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The prevalence and outcomes of inflammatory bowel disease among patients with cytomegalovirus disease

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ABSTRACT

Aims: Cytomegalovirus (CMV) colitis in individuals with inflammatory bowel disease (IBD) is a serious condition. The present study evaluated the prevalence and outcome of IBD-CMV colitis among patients with CMV disease.

Methods: We performed a retrospective study to evaluate the patients with IBD and CMV colitis between January 1, 2017, and December 31, 2022. We identified IBD-CMV colitis based on the presence of CMV in tissue or a polymerase chain reaction (PCR) result of ≥1000 copies/mL with no other clinical explanations. The frequency of IBD-CMV colitis, relapse rate, requirement of surgical interventions, and associated mortality were assessed.

Results: Out of 163 patients with CMV disease screened, 28 (17.2%) were diagnosed with CMV colitis and IBD [median age: 54 (19-67) years, male: 77%]. The frequency of ulcerative colitis and Crohn's disease was 93% and 7%, respectively. Most CMV PCR assays (97%) were performed using serum, whereas the remaining tests were performed using serum and tissue samples. CMV was not detected via immunohistochemistry or hematoxylin-eosin staining in any patient. Antiviral treatment was initiated in 74% of the patients and lasted a median of 20 days (6-32 days). No surgical interventions or disease-related deaths were identified.

Conclusions: This electronic medical records study showed that IBD-CMV colitis was a rare disease among patients with CMV disease and generally followed a favorable course.

Introduction

Cytomegalovirus (CMV) is a virus classified within the Betaherpesvirinae subgroup of the Herpesviridae family. It is primarily known for causing asymptomatic infections. Following primary infection, CMV can establish latency within the host and reactivate in response to various stimuli. In healthy individuals with an intact immune system, CMV does not typically cause significant complications. However, the virus can lead to multiorgan dysfunction in individuals with compromised immune systems. Additionally, CMV is associated with several diseases linked to chronic inflammation, including coronary artery disease, exacerbations of inflammatory bowel disease (IBD), multiple sclerosis, certain cancers, and immunosenescence in older people (1).

Patients with CMV infection may exhibit signs and symptoms associated with the disease. The colon is one of

the target organs affected by the CMV disease (2). CMV colitis occurs in approximately 0.05-10% of patients with active IBD. Although a definitive correlation between Crohn's disease and CMV colitis does not exist, CMV colitis is often observed in patients experiencing severe or steroid-refractory ulcerative colitis (UC) (3-6). Whether CMV is a causative factor for UC exacerbations remains to be clearly defined (7). Moreover, numerous studies have identified CMV colitis as a significant risk factor for cases of UC that do not respond to steroid treatment (8,9).

Patients diagnosed with CMV and IBD receive treatment and follow-up care. However, the available data regarding the prevalence of IBD-CMV colitis is sparse in the local context. Accordingly, this study aimed to evaluate the burden and outcomes of IBD-CMV colitis among patients experiencing CMV disease.

Methods

Study design

This study was conducted in a tertiary care hospital and retrospectively evaluated patients who presented with steroid-refractory IBD exacerbation and CMV colitis between January 1, 2017, and December 31, 2022. Patients with IBD-CMV colitis were identified from diagnoses of CMV disease in the Department of Infectious Diseases and Clinical Microbiology. The study was approved by the University of Health Sciences Türkiye, Gülhane Training and Research Hospital of Local Ethics Committee (decision no: 2022/96, date: 17.05.2023). The study protocol conforms to the Declaration of Helsinki and good clinical practice guidelines.

Inclusion and exclusion criteria

The study included female and male patients aged 18 years and older who presented to the infectious disease and clinical microbiology clinic and outpatient department with steroid-refractory IBD exacerbations. Eligible participants exhibited the following criteria: Negative blood and stool cultures, histopathological evidence of CMV, serum or tissue CMV polymerase chain reaction (PCR) ≥1000 copies/mL, and no indications of *Clostridium* difficile or *Entamoeba histolytica* infections. Patients younger than 18 years, with an identified colitis pathogen, having serum CMV PCR <1000 copies/mL, or with insufficient information in the electronic medical records were excluded.

Data collection

We used the inpatient and outpatient records to obtain data on demographic characteristics, primary diagnoses and treatments, symptoms at admission, interventions, culture results, stool analyses, serum and tissue CMV PCR levels, colonoscopy findings, and biopsy reports.

Criteria for cytomegalovirus colitis

The case definition was based on a consensus report on the diagnosis and treatment of CMV in Türkiye (10). This report recommends antiviral therapy in symptomatic patients with IBD based on a CMV PCR test or biopsy result (10). The criteria for CMV colitis used in this study were evidence of CMV in tissues (8) or detection of CMV PCR ≥1000 copies/mL in serum or tissue (11) with no other causes explaining the clinical course.

Criteria for treatment termination

The criteria for terminating the CMV colitis treatment in the clinic where the present study was performed included weekly virologic assessment by serum CMV PCR test. Treatment continued until the initial clinical symptoms and CMV viremia were resolved (12).

Prognosis assessment

A relapse was defined as a CMV colitis within 3 months after remission. Colitis beyond 3 months was regarded as a new episode and included in this study (12). CMV-associated surgery was defined as any intestinal surgical procedure conducted within 6 months of a confirmed diagnosis of CMV colitis (5). Death within six weeks after CMV colitis that could not be explained by other causes was classified as CMV-related mortality (13).

Study endpoints

The primary objective of this study was to evaluate the prevalence of IBD among patients experiencing CMV disease. For this purpose, we explored the underlying disease in patients with CMV disease. The secondary endpoints were the rates of relapse, surgical intervention, and mortality related to poor prognostic outcomes in patients with IBD and CMV colitis.

Statistical Analysis

The data were analyzed using the IBM SPSS Statistics 22.0 (SPSS Inc, Chicago, IL). The distribution of the data was evaluated using the Kolmogorov-Smirnov test. Categorical variables were presented as frequency and percentage. Continuous variables with normal distribution were presented as mean±standard deviation. Non-normally distributed variables were presented as median (minimum-maximum).

Results

Basic characteristics

We identified 163 patients diagnosed with CMV disease over 6 years. Of them, 28 (17.2%) were classified as CMV colitis in patients diagnosed with IBH. Of the patients with IBH, 93% were diagnosed with UC and 7% with Crohn's disease. The median age was 54 (19 to 67) years and 77% of the patients were male. The median time since IBD diagnosis was 3 months (1-180

months), and the median duration of IBD treatment was 2.5 months (1-180 months). The patients reported diarrhea, bloody diarrhea, and fever by 57%, 37%, and 14%, respectively.

Diagnostic management

CMV PCR assays were performed in serum by 97% and in serum and tissue samples together by 3%. The median serum CMV PCR level was 4260 copies/mL (1000-85200 copies/mL). CMV was not detected by immunohistochemistry and hematoxylin-eosin staining in any biopsy sample in which CMV PCR assay was positive.

Treatment processes

In total, 26% of the patients were not readmitted for antiviral treatment. Antiviral therapy was initiated in 74% of the patients and maintained for an average of 20 days (6-32 days). Adverse effects were noted in 38.5% of the patients, such as anemia (42%), cytopenia (30%), pancytopenia (10%), and thrombocytopenia (10%). No antiviral treatment was modified due to observed side effects.

Prognostic results

No surgical interventions, CMV-related mortality, or relapse were observed during the follow-up period. Notably, only one patient succumbed to complications of Coronavirus disease-2019.

Discussion

CMV colitis is distinguished by diarrhea, fever, and abdominal pain, with approximately 53% of cases presenting as bloody (14). Therefore, clinically differentiating between CMV colitis and IBD exacerbation is challenging. These symptoms, which can complicate clinical distinction, were frequently recorded in the present study.

There are different perspectives on the investigation of CMV colitis during IBD exacerbations. Some experts advise against routine testing for CMV replication, noting that CMV infection is relatively uncommon in active IBD cases (15,16). Maher and Nassar (17) argued that acute CMV infection is often overlooked in patients with IBD and highlighted the need to rule out this infection before initiating aggressive immunotherapy. Similarly, Weng et al. (3) emphasized the importance of routine histopathological examinations and/or CMV PCR tests in patients with refractory colitis. We systematically evaluated CMV colitis in all patients suspected of experiencing IBD exacerbation.

The prevalence of IBD among patients diagnosed with CMV disease remains uncertain. The present 6-year follow-up retrospective study showed that IBD was present in 17.2% of patients with CMV colitis. Unfortunately, this finding cannot be compared with the existing literature because no previous study specifically addressed the prevalence of underlying conditions in this patient population. These findings suggest that IBD is not a frequent underlying condition in individuals experiencing CMV colitis.

A consensus report on CMV diagnosis and treatment in Türkiye determined the definite and high-probability diagnostic criteria for CMV colitis in solid organ transplant recipients (10). The report clarified that the proposed criteria mentioned were inappropriate for use in patients with IBD because of ongoing inflammation. The study also stated that there was no recognized gold-standard diagnostic method for identifying CMV colitis in patients with IBD (10). We defined the cases in the current study using the guidance of the latest consensus report (10).

The sensitivity and specificity of molecular methods for diagnosing CMV colitis can vary significantly. Kredel et al. (18) compared serum CMV PCR, immunohistochemistry, and hematoxylin-eosin staining and found sensitivities of 1.0, 0.67, and 0.17, respectively, with specificities of 0.94 and 0.98 for the latter two methods. They recommended serum CMV PCR as the preferred diagnostic approach. Additionally, a prospective study conducted in Türkiye indicated low sensitivity but high specificity for CMV PCR in tissue and blood samples (19). The current literature revealed a lack of comprehensive information regarding the cut-off PCR level necessary for diagnosis. In the sole prospective study available, Ormeci et al. (11) proposed a 1000 copies/mL threshold for CMV PCR to diagnose CMV disease in patients with steroid-refractory IBD. Based on recent studies, a definitive diagnosis of CMV colitis can be made using tissue assays. Moreover, serum PCR can be used to exclude the disease, as was recommended in a consensus report (10). In the present study, this approach was an exclusion criterion for patients in the studied facility when a biopsy was unavailable. This proactive measure helps reduce the risk of serious complications associated with CMV colitis.

Antiviral therapy has proven beneficial for patients with steroid-refractory UC because it can significantly decrease the need for surgical intervention (8). For optimal outcomes, intravenous ganciclovir and/or oral valganciclovir should be administered for 2 to 3 weeks (8). Regarding treatment duration, intravenous ganciclovir for 2 weeks is more effective than intravenous ganciclovir for 1 week plus oral valganciclovir for 1 week (20). In the clinic where the present study was performed, intravenous ganciclovir was given priority over oral treatment in patients with IBD. Consistent with this, the patients received intravenous ganciclovir for 3 weeks on average.

CMV colitis presents a significant threat in immunosuppressed patients, exhibiting a mortality rate that varies between 35.7% and 71.4% depending on the specific characteristics of the patient population (21,22). Recent findings by Jung et al. (23) indicate that relapse occurs in approximately 10% of cases despite antiviral treatment. This phenomenon has been linked to the presence of hematological malignancies and UC. Additionally, Hendler et al. (24) demonstrated that CMV infection was associated with a 2.3-fold increase in mortality among patients

with UC, a 4.6-fold increase in mortality among individuals with Crohn's disease, and a 2.5-fold increase in colectomy in patients with UC. In the present six-year longitudinal study, we observed that CMV colitis exhibited a progressive course among patients with IBD but generally resulted in favorable outcomes. Notably, no patient required surgical intervention, and there were no relapses. Regrettably, one patient succumbed to causes unrelated to CMV or IBD.

The limitations of this study include the small sample size and the lack of biopsies in a significant number of patients. These factors may impact the generalizability of our findings and warrant careful consideration when interpreting the results.

Conclusion

The present study showed that an IBD diagnosis was rare in patients with CMV. The observed cases typically followed a positive clinical course. Prospective studies are needed to determine the true prevalence of IBD patients with CMV, along with standardization of treatment and follow-up.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Gülhane Training and Research Hospital of Local Ethics Committee (decision no: 2022/96, date: 17.05.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.K., C.B., G.F., G.Ç., Concept: Z.K., C.B., Design: Z.K., C.B., Data Collection or Processing: Z.K., C.B., G.F., G.Ç., Analysis or Interpretation: Z.K., C.B., Literature Search: Z.K., C.B., G.F., G.Ç., Writing: Z.K., C.B., G.F., G.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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