A Thai Man with Chronic Diarrhea for 2 Years

Wuthiphong Chaiphornphathana, M.D.
Chinnavat Suthivana, M.D.
Winyoo jantrasoontragul, M.D.

ABSTRACT

Cytomegalovirus infection occurs in immunocompromised patients or previously treated with systemic corticosteroids or immunosuppressant. However, CMV infection may occur in immunocompetent patients, which is recognized as a rare condition. We report a case of cytomegalovirus (CMV) colitis in case of steroid naive ulcerative colitis (UC) after mesalamine treatment for 24 months. A review of previous case coincident CMV and UC are explored. Only six previous cases of CMV colitis were reported in patients naive to systemic corticosteroids. We also discuss the relationship between CMV infection and UC as well as the diagnosis, treatment, patient characteristic and outcome. Cytomegalovirus infection should be included in the differential diagnosis of steroid naive UC patients with refractory to conventional non steroids regimen.

Key words: Cytomegalovirus, Steroid-Naïve, Ulcerative Colitis

A married man 49 years old, Ang-thong Province, Thailand.

Chief complaint: chronic diarrhea for more than 2 years.

Present illness: Two years ago, he had non-specific abdominal pain at lower abdomen and mucous bloody stool. He defecated more than 10 times per day, both at night and during the daytime. He had urgency of defecation and tenesmus. Other symptoms were nausea, vomiting and non-shivering low grade fever. He visited many physicians and got many kinds of drugs, such as antibiotics and oral rehydration solution but the symptoms was still worse. He lost weight in about 8 kilograms (kg) in one month. He went to other private and University Hospital for more investigations such as stool exam and culture, biochemistry blood tests, HIV antibody test, and colonoscopy. The biopsy of colonic mucosa was done and he got the treatment with mesalamine (250 mg) 1 tab tid pc for 3 months. He felt better, less diarrhea about 5-6 times per day but his body weight did not increase. So, he had to do the 2nd colonoscopy and biopsy. He continued the treatment with the increased dose of mesalamine; (250 mg) 2 tablets in the morning and evening plus 1 tablet after lunch. His symptoms were still not improved. After he had taken this drug for two years, he was treated
with steroid rectal suppository before bedtime since one month ago but he still had symptoms. At last, he came to Bhumibol Hospital for proper treatment.

**Past history:** He had history of prolapsed internal hemorrhoid grade 2 for 20 years which occasionally bled.

**Personal history:** He had no alcohol drink, and had no history of homosexual activity. He refused herbal medications. He was a nonsmoker. There was no anyone in his family had the similar symptoms.

**Physical examinations**

**General appearance:** middle aged man, well nourished, and no apparent distress, normal consciousness and well cooperative.

**Vital signs:** temperature of 36.5°C, pulse rate 76 beats/min, respiratory rate of 22/ min, blood pressure 138/89 mmHg.

**HEENT:** mild pale conjunctiva, no icteric sclera and no cervical lymph node enlargement

**Heart and Lung:** regular heart rate, normal heart sound and normal breath sound

**Abdomen:** mild bulging, normal bowel sound, soft, no tenderness, no guarding, no rebound tenderness, no hepato-splenomegaly.

**Extremities:** no edema

**Rectal examination:** normal appearance of perineum, no rectal mass, normal internal and external rectal sphincter tone, mucous yellow brown colored stool.

**Investigations**

**CBC:** Hb 9.5 g/dl, Hct 29.8 %, WBC 12,100 / ul, N 85%, L 10%, M 5%, platelet. 500,000 / ul, MCV 68.6 , MCH 21.8 MCHC 31.7, RDW 17.5.

**Peripheral Blood Smear:** hypochromic microcytic blood picture, no anisopoikilocysis.

**Urinalysis:** clear yellow color, sp gr 1015, protein and glucose were negative, no WBC and no RBC.

**Stool examination:** mucus and watery, WBC20-30 / HPF, RBC 30-50 / HPF, stool occult was positive, stool parasite absent for 3 days.

**Blood chemistry:** BUN 17 mg/dl, Cr 0.9 mg/dl, Na 138 mmol/l, K 4.0 mmol/l, Cl 106 mmol/l, CO2 24 mmol/l, total protein 7.2 g/dl, albumin 3.8 g/dl, total bilirubin 0.2 mg/dl, direct bilirubin 0.1 mg/dl, SGOT 15 u/l, SGPT 35 u/l, alkaline phosphatase 83 u/l

**AntiHIV:** negative

**Stool culture:** No enteric pathogen

**Stool for C. difficile toxin:** Toxin A negative

**CMV study:** CMV IgG EIA 11.8 IU/ML (<0.5 IU/ML), CMV IgM EIA negative

**CMV viral load:** < 400 copies/ml

**ESR:** 87 mm/hr, CRP negative

**Colonoscopy findings as shown (Figure 1A-D):**

Endoscopy was done up to cecal area. The mucosa from cecum downward to transverse colon looked normal. The colonic mucosa at the splenic flexure level appeared diffuse erythematous, swelling, granularity and friable with multiple superficial ulcerations and whitish exudates as well as multiple polypoid lesions diameter varies from 0.5-4 cm in size. The colonic multiple random biopsies were done at distal sigmoid downward to the rectum.

**Pathological report as shown (Figure 2A, B):**

- **Colonic mucosa:** focal erosion, mucin depletion, and ulceration. Diffuse or mixed acute and together with diffuse cryptitis and abscess. Epithelium revealed reactive atypia. Glandular architecture was distorted. Dysplasia was not seen.

- **Poly like lesion:** multiple fragments of granulation tissue mixed with clumps of fibrin and red blood cells. They contained proliferated vessels and numerous inflammatory cells. Scattered enlarged cells containing intranuclear eosinophilic inclusion were detected among the proliferated vessels.

**Pathological diagnosis**

1. Moderate chronic and acute colitis with ulcer, ulcerative colitis.

2. Granulation tissue with atypical cell compatible with cytomegalovirus inclusion.

**Final diagnosis**

Cytomegalovirus colitis complicating ulcerative colitis.

**Treatment**

Ganciclovir 250 mg/kg per day administered in 2 divided doses, daily, for 3 weeks, plus mesalamine(250) 1 tablet oral t.i.d. pc then his diarrheal symptom had improved from 10 bowel movements/day to 2-3 /day and formed stool in one week.

**DISCUSSION**

This patient was diagnosed as ulcerative colitis (UC), and treated by mesalamine (250mg) with a par-
A Thai Man with Chronic Diarrhea for 2 Years

Figure 1 A-D

Figure 2 A, B Biopsy demonstrating CMV intranuclear inclusion with surrounding clear halo at arrowhead (H&E stain).
tial response. Cause of partial response might be due to the 2 reasons:

1. The sub-optimal dose of mesalamine, regarding to the severity of UC by Trulove and Witt criterias. This patient was classified in the severe grade and should be treated with systemic steroid such as oral prednisolone 40-60 mg/day combined with mesalamine (2-4.8 gm/day) for induction remission and

2. The superimposed infections such as Clostridium difficile or CMV.

Human cytomegalovirus (CMV), originally called human salivary gland virus, was described in 1956. CMV belongs to family Herpesviridae, whose members share a similar genome and virion structure as well as the ability to establish persistent infection with intermittent reactivation. The viral particle is approximately 200 nm in diameter. Several cell types are permissive for CMV replication during natural infection, including endothelial, epithelial cells, fibroblasts, monocyte and dendritic cells. Portals of entry include mucosal surfaces of the upper respiratory, gastrointestinal, and genital tracts after exposure to infectious secretions. The virus disseminates widely via polymorphonuclear leukocytes. Ductal epithelial cells support productive infection resulting in release of infectious virus into secretion such as saliva, breast milk, urine and genital fluids. The host immune response clears viremia within months of primary infection in normal healthy adults. However, CMV remains latent for the lifetime of the host, reactivating intermittently(6).

CMV have a common infection, 40-100% of adults worldwide can detected CMV antibody(2). Diarrhea, hematochezia, tenesmus, abdominal pain, associated with fever, malaise, anorexia and weight loss with wide range of severity were the main symptoms of colon involvements(3). The majority of CMV active disease occurs in immunodeficient patients(4). It has rarely been reported in immunocompetent subjects. All of non UC immunocompetent cases were preceded by some form of mucosal injury i.e. Shigella dysentery, anal intercourse, allergic colitis, amebiasis, and hypotension. All of them had spontaneous resolution in 2-4 weeks(5). It is unclear why some immunocompetent individuals develop CMV colitis. One possibility is that disruption of the colonic mucosa can predispose patients to colonic CMV disease(6). Vogel and colleagues demonstrated in vivo and in vitro that CMV had a propensity to infect proliferating endothelial cells

in inflamed, damaged tissue(7). Infected cells are usually found in ulcer beds or areas of granulation tissue(8). GI-CMV disease, the gross appearance and location of the lesion are similar regardless of the cause of the immunodeficiency. Endoscopic findings reveal ulceration, erosion, and mucosal hemorrhage which are the primary macroscopic findings(1).

Diagnosis can be made with high degree of suspicious because the presentation of CMV colitis is similar to UC flare(11). IgM class and PCR of CMV antigen in urine, culture of the organism from blood, urine, or oropharynx may be the indicators of recent infection, but they do not prove CMV colitis(9). Typical intranuclear and intracytoplasmic inclusion on routine H&E stains, is the gold standard method for determining the presence of active disease(3,10). Immunohistochemical staining, improves the detection rate of CMV by greater than fivefold in patients with refractory and non-refractory UC(10).

**Cytomegalovirus Colitis and UC**

The prevalence of CMV superinfection in patients with IBD is generally low (0.8% to 3.4%). Since 1961, Powell et al. first described a patient with UC and cytomegalic inclusion disease(11). There have been a series of anecdotal case reports and small studies describing the presence of CMV in patients with new onset and long standing UC. The role of CMV infection in patients with UC is controversial(10). Acute ulcerative proctocolitis can be trigger by primary CMV infection and IBD can develop as a result of primary infection with CMV(12). Exacerbation of UC may be associated with secondary CMV infection(13). CMV infection must be considered in steroid-refractory UC(10). In steroid-naive UC patient, CMV colitis is rare; only 6 cases were report in literatures(12,14-17) and showed in Table 1. Involvement can occured regardless of severity and location of the whole colon.(17) As previous reported cases, the deterioration and refractory to the treatment of UC in this patient was associated with CMV, although the virus was not detected after several times of colonic biopsy until the last examination. The improvement of his condition after Ganciclovir therapy supported of CMV as true pathogen. Before antiviral therapy era, the mortality rate was 33% and 80% of the 15 patients required surgical intervention. After Ganciclovir therapy, there was no death case reported, and the surgical treatment was required only 5 of 19 patients (26%)(17).
CONCLUSION

This case report demonstrates of CMV colitis superimposed on ulcerative colitis in the absence of any systemic corticosteroid therapy. Therefore, in refractory UC patients, the other diagnoses including CMV should be considered in the differential diagnosis regardless of previous or concurrent corticosteroid use. Early colonoscopy with multiple stepwise randomized biopsy should be performed to detect any microscopic features of secondary CMV infection or other pathogens. Correct diagnosis of CMV colitis and proper treatment with Ganciclovir can improve the clinical conditions.

REFERENCES