no focal neurological deficits and meningeal signs were absent. The patient was admitted and investigated to evaluate the cause of raised intracranial pressure.

Magnetic resonance imaging (MRI)Brain Plain and Contrast Study showed mild meningeal enhancement with normal venogram. Cerebrospinal fluid (CSF) was under high pressure (280 mm of water) with 30 cells (80% lymphocytes and 20% neutrophils), protein was 53 mg%, glucose was 12 mg% and chlorides were 125 mg%. CSF India Ink preparation and latex agglutination test for cryptoccocus was positive (1:16 dilution). CSF cultures (fungal) showed growth of *Cryptoccocus neoformans*.

Routine hematological investigations revealed moderate anemia and lymphocytopenia (Hb 6.6 gm/dl, total WBC count 9100 cells/mm^3 with polymorphs 95%, lymphocytes 5% and ESR 2 mm/1^{st} hr). Peripheral smear showed microcytic hypochromic

anemia with lymphopenia. As the lymphocyte count was low on two occasions, absolute CD4 count was done and was found to be very low at 44 cells/μl (normal 354–1100 cells/μl). Tests for human immunodeficiency virus (HIV) with enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) were negative.

At the same time, we found that her total serum protein was 3.4 gm%, with albumin 1.5 gm%. Renal parameters, serum bilurubin and liver enzymes were normal. There was no evidence of proteinuria. Ultrasound of chest and abdomen showed mild bilateral pleural effusions and ascitis with normal liver and kidneys.

As the patient had low protein we also assessed the levels of various serum globulins. Serum immunoglobulins were low IgG-793 (normal 800–1700 mg/dl), IgA-126 (100–490 mg/dl) and IgM-38 gm/L (50–320 mg/dl). Serum ceruloplasmin was 14.7 mg/dl (normal 13–36 mg/dl). On iron studies, although the serum iron was low at 8.0 mg/dl (normal 49–151 mg/dl), total iron binding capacity was 241 mcg/dl (normal 250–400 mcg/dl), indicating low serum transferrin levels. On further investigations, the lipid profile showed total cholesterol of 129 mg/dl (normal range 160–200), low-density lipoprotein cholesterol 86 mg/dl (normal range 100–129 mg/dl), very low-density lipoprotein cholesterol 13 mg/dl (normal range 5–40 mg//dl) and Triglycerides 65 mg/dl (normal<150 mg/dl), suggestive of hypocholesterolemia.

We started investigating the patient for causes of a combination of protein losing enteropathy, hypocholesterolemia and lymphopenia. Stool examination for giardiasis was negative. A diagnosis of intestinal lymphangiectasia was suspected in view of deficient humoral and cellular immunity with low albumin. The patient was subjected to upper gastrointestinal (GI) endoscopy, which showed a whitish granular appearance of mucosa in the duodenum with white-tipped villi, scattered white spots, white nodules and submucosal elevations [Figure 1], suggestive of lymphangiectasia. The biopsy from duodenal mucosa showed dilated intramucosal and submucosal lacteals, which confirmed the diagnosis [Figure 2]. The patient was treated with IV amphotercin 0.7 mg/kg/day and flucytosine 100 mg/kg/day in divided doses for a period of 2 weeks followed by repeat CSF analysis, which showed persistent antigen; hence, antifungals were continued for another 8 weeks. She was also treated with a low-fat, high-protein diet supplemented with medium chain triglycerides. There was remarkable improvement in her general condition and meningitis resolved. CSF analysis at the end of 10 weeks was normal. She was continued on oral flucanozole 200 mg twice daily as per the Center for Disease Control (CDC) guidelines for management of cryptococcal meningitis in immunocompromised patients. Henceforth, she is under regular follow-up and there is mild improvement in her CD4 count at 3 months (100 cells/μl). Till date, she is on maintenance doses of oral fluconazole and is asymptomatic.

Discussion

Cryptoccocal meningitis is the most common form of fungal meningitis, and is caused by *Cryptoccocus neoformans*. [4] It is commonly encountered in immunocompromised patients with impaired cell-mediated immunity. This possibility should always be considered in any patient presenting with chronic meningitis with an underlying immunocompromised state. In an HIV infection, it usually occurs in the advanced stages, when the CD4 count falls below 100 cell/mm^3. It also occurs in non-HIV patients who are immunodeficient due to corticosteroid therapy, lymphoproliferative disorders, renal failure/dialysis, cirrhosis, hypogammaglobulinemia, sarcoidosis, diabetes mellitus, idiopathic CD4+ lymphocytopenia and, rarely, in healthy individuals with no obvious predisposing factors.[5]

Intestinal lymphangiectasia is a rare disorder, characterized by dilated intestinal lacteals resulting in lymph leakage into the small bowel.[1] The etiology can be either primary (Waldmann's syndrome) or secondary due to an underlying cause. Protein-losing enteropathies, associated with intestinal lymphangiectasia may arise secondary to constrictive pericarditis, intestinal lymphoma, lymphenteric fistula, Whipple's disease, Crohn's disease, sarcoidosis, intestinal tuberculosis, giardiasis,[6] systemic sclerosis radiation and/or

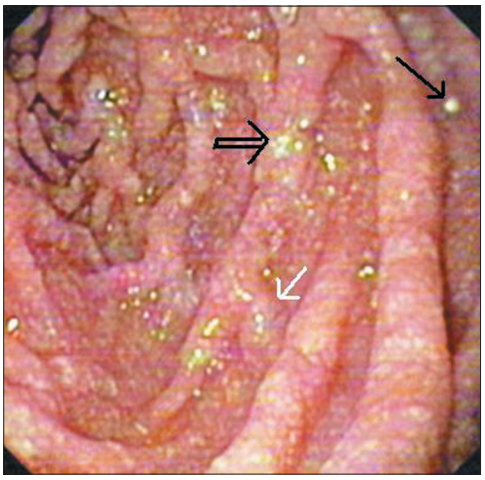

Figure 1: Upper gastrointestinal endoscopy pictures revealing whitish granular appearance of duodenal mucosa with white-tipped villi (open black arrow), scattered white spots, white nodules (solid black arrow) and submucosal elevations (white arrow)

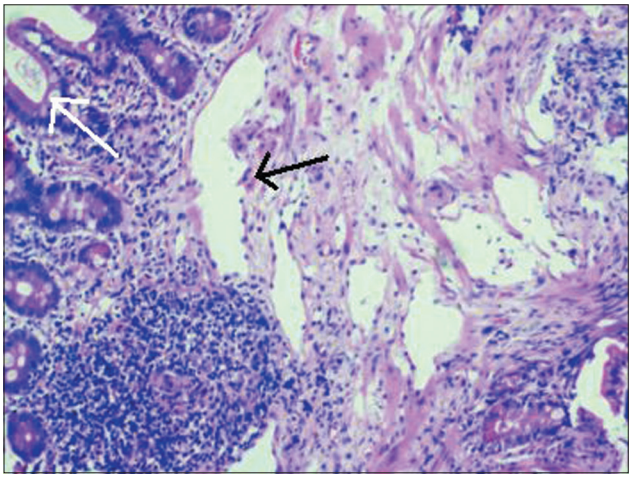

Figure 2: Histopathology of the upper duodenal mucosa with hematoxylin stain shows dilated intramucosal (white arrow) and submucosal lacteals (black arrow)

chemotherapy with retroperitoneal fibrosis[7] or cirrhosis.[8] The PIL usually presents in children below 3 years of age, but may be diagnosed in older adults too. Clinical manifestations include abdominal pain, nausea, vomiting, chronic diarrhea, failure to thrive, growth retardation and, rarely, an abdominal mass due to bowel edema. Other manifestations include lymphedema, edema due to hypoproteinemia, anasarca, ascites and pleural effusions. Rarely, it may be totally asymptomatic. Laboratory findings include decreased serum total protein and albumin along with decreased immunoglobulin levels. The number of lymphocytes, especially CD4+ and CD8+ lymphocytes, is decreased in almost every patient. In spite of hypogammaglobulinemia and lymphopenia, pyogenic bacterial infections and opportunistic infections are uncommon.[1]

Only two cases of disseminated cryptoccocal meningitis and osteomyelitis in patients with lymphangiectasia have been reported in the literature so far.[3,9] Our case is the first report of primary cryptoccocal meningitis without features of dissemination of infection to other organs as a primary manifestation of intestinal lymphangiectasia. Seronegativity to HIV and lymphopenia, reduced CD4 count, low level of serum immunoglobulins indicating a combined deficiency of humoral and cell-mediated immunity, the associated features of malabsorption syndrome like low levels of serum albumin, total cholesterol, transferrin and ceruloplasmin has led to the suspicion of the presence of primary lymphangiectasia. An upper GI endoscopy and biopsy confirmed the diagnosis. The management of our patient included a low-fat, high-protein diet supplemented with medium chain triglycerides, which resulted in the reversal of clinical and biochemical signs. A small bowel resection is useful in rare cases in which intestinal lymphangiectasia is segmental and localized.

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