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REVIEW ARTICLE

Coexisting cytomegalovirus infection in immunocompetent patients with *Clostridium difficile* colitis

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Abstract Cytomegalovirus (CMV) colitis usually occurs in immunocompromised patients with human immunodeficiency virus infection, organ transplantation, and malignancy receiving chemotherapy or ulcerative colitis receiving immunosuppressive agents. However, CMV colitis is increasingly recognized in immunocompetent hosts. Notably, CMV colitis coexisting with *Clostridium difficile* infection (CDI) in apparently healthy individuals has been published in recent years, which could result in high morbidity and mortality. CMV colitis is a rare but possible differential diagnosis in immunocompetent patients with abdominal pain, watery, or especially bloody diarrhea, which could be refractory to standard treatment for CDI. As a characteristic of CDI, however, pseudomembranous colitis may be only caused by CMV infection. Real-time CMV-polymerase chain reaction (PCR) for blood and stool samples may be a useful and noninvasive diagnostic strategy to identify CMV infection when treatment of CDI eventually fails to show significant benefits. Quantitative CMV-PCR in mucosal biopsies may increase the diagnostic yield of traditional histopathology. CMV colitis is potentially life-threatening if severe complications occur, such as sepsis secondary to colitis, massive colorectal bleeding, toxic megacolon, and colonic perforation, so that may necessitate preemptive antiviral treatment for those who are positive for CMV-PCR in blood and/or stool samples while pending histological diagnosis.

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Background

Cytomegalovirus (CMV) is a highly prevalent and globally distributed virus. CMV infection in healthy adults is usually asymptomatic or causes a mildly infectious mononucleosis-like syndrome. CMV then usually becomes dormant until reactivation in patients with severely immunocompromised status, who may potentially develop invasive CMV disease with a wide range of manifestations, most commonly colorectal infection with hemorrhagic ulceration. Two coexistent entities—CMV colitis and *Clostridium difficile* colitis—have usually been reported among immunocompromised patients, who have human immunodeficiency virus infection, organ transplantation, hematologic malignancy, solitary organ cancer, or inflammatory bowel disease receiving immunosuppressive agents.[1–9] For example, Florescu et al[8] reviewed nine patients who developed *C. difficile* and CMV colitis; among them, eight patients were immunocompromised: four transplant recipients, two oncology patients, one patient with advanced acquired immunodeficiency syndrome, and one on an immunosuppressive regimen for severe ulcerative colitis. Besides, CMV colitis can mimic or present as pseudomembranous colitis in immunocompromised patients.[10–14]

CMV gastrointestinal disease rarely occurs in immunocompetent patients and could resolve completely without the use of antiviral drugs, if the immunity is obtained.[15] In addition, CMV colitis is increasingly recognized in apparently immunocompetent patients in some immunomodulating conditions, such as elderly, pregnancy, chronic renal failure, coronary artery disease, ischemic heart disease, congestive heart failure, diabetes mellitus, steroid use, blood transfusion, and prolonged stay in the intensive care units (ICUs).[15–28] However, CMV colitis in these patients has often been neglected by clinical physicians.[28] Therefore, this review article will mainly focus on English literature of CMV colitis coexisting, following, or followed by *C. difficile* colitis among previously healthy or apparently immunocompetent adult patients. We will also review those cases of CMV colitis presenting as a sole cause of pseudomembranous colitis without *C. difficile* infection (CDI).

Epidemiology of CMV colitis in immunocompetent patients

One systemic review identified only 91 immunocompetent patients with gastrointestinal CMV infections for the period of 1950–2007.[25] Another literature review from 1980 to 2003 identified 44 immunocompetent patients with CMV colitis. Among them, spontaneous remission occurred in 31.8%, mostly individuals <55 years old.[21] In Korea, 51 immunocompetent patients with CMV colitis, including 11 ICU patients and 17.6% with spontaneous remission, were diagnosed at a tertiary care university hospital between January 1995 and February 2014.[23] In specific hospital ICU units, CMV colitis was diagnosed in 14 previously immunocompetent ICU patients at a teaching hospital in Brazil from January 2000 to March 2013.[27] While in Taiwan, with intention to diagnosis, CMV colitis was detected in 18 ICU patients at a teaching hospital from January 2011 through June 2013.[28] Among them, three patients had malignancy. The biopsy-proven diagnosis was made for eight patients. Other probable cases were diagnosed based on clinical symptoms with detection of blood CMV DNA plus either colonoscopic findings or detection of CMV DNA in stool samples.[28] Traditionally, CMV colitis was easily neglected and underdiagnosed in ICU patients with chronic critical illness, particularly with chronic renal failure.[23,27,28]

Epidemiology of *C. difficile* colitis

Diseases caused by *C. difficile* range from mild diarrhea to potentially life-threatening pseudomembranous colitis. CDIs occur primarily in hospitalized patients with risk factors such as concomitant or recent use of antibiotics.[29] The colonization rate of *C. difficile* in adult hospitalized patients shows geographic variation, ranging from 4.4% to 23.2%.[30] The hypervirulent *C. difficile* strains such as the epidemic clone (027/NAP1/BI) has partly contributed to change the CDI epidemiology to worldwide dissemination.[31] In particular, elderly patients in surgical wards and ICUs are at significant risk of developing CDI.[32] After 2006, a 47% increase in the rate of CDI was noted in the USA.[33] In a cohort of hospitalized older adults in Michigan, impaired functional status was an independent risk factor for severe CDI.[34] In one study in Korea between January 2007 and July 2012, 55% of colitis in elderly people in long-term care facilities was caused by CDI, whereas nonspecific colitis was most common (63%) in elderly people in local communities.[35] Diagnosis of CDI is based on the identification of *C. difficile* toxins A and B in diarrheal stool. First-line antibiotics for CDI treatment are metronidazole and vancomycin.[36] Fidaxomicin, a macrolide antibiotic, has been shown to be significantly effective in treating CDI compared with vancomycin.[37] For recurrence and relapse of CDI, rifaximin and tigecycline have yielded some positive outcomes against *C. difficile*.[38] Fecal microbiota transplant is an alternative therapy for CDI that is effective and promising in multiple CDI recurrences.[39]

Coexisting CMV and *C. difficile* colitis

A history of cytomegalovirus infection has been recognized as one of the significant risk factors for *C. difficile* colonization.[30,40] Adult patients colonized with toxigenic *C. difficile* were prone to the subsequent development of *C. difficile*-associated diarrhea.[30] Critically ill patients and elderly patients are at an increased risk of developing diarrheal illness like CDI and CMV colitis. Literature of coexisting CMV and *C. difficile* colitis have been reported in immunocompetent patients, mostly in the years after 2010 (Table 1), implying that effective alerts are increasing to current physicians. Presenting symptoms of both diseases included fever, diarrhea, gastrointestinal bleeding, and abdominal pain, with predominance of severe watery diarrhea for CD, and bloody stool and occasional massive bleeding for CMV colitis. Both may cause toxic megacolon and bowel perforation, leading to a poor prognosis.[51] However, we propose that the clinical features of colitis caused by both etiologies could vary with the following scenarios (Table 1).

Table 1 The clinical features of cytomegalovirus colitis coexisting, following, or mimicking Clostridium difficile colitis in the immunocompetent patients.

Case	Age/sex	Diarrhea	Diagnosis modality positive for		Time lag of 2nd diagnosis	Therapy	Outcome	Y of reference
			CDI	CMV colitis				
CMV colitis coexisting CDI with refractory pseudomembranous colitis								
1	78/F	Bloody	Stool toxin[a]	Colon biopsy[b] Immunostain[c]	>3 wk	Me,V, Fi, S, G, TC	Recovery	2012[41]
2	82/M	Bloody	Stool toxin[a]	Colon biopsy[b] Immunostain[c] CMV-PCR(1)[d]	3 d	Me, G, Vg	Recovery	2014[28]
3	53	Watery	Stool toxin[a]	CMV-IgM[b] Colon biopsy[c]	—	Me, V, R, S, G	Recovery	2014[42]
4	63/F	Watery	Stool toxin[a]	CMV-PCR(1)[b] Immunostain[c]	>7 d	Me, V, S, G	Recovery	2015[43]
CMV colitis coexisting CDI with refractory nonpseudomembranous colitis								
5	81/M	Bloody	Stool toxin[a]	Colon biopsy[b] CMV-PCR (1)[c]	—	Me, V, G	Recovery	2009[44]
6	37/F	Watery	Stool toxin[a]	Colon biopsy[b] Antigenemia[c]	>2 wk	Me, V, G, Fc	Recovery	2013[45]
7	85/M	Watery	Stool culture[a]	Colon biopsy[b] immunostain[c]	—	Me, V, G	Recovery	2014[46]
8	60/F	Bloody	Stool culture[a]	Immunostain[b] CMV-igm[c]	>10 d	Me, no antiviral	Recovery	2015[15]
9	90/M	Bloody	Stool toxin[a]	Colon biopsy[b] Immunostain[c]	14 d	M, G	Recovery	2015[47]
CMV colitis following successful therapy for CDI								
10	83/F	Some blood	Stool culture[a]	Colon biopsy[b] CMV-IgM[c]	—	V, G	Died[e]	1992[48]
11	74/F	Bloody	Stool toxin[a]	CMV-PCR (1)[b] 2nd colonoscopy-immunostain[c]	3 wk	Me, G	Died[f]	2014[28]
CMV colitis as a cause of pseudomembranous colitis without CDI								
12	63/M	—	Colonoscopy[a] and biopsy[b]	CMV-PCR(1–3)[c] Immunostain[d]	No time lag	V, no antiviral	Died[g]	2000[49]
13	29/M	Watery	Colonoscopic finding[a]	2nd colonoscopy with biopsy[b]	—	Me, G	Recovery	2011[50]
14	69/M	Watery	Colonoscopic finding[a]	CMV-PCR(1–2)[b] Immunostain[c]	9 d	Me, V, G	Died[h]	2014[28]

[e] Postmortem examination revealed severe pneumonia and inflamed colitis but without CMV inclusion bodies.
[f] Ganciclovir was delayed to commence 3 weeks after CMV diagnosis but was discontinued due to worsening leukopenia, and thus failed to give improvement.
[g] Postmortem examination revealed CMV myocarditis, pneumonitis, and colitis.
[h] Patient had symptomatic improvement of CMV colitis but died due to other comorbidities.
CDI = *Clostridium difficile* infection; CMV = cytomegalovirus; colon biopsy = histopathological findings of colonic mucosa with hematoxylin and eosin stain; F = female; Fc = foscarnet; Fi = fidaxomicin; G = ganciclovir; IgM = immunoglobulin M; immunostain = CMV immunohistochemical staining; M = male; Me = metronidazole; PCR = polymerase chain reaction for samples of (1) = blood, (2) = stool, and (3) = mucosal biopsies; R = rifaximin; S = stool microbiota transplant; stool toxin = *Clostridium difficile* toxin assay for stool sample; TC = total colectomy; V = vancomycin; Vg = valganciclovir.
[a,b,c,d] Sequential order of positive diagnosis modalities.

CDI with refractory pseudomembranous colitis

CDI with pseudomembranous colitis unresponsive to metronidazole and vancomycin therapy may need fecal transplantation to overcome the severe colitis. However, concomitant CMV colitis may partly contribute the refractory course and necessity simultaneous ganciclovir therapy to completely resolve the colitis.[42] We previously reported an 82-year-old man who had coexistent CMV and CDI-associated pseudomembranous colitis (Figure 1).[28] Moreover, Kurtz and Morgan[41] reported an immunocompetent elderly woman with CDI, which was unresponsive to metronidazole, vancomycin, fidaxomicin, and stool transplant due to concomitant CMV colitis. We also reported a case of toxic megacolon leading to respiratory failure, which developed after therapy with metronidazole, vancomycin, and fecal microbiota transplants for CDI-associated pseudomembranous colitis. An immunostaining study was performed on the initial colon mucosal biopsy and it confirmed concomitant CMV colitis with CDI.[43]

CDI with refractory colorectal ulcers or diffuse colitis without pseudomembranes

Nonimmunosuppressed patients with prolonged ICU stay due to chronic critical illness are at a high risk for both CDI and CMV colitis. Of the two diagnoses, CMV is likely missed

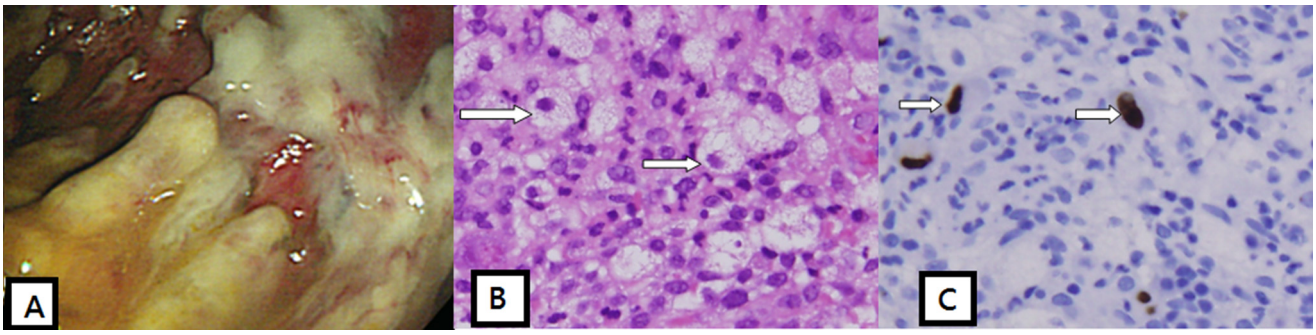

Figure 1. Colonoscopic findings showing: (A) pseudomembranous colitis; (B) colon mucosal biopsy showing enlarged atypical lymphocytes with eosinophilic inclusion bodies (arrow); and (C) positive for cytomegalovirus immunostaining (arrow). The results of blood cytomegalovirus-polymerase chain reaction and stool *Clostridium* toxin assay were both positive.

more often because a biopsy or immunostaining is required to confirm the diagnosis, while CDI can be diagnosed based on noninvasive fecal *C. difficile* toxin assay.[8] Many clinicians would only treat CDI for a patient with severe diarrhea and positive *C. difficile* toxin in the stool.

Concomitant CDI and CMV colitis may sometimes manifest with diffuse colitis without pseudomembranes, which was refractory to first-line antibiotics for CDI treatment.[15,44–47] For example, Harano et al[15] reported a 60-year-old immunocompetent woman who presented with abdominal pain and bloody diarrhea due to colorectal erosion and ulceration with positive stool isolate of *C. difficile*. Administration of metronidazole did not improve her symptoms. Endoscopic biopsy with immunostaining revealed CMV colitis. Hung et al[46] reported CMV colitis with the presentation of watery diarrhea and stool culture positive for *C. difficile*, but diarrhea persisted despite oral metronidazole and vancomycin therapy. Chen et al[47] presented a 90-year-old, critically ill, immunocompetent patient, who had multiple refractory *C. difficile*-infected ulcers in the sigmoid colon and biopsy confirmed CMV colitis. This scenario was similar to a patient of lower lip squamous cell carcinoma who had diffuse pancolitis unresponsive to metronidazole, vancomycin enemas, and later fidaxomicin, even though his stool *C. difficile* toxin became negative conversion. At this point, the CMV polymerase chain reaction (PCR) in his stool and blood were positive, and pre-emptive therapy with valganciclovir resulted in rapid clinical response and uneventful recovery.[9]

CMV colitis following successful therapy for CDI

Persistent diarrhea or relapse of intestinal symptoms after appropriate antimicrobial therapy for CDI may not necessarily indicate ineffective therapy for refractory course of CDI. Jawad[48] reported a patient with diarrhea and her stool culture was positive for *C. difficile*. Oral vancomycin rendered her stool negative but some bloody diarrhea occurred due to sequential CMV colitis. We previously reported a patient who had a therapeutic response to initial *C. difficile*—associated pseudomembranous colitis but the symptoms relapsed 3 weeks later due to the emergence of CMV-associated colon ulceration.[28] This scenario might be related to the reactivation of latent CMV infection in conditions of immunomodulation caused by pseudomembranous colitis.

CDI following successful therapy for CMV colitis

This rare scenario was reported in an elderly patient with adult T-cell leukemia lymphoma, who developed CMV colitis on Day 5 of chemotherapy. After 2 weeks of successful ganciclovir therapy, the patient developed diarrhea again with CDI-associated pseudomembranous colitis instead of CMV colitis. At that time, CMV antigenemia and a histologic study for CMV were negative.[2]

CMV colitis as a cause of pseudomembranous colitis without CDI

In addition to manifesting with solitary ulcer, multiple ulcers, diffuse colitis, and polypoid lesions, occasionally CMV colitis may present with pseudomembranes, leading to a misdiagnosis as CDI-associated pseudomembranous colitis.[26,52] This scenario should be considered particularly when *C. difficile* toxin assays or cultures are negative.[49,50] We previously described a patient who had CMV-associated pseudomembranous colitis (Figure 2), as the result of the *Clostridium* toxin assay was negative and the patient experienced a poor response to oral metronidazole therapy.[28]

Current diagnosis and treatment of CMV colitis

Historically, the diagnostic gold standard for CMV colitis is the direct histopathological identification of the Cowdry owl eye inclusion bodies in colonic biopsies or the use of immunohistochemistry (IHC) staining. Although CMV antigenemia and blood CMV-PCR showed low sensitivity (<50%) for diagnosing CMV colitis, the specificity values were high (>80%).[53] In the presence of significant colon ulcers, however, the sensitivity of CMV antigenemia or PCR for diagnosing CMV colitis rose to 67.3%.[53] Real time PCR for CMV DNA quantification in the blood and stool as well as in the colonic biopsy is currently considered as a useful diagnostic tool.[54] The accuracy of these diagnostic modalities compared with the diagnostic gold standard are summarized in Table 2.

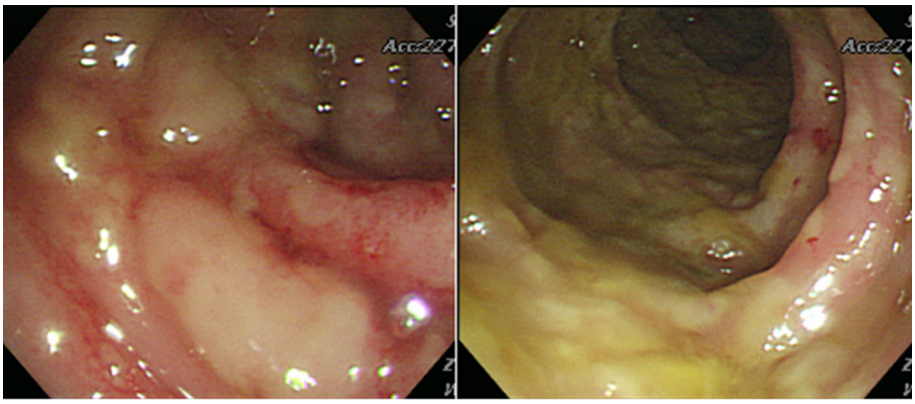

Figure 2. Colonoscopic finding is showing colitis with pseudomembranes. The cytomegalovirus-polymerase chain reaction for blood and stool were positive. The stool *Clostridium* toxin assay was negative. The histopathological findings were consistent with pseudomembranous colitis but immunostains confirmed cytomegalovirus colitis (not shown).

CMV-PCR in colonic mucosal biopsies

Yoshino et al[55] reported that quantitative real-time PCR (qPCR) for detecting CMV infection in inflamed colonic mucosa is useful for accurate diagnosis of CMV infection. Mills et al[56] reported that CMV DNA was detected by PCR in 90.9% (30/33) of IHC-positive and 14.5% (8/55) of IHC-negative mucosal biopsies, respectively. Their study indicated that CMV-PCR in gastrointestinal mucosal biopsies complements IHC and has the potential to identify additional patients who may benefit from anti-CMV therapy. McCoy et al[57] further reported that qPCR is highly sensitive and specific to aid in the early diagnosis of CMV infection on equivocal gastrointestinal biopsies. The mean value of CMV DNA load in gastrointestinal biopsies was 3845 copies/μg total DNA (range, 15—15,500 copies/μg total DNA). However, the cutoff values for diagnosis of CMV colitis were not determined.[61]

It should be highlighted that negative histopathological findings of small colonic mucosal biopsies could not definitively exclude the diagnosis of CMV colitis. Theoretically, multiple biopsy specimens from longitudinal ulcers or diffuse colitis combined with qPCR in mucosal biopsies could increase the diagnostic yield of CMV colitis, especially in those patients known for positive CMV-PCR for blood and/or stool samples.

CMV real-time PCR for blood samples

Quantification of plasma CMV DNA by real-time PCR is a noninvasive method of aiding diagnosis and can be used to monitor the treatment of CMV infection in immunocompetent patients.[20,62] Concordance between plasma real-time PCR and the pp65 antigenemia assay was 82.2%.[63] However, plasma real-time PCR is more sensitive than the antigenemia assay for monitoring active CMV infection.[63,64] However, blood CMV-PCR stands for CMV reactivation, and further direct evidences of CMV colitis by other diagnostic tools are required.

CMV real-time PCR for fecal samples

Michel et al[58] first adopted CMV-PCR for stool specimens as a diagnostic tool for patients with suspected CMV colitis.

Table 2 The diagnostic test evaluation of new diagnostic modalities for cytomegalovirus colitis or digestive tract infections.

CMV diagnostic modalities	Gold standard	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
Antigenemia in UC patients[53]	Histopathology	47.0	81.7	59.1	73.0
PCR for blood in UC patients[53]	Histopathology	44.3	87.9	67.3	73.6
Real-time (qPCR) in colon mucosal biopsies[55]	Histopathology	100	50.0	23.5	100
Real-time (qPCR) in digestive mucosal biopsies[56]	Histopathology	90.9	85.5	79.0	94.0
Real-time (qPCR) in digestive mucosal biopsies[57]	Histopathology	96.7	98.7	98.9	96.3
PCR for stool[58]	Histopathology	100	94.1	80.0	100
PCR for stool[59]	PCR in colon mucosal biopsies	83.3	93.3	83.3	93.3
Real-time (qPCR) for stool[60]	Histopathology	66.7	95.7	80.0	91.8

CMV = cytomegalovirus; qPCR = quantitative polymerase chain reaction; UC = ulcerative colitis.

They concluded that the absence of CMV DNA in stool samples may prove useful in ruling out CMV-related colitis. Thereafter, Boom et al[65] quantified CMV DNA loads in clinical fecal specimens to monitor the efficacy of antiviral treatment. In a small pilot study, the sensitivity, specificity, and accuracy of the PCR-based stool test for detection of CMV DNA compared with PCR-based detection of CMV in mucosal biopsies were 83%, 93%, and 90%, respectively.[59] We also found qualitative CMV-PCR for stool samples helpful in aiding the diagnosis of CMV colitis.[28] In a recent study from Germany, quantitative CMV real-time PCR in fecal samples was positive in eight out of 12 patients of CMV intestinal disease (sensitivity, 67%), and was negative in the non-CMV group (45/47), indicating a good specificity of 96%.[60] Therefore, negative CMV PCR results from fecal samples cannot exclude CMV intestinal disease, whereas positive fecal PCR results could facilitate an earlier detection of ongoing CMV infections and might help to circumvent invasive biopsy via endoscopy. Otherwise, fecal PCR may guide a pre-emptive therapy for life-threatening conditions, such as massive colonic bleeding, when a conclusive histopathological proof of CMV infection is not yet available.[28]

Strategy for diagnosis and controversy in treatment of CMV colitis

The development of abdominal pain, fever, watery diarrhea, and bleeding stool in a critically ill patient should prompt the clinician to consider the diagnosis of CMV and CDI-associated colitis. Diagnostic strategy could be designed as follows.

If standard stool pathogens and *C. difficile* toxin studies are nondiagnostic, endoscopic evaluation and CMV-PCR for blood and stool samples should be obtained. Quantitative CMV-PCR in mucosal biopsies seems to be a useful tool for diagnosis when combined with blood/stool PCR and endoscopic findings. In another way, if the results of stool *C. difficile* toxin assay are positive, the possibility of coexistent or sequential CMV colitis should not be neglected. For those patients with a diagnosis of *Clostridium* colitis but who are unresponsive or partially responsive to therapy with metronidazole and/or vancomycin, and especially if CMV-PCR for blood and/or stool samples was positive, then re-evaluation of the initial colon mucosal biopsies using qPCR for CMV would be helpful.

It is possible that complete resolution of colonic ulceration could be spontaneously achieved without use of antiviral drugs in some immunocompromised or immunocompetent patients with CMV colitis.[15,21,23] However, if CMV infection is confirmed, ganciclovir therapy should be initiated without delay in critically ill patients to avoid severe complications of colorectal massive bleeding and perforation. Most of the reported cases of CMV colitis coexisting or following CDI as well as presenting as pseudomembranous colitis had good clinical outcomes under appropriate medical therapy (Table 1). If bowel perforation occurs, prompt surgical resection is indicated.[66]

Conclusion

Currently, CMV colitis is increasingly recognized in immunocompetent patients, manifesting with symptoms similar to or consistent with CDI-associated pseudomembranous colitis. CMV colitis most commonly presents with bloody stool in chronic status of critically ill patients with immunomodulating comorbidities, whereas *C. difficile* may produce severe watery diarrhea in those exposed to broad spectrum antibiotics. Coexisting CMV in the apparently CDI-associated colitis could correspond to intractable colorectal symptoms. If CMV-PCR for blood and stool samples were positive, endoscopic biopsy with immunostaining of mucosal specimens is a definitive procedure for diagnosing CMV colitis, even in a case of pseudomembranous colitis or a case positive for fecal *C. difficile* toxin assay. In cases of coexisting CMV and *C. difficile* colitis, ganciclovir therapy for CMV colitis in time may circumvent the unnecessary second-line therapeutic method or fecal transplantation for CDI, supposing that persistent diarrhea was not due to treatment failure for *C. difficile*.

Conflicts of interest

All contributing authors declare no financial interests related to the material in the manuscript.

Ethical consent

The figures cited in the current review were approved by the institutional review board of Chi Mei Medical Center, Tainan, Taiwan (no. 10207-005).

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