CASE REPORT

Mycobacterium ulcerans infection as a cause of chronic diarrhea in an AIDS patient: A case report

Jin-Gook Huh, You-Sun Kim, Jong-Sung Lee, Tae-Yeob Jeong, Soo-Hyung Ryu, Jung-Hwan Lee, Jeong-Seop Moon, Yun-Kyung Kang, Myung-Shup Shim, Myoung-Don Oh

Jin-Gook Huh, You-Sun Kim, Jong-Sung Lee, Tae-Yeob Jeong, Soo-Hyung Ryu, Jung-Hwan Lee, Jeong-Seop Moon, Department of Internal Medicine, Inje University College of Medicine, Seoul 100-032, South Korea
Yun-Kyung Kang, Department of Pathology, Inje University College of Medicine, Seoul 100-032, South Korea
Myung-Shup Shim, Korean Institute of Tuberculosis, Seoul, South Korea
Myoung-Don Oh, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea
Correspondence to: You-Sun Kim, MD, PhD, Department of Internal Medicine, Inje University College of Medicine, Seoul Paik Hospital, Joong-gu, Jeo-dong 2-ga 85, Seoul 100-032, South Korea. yousunk69@korea.com
Telephone: +82-2-22700012 Fax: +82-2-22700579
Received: July 23, 2007   Revised: October 13, 2007

Abstract

Chronic diarrhea is one of the most frequent gastro-intestinal manifestations in acquired immunodeficiency syndrome (AIDS). Protozoa and nontuberculous mycobacteria (NTM) are opportunistic pathogens that can easily infect these patients. Among the NTM, *Mycobacterium avium* complex (MAC) is the most frequently observed pathogen in HIV-infected patients. However, NTMs other than MAC have not been reported as a gastrointestinal pathogen as yet. We present a case of chronic diarrhea in an AIDS patient in whom *Mycobacterium ulcerans* and *cryptosporidium* co-infection is evidenced from colonic tissue.

INTRODUCTION

HIV infection, which frequently involves the gastro-intestinal tract, may be associated with diarrhea, abdominal pain, esophageal symptoms, malabsorption, and weight loss[1,2]. The gastrointestinal tract is the major target for pathogens in HIV-infected patients and as many as a third of patients with AIDS are initially seen by a gastroenterologist[3]. In those instances, diarrhea is the most frequent manifestation in AIDS and HIV-positive patients. Diarrhea has been reported to be present at the same time during their illness in as many as 80% of North American patients with AIDS, and the prevalence may approach to 100% in developing countries, causing a significant morbidity and mortality[4-6]. Those suffering from chronic diarrhea tend to have a low quality of life and seem to have higher annual health costs. Typical infectious diseases affecting the intestinal tract in HIV-infected patients are caused by protozoa (*Microsporidium, Cryptosporidium*), bacteria (*Clostridium difficile, Salmonella, Shigella, Campylobacter*, and MAC), viruses (Cytomegalovirus, Herpes simplex) and fungi (*Candida species*). Before the HIV epidemic, NTM was an unusual cause of disease in humans. Nowadays, however, NTM especially MAC, is one of the most common causes of intestinal bacterial infection in AIDS patients[2,7]. But non-MAC NTMs, including *Mycobacterium ulcerans*, have not been reported as a pathogen in the gastrointestinal tract.

We report herein a case of colonic infection with an unusual NTM, *Mycobacterium ulcerans*, which caused chronic diarrhea in a patient with AIDS.

CASE REPORT

A 40-year-old man complained of persistent diarrhea associated with a 9 kg weight loss during the last 3 mo. He described his diarrhea as watery stools that occurred five to six times per day, especially at night. There was no previous history of travel, food, medication, or any medical or familial disease. He denied melena or hematochezia. On physical examination, the patient had a chronic ill-looking appearance but there were no remarkable findings except for a slightly dehydrated tongue. His blood pressure was 110/70 mmHg, pulse was 70 beats per minute, respiratory rate was 20 breaths per minute, and temperature was 36.2℃. His height was 167 cm and weight was 54 kg. The abdomen was soft and nontender
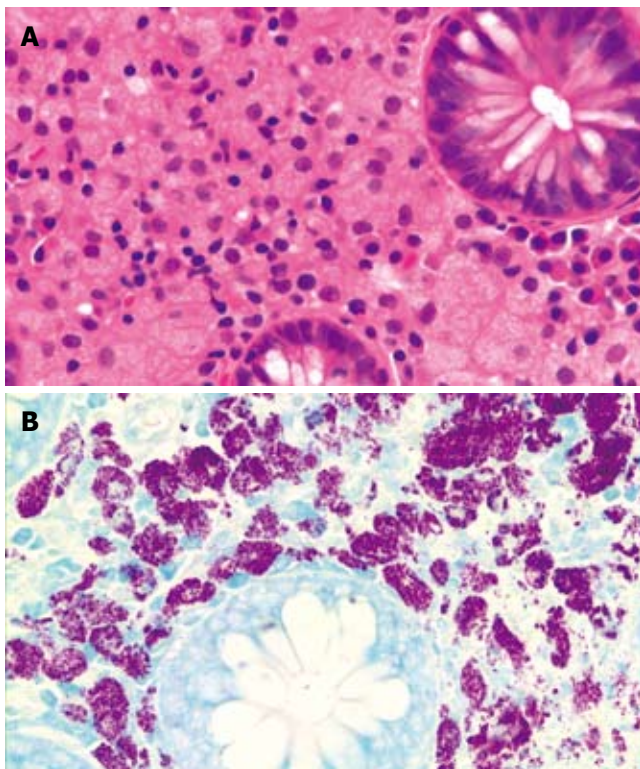
Figure 1 Pathologic examination of biopsy specimen from sigmoid colon revealing foamy histiocytic collections in lamina propria by hematoxylin and eosion stain (**A** × 400) and innumerable acid-fast bacilli collections by Ziehl-Neelsen stain (**B** × 400).
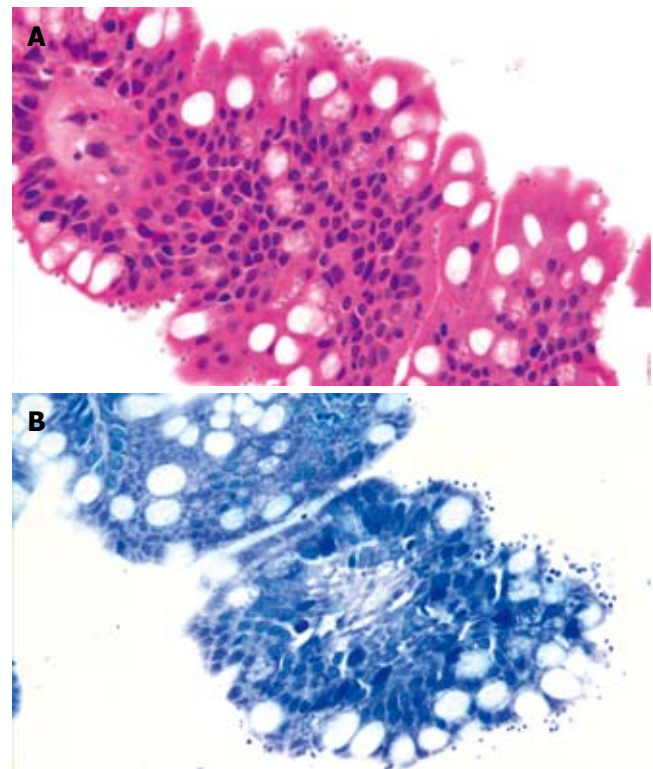

Figure 2 Pathologic examination of biopsy specimen from terminal ileum showing many tiny organisms of the *Cryptosporidium* species with mild chronic inflammation on the surface of the luminal border of the crypt epithelial cells by hematoxylin and eosion stain (**A** × 400) and Giemsa stain (**B** × 400).

without hepatosplenomegaly. The bowel sound was slightly increased. Rectal examination revealed no palpable masses or blood clots. The hemoglobin level was 14.4 g/dL, white blood cell count was $4200/mm^3$, and platelet count was $159\,000/mm^3$. The serum electrolyte levels, urinalysis, and tests of renal, liver, and thyroid function were normal. The C-reactive protein level was 0.1 mg/dL. Stool examinations for ova, parasites, bacterial pathogens, and *Clostridium difficile* toxin were negative. Colonoscopy showed normal findings but a blind mucosal biopsy was done at the terminal ileum and sigmoid colon to evaluate the chronic diarrhea. Also, anti-HIV antibody was checked to rule out AIDS, which is an important cause of chronic diarrhea. The result of anti-HIV antibody was positive. CD4 T cell count was $168/mm^3$. We asked the patient about his medical history again and he admitted to an HIV positive history to us. He was diagnosed with AIDS at another hospital in 2002 and treated with highly active antiretroviral therapy (HAART). However, he voluntarily discontinued his treatment in 2004. The biopsy specimen from the sigmoid colon demonstrated foamy histiocytic collections in lamina propria by hematoxylin and eosin stain and revealed innumerable acid-fast bacilli collections by Ziehl-Neelsen stain (Figure 1). The possibility of NTM on colonic biopsy would have to be considered instead of *Mycobacterium tuberculosis* because of innumerable acid-fast bacilli collections. The biopsy specimen from the terminal ileum demonstrated mild chronic inflammation with protozoa infection consistent with cryptosporidiosis (Figure 2). To further evaluate the small bowel, a capsule
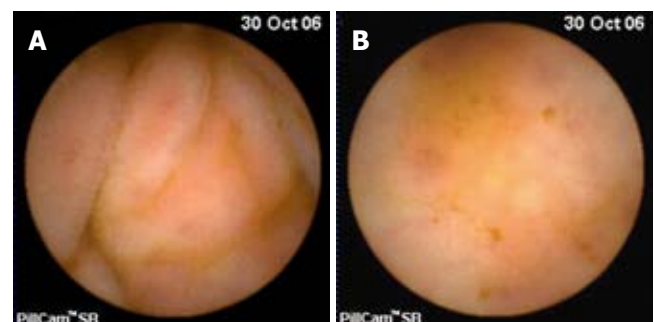

Figure 3 Capsule endoscopic findings of small bowel showing mild edematous (**A**) and hyperemic (**B**) mucosal change.

endoscopy was performed. The whole small bowel showed mild edematous and hyperemic mucosal change (Figure 3).

PCR-restriction fragment length polymorphism analysis (PRA)

To identify the species of NTM, we used PCR-restriction fragment length polymorphism of the rpoB gene. PRA offers an easy, rapid, and inexpensive way to identify *Mycobacterium* species in a single experiment. Recently, Lee et al[8] chose the rpoB gene as a target and the restriction analysis of a 360-bp fragment within the rpoB gene after single Msp I digestion showed that it was highly effective for differentiating most *Mycobacterium*. They suggested that PRA using the novel region of the rpoB gene is more simple, rapid, and accurate versus other
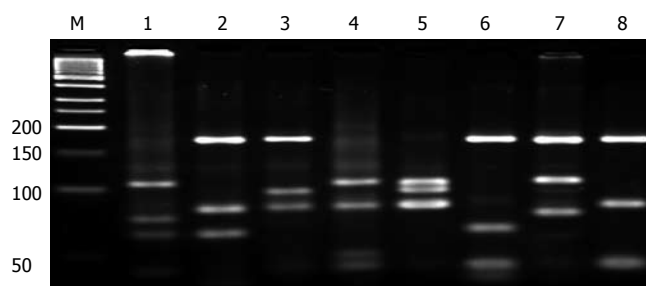
Figure 4 Identification of the species of NTM by PCR-restriction fragment length polymorphism of the rpoB gene. Lane: M, DNA size marker; lane1, M. ulcerans; lane 2, *M. tuberculosis*; lane 3, *M. intracellulare*; lane 4, *M. avium*; lane 5, *M. abscessus*; lame 6, *M. kansasii*; lane 7, *M. fortuitum*; lane 8, *M. gordonae.*

conventional methods such as chromatography or DNA sequence analysis. Briefly, we got the genomic DNA from paraffin-embedded colonic specimen. PCR was carried out with 10 ng genomic DNA, 10 pmol of each primer, 5'-TCAAGGAGAAGCGCTACGA-3' (RPO5') and 5'-GGATGTTGATCAGGGTCTGC-3' (RPO3') and DyNAzyme II DNA polymerase (FINNZYMESY, Espoo, Finland) resulted in a 360-bp PCR product. After successful amplification, the PCR products were subjected to restriction enzyme digestion with 5U of Msp I (Boehringer Mannheim Biochemicals, Mannheim, Germany). For interpreting the PRA profile generated by each species, a 50-bp ladder DNA size marker (Boehringer Mannheim) was used. From the PRA, we discovered that the NTM species was *Mycobacterium ulcerans* (Figure 4).

The patient was diagnosed with *Mycobacterium ulcerans* and *cryptosporidium* co-infection. He was treated with clarithromycin and ethambutol to target the NTM and with HAART for underlying AIDS. After three months of treatment for NTM, the patient said that his diarrhea was much improved.

DISCUSSION

Since the discovery of AIDS in 1981, HIV infection has spread quickly and become a very serious health problem for humans, not only in Western world, but also in Asian area. Since the first case of HIV infection was reported in Korea at 1985, the number of those infected with HIV has steadily increased. Despite the introduction of HAART, diarrhea remains a common disease manifestation related to HIV infection and is a diagnostic problem. The incidence of chronic diarrhea in AIDS patients does not change after HAART[9]. In other words, the incidence of opportunistic infections is still too high to ignore them. Opportunistic infections are responsible for 68%-85% of diarrhea in HIV-infected patients[7,10].

Initially, we did not know the exact medical history of the patient. However, HIV-related diarrhea must be included in evaluating chronic diarrhea, especially when it is associated with weight loss. Therefore, we performed a routine serologic test for HIV infection. Patients with chronic diarrhea in HIV-infected persons often cause a difficult diagnostic problem. There are proved pathogens or causes of drugs including protease inhibitors, but no causes of diarrhea are commonly encountered. The

usefulness of endoscope in evaluating diarrhea in HIV-infected patients has been well investigated[11-13]. Because of the common involvement of the small bowel, colonoscopy is preferred to flexible sigmoidoscopy in HIV-infected patients with chronic, unexplained diarrhea[13]. Although colonoscopy is frequently performed in these patients, the usefulness of biopsy of normal mucosa is uncertain. Shah *et al*[14] suggested that colonoscopy with biopsy is a useful tool in the investigation of patients with chronic diarrhea, which yields a histological diagnosis in 31% of patients. In our case, we performed a blind biopsy from normal mucosa, because the serology for HIV was positive, and we thought that the histological evaluation would give us good information for the proper diagnosis. With the histological diagnosis, we had a clue as to how to properly treat the patient. This is in accordance with the suggestion of Shah *et al*[14] that colonoscopy with biopsy is a useful tool in the investigation of patients with chronic diarrhea, not only from the abnormal mucosal lesion but also from the normal one.

NTMs are ubiquitous organisms that are different from tuberculosis and represented by more than 65 different species[15]. The most frequent forms of NTM include *Mycobacterium avium* complex (MAC, 61%), *Mycobacterium fortuitum* (19%) and *Mycobacterium kansasii* (10%), with smaller percentages of *Mycobacterium gordonae* and *Mycobacterium chelonae*[15,16]. Mycobacterial involvement of the bowel either by tuberculosis or MAC may lead to diarrhea. Antony *et al*[17] reported that MAC is the most commonly identified organism in patients with chronic diarrhea and low CD4 lymphocyte counts. Although tuberculosis appears to be symptomatic in all cases, a large number of patients with MAC have an asymptomatic infection of the gut. Endoscopic findings of MAC infection may be nonspecific. Sun *et al*[18] reviewed 55 reported cases of MAC infection with an endoscopic description which involved the gastrointestinal tract in AIDS patients, and found that the most common endoscopic finding is multiple raised nodules (38%) in the involved sites. The other endoscopic findings of MAC infection include normal findings (36%), erythemas (13%), ulcerations (11%), edemas (11%), friabilities (11%), reduced mucosal vascular patterns (9%), erosions (4%), confluent nodules (4%), strictures (2%), and aphthous erosions (2%). Therefore, for a definitive diagnosis in symptomatic patients, especially those without typical endoscopic findings, it is essential to obtain tissue specimens for histopathologic examination and microbiologic culture. Isolates of *Mycobacterium* from tissue biopsies or blood are almost always indicative of the disease[19]. The organism is readily seen on biopsy specimens with acid-fast staining, and the number of organisms is often striking. Rarely, a NTM other than a MAC has been isolated upon a colonic biopsy in a HIV patient[19]. In our case, a very rare NTM, *Mycobacterium ulcerans*, was isolated in colonic mucosa, and it is presumed to be the cause for the patient's chronic diarrhea. Many clinical syndromes are similar to those seen with MAC and only can be differentiated by identification of the organism, like PRA or DNA sequence analysis[20].

Mycobacterium ulcerans is known to cause skin diseases, such as Buruli ulcer, an important health problem in

several West African countries. Although the disease is known to be associated with contaminated water, the mode of transmission has not yet been understood[21,22]. *Mycobacterium ulcerans* produces the toxin mycolactone, which induces necrosis and ulceration by its own cytotoxic and immunosuppressive properties. HIV infection has not been reported as a risk factor for Buruli ulcer[23]. However, severe clinical forms of the disease have been described in HIV-positive patients[24]. To our knowledge, this is the first case of colonic infection with *Mycobacterium ulcerans*, which caused chronic diarrhea in a patient with AIDS.

In conclusion, *Mycobacterium ulcerans* and *crypto-sporidium* co-infection is the cause of chronic diarrhea in AIDS patients. Serologic test of HIV must be performed when evaluating chronic diarrhea, especially when it is associated with significant weight loss. We think that colonoscopy with routine biopsy is a useful tool for accurate diagnosis of chronic diarrhea.

REFERENCES

1   **Smith PD**, Quinn TC, Strober W, Janoff EN, Masur H. Gastrointestinal infections in AIDS. *Ann intern Med* 1992; **116**: 63-77

2   **Dworkin B**, Wormser GP, Rosenthal WS, Heier SK, Braunstein M, Weiss L, Jankowski R, Levy D, Weiselberg S. Gastrointestinal manifestations of the acquired immunodeficiency syndrome: a review of 22 cases. *Am J Gastroenterol* 1985; **80**: 774-778

3   **Dancygier H**. AIDS and gastrointestinal endoscopy. *Endoscopy* 1992; **24**: 169-175

4   **Mayer HB**, Wanke CA. Diagnostic strategies in HIV-infected patients with diarrhea. *AIDS* 1994; **8**: 1639-1648

5   **Orenstein JM**, Chiang J, Steinberg W, Smith PD, Rotterdam H, Kotler DP. Intestinal microsporisdiosis as a cause of diarrhea in human immunodeficiency virus-infected patients. *Hum pathol* 1990; **21**: 475-481

6   **Colebunders R**, Francis H, Mann JM, Bila KM, Izaley L, Kimputu L, Behets F, Van der Groen G, Quinn TC, Curran JW, Piot P. Persistent diarrhea, strongly associated with HIV infection in Kinshasa, Zaire. *Am J Gastroenterol* 1987; **82**: 859-864

7   **Blanshard C**, Gazzard BG. Natural history and prognosis of diarrhea of unknown cause in patients with acquired immunodeficiency syndrome (AIDS). *Gut* 1995; **36**: 283-286

8   **Lee H**, Park HJ, Cho SN, Bai GH, Kim SJ. Species identification of mycobacteria by PCR-restriction fragment length polymorphism of the rpoB gene. *J Clin Microbiol* 2000; **38**: 2966-2971

9   **Call SA**, Heudebert G, Saag M, Wilcox CM. The changing etiology of chronic diarrhea in HIV-infected patients with CD4 cell counts less than 200 cells/mm3. *Am J Gastroenterol* 2000; **95**: 3142-3146

10   **Laughon BE**, Druckman DA, Vernon A, Quinn TC, Polk BF, Modlin JF, Yolken RH, Bartlett JG. Prevalence of enteric pathogens in homosexual men with and without acquired immunodeficiency syndrome. *Gastroenterol* 1988; **94**: 984-993

11   **Kearney DJ**, Steuerwald M, Koch J, Cello JP. A prospective study of endoscopy in HIV-associated diarrhea. *Am J Gastroenterol* 1999; **94**: 596-602

12   **Bini EJ**, Cohen J. Diagnostic yield and cost-effectiveness of endoscopy in chronic human immunodeficiency virus-related diarrhea. *Gastrointest Endosc* 1998; **48**: 354-361

13   **Bini EJ**, Weinshel EH. Endoscopic evaluation of chronic human immunodeficiency virus-related diarrhea: Is colonoscopy superior to flexible sigmoidoscopy? *Am J Gastroenterol* 1998; **93**: 56-60

14   **Shah RJ**, Fenoglio-Preiser C, Bleau BL, Giannella RA. Usefulness of colonoscopy with biopsy in the evaluation of patients with chronic diarrhea. *Am J Gastroenterol* 2001; **96**: 1091-1095

15   **Guide SV**, Holland SM. Host susceptibility factors in mycobacterial infections. *Infect Dis Clin North Am* 2002; **16**: 163-186

16   **Phillips MS**, von Reyn CF. Nosocomial infections due to nontuberculous mycobacteria. *Clin Infect Dis* 2001; **33**: 1363-1374

17   **Antony MA**, Brandt LJ, Klein RS, Bernstein LH. Infectious diarrhea in patients with AIDS. *Dig Dis Sci* 1988; **33**: 1141-1146

18   **Sun HY**, Chen MY, Wu MS, Hsieh SM, Fang CT, Hung CC, Chang SC. Endoscopic appearance of GI mycobacteriosis caused by the *Mycobacterium avium* complex in a patient with AIDS: case report and review. *Gastrointest Endosc* 2005; **61**: 775-779

19   **Yates MD**, Pozniak A, Uttley AH, Clarke R, Grange JM. Isolation of environmental mycobacteria from clinical specimens in south-east England: 1973-1993. *Int J Tuberc Lung Dis* 1997; **1**: 75-80

20   **Jones D**, Havlir DV. Nontuberculous mycobacteria in the HIV infected patient. *Clin Chest Med* 2002; **23**: 665-674

21   **Sizaire V**, Nackers F, Comte E, Portaels F. *Mycobacterium ulcerans* infection: control, diagnosis, and treatment. *Lancet Infect Dis* 2006; **6**: 288-296

22   **van der Werf TS**, Stienstra Y, Johnson RC, Phillips R, Adjei O, Fleischer B, Wansbrough-Jones MH, Johnson PD, Portaels F, van der Graaf WT, Asiedu K. *Mycobacterium ulcerans* disease. *Bull World Health Organ* 2005; **83**: 785-791

23   **Raghunathan PL**, Whitney EA, Asamoa K, Stienstra Y, Taylor TH Jr, Amofah GK, Ofori-Adjei D, Dobos K, Guarner J, Martin S, Pathak S, Klutse E, Etuaful S, van der Graaf WT, van der Werf TS, King CH, Tappero JW, Ashford DA. Risk factors for Buruli ulcer disease (*Mycobacterium ulcerans* infection): results from a case-control study in Ghana. *Clin Infect Dis* 2005; **40**: 1445-1453

24   **Johnson RC**, Ifebe D, Hans-Moevi A, Kestens L, Houessou R, Guedenon A, Meyers WM, Portaels F. Disseminated *Mycobacterium ulcerans* disease in an HIV-positive patient: a case study. *AIDS* 2002; **16**: 1704-1705