Chronic diarrhea caused by *Blastocystis hominis* and *Cryptosporidium sp.* in immunocompetent patient-a case report

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Abstract. *Blastocystis hominis* and *Cryptosporidium sp.* are commonly associated with immunocompromised patients. Severe clinical manifestation can be produced by this organism. It varies according to immune status, and subtype of this organism. Unfortunately, we found an immunocompetent patient with chronic diarrhea caused by this organism. A 38-year old male was admitted to Adam Malik General Hospital because of watery diarrhea since four days ago. Administration of fluid replacement was done to this patient, but the frequency of diarrhea did not decrease. Loperamide as anti-spasmodic was also given in each episode of diarrhea. Surprisingly, fecal smear examination revealed that this patient positive for *Blastocystis hominis* and *Cryptosporidium sp.* Thus, diarrhea was resolved for four days without giving any anti-parasitic drugs to the patient.

1. Introduction

*Blastocystis hominis* is an intestinal parasite which found throughout the country with prevalence different in each study, 60% in developing countries and 5-20% in the developed country.[1] This organism has been re-classified as Stramenopila (not as protozoa) and consists of nine distinct subtypes. Reservoir host of this organism is human. Clinical manifestations are associated with a subtype of this organism and immune status of the host.[2] It explains why clinical manifestation caused by this organism usually found in the immunocompromised patient. Diagnosis can be made by using fecal specimen with iron hematoxyline or trichrome stain under a microscope. Symptoms vary in presentation, such as diarrhea, as the primary symptom, abdominal discomfort, anorexia, and flatulence. But, Blastocystis infection controversially produces symptom, particularly in immunocompetent hosts and eradication is still debatable.[3,4]

*Cryptosporidium sp.* is widely recognized as an organism related to an immunocompromised condition which infects lung and gastrointestinal tract. *Cryptosporidium hominis* and *Cryptosporidium parvum* are associated with human infection, but between these two species are indistinguishable.[5] Evidently, Cryptosporidium can cause severe diarrhea, particularly in children population and immunocompromised hosts. In immunocompetent population, approximately there are 6.1 % of diarrheal disease caused by Cryptosporidium. Cryptosporidium proliferates inside the microvillus layer of the small intestine; it explains this infection could affect intestinal absorption and lead to...
malnutrition.[6,7] Blastocystis hominis and Cryptosporidium sp. are parasitic intestinal infection associated with weak immune status.[8]

2. Findings
A 38-year old male was admitted to Adam Malik General Hospital for watery diarrhea lasting for four days with 5-6 episodes a day. He was complaining about his fatigue, nausea, anorexia, and abdominal cramps since several days before diarrhea occurred. Elevation of body temperature was noted to this patient (39.0°C), other vital signs were normal. The composition of his feces was consist of mostly water. No abnormal finding was found in chest X-ray. Blood workup showed no leukocyte elevation (6,140/µL) but mildly reduction thrombocyte (189,000/µL). He was also not anemic (17.6 g/dL) and his hematocrit was a little higher than normal man (52%). He excluded from immunocompromised condition by doing several tests, such as anti-retrovirus antibody was negative, surface antigen of hepatitis b virus (HBsAg) was also negative, kidney function test (ureum= 43 mg/dL, Creatinine= 2.27 mg/dL), blood glucose was normal, and another condition especially can be diagnosed by using anamnesis and physical diagnostic was not found. The electrolyte was also normal in this patient. This patient was also diagnosed with asthma but routinely using maintenance medication and exacerbation never ensued.

During hospitalization, fluid replacement therapy using ringer lactate was done. Nevertheless, there was no change in diarrhea frequency and feces texture. For symptomatic treatment, loperamide was used to treat abdominal cramp and to decrease the frequency of diarrhea. At the second day of admission, fecal smear examination was positive for Blastocystis hominis and Cryptosporidium sp. We did not give the patients with antiparasitic drugs, fortunately, the episodes of diarrhea were decreased. At the fourth day of hospitalization, the diarrhea was resolved without any additional symptom.

3. Discussion
Blastocystis hominis has been considered as yeast, fungi, or protozoa but based on molecular studies this organism is newly reclassified as Stramenopila. It infects lower intestine of humans and animals. Blastocystis role causing various gastrointestinal tract symptom is still debatable. In immunocompetent patient, this organism can cause self-limited disease, predominantly adult patients.[9-11] Several subtypes exist based on host. There are approximately nine subtypes, subtype 1,2,3, and four are common with the human infection.[12-13] Its life cycle consists of several different
forms, such as vacuolar, vacuolar, multivacuolar, granular, ameboid, and cystic defined as morphologic stages in Blastocystis. The cyst stage is an infective form and survives at room temperature for 19 days, but it is still fragile in cold and heat.[14] watery diarrhea, cramping abdominal pain, flatulence, and vomiting/nausea are commonly found in Blastocystis infection. Several studies showed that there was a positive relationship between this parasite and some immune-mediated intestinal condition. Extraintestinal symptom, particularly urticaria, can be induced by this organism.[15-16]

Cryptosporidiosis is an infection caused by apicomplexan protozoa, called Cryptosporidium sp. Cryptosporidium parvum and Cryptosporidium hominis are common species associated with human infection. Worldwide, this organism as a major causative agent inducing watery diarrhea in several populations, mainly in an immunocompromised patient.[17] Sporulated oocyst of Cryptosporidium sp. is an infective stage of this organism. Excystation of oocyst occurs and sporozoites invade enterocytes in the upper part of small intestine. Prevalence of cryptosporidiosis is related to CD4+ count.[18,19]

The immune system is divided into three components, nonspecific immunity (skin and other mucosal barriers), the innate immune system (soluble factors and cells), and adaptive immune system.[20] Toll-like receptors and complement will recognize Blastocystis hominis and Cryptosporidium sp. as antigen. After recognition T cell maturation will ensue. It explains why this infection is related to the function of T cell.[5,21]

Certain studies showed that special mechanism involved in the pathogenesis of Blastocystis infection. There was reported that interaction between cysteine protease and enterocytes related to the inflammatory condition. This substance induces elevation of the pro-inflammatory cytokine, IL-8. Albeit, through several studies the pathogenesis of this organism is not precisely explained.[22,23]

Numerous studies showed that clinical manifestations of this infection are related to the subtype of Blastocystis, for example, subtype 1 is more associated with asymptomatic disease while an infection caused by subtype two could produce symptom, one study revealed that 100% of patients had diarrhea. Subtype 8 infection is a rare but commonly producing severe symptom. Subtype 3 infection is commonly found in human, but it was sometimes producing symptoms. Contradictory studies were also reported, in rat subtype one was related to the symptoms, but there were also strain in subtype 3 and four not related to the symptom. The genome of subtype seven has been fully discovered; some location was also noted in producing important protein for host protease inhibition, this protein could induce a change in intestinal homeostasis. Further studies are needed for unknown pathogenicity in this infection. Age is considered as an independent factor related to Blastocystosis, histological examination of the colon and cecum exhibited positive infiltration of inflammatory cell, oedematous lamina propria, and mild mucosal disruption. The findings commonly found in juvenile mice. Also, host genotype, parasite load, host response, and dysbiosis are another factors influencing the pathogenesis of this infection.[24,25]

By using PCR technique, pathogenesis of Cryptosporidium had been led to a better understanding. There is two major genotype of C.parvum (genotype one has capability causing infection in human and animal, genotype two just infects human).[26] It is evident that cell-mediated immunity has a big role in eradicating Cryptosporidium. Elevation of humoral immune response was also found in this infection, but it remains elusive. In vitro studies revealed that certain cytokines, IFN-γ, IL-12, and TNF-α, were related to favorable immune response, especially against this infection. Innate immune response is also used to eradicate this infection, resolution of this infection can occur even in a patient with impaired T cell function, particularly AIDS patient. Meanwhile, the efficiency of medication to eradicate this organism are still questionable, especially for the immunocompromised patient.[27] Through a genetic study, a study conducted in Bangladesh found the genetic predisposition to cryptosporidiosis, B*15 HLA I allele and DQB1*0301 HLA II allele.[28]

The latest studies stated that several immune mechanisms have a big role in eradicating Cryptosporidium. Since penetration occurs by this organism, the immune system recognizes the antigen by using TLR leads to chemokine production (dependent NF-κB pathway). Antimicrobial
peptides are also decreased in Cryptosporidium infection, especially human β-defensin (HBD) -1. Polymorphisms of mbl2 encoded mannose-binding lectin (MBL) increased susceptibility to this infection. Meanwhile, prostaglandin and substance P were upregulated, especially in jejunal biopsies from AIDS patient.[29] Some antigens might be able to boost humoral and cell-mediated immunity has been revealed, such as gp900, p23/27, gp40, and gp15/17.[30]

4. Conclusions
To conclude, diarrhea caused by Blastocystis hominis and Cryptosporidium sp. still need further study, particularly in an immunocompetent patient. It is noted that these infections are related to T cell function, but many factors can influence the pathogenesis. Through genetic studies, several subtypes have been proved to cause severe disease. This patient had suffered from diarrhea caused by these organisms but not an immunocompromised patient. No anti-parasitic drug was applied to this patient. After four days of hospitalization, this patient was discharged from the hospital. Subtype examination could not be done because the limitation of using PCR-based technique here.

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