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Original Article

CMV colitis in children: Single-center experience

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Abstract

Objective: CMV colitis in children is very rare. We aimed to evaluate the clinical and histopathological findings of the patients with CMV colitis.

Methods: This was a single-center retrospective study. We enrolled the patients who were histopathologically diagnosed with CMV colitis between January 2010 and April 2022. We investigated their clinical and histopathological findings.

Results: In total 67 patients with diarrhea had positive CMV IgM/ PCR. We enrolled 6 of them who had histopathologic findings of CMV infection determined by Hematoxylin-eosin and immunohistochemistry (IHC) staining. Three (50%) of the patients were female. Two of the patients had no immunodeficiency or underlying disease. The underlying diseases were ulcerative colitis (UC) in 3 (50%) children and common variable immunodeficiency in one (16.6%) of the children. The most common symptoms were bloody diarrhea and hypoalbuminemia. CMV IgM and IgG were positive only in one patient. However, all patients had positive CMV PCR. The affected colon mucosa appeared friable and oedematous in all patients. Two patients (33.3%) had polyps in the transverse and descending colon, three patients (50%) had multiple ulcers in the sigmoid colon, and one patient (16.6%) had erythema in the sigmoid colon. All six patients had positive IHC staining in the colonic tissue. All patients were treated with ganciclovir. Four patients improved however, two patients required colectomy in the follow-up.

Conclusion: CMV colitis may be seen in both immunosuppressive and immunocompetent patients. CMV colitis should be considered especially in the combination of bloody diarrhea and hypoalbuminemia. Early diagnosis is mandatory for the successful treatment and outcome of the disease.

Keywords: Child, CMV infection, colitis

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INTRODUCTION

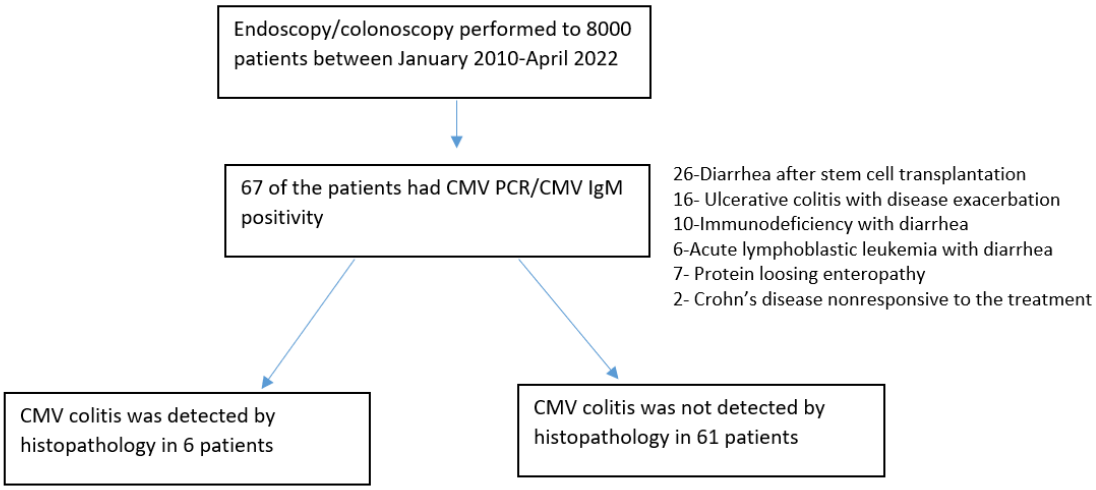
Cytomegalovirus (CMV) is a double-stranded DNA virus and a member of the herpes virus family. Its seroprevalence varies between 40-70% in the general population (1). CMV infection is characterized by asymptomatic, mild, and self-limited disease in healthy individuals. However, it can be reactivated in both immunocompetent and immunosuppressed persons and may result in severe disease. Reactivation occurs at any time during life, especially in cases of systemic immunosuppression, acquired immunodeficiency, organ transplantation, or inflammatory bowel disease (IBD). CMV infection may also develop as a primary infection in immunocompetent patients (2). Gastrointestinal system involvement may be severe in CMV infection. Especially colon and esophagus are the most common sites (2-8).

CMV infection is frequent in hospitalized adults with IBD varying from 0.5% to 3.4% (9,10). It is much more frequent in IBD patients with severe colitis and >30% in steroid-resistant IBD patients (7). However, the data on CMV colitis in children is scarce. CMV colitis usually presents with low-grade fever, watery diarrhea, hematochezia, weight loss, and abdominal pain. CMV infection can lead to extensive mucosal hemorrhage, ulceration, and erosion in the gastrointestinal tract. Widespread mucosal bleeding and intestinal perforation can be life-threatening. The lesions' pathogenesis is unclear, but tissue inflammation, necrosis, ischemic mucosal damage due to endothelial involvement, and regional autoimmunity may play a role (3). CMV infection may rarely lead to protein-losing enteropathy (11-17).

Diagnosis of CMV is difficult, and high clinical suspicion is needed. CMV colitis can be detected by hematoxylin and eosin (H&E) or immunohistochemistry (IHC) staining in endoscopic biopsies (18,19). CMV-infected cells show a typical "Owl-eyes" appearance with H&E staining characterized by enlarged cells, large eosinophilic inclusions that are sometimes surrounded by a clear halo, and smaller cytoplasmic inclusions. These cells are very specific for CMV infection (92–100%), but with poor sensitivity (10–87%) (20). CMV-specific IHC is the gold standard for diagnosis of end-organ CMV diseases, however, an invasive procedure is required to obtain tissue specimens (18).

Many factors such as mucosal inflammation, use of immunosuppressant drugs, and malnutrition may lead to reactivation of CMV infection in patients with IBD. Therefore, antiviral therapy should be given to immunosuppressed patients and immunocompetent patients with severe diseases (20). Here, we present clinical data of our patients with CMV colitis. We also aimed to evaluate the clinical and histopathological findings of these patients.

Figure 1. Study Flow-Chart



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MATERIALS AND METHODS

This study was approved by the local ethical committee (Approval Number: E2-22-1715). We conducted a retrospective review of children who underwent endoscopy/sigmoidoscopy or colonoscopy in a single tertiary center between January 2010 and April 2022. We searched our endoscopy database (Endocam) via the terms ‘’cytomegalovirus, CMV, CMV colitis’’, and patients' files to collect the data. Additionally, we searched our endoscopic histopathology reports for CMV infection.

We included the patients between 0-18 years who underwent endoscopy/sigmoidoscopy or colonoscopy. All included children had positive serum CMV PCR and histologic presence of viral cytopathic effects with H&E stain or IHC in endoscopic biopsies. Demographic, medical, laboratory, endoscopic, and histopathologic findings were recorded. The drugs used in the treatment of CMV infection and clinical outcomes were retrieved. We excluded the children who did not show the histopathologic presence of CMV infection in endoscopic biopsies, despite positive serum CMV serology/PCR.

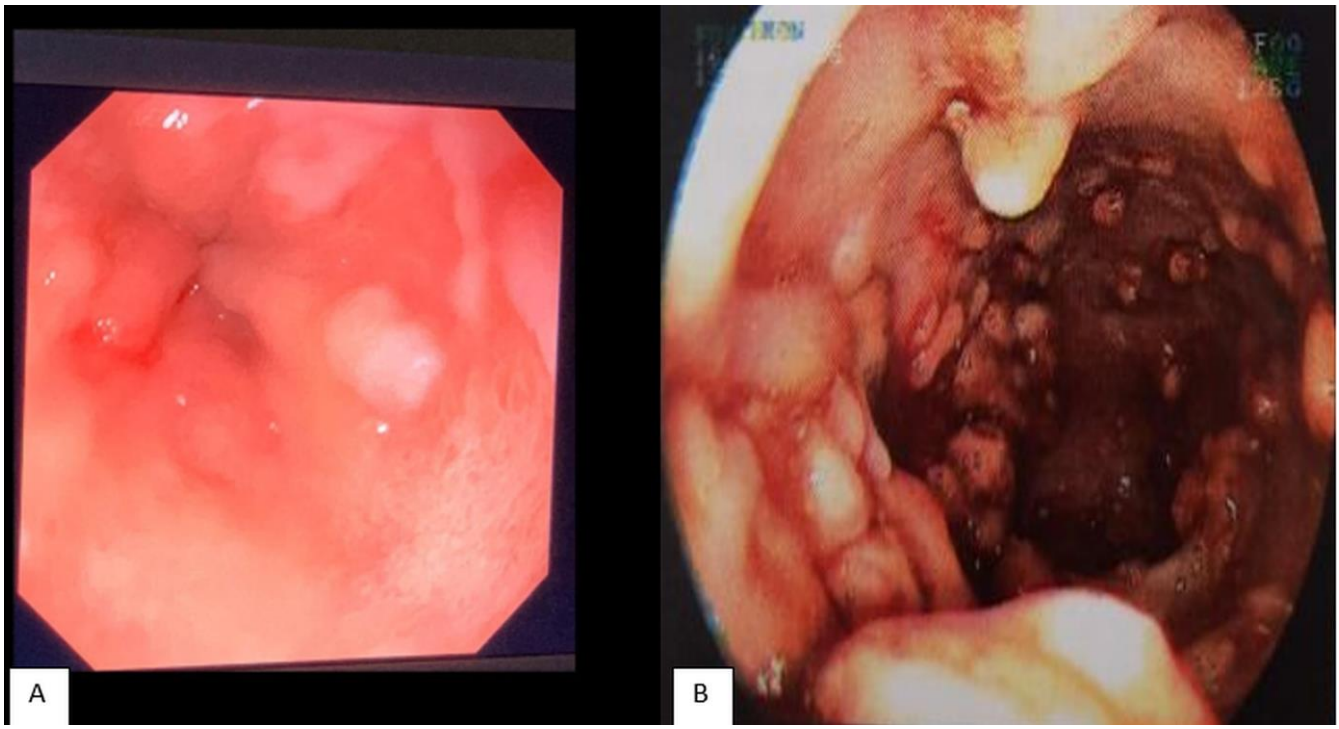

Figure 2. A: Erythema and friability in colon mucosa, B: Colonic polyps which have positive tissue CMV-PCR

For CMV detection in the tissue (Zeta-8B 1.2/1G5.2/2D4 mouse monoclonal antibody, dilution:1/100), Ventana BenchMark Ultra was used. After antigen retrieval treatment with EDTA solution, the CMV antibody was manually applied and incubated for 56 minutes. Enrichment was done with Ventana Amplification Kit. The BMK Ultraview DAB paraffin kit was then used for staining. Also, counterstaining was performed as part of the automated staining protocol using hematoxylin. After staining, the slides were washed, dehydrated in graded alcohol and xylene, mounted, and coverslipped. The presence of nuclear staining for the CMV antibody was considered to be positive.

Statistical analysis:

Data were analyzed using SPSS software (IBM SPSS version 20, Armonk, NY, USA). Continuous variables were reported as mean±standard deviation (SD) or median and range; categorical variables were reported as count (percentage).

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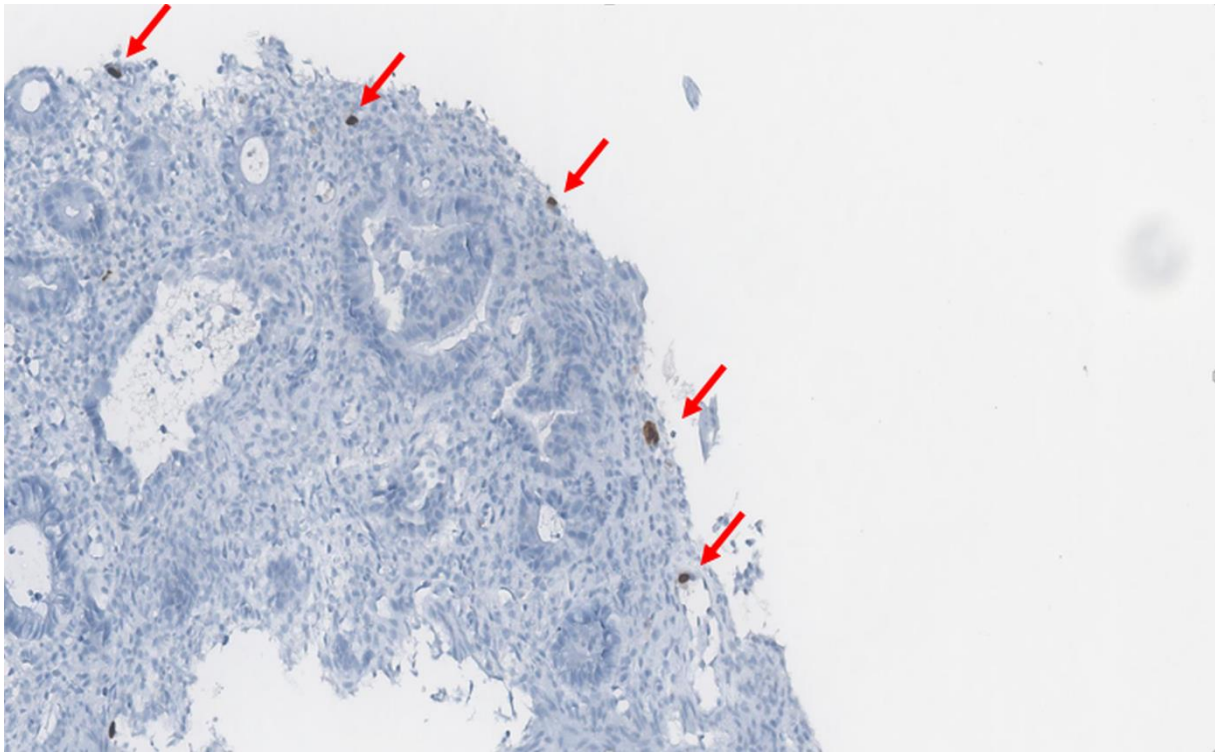

Figure 3. Immunohistochemistry staining (20×objective) was performed 1/100 diluted Zeta-8B 1.2/1G5.2/2D4 mouse monoclonal antibody and showed strong focal CMV immunoreactivity with brownish areas

RESULTS

During the study period, 8000 endoscopy/sigmoidoscopy or colonoscopy was performed. Sixty-seven of the patients had positive CMV serology/PCR. The distribution of the patients with positive CMV serology/PCR whose endoscopy/colonoscopy was performed is shown in Figure 1. We did not find the CMV histopathologic findings in 61 of the patients. There were only six (0.075%) patients with positive CMV PCR and colonic tissue involvement demonstrated by histopathologic examination. These six patients were included in the study. The mean age of the children was 99.5 months (min 1 month, max 198 months). Three of the patients (50%) were female. All of the patients presented with bloody diarrhea. Three of the patients (50%) had severe edema. The underlying disease was ulcerative colitis (UC) in 3 (50%) children, common variable immunodeficiency in one (16.6%) of the children. There was no underlying disease in two (33.3%) of the children. Table 1 summarizes the demographic and clinical features of the patients. Median hemoglobin level was 9.9 g/dL (min 8-max 11.5), white blood cell 6000 mm^3 (min 4450-max 9100), platelet $321x10^9$/L (min 206- max 546). Mean absolute neutrophil count was $3.1\pm1.5x10^9$/L (min 1.2-max 5.4), absolute lymphocyte count was $2.5\pm1.2x10^9$/L (min 1.2-max 4.1). Alanine aminotransferase (52 U/L, N: 0-41) and aspartate aminotransferase 49 U/L (N: 0-73) levels were elevated in only one child. Bilirubin levels were normal in all six children. Albumin levels were low in 5 of the patients, the mean albumin level was a median of 2.2 g/L (min 1.8-max 4, normal values 3.2-4.8). All patients had erythrocytes in stool examination. Only one patient with UC had entamoeba histolytica trophozoites in stool microscopy. Adenovirus, rotavirus, clostridium difficile toxin A and B, and cryptosporidium parvum were all negative in stool microscopic examination of the patients. The sedimentation rate was normal in all of the children, however, CRP levels were elevated in four (66.6%) of them. One patient had CMV IgM and IgG positivity. The other five patients had negative CMV IgM and IgG serology. Median serum CMV PCR at admission was 2690 copies/mL (min 116-max

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15.855). The median CMV viral load at the time of the CMV colitis diagnosis was 9419 copies/mL (min 4520-max 15.855). Tissue CMV PCR was performed on two of the patients, one of them had 4.398.543, other had 450.000 copies of CMV. Abdominal ultrasonography was normal in four (66.6%) of the patients, however, the other two patients with ulcerative colitis had increased bowel thickness in the colon.

We have performed upper gastrointestinal system endoscopy (UGE) in five of these patients. Two of them had normal UGE, however, two of them had erythema in the esophagus, diffuse white plaques, and nodularity in the antrum. One patient had erythema in the corpus and antrum. The histopathologic investigation was normal in one patient, chronic gastritis in one, edema in the esophagus and Helicobacter pylori (Hp) in one, Hp in one, chronic gastritis and Hp in one patient. All six patients had colonoscopy/rectosigmoidoscopy. The affected mucosa appeared friable and oedematous in all patients. Additionally, two patients (33.3%) had polyps in the transverse, descending and sigmoid colon (Figure 2), three patients (50%) had multiple ulcers in the sigmoid colon, and one patient (16.6%) had erythema in the sigmoid colon. All six patients had positive IHC staining in the colonic tissue (Figure 3). Histopathologic examination revealed chronic active inflammation in one patient, the other five patients had cryptitis, crypt abscess, crypt distortion, and infiltration with polymorphonuclear leukocytes (PNL) in colonic biopsies. Table 2 summarised the endoscopic and histopathological findings of the patients. The median time to diagnosis for CMV was 31.5 days (min 6-max 90 days). All patients were treated with ganciclovir, and in 4 patients treatment was continued with valganciclovir. The median duration of the therapy was 2.2 months (min 14 days- max 6 months). The median time to the improvement of diarrhea was 12.5 days (min 10- max 20 days). The median normalization time of albumin levels after treatment was 15 days (min 10- max 75 days). After treatment four of the patients improved, however, colectomy was performed in two patients. One of them (Patient 5) with UC had CMV positivity in the colonic polyps. He had completed antiviral treatment and showed clinical improvement. However, two years after the first treatment, he had an acute exacerbation of the UC disease, and colonoscopy and histopathology revealed CMV recurrence in the colonic polyps again. He did not respond to antiviral treatment and ultimately colectomy was performed. The other patient (Patient 4) with immunodeficiency had positive CMV involvement in the colon after six months of the treatment, and colectomy was needed to improve the outcome (Table 3).

DISCUSSION

In our study, the majority of the patients had hypoalbuminemia, edema, and protein-losing enteropathy (PLE) associated with CMV. PLE is a rare clinical condition characterized by massive leakage of protein-rich fluids across the eroded epithelium in the gastrointestinal tract. The diagnosis is based on the exclusion of other causes of hypoproteinemia. We did not find any other causes of PLE in the patients. PLE in CMV infection was rarely reported in adults (11) and children (12-17). Clinicians may overlook CMV and a high index of suspicion is needed in cases with bloody diarrhea and PLE. Serology can be used as a screening test, but, a follow-up serum CMV titer is more useful to diagnose the infection. Serology may yield false-negative results in local CMV infection. We detected only one patient with positive CMV IgM serology at admission while the others had negative CMV IgM or IgG serology. Detection of CMV DNA by PCR in tissue biopsies is a useful method for the final diagnosis. CMV colitis is a well-known clinical entity in immunosuppressed patients with diarrhea. However severe colitis secondary to CMV infection may also occur in the immunocompetent hosts (4,21-24). Klauber et al. reviewed 13 immunocompetent adult patients with CMV colitis. All of these patients had diarrhea, and 11 of them had bleeding or bloody diarrhea. The mortality rate was 26.7% and they concluded that CMV colitis in immunocompetent patients is rare, but potentially severe and may lead to significant morbidity (22). Another study showed that the most common symptoms in CMV colitis were melena in the immunocompetent group and diarrhea in the immunocompromised group (24). Our patients with

CMV colitis presented with bloody diarrhea from infancy to adolescent age, both in immunocompetent and immunosuppressed patients.

Table 1. Demographic, clinical, and laboratory findings of the patients

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**
Age, gender	1 month, M	1 year, F	16 years, M	2 years, M	14 years, F	16.5 years, F
Symptoms	Fever, bloody diarrhea	Bloody diarrhea	Bloody diarrhea	Fever, bloody diarrhea	Bloody diarrhea	Bloody diarrhea
Underlying disease	No	No	Ulcerative colitis	CVID	Ulcerative colitis	Ulcerative colitis
Physical examination	Diffuse edema	Diffuse edema	Normal	Diffuse edema	Normal	Normal
Hemoglobin(g/dL)	9.5	10.3	11.5	8	11.4	9.1
WBC (x10^9/L)	8.3	4.4	5.2	5.7	6.3	9.1
Platelet (x10^9/L)	352	337	546	262	227	206
Absolute neutrophil count	3370	1740	3300	1200	4100	5400
Absolute lymphocyte count	4180	2200	1200	3900	1300	2400
Total protein (N: 67-84 g/L)	2.7	3.2	6.2	4.8	5.1	7.2
Albumin (N: 32-48 g/L)	1.8	2	3.4	2.1	2.4	4
ALT (N: 0-31 U/L)	52	27	13	10	13	12
AST (N: 0-36 U/L)	49	31	21	28	15	15
Sedimentation (mm/h)	-	-	22	-	11	21
CRP (N: 0-5 mg/dL)	129	104	23	69	0.1	0.5
CMV IgM	Neg	Neg	Neg	Neg	Neg	Positive
CMV IgG	Neg	Neg	Neg	Neg	Neg	Positive
Serum CMV PCR at admission (copy/mL)	116	280	15855	2690	9419	-
Serum CMV PCR at diagnosis (copy/mL)	7277	457631	15855	4520	9419	-
Tissue CMV PCR (copy)	4398543	-	-	-	-	4500000

ALT; Alanine aminotransferase, AST; Aspartate aminotransferase, CRP; C-reactive protein, CVID; Common variable immunodeficiency, WBC; White blood cell

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Table 2. Endoscopic and colonoscopic findings of the patients with CMV colitis

	Endoscopy	Colonoscopy	Endoscopic histopathology	Colonoscopic histopathology
P1	-	Erythema and friability	-	Chronic active inflammation, CMV positivity
P2	Normal	Ulcer, friability, and erythema	Active chronic gastritis	Cryptitis, crypt abscess, crypt distortion, PNL, CMV positivity
P3	Erythema, white plaques in the esophagus, antral nodularity	Polyps in the transverse and descending colon, erythema, and friability	Edema in the esophagus and Helicobacter pylori infection	Cryptitis, crypt abscess, crypt distortion, PNL, CMV positivity
P4	Erythema, white plaques in the esophagus, antral nodularity	Polyps in transverse, descending and sigmoid colon, erythema	Helicobacter pylori infection	Cryptitis, crypt abscess, crypt distortion, PNL, CMV positivity
P5	Erythema in corpus and antrum	Ulcers and friability	Chronic gastritis, Helicobacter pylori infection	Cryptitis, crypt abscess, crypt distortion, PNL, CMV positivity
P6	Normal	Erythema	Normal	Cryptitis, crypt abscess, crypt distortion, PNL, CMV positivity

P: Patient, PNL: Polymorphonuclear leukocytes

UC was the underlying disease in half of our patients. CMV infection was shown to be significantly more prevalent in patients with UC who required colectomy at 1 year in a retrospective multicenter study. A higher risk for colectomy was observed during hospitalization (5). CMV is frequently detected in the colonic tissue of UC patients in surgical specimens (25). It is not clear whether CMV reactivation in IBD may lead to exacerbation of the disease or vice versa (9,19). Immunosuppressive drugs like systemic corticosteroids, thiopurines, and methotrexate may be associated with CMV reactivation in patients with UC (26, 27). Clinical and endoscopic features of CMV colitis are nonspecific, but rapid diagnosis and treatment is mandatory especially in immunosuppressive patients. CMV colitis in IBD is associated with a more severe disease. Patients with ulcerative colitis exacerbation and CMV infection are more resistant to treatment with corticosteroids than non-infected patients. CMV viral load in colonic tissue affects the outcome. Positive tissue CMV PCR or high-grade CMV colitis characterized by the presence of inclusion bodies and/ or positive IHC in colonic biopsies represents an increased risk of colectomy. Patients with high tissue CMV viral load may benefit from antiviral treatment without additional UC therapy. However, patients with low viral load [<5500 copies/µg DNA] would improve by intensifying UC therapy (28). Following this, we have used ganciclovir treatment

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in all patients. PLE with intractable diarrhea and hypoalbuminemia improved with ganciclovir treatment. But, the treatment was not effective in two patients with colonic polyps who required colectomy. Early diagnosis of CMV colitis improves survival, therefore clinicians should be aware of this entity (24).

Table 3. The time to diagnosis, treatment, and outcome of the patients

	Time to diagnosis (Day)	**Treatment**	**Treatment duration (Day)**	**Time to diarrhea improvement (day)**	**Time to albumin improvement (day)**	**Outcome**
P1	33	G	180	15	12	improved
P2	60	G, V	30	10	10	improved
P3	15	G,V	90	10	15	improved
P4	30	G, V	40	-	30	colectomy
P5	90	G	14	-	75	colectomy
P6	6	G, V	150	20	-	improved

P: patient, G: ganciclovir, V: valganciclovir

CONCLUSION

CMV infection should be suspected in every child who presents with bloody diarrhea and PLE. Serologic screening may be misleading and tissue CMV PCR can facilitate the diagnosis. Ganciclovir or valganciclovir treatments may be life-saving in patients with severe and intractable diarrhea.

Conflict of interest: The authors declare no conflict of interest.

Ethics Committee Approval: Our hospital's ethics committee, approval number: E2-22-1715

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Peer-review: Externally peer-reviewed

Authorship Contributions: Concept; AMD, CA -Design; AMD, CA, BH, SD, SKY, EK -Supervision; AMD, SKY - Funding; -None; -Materials; AMD, CA, BH, EK -Data collection &/or processing; AMD, CA, BH - Analysis and/ or interpretation; AMD - Literature search; AMD -Writing; AMD- Critical review; SD.

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