sciendo

PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B,
Vol. 76 (2022), No. 5/6 (740/741), pp. 585–594.

DOI: 10.2478/prolas-2022-0091

Review

A QUICK GUIDE TO DIAGNOSIS AND TREATMENT OF CYTOMEGALOVIRUS INFECTION IN THE GUT: CURRENT DILEMMAS

Iļja Drjagunovs[1,2], Sniedze Laivacuma[1,4,5,#], Indra Zeltiņa[1,5], and Aleksejs Derovs[1,3,4,5]

[1] Department of Infectology, Rīga Stradiņš University, 16 Dzirciema Str., Rīga, LV-1007, LATVIA

[2] Pauls Stradiņš Clinical University Hospital, 13 Pilsoņu Str., Rīga, LV-1002, LATVIA

[3] Department of Internal Diseases, Rīga Stradiņš University, 16 Dzirciema Str., Rīga, LV-1007, LATVIA

[4] JSC Veselības centru apvienība, 16 A. Saharova Str., Rīga, LV-1021, LATVIA

[5] Rīga East University Hospital, 2 Hipokrāta Str., Rīga, LV-1038, LATVIA

[#] Corresponding author, Sniedze.Laivacuma@rsu.lv

Communicated by Ludmila Vīksna

Cytomegalovirus is a ubiquitous herpesvirus, which, after often asymptomatic primary infection, establishes a life-long latency in different organs, including gut. As there is a close synergistic relationship between mucosal inflammation and viral expression, particularly in patients suffering from inflammatory bowel disease, it is often challenging to distinguish subclinical cytomegalovirus replication from cytomegalovirus-mediated colitis. The outcome for patients with cytomegalovirus reactivation appears to be worse than that for patients without reactivation, but the true role of cytomegalovirus is not entirely clear, as is the dilemma whether specific treatment with antivirals alters the course of inflammatory bowel disease. This review focuses on gastrointestinal tract cytomegalovirus disease, with special emphasis on diagnostic and treatment considerations of cytomegalovirus colitis in patients with inflammatory bowel disease.

Keywords: *CVM, inflammatory bowel disease, ulcerative colitis, ganciclovir.*

INTRODUCTION

Cytomegalovirus (CMV), an encapsulated double-stranded DNA virus of the *Betaherpesvirinae* subfamily of herpesviruses, is a common, ubiquitous pathogen, generally innocuous in healthy individuals (O'Hara *et al.*, 2017). Following primary infection, the virus establishes latency in haematopoietic progenitor cells and myeloid lineage cells (Goodrum *et al.*, 2016). The latent state permits life-long persistence of the viral genome marked by sporadic bouts of reactivation, which allows for periods of typically subclinical virus shedding (Britt *et al.*, 2008). Of all herpes viruses, CMV harbours the largest number of genes dedicated to evading innate and adaptive immunity in the host (Gupta *et al.*, 2021). A broad range of cells are infected including the parenchyma and connective tissue cells of gastrointestinal (GI) organs. The varied manifestations of CMV disease are, in part, related to its diverse cellular tropism.

CMV transmission usually requires close and prolonged contact with body fluids, such as urine, saliva, semen, vaginal fluid, and breastmilk, but can occur through blood/tissue, and occupational exposure as well. Approximately 59% of the population older than six years of age has been exposed to CMV, with an increase in the population's seroprevalence with advancing age and lower income (Bartlett *et al.*, 2018).

Primary CMV infection is often asymptomatic or subclinical in immunocompetent individuals. When symptomatic, in adults it is often described as a self-limiting mononucleosis-like syndrome, characterised by fever, rash, and leukocytosis, with less prominent cervical lymphadenopathy than that caused by Epstein-Barr virus (Nolan *et al.*, 2017).

Organ involvement is uncommon in immunocompetent hosts, although both disseminated and tissue-invasive CMV

have been documented and described (Karigane *et al.,* 2014; Sue *et al.*, 2016). In contrast, CMV is an important opportunistic pathogen in immunocompromised hosts, particularly those with acquired immunodeficiency syndrome (AIDS), recipients of solid and bone marrow transplants, those receiving immunosuppressive therapy, including patients with inflammatory bowel diseases (IBD), and patients with malignancies, especially those under chemotherapy or with haematological malignancies, causing significant morbidity and mortality (Ozaki *et al.*, 2013; Wang *et al.*, 2016). These patients tend to develop severe organ-specific or disseminated CMV manifestations, such as pneumonitis, retinitis, and colitis.

Caution must be exercised whenever analysing published literature describing invasive CMV disease in immunocompetent patients as different studies include patients with endocrinopathies, for example, diabetes mellitus (DM), lymphoproliferative and nonhematological malignancies, end-stage renal disease, autoimmune diseases, and pregnancy in the immunocompetent group, although such comorbidities could serve as potential immune-modulating and predisposing factors to severe CMV disease (Galiatsatos *et al.*, 2005; Ko *et al.*, 2015). Thus, with the increasing prevalence of such factors in the general population, further studies are warranted to clarify the underlying pathophysiology of CMV diseases in these "immunocompetent" (or "non-immunocompromised") but high-risk populations.

In the context of CMV and GI tract, overall, the lower GI tract is the most common site of involvement, however, in the recent past, CMV disease with more involvement of the upper GI tract in both immunocompetent and immunocompromised individuals has been increasingly recognised (Hwang *et al.*, 2006).

UPPER GI TRACT

CMV disease presents throughout the upper GI tract (the mouth, pharynx, oesophagus, stomach, and small intestine). Previous studies have shown that the most affected sites of upper GI CMV disease are the mid-distal esophagus (88%) (Wang *et al.*, 2016) and the gastric antrum (84%) (Bonetti *et al.*, 2011).

The clinical presentation of upper GI CMV disease is highly variable and depends on its location and severity. Wang *et al.* (2016) found that odynophagia/dysphagia (44%) and epigastric pain (31%) were the most common symptoms in patients with CMV esophagitis, while according to another study (Péter *et al.* 2004), abdominal pain (39%), anaemia/GI bleeding (20%), and nausea/vomiting (13%) were the most frequent complaints in patients with CMV gastritis/duodenitis. Moreover, in up to 7% of the cases, upper GI CMV disease may be asymptomatic.

Patients with CMV disease in the small intestine often present with diarrhea and generalised abdominal pain (Karigane *et al.*, 2014). Intestinal CMV disease may mimic IBD through endoscopy and imaging (Hsieh *et al.*, 2016). Haemorrhage and perforation have been reported but are rare (Cha *et al.*, 2010).

The endoscopic appearance of upper GI CMV disease is often non-specific ranging from normal or minimal inflamed mucosa to deep ulceration (Bonetti *et al.*, 2011; Ozaki *et al.*, 2013). In CMV esophagitis, well-demarcated serpiginous ulcers are more common than mucosal inflammation (88% vs. 63%) (Wang *et al.*, 2016), whereas in gastroduodenal disease inflammatory changes may exceed ulceration (54% vs. 18%) (Peter *et al.*, 2004). Despite the location in the GI tract, erosions and ulcers tend to be multiple (Bonetti *et al.*, 2011; Wang *et al.*, 2016). Extensive and deep ulceration can also be present and may lead to serious GI complications, such as perforation and massive bleeding (Ozaki *et al.*, 2013; Marques *et al.*, 2017).

LOWER GI TRACT

The most common clinical presentation of GI CMV disease is colitis, which typically causes diarrhea, haematochezia, fever, tenesmus, urgency, and abdominal pain (Ko *et al.*, 2015).

A meta-analysis (Galiatsatos *et al.* 2005) showed that 36% of critically ill "immunocompetent" patients in an intensive care unit had CMV end-organ disease. The mean age of "immunocompetent" patients with CMV disease was observed to range between 64 and 75 years and most patients had underlying immune-modulating conditions, such as chronic kidney disease, DM, or cardiomyopathy (Siciliano *et al.* 2014; Bernard *et al.* 2015). The in-hospital mortality of these patients, probably affected by comorbidities, was 71.4% despite treatment.

In IBD, the symptoms of CMV colitis tend to mimic IBD exacerbation [abdominal pain, anorexia, malaise, nausea, vomiting, diarrhea, and bleeding], and can potentially, although rarely (about 1% of cases), cause colonic perforation (Bontà *et al.*, 2016).

RELATIONSHIP BETWEEN CMV AND IBD

The association between CMV and IBD was first described by Powell *et al.* (1961) in a patient with ulcerative colitis (UC) and cytomegalic inclusion disease. Since then, the question of whether CMV is an active pathogen or 'an innocent bystander' in IBD patients remains controversial (Lawlor *et al.*, 2010). Interpretation of existing results is limited due to the small and retrospective design of most studies, different diagnostic methods for detecting CMV and different classifications for the severity of concomitant IBD.

CMV colitis occurs in "seropositive" patients with IBD. Generally, CMV does not appear to interfere with the clinical evolution of Crohn's disease (CD), and its involvement in UC is still debatable, especially in severe flare-ups (Ayre *et al.*, 2009).

CMV prevalence in CD. According to Hommes *et al.* (2002) and D'Ovidio *et al.* (2008), CMV seropositivity in CD patients does not differ from other populations and reaches 70%; however; CMV disease is rare in CD, making the virus an unlikely aetiological factor in the *de novo* development of IBD (Kim *et al.*, 2010).

Most studies in the field consistently report that the majority of CD patients are negative for CMV upon immunohistochemistry (IHC) staining, the mainstay of tissue-invasive CMV diagnosis, while CMV DNA in tissue or stool sample is positive in < 5% of patients (Knösel *et al.*, 2009; Kim *et al*., 2010). However, an exception was in a study (Wakefield *et al.*, 1992) that used highly sensitive PCR (detection threshold < 10 copies of CMV DNA), detecting CMV in 66% of individuals with CD and in 29% of controls, and thus showing no association between CMV DNA and CD activity, along with the suggestion that small quantities of viral DNA are not clinically relevant even in patients with UC.

Nakase *et al.* (2010) proposed that these findings could be related to some pathophysiologic aspects of CD and CMV, specifically that tumour necrosis factor-α (TNFα) is significantly associated with CMV infection or reactivation in IBD, while interferon-γ (IFNγ) released from CD4+ Th1 cells (Fuss *et al.*, 1996) could suppress CMV reactivation. As CD is considered a Th1-type inflammatory process with high expression of IFNγ, this could possibly explain the different prevalence of CMV disease in UC and CD.

CMV prevalence in UC. Although prevalence of latent CMV in UC is similar to CD, approximately 70% (Domènech *et al.*, 2008), recent data have suggested that CMV infection increased the risk of hospitalisation attributable to UC exacerbation 8.2-fold, and patients with histories of CMV colitis within the three months prior to commencement of infliximab therapy were 6.47-fold more likely not to respond to such therapy (Park *et al.*, 2013; Matsumoto *et al.*, 2014).

Patients in remission or with mild-moderate UC did not show an increased risk of CMV colitis, determined by negative haematoxylin and eosin (HE) and IHC findings (Domènech *et al.*, 2008; Kim *et al.*, 2010) or IHC in colectomy patients undergoing surgery for dysplasia or cancer (Kojima *et al.*, 2006).

The most extensive literature is on severe and/or steroid-refractory UC. As these terms are used interchangeably in different studies and are not defined clearly, the results are difficult to interpret (Lawlor *et al.*, 2010).

Severe colitis. According only to CMV antigenaemia, prevalence of CMV disease is reported around 34% (Wada *et al.*, 2003), while with HE or IHC alone in colonic mucosa prevalence decreased to 3% (Vega *et al.*, 1999). The combination of both serological tests and rectal biopsies found a CMV disease prevalence of around 20% (Criscuoli *et al.*, 2004; Kishore *et al.*, 2004). Identified risk factors include female gender, older age, pancolonic disease with active inflammation at histology and azathioprine therapy (Kojima *et al.*, 2006).

Severe steroid-resistant colitis. Retrospective study by Papadakis *et al.* (2001) showed a 0.5% prevalence of CMV disease according to HE, which increased dramatically when combining HE and IHC with antigenaemia (20%–40%) (Maconi *et al.*, 2005; Kojima *et al.*, 2006; Domènech *et al.*, 2008). As there is a poor correlation between blood and colonic viral DNA load (60% and 38%, respectively), possibly due to a specific CMV genotype with a particular colonic tropism and pathogenic character, as proposed by Criscuoli *et al.* (2011), a blood test alone should not guide clinical decision-making whether to start or withhold antiviral treatment (Pofelski *et al.*, 2007; Yoshino *et al.*, 2007).

Urgent colectomy for colitis. A higher prevalence of CMV could be expected in these patients due to a more severe course of their disease, but the prevalence studies using HE or IHC for CMV detection in mucosal samples ranged between 11.5% and 27% (Alcalá *et al.*, 2000; Maconi *et al.*, 2005), similarly to the previous groups.

Experimental studies suggest that CMV reaches the intestinal mucosa through persistence in migrating monocytes and then colonises the colonic cells, acquiring particular affinity for the inflammatory sites, probably due to the presence of pro-inflammatory cytokines (IFNγ and TNFα) produced by macrophages and T-cells in active UC (Hommes *et al.*, 2004; Simon *et al.*, 2005). Roblin *et al.* (2011) proposed that CMV can appear only in inflamed tissue and is not found in healthy tissue, thus leading other authors to suggest that the positivity of CMV DNA in the colonic mucosa in patients with refractory UC indicates uncontrolled intestinal inflammation, necessitating a change in immunosuppressive therapy (Hakase *et al.*, 2011).

Coincidental detection of primary CMV colitis at the first manifestation of IBD (Diepersloot *et al.*, 1990; Orvar *et al.*, 1993), in IBD patients without immunosuppression (Rachima *et al.*, 1998; Streetz *et al.*, 2003), and even disseminated CMV infection in CD (Helbling *et al.*, 2002) has been rarely reported.

ESTABLISHING DIAGNOSIS

To the best of our knowledge, there are more than 20 different methods to diagnose CMV infection and/or intestinal disease, mainly caused by the fact that still no single gold standard exists for establishing clinically relevant CMV disease in IBD (Table 1). As CMV-seropositive patients receiving immunosuppressants are at risk of end-organ reactivation, the latest European Crohn's and Colitis Organisation (ECCO) guidelines on the prevention, diagnosis, and management of infections in IBD recommend measurement of CMV-specific IgG antibodies for all IBD patients, preferably at disease diagnosis or at least before starting or while being treated with immunosuppressive agents, if baseline measurements are missing (Kucharzik *et al.*, 2021), in order

Table 1. Characteristics of diagnostic tests for CMV colitis (adapted from Römkens *et al.*, 2016; Park *et al.*, 2017)

Diagnostic test	Pros	Cons	Sensitivity, %	Specificity, %
CytomegalovirusIgG class antibodies	Helps to distinguish patients with risk for CMV colitis	Systemic, not providing information about intestinal disease	98–100	96–99
Antigen (pp65) detection assay	Takes a short time to perform (24 hour) Helpful for predicting clinical course of CMV colitis	Systemic, not providing information about intestinal disease	47–67	82–90
Cytomegalovirus DNA (PCR in blood)	Non-invasive method (endoscopy not required)	No cut-off value for the diagnosis yet established	44	88
CMV DNA (PCR in tissue)	Very high sensitivity for CMV detection in colon	Cut-off value not yet clear Uncertain clinical significance	65–100	40–100
CMV DNA (PCR in stool)	Non-invasive method (endoscopy not required) Quantification possible	Little experience with the method	83	93
Viral culture	High sensitivity and specificity	Long turnaround time (2–4 weeks)	45–78	89–100
Histological examination – HE staining	Highly specific, proves intestinal disease	Invasive Time-consuming Requires several tissue samples and skilled pathologist	10–87	92–100
Histological examination – IHC staining	Highly specific, proves intestinal disease More sensitive than HE	Invasive Long turnaround time (3–5 days) Requires several tissue samples and skilled pathologist	93	92–100

CMV, cytomegalovirus; IgG, immunoglobulin G; PCR, polymerase chain reaction; HE, hematoxylin and eosin; IHC, immunohistochemistry.

to potentially identify patients who are at risk of acquiring a new CMV infection (seronegative) or reactivation (seropositive) (Liu *et al.*, 2014). However, serology has no diagnostic value for CMV colitis due to high seroprevalence of CMV within the adult population and thus cannot replace invasive endoscopic procedures for pathological confirmation of CMV colitis (McCoy *et al.*, 2014).

Generally, patients with refractory IBD should be tested for CMV colitis, especially if they are failing immunosuppressive therapy, as multiple studies have concluded that concurrent CMV colitis is associated with a major risk of poorer outcomes, including toxic megacolon, colectomy, rescue therapy, and increased rate of disease flares (Lee *et al.*, 2016; Cohen *et al.*, 2018; Schenk *et al.*, 2019).

Active CMV colitis is usually diagnosed by endoscopic CMV detection in colonic tissue, histological tests including HE and IHC stains, and/or tissue PCR, although blood-based CMV antigenaemia assay and blood PCR (bPCR) have been extensively studied recently and could have some practical implications as well.

Typical endoscopic findings of CMV colitis are microerosions and deep ulcers (Ljungman *et al.*, 2002). Pseudotumoral lesions as an endoscopic finding for CMV GI tract infection have been reported by others and are postulated to be due to infection of stromal and epithelial cells resulting in hyperplastic changes (Bonetti *et al.*, 2015). However, most studies in patients with IBD, specifically in active UC, have not found specific endoscopic features (Yoshino *et al.*, 2007; Roblin *et al.*, 2011).

When assessing for CMV colitis, biopsy location and number appear to be important. Zidar *et al.* (2015) compared specimens collected from the colonic ulcer base and edge, and from uninvolved mucosa, which showed no significant difference between the ulcer base and edge in terms of the highest densities of CMV-positive cells. However, the uninvolved mucosa was IHC-negative for CMV and either PCR-negative, or very low (0 to 3 viral copies/mg tissue), supporting previous findings of Roblin *et al.* (2011), and suggesting that the most appropriate biopsy sites seem to be ulcer base and edge.

Left-colon biopsies identify most UC patients with CMV. Conversely, in CD many patients had CMV detectable only in right-colon biopsies. In terms of the adequate specimen number, McCurdy *et al.* (2015) proposed that 11 sigmoidoscopic biopsies be taken for UC diagnosis, and 16 colonoscopic biopsies for CD diagnosis to achieve an 80% probability of CMV detection. However, such high numbers are associated with risks of haemorrhage and perforation, thus highlighting the importance of the location of biopsies.

HE staining is the primary diagnostic test performed in patients suspected of having invasive CMV disease and has the ability to show the typical viral inclusions highly specific for CMV colitis known as “owl’s eye” inclusions — the nuclei of cytomegalic cells containing CMV inclusion bodies are surrounded by clear cytoplasm (Park *et al.*, 2017). However, the HE method has been shown to have lower sensitivity compared to IHC and tissue polymerase chain reaction (tPCR), possibly due to the rarity of finding these inclusion bodies within the relatively small amount of

tissue biopsied (Gauss *et al.*, 2015; Tandon *et al.*, 2017). Atypical features such as eccentric or smudged nuclei, perinuclear amphophilic zones (Yan *et al.*, 2014), and cells with basophilic inclusions that are up to twice the size of their non-infected neighbours and do not have the classic halo appearance (Zidar *et al.*, 2015), have been documented as well.

Numerous studies have confirmed that the gold standard for detection of CMV in GI mucosal biopsies is CMV-specific IHC staining, labelling CMV antigen in infected cells (Mills *et al.*, 2013; Zidar *et al.*, 2015; Juric-Sekhar *et al.*, 2017), which is a highly sensitive and specific test. Thus, according to ECCO guidelines, IHC should be performed in any clinical suspicion or consistent findings in the HE staining (Kucharzik *et al.*, 2021). The inclusions in IHC tend to be nuclear, occasionally cytoplasmic, mainly within endothelial cells.

Whereas quantitative CMV bPCR implies for diagnosis of systemic infection, tPCR has been shown to be more sensitive than IHC, and ECCO guidelines recommend it as, possibly, the standard test for confirming active CMV infection [colitis] in IBD patients, along with IHC (Kucharzik *et al.*, 2021). This method is fast and objective, although not well standardised yet (Bernard *et al.*, 2015). However, using tPCR for diagnosis of CMV colitis is controversial (Zidar *et al.*, 2015). One source of controversy is related to the difference between fresh and formalin-fixed, paraffin-embedded tissue (FFPE) when performing tPCR, as fresh tissue is often hard to obtain in clinical practice. A study by Mills *et al.* (2013) showed that CMV PCR on FFPE GI biopsies complements IHC, and therefore can be used instead of fresh tissue. Another aspect to consider is that CMV remains latent within leukocytes after a primary infection, meaning that a positive result does not necessarily indicate an active infection due to very high sensitivity, although tPCR is crucial when IHC is negative in patients with strong clinical suspicion of active CMV colitis. Overall, authors agree that there is still a need to define a cut-off for PCR within GI biopsies as no clear criteria differentiating between a latent CMV infection and CMV disease are yet available. According to Ciccocioppo *et al.* (2015), a mucosal viral load greater than 10^3 copies/10^5 cells was associated with refractoriness to treatment, whereas Roblin *et al.* (2011) found that a viral load of 250 copies/mg of tissue predicted the resistance of patients with active UC to continuous intravenous (IV) steroids, infliximab, and cyclosporine.

Finally, given the reduced sensitivity of HE staining, ECCO guidelines consistently propose that IHC, possibly tPCR, or both are essential for detecting CMV colitis in IBD and should be considered as standard tests (Tandon *et al.*, 2017; Kucharzik *et al.*, 2021).

Blood-based CMV detection tests studied in patients with IBD include CMV antigenaemia assay and bPCR, although both tests are of limited value in UC patients, as such patients have lower levels of CMV than do transplant recipients. The CMV antigenaemia assay semi-quantitatively detects the pp65 antigen in polymorphonuclear leucocytes (PMNs) of peripheral blood. CMV antigen-positive PMNs develop when antigens produced by CMV-infected cells are absorbed by the nuclei of PMNs, indicating systemic CMV reactivation. A positive result is defined as at least one pp65-positive cell per 2×10^5 PMNs and may depend on disease severity and the doses of immunosuppressants prescribed; no cut-off value for diagnosis of CMV colitis has yet been established (Park *et al.*, 2017). It should be noted that false negative results can occur in neutropenic patients (Nakase *et al.*, 2008).

CMV DNA in serum, measured by bPCR, may be diagnostic, but no cut-off value separating latent from active infection has yet been defined. Cut-offs in post-transplant patients vary from 4000 to 10 000 IU/ml (Emery *et al.*, 2013; Kotton *et al.*, 2013). In a study by Kim *et al.* (2013) on diagnosing suspected CMV colitis in patients with moderate-to-severe UC, serum CMV DNA PCR positivity was defined as > 250 copies/ml. Notably, both the CMV antigenaemia assay and bPCR were diagnostically useful in UC patients with endoscopically significant ulcers; the tests predicted CMV colitis with 67.3% sensitivity and 75.7% specificity in such patients. Furthermore, CMV antigenaemia-positivity was significantly associated with the need for subsequent colectomy in patients with UC and CMV colitis, suggesting that the test usefully predicted the clinical course of the disease. Similarly, Chun *et al.* (2015) found that two pp65-positive cells on CMV antigenaemia assay were significantly associated with refractoriness to corticosteroid therapy, affording a sensitivity of 66.7% and a specificity of 90.3%.

These findings suggest that while the low sensitivity of the CMV antigenaemia assay renders it difficult to replace endoscopic biopsy with the assay, the high specificity might aid in early diagnosis of severe CMV colitis cases that require prompt treatment prior to time-consuming IHC staining. According to Chang *et al.* (2015), as CMV infection is associated with poor responses to steroids and infliximab, CMV antigenaemia-positivity prior to the administration of such drugs in the acute exacerbation of UC might usefully predict candidates for early CMV rescue therapy, while ECCO guidelines suggest that blood-based CMV tests may be performed in addition to tissue-based tests when considering cessation of immunosuppressive therapy (Kucharzik *et al.*, 2021).

Viral culture was previously regarded as the gold standard in CMV detection, and despite its relatively high sensitivity and specificity to identify CMV in colonic tissue, this method is not used in clinical practice anymore as results take 2 to 4 weeks to obtain (Garrido *et al.*, 2013).

Furthermore, there is a need to develop non-invasive molecular tests for diagnosis of CMV colitis, and stool PCR may become the non-invasive diagnostic test of choice (Goodman *et al.*, 2015), but to date, the sensitivity of the assays is too low, leading to false-negative results, even in allograft patients with high viral load in the tissue (Sun *et al.*,

2015). Either way, a high index of suspicion is needed for diagnosis of CMV colitis in immunocompromised as well as immunocompetent patients.

TREATMENT — FEASIBLE OR FUTILE?

CMV is frequently detected in colonic tissue of IBD patients who are refractory to immunosuppressants, and thus could be involved in the pathophysiology of steroid refractoriness (Lee *et al.*, 2016; Nowacki *et al.*, 2018). There have been no studies specifically designed to address immunosuppressive treatment in this clinical scenario.

In a study by Shukla *et al.* (2017), corticosteroids (OR = 2.10, 95% CI = 1.31–3.37) and azathioprine (OR = 1.76, 95% CI = 1.21–2.57) were shown as independent predictive factors of CMV reactivation in the colon, which in turn may aggravate moderate or severe attacks of IBD.

Based on this indirect information, several therapeutic schedules have been proposed, such as rapid steroid tapering (Inokuchi *et al.*, 2014; Cohen *et al.*, 2018) or administration of infliximab, which is considered to have a lower risk of CMV reactivation compared to other immunosuppressants (McCurdy *et al.*, 2015; Shukla *et al.*, 2017). Recently, case reports by Rawa-Gołębiewska *et al.* (2019) and Hommel *et al.* (2020) proposed vedolizumab for the treatment of steroid-resistant UC with CMV reactivation, although its efficacy has not been previously shown in large cohorts.

Although immunosuppressants could theoretically worsen the outcome of CMV colitis, numerous case series and retrospective cohorts have shown that they are still mostly maintained for control of disease activity (McCurdy *et al.*, 2015; Cohen *et al.*, 2018; Nowacki *et al.*, 2018). Moreover, in patients with low CMV viral load and a low number of IHC-positive cells in the colon, CMV clearance may parallel the achievement of remission induced by immunosuppressants, even in patients who do not receive antivirals (Clos-Parals *et al.*, 2019). A case-control study by Levin *et al.* (2017) reported that immunosuppressant discontinuation and administration of antivirals achieved remission and colectomy rates similar to refractory patients without CMV managed with standard rescue therapy. Thus, the best therapeutic schedule for CMV reactivation in refractory UC remains to be determined.

Case reports have described primary disseminated CMV infection, characterised by a mononucleosis-like syndrome with positive serum CMV DNA PCR, fever, leukopenia, thrombocytopenia, and transaminitis, in UC patients receiving immunosuppressants (Torres *et al.*, 2018; Fakhreddine *et al.*, 2019). In such cases, discontinuation of immunosuppressive therapy is recommended.

Meta-analyses by Kopylov *et al.* (2014) and Shukla *et al.* (2015) revealed contradictory results regarding the benefits of antiviral therapy in CMV reactivation in IBD, probably due to differences in CMV burden, and thus supporting the concept that CMV is 'an innocent bystander' in patients with low CMV burdens but an active pathogen in those with high CMV burdens. The latest ECCO guidelines state that there is limited information on the relationship between the evolution of UC and tissue viral load, as measured by number of viral inclusions in IHC (Jones *et al.*, 2015; Zagórowicz *et al.*, 2016) or CMV DNA copies (Roblin *et al.*, 2011). Although some studies demonstrated that the higher the colonic viral load, the higher the risk of colectomy in patients with UC, supporting the benefit of antiviral therapy in cases of CMV reactivation, an exact threshold to determine which patients might benefit from antiviral therapy is currently unknown.

For example, a study by Jones *et al.* (2015) classified IBD patients into a high-grade CMV density group (five or more viral inclusions on IHC in each biopsy specimen); a low-grade CMV density group (fewer than five inclusions); and a control group (CMV-negative). The colectomy rates for patients in the low-grade CMV density group did not differ, regardless of whether antiviral therapy was prescribed. However, in the high-grade CMV density group, the colectomy rates were significantly higher in patients not on antiviral therapy (83% compared to 44% in those on therapy). Therefore, antiviral therapy may be indicated for cases of steroid-refractory or -dependent UC with high-grade CMV infection, and for those with > 250 CMV DNA copies/mg of tissue or low-grade CMV infection (evidenced by few inclusions or 10 to 250 DNA copies/mg of tissue) with endoscopically large ulcers (> 5 mm) (Fig. 1) (Shukla *et al.*, 2015; Pillet *et al.*, 2016).

The drug of choice for CMV colitis in adults is intravenous ganciclovir (5 mg/kg twice daily) for 5–10 days, followed by oral prodrug valganciclovir (900 mg twice daily) for the remainder of the 2–3-week course. An earlier transition to oral treatment is possible depending on the treatment response (Kucharzik *et al.*, 2021).

In paediatric patients, it is recommended to complete a full 2–3-week course of intravenous ganciclovir, as an early switch to oral treatment could promote CMV reactivation (Jain *et al.*, 2016).

The common side effects of ganciclovir, namely neutropaenia and thrombocytopaenia [also manifestations of systemic CMV], can add complexity to management. Such situations require a multidisciplinary approach, including engagement with infectious disease specialists. Hence, full blood count must be monitored regularly in patients on ganciclovir. Foscarnet, administered intravenously (90 mg/kg) twice daily for 2 to 3 weeks, may serve as a secondary treatment for ganciclovir-intolerant patients or in uncommon cases of ganciclovir-resistant CMV, mostly due to mutations in the viral UL97 kinase gene; the principal side-effect is nephrotoxicity. Concomitant administration of normal saline may reduce the risk of irreversible renal damage (Kucharzik *et al.*, 2021).

Pharmacokinetic and pharmacodynamic properties of antiviral medications are not discussed as it is beyond the scope of this paper.

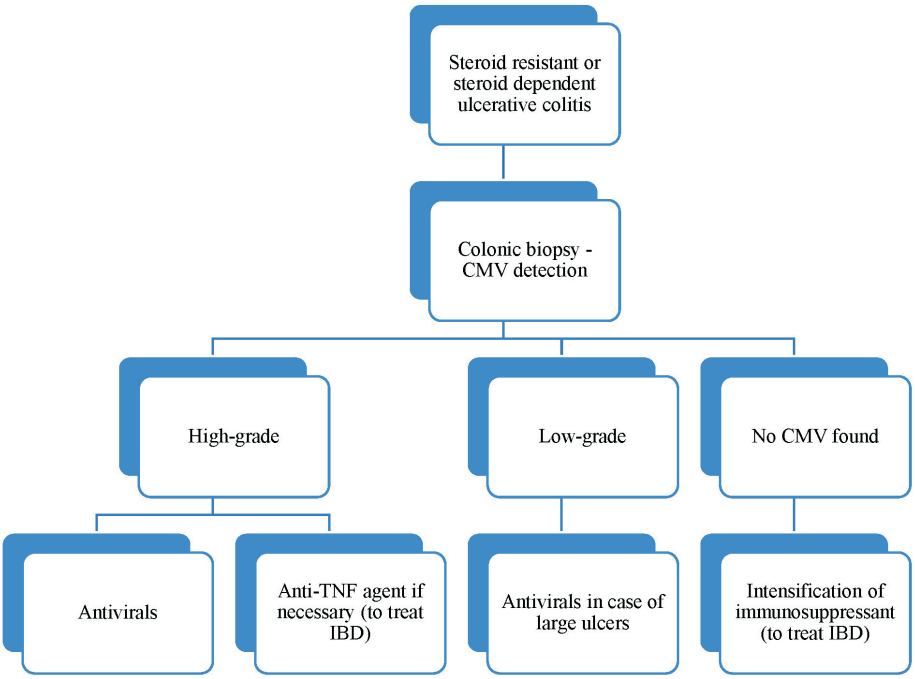

Fig. 1. A proposed management algorithm for cytomegalovirus (CMV) colitis in ulcerative colitis (UC) patients (adapted from Park *et al.*, 2017).

Follow-ups and monitoring standards after treatment of CMV colitis remain to be established. According to ECCO guidelines, blood-based CMV tests may be performed in addition to tissue-based tests when considering cessation of immunosuppressive therapy, although no cut-offs have yet been established (Kucharzik *et al.*, 2021). It is unclear whether follow-up endoscopy is required to confirm clearance of CMV antigens after treatment of CMV colitis.

Whether medical treatment is necessary for other immunocompetent patients is debatable. Antiviral medications have considerable side effects, however, untreated CMV disease is associated with higher morbidity and mortality. Fyock *et al.* (2014) suggested that an immunocompetent patient should only be given antiviral treatment if it is a male over 55 years of age or if the patient has immune-modulating comorbidities. As many reports have described a rapid clinical improvement after starting therapy (Hasegawa *et al.*, 2015; Levin *et al.*, 2017), it is a common practice to treat "immunocompetent" patients who have severe CMV colitis, at least until further studies can be done.

CONCLUSIONS

CMV is a common infection in the general population, and a relatively common end-organ infectious complication in both immunocompromised and "non-immunocompromised" patients. In IBD, especially UC, patients, reactivation of CMV is associated with severe colitis, often leading to deterioration in their clinical evolution. As reactivation is triggered by clinical stimuli, including the use of immunosuppressants and exacerbation of mucosal inflammation, CMV screening is required only for a subset of patients, thus a high index of suspicion is crucial. Diagnosis of CMV colitis generally relies on histological IHC staining and colonic tissue PCR; blood-based tests such as the CMV antigenaemia assay or PCR may aid in early diagnosis and predict the clinical course, although no clear cut-offs have yet been established. Prescription of antiviral medications may be based on the colon viral load or number of inclusions seen on IHC staining. However, when such assessment is practically difficult, an endoscopically large ulcers may aid in decision-making. Anti-TNF agents as a step-up therapy may be considered to treat CMV reactivation-associated flare-ups in UC patients with high CMV burden, in combination with antiviral treatment. Non-invasive CMV diagnostic tests are being developed and will hopefully improve the care of patients with CMV colitis.

REFERENCES

Alcalá, M. J., Casellas, F., Pallarés, J., de Torres, I., Malagelada, J. R. (2000). Infection by cytomegalovirus in patients with ulcerative colitis requiring colonic resection. *Med. Clin.* (Barc), **114**, 201–204.

Ayre, K., Warren, B. F., Jeffery, K., Travis, S. P. (2009). The role of CMV in steroid-resistant ulcerative colitis: A systematic review. *J. Crohns Colitis*, **3** (3), 141–148.

Bartlett, A. W., Hall, B. M., Palasanthiran, P., McMullan, B., Shand, A. W., Rawlinson, W. D. (2018). Recognition, treatment, and sequelae of congenital cytomegalovirus in Australia: An observational study. *J. Clin. Virol.*, **108**, 121–125.

Bernard, S., Germi, R., Lupo, J., Laverrière, M. H., Masse, V., Morand, P., Gavazzi, G. (2015). Symptomatic cytomegalovirus gastrointestinal infection with positive quantitative real-time PCR findings in apparently immuno-competent patients: A case series. *Clin. Microbiol. Infect.*, **21** (12), 1121.e1–e7.

Bonetti, L., Barresi, V., Bertani, A., Maccio, L., Palmiere, C. (2015). Human cytomegalovirus induced pseudotumor of upper gastrointestinal tract mucosa: Effects of long-term chronic disease? *J. Med. Virol.*, **87**, 1041–1045.

Bonetti, L. R., Losi, L., Gregorio, C., Bertani, A., Merighi, A., Bettelli, S., Scuri, M., Maiorana, A. (2011). Cytomegalovirus infection of the upper gastrointestinal tract: A clinical and pathological study of 30 cases. *Scand. J. Gastroenterol.*, **46**, 1228–1235.

Bontà, J., Zeitz, J., Frei, P., Biedermann, L., Sulz, M. C., Vavricka, S. R., Scharl, S., Fried, M., Rogler, G., Scharl, M. (2016). Cytomegalovirus dis-

ease in inflammatory bowel disease: Epidemiology and disease characteristics in a large single-centre experience. *Eur. J. Gastroenterol. Hepatol*., **28**, 1329–1334.

Britt, W. (2008). Manifestations of human cytomegalovirus infection: Proposed mechanisms of acute and chronic disease. *Curr. Top. Microbiol. Immunol*., **325**, 417–470.

Cha, J. M., Lee, J., Choe, J. W., Joo, K. R., Jung, S. W., Shin, H. P., Choi, S. I. (2010). Cytomegalovirus enteritis causing ileal perforation in an elderly immunocompetent individual. *Yonsei Med. J.,* **51**, 279–283.

Chang, S., Cheon, J. H. (2015). A clinical significance of assessing cytomegalovirus infection status in patients with ulcerative colitis. *Intest Res*., **13**, 2–3.

Chun, J., Lee, C., Kwon, J. E., Hwang, S. W., Kim, S. G., Kim, J. S., Jung, H. C., Im, J.P. (2015). Usefulness of the cytomegalovirus antigenemia assay in patients with ulcerative colitis. *Intest Res*., **13**, 50–59.

Ciccocioppo, R., Racca, F., Paolucci, S., Campanini, G., Pozzi, L., Betti, E., Riboni, R., Vanoli, A., Baldanti, F., Corazza, G. R. (2015). Human cytomegalovirus and Epstein-Barr virus infection in inflammatory bowel disease: Need for mucosal viral load measurement. *World J. Gastroenterol*., **21**, 1915–1926.

Clos-Parals, A., Rodríguez-Martínez, P., Cañete, F., Mañosa, M., Ruiz-Cerulla, A., Paúles, J., Llaó, J., Gordillo, J., Fumagalli, C., Garcia-Plnella, E., *et al.* (2019). Prognostic value of the burden of cytomegalovirus colonic reactivation evaluated by immunohistochemical staining in patients with active ulcerative colitis. *J. Crohns Colitis*, **13**, 385–388.

Cohen, S., Martinez-Vinson, C., Aloi, M., Turner, D., Assa, A., de Ridder, L., Wolters, V., de Meij, T., Alvisi, P., Bronsky, J. (2018). Pediatric IBD Porto Group of ESPGHAN. Cytomegalovirus infection in pediatric severe ulcerative colitis: A multicenter study from the pediatric inflammatory bowel disease Porto group of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. *Pediatr. Infect. Dis. J*., **37**, 197–201.

Criscuoli, V., Casà, A., Orlando, A., Pecoraro, G., Oliva, L., Traina, M., Rizzo, A., Cottone, M. (2004). Severe acute colitis associated with CMV: A prevalence study. *Dig. Liver Dis*., **36**, 818–820.

Criscuoli, V., Rizzuto, M. R., Montalbano, L., Gallo, E., Cottone, M. (2011). Natural history of cytomegalovirus infection in a series of patients diagnosed with moderate-severe ulcerative colitis. *World J. Gastroenterol*., **17**, 633–638.

D'Ovidio, V., Vernia, P., Gentile, G., Capobianchi, A, Marcheggiano, A., Viscido, A., Martino, P., Caprilli, R. (2008). Cytomegalovirus infection in inflammatory bowel disease patients undergoing anti-TNFalpha therapy. *J. Clin. Virol*., **43**, 180–183.

Diepersloot, R. J., Kroes, A. C., Visser, W., Jiwa, N. M., Rothbarth, P. H. (1990). Acute ulcerative proctocolitis associated with primary cytomegalovirus infection. *Arch. Intern. Med*., **150**, 1749–1751.

Domènech, E., Vega, R., Ojanguren, I., Hernández, A., Garcia-Planella, E., Bernal, I., Rosinach, M., Boix, J., Cabré, E., Gassull, M. A. (2008). Cytomegalovirus infection in ulcerative colitis: A prospective, comparative study on prevalence and diagnostic strategy. *Inflamm. Bowel Dis*., **14**, 1373–1379.

Emery, V., Zuckerman, M., Jackson, G., Aitken, C., Osman, H., Pagliuca, A., Potter, M., Peggs, K., Clark, A. (2013). Management of cytomegalovirus infection in haemopoietic stem cell transplantation. *Brit. J. Haematol*., **162**, 25–39.

Fakhreddine, A. Y., Frenette, C. T., Konijeti, G. G. (2019). A practical review of cytomegalovirus in gastroenterology and hepatology. *Gastroenterol. Res. Pract*., **2019**, 6156581.

Fuss, I. J., Neurath, M., Boirivant, M., Klein, J. S., de la Motte, C., Strong, S. A., Fiocchi, C., Strober, W. (1996). Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease. Crohn's disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. *J. Immunol*., **157**, 1261–1270.

Fyock, C., Gaitanis, M., Gao, J., Resnick, M., Shah, S. (2014). Gastrointestinal CMV in an elderly, immunocompetent patient. *Rhode Island Med. J.,* **97** (6), 53–56.

Galiatsatos, P., Shrier, I., Lamoureux, E., Szilagyi, A. (2005). Meta-analysis of outcome of cytomegalovirus colitis in immunocompetent hosts. *Dig. Dis. Sci.,* **50**, 609–616.

Garrido, E., Carrera, E., Manzano, R., Lopez-Sanroman, A. (2013). Clinical significance of cytomegalovirus infection in patients with inflammatory bowel disease. *World J. Gastroenterol*., **19** (1), 17–25. DOI:10.3748/wjg.v19.i1.17.

Gauss, A., Rosenstiel, S., Schnitzler, P., Hinz, U., Rehlen, T., Kadmon, M., Ehehalt, R., Stremmel, W., Zawierucha, A. (2015). Intestinal cytomegalovirus infection in patients hospitalized for exacerbation of inflammatory bowel disease: A 10-year tertiary referral center experience. *Eur. J. Gastroenterol. Hepatol*., **27** (6), 712–720.

Goodman, A. L., Murray, C. D., Watkins, J., Griffiths, P. D., Webster, D. P. (2015). CMV in the gut: A critical review of CMV detection in the immunocompetent host with colitis. *Eur. J. Clin. Microbiol. Infect. Dis*., **34** (1), 13–18.

Goodrum, F. (2016). Human cytomegalovirus latency: Approaching the Gordian knot. *Annu. Rev. Virol*., **3**, 333–357.

Gupta, M., Shorman, M. (2022). Cytomegalovirus. In: *Treasure Island (FL).* StatPearls Publishing, 2022 May. https://www.ncbi.nlm.nih.gov/books/NBK459185/?report=classic

Hasegawa, T., Aomatsu, K., Nakamura, M., Aomatsu, N., Aomatsu, K. (2015). Cytomegalovirus colitis followed by ischemic colitis in a non-immunocompromised adult: A case report. *World J. Gastroenterol*., **21** (12), 3750–3754.

Helbling, D., Breitbach, T. H., Krause, M. (2002). Disseminated cytomegalovirus infection in Crohn's disease following anti-tumour necrosis factor therapy. *Eur. J. Gastroenterol. Hepatol.,* **14**, 1393–1395.

Hommel, C., Pillet, S., Rahier, J. F. (2020). Comment on: 'Resolution of CMV infection in the bowel on vedolizumab therapy'. *J. Crohns Colitis*, **14**, 148–149.

Hommes, D. W., Sterringa, G., Boom, R. (2002). Incidence and outcome of cytomegalovirus infection in patients with inflammatory bowel disease. *Gastroenterology*, **122**, A1287.

Hommes, D. W., Sterringa, G., van Deventer, S. J., Tytgat, G. N., Weel, J. (2004). The pathogenicity of cytomegalovirus in inflammatory bowel disease: a systematic review and evidence-based recommendations for future research. *Inflamm. Bowel Dis*., **10**, 245–250.

Hsieh, C.-L., Tu, C.-H., Tsai, M.-H., Liang, C.-W., Wang, H.-P., Tseng, P.-H. (2016). Cytomegalovirus enteritis in immunocompetent patients: Report of two cases diagnosed using single-balloon enteroscopy. *Adv. Digest. Med*., **3** (3), 135–140.

Hwang, J. B., Park, M. H., Lee, B. Y., Choi, W. J., Kim, C. S., Lee, S. L., Kang, U. (2006). Clinical quiz. Cytomegalovirus infection. *J. Pediatr. Gastroenterol. Nutr.,* **42** (05), 607–608.

Inokuchi, T., Kato, J., Hiraoka, S., Suzuki, H., Nakarai, A., Hirakawa, T., Akita, M., Takahashi, S., Harada, K., Okada, H. (2014). Long-term follow-up of ulcerative colitis patients treated on the basis of their cytomegalovirus antigen status. *World J. Gastroenterol*., **20**, 509–517.

Jain, R., Trehan, A., Mishra, B., Singh, R., Saud, B., Bansal, D. (2016). Cytomegalovirus disease in children with acute lymphoblastic leukemia. *Pediatr. Hematol. Oncol.,* **33** (4), 239–247.

Jones, A., McCurdy, J. D., Loftus, E. V. Jr, Bruining, D. H., Enders, F. T., Killian, J. M., Smyrk, T. C. (2015). Effects of antiviral therapy for patients with inflammatory bowel disease and a positive intestinal biopsy for cytomegalovirus. *Clin. Gastroenterol. Hepatol*., **13**, 949–955.

Juric-Sekhar, G., Upton, M. P., Swanson, P. E., Westerhoff, M. (2017). Cytomegalovirus (CMV) in gastrointestinal mucosal biopsies: Should a pathologist perform CMV immunohistochemistry if the clinician requests it? *Hum. Pathol*., **60**, 11–15.

Karigane, D., Takaya, S., Seki, Y., Matsumoto, Y., Onose, A., Kosakai, A., Sugaya, N., Mori, T. (2014). Cytomegalovirus enteritis in immunocompetent subjects: A case report and review of the literature. *J. Infect. Chemother*., **20** (5), 325–329.

Kim, C. H., Bahng, S., Kang, K. J., Ku, B. H., Jo, Y. C., Kim, J. Y., Chang, D. K., Son, H. J., Rhee, P. L., Kim, J. J., *et al.* (2010). Cytomegalovirus colitis in patients without inflammatory bowel disease: A single center study. *Scand. J. Gastroenterol*., **45**, 1295–1301.

Kim, J. W., Boo, S. J., Ye, B. D., Kim, C. L., Yang, S. K., Kim, J., Kim, S. A., Park, S. H., Park, S. K., Yang, D. H., *et al.* (2014). Clinical utility of cytomegalovirus antigenaemia assay and blood cytomegalovirus DNA PCR for cytomegaloviral colitis patients with moderate to severe ulcerative colitis. *J. Crohns Colitis*, **8**, 693–701.

Kishore, J., Ghoshal, U., Ghoshal, U. C., Krishnani, N., Kumar, S., Singh, M., Ayyagari, A. (2004). Infection with cytomegalovirus in patients with inflammatory bowel disease: Prevalence, clinical significance and outcome. *J. Med. Microbiol*., **53**, 1155–1160.

Knösel, T., Schewe, C., Petersen, N., Dietel, M., Petersen, I. (2009). Prevalence of infectious pathogens in Crohn's disease. *Pathol. Res. Pract*., **205**, 223–230.

Ko, J. H., Peck, K. R., Lee, W. J., Lee, J. Y., Cho, S. Y., Ha, Y. E., Kang, C.-I., Chung, D. R., Kim, Y.H., Lee, N. Y. (2015). Clinical presentation and risk factors for cytomegalovirus colitis in immunocompetent adult patients. *Clin. Infect. Dis*., **60** (6), e20–e26.

Kojima, T., Watanabe, T., Hata, K., Shinozaki, M., Yokoyama, T., Nagawa, H. (2006). Cytomegalovirus infection in ulcerative colitis. *Scand J. Gastroenterol*., **41**, 706–711.

Kopylov, U., Eliakim-Raz, N., Szilagy, A., Seidman, E., Ben-Horin, S., Katz, L. (2014). Antiviral therapy in cytomegalovirus-positive ulcerative colitis: A systematic review and meta-analysis. *World J. Gastroenterol*., **20**, 2695–2703.

Kotton, C. N., Kumar, D., Caliendo, A. M., Asberg, A., Chou, S., Danziger, Isakov, L., Humar, A., Transplantation Society International CMV Consensus Group. (2013). Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation*, **96**, 333–360.

Kucharzik, T., Ellul, P., Greuter, T., Rahier, J. F., Verstockt, B., Abreu, C., Albuquerque, A., Allocca, M., Esteve, M., Farraye, F. A., *et al.* (2021). ECCO Guidelines on the prevention, diagnosis, and management of infections in inflammatory bowel disease. *J. Crohns Colitis*, **15** (6), 879–913. DOI: 10.1093/ecco-jcc/jjab052.

Lawlor, G. , Moss, A. C. (2010). Cytomegalovirus in inflammatory bowel disease: pathogen or innocent bystander? *Inflamm. Bowel Dis.,* **16**, 1620–1627.

Lee, H. S., Park, S. H., Kim, S. H., Kim, J., Choi, J., Lee, H. J., Kim, W. S., Lee, J.-M., Kwak, M. S., Hwang, S. W., *et al.* (2016). Risk factors and clinical outcomes associated with cytomegalovirus colitis in patients with acute severe ulcerative colitis. *Inflamm. Bowel Dis*., **22**, 912–918.

Levin, A., Yaari, S., Stoff, R., Caplan, O., Wolf, D. G., Israeli, E. (2017). Diagnosis of cytomegalovirus infection during exacerbation of ulcerative colitis. *Digestion*, **96**, 142–148.

Liu, P. Y., Cheng, S. B., Lin, C. C., Lin, C. H., Chang, S. N., Cheng, C. Y., Shi, Z. Y., Tung, K. C., Wu, M. J. (2014). Cytomegalovirus disease after liver transplantation: A nationwide population-based study. *Transplant Proc*., **46** (3), 832–834.

Ljungman, P., Griffiths, P., Paya, C. (2002). Definitions of cytomegalovirus infection and disease in transplant recipients. *Clin. Infect. Dis*., **34**, 1094–1097.

Maconi, G., Colombo, E., Zerbi, P., Sampietro, G. M., Fociani, P., Bosani, M., Cassinotti, A., Casini, V., Russo, A., Ardizzone, S., *et al.* (2005). Prevalence, detection rate and outcome of cytomegalovirus infection in ulcerative colitis patients requiring colonic resection. *Dig. Liver Dis*., **37**, 418–423.

Marques, S., Carmo, J., Pinto, D., Bispo, M., Ramos, S., Chagas, C. (2017). Cytomegalovirus disease of the upper gastrointestinal tract: A 10-year retrospective study. *GE Portuguese J. Gastroenterol*., **24** (6), 262–268.

Matsumoto, S., Yoshida, Y. (2014). What are the factors that affect hospitalization and surgery for aggravation of ulcerative colitis? *Eur. J. Gastroenterol. Hepatol.*, **26**, 282–287.

McCoy, M. H., Post, K., Sen, J. D., Chang, H. Y., Zhao, Z., Fan, R., Chen, S., Leland, D., Cheng, L., Lin, J. (2014). qPCR increases sensitivity to detect cytomegalovirus in formalin-fixed, paraffin-embedded tissue of gastrointestinal biopsies. *Hum. Pathol*., **45** (1), 48–53.

McCurdy, J. D., Enders, F. T., Jones, A., Killian, J. M., Loftus, E. V., Bruining, D. H., Smyrk, T. C. (2015). Detection of cytomegalovirus in patients with inflammatory bowel disease: Where to biopsy and how many biopsies? *Inflamm. Bowel Dis*., **21**, 2833–2838.

McCurdy, J. D., Jones, A., Enders, F. T. Killian, J. M., Loftus, Jr., E. V., Smyrk, T. C., Bruining, D. H. (2015). A model for identifying cytomegalovirus in patients with inflammatory bowel disease. *Clin. Gastroenterol. Hepatol.,* **13**, 131–137.

Mills, A. M., Guo, F. P., Copland, A. P., Pai, R. K., Pinsky, B. A. (2013). A comparison of CMV detection in gastrointestinal mucosal biopsies using immunohistochemistry and PCR performed on formalin-fixed, paraffin-embedded tissue. *Amer. J. Surg. Pathol*., **37** (7), 995–1000.

Nakase, H., Matsumura, K., Yoshino, T., Chiba, T. (2008). Systematic review: Cytomegalovirus infection in inflammatory bowel disease. *J. Gastroenterol*., **43**, 735–740.

Nakase, H., Yoshino, T., Honzawa, Y, Chiba, T. (2010). Low prevalence of CMV infection in patients with Crohn's disease in comparison with ulcerative colitis: Effect of different immune response on prevalence of CMV infection. *Dig. Dis. Sci.,* **55**, 1498–1499.

Nakase, H., Yoshino, T., Matumura, K., Honzawa, Y., Yamamoto, S., Matsuura, M., Chiba, T. (2011). Positive finding of colonic polymerase chain reaction for cytomegalovirus DNA is not false positive but a warning for treating patients with ulcerative colitis refractory to immunosuppressive therapies. *Inflamm. Bowel Dis*., **17**, E13–E14.

Nolan, N., Halai, U. A., Regunath, H., Smith, L., Rojas-Moreno, C., Salzer, W. (2017). Primary cytomegalovirus infection in immunocompetent adults in the United States: A case series. *IDCases*, **10**, 123–126.

Nowacki, T. M., Bettenworth, D., Meister, T., Heidemann, J., Lewnze, F., Schidt, H. H., Heinzow, H. S. (2018). Novel score predicts risk for cytomegalovirus infection in ulcerative colitis. *J. Clin. Virol*., **105**, 103–108.

O'Hara, K. M., Pontrelli, G., Kunstel, K. L. (2017). An introduction to gastrointestinal tract CMV disease. *J. Amer. Acad. Phys. Assist*., **30** (10), 48–52.

Orvar, K., Murray, J., Carmen, G., Conklin, J. (1993). Cytomegalovirus infection associated with onset of inflammatory bowel disease. *Dig. Dis. Sci*., **38**, 2307–2310.

Ozaki, T., Yamashita, H., Kaneko, S., Yorifuji, H., Takahashi, H., Ueda, Y., Takahashi, Y., Kaneko, H., Kano, T., Mimori, A. (2013). Cytomegalovirus disease of the upper gastrointestinal tract in patients with rheumatic diseases: A case series and literature review. *Clin. Rheumatol*., **32**, 1683–1690.

Papadakis, K. A., Tung, J. K., Binder, S. W., Kam, L. Y., Abreu, M. T., Targan, S. R., Vasiliauskas, E. A. (2001). Outcome of cytomegalovirus infections in patients with inflammatory bowel disease. *Amer. J. Gastroenterol*., **96**, 2137–2142.

Park, S. C., Jeen, Y. M., Jeen, Y. T. (2017). Approach to cytomegalovirus infections in patients with ulcerative colitis [published correction appears in *Korean J. Intern. Med.* 2021 May; **36** (3), 751]. *Korean J. Intern. Med*., 2017; **32** (3), 383–392.

Park, S. H., Yang, S. K., Hong, S. M., Park, S. K., Kim, J. W., Lee, H. J., Yang, D. H., Jung, K. W., Kim, K. J., Ye, B. D., Byeon, J. S. (2013). Severe disease activity and cytomegalovirus colitis are predictive of a nonresponse to infliximab in patients with ulcerative colitis. *Dig. Dis. Sci*., **58**, 3592–3599.

Powell, R. D., Warner, N. E., Levine, R. S., Kirsner, J. B. (1961). Cytomegalic inclusion disease and ulcerative colitis; report of a case in a young adult. *Amer. J. Med.*, **30**, 334–340.

Péter, A., Telkes, G., Varga, M., Sįrvįry, E., Kovalszky, I. (2004). Endoscopic diagnosis of cytomegalovirus infection of upper gastrointestinal tract in solid organ transplant recipients: Hungarian single-center experience. *Clin. Transplant*., **18**, 580–584.

Pillet, S., Pozzetto, B., Roblin, X. (2016). Cytomegalovirus and ulcerative colitis: Place of antiviral therapy. *World J. Gastroenterol*., **22**, 2030–2045.

Pofelski, J., Heluwaert, F., Roblin, X., Morand, P., Gratacap, B., Germain, E., Brion, J. P., Salon, C., Bonaz, B. (2007). Cytomegalovirus and cryptogenic inflammatory bowel disease. *Gastroenterol. Clin. Biol*., **31**, 292–296.

Rachima, C., Maoz, E., Apter, S., Thaler, M., Grossman, E., Rosenthal, T. (1998). Cytomegalovirus infection associated with ulcerative colitis in immunocompetent individuals. *Postgrad. Med. J*., **74**, 486–489.

Rawa-Gołębiewska, A., Lenarcik, M., Zagórowicz, E. (2019). Resolution of CMV infection in the bowel on vedolizumab therapy. *J. Crohns Colitis*, **13**, 1234–1245.

Roblin, X., Pillet, S., Oussalah, A., Berthelot, P., Del Tedesco, E., Phelip, J. M., Chambonnière, M. L., Garraud, O., Peyrin-Biroulet, L., Pozzetto, B. (2011). Cytomegalovirus load in inflamed intestinal tissue is predictive of resistance to immunosuppressive therapy in ulcerative colitis. *Amer. J. Gastroenterol*., **106**, 2001–2008.

Römkens, T. E., Bulte, G. J., Nissen, L. H., Drenth, J. P. (2016). Cytomegalovirus in inflammatory bowel disease: A systematic review. *World J. Gastroenterol*., **22** (3), 1321–1330. DOI:10.3748/wjg.v22.i3.1321.

Schenk, W., Klugmann, T., Borkenhagen, A., Klecker, C., Dietel, P., Kirshner, R., Schneider, E., Bruns, T., Stallmach, A., Teich, N. (2019). The detection of the cytomegalovirus DNA in the colonic mucosa of patients with ulcerative colitis is associated with increased long-term risk of proctocolectomy: Results from an outpatient IBD clinic. *Int. J. Colorectal Dis*., **34**, 393–400.

Shukla, T., Singh, S., Loftus, E. V. Jr, Bruining, D. H., McCurdy, J. D. (2015). Antiviral therapy in steroid-refractory ulcerative colitis with cytomegalovirus: Systematic review and meta-analysis. *Inflamm. Bowel Dis*., **21**, 2718–2725.

Shukla, T., Singh, S., Tandon, P., McCurdy, J. D. (2017). Corticosteroids and thiopurines but not tumor necrosis factor antagonists are associated with cytomegalovirus reactivation in inflammatory bowel disease. A systematic review and meta-analysis. *J. Clin. Gastroenterol*., **51**, 394–401.

Siciliano, R. F., Castelli, J. B., Randi, B. A., Vieira, R. D., Strabelli, T. M. V. (2014). Cytomegalovirus colitis in immunocompetent critically ill patients. *Int. J. Infect. Dis*., **20**, 71–73.

Simon, C. O., Seckert, C. K., Dreis, D., Reddehase, M. J., Grzimek, N. K. (2005). Role for tumor necrosis factor alpha in murine cytomegalovirus transcriptional reactivation in latently infected lungs. *J. Virol.,***79**, 326–340.

Streetz, K. L., Buhr, T., Wedemeyer, H., Bleck, J., Schedel, I., Manns, M. P., Göke, M. N. (2003). Acute CMV-colitis in a patient with a history of ulcerative colitis. *Scand. J. Gastroenterol*., **38**, 119–122.

Sue, P., Salazar-Austin, N., McDonald, O., Rishi, A., Cornish, T. C., Artav-Boger, R. (2016). Cytomegalovirus enterocolitis in immunocompetent young children. A report of two cases and review of literature. *Pediatric Infect. Dis. J*., **35**, 573–576.

Sun, Y.-Q., Xu, L.-P., Han, T.-T., Zhang, X.-H., Wang, Y., Han, W., Wang, F.-R., Wang, J.-Z., Chen, H., Chen, Y.-H., *et al.* (2015). Detection of human cytomegalovirus (CMV) DNA in feces has limited value in predicting CMV enteritis in patients with intestinal graft-versus-host disease after allogeneic stem cell transplantation. *Transpl. Infect. Dis*., **17**, 655–661. DOI: 10.1111/tid.12420.

Tandon, P., James, P., Cordeiro, E., Mallick, R., Shukla, T., McCurdy, J. D. (2017). Diagnostic accuracy of blood-based tests and histopathology for cytomegalovirus reactivation in inflammatory bowel disease: A systematic review and meta-analysis. *Inflamm. Bowel Dis*., **23** (4), 551–560.

Torres, P., Lobatón, T., Cañete, F., Clos, A., Mañosa, M., Cabré, E., Domènech, E. (2018). Cytomegalovirus primoinfection in inflammatory bowel disease. *Gastroenterol. Hepatol*., **41**, 453–454.

Vega, R., Bertrán, X., Menacho, M., Domènech, E., Moreno de Vega, V., Hombrados, M., Cabré, E., Ojanguren, I., Gassull, M. A. (1999). Cytomegalovirus infection in patients with inflammatory bowel disease. *Amer. J. Gastroenterol*., **94**, 1053–1056.

Wada, Y., Matsui, T., Matake, H., Sakurai, T., Yamamoto, J., Kikuchi, Y., Yorioka, M., Tsuda, S., Yao, T., Yao, S., *et al*. (2003). Intractable ulcerative colitis caused by cytomegalovirus infection: A prospective study on prevalence, diagnosis, and treatment. *Dis. Colon Rectum*, **46**, S59–S65.

Wakefield, A. J., Fox, J. D., Sawyerr, A. M., Taylor, J. E., Sweenie, C. H., Smith, M., Emery, V. C., Hudson, M., Tedder, R. S., Pounder, R. E. (1992). Detection of herpesvirus DNA in the large intestine of patients with ulcerative colitis and Crohn's disease using the nested polymerase chain reaction. *J. Med. Virol.,* **38**, 183–190.

Wang, H. W., Kuo, C. J., Lin, W. R., Hsu, C. M., Ho, Y. P., Lin, C. J., Su, M. Y., Chiu, C. T., Wang, C. L., Chen, K. H. (2016). The clinical characteristics and manifestations of cytomegalovirus esophagitis. *Dis. Esophagus,* **29**, 392–399.

Yan, Z., Wang, L., Dennis, J., Doern, C., Baker, J., Park, J. Y. (2014). Clinical significance of isolated cytomegalovirus-infected gastrointestinal cells. *Int. J. Surg. Pathol*., **22** (6), 492–498.

Yoshino, T., Nakase, H., Ueno, S., Uza, N., Inoue, S., Mikami, S., Matsuura, M., Ohmori, K., Sakurai, T., Nagayama, S., *et al.* (2007). Usefulness of quantitative real-time PCR assay for early detection of cytomegalovirus infection in patients with ulcerative colitis refractory to immunosuppressive therapies. *Inflamm. Bowel Dis.,***13**, 1516–1521.

Zagórowicz, E., Bugajski, M., Wieszczy, P., Pietrzak, A., Magdziak, A., Mróz, A. (2016). Cytomegalovirus infection in ulcerative colitis is related to severe inflammation and a high count of cytomegalovirus-positive cells in biopsy is a risk factor for colectomy. *J. Crohns Colitis*, **10**, 1205–1211.

Zidar, N., Ferkolj, I., Tepeš, K., Štabuc, B., Kojc, N., Uršič, T., Petrovec, M. (2015). Diagnosing cytomegalovirus in patients with inflammatory bowel disease — by immunohistochemistry or polymerase chain reaction? *Virchows Arch.*, **466** (5), 533–539.

Received 2 May 2022
Accepted in the final form 15 May 2022

ĪSS CEĻVEDIS CITOMEGALOVĪRUSA ZARNU INFEKCIJAS DIAGNOSTIKAI UN ĀRSTĒŠANAI: ŠĪ BRĪŽA DILEMMAS

Citomegalovīruss ir visuresošs herpes grupas vīruss, kas pēc bieži vien asimptomātiskas primārās infekcijas pāriet latentā stāvoklī dažādos orgānos, tostarp zarnās. Tā kā pastāv cieša sinerģiska saikne starp gļotādas iekaisumu un vīrusa ekspresiju, īpaši pacientiem ar iekaisīgām zarnu slimībām, bieži ir grūti atšķirt subklīnisku citomegalovīrusa replikāciju no citomegalovīrusa izraisīta kolīta. Šķiet, ka iznākums pacientiem ar citomegalovīrusa reaktivāciju ir sliktāks nekā pacientiem bez reaktivācijas, taču citomegalovīrusa patiesā loma nav pilnībā skaidra, tāpat kā dilemma, vai specifisko pretvīrusu līdzekļu pielietošana izmaina iekaisīgu zarnu slimību gaitu. Šajā pārskatā galvenā uzmanība pievērsta citomegalovīrusa izpausmēm kuņģa–zarnu traktā, īpašu uzsvaru liekot uz citomegalovīrusa kolīta diagnostikas un ārstēšanas apsvērumiem pacientiem ar iekaisīgām zarnu slimībām.