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The Possible Role of HCMV in Inflammatory Bowel Diseases in Sample of Iraqi patients

Alaa H. Fadhil *MSc*, **Haider S. Kadhim**[1] *PhD*, **Raghad J. Hussain**[2] *FICMS*, **Sazan A. Al-Atrooshi**[3] *FICMS*

[1]Dept. of Microbiology, College of Medicine, Al-Nahrain University, Baghdad, Iraq, [2]Gastroenterology and Hepatology Teaching Hospital, Baghdad, Iraq, [3]Dept. of Pathology and Forensic medicine, College of Medicine, University of Baghdad, Baghdad, Iraq

Abstract

Background Human cytomegalovirus (HCMV) reactivation is one of the most risks that occur in immunosuppressed patients. The association and role of CMV and inflammatory bowel disease (IBD) exacerbation is still controversy.

Objective To investigate the rate of occurrence and role of HCMV in patients with IBD including demographic and clinical features.

Methods A cross sectional study involved sixty-five (65) IBD patients whom divided into 9 Crohn's disease patients and 56 ulcerative colitis patients. The detection of local CMV reactivation (colon) was based on the presence of early and immediately early antigens (nonstructural proteins). The positive results for HCMV reactivation was considered according on Immunohistochemistry (IHC) and/or serological enzyme linked immunosorbent assay (ELISA) results.

Results Among the 65 eligible IBD patients, nine patients (13.85%) gave positive result for IHC, compared to 56 patients (86.15%) with negative result. On the other hand, only two patients (3.08%) had a positive result for anti-HCMV IgM antibody, while almost all patients (except one) were positive for anti-HCMV IgG antibody. There was a significant difference between positive HCMV and patients with long duration of IBD and non-response to treatment.

Conclusion IBD and its treatment may put those patients at risk of HCMV reactivation. Colonic active CMV was detected particularly in sever UC patients and significantly in patients with disease duration above 5 years and not response to treatment based on IHC technique for IE and E HCMV proteins detection.

Keywords Cytomegalovirus, inflammatory bowel disease, ulcerative colitis, Crohn's disease, immunohistochemistry

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List of abbreviations: CDAI = Crohn's Disease Activity Index, CID = Cytomegalic inclusion disease, CMI = Cell mediated immunity, HCMV = Human Cytomegalovirus, HIV = Human Immunodeficiency virus, E = Early, H&E = Hematoxylin and eosin, IE = Immediate early, IHC = Immunohistochemistry, PCR = Polymerase chain reaction, pp65 = Phosphoprotein 65, TRL = Terminal repeat long, UL = Unique long, US = Unique short

Introduction

Inflammatory bowel diseases (IBDs), which include ulcerative colitis (UC) and Crohn's disease (CD), consist of chronic relapsing and nonspecific inflammatory diseases of unknown etiology that affect the digestive tract [(1)]. Multimodal approach of immunosuppressive treatment

(immunomodulators and biological agents) that used to minimize symptoms and prevent complications have suppressed the immunity in these patients which increase their risk of opportunistic infections [2-4]. Human cytomegalovirus (HCMV) is considered as one of the most common viral gastrointestinal pathogens in IBD patients [5]. Cytomegalovirus (CMV) belongs to the Herpesviridae family and represents as a common viral infection in humans, with infection level ranging from 40% in the developed countries to 100% in developing countries [6]. After primary infection, this virus is known to maintaining a persistent, long-life infection of the host, often as a latent form that can be found in different cell types [7].

HCMV infection is of particular interest in IBD that combine inflammation in the colon and the long-term maintenance of immunosuppressive therapy; both of which can reactivate latent CMV [8]. In the immunosuppressed patient with IBD, the clinical symptoms can mimic an acute exacerbation, and it is important to differentiate CMV colitis from an IBD flare-up because untreated CMV infection in these patients can lead to fulminant colitis, requiring colectomy or resulting in death [10].

Several studies have established an association between severe steroid-refractory IBD and CMV infection [11,12]; however, international guidelines from both the American College of Gastroenterology (ACG) and The European Crohn's and Colitis Organization (ECCO), which recommend as the CMV colitis should be excluded in patients with acute steroid resistance before increasing treatment dosage [13,14].

HCMV infection can be detected in both serum and tissue according to detection method. However, serum anti-CMV IgG antibodies have high specificity and sensitivity for latent infection, and IgM antibodies for acute infection or reactivation of CMV infection with viremia, but this does not correlate with active CMV colitis [15].

ECCO recommended tissue polymerase chain reaction (PCR) or histopathology combined with immunohistochemistry (IHC), using monoclonal antibodies against CMV immediate early antigen) are highly specific and sensitive for diagnosing CMV colitis in IBD [13].

There are several studies about the incidence of CMV in different parts of Iraq, Al-Obaidi in 2008 [16] studied about 32 patients with colorectal adenocarcinoma and 8 with colorectal hyperplastic polyps. Normal tissues of tumor margin were considered as control. IHC staining technique used to detect HCMV early antigens in a tissue by using specific monoclonal antibodies. CMV early Ag was detected in 5 (15.6%) out of 32 colorectal adenocarcinoma, while the other 8 patients with colorectal hyperplastic polyps and control were negative for the virus. Another study was reported by Shamran et al. in 2015 [17] was detect CMV Ags in glioma patients by using different monoclonal antibodies against different virus Ags, this study showed about 33 (91.67%), 28 (77.78%) and 26 (72.22%) out of 36 glioma samples were positive for EI-72, pp65 and late antigen respectively. In the recent study by Al-Toban et al. in 2018 [18] a sixty-one patients with acute leukemia. Forty-eight of them evaluated while induction chemotherapy (group I), while 13 post allogeneic stem cell transplantation patients, and 30 apparently healthy individuals as (control group). In this study, real-time PCR used to detect and quantitatively CMV DNA and about 12 (25%) out of 48 patients in group I, two (15.4%) out of the 13 patients in group II, and 2 (6.7%) out of 30 in the control group had positive cytomegalovirus viremia.

The aims of this study were to explore the association of HCMV infection in patients with IBD and to review the correlation of CMV infection with various demographic, therapeutic and clinical features in IBD patients.

Methods

Patients

This cross-sectional study involved sixty-five (65) inflammatory bowel disease patients whom divided into 9 CD patients and 56 UC patients. Informed consent was obtained from each patient. All patients were recruited from one hospital in Baghdad: The Gastroenterology and Hepatology Teaching Hospital/Colonoscopy Unit in the period from September, 2017 to September, 2018. Diagnosis of UC and CD was based on the presence of clinical, endoscopic, radiologic and histologic features to classify those IBD patients according to histopathologists' reports. The local Institutional Review Board (IRB) had ethically approved this study. All data were collected on patients using case note review and a questionnaire sheet that include patient demographics, age at IBD symptom onset, history, diagnosis (sign and symptoms, endoscopical and histopathological finding), medications and about other diseases. In addition to that CD activity index and partial myoscore used for CD and UC respectively, to evaluate the severity of diseases.

Samples collection

Tissue biopsies were collected during endoscopy of patients for histopathological examination to confirm all baseline data needed for this study and to obtain a tissue section slides for IHC technique. Also, blood samples were collected from each patient for serum preparation that used for detection of anti-HCMV IgM and IgG antibodies by enzyme linked immunosorbent assay (ELISA) technique.

Histopathology

Formalin fixed paraffin embedded blocks were cut into sections (5 µm thickness) used to prepare slides for Hematoxylin and Eosin staining to demonstrate typical CMV inclusions. Furthermore, two other slides were performed for IHC with two specific monoclonal Mouse Anti-Cytomegalovirus Clones (CCH2 and DDG9) to detect of early and immediate early antigens of HCMV respectively to increase the diagnostic yield of histopathology. Sections on positively charged slides were placed vertically in hot air oven at 65°C overnight. Two antigen retrieval steps done by used Trypsin as enzymatic and high pH solution (Dako) for heat protocol. A diluted primary antibody (1:50) was placed onto the tissue section and incubated for 60 minutes at room temperature in humid chamber, followed by the appropriate detection kit Dako anti–mouse HRP). Sections were analyzed via conventional light microscopy. The immunostained slides were evaluated for the presence of nuclear staining for the HCMV early antigen, sometimes accompanied by cytoplasmic staining.

Serology

An indirect ELISA were used to detect anti-CMV IgM and IgG antibodies in all patients' serum by using a commercially available kit (Forsight, USA). The positive and negative controls provided with the kit.

Statistical analysis

The statistical analysis of this study performed with (SPSS) 20.0 and Microsoft Excel 2010. Categorical data formulated as count and percentage. Chi-square test was used to describe the association between positive CMV with demographic and clinical data. Alternatively, kappa test was used to describe the agreement between diagnostic tests. The lower level of accepted statistically significant difference is below 0.05.

Results

Sixty-five patients diagnosed with active IBD (56 with UC and 9 with CD) were enrolled in this cross-sectional study. At the time of assessment, the mean age was 40.74±13.47 (range: 14-69) years. Male patients represented 46.15% of the patients (30 out of 65) and Smokers represented only a small minority of patients (5/65, 7.69%). The clinical characteristics of patients with or without HCMV are shown in Table 1. The patients were different in duration of diseases, severity of disease (mild, moderate, sever), type and response to treatment and disease extension.

CMV infection with IBD patients

Nine (13.85%) of the 65 IBD patients had CMV infection (all of them with UC) however; there is no significant difference between two types of IBD. CMV Ag was detected by IHC in tissue sample while in sera all those patients exhibited a positive Anti-CMV IgG Ab and only 2 out of 9 patients were detected with Anti-CMV IgM Ab.

Table 1. Clinical characteristics of the study population

Variable		Frequency	Percentage
Type of Disease	UC	56	86.15%
	CD	9	13.85%
Degree of Disease	Severe	29	44.62%
	Moderate	22	33.85%
	Mild	14	21.54%
Duration of disease (year)	<3	28	43.08%
	3-5	16	24.62%
	>5	21	32.31%
Response to treatment	Yes	37	61.66%
	No	23	38.34%
Type of treatment	Non biological	54	83.31%
	Biological	6	9.23%
	No treatment	5	7.69%
Disease extension	Left side colon	9	13.85%
	Proctitis	33	50.77%
	Pancolitis	23	35.38%

UC: Ulcerative colitis, CD: Crohn's disease

Possible risk factors associated with CMV reactivation

There was no significant difference in terms of age, sex, and smoking between CMV-positive and negative IBD patients ($p > 0.05$). Although, all 9 CMV-positive patients were among UC patients there was no significant difference between CMV infection and two types of IBDs. Severity of disease had shown no significant association with CMV infection although about seven CMV-positive patients out of 9 with severe illness. Only 60 patients had received treatment and about 7 (30.44%) of CMV-positive among non-response compared with only one patient among responsive was shown a highly significant differences ($p = 0.002$) with positive CMV patients. Of the 9 CMV-positive patients, seven were receiving Non-biological treatment; one was received biological treatment and one without treatment with no significant difference ($p > 0.05$). There was no significant difference in the frequency of CMV infection with respect to the disease extension of IBD ($p > 0.05$) although about 6 of CMV infection patients had proctitis involvement among 2 had pancolitis and one with left side colon. Six of the 9 CMV-positive patients had a long disease duration above 5 years shown a significant association ($p = 0.042$) than that in CMV negative patients. Risk factors for CMV infection with IBD are listed in table 2.

Table 2. Risk factors for HCMV infection with IBD

Variable		CMV		P-value
		Negative (%)	Positive (%)	
Disease	Ulcerative Colitis	47 (83.9)	9 (16.1)	0.195
	Crohn's disease	9 (100)	0 (0.0)	
Disease severity	Mild	13 (92.86)	1 (7.14)	0.095*
	Moderate	21 (95.45)	1 (4.55)	
	Severe	22 (75.86)	7 (24.14)	
Disease duration (years)	<3	27 (96.43)	1 (3.57)	0.042*
	3-5	14 (87.5)	2 (12.5)	
	>5	15 (71.43)	6 (28.57)	
Response to treatment	No	16 (69.56)	7 (30.44)	0.002**
	Yes	36 (97.29)	1 (2.71)	

*P < 0.05, ** P < 0.01

Discussion

The first published case report of HCMV associated with UC has been in 1961 lead to raise the question of whether the CMV detected was the primary cause of the patient's deterioration or a by-product of ''Ulcerative colitis, debility and the therapeutic use of adrenal cortical steroids.'' In the last 50 years this subject has become a topic in IBD literature [19].

Historically, symptomatic CMV disease was observed in immunocompromised patients; in newborns, following solid organ transplantation, in cases with human Immunodeficiency virus (HIV), or patients on immunosuppressive medications [20,21]. Numerous case series have also been reported of CMV detection in patients with severe IBD unresponsive to standard immunosuppressive therapy [22,23].

In the current study, the prevalence of HCMV in patients with IBD was 13.85%. This rate was agreement with a study in 2009 by Maher and Nassar in KSA, which detected HCMV in 9 out of 72 (12.5%) with same method of diagnosis in active IBD patients [24], Ormeci et al. 2016 in Istanbul was detect 13 out of 85 (15.4%) of IBD patients had HCMV infection [25], and Yadegarynia et al. 2018 in Iran six out 86 (7%) patients with UC the virus was detected by qPCR for colonoscopic biopsy [26].

Among 9 positive patients of IHC results, which expressed HCMV antigens (all of them had Anti-CMV IgG antibodies), only two patients had Anti-CMV IgM this situation may be due to immunosuppression status sometimes may not show IgM response as well as lower of sensitivity comparison to IHC [27,28]. Similar finding by Roblin et al. in 2011 was reported 16 patients with CMV colitis, all had serum anti-CMV IgG antibodies but none had anti-CMV IgM antibodies, although three had CMV DNA in their blood [29]. In addition, Iida et al. in 2013 found none of the 79 patients they reported with moderate or severe UC, who were anti CMV IgG antibody positive, had serum IgM antibodies to CMV [30]. Also, Gauss et al. (2015) 10-year retrospective cohort study for 294 patients with exacerbated IBD reported one patient with highly positive CMV pp65 was in the blood however CMV IgM test gave negative result [31].

According to type and severity of disease many studies have linked CMV with severe UC with prevalence ranged from 16-34% when used various diagnosis methods [12,23,30,32,33]. In case-control study performed on 226 IBD patients (83.6%), Yi et al. (2013) showed that CMV reactivation was significantly associated with severe UC patients [34]. Although, in this study there is no significant statistical difference all positive HCMV E and IE antigens IHC detected only in UC patients and about (77.7%) of severe

disease, these finding may be due to different cytokines profile of CD and UC: in CD Th 1 and Th 17 CD4+ cells differentiation with massive antiviral cytokines (IFN-γ). While there is a limited secretion of these cytokines in UC [35]. Different finding by Ormeci et al. in 2016 was reported Thirteen (15.4%) of the 85 IBD patients had CMV infection (5/42 with CD and 8/43 with UC) with no significantly different between two types of IBD [25].

Several studies and meta-analysis including 11 studies with 867 IBD patients have established an association between severe steroid-refractory IBD and CMV infection [11,12,36]. Roblin et al. in 2011 in a prospective study for 42 patients with moderate to severe UC on IV steroid treatment showed an association between CMV detection in inflamed area with resistance to steroid [29]. In this study, the association found with highly significant statistical difference (p=0.002) among seven non-response UC patients with positive for HCMV (87.5%) out from 8 positive patients takes a treatment. This association is still unclear and may be due to viral mechanism which has a role in worsening the inflammation [37].

In this study, the disease duration by years was classified to intervals (<3, 3-5, >5) according to other previous studies [31,38]. Patients with long disease duration above 5 years showed higher proportion of HCMV positive patients (28.57%) than either those with less than 3 years duration (12.5%) or those with 3-5 years duration (3.57%) with a significant difference (p=0.014), the explanation of this association may be due to CMV infection, reactivation of latent virus is a more probable event during attacks of intestinal inflammation and use of immunosuppression treatment for long period [39,40]. This significance also reported by recent study by Makarchuk et al. in 2017 during study a group of IBD patients for 6 years that about 35% of CMV infected patients were with long disease duration ≥ 5 years [38].

According to all evidences about CMV infection in patients with IBD, the management of CMV infection in IBD patients was based on the guidelines from both the ACG and ECCO, which recommend as follows: the CMV colitis should be excluded by tissue PCR or IHC in patients with acute steroid resistance before increasing treatment dosage. In patients with severe steroid resistance with detection of colonic CMV the antiviral therapy should be initiated with discontinuation of immunomodulatory agents until improve of colitis symptoms, While immunomodulatory therapy must be discontinued during systemic CMV disease [13,14].

The major findings of this study are as follows: (a) Colonic HCMV reactivation (HCMV Colitis) can occur in some IBD patients; (b) HCMV appears to have a significant role in a subgroup of IBD patients particularly refractory patients with long disease duration (>5 years) than other IBD patients; (c) The patients with severe refractory, proctosigmoiditis and older >30 year appeared to be more susceptible to HCMV reactivation; (d) The use of HCMV IE and E proteins IHC reflects the reliable method to diagnose colonic local HCMV reactivation rather than depended on H&E or serology; (e) There is a high seroprevalence of HCMV among Iraqi Patients.

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Author contribution

Fadhil: Collection of specimens, slides preparation, H&E with IHC staining and doing ELISA, preparing the manuscript and references. Dr. Kadhim: supervised the work, edit and finalize the manuscript. Dr. Al-Akayshee: Consultant Gastro and Hepatology helped in selection and providing of samples. Dr. Mirza: Consultant pathologist help in providing the histopathology reports and IHC staining results.

Conflict of interest

Authors declare no conflict of interest.

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References

1. Vilela EG, Osvaldo H, Martins FP, et al. Evaluation of inflammatory activity in Crohn's disease and ulcerative colitis. World J Gastroenterol. 2012; 18(9): 872-81. doi: 10.3748/wjg.v18.i9.872.
2. Dave M, Purohit T, Razonable R, et al. Opportunistic infections due to inflammatory bowel disease therapy. Inflamm Bowel Dis. 2014; 20(1): 196-212. doi: 10.1097/MIB.0b013e3182a827d2.
3. Azie N, Neofytos D, Pfaller M, et al. The PATH (prospective antifungal therapy) alliance(R) registry and invasive fungal infections: update 2012. Diagn Microbiol Infect Dis. 2012; 73(4): 293-300. doi:10.1016/j.diagmicrobio.2012.06.012.
4. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREATTM registry. Am J Gastroenterol. 2012; 107(9): 1409-22. doi: 10.1038/ajg.2012.218.
5. Christidou A, Zambeli E, Mantzaris G. Cytomegalovirus and inflammatory bowel disease: pathogenicity, diagnosis and treatment. Ann Gastroentol. 2007; 20(2): 110-5.
6. Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. Rev Med Virol. 2010; 20(4): 202-13. doi: 10.1002/rmv.655.
7. You DM, Johnson MD. Cytomegalovirus infection and the gastrointestinal tract. Curr Gastroenterol Rep. 2012; 14(4): 334-42. doi: 10.1007/s11894-012-0266-4.
8. Kandiel A, Lashner B. Cytomegalovirus colitis complicating inflammatory bowel disease. Am J Gastroenterol 2006; 101(12): 2857-65 doi: 10.1111/j.1572-0241.2006.00869.x.
9. Goodman AL, Murray CD, Watkins J, et al. CMV in the gut: a critical review of CMV detection in the immunocompetent host with colitis. Eur J Clin Microbiol Infect Dis. 2015; 34(1): 13-18. doi: 10.1007/s10096-014-2212-x.
10. Papadakis KA, Tung JK, Binder SW, et al. Outcome of cytomegalovirus infections in patients with inflammatory bowel disease. Am J Gastroenterol. 2001; 96(7): 2137. Available from: doi: 10.1111/j.1572-0241.2001.03949.x.
11. Domènech E, Vega R, Ojanguren I, et al. Cytomegalovirus infection in ulcerative colitis: a prospective, comparative study on prevalence and diagnostic strategy. Inflamm Bowel Dis. 2008; 14(10): 1373-9. doi: 10.1002/ibd.20498.
12. Park SC, Jeen YM, Jeen YT. Approach to cytomegalovirus infections in patients with ulcerative colitis. Korean J Intern Med. 2017; 32(3): 383-92. doi: 10.3904/kjim.2017.087.
13. Rahier JF, Magro F, Abreu C, et al. European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis. 2014; 8(6): 443-68. doi: 10.1016/j.crohns.2013.12.013.
14. Landsman MJ, Sultan M, Stevens M, et al. Diagnosis and management of common gastrointestinal tract infectious diseases in ulcerative colitis and Crohn's disease patients. Inflamm Bowel Dis. 2014; 20(12): 2503-10. doi: 10.1097/MIB.0000000000000140.
15. Garrido E, Carrera E, Manzano R, et al. Clinical significance of cytomegalovirus infection in patients with inflammatory bowel disease World J Gastroenterol. 2013; 19(1): 17-25. doi: 10.3748/wjg.v19.i1.17.
16. Al-Obaidi AB. Human Cytomegalovirus and Colorectal Adenocarcinoma: Any Association? IRAQI J Med Sci. 2008; 6(2): 54-7.
17. Shamran HA, Kadhim HS, Hussain AR, et al. Detection of human cytomegalovirus in different histopathological types of glioma in Iraqi patients. Biomed Res Int. 2015; 2015: 642652. doi: 10.1155/2015/642652.
18. Al-Toban HA, Al-Marsomy HD, Al-Obaidi AB, et al. Molecular detection of cytomegalovirus in a sample of Iraqi patients with acute leukemia and stem cell transplantation. Iraqi J Med Sci. 2018; 16(3), 344-52. doi: 10.22578/IJMS.16.3.14.
19. Powell RD, Warner NE, Levine RS, et al. Cytomegalic inclusion disease and ulcerative colitis; report of a case in a young adult. Am J Med. 1961; 30: 334-40. doi: 10.1016/0002-9343(61)90105-x.
20. Alford CA, Stagno S, Pass RF, et al. Congenital and perinatal cytomegalovirus infections. Rev Infect Dis. 1990; 12(suppl 7): S745–53. doi: 10.1093/clinids/12.supplement_7.s745.
21. Nelson MR, Erskine D, Hawkins DA, et al. Treatment with corticosteroids—a risk factor for the development of clinical cytomegalovirus disease in AIDS. AIDS. 1993; 7(3): 375-8. doi: 10.1097/00002030-199303000-00011
22. Maconi G, Colombo E, Zerbi P, et al. Prevalence, detection rate and outcome of cytomegalovirus infection in ulcerative colitis patients requiring colonic resection. Dig Liver Dis. 2005; 37(6): 418–23. doi: 10.1016/j.dld.2005.01.011.
23. Ayre K, Warren B, Jeffrey K, Travis SP. The role of CMV in steroid-resistant ulcerative colitis: a systematic review. J Crohns Colitis. 2009; 3(3): 141-8. doi: 10.1016/j.crohns.2009.03.002.
24. Maher MM, Nassar MI. Acute cytomegalovirus infection is a risk factor in refractory and complicated inflammatory bowel disease. Dig Dis Sci. 2009; 54(11): 2456-62. doi: 10.1007/s10620-008-0639-6.
25. 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(5): 858–65.
26. Yadegarynia D, Tehrani S, Roohi M, et al. Prevalence of cytomegalovirus infection in patients with ulcerative colitis: a prospective cross-sectional study in Tehran, Iran. Iran J Microbiol. 2018; 10(5): 342-7.
27. de la Hoz RE, Stephens G, Sherlock C. Diagnosis and treatment approaches of CMV infections in adult patients. J Clin Virol. 2002; 25 Suppl 2: S1-12. doi: 10.1016/s1386-6532(02)00091-4
28. Kotton CN, Fishman JA. Viral infection in the renal transplant recipient. J Am Soc Nephrol. 2005; 16(6): 1758-74. doi: 10.1681/ASN.2004121113.
29. 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(11): 2001-8. doi: 10.1038/ajg.2011.202.
30. 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(6): 1156-63. doi: 10.1097/MIB.0b013e31828075ce.
31. Gauss A, Rosenstiel S, Schnitzler P, et al. Intestinal cytomegalovirus infection in patients hospitalized for exacerbation of inflammatory bowel disease: a 10-year tertiary referral center experience. Eur J Gastroenterol Hepatol. 2015; 27: 712–20.
32. Lombardi G, Garofoli F, Stronati M. Congenital cytomegalovirus infection: treatment, sequelae and follow-up. J Matern Fetal Neonatal Med. 2010; 23(3):45-48. doi: 10.3109/14767058.2010.506753.
33. Kambham N, Vij R, Cartwright CA, et al. Cytomegalovirus infection in steroid-refractory ulcerative colitis: a case-control study. Am J Surg Pathol 2004; 28(3): 365-73. doi: 10.1097/00000478-200403000-00009
34. Yi F, Zhao J, Luckheeram RV, et al. The prevalence and risk factors of cytomegalovirus infection in inflammatory bowel disease in Wuhan, Central China. Virol J. 2013; 10: 43. doi: 10.1186/1743-422X-10-43.
35. Strober W, Fuss IJ. Proinflammatory cytokines in the pathogenesis of inflammatory bowel diseases. Gastroenterology. 2011; 140(6): 1756-67. doi: 10.1053/j.gastro.2011.02.016.
36. Wu XW, Wu L, Ji HZ, et al. Relationship between Cytomegalovirus Infection and Steroid Resistance in Inflammatory Bowel Disease: A Meta-Analysis. Dig Dis Sci. 2015; 60(11): 3203-8. doi: 10.1007/s10620-015-3733-6.
37. Yi HA, Kim MS, Jang SY, et al. Cellular signals involved in cyclooxygenase-2 expression induced by human cytomegalovirus. Virus Res. 2009; 146(1-2): 89-96. doi: 10.1016/j.virusres.2009.09.004.
38. Makarchuk P, Belousova E, Volchkova E, et al. P517 Features of cytomegalovirus infection in inflammatory bowel disease, Journal of Crohn's and Colitis. 2017; 11(1): S343. doi: https://doi.org/10.1093/ecco-jcc/jjx002.641
39. Kim JJ, Simpson N, Klipfel N, et al. Cytomegalovirus infection in patients with active inflammatory bowel disease. Dig Dis Sci. 2010; 55(4): 1059-65. doi: 10.1007/s10620-010-1126-4.
40. Lawlor G, Moss AC. Cytomegalovirus in inflammatory bowel disease: pathogen or innocent bystander?. Inflamm Bowel Dis. 2010; 16(9): 1620-7. doi: 10.1002/ibd.21275.

Correspondence to Alaa H. Fadhil
E-mail: alaa.h.fadhil@gmail.com
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