

# İMMÜNKOMPETAN BİR HASTADA HAYATI TEHDİT EDEN SİTOMEGALOVİRÜS KOLİTİ: BİR OLGU SUNUMU

## Life-Threatening Cytomegalovirus Colitis In An Immunocompetent Patient: A Case Report

Sevinç Şahin<sup>1</sup>, Esra Özhamam<sup>2</sup>, Sezer Kulaçoğlu<sup>2</sup>, Selda Seçkin<sup>1</sup>

### ÖZET

Sitomegalovirüs, çoğunlukla immün yetmezliği olan hastalarda ve nadiren de immün-kompetan kişilerde gastrointestinal sistemin herhangi bir yerinde enfeksiyona yol açabilen fırsatçı bir virüstür. Sitomegalovirüs enfeksiyonu immün yetmezliği olan hastalarda hemen her zaman agresif bir seyir gösterir iken tersine immünkompetan bireylerde genellikle kendi kendini sınırlayan bir seyir gösterir. Ancak bazen immünkompetan kişilerde de ciddi tablolara neden olabilir. Biz bu olgu sunumunda 79 yaşında immünkompetan erkek hastada görülen hayati tehdit eden sitomegalovirüs enfeksiyonunu sunuyoruz. Sitomegalovirüs koliti karın ağrısı, diare, hematokezya, melena veya ateş gibi klinik semptomlar ile kendini gösterebilir. Endoskopik olarak, ülserasyon, obstruktif psödomembran oluşumu, mukozal kanama ve/veya inflamatuvar kitleler görülebilir. Histopatolojik olarak, minimal inflamasyondan derin ülserlere veya yaygın nekrozlara kadar değişen geniş bir spektrumda inflamatuvar süreç gözlemlenebilir. Karakteristik histopatolojik özelliği intranükleer veya intrasitoplazmik "baykuş gözü" şeklindeki viral inklüzyonlardır. Bu bildiride ayrıca immünkompetan bireylerde görülen sitomegalovirüs enfeksiyonu ve ayırıcı tanı ile ilgili kısa bir özet de sunulmuştur.

**Anahtar kelimeler:** *Sitomegalovirüs, Kolit, Fırsatçı enfeksiyonlar*

### ABSTRACT

Cytomegalovirus is an opportunistic virus that can cause infection in any part of the gastrointestinal tract, mostly in immunocompromised patients and rarely in immunocompetent individuals. Cytomegalovirus infection almost always shows an aggressive course in immunocompromised patients, in contrary it is usually self-limited in immunocompetent individuals. But sometimes it produces severe manifestations in immunocompetent patients. Herein, we report a case of life-threatening cytomegalovirus colitis in an immunocompetent 79 year-old man. Cytomegalovirus colitis can be presented with clinical symptoms like abdominal pain, diarrhea, hematochezia, melena or fever. In endoscopic examination, ulceration, obstructive pseudomembrane formation, mucosal bleeding and/or inflammatory masses can be detected.

<sup>1</sup>Bozok Üniversitesi Araştırma ve Uygulama Hastanesi Tıbbi Patoloji Anabilim Dalı  
Yozgat

<sup>2</sup>Ankara Numune Eğitim ve Araştırma Hastanesi Patoloji Kliniği  
Ankara

Sevinç Şahin, Yrd. Doç. Dr.  
Esra Özhamam, Uzm. Dr.  
Sezer Kulaçoğlu, Doç. Dr.  
Selda Seçkin, Prof. Dr.

#### İletişim:

Yrd. Doç. Dr. Sevinç Şahin  
Bozok Üniversitesi Araştırma ve Uygulama Hastanesi Tıbbi Patoloji Anabilim Dalı, Yozgat  
Tel: 0 555 557 69 46  
e-mail:  
sevcelik82@gmail.com

Geliş tarihi/Received:01.09.2012  
Kabul tarihi/Accepted:09.02.2013

Histopathologically, inflammatory processes ranging from minimal inflammation to deep ulcers or extensive necrosis can be observed in a wide spectrum. The characteristic histopathological feature is intranuclear or intracytoplasmic “owl’s eye” viral inclusions. A brief summary about cytomegalovirus infection in immunocompetent individuals and differential diagnosis are also given in this report.

**Key words:** *Cytomegalovirus, Colitis, Opportunistic infections*

## INTRODUCTION

CMV, a  $\beta$ -group herpesvirus, can cause various manifestations in congenital or acquired (AIDS, solid organ or bone marrow transplantation, etc.) immunocompromised patients as well as rarely in immunocompetent individuals (1-2). Immunocompromised patients are usually presented with life-threatening lung and intestinal infections. However, CMV infection in immunocompetent patients is generally self-limited and infectious mononucleosis-like clinical findings as fever, atypical lymphocytosis, lymphadenopathy and hepatomegaly are usually observed (3). Although rare in the literature, CMV has been reported to cause severe clinical manifestations like colitis, meningitis, encephalitis, transverse myelitis, thrombocytopenia, hemolytic anemia, uveitis, pericarditis, myocarditis, and pneumonia in immunocompetent individuals (3-4).

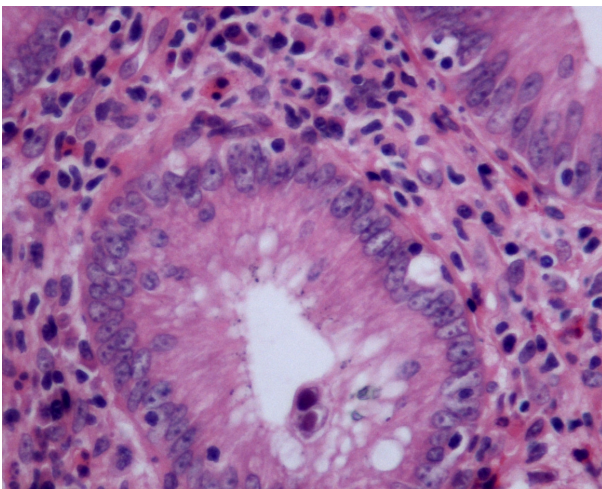
CMV infection may develop anywhere in the gastrointestinal tract but the most common site is the colon (3, 5-6). CMV can affect colon primarily as well as secondary to inflammatory bowel diseases that lead to high mortality due to toxic megacolon and/or exacerbations of the underlying disease (2, 4). Watery or bloody diarrhea, abdominal pain, fever and weight loss are the most common clinical symptoms in CMV colitis. Haematochezia, melena, nausea, and vomiting may also be seen (5, 7). CMV colitis can cause a wide variety of gross lesions in colon (7). The most common lesion is ulceration, either single or multiple and, either superficial or deep (9). Extensive and deep ulcers may

cause intestinal pseudo-obstruction, toxic megacolon and/or perforation (2). Segmental ulcerative lesions and linear ulcers mimicking Crohn’s disease may be seen as well. Mucosal hemorrhage, erosion, edema, pseudomembranes, and obstructive inflammatory masses are the other possible lesions that can be detected grossly (7).

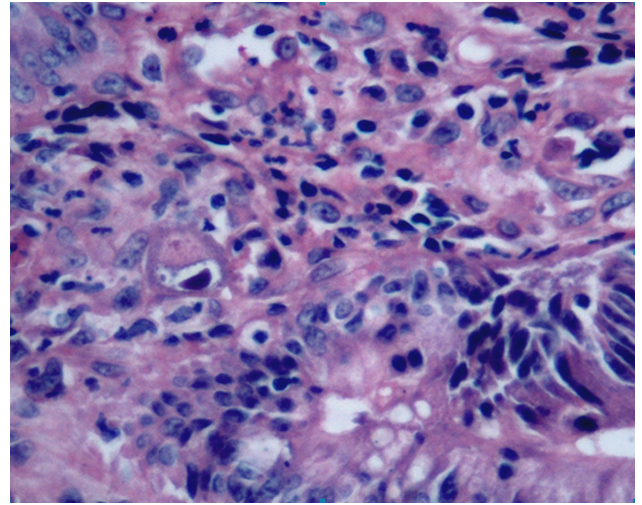
Various nonspecific histological findings ranging from minimal inflammation to deep ulcers, necrosis and extensive granulation tissue can be observed in CMV colitis (7). Both nuclear and cytoplasmic enlargement, and nuclear pleomorphism are usually detected in the affected cells, hence the name “cytomegalovirus” (7). The characteristic histologic feature is basophilic “owl’s eye” intranuclear or intracytoplasmic inclusions with peripheral clear halo, visible on routine hematoxylin and eosin (H&E) preparations (7). Small, granular, basophilic to amphophilic intracytoplasmic inclusions may be seen as well (8). Inclusions are preferentially found in endothelial cells and stromal cells, and only rarely in epithelial cells (7). It is suggested that the tendency of CMV affecting the endothelial cells may lead to activate some inflammatory mediators that cause thrombosis and subsequent bowel ischemia (2). Cryptitis, crypt abscesses, crypt atrophy, crypt loss, apoptotic enterocytes and mixed inflammatory cells including numerous neutrophils in the lamina propria can be seen (2,7). But, while examining the biopsies of severely immunocompromised patients, it should be noted that solely viral inclusions may be observed without any inflammatory reaction (2,7).

## CASE REPORT

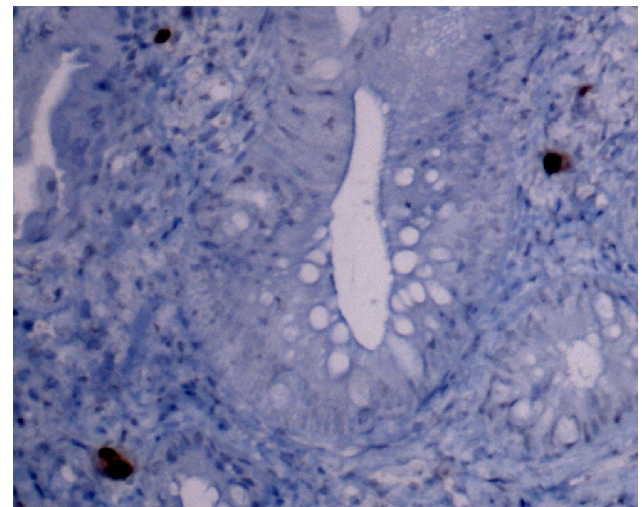
79-year-old male patient was admitted to the emergency department with bloody diarrhea. He had benign prostatic hyperplasia and congestive heart failure, and had no other health problems known. Laboratory investigations showed neutrophilia (74.8%), anemia (haemoglobin 8.7 g/dL), and thrombocytopenia ( $124 \times 10^3/\mu\text{l}$ ), hypernatremia (148 mmol/L), hypokalemia (3.1 mmol/L), hypocalcemia (7.78 mg/dL), and elevated lactate dehydrogenase (261 U/L). Doppler ultrasound examination excluded mesenteric vascular disease. Colonoscopy revealed extensive ulceration and two polypoid lesions measured 0.8 cm and 0.6 cm in diameter, in rectosigmoid colon. Mucosal colon biopsies showed ulceration, acute inflammation, granulation tissue, cryptitis and crypt abscesses. The “owl’s eye” intranuclear viral inclusions and granular eosinophilic intracytoplasmic viral inclusions were detected in the stroma and glandular epithelium, especially in the ulceration base and in the granulation tissue (Figure 1-2). CMV immunostain was positive in a few cells (Figure 3). The histopathological examination was consistent with CMV colitis that was supported by immunohistochemistry. The patient died in a short time by cardiac arrest, thus further clinical information could not be obtained.



**Figure 1.** The characteristic intranuclear “owl’s eye” viral inclusion in glandular epithelium, (H&E, x400).



**Figure 2.** The mixed inflammatory cells including neutrophils in the lamina propria, intranuclear “owl’s eye” viral inclusion and intracytoplasmic eosinophilic granular viral inclusions in the stromal cells, (H&E, x400).



**Figure 3.** The nuclear positivity with CMV immunostain in a few cells, (x400).

## DISCUSSION

The manifestations and complications of CMV infection in immunocompromised patients are well known, whereas, relatively little knowledge or attention is available on the morbidity and mortality of CMV infection in immunocompetent patients. Rafailidis et al. reviewed that severe CMV infection could affect almost every system in immunocompetent patients, the most common system was the gastrointestinal tract and the most common site was the colon (3). The other affected systems and manifestations caused by CMV were given as the central nervous system (meningitis, encephalitis, myelitis, nerve palsies, myeloradiculopathy), hematological manifestations (hemolytic anaemia and thrombocytopenia), the eye (uveitis, retinitis), liver (hepatitis), lung (pneumonitis) and thrombosis of the arterial and venous system (deep venous thrombosis, portal vein thrombosis, pulmonary embolism) in a decreasing order of frequency (3). The mortality rate varies between 6.2% and 32% in the literature in immunocompetent patients with CMV colitis (3). And it is suggested in the literature that the prognosis of the disease is inversely related to the age of the patient. In a study about the outcome of the CMV colitis in immunocompetent hosts, the rate of spontaneous remission of the patients younger than 55 year-old was higher than the older patients (9). And, the mortality rate was higher among the elderly hosts (9). The higher mortality rate may be associated with the decline in humoral and cellular immunity due to immune modulating conditions (diabetes mellitus, renal failure, malignancies, etc.), and the higher prevalence of co-morbidity in older patients (5, 9). Although there was no known disease suppressing the immune system in our case, it is probable that some unknown immune modulating conditions might coexist with CMV colitis in our elderly (79 year-old) patient.

The initial diagnosis of CMV colitis is sometimes aided only by identification of viral inclusions by pathologists in colonoscopic biopsies. The histologic differential diagnosis of CMV includes other viral infections, especially adenovirus and herpes simplex virus (HSV)

(7). Adenovirus colitis is common in children associated with humoral immunodeficiency or rota virus, and in immunocompromised patients with AIDS or bone marrow transplantation (7, 10). Adenovirus inclusions are usually crescent or targetoid shaped, homogeneous, smudgy, eosinophilic intranuclear inclusions (2, 7). They are generally located in the surface epithelium, characteristically involving goblet cells (2, 7, 10). However, CMV inclusions have an "owl's eye" morphology, and they are generally located in endothelial or stromal cells, and either in the nucleus or cytoplasm, and are often found deep in ulcer bases (7). HSV infection may occur throughout the gastrointestinal tract mostly in the esophagus and anorectum, especially in immunocompromised patients and homosexual men (2, 7). HSV inclusions are intranuclear and consisting of a smudged, groundglass nucleus with peripheral darker, marginated chromatin (2,7 ). Similar to adenovirus, HSV inclusions are generally located in the surface epithelium and at the edges of ulcers (2, 7).

As mentioned previously, CMV is a mimicker of Crohn's disease both grossly and microscopically. The diagnosis of CMV infection can be confirmed by detecting the inclusions, but it should be noted that the two may coexist (2, 7). CMV infection and graft-versus-host disease (GVHD) in transplant patients may be indistinguishable, because they have similar clinical and histopathological features. Also, these conditions may coincide (7). The presence of viable nests of endocrine cells, abundant apoptotic bodies associated with crypt necrosis and crypt loss, and minimal inflammation favor GVHD (7).

In biopsy specimens, the diagnosis of CMV colitis may be easily missed when only rare inclusions are present. Thus, CMV infection can not be ruled out when there is no viral inclusion detected. Use of immunohistochemistry and examination of multiple serial sections are recommended when evaluating the colonic biopsy for CMV infection (2, 7).

Also, serologic studies, antigen tests, PCR assays, in situ hybridization, and viral culture can be used for diagnosis. But the isolation of CMV in culture has a limited utility for the diagnosis since virus may be excreted for a long time after primary infection, thus it does not indicate active infection (7).

There are some specific antiviral agents against CMV infection. But there is no consensus in the literature as to whether drug use is necessary or not for CMV infection in immunocompetent patients because of the potential toxicity (myelosuppression, hepatotoxicity, infertility, etc.) of therapy and the possible self-limited course of the disease (3). However, the physicians generally tend to use antiviral treatment for severe cases with colon, ocular and lung involvement, and meningoencephalitis (3). The benefits of specific antiviral therapy should be weighed against the adverse effects before initiating the therapy.

In conclusion, it should be noted that CMV infection can cause severe life-threatening manifestations in immunocompetent hosts as well as immunocompromised patients. And, CMV colitis should be taken into consideration, especially in the elderly patients with severe diarrhea who do not suffer from neither chronic inflammatory bowel disease nor immunodeficiency. The colonoscopic biopsies that constitute the majority of routine pathological specimens, especially the biopsies of patients with severe diarrhea, bloody stools and ulceration in colon, should be examined carefully for viral inclusions that are crucial for the definite diagnosis and treatment.

## REFERENCES

1. Mervan B. Evaluation of cytomegalovirus infection cases followed in hospital. *Bakırköy Tıp Dergisi* 2013; 9(1):39-41.

2. Lamps LW. Infectious Diseases of the Colon. In: *Lacobuzio-Donahue CA, Montgomery E, eds.*

*Gastrointestinal and Liver Pathology*. 2nd ed. Philadelphia: Elsevier Saunders, 2012;297-304.

3. Rafailidis PI, Mourtzoukou EG, Varbobitis IC, Falagas ME. Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review. *Virology* 2008;5(3):47-55.

4. Momin N, Telisinghe PU, Chong VH. Cytomegalovirus colitis in immunocompetent patients. *Singapore Med J* 2011;52(9):170-2.

5. Galiatsatos P, Shrier I, Lamoureux E, Szilagyi A. Meta-analysis of outcome of cytomegalovirus colitis in immunocompetent hosts. *Dig Dis Sci* 2005; 50(4):609-16.

6. Karakozis S, Gongora E, Caceres M, Brun E, Cook JW. Life-threatening cytomegalovirus colitis in the immunocompetent patient: report of a case and review of the literature. *Dis Colon Rectum* 2001; 44(11):1716-20.

7. Lamps LW. Infectious Disorders of the GI Tract. In: *Odze RD, Goldblum RJ, eds. Surgical Pathology of the GI Tract, Liver, Biliary Tract and Pancreas*. 2nd ed. Philadelphia: Elsevier Saunders, 2009:52-80.

8. Wang HH. Diagnostic Cytology of the GI Tract. In: *Odze RD, Goldblum RJ, eds. Surgical Pathology of the GI Tract, Liver, Biliary Tract and Pancreas*. 2nd ed. Philadelphia: Elsevier Saunders, 2009:42.

9. Carter D, Olchovsky D, Pokroy R, Ezra D. Cytomegalovirus-associated colitis causing diarrhea in an immunocompetent patient. *World J Gastroenterol* 2006; 12(42):6898-9.

10. Yan Z, Nguyen S, Poles M, et al. Adenovirus colitis in human immunodeficiency virus infection: an underdiagnosed entity. *Am J Surg Pathol* 1998; 22(9):101-6.