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A Descriptive Analysis of Clinical and Endoscopic Findings in Pediatric Patients with Gastrointestinal Cytomegalovirus Infection

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Abstract

Background: Cytomegalovirus (CMV) is a common viral infection, with gastrointestinal CMV infection primarily seen in individuals with weakened immune systems, impacting the clinical outcomes of affected patients. This study aim to evaluate the clinical manifestations, endoscopic findings, and underlying causes among pediatric cases with gastrointestinal CMV infection.

Methods: This retrospective study included all pediatric patients diagnosed with GI-CMV who were referred to Akbar Children's Hospital in Mashhad, Iran, and met the study's criteria. The criteria included pediatric patients who underwent endoscopic examinations. Comprehensive checklists were used to document symptoms, clinical presentations, medical histories, and endoscopic findings, with data extracted from patient records. Statistical analysis was performed using SPSS software version 23, with statistical significance set at $p < 0.05$.

Results: In a study of 17 patients initially admitted with a probable diagnosis of CMV, 12 (70.6%) were confirmed to have CMV during follow-up. The group consisted of 9 girls (75%) and 3 boys (25%), with a mean age of 42.75 months (SD ± 31.95). Most patients (83.3%) were discharged with partial recovery, and CMV infection was confirmed in 70.6% of cases. Pathology revealed that 75% had gastric involvement. The most common initial symptom was bloody vomiting (26%), followed by fever and diarrhea (13%). Ganciclovir was administered to all patients, and 8.33% received Prednisolone as well. Most patients exhibited elevated white blood cell counts, and liver enzymes and albumin levels were also impaired.

Conclusion: Symptoms of CMV colitis tend to be nonspecific and can manifest across a spectrum ranging from mild to severe presentations. Notably, CMV-positive patients are predisposed to more severe forms of colitis, with prolonged hospitalizations and concomitant febrile episodes frequently noted in cases of CMV colitis associated with underlying inflammatory bowel disease (IBD).

Key Words: Cytomegalovirus infection, Gastrointestinal disorders, Pediatric.

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1- INTRODUCTION

Cytomegalovirus (CMV) is a widespread viral infection prevalent in the general population. The seroprevalence of CMV varies between 40% and 100%, and it is influenced by age and geographic distribution (1). In a study conducted in Iran, CMV was diagnosed by polymerase chain reaction (PCR) in 7% of patients with ulcerative colitis (UC) (2). While CMV typically causes self-limiting disease in healthy individuals, it can lead to severe systemic illness in immunocompromised patients. CMV colitis primarily affects individuals with compromised immunity and is known to impact the clinical outcomes of these patients (3).

Following the initial infection, which can be symptomatic or asymptomatic, the virus enters a latent phase, persisting in human hosts for life (4). Various cells in the gastrointestinal (GI) organs, including those of the parenchyma and connective tissue, can become infected. CMV transmission occurs through sexual contact, blood/tissue exposure, perinatal routes, and close contact. Immune suppression, resulting from conditions like leukopenia, organ transplantation, AIDS, and immunosuppressive medications, poses a significant risk factor for symptomatic CMV infection (5).

CMV infection can affect multiple organs, with GI involvement being common (6). Symptoms and signs often mimic those of other infectious and inflammatory causes. Individuals with upper GI-CMV disease typically exhibit ulcerations throughout the GI tract, including painful ulcers in the mouth and throat due to CMV infection. Colitis is the most prevalent clinical presentation of GI-CMV disease, manifesting as diarrhea, hematochezia, fever, tenesmus, urgency, and abdominal pain, often with colonic ulcers resembling inflammatory bowel disease (IBD) (5). The gold standard for CMV detection in gastrointestinal mucosal biopsies is the use of CMV-specific immunohistochemistry (IHC), which identifies CMV antigens in infected cells (7). However, PCR testing of colonic tissue has demonstrated greater sensitivity compared to IHC. The European Crohn's and Colitis Organization (ECCO) guidelines recommend the use of PCR in GI tissue biopsies for the diagnosis of CMV colitis in IBD patients (8). Although this method is rapid, objective, and standardized, the application of PCR for diagnosing CMV colitis remains controversial (9).

CMV colitis is a frequent infectious complication among immunocompromised patients (10), with IBD being a common predisposing condition. The prevalence of CMV disease in IBD ranges from 1.5% to 4.5% (11). The first reported case of CMV colitis in IBD dates back to 1993, involving a 14-year-old boy with ulcerative colitis who underwent colectomy (12). Studies have shown that CMV-positive children with severe acute colitis are less responsive to corticosteroid treatment and more likely to require colectomy within 12 months compared to CMV-negative counterparts (13).

In managing acute colitis in children, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommends endoscopic evaluation in steroid-refractory cases to rule out CMV infection. Furthermore, staining and examination of colon biopsies for CMV using IHC are advised (14).

A study of 23 cases of CMV enterocolitis among immunocompetent children indicated that these patients typically present with leukocytosis, thrombocytosis, watery or bloody diarrhea, and may require colectomy (15). Prolonged hospitalization and fever are also associated with CMV colitis in IBD, with higher odds of in-hospital mortality for IBD patients with CMV infection compared to those without CMV (16, 17).

Endoscopic findings of CMV colitis are generally nonspecific, with distinct punched-out ulcers being a notable feature (18). Irregular and cobblestone-like ulcerations have also been associated with CMV colitis (19). The gold standard for diagnosing CMV in gastrointestinal mucosal biopsies is CMV-specific IHC, indicating CMV antigens in infected cells (7).

The recommended treatment for CMV colitis in adults is oral or intravenous ganciclovir at a dosage of 5 mg/kg twice daily, followed by oral valganciclovir after 3-5 days of intravenous therapy (8). In pediatric cases, injectable ganciclovir is suggested for 14-21 days to prevent CMV reactivation during the transition from intravenous to oral therapy (20). Foscarnet may be used as an alternative in cases of resistance or intolerance to ganciclovir (21). Combining antiviral therapy with granulocyte and monocyte adsorptive apheresis (GMAA) in kidney transplant recipients has demonstrated efficacy in reducing the treatment duration for CMV infection without significant adverse effects (22).

The debate over the necessity of antiviral intervention in individuals with intact immune function continuses. Noteworthy side effects of antiviral drugs include myeloid lineage suppression, central nervous system disturbances, hepatotoxicity, and nephrotoxicity (23). However, untreated CMV disease is linked to increased complications and mortality rates. It is suggested that antiviral treatment for individuals with normal immune function should be considered primarily for males aged over 55 or those with immune-affecting comorbidities such as diabetes or chronic renal disease (24).

In patients with ulcerative colitis, regardless of age, CMV infection is often associated with severe colitis and is indicative of unfavorable clinical outcomes. A high clinical suspicion is necessary for timely diagnosis, and subsequent treatment necessitates meticulous attention due to its significant impact on the clinical prognosis for such patients. While several researchers from various regions have reported on the prevalence of CMV infection among patients with IBD (25-27), there is a paucity of data specifically concerning this issue in Iran, particularly in the pediatric population (2). Given the widespread prevalence of CMV in the general population and its frequent occurrence as an infectious complication among immunocompromised patients, along with the wide range of etiological factors associated with CMV colitis and other gastrointestinal disorders, this study aims to provide a comprehensive assessment encompassing clinical and endoscopic findings, as well as the underlying etiology in pediatric patients with GI-CMV infection. This analysis seeks to enhance diagnostic accuracy and prognosis when dealing with such patients, thereby reducing unnecessary healthcare costs.

2-METHODS

In this retrospective study, all children who underwent endoscopic examination at Akbar Children's Hospital in Mashhad, Iran from 2018 to 2022 and met the inclusion criteria were included in the study through a census method. The inclusion criteria included all pediatric patients who underwent endoscopic examination. Individuals lacking relevant documentation in their medical records were excluded from the study. Initially, 17 patients were admitted with a probable diagnosis of CMV, of which 12 were treated with a definite diagnosis of CMV during follow-up.

Data were collected using checklists that documented the patients' clinical symptoms, previous medical history, and endoscopic findings. Information was recorded by extracting relevant data from medical records into these checklists.

Following data collection, the information was entered into SPSS software version 23, and appropriate tables and graphs were employed for data visualization and description. For the comparison of quantitative variables, t-tests or their nonparametric equivalents were utilized, depending on the distribution type. A significance level of less than 0.05 was considered statistically significant.

2-1.ETHICAL CONSIDERATIONS

All stages of the study adhered to the ethical principles of the Helsinki Declaration and were approved by the Ethics Committee of Mashhad University of Medical Sciences (Ethics Code: IR.MUMS.MEDICAL.REC.1401.614).

3-RESULTS

This study aimed to descriptively investigate the clinical, endoscopic findings, and underlying causes of gastrointestinal cytomegalovirus infection in children. Initially, 17 patients were admitted with a probable diagnosis of CMV, of which 12 (70.6%) were treated with a definitive diagnosis of CMV during follow-up. In patients whose CMV was negative, 2 were diagnosed with Crohn's disease during follow-up.

Table-1. The consequence of patients with GI-CMV infection.

CMV test Frequency (%)	Positive	12 (70.6)
	Negative	5 (29.4)
Final diagnosis of patients who tested negative for CMV Frequency (%)	IBD	2(40.0)
	Hepatoblastoma	1(20.0)
	Liver Mesenchymal Hamartoma (LMH)	1(20.0)
	Chronic granulomatous disease	1(20.0)
Consequence Frequency (%)	Death	2(16.7)
	Discharge	10(83.3)
Symptoms of patients with gastrointestinal cytomegalovirus infection Frequency (%)	Hematemesis	6(26.0)
	Edema	2(8.7)
	Diarrhea	3(13.0)
	Anorexia	2(8.7)
	Vomiting	2(8.7)
	Fever	3(13.0)
	Lethargy and decreased level of consciousness	2(8.7)
	Epigastric pain	1(4.3)
	Palor	1(4.3)
	Abdominal swelling (ascites)	1(4.3)
The final diagnosis of patients with GI-CMV infection Frequency (%)	CMV / duodenitis	1(8.33)
	CMV /Esophagitis	1(8.33)
	CMV /Esophagitis & stomach	1(8.33)
	CMV / stomach	9(75.0)
drugs used Frequency (%)	Ganciclovir	12(100.0)
	Prednisolone	1(8.33)

The study, conducted with a sample size of 12 people, included 9 girls (75%) and 3 boys (25%) with a mean age of 42.75 ± 31.95 months ranging from3 to 96 months old. One CMV positive patient had a history of congenital infection. 83.3% of patients were discharged from the hospital with partial recovery. In the studied population, 26% of the patients reported bleeding symptoms such as hematemesis and nasal bleeding, as well as reduced platelet levels. Additionally, 13.0% exhibited edema and vomiting, alongside other symptoms including diarrhea, anorexia, lethargy, decreased level of consciousness, and neck and abdominal swelling. As shown in Table 1, 75% of patients had gastric involvement. Ganciclovir was the primary drug used in these patients. It was used in 100% of patients. In 8.33% of patients, in addition to Ganciclovir, Prednisolone was also used (Table 1).The patients' tests results are summarized in Table 2. The majority had high WBC. Counts. Liver enzymes, albumin, and platelets were impaired in most patients. Complete blood count (CBC) tests showed elevated white blood cell (WBC) levels, along with reduced red blood cell (RBC) and platelet (PLT) counts. Renal function was normal across the patients, but the inflammatory marker erythrocyte sedimentation rate (ESR) was elevated in most cases, while C-reactive protein (CRP) levels were within the normal range for most.

Table-2. The laboratory findings in patients with GI-CMV infection.

	Minimum	Maximum	Mean	Standard Deviation
Blood sugar (BS)	76	101	87.83	8.305
Urea	16	38	24.43	7.138
Creatinine	0.30	0.60	0.49	0.10
Triglycerides	195.00	250.00	222.50	38.89
Cholesterol	80.00	80.00	80.00	.
Sodium	131.00	142.20	137.42	4.34
Potassium	3.70	5.00	4.40	0.43
Albumin	2.00	4.50	3.30	1.02
Total protein	4.00	6.80	5.30	1.41
Total Bilirubin	0.60	2.30	1.45	1.20
Direct Bilirubin	0.14	1.40	0.77	0.89
AST	24.00	211.00	66.66	73.41
ALT	7.00	182.00	69.66	86.72
ALP	139.00	640.00	367.00	207.30
LDH	443.00	759.00	601.00	223.44
Lactate	6.90	6.90	6.9000	.
Ammonia	51.90	100.30	76.1000	34.22
PT	11.00	13.00	12.66	0.81
INR	0.77	1.00	0.96	0.09
PTT	29.00	48.00	34.66	6.91
WBC	5.50	23.23	14.00	5.34
Hemoglobin	8.30	14.30	11.58	2.25
Platelet	7.00	478.00	338.28	161.83
PMN (Polymorphonuclear)	17.00	79.00	44.78	18.85
Lymphocyte	16.00	73.00	43.04	18.64
ESR	1.00	88.00	26.40	36.25
Gamma-Glutamyl Transferase	0.00	43.00	21.50	30.40

Serum albumin levels were normal in all evaluated patients. Liver function tests were abnormal in half of the patients, with median prothrombin time (PT), activated partial thromboplastin time (PTT), international normalized ratio (INR), as well as total and direct bilirubin levels being outside normal ranges. Some patients exhibited elevated bilirubin levels (Total Bilirubin = 1.4), likely indicating clinical jaundice (Table 2).

The results of endoscopic and colonoscopic examinations in patients diagnosed with CMV are presented in Table 3. Pathological findings from endoscopic and colonoscopic biopsy samples for these patients are detailed in Table 4. Finally, summarizes the diagnoses of patients before and after undergoing endoscopy and colonoscopy.(Table 5)

Table-3. Endoscopic and colonoscopy results in patients with GI-CMV infection.

Esophagus	Stomach	Duodenum	Colon	Rectum
White and fragile secretions (n=2)	Enteral nodularity	Duodenal bubble swelling (n=3)	Pattern of chronic active colitis (n=2)	Pattern of chronic active crypt-destructive colitis (n=2)
Esophagitis (n=2)	Gastritis		Pattern of acute active colitis	Pattern of acute active crypt-destructive colitis
Esophagitis and ulceration	Mucosal nodularity in the antrum, Polyp in the antrum			
	Erythema, ulceration, and bleeding (n=3)			
	Mucosal varioliform lesions, edema, erythema			

Table-4. Pathological results of endoscopic and colonoscopic biopsy samples in patients with GI-CMV infection.

Esophagus	Duodenum	Stomach	Colon	Rectum
Unexplained (n=5)	Unexplained(n=3)	Unexplained (n=2)	Unexplained	Unexplained
Insufficient sample	Insufficient sample	Insufficient sample	Chronic active colitis (n=3)	chronic active crypt-destructive colitis (n=3)
Hyperplasia of basal cells with large, hyperchromatic nuclei	Nodular hyperplasia of lymphoid tissue	Chronic superficial gastritis		
Active and severe erosive swelling	Mild chronic duodenitis	Mild gastritis		
Mild reflux esophagitis	Severe duodenitis with villous atrophy and ulcer	Active gastritis ulcer due to CMV (n=3)		
Severe reflux esophagitis	Foveolar hyperplasia with mild edema	Acute gastritis, Ulcer and Helicobacter pylori-negative		
Mild superficial gastritis with epithelium cytokine expression	Chronic atrophic duodenitis due to anti-TTG	Hyperplastic gastric polyps		
	Non-atrophic duodenitis (anti-TTG)			

Table-5. Diagnosis of disease before and after endoscopy and colonoscopy in patients with GI-CMV infection.

Diagnosis of disease before procedure	Diagnosis of disease after procedure
Protein-losing enteropathy	Protein-losing enteropathy
Peptic ulcer (n=3)	Peptic ulcer (n=3)
GI bleeding (n=6)	Esophagitis (n=5), Enteral polyp (n=1)
Menetrier disease	Menetrier disease
Malabsorption and growth disorder	Severe duodenitis with villous atrophy and ulcer (CMV)
Autoimmune hepatitis	Autoimmune hepatitis

4- DISSCATION

This study aimed to conduct a descriptive investigation of clinical, endoscopic findings and underlying causes of gastrointestinal cytomegalovirus infection in children. Initially, 17 patients were hospitalized with a probable diagnosis of CMV, of which 12 patients (70.6%) were definitively diagnosed with CMV during follow-up. In patients whose CMV tests were negative, it was found during follow-up that 2 patients were diagnosed with Crohn's disease. The study, included 12 patients, consisting of 9 girls (75%) and 3 boys (25%) with a mean age of 42.75 ± 31.95 months. The youngest patient was 3 months old, and the oldest was 96 months old. 83.3% of patients were discharged from the hospital with partial recovery with 70.6% testing positive for gastrointestinal cytomegalovirus infection. 75% of patients had gastric involvement. In the study population, the distribution of symptoms of the disease, in order of frequency, the most common initial symptom was reported to be vomiting blood with 26%. Fever and diarrhea were in second place in terms of frequency with 13%. In the patients under study, the majority of people with 75% reported stomach involvement. Ganciclovir was the most important drug used in these patients, being used in 100% of patients. In 33.8% of patients, in addition to Ganciclovir, Prednisolone was also used. The majority had high WBC. Also, liver enzymes and albumin were impaired in the majority of patients.

CMV initiates with a primary infection followed by a latent phase (6). While most individuals with CMV infection are either asymptomatic or display general symptoms resembling mononucleosis-like syndrome (4), severe infections have been documented in immunocompetent patients, with the GI tract being a common site of involvement (28). Patients with CMV colitis typically present with fever, abdominal pain, watery diarrhea, hematochezia, severe hemorrhaging, and occasionally colonic distension and perforation (5). Studies suggest that GI bleeding is predominant in immunocompetent patients, whereas diarrhea is the primary symptom in immunocompromised patients (6,29). CMV's ability to infect vascular endothelium can lead to mucosal ischemic damage resulting in bleeding (30). In a study focusing on children with CMV-related protein-losing enteropathy, Ferrua et al. identified evidence of CMV infection through non-invasive techniques in 88.9% of immunocompetent and 95.5% of immunosuppressed patients. Notably, digestive symptoms were more pronounced in immunocompetent children, particularly vomiting (31).

The discharge rate in the present study for CMV-infected patients was high, with 70.6% demonstrating positive results for GI-CMV infection upon final testing. Contrary to findings from previous studies

indicating poor outcomes in patients with IBD associated with CMV hospitalizations (16, 17), a notable 82.4% of patients in our study exhibited improvements and were discharged.

A study involving thirty-eight patients aged between three days and twelve years highlighted esophagitis and small bowel pathology as prevalent conditions, despite CMV presence throughout the GI system. Invasive GI-CMV affliction in children was mainly linked to HIV or significant lower GI inflammation in infants under six months, with a mortality rate of 32% (32). In our research concerning final diagnoses of patients with GI-CMV infection, 11.76% presented with GI bleeding while another 11.76% were diagnosed with Crohn's disease or IBD, with a mortality rate of 17.6%. Valganciclovir emerged as the most commonly prescribed medication in these cases. Another study analyzing 254,839 hospitalizations related to IBD revealed an overall CMV infection prevalence of 0.3%, with about two-thirds of infected patients having UC, correlating with a 3.6-fold heightened risk of CMV contraction. The presence of CMV infection significantly correlated with elevated in-hospital mortality rates and severe IBD cases (33). In our study, the mortality rate stood at 17.6%, pointing to the crucial role of timely diagnosis and appropriate medication in reducing mortality rates.

In our research, the majority of patients exhibited heightened WBC counts, while RBC and platelet levels were decreased. The patients demonstrated normal renal function, thyroid function, and serum albumin levels. Notably, elevated ESR was prevalent among most cases, whereas CRP levels remained within normal limits for the majority of patients. Liver function tests indicated abnormalities in half of the patients, with mean PT, PTT, INR, total bilirubin, and direct bilirubin levels falling outside the accepted ranges. Prognostic indicators for mortality included elevated WBC counts, decreased RBC counts, reduced platelet levels, liver enzyme disturbances, as well as occurrences of hematemesis and epistaxis. A study involving patients with GI-CMV diseases revealed that nearly half of the patients were immunocompromised. The overall in-hospital mortality rate stood at 20.8%, with CMV enteritis displaying the highest mortality rate at 23.3%. Factors predictive of in-hospital mortality included age, immune status, serum albumin levels, platelet counts, GI bleeding, time-to-diagnosis, and combination therapy (34).

Our study revealed various endoscopic and colonoscopic findings in CMV-diagnosed patients, such as esophagitis in the esophagus, ulcers and antral nodularity in the stomach, duodenitis in the duodenum, and both chronic and acute active colitis in the colon. Additionally, the rectum showed signs of chronic and acute active destructive colitis. Endoscopic features of CMV colitis are diverse and include diffuse erythema, hemorrhagic spots, ischemia, erosions, ulcers, strictures, polypoids, pseudomembranes, and pseudotumors. Specific colonoscopic findings of CMV ulcers comprised irregular ulceration, map-like appearance, wide mucosal defect, punched-out ulceration, and longitudinal ulceration (35). Chaemsupaphan et al.’s study on immunocompetent patients suggested that the ischemic process might be exacerbated by a hypoperfusion state induced by underlying conditions, leading to increased bleeding. The presence of the "single-stripe sign," typically seen in patients with ischemic colitis, in some GI-CMV patients supported this hypothesis (6). Overall, diagnosing GI-CMV diseases poses challenges due to the varied presentations, diverse endoscopic findings, biopsy sites, and laboratory techniques. Symptoms and laboratory parameters may not be distinctive from other infectious disease

etiologies. Despite variable ulcers being the predominant endoscopic feature of CMV infection, diagnosis based solely on endoscopic findings can be arduous (34).

The strength of this study lies in the sampling from a prominent referral hospital in eastern Iran, attracting patients nationwide. Nevertheless, notable weaknesses include a retrospective study design, and a limited sample size.

5- CONCLUSION

The majority of patients diagnosed with GI-CMV infection were discharged from the hospital showing signs of improvement, with GI-CMV infection being detected in 70.6% of the cases. The findings of this study underscore the significance of monitoring laboratory parameters and patient symptoms upon admission to facilitate prompt diagnosis and treatment of individuals with GI-CMV infection, thereby aiding in preventing further transmission. Thus, the evaluation of WBC counts, RBC levels, platelet counts, inflammatory markers such as ESR and CRP, liver enzymes, and patient symptoms is deemed valuable in the diagnostic assessment of patients with GI-CMV infection.

6- CONFLICT OF INTEREST

The authors declare that they have no financial or non-financial interests to this close.

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