Dicle Tıp Dergisi / Dicle Med J (2023) 50 (2) : 203-210

www.diclemedj.org

Original Article / Özgün Araştırma

Importance of using tissue PCR to diagnose CMV colitis in ulcerative colitis

Tuba Erürker Öztürk[1], Murat Kıyıcı[2], Macit Gülten[2], Enver Dolar[2], Selim Gürel[2], Selim Giray Nak[2], Fatih Eren[2]

1 Denizli State Hospital Department of Gastroenterology, Denizli, Turkey

2 Uludag University Medicine Faculty Department of Gastroenterology, Uludag University Medicine Faculty Hospital, Bursa, Turkey

Received: 11.06.2022; Revised: 07.03.2023; Accepted: 08.05.2023

Abstract

Objective: To show the importance of tissue Cytomegalovirus (CMV) PCR to diagnose CMV infection in patients with treatment-resistant ulcerative colitis.

Methods: Fifteen patients who had previously been diagnosed as ulcerative colitis with clinical, endoscopic, histological, and radiological criteria and who had referred to our clinic with acute exacerbation who were diagnosed with CMV colitis and received CMV treatment, were evaluated retrospectively. After the demographic and clinical characteristics of the patients were noted, Mayo scores were evaluated to determine ulcerative colitis activity. Patients' age, gender, laboratory values, type of colitis, and Mayo scores were recorded. Biopsy results, CMV IgM, serum, and tissue CMV DNA levels were noted. Descriptive statistical parameters of the demographical data were calculated.

Results: Eleven of the patients were male, and four were female. The mean age of the patients was 42±11,3. The mean duration of the disease was 28±46 months. Twelve patients had pancolitis, and three patients had distal colitis. All patients' Mayo score was 12 points. All patients were steroid-resistant, and none had previously received biological agent therapy. 7 of 15 patients had serum CMV DNA levels over 1000 copies/mL. Tissue CMV DNA levels of 8 patients were found higher than 250 copies/mg, although serum CMV DNA levels were below 1000 copies/mL. Pathology samples of 11 patients were evaluated, and CMV inclusion bodies were not detected. All patients received ganciclovir for CMV treatment. After treatment, CMV DNA of all patients was negative, and diarrhea and inflammation markers were reduced.

Conclusion: For the diagnosis of CMV, CMV-PCR in colon tissue specimens should also be considered in addition to endoscopic appearance and serum CMV DNA levels.

Keywords: CMV DNA; PCR; Ulcerative colitis; CMV colitis; Cytomegalovirus

DOI: 10.5798/dicletip.1313321

Correspondence / Yazışma Adresi: *Tuba Erürker Öztürk, Denizli State Hospital Department of Gastroenterology, Denizli, Turkey e-mail: drozturktuba@gmail.com*

Ülseratif kolitli hastalarda CMV tanısında doku PCR'ın önemi

Öz

Amaç: Tedaviye dirençli ülseratif kolit hastalarında Cytomegalovirus (CMV) enfeksiyonu tanısı koyarken doku CMV PCR düzeyinin daha önemli olduğunu göstermektir.

Yöntemler: Klinik, endoskopik, histoloji ve radyolojik kriterlere göre daha önce ülseratif kolit tanısı almış akut alevlenme ile tarafımıza refere edilmiş CMV kolit saptanıp CMV tedavisi alan 15 hastanın dosyası retrospektif olarak değerlendirildi. Hastaların demografik ve klinik bulguları not edildikten sonra ülseratif kolit aktivasyonu Mayo skoruna göre sınıflandırıldı. Hastaların yaşı, cinsiyeti, laboratuvar değerleri, kolitin tipi, ve Mayo skoru kaydedildi. Biyopsi sonuçları, CMV IgM, serum ve doku CMV DNA düzeyleri değerlendirildi. Demografik dataların disktriptif istatistiksel parametreleri hesaplandı.

Bulgular: 15 hastanın 11'i erkek, 4'ü kadındı. Hastaların ortalama yaşları 42±11,3 yıldı. Ortalama ülseratif kolit hastalık süreleri 28±46 aydı. 12 hastanın hastalık tutulumu pankolit 3 hastanın ise distal kolit şeklinde idi. Tüm hastalar steroide dirençli hastalardı ve daha önce biyolojik ajan tedavisi kullanmamışlardı. 15 hastanın 7'inde serum CMV DNA düzeyi 1000 kopya/mL'nin üzerindeydi. 8 hastanın da serim CMV DNA düzeyi 1000 kopya/mL'nin altında olmasına rağmen doku CMV DNA düzeyleri 250 kopya/mg'ın üzerindeydi. 11 hastanın patoloji sonuçları değerlendirildi. Patoloji örneklerinde CMV inklüzyon cisimcikleri izlenmedi. Tüm hastalara CMV tedavisi için gansiklovir tedavisi verildi. Tedavi sonrasında serum CMV DNA düzeyleri negatifti. Hastaların dışkılama sayıları günde 1-2 kez olmak üzere normal kıvamdaydı ve inflamasyon belirteçleri normal seviyelere gerilemişti.

Sonuç: CMV kolitinin tanısı için kolonun tipik endoskopik görünümü ve serum CMV DNA düzeyi kadar doku CMV DNA düzeyi de göz önünde tutulmalıdır.

Anahtar kelimeler: CMV DNA, PCR, Ülseratif kolit, CMV koliti, Cytomegalovirus.

INTRODUCTION

Cytomegalovirus (CMV), a member of the herpesviral family, is double-stranded and enveloped DNA virus. This virus has a high transmission rate (60-90%) and a long latency in the body[1]. In 15.4-34% of patients with inflammatory bowel diseases (IBDs) who received steroids and/or other immunosuppressive therapies, CMV can lead to viral gastroenteritis[2].

Activation of the virus can be caused by many factors such as psychological stress, fever, trauma, or immunosuppressive treatment. CMVs replicate slowly and are characterized by causing late cell pathology. The endoscopic appearance of CMV colitis could be various. The most common lesion is an ulcer. Ulcers could be superficial or deep, single, or multiple[3,4]. Diffusive and deep ulcers can cause intestinal pseudoobstruction, perforation, and/or toxic megacolon. Segmental ulcerative erosions and linear ulcers can be confused with the endoscopic appearance of Crohn's disease. Mucosal hemorrhage, edema, erosions, pseudomembranes, and obstructive inflammatory masses are other possible lesions that can be seen macroscopically in endoscopy. Diagnosis can be made easily by observing several inclusion bodies in the biopsy specimen. However, the absence of inclusion bodies does not exclude CMV infection. Another diagnostic method to show CMV is immunochemistry. Serological tests, antigen tests, PCR, in situ hybridization, and viral culture are the other tests that can be used to diagnose CMV[5-7]. Isolation of CMV in culture is not useful for diagnosis because CMV can survive for a long time after the primer infection, and therefore it can't show active infection. Histology and hematoxylin-eosin (H&E) staining of intranuclear inclusion bodies in patients with ulcerative colitis has been reported as significant for CMV diagnosis according to the current European Crohn's and Colitis Organization guidelines[8]. PCR is the most sensitive method for diagnosing most viral infections, including CMV infection[9]. The cut-off value of both tissue and

serum CMV DNA has not yet been determined, but values above 250 copies / mL seem appropriate for CMV colitis[10-11].

In our study, we aimed to emphasize the importance of tissue CMV DNA level for diagnosis CMV colitis in patients with steroid-resistant ulcerative colitis.

METHODS

All ulcerative colitis patients hospitalized between 2014 and 2017 with acute exacerbation were screened. Patients were examined for opportunistic infections due to acute exacerbation. All patients underwent colonoscopy. In addition, both serum CMV and tissue CMV levels were studied from these patients. Fifteen patients with high serum and/or tissue CMV levels were included in the study. Patients with Clostridium difficile infection and negative serum and/or tissue CMV levels were excluded from the study. Fifteen patients who were hospitalized with ulcerative colitis diagnosis between 2014 and 2017 at the Gastroenterology Clinic of Uludag University Medicine Faculty Hospital were reviewed retrospectively. This study was carried out after the approval of the Local Ethics Committee (2017-4/47). Fifteen patients who were previously diagnosed ulcerative colitis with clinically, endoscopically, histologically, and radiologically criteria, and who referred to our clinic with acute exacerbation were evaluated. The mean age of the patients was 42 ± 11.3 (range:20-59). 11 of the patients were male, and four were female. All of the patients referred to our clinic with activation. All patients Mayo score was 12 points. The mean duration of the disease was 28±46,5 (range: 2-192) months. Twelve patients (80%) had pancolitis, and three patients had distal colitis. All patients were steroid-resistant, and none had previously received biological agent therapy. All patients had 4 gr/ day mesalamine, 60 mg/day methylprednisolone and 100mg/day azathioprine. The demographic characteristics and treatments of the patients are shown in the table (Table 1).

Table I: Demographic and clinical characteristics of the patients

	Ulcerative colitis (n=15)
Sex (male/female)	11/4
Average age (years) ± SD	42±11.3(range: 20-59)
Duration of the disease (months)	28±46,5(range: 2-192)
Type of colitis	
• Pancolitis	12 (80%)
• Distal colitis	3
Severity of the disease	
• Severe	15 (100%)
• Other	0
Treatment	
• MES-CS-immunomodulator	15 (100%)
• Anti-TNF	0

After the demographic and clinical characteristics of the patients were noted, Mayo scores were evaluated to determine ulcerative colitis activity. Patients' age, gender, laboratory values, and Mayo scores were recorded. Corticosteroid resistance was defined as the absence of healing despite steroid use at 30 mg or more for at least two weeks[5]. Gastric microscopy, gastric amoeba antigen, Clostridium difficile toxin A-B test, gaita culture, and serum CMV DNA levels were routinely examined in all patients who were referred due to acute ulcerative colitis. Current treatments and medications were mesalamine (Salofalk, Ali Raif Medical, Istanbul, Turkey), methylprednisolone (Prednol, Mustafa Nevzat Medical, Istanbul Turkey), azathioprine (Imuran, GlaxoSmithKline, Boronia Victoria, Australia). All patients were evaluated with colonoscopy. Patients with inflammation up to the proximal part of the hepatic flexure were evaluated as pancolitis, and those with inflammation up to the splenic flexure were evaluated as distal (left-sided) colitis[5]. During a colonoscopy, samples were taken for both pathology and CMV DNA from the activated mucosa. Clinical, laboratory, and endoscopic findings were used to assess the remission.

Detection of CMV in serum and tissue specimens

Quantitative evaluation of CMV DNA in serum and tissue was performed with Abbott M200Sp CMV DNA Real-Time PCR Test (Abbott Diagnostics GmbH, Chicago, USA). Plasma and serum samples

were used directly. At least four mucosal biopsies were taken from the ulcerative area. Biopsy specimens were also examined for CMV inclusion bodies.

Diagnosis and treatment protocol of CMV infection

CMV infection was diagnosed with the presence of one or more criteria (plasma or tissue CMV DNA positivity or staining of inclusion bodies with H&E). Serum CMV DNA lower limit value was determined as 1000 copies / mL and tissue CMV DNA lower limit value was determined 250 copies/mg[11]. All patients were evaluated as CMV colitis. CMV DNA was studied in 13 tissue samples of 15 patients. 7 of 15 patients had serum CMV-DNA levels over 1000 copies / mL. Pathology samples of 10 patients were evaluated, and CMV inclusion bodies weren't detected. Ganciclovir (Cymevene, Roche Products Limited, Welwyn Garden City, UK) was administered for three weeks to treat CMV infection. During this time, the dose of steroids was reduced stepwise.

Statistical Analysis

SPSS program (2015) version 23 was used for statistical analysis. Descriptive statistical parameters (mean, standard deviation, median frequency, ratio, and min-max) of the study data were calculated. The Shapiro-Wilks and Anderson-Darling tests were used for testing normality. Non-parametric tests were used for non-normal distributed data.

RESULTS

Fifteen patients with steroid-resistant ulcerative colitis with serum CMV DNA levels>1000 copies/mL or tissue CMV DNA levels>250 copies/mg were treated with 5 mg/kg ganciclovir. Tissue CMV DNA levels of 8 patients were found higher than 250 copies/mg, although serum CMV DNA levels were below 1000 copies/mL. The pathologic specimens of 11 patients were evaluated for CMV inclusion bodies, but inclusion bodies weren't seen. Pathologic specimens could not be evaluated immunohistochemically due to technical insufficiency. Tissue CMV DNA was studied in 13 patients, and the lowest value was determined as 1735 copies/mg. This diagnosis was not supported by pathology in patients diagnosed with tissue CMV DNA levels. This may be due to technical inadequacy, inappropriate sampling, or inexperience in evaluating.

The characteristics of the patients diagnosed with steroid-resistant CMV colitis are described in the table (Table 2). The appearance of CMV colitis in colonoscopy was showed in image 1-3.

Table II: Characteristics of patients with resistant ulcerative colitis with tissue CMV levels higher than 1,000 copies/mg

Patient number	Age-sex	Type of colitis	CMV IgM	Serum CMV DNA (copies/mL)	Tissue CMV DNA (copies/mg)	CMV pathology
1	51-M	Pancolitis	Negative	<20	9.599,8	Negative
2	53-M	Pancolitis	Negative	51.618	1.096.492,4	Negative
3	55-M	Pancolitis	Unknown	3.055	Not performed	Not performed
4	20-F	Pancolitis	Negative	1.190	4,334	Negative
5	47-M	Pancolitis	Unknown	4.651	155.786,4	Negative
6	59-M	Pancolitis	Positive	6.367	Not performed	Not performed
7	29-M	Pancolitis	Unknown	5.407	17.959,8	Negative
8	40-M	Pancolitis	Negative	50	5.153,8	Negative
9	46-F	Pancolitis	Positive	108	18.211,6	Negative
10	27-F	Pancolitis	Unknown	123	5.170,9	Negative
11	50-F	Distal colitis	Unknown	313	25.066,1	Negative
12	47-M	Distal colitis	Negative	13.647	5.361,4	Not performed
13	40-M	Pancolitis	Unknown	44	1.735,9	Not performed
14	39-M	Pancolitis	Unknown	705	449.457,8	Negative
15	35-M	Distal colitis	Negative	91	174.150,8	Negative

Antiviral therapy was initiated regardless of the tissue CMV DNA level in 8 patients with serum CMV DNA levels < 1000 copies/mL. In 8 patients, tissue CMV DNA level was determined to be over 250 copies/mg, and antiviral treatment was initiated. Fifteen patients were treated with ganciclovir for three weeks. Serum and tissue CMV DNA levels were found negative after treatment.

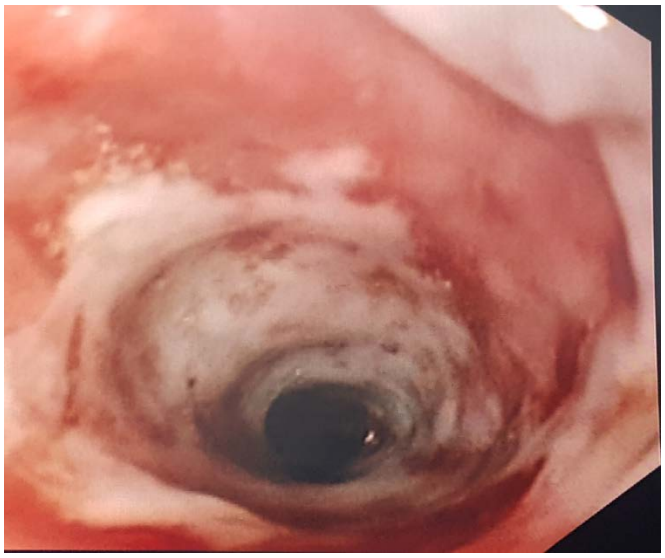

Figure 1: Ulcers apperance of CMV colitis in colonoscopy

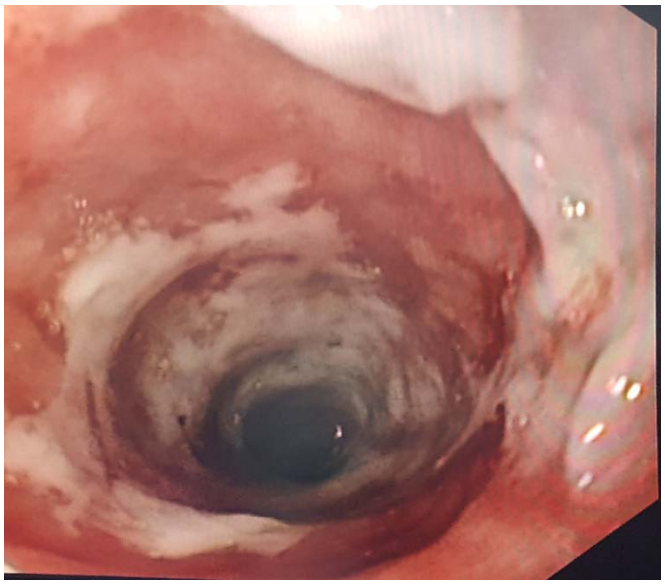

Figure 2: Erythematous and edematous appearance of CMV colitis in colonoscopy

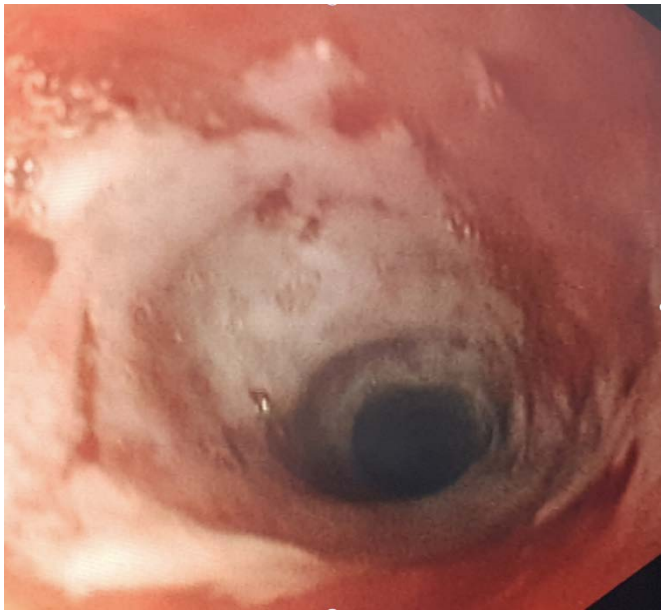

Figure 3: Apperance of CMV colitis in colonoscopy

DISCUSSION

Ulcerative colitis has been known since the 1900s. However, aminosalicylates were found to be effective for the treatment of this disease in the 1940s[11,12,26]. Resistance in the treatment of this disease is one of the important problems encountered. The association of CMV with ulcerative colitis is known from the 1960s, but it is important to detect the virus prior to antiviral treatment.

In patients with ulcerative colitis, CMV infection was first reported in the USA in 1961[13]. Since then, CMV infection is being investigated in ulcerative colitis patients. However, an effective diagnostic method is still controversial. It is controversial whether CMV reactivation increases inflammation in patients with IBD or whether it is only a surrogate marker for IBD[14]. In a prospective study, it was shown that CMV infection was seen in 4.5% of new-onset ulcerative colitis, suggesting that immunosuppressive drugs may be a significant risk factor for CMV infection[15]. However, it is also possible that CMV is an "innocent audience" in the background of the colon mucosa during an active IBD period. For this reason, routine CMV tests are not recommended for all patients

with ulcerative colitis. However, during the steroid-resistant colitis or acute exacerbations treated with steroid therapy, PCR or immunohistochemical methods should be used to evaluate CMV. Several studies have used many different methods to diagnose CMV infection in steroid-resistant ulcerative colitis. Although studies have shown that tissue CMV DNA testing in mucosal biopsies is the most sensitive method for detecting CMV colitis, it is not explicitly stated which approach is better[16-19]. Detection of CMV DNA by PCR analysis in mucosal biopsies has been described as the most sensitive method in patients with CMV enteritis[20-22]. Although serum CMV DNA is negative, CMV infection can be detected in tissue samples. Although the serum CMV DNA level of a patient in our study was negative, the tissue CMV DNA level was found to be 9599,8 copies/mg.

Our study was a retrospective study that patients who referred to the hospital with acute exacerbations and with steroid-resistant ulcerative colitis were evaluated. Since our study is retrospective, some patient's tissue CMV DNA and pathology assessments were missing. The possibility of acute gastroenteritis caused by other infections was excluded, and patients were evaluated for CMV colitis. Despite the steroid treatment, the daily bloody stool frequency of these patients was six or more, and the general clinics were not improved.

Serum CMV DNA levels were studied in all patients. Antiviral therapy was initiated regardless of the tissue CMV DNA level in 7 patients with serum CMV DNA levels>1000 copies/mL. In 8 patients, tissue CMV DNA level was determined to be over 250 copies/mg, and antiviral treatment was initiated. The most recommended diagnostic method is to show inclusion bodies with immunohistochemical staining in pathology specimens[23,24,27].In our study, the pathologic specimens of 11 patients were evaluated for CMV inclusion bodies, but inclusion bodies weren't seen. Pathologic specimens could not be evaluated immunohistochemically due to technical insufficiency. The viral culture wasn't studied patients, which is a gold standard method for CMV treatment. Since virus infection in culture could last for weeks, it is not a practical method; routine usage is not recommended[25]. There is no serum and tissue CMV DNA lower limit value that was determined for CMV colitis diagnosis. Most of the studies suggest the lower limit value for tissue CMV DNA as 250 copies/mg. In our study, tissue CMV DNA was studied in 13 patients, and the lowest value was determined as 1735 copies/mg. This diagnosis was not supported by pathology in patients diagnosed with tissue CMV DNA levels. This may be due to technical inadequacy, inappropriate sampling, or inexperience in evaluating.

In Beswick et al's review they stated that the evaluation of CMV infection in acute exacerbation in IBD is necessary for disease management and treatment selection. Also detection of CMV should be assessed a poorer prognosis for this group of patients. Because of CMV PCR has a high false-positive rate they recommend to use immunohistochemical analysis for diagnose[28].

Mourad et al's suggest that it is important to keep a high clinical suspicion for CMV infection who has acute excerbation of UC. This group of patients are presenting with worsening of their gastrointestinal symptoms, regardless of their immunosuppression treatment. A delay in the diagnosis and subsequent management could be associated with poor outcomes, including increased colectomy rates. If patients have multiple inclusion bodies, they have started antiviral treatment regardless of CMV tissue PCR or positive IHC stains. If the inclusion bodies are negative and patients have high CMV tissue PCR [>250 copies/mg of tissue] or high IHC staining [>four cells/ section], then they

would also propose the endication of anti-viral therapy[29].

Goetgebuer et al. defined most Dutch gastroenterologists acknowledge the importance of CMV colitis in IBD. They have given the initiation of treatment according to tissue CMV PCR or pathology species[30].

Kwon et al. found a high rate of CMV infection in IBD in their study. It has been reported that the diagnosis of CMV infection is cost-effective by reducing patient morbidity and hospitalization rates[31].

However, despite the low serum CMV DNA levels, the high levels of tissue CMV DNA are noteworthy. This indicates that tissue CMV DNA level is more valuable data for the diagnosis of CMV colitis. This can be better demonstrated with more patients and multicenter studies.

CMV infection should also be considered in treatment-resistant patients and in patients who develop acute attacks while under treatment. For the diagnosis of CMV, CMV-PCR in colon tissue specimens should also be considered. In addition to endoscopic appearance and serum CMV DNA levels.

Ethics Committee Approval: Fifteen patients who were hospitalized with ulcerative colitis diagnosis between 2014 and 2017 at the Gastroenterology Clinic of …. were reviewed retrospectively. This study was carried out after the approval of the Local Ethics Committee (2017-4/47).

Conflict of Interest: The authors declared no conflicts of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Staras SA, Dollard SC, Radford KW, et al. Seroprevalence of cytomegalovirus infection in the United States, 1988-1994. Clin Infect Dis 2006; 43: 1143-51.

2. Papadakis KA, Tung JK, Binder SW, et al. Outcome of cytomegalovirus infections in patients with inflammatory bowel disease. Am J Gastroenterol 2001; 96: 2137-42.

3. Odze RD, Goldblum JR. Surgical pathology of the GI tract, liver, biliary tract, and pancreas. 2nd ed. Philadelphia: W.B. Saunders/Elsevier, 2009; 52-53.

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

5. Iida T, Ikeya K, Watanabe F, et al. Looking for endoscopic features of cytomegalovirus colitis: a study of 187 patients with active ulcerative colitis, positive and negative for cytomegalovirus. Inflamm Bowel Dis 2013; 19: 1156-63.

6. Omiya M, Matsushita M, Tanaka T, Kawamata s, Okazaki K. The absence of large ulcer predicts latent cytomegalovirus infection in ulcerative colitis with positive mucosal viral assay. Intern Med 2010; 49: 2277-82.

7. Suzuki H, Kato J, Kuriyama M, et al. Specific endoscopic features of ulcerative colitis complicated by cytomegalovirus infection. World J Gastroenterol 2010; 16: 1245-51.

8. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis 2014; 8: 443-68.

9. Storch GA, Buller RS, Bailey TC, et al. Comparison of PCR and pp65 antigenemia assay with quantitative shell vial culture for detection of cytomegalovirus in blood leukocytes from solid-organ transplant recipients. J Clin Microbiol 1994; 32: 997-1003.

10. Roblin X, Pillet S, Oussalah A, et al. Cytomegalovirus load in inflamed intestinal tissue is predictive of resistance to immunosuppressive therapy in ulcerative colitis. Am J Gastroenterol 2011; 106: 2001-8.

11. Sager K, Alam S, Bond A, Chinnappan L, Probert CS. Review article: cytomegalovirus and inflammatory bowel disease. Aliment Pharmacol Ther 2015; 41: 725-33.

12. Wilks S, Moxon W. Lectures on pathological anatomy. London: Longmans, Green, 1889.

13. Powell RD, Warner NE, Levine RS, Kirsner JB. Cytomegalic inclusion disease and ulcerative colitis; report of a case in a young adult. Am J Med 1961; 30: 334-40.

14. Lawlor G, Moss AC. Cytomegalovirus in inflammatory bowel disease: pathogen or innocent bystander? Inflamm Bowel Dis 2010; 16: 1620-7.

15. Kim YS, Kim YH, Kim JS, et al. Cytomegalovirus infection in patients with new onset ulcerative colitis: a prospective study. Hepatogastroenterology 2012; 59: 1098-01.

16. Cotte L, Drouet E, Bissuel F, Denoyel A, Trepo C. Diagnostic value of amplification of human cytomegalovirus DNA from gastrointestinal biopsies from human immunodeficiency virus-infected patients. J Clin Microbiol 1993; 31: 2066-9.

17. Hommes DW, Sterringa G, van Deventer SJ, Tytgat GNJ, Weel J. The pathogenicity of cytomegalovirus in inflammatory bowel disease: a systematic review and evidence-based recommendations for future research. Inflamm Bowel Dis 2004; 10: 245-50.

18. Kandiel A, Lashner B. Cytomegalovirus colitis complicating inflammatory bowel disease. Am J Gastroenterol 2006; 101: 2857-65.

19. Kou T, Nakase H, Tamaki H, et al. Cytomegalovirus infection in patients with ulcerative colitis diagnosed by quantitative real-time PCR analysis. Dig Dis Sci 2006; 51: 1052-5.

20. Rahbar A, Bostrom L, Lagerstedt U, et al. Evidence of active cytomegalovirus infection and increased production of IL-6 in tissue specimens obtained from patients with inflammatory bowel diseases. Inflamm Bowel Dis 2003; 9: 154-161.

21. Robey SS, Gage WR, Kuhajda FP. Comparison of immunoperoxidase and DNA in situ hybridization techniques in the diagnosis of cytomegalovirus colitis. Am J Clin Pathol 1988; 89: 666-71.

22. Wakefield AJ, Fox JD, Sawyerr AM, et al. Detection of herpesvirus DNA in the large intestine of patients with ulcerative colitis and Crohn's disease using the nested polymerase chain reaction. J Med Virol 1992; 38: 183-90.

23. Garrido E, Carrera E, Manzano R, Lopez-Sanroman A. Clinical significance of cytomegalovirus infection in patients with inflammatory bowel disease. World J Gastroenterol 2013; 19: 17-25.

24. Ormeci AC, Akyuz F, Baran B, et al. Steroid-refractory inflammatory bowel disease is a risk factor for CMV infection. Eur Rev Med Pharmacol Sci 2016; 20: 858-65.

25. Landry ML, Ferguson D. Comparison of quantitative cytomegalovirus antigenemia assay with culture methods and correlation with clinical disease. J Clin Microbiol 1993; 31: 2851-6.

26. Göral V. Endoscopic Features of Ulcerative Colitis. Türkiye Klinikleri J. Gastroenterohepatol-Special Topics 2009; 2 (1):34-40.

27. Kelle İ, Erdinç M. General Features of Antiviral Drugs. Erdinç M, editör. Viral Enfeksiyonlarda Güncel Tedavi Yaklaşımları ve İmmünizasyon. 1. Baskı. Ankara: Türkiye Klinikleri; 2021. p.8-30.

28. Beswick L, Ye B and van Langenberg D. Toward an Algorithm for the Diagnosis and Management of CMV in Patients with Colitis. Inflamm Bowel Dis 2016;22:2966–76.

29. Mourad FH, Hashash JG, Kariyawasam VJ, Leong RW. Ulcerative Colitis and Cytomegalovirus Infection: From A to Z. Journal of Crohn's and Colitis, 2020, 1162–71.

30. Goetgebuer RL, van der Woude CD, Bakker L, et al. The diagnosis and management of CMV colitis in IBD patients shows high practice variation: a national survey among gastroenterologists. Scand J Gastroenterol 2022 Nov; 57(11):1321-1326.

31. Kwon J, Flux D, Farraye FA, Kröner PT. Cytomegalovirus-related colitis in patients with inflammatory bowel disease. Int J Colorectal Dis. 2022 Mar; 37(3): 685-691.