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REVIEW

Cytomegalovirus Pneumonia in Inflammatory Bowel Disease: Literature Review and Clinical Recommendations

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Aim: The objective was to elucidate the correlation between CMVP and immunosuppressive therapy in IBD patients, we hope this review could expand on the significance of CMV as an opportunistic pathogen and the potential impact on morbidity and mortality in IBD patients.

Methods: Records and clinical trajectories linked to CMVP in IBD patients were extracted from the PubMed database, irrespective of language barriers. The reference lists incorporated in these studies were manually inspected. Conclusions were generated using straightforward descriptive analysis.

Results: In total, 18 IBD patients, including Crohn's disease (CD, 67%) and Ulcerative Colitis (UC, 33%), affected by CMVP were identified from 17 published articles. A minority of these patients (17%) exhibited active disease, whereas the majority (83%) presented with quiescent disease. Fever (100%) and dyspnea (44%) emerged as the most prevalent clinical symptoms. All the patients had undergone immunosuppressive therapy. A significant proportion, up to 89%, had received thiopurine treatment prior to the CMVP diagnosis. Interestingly, none of the patients were subjected to biological therapy. Half of the patients manifested with Hemophagocytic Lymphohistiocytosis (HLH). Almost all patients (94%) were administered antiviral treatment and a substantial 83% experienced full recovery. Immunosuppressive agents were either tapered or discontinued altogether. A subset of patients, 17%, suffered fatal outcomes.

Conclusion: Our findings underscore the need for heightened suspicion of CMVP in IBD patients who exhibit symptoms such as fever and dyspnea. During the COVID-19 pandemic, CMVP should be considered a potential differential diagnosis. It was observed that CMVP primarily transpires during CD remission. Azathioprine emerged as the predominant immunosuppressant linked to CMV reactivation. The prompt application of effective antiviral therapy can substantially enhance patient outcomes. CMV vaccine might serve as a viable prevention strategy.

Keywords: CMV, cytomegalovirus pneumonia, inflammatory bowel disease, ulcerative colitis, Crohn's disease

Introduction

Cytomegalovirus (CMV) is a double-stranded DNA virus, part of the Herpesviridae family, and commonly infects humans. This virus can establish a lifelong latent state in healthy individuals, with potential for reactivation leading to either subclinical or clinical infection. While CMV infection often presents as asymptomatic in immunocompetent individuals, it can lead to severe clinical complications in those who are immunocompromised. This is particularly observed in individuals receiving steroids or immunosuppressive therapy, as these treatments can facilitate CMV reactivation.[1,2]

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The gastrointestinal tract is a frequently involved system in Cytomegalovirus (CMV) infections. It has been noted that patients diagnosed with Inflammatory Bowel Disease (IBD) exhibit a heightened risk ratio for CMV reactivation. Roughly 34.5% of patients diagnosed with IBD exhibit CMV colitis as confirmed by quantitative real-time PCR.[3] CMV infection is also a potential contributor to instances of therapy-resistant IBD.[4] According to recent guidelines published by the European Crohn's and Colitis Organisation (ECCO),[5] CMV colitis is linked to a higher risk of surgical intervention and mortality among patients with active IBD. Implementing effective antiviral therapy can significantly improve patient outcomes. Multiple risk factors are widely recognized for this increase, including extensive usage of immunosuppressants[6,7] and impaired T-cell immunity. T-cell responses are critical in controlling CMV,[8] and the activation of CMV-specific T-cells may lead to unchecked viral replication.[9] Furthermore, the propensity of CMV to target sites of inflammation is another significant factor.[10] CMV reactivation is often induced and sustained by inflamed mucosa.

The lungs are among the most frequently involved organs in CMV infections.[11] CMV may initially seed in the oropharyngeal cavity before infecting the lungs. Its primary mode of spread is via cell-to-cell infection through innate immune cells, which aids in establishing latency within the host.[12] Beyond inhalation of infectious body fluids, systemic CMV infection can also lead to pneumonia in the lungs.[13] The lungs and the gastrointestinal tract share the same embryological origin, tracing back to the ancestral intestine.[14] The similarities in immune systems between the lungs and intestines might facilitate pulmonary involvement.[15] Current evidence suggests that the prevalence of CMV pneumonia (CMVP) in immunocompromised hosts can reach up to 60%, which could be attributed to severe immunosuppression.[16] Indeed, symptomatic CMVP infections are more commonly identified in immunocompromised patients.[17]

Over the past decade, there has been a surfeit of therapeutic advancements in the treatment of IBD. These developments have revolutionized IBD management, enabling the induction of intestinal mucosal healing and potentially altering disease progression. Despite the high mortality associated with CMVP in patients with IBD, there is scant information about the manifestation of CMVP in IBD patients who are subjected to immunosuppressive therapy.[18,19] The optimal treatment strategy has yet to be definitively determined, indicating a clear need for additional data and research to address this knowledge gap.

The primary objective of this study is to scrutinize the existing literature, aiming to delineate the clinical characteristics, diagnostic procedures, and treatment approaches pertinent to CMV infections among IBD patients. Through this comprehensive review, we anticipate extending our understanding of the implications of CMV as an opportunistic pathogen, as well as providing pragmatic clinical recommendations for the prevention and management of CMV infections in patients with IBD.

Methods

This study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[20] A comprehensive search of the PubMed database was performed, collecting pertinent literature up to September 2022. The search terms utilized included "Cytomegalovirus" or "CMV" and "inflammatory bowel disease" or "Crohn's disease" or "ulcerative colitis" or "IBD".

First, titles and abstracts were screened to identify potentially relevant papers. Studies not meeting inclusion criteria were excluded. Second, we read them in their entirety to assess their appropriateness for inclusion. Articles selected for inclusion met specific criteria, namely, they provided detailed information on IBD patients with CMVP. In addition, the references cited in these articles were reviewed to discover potentially relevant studies. The retrieved studies were manually scrutinized to assess their suitability for inclusion. Conversely, non-relevant articles were excluded based on the following criteria: (1) cases with underlying congenital CMV infections, (2) IBD patients without CMVP, (3) patients with CMVP but not arising from IBD, and (4) those with unavailable or incomplete data.

CMVP was diagnosed according to specific criteria: (1) Symptoms including, but not limited to, dyspnea, fever, cough, and hypoxia; (2) Radiological or post-mortem findings of pneumonia; (3) The presence of pp65 antigenemia and/or CMV DNA in the blood and/or respiratory samples, as well as anti-CMV antibodies of IgM and IgG titers; (4) CMV inclusion bodies found in lung specimen histopathology; (5) Positive CMV cultures in lung and/or respiratory samples; and (6) Positive CMV in situ hybridization on lung specimens.[21,22]

Statistical analysis was performed with data summarized using descriptive statistics, including frequency and means. Calculations were conducted using Microsoft Excel.

Results

The initial literature search yielded a total of 810 articles. We screened these preliminary results for relevance based on two key criteria: topical relevance and descriptions of patient cases. This step resulted in 32 pertinent articles. Furthermore, in all the remaining articles, CMVP was confirmed based on predefined criteria. Ultimately, 17 articles comprising 18 case reports met the predetermined inclusion criteria. The process of literature search and evaluation is illustrated in Figure 1. All extracted clinical data are presented in Table 1.

The patient cohort predominantly comprised females (72%) with a median age of 37 years (range: 18–77 years). Among the patients, 67% had Crohn's Disease (CD), and 33% suffered from Ulcerative Colitis (UC). Notably, 17% (UC=2, CD=1) of the patients had active disease, while 83% (UC=4, CD=11) presented with quiescent disease. Among the three patients with confirmed active IBD, characteristic cytomegalic cells were identified in the colonic autopsy specimens of a UC patient. All patients had received immunosuppressants such as prednisone (22%), 6-mercaptopurine (6-MP) (11%), azathioprine (AZA) (78%), and/or cyclosporine A (CSA) (11%) prior to the CMV onset. Notably, 89% of patients were administered thiopurines in combination with either glucocorticoids (n=2) or 5-aminosalicylates (n=6), with no patients receiving biologics.

The most frequently reported symptoms were fever (100%), varied degrees of dyspnea (44%), and cough (33%). Additional non-specific symptoms included breathlessness (11%) and pharyngeal discomfort (17%), while approximately one-fourth of the patients (23%) experienced no respiratory symptoms.

Serological tests were predominantly employed for diagnosing CMV infection, with 94% of the patients being CMV seropositive. The Bronchoalveolar lavage fluid (BALF)CMV DNA and blood CMV DNA were positive in 34% and 50% of the patients, respectively. BALF CMV DNA test serves as a valuable complement to CMV serological diagnosis,

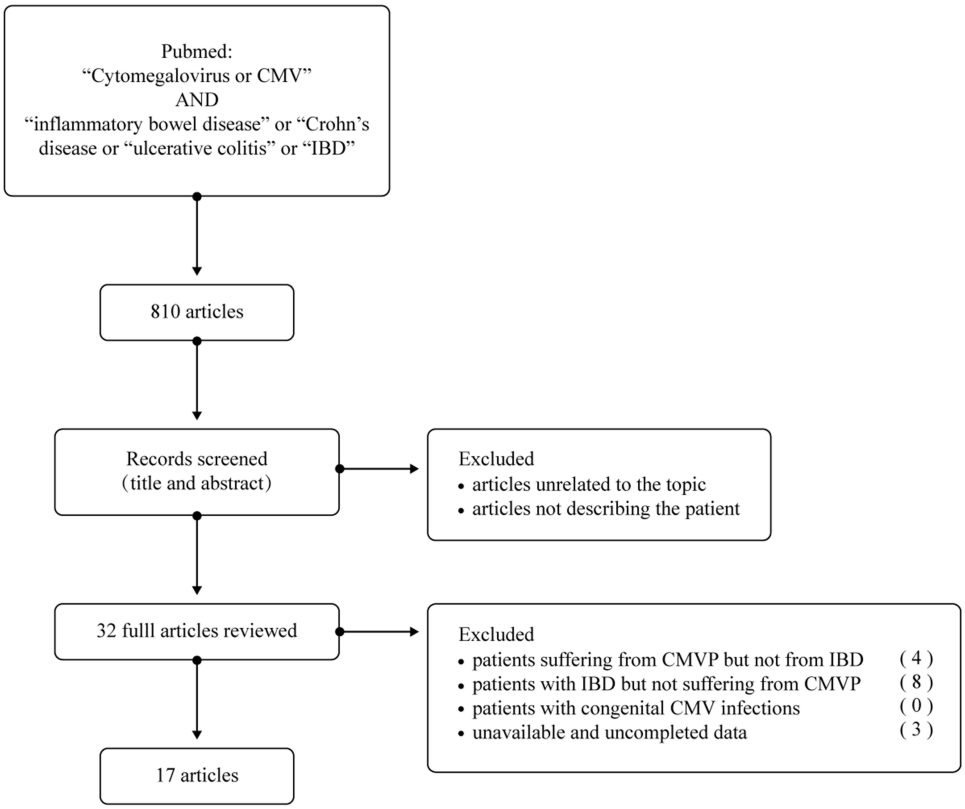

Figure 1 Flow chart of the literature search. The search led to 17 articles describing patient cases of CMVP. In total, 18 patient cases were included from literature.

Table 1 Main Characteristics, Therapy, and Outcome of IBD Patients with CMV Pneumonia

Study	Number of the Patient	Sex/ Age	Disease Type/ Duration	Disease Activity of IBD	Previous Medication	Symptoms and Treatment	CMV Diagnosis	Radiological Findings	Outcome	HLH
Sijpkens et al, 1996[23]	1	F/20	CD (3 years)	Remission	Steroids and 5-ASA (NR,3 years); AZA (NR, 19 months)	Fever, headache, mild dyspnea, nonproductive cough, weakness GCV	Blood CMV IgM+, blood CMV IgG+	Bilateral interstitial infiltrates/ X-ray	Cured, AZA stopped	Yes
Papadakis et al, 2001[24]	1	M/51	CD (23 years)	Activity	CSA, 6-MP, steroids, 5-ASA (NR)	Fever, dyspnea, diarrhea G-CSF, GCV, trimethoprim, sulfamethoxazole, antibiotics	Blood CMV IgM+, bronchoscopic biopsies CMV+, CMV culture in BAL +	NR	Died, 6-MP stopped multisystem failure	No
Hookey et al, 2003[25]	1	F/19	CD (9 years)	Remission	6-MP (50 mg/d,18 months)	Fever, chills, cough GCV, immunoglobulins, corticosteroids	CMV culture in BAL+, CMV IHC in BAL+	Bilateral, diffuse, mixed air-space and interstitial appearance / X-ray	Cured,6-MP stopped	No
Sato et al, 2007[26]	1	M/77	UC (6 months)	Activity	Steroids and 5-ASA (NR, 3 years); AZA (NR, 19 months)	High fever, dyspnea, diarrhea GCV	Blood CMV PP65 +, lung and colon autospies CMV+	Ground glass appearance of both lungs/ X-ray and CT	Died, respiratory failure, and severe anemia	No
Piton et al, 2008[27]	1	F/18	UC (2 years)	Activity	5-ASA (NR, 2 years), steroids (NR, 15 days), CSA (NR,3 days)	Fever, diarrhea, dysphagia, abdominal pain GCV	Blood CMV pp65 +, blood CMV IgM +, blood CMV IgG+, blood CMV DNA + CMV inclusion in BAL +	Interstitial pneumonia/ X-ray	Cured, steroids tapered; CSA reduced	No
de Boer et al, 2008[28]	1	F/26	CD (16 years)	Remission	AZA (100mg/d, 10 years) and 5-ASA (1500mg/d, 10 years), steroids (NR)	Fever, myalgia, cough, and diarrhea Aminopenicillin, aminoglycoside	Blood CMV IgM+, blood CMV IgG+	Bilateral pneumonia/CT	Cured, AZA and 5-ASA stopped	No
Wolschke et al, 2010[29]	1	F/28	CD (11 years)	Remission	AZA (NR, 2 years)	Fever, dyspnea, cough CSA, GCV, prednisone, etoposide	BAL CMV DNA+, blood CMV DNA+	Bilateral pleural effusion infiltrates /CT	Cured, stopping AZA not reported	Yes

Presti et al, 2011[30]	1	F/32	CD (6 years)	Remission	AZA (2.2mg/kg/day, 8 months)	Fever methylprednisolone, GCV, valganciclovir	Blood CMV DNA +	Bilateral infiltrates/ X-ray	Cured, AZA stopped	Yes
van Langenberg et al, 2011[31]	2	F/35	UC (NR)	Remission	AZA (100mg/d, 2 years)	Fever, cough, lethargy, GCV, hydrocortisone	Blood/ bronchial CMV IgM + Blood/ bronchial CMV DNA +	Bilateral consolidation/ X-ray	Cured, AZA stopped	Yes
		M/28	CD (NR)		AZA (150mg/d, 2 years)	Fevers, sore throat, fatigue, GCV		Bilateral, patchy alveolar opacification/ CT		
N'Guyen et al, 2011[32]	1	F/38	CD (NR)	Remission	AZA (NR, 2 years)	Fever GCV, valganciclovir, foscarnet, polyvalent, immunoglobulins	Blood CMV IgM+, Blood CMV IgG+, BAL CMV DNA +	Bilateral involvement	Died, died during emergency surgery for necrotic gastric ulcers	Yes
Abbey et al, 2014[33]	1	M/51	CD (8 years)	Remission	AZA (NR, 5 years)	Shortness of breath, dyspnoea, and fever GCV	Blood CMV IgM+, blood CMV DNA+, CMV respiratory culture +	Small bilateral pleural effusions and bilateral basal lung consolidation/ CT	Cured, AZA stopped	No
Stack et al, 2016[34]	1	F/35	CD (3 years)	Remission	AZA (200mg/d, 3 years)	Fever, tachycardia GCV	Blood CMV IgM +, blood CMV IgG +, blood CMV DNA +	Right upper lobe lesion/ x-ray	Cured, AZA stopped	No
Divithotawela et al, 2016[35]	1	F/44	UC (NR)	Remission	AZA (150 mg/d, NR) and mesalazine (4.8 g/d, NR)	Fever, headache, delirium, and dyspnea GCV, vancomycin, meropenem, oral doxycycline, oseltamivir, CMV immunoglobulin, methylprednisolone, and anakinra	Blood CMV DNA+, BAL CMV DNA +	Bilateral consolidation/ CT	Cured, AZA stopped	Yes
Vakkalagadda et al, 2017[36]	1	F/59	UC (NR)	Remission	AZA and mesalamine (NR)	Fever, sore throat, and worsening shortness of breath GCV, GSF	Blood CMV IgM +, BAL CMV DNA +	Bilateral diffuse ground glass lung opacities /CT	Cured, AZA stopped	Yes

(*Continued*)

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Table 1 (Continued).

Study	Number of the Patient	Sex/ Age	Disease Type/ Duration	Disease Activity of IBD	Previous Medication	Symptoms and Treatment	CMV Diagnosis	Radiological Findings	Outcome	HLH
Cockbain et al, 2019[37]	1	M/50	UC (5 years)/ HIV (16 years)	Remission	Mesalazine and AZA (100 mg/d, NR)	Fever, sore throat, diarrhea GCV, corticosteroid	Blood CMV DNA +	Widespread bilateral interstitial changes / X-ray/CT	Cured, AZA stopped	Yes
Hawthorne et al, 2021[38]	1	F/27	CD (9 years)	Remission	AZA (75mg/d, 9 years)	Fever, tachycardia antibiotics, GCV, cotrimoxazole	Blood CMV IgG +, blood CMV IgM +	Bilateral ground glass opacification involving all lung fields/CT	Cured, AZA stopped	No
Voet et al, 2021[39]	1	F/28	CD (NR)	Remission	AZA (NR, 4 years)	Fever, diarrhea, cough, and visual disturbances GCV, valganciclovir	Blood CMV DNA + blood CMV IgG +, blood CMV IgM +	Lymphangitis / CT	Cured, AZA stopped	No

Abbreviations: 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; AZA, azathioprine; BAL, bronchoalveolar lavage; CD, Crohn's Disease; CSA, cyclosporin A; CMV, Cytomegalovirus; F, female; G-CSF, granulocyte colony-stimulating factor; GCV, ganciclovir; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; IHC, immunohistochemistry; M, male; UC, ulcerative colitis; NR, not reported.

substantially enhancing diagnostic accuracy. Radiographic findings indicated pulmonary lesions manifesting as bilateral interstitial infiltrates (78%), ground-glass opacity (17%), and consolidation (17%). As for the treatment regimen, ganciclovir was administered to nearly all patients (94%) immediately after the diagnosis of CMVP, only one patient recovered in the absence of antiviral treatment. The average course of antiviral therapy was 22 days (5–42 days). Concurrent immunosuppressive therapy (100%) was either tapered (glucocorticoid) or discontinued (AZA,6-MP, or CsA). Notably, half of the patients (50%) developed complications from Hemophagocytic Lymphohistiocytosis (HLH). Regrettably, the mortality rate was 17%, with three patients succumbing to organ failure.

Discussion

Patients with Inflammatory Bowel Disease (IBD) present an increased susceptibility to Cytomegalovirus (CMV) infection, with 45 to 100% of IBD patients harboring latent CMV infections.[40] It is widely acknowledged that immunologic dysregulation plays a significant role in the pathogenesis of IBD,[41] thus predisposing these patients to opportunistic infections such as CMV, either via primary infection or reactivation of latent virus under immunocompromised states.

Despite the heterogeneous immunotypes associated with different IBD subtypes, it remains uncertain whether these variations influence the incidence of CMV Pneumonia (CMVP). The present study indicates that Crohn's Disease (CD) is the subtype most frequently associated with CMVP, aligning with a prior systematic review.[18] This review involved 13 IBD patients, out of which 10 were diagnosed with CD concurrent with CMVP. This trend may be attributed to the increased odds of CD patients to immunosuppressive therapy. Existing epidemiological data reveal that approximately 76.6% of Ulcerative Colitis (UC) patients experience a mild to moderate disease course.[42] As such, 5-aminosalicylic acid (5-ASA) serves as the first-line treatment for this patient group, exerting no significant impact on immunity.[43] Meta-analyses have corroborated the safety and efficacy of 5-ASA in mitigating the risk of CMV reactivation,[44] which may explain the lower incidence of CMVP among UC patients.

Nevertheless, contradictory evidence exists in the literature. For instance, Romkens et al suggested that UC patients might exhibit a higher susceptibility to CMV-associated infections and intestinal diseases than those with CD.[19] CMV reactivation in these patients is often facilitated by compromised intestinal immune barriers and immunosuppression.[45] From an immunological perspective, UC is associated with increased production of pro-inflammatory cytokines in response to gut microbes.[46] It is well-documented that CMV activation occurs in monocytes and dendritic cells under the influence of TNF and IFN.[47] Consequently, interactions between CMV and inflammation exacerbate intestinal damage.[48] These observations necessitate further research to elucidate the underlying mechanisms.

The prevailing evidence suggests that CMVP predominantly transpires during the remission phase in IBD patients, an observation that aligns with prior studies.[18,49] Interestingly, intestinal inflammation does not appear to be related to the risk of CMVP onset. Notably, a significantly elevated incidence of CMVP was identified in patients with inactive IBD who were under thiopurine monotherapy, suggesting that advanced immunosuppression is a primary driver of increased CMVP incidence.[50]

Clinically, CMVP primarily affects the lung interstitium. Radiological signs of CMVP can often be atypical, encompassing a spectrum from diffuse interstitial infiltrates and ground-glass opacities to small nodules or a crazy-paving pattern on computed tomography.[51,52] Pulmonary pathology in IBD patients lacks consensus and has been ascribed to drug toxicity, immune-related causes, or an obscure inflammatory association with gut disease. Nevertheless, it is crucial to bear in mind that authentic IBD-associated interstitial lung disease is infrequent. The history of drug usage should always be scrutinized in the management of IBD patients presenting with interstitial lung disease characteristics.[53] Certain medications, including sulfasalazine,[54] mesalamine,[54] thiopurines,[55] methotrexate,[56] as well as the biologic,[57,58] can induce lung injury if utilized for IBD treatment. Differentiating between lung disease stemming from IBD and that caused by medications remains a formidable challenge. Despite the difficulties in procuring pathological evidence of CMVP, a diagnosis typically necessitates the combination of positive CMV serostatus and viral DNA in blood and/or bronchoalveolar lavage samples. Lung biopsy may facilitate the direct detection of CMV infection via immunohistopathology.

CMVP symptoms can range from being asymptomatic to nonspecific, including manifestations such as dry cough, breathlessness, exertional dyspnea, and fevers.[59] Respiratory symptoms are typically insidious and progressive.[54] In the current study, prolonged fever emerged as the most prominent symptom. Intriguingly, in some instances, patients displayed no cough or respiratory symptoms, while bilateral basilar patchy/interstitial infiltrates predominantly appeared on chest radiographs. The presenting signs and symptoms of CMVP are usually nonspecific, often leading to delayed diagnosis due to their uncharacteristic nature. From our perspective, we assert that CMVP should be contemplated in the differential diagnosis for immunosuppressed patients presenting with fever and dyspnea. Further, more diagnostic modalities such as high-resolution lung CT and fiberoptic bronchoscopy should be deployed. Importantly, in the context of the ongoing COVID-19 pandemic, COVID-19 should be incorporated into the differential diagnosis as its clinical symptoms and imaging findings bear similarity to those of CMVP.[60]

Immunosuppression induced by medications paves the way for viral reactivation. Pharmaceuticals frequently employed in managing IBD, such as biological agents, glucocorticoids, and azathioprine, have been shown to maintain the body in a state of immune inhibition.[5] CMV disease can manifest when host immunity is compromised. It is widely accepted that recent exposure to corticosteroids or thiopurines, but not anti-TNF agents, constitutes a significant risk factor.[61] The protracted use of high-dose corticosteroid therapy elevates the risk of CMVP.[62] Studies have reported that steroids can stimulate the transcription of immediate-early (IE) genes while downregulating the activity of lymphocytes and monocytes, in parallel with CMV reactivation implicated in steroid resistance.[63] The potential mechanism encompasses a marked increase in pro-inflammatory cytokines and altered glucocorticoid receptor expression, which may exacerbate ulcerative colitis (UC). In contrast, combination therapies for IBD have been associated with a higher risk of severe infection, especially when corticosteroids are used in conjunction with TNF antagonists.[64] A greater prednisolone dosage (>32 mg/d) used in combination with immunosuppressants can potentially shorten the duration of CMV reactivation and serve as a predictor of CMVP.[65]

In this study, we discerned a strong correlation between thiopurines and CMV infection. The most frequently observed adverse effects of AZA/6-MP are opportunistic infections.[66] Although reports of CMV reactivation exist, a definitive causal relationship remains unestablished. Prior literature suggests that thiopurines augment the risk of viral infections[67] and severe systemic CMV infection when on immunosuppressive medication,[68] a scenario potentially attributable to thiopurine-induced lymphopenia.[69] Thiopurines may induce apoptosis of activated T-cells[70] and mitigate the T-cell response to infectious agents. For patients receiving thiopurine therapy, viral infections like cytomegalovirus, Epstein-Barr (EB) virus, and herpes simplex virus pose a significant concern.[71] A systematic review reported a worse prognosis in CMVP patients with IBD;[18] even a minimal dose of azathioprine could induce significant CMVP by facilitating sufficient immunosuppression, a phenomenon attributed to slow drug metabolism.[38] Consequently, in clinical practice, screening for thiopurine methyltransferase (TPMT) and Nudix hydrolase (NUDT15) genetic polymorphisms prior to initiating azathioprine can enhance patient therapeutic response while minimizing side effects.[72] Miechowiecki et al[73] described a case of acute CMV infection in a patient with Crohn's disease (CD) in remission under azathioprine therapy who recovered following antiviral and symptomatic therapy. This finding indicates that IBD patients undergoing long-term thiopurine therapy may be more vulnerable to severe CMV disease.

Recent studies have illuminated a decline in CMV infections among IBD patients, indicative of a transition from conventional corticosteroid-based therapies to more effective agents with desirable safety profiles and minimal side effects.[74] Biologic drugs have emerged as a prevalent and often essential therapeutic option in IBD management. Beyond TNF-α inhibitors, integrin receptor antagonists and IL-12 and IL-23 antagonists are comparably utilized.[75] Our review of the literature yielded no instances of CMVP related to biologics. The association between TNF-α inhibitors and CMV infections has not been systematically explored. However, it is recognized that TNF-α plays a vital role in controlling viral infection, eliciting CMV from latency to active infection, with the risk of CMV disease correlating with TNF-a levels.[76,77] Theoretically, TNF-blockade treatment could promote viral reactivation through TNF depletion.[77] Nevertheless, numerous instances have demonstrated that CMV activation remains unaffected by anti-TNF therapy.[78,79] Reports suggest that TNF-α inhibitors could mitigate CMV viral load via TNF-α reduction.[80] TNF-α inhibitors might also be effective in treating the underlying disease activity that accompanies inflammation-induced CMV replication in colon tissue.[81] Short-term infliximab treatment (<14w) exerts minimal influence on the risk of latent

CMV reactivation.[82] Therefore, TNF-α inhibitors like infliximab and adalimumab may be suitable for severe ulcerative colitis in the context of CMV infection.[44] Likewise, anti-TNF monotherapy has been linked with a lower risk of opportunistic viral infections compared to thiopurine monotherapy.[67]

Anti-integrin monoclonal antibodies, such as vedolizumab, are acknowledged to be efficacious in the treatment of IBD. Despite respiratory tract infections being the most common adverse events (AEs), there is no definitive evidence linking them to vedolizumab.[83,84] Generally, gut-selective mechanisms underpin its safety profile.[85,86] Vedolizumab demonstrates commendable biosafety during IBD flare-ups associated with CMV infection.[87,88] Hommel et al reported a patient with active UC and colonic CMV reactivation who, following treatment with ganciclovir and vedolizumab, achieved clinical remission and experienced a reduction in gut viral load.[89] In vivo, vedolizumab inhibits the recruitment of CMV-infected monocytes to the mucosa and modulates leukocyte trafficking.[90] Moreover, it can be safely administered to IBD patients with severe COVID-19 infections, further highlighting its robust safety.[91] However, one single-center clinical study noted a heightened risk of CMV reactivation in CMV seropositive UC patients administered vedolizumab compared to those receiving TNF-α inhibitors, yet the observation remained unelucidated.[92] Data on CMV infection and vedolizumab use are, to date, still scarce.

Ustekinumab, a fully human monoclonal antibody targeting interleukin-12/23p40, is deemed a cornerstone in inducing and maintaining remission in moderate to severe IBD patients. Long-term follow-up studies have corroborated the effectiveness and safety of ustekinumab in UC and CD patients.[93,94] Adverse effects are well-tolerated with ustekinumab, and its profile mirrors that of the placebo. The most frequently encountered adverse reactions include nasopharyngitis and upper respiratory tract infections.[94] Tuberculosis infections have not been reported. Discontinuation of ustekinumab in patients with pneumonia is not requisite.[95] Ustekinumab appears to be safe in situations of induced or exacerbated infection. Recently, Despotes et al described a CD patient with interstitial lung disease secondary to ustekinumab.[96] In this case, pneumonia was attributed to ustekinumab following the ruling out of infections. The patient's lung function recovered post high-dose steroid treatment. In summary, the safety of newer non-TNF-α biologics warrants more comprehensive scrutiny.

Hemophagocytic lymphohistiocytosis (HLH) represents a multisystem inflammatory syndrome induced by secondary immune disorders. The most frequent cause of secondary HLH is infection, with CMV and EBV infections being considered the most common triggers for HLH.[97] It has been documented that IBD is the most prevalent comorbidity (20 out of 35 cases) in CMV-associated HLH patients.[98] In our study, HLH was persistently observed in approximately half of the patient population, corroborating the argument that immunosuppressive treatments and immune-related comorbidities significantly escalate the risk. The high incidence of HLH could potentially explain the unfavorable prognosis of CMVP in patients suffering from IBD. Following antiviral treatment, most patients experienced favorable outcomes, evidenced by high survival rates, underscoring the cruciality of early diagnosis and intervention. Interestingly, we acknowledge recent reports concerning HLH induced by COVID-19, where even a mild COVID-19 infection could hyperactivate the immune response and trigger HLH.[99] In the era of COVID-19, HLH should be considered in patients presenting with signs of liver injury and high fever subsequent to COVID-19 infection.

The necessity of antiviral drugs for CMVP is a well-recognized concept, with first-line treatment typically involving the intravenous administration of ganciclovir or its prodrug, valganciclovir, for 2–3 weeks. Symptomatic disseminated viral infections, encompassing pneumonia, mandate antiviral therapy alongside the tapering of all immunosuppressants.[81] Given the severe impact of immunosuppression on systemic immunity in IBD patients, cessation of immunosuppressives, particularly azathioprine, warrants strong consideration, especially in cases where intestinal symptoms are not pronounced. Although TNF-α inhibitors exhibit a sound biosafety profile, the management of novel biological agents such as Vedolizumab and Ustekinumab remains an area of uncertainty, calling for additional research. Therefore, expedited treatment with ganciclovir coupled with the discontinuation of immunosuppressive therapy may enhance IBD symptomatology and avert complications and mortality in the majority of patients.

CMV infection imposes a considerable disease burden on immunocompromised individuals. Given the deleterious side effects and potential resistance encountered with antiviral agents, the use of neutralizing antibodies emerges as an appealing strategy for conferring protection, and as potential therapeutics and prophylactics against CMV.[100] There is a pressing need for an effective human CMV vaccine, which could substantially prevent CMV infection and associated

diseases, thereby mitigating numerous severe and disabling consequences, particularly in newborns and immunocompromised individuals.[101] As far back as the 1970s, efforts to develop HCMV vaccines commenced. Despite the absence of a licensed HCMV vaccine, trials persist.[102] Multiple candidate vaccines, including live-attenuated vaccines, chimeric peptidic vaccines, and recombinant subunit vaccines, have demonstrated favorable biosafety profiles and promising clinical results in trials.[103] Even though IBD patients have not been incorporated into clinical trials,[104] novel vaccine technologies, analogous to those effective against COVID-19, may facilitate the creation of a therapeutic vaccine against CMV, leading to improvements in the health of immunocompromised patients, inclusive of those with IBD.

Conclusion

In conclusion, cytomegalovirus pneumonia (CMVP) poses a grave complication in immunocompromised IBD patients undergoing thiopurine treatment, associated with elevated morbidity and mortality rates. Diagnosing CMVP in clinical settings proves arduous due to its potential to manifest with nonspecific clinical and radiological features akin to those of drug-induced or COVID-19 pneumonia. Hence, CMV infection should be contemplated as a differential diagnosis in IBD patients who exhibit respiratory symptoms. Prompt diagnosis and assertive antiviral intervention ameliorate the prognosis. Nevertheless, our understanding of CMV infection in the context of novel biological agents remains sparse, necessitating additional data and research to bridge this knowledge gap. This underscores the need for future research and could offer valuable insights for subsequent studies.

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Disclosure

The authors declare no conflicts of interest in this work.

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