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CMV Infection in Pediatric IBD

Anat Yerushalmy-Feler[1,2] · Sharona Kern-Isaacs[2] · Shlomi Cohen[1,2]

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Abstract

Purpose of Review Patients with inflammatory bowel disease (IBD) are predisposed to infections. Cytomegalovirus (CMV) colitis in adult IBD patients, particularly ulcerative colitis (UC), is related to severe or steroid-refractory disease. The aim of this review is to summarize the data on the prevalence and role of CMV colitis in children with IBD.

Recent Findings Data on CMV colitis in children continue to be very limited due to its rarity. As in adults, children with coexisting UC and CMV tend to have more severe colitis, are resistant to corticosteroids, and are at high risk for colectomies on short- and long-term follow-up.

Summary In children, as in adults, the significance of CMV colitis, in terms of whether CMV is a pathogen that aggravates acute severe colitis or simply reflects disease severity, is still unknown.

Keywords CMV · Crohn's disease · Ulcerative colitis · IBD · Children · Adults

Introduction

Cytomegalovirus (CMV) is a member of the herpesviridae family. The seroprevalence of CMV in the general population varies between 40 and 100% and is greatly influenced by age and geographic distribution [1, 2]. CMV usually causes mild and self-limited disease in healthy children and adults, but it may result in a severe systemic disease (e.g., pneumonitis, hepatitis, and colitis) in immunocompromised patients. The latter include those receiving immunosuppressive medications after bone marrow or solid organ transplantation or for other indications (e.g., chronic inflammatory conditions) [3].

Patients with inflammatory bowel disease (IBD) are predisposed to infections due to their intestinal inflammation or to their receiving immunosuppression therapy. CMV infection, mainly CMV colitis, occurs most commonly in severe or steroid-refractory disease, and it is believed to negatively affect the clinical outcome of those patients. There is ongoing debate among gastroenterologists on the significance of CMV colitis among adults, specifically, whether CMV is a pathogen that aggravates acute severe colitis or whether it simply reflects disease severity [4]. The objective of this paper is to present contemporary approaches to the diagnosis and treatment of CMV infection in children with IBD. Unfortunately, current data on the prevalence and role of CMV colitis in pediatric IBD are so sparse that clinicians extrapolate therapeutic guidelines from those of adults with IBD. For this reason, we will present the data on CMV in adults with IBD and then consider them from a pediatric perspective.

Epidemiology

CMV infection is defined by a positive serum polymerase chain reaction (PCR) or by the detection of CMV antigens or antibodies in serum. CMV disease is a clinical condition in which CMV infection is accompanied by specific clinical symptoms that include, but are not necessarily limited to, fever, lymph node swelling, and hepatosplenomegaly [5, 6]. The prevalence of CMV infection and disease coexisting with IBD is not clear. In one systematic review, the prevalence rates varied widely, depending upon the definitions that were used for CMV infection and disease [3].

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✉ Shlomi Cohen
shlomico@tlvmc.gov.il

[1] Pediatric Gastroenterology Unit, "Dana-Dwek" Children's Hospital, Tel Aviv Sourasky Medical Center, 6 Weizman Street, 6423906 Tel Aviv, Israel

[2] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

In general, CMV disease occurs more frequently in ulcerative colitis (UC) than in Crohn's disease (CD). The prevalence of CMV reactivation in IBD patients ranges from 1.5 to 4.5% in mixed samples of UC and CD patients [7, 8], to 22.7% in a sample limited to UC patients [9], and up to 33.6% of UC patients during an episode of acute severe colitis [10]. The highest prevalence rates were reported when defining CMV infection by a positive serum PCR and diagnosing CMV intestinal disease by a tissue PCR that showed > 10 copies/mg tissue [3].

Risk Factors

Several risk factors for CMV colitis in adult IBD patients have been identified. Gauss et al. reported an association between CMV colitis and older age [9]. A similar association was recently found in some additional studies [11, 12] but not in others [13]. In a meta-analysis by Zhang et al. [14], IBD patients with CMV colitis presented with shorter IBD disease duration. In agreement with that finding, a retrospective study by Gauss et al. showed that the occurrence of CMV infection was associated with disease duration of less than 60 months [9]. In the setting of acute severe colitis, a higher endoscopic score (Mayo score) [10], as well as the extent of disease (i.e., pancolitis) [15], was associated with the risk of infection with CMV colitis.

Immunosuppression has a significant role in increasing the risk of CMV colitis in IBD. High doses of systemic corticosteroids administered for greater than 1 month were an independent risk factor for CMV-associated colitis in patients with active UC [15]. Notably, prior to the diagnosis of CMV colitis, patients with coexisting acute severe UC and CMV disease received significantly higher doses of corticosteroids than CMV-negative patients [10]. Other studies also confirmed previous findings of the association of corticosteroids and other immunomodulators (i.e., thiopurines and methotrexate) with CMV disease in patients with IBD [11, 16].

Patients treated with anti-TNF agents have also been studied. While increased susceptibility to infectious agents has been associated with anti-TNF agents, several recent studies, including a systematic review and meta-analysis, have shown no association between increased CMV disease susceptibility and anti-TNF agents [11, 16–18]. In addition, TNF-alpha has been shown to support viral replication in vitro [19], a finding that has raised the assumption that TNF antagonists might suppress CMV reactivation. A reasonable conclusion is that these agents should be preferred over other immunosuppressive therapies when treating CMV-related colitis.

Although the common concept is that immunosuppressive therapy is a risk factor for CMV reactivation, a recent study [20] found CMV reactivation to be more common not only in newly diagnosed IBD patients but also in untreated patients compared to controls, suggesting that CMV may have served as a predisposing agent to the initiation of the mucosal inflammation of IBD in those cases.

Clinical Features

Symptoms of CMV colitis may mimic IBD flares and include abdominal pain, diarrhea, and rectal bleeding [21]. In their meta-analysis [14], Zhang et al. found that CMV-positive patients presented with significantly higher susceptibility to severe colitis, pancolitis, and colectomy. During hospital admission, variables associated with CMV infection, besides older age and short disease duration, were lower blood leukocyte count, recent immunosuppressive therapy, and prolonged hospitalization [9], as well as the presence of fever [13]. Most important, however, the patients with CMV colitis did not present with the classical symptoms of CMV viremia (such as pharyngitis, lymphadenopathy, and splenomegaly.

CMV may be a potential cause of steroid resistance in IBD [12, 22–25]. One meta-analysis reported a steroid resistance rate as high as 70% in CMV-positive IBD patients compared to a rate of 35% in CMV-negative IBD patients [26].

IBD patients with CMV disease have been found to be more likely to develop *Clostridium difficile* infection than CMV-negative IBD patients [27]. The concurrence of CMV and *Clostridium difficile* infection was associated with poorer outcomes, such as decreased colectomy-free survival [27]. Those authors suggested testing IBD patients with CMV for *Clostridium difficile* infection in order to manage the illness aggressively in cases of concurrent active infection.

In addition to higher rate of colectomies, patients with acute severe UC and coexisting CMV experience poorer outcomes and a greater need for rescue therapy such as infliximab or cyclosporine [10]. In-hospital mortality was found to be seven times higher for IBD patients with CMV compared to IBD patients without CMV, and healthcare resource utilization (length of stay and total hospital charge) was significantly increased for the former patients [28]. On the contrary, a later study reported that CMV in UC patients was associated with longer hospitalization but not correlated with higher mortality rates or with increased colorectal surgery [29]. This clinical presentation of CMV colitis in IBD might be affected by the tissue viral load. This association was demonstrated in a retrospective study that showed no difference in the clinical course between CMV-negative and CMV-positive IBD patients who had low viral loads in tissue [12].

Endoscopic Features

The findings of studies on characteristic endoscopic findings in CMV colitis in IBD patients have produced

conflicting results. One retrospective study of 149 UC patients [15] noted that a punched-out ulcer was the only significant independent predictor of CMV colitis visualized on endoscopy. Histologically, the number of CMV inclusion bodies was reportedly significantly higher in patients with punched-out lesions [30]. In addition to punched-out lesions, irregular ulceration and cobblestone-like appearance were also associated with CMV [30]. A good correlation was also found between endoscopic scores and tissue PCR positive for CMV [12].

Diagnosis

The "gold standard" method for diagnosing CMV colitis in patients with IBD is the subject of many studies. One study [31] found blood PCR to be in high agreement with immunohistochemistry (IHC) in diagnosing CMV, but most studies agree that only the detection of CMV in the intestinal tissue (CMV disease), and not in blood (CMV infection), is clinically meaningful in IBD [32, 33].

The optimal sites for endoscopic biopsy for CMV infection were found to be at the base and the edge of ulcers [34]. Hematoxylin and eosin staining is insufficient for the diagnosis of CMV colitis, having been found to have low sensitivity compared to IHC and PCR [9, 32] since large cells with viral inclusions or the typical "owl eye's appearance" do not always exist. Therefore, the accepted methods of diagnosing CMV colitis are tissue IHC or PCR. The density of positive cells as determined by IHC was reported to correlate well with the number of viral copies as determined by PCR [34]. PCR methodology, however, is considered more sensitive than IHC [13, 23], with a high correlation between macroscopically damaged areas and the areas with the highest viral loads. In spite of the concerns that PCR could be reflecting latent rather than active infection, PCR is recommended [35] in cases when IHC is negative, but only when there is a strong clinical suspicion of CMV reactivation. In an attempt to establish a mucosal viral load measurement in PCR as a standard for diagnosing CMV colitis, peak values of mucosal viral loads greater than 10^3 copies/10^5 cells were found to be associated with refractoriness to treatment [23]. In another study, a viral load of 250 copies/mg of tissue was shown to be a predictor of steroid-resistant disease [36].

In adults, according to the European Crohn's and Colitis Organization (ECCO) [6], blood CMV serology can be used to identify patients at risk for CMV reactivation. PCR is the most commonly used technique for CMV colitis: it has the advantages of rapid and quantitative results and high sensitivity. Histopathology combined with IHC is also highly specific and sensitive.

Treatment of CMV Colitis

Antiviral therapy for CMV colitis includes intravenous ganciclovir. According to ECCO guidelines [6], a switch to oral valganciclovir for the remainder of the 2–3-week course may be considered after 3–5 days. Foscarnet is an alternative in cases of ganciclovir resistance or intolerance. In a retrospective study of 50 patients [37], those with high-grade disease (≥ 5 inclusions in a single fragment) who received antiviral therapy were significantly less likely to require colectomy within 1 year of diagnosis compared to patients with low-grade disease who showed only modest improvement under antiviral therapy. This discrepancy probably reflects the fact that the pathogenic role of CMV is more definite in a high-grade CMV disease. Improved clinical outcome, including decreased rates of colectomies in patients who received antiviral therapy, was observed in other studies [12, 22, 38], but anti-CMV therapy as a single therapy did not always achieve clinical response in UC [12]. In steroid-dependent or refractory disease, patients who received antiviral therapy were more likely to be in remission at 1 year [39] with a significant reduction in colectomy risk [40]. The same significant findings were not present when the analysis encompassed all UC patients, not simply those who were exclusively corticosteroid-refractory. Contrarily, different results were obtained by Zagorowic et al. [31], who found no evidence of a positive effect of ganciclovir in patients with in five or more IHC-positive cells. While it was beneficial in the short term, ganciclovir showed marginal efficacy for long-term outcome [41]. In a systematic review and meta-analysis of comparative cohort and case-control studies published by Kopylov et al. [2], no positive association between antiviral therapy and a favorable outcome was demonstrated. As for the acceptable treatment in IBD flares, Kopylov et al.'s multicenter retrospective study of hospitalized CMV-positive patients with UC [42•] found that rescue immunosuppressive drugs given for acute severe UC, such as infliximab or cyclosporine, are not associated with additional risk for colectomy over antiviral therapy alone. Treatment on a case-by-case basis is appropriate: it has been suggested the patients who do not respond to standard therapy for IBD be treated with the addition of ganciclovir if CMV is detected in colonic tissue [21].

The Pediatric Perspective

The first pediatric case of CMV colitis in IBD was described in 1993, and it involved a 14-year-old boy with UC who underwent colectomy [33]. The pathological examination of the colon specimen revealed CMV in the intestinal mucosa. A few more case reports of CMV disease in pediatric IBD were published subsequently [43–45]. One case series included six children with IBD who developed a concomitant CMV colitis

that was diagnosed by endoscopy and tissue PCR and confirmed by IHC [46]. Five of the children were steroid resistant, and one was infliximab resistant.

Studies on CMV infection complicating acute severe colitis in children are scarce. Cohen et al. [47••] recently published a multicenter retrospective case-controlled study comparing the outcomes of CMV-positive children with acute severe colitis to CMV-negative children with acute severe colitis. Similar to the adult associations described above, more CMV-positive children were resistant to corticosteroids. By 12 months, 5 (33%) CMV-positive and 5 (13%) CMV-negative patients ($p = 0.049$), required colectomy, but the difference did not reach a level of significance on multivariate analysis, probably due to the small number of patients.

In its guidelines for the management of acute severe colitis, the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition [33] recommends performing an endoscopic examination in children with steroid-resistant colitis in order to exclude a CMV diagnosis. It is also recommended that colonic biopsies should be stained for CMV by IHC.

Summary and Conclusion

CMV is one of the infectious complications in patients with IBD. It is associated with severe colitis in both children and adult IBD patients and a high rate of colectomies during short- and long-term follow-up. Antiviral treatment of CMV may improve the outcome of these patients. However, the debate on the significance of CMV colitis, specifically, whether CMV is a pathogen that aggravates acute severe colitis or whether it simply reflects disease severity, is still ongoing.

Compliance with Ethical Standards

Conflict of Interest Anat Yerushalmy-Feler, Sharona Kern-Isaacs, and Shlomi Cohen declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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