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Review Article

Factors Associated with Cytomegalovirus (CMV) Procto-Colitis in Immunocompetent Adults: A Systematic Review

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ABSTRACT

Objective: The pathophysiology of CMV procto-colitis in immunocompetent adults is poorly understood. We aimed to systematically review the literature to explore factors, presenting symptoms and endoscopy findings associated with CMV procto-colitis in immunocompetent adults.

Methods: Following PRISMA guidelines, we conducted a narrative systematic review by searching MEDLINE, EMBASE, EMCARE and CINAHL for manuscripts published up to August 2023. One author screened manuscript abstracts; two authors independently conducted a full text review. We included manuscripts which included primary data of immunocompetent adults with CMV procto-colitis except case reports. Quality and risk of bias was assessed independently by two authors using the Joanna Briggs institute critical appraisal tools.

Results: 8 manuscripts were included in the final review from the USA (n=2), China (n=2), Korea (n=2), India (n=1) and Brazil (n=1) and consisted of 6 case series, one case-control study and one cross-sectional study published between 1988-2022. We identified demographic and behavioural factors (older age, lower BMI, receptive anal sex), infection factors (urinary tract infections, shigellosis, Hepatitis C, COVID-19, sepsis, antimicrobial use), medical conditions (cardiovascular disease, respiratory disease, renal disease, auto-immune disease, diabetes) and hospitalisation factors (intensive care admission, longer length of hospital stay) associated with CMV procto-colitis in immunocompetent adults. Patients presented with rectal bleeding, diarrhoea, melaena, fever, nausea/vomiting, abdominal pain/bloating and constipation. Large bowel endoscopy findings were ulcers, erosions, and erythema and polyp/mass lesions.

Conclusion: We have highlighted factors, presenting symptoms and endoscopy findings associated with CMV procto-colitis in immunocompetent patients which provides insight for clinical guideline development and future research.

Keywords: Cytomegalovirus, CMV, Immunocompetent, non-immunocompromised, colitis, proctitis, gastrointestinal

INTRODUCTION

Cytomegalovirus (CMV) is a member of the herpes virus family which can cause a mononucleosis like-illness and has a high serology prevalence of 60-100% in most communities [1, 2]. Transmission occurs in a bimodal peak, the first peak in infancy likely related to placental transmission and horizontal spread amongst infants, and the second peak in young adulthood related to kissing and sexual transmission [3]. Following initial infection, CMV becomes latent and reactivation is well described in immunocompromised individuals such as those with advanced HIV infection, solid organ transplant, haematological and other malignancies, and undergoing chemotherapy and other immunosuppressants [3-8]. Reactivation can result in end organ disease including the retina, liver, lungs, central nervous system and gastrointestinal system [9]. Community seroprevalence indicates reactivation is usually the likely source of end-organ disease, although primary infection may contribute to a minority of cases [10].

Diagnosis of CMV procto-colitis is made by observation of viral inclusions on hematoxylin and eosin (H&E) staining of colonic/rectal mucosa histology, or immunohistochemistry staining. However H&E staining has a lower sensitivity (84%) and may be missed due to sampling error, for example due to a small histology specimen, while immunohistochemistry staining is the gold standard with higher sensitivity and specificity but requires clinicians to have a high degree of suspicion of CMV in order to request the appropriate investigation [11, 12]. Recent advances in PCR technology has made this available for the detection of CMV in histological samples however there is controversy about its use particularly regarding availability of fresh samples versus formalin-fixed, paraffin embedded tissue samples, and the potential for false-positive results given the high sensitivity and residual CMV DNA in tissue lymphocytes especially where there is inflammation [13].

Main Points:

We have explored and highlighted demographic and behavioural factors (older age, lower BMI, receptive anal sex), infection factors (urinary tract infections, shigellosis, Hepatitis C, COVID-19, sepsis, antimicrobial use), medical conditions (cardiovascular disease, respiratory disease, renal disease, auto-immune disease, diabetes) and hospitalisation factors (intensive care admission, longer length of hospital stay) and presenting symptoms and large bowel endoscopy findings associated with CMV procto-colitis in immunocompetent adults.

Severe manifestations of reactivated CMV in immunocompetent patients have been shown to be more common than previously believed, including the gastrointestinal tract (colitis), the central nervous system (meningitis, encephalitis, transverse myelitis), haematological disorders (haemolytic anaemia, thrombocytopenia, thrombosis of the venous or arterial vascular system), ocular involvement (uveitis), and lung disease (pneumonitis) [9]. CMV procto-colitis is well described in association with inflammatory bowel disease (IBD) [14]. Reactivation of CMV can be associated with flares in IBD, and is associated with older age, shorter IBD duration and pancolitis [14-16].

While CMV procto-colitis may be rare in immunocompetent adults, its sequelae can be severe requiring antiviral therapy and can be fatal [17]. The aim of this systematic review was to explore any factors including presenting symptoms and colonoscopy findings associated with CMV proctocolitis in immunocompetent adults to provide insights into the pathophysiology and inform future guidelines and research.

MATERIALS AND METHOD

Search Strategy and Selection

A systematic review of the literature was conducted in September 2023 using PRISMA guidelines to explore any factors associated with CMV in immunocompetent adults. We searched four bibliographic databases (MEDLINE, EMBASE and EMCARE via the Ovid interface; CINALH via the EBSCO host interface) to identify eligible manuscripts using the following search terms: (Cytomegalovirus OR CMV) AND (immunocompetent OR non-immunodeficient OR non-immunocompromised OR non-immunosuppressed OR nonimmunodeficient OR nonimmunocompromised OR nonimmunosuppressed) AND (proctitis OR colitis OR proctocolitis OR procto-colitis OR GI infection OR gastrointestinal). Manuscripts meeting the following criteria were included in our review: participants were immunocompetent, had a diagnosis of procto-colitis caused by CMV diagnosed using either immunohistochemistry staining or typical owl's eye and intracytoplasmic CMV inclusions on hematoxylin and eosin staining. We only included manuscripts written in English language, containing primary data where at least one variable (either observed or comparable) with Cytomegalovirus was explored and publication date was not

restricted. As we primarily wanted to explore factors associated with proctocolitis, we excluded manuscripts which reported the whole gastrointestinal tract where data on rectal infection could not be extracted separately, and participant populations under the age of 16. For the purposes of this study, we defined immune-suppressed as either living with HIV infection, solid organ transplant, haematological and other malignancies, and undergoing chemotherapy and other immunosuppressant or bone marrow suppressant therapy, or any genetic disorder causing immunosuppression. Where manuscripts contained mixed populations of immunocompetent and immunocompromised, we only extracted and analysed data from immunocompetent individuals. Manuscripts were excluded if the authors had included data on patients with solid organ transplants, haematological malignancies, on immunosuppressive therapy (such as chemotherapy), or were living with HIV. Manuscripts reporting on all other conditions were included. All types of study where primary data were reported were included except for case reports which were excluded due to their inherent bias and inherent inability to control for confounding factors. Conference abstracts, editorials, conference posters, review articles, opinion articles and grey literature were excluded due to their lack of peer review.

A staged process was used for screening and selection of manuscripts for the final review. Each record from the initial search of citations was imported into Rayyan software and duplicate citations were removed. Manuscripts abstracts were screened by the primary researcher (TB) and then full text manuscripts were then assessed for eligibility independently by the primary researcher (TB) and an associate researcher (KL). Any discrepancies were discussed (TB, KL and DR) for a final decision regarding eligibility.

Quality Assessment, Risk of Bias Assessment and Data Synthesis

Quality assessment and risk of bias was assessed for each manuscript independently by the primary researcher (TB) and the associate researcher (KL) using the Joanna Briggs Institute (JBI) critical appraisal checklists [18]. The final manuscripts were graded and marked either include, exclude or seek further information. Any discrepancies or manuscripts not reaching quality assessment threshold was discussed collectively (by TB, KL and DR) for a final decision. We synthesized and tabulated narrative data from the manuscripts. The review protocol was registered on PROSPERO (CRD42023455014).

RESULTS

The initial search identified 1001 citations, 336 duplicate citations were removed, 665 abstracts were screened for eligibility and 476 were excluded. We assessed 22 full text manuscripts for eligibility and 14 manuscripts were excluded. In total, 8 manuscripts were included in the final review [19-26] (Figure 1). Risk of bias was determined to be low in 4 manuscripts, moderate in 1 manuscript and high in 3 manuscripts. (Supplementary table 1) The manuscripts were from the USA (n=2), China (n=2), Korea (n=2), India (n=1) and Brazil (n=1) and included were 6 case series, one case control study and one cross sectional study published between 1988 and 2022 (Table 1). In total, there were 165 patients with CMV procto-colitis.

Demographic and Behavioural Factors

We found that CMV procto-colitis was associated with increasing age, lower body mass index and receptive anal intercourse [19, 24, 25] (Table 2).

Infection Factors

We found that infection (including urinary tract infection, shigellosis, hepatitis C, COVID-19, sepsis) and preceding anti-biotic use was associated with CMV procto-colitis [19, 21, 23, 24].

Medical Conditions

Our review has identified the following medical problems associated with CMV procto-colitis: cardiovascular (including coronary disease, cardiomyopathy, cerebrovascular disease and hypertension), respiratory disease (including pneumonia, COPD, pulmonary hypertension), renal disease (including acute/chronic renal impairment and dialysis), autoimmune disease (including rheumatological), sepsis and diabetes mellitus [19-26].

Symptoms

Patients with CMV procto-colitis presented with: rectal bleeding, diarrhoea and melaena, fever, nausea/vomiting, abdominal pain/bloating and constipation [19-26].

Colonoscopy Findings

Where lower bowel endoscopy was reported, patients with CMV procto-colitis were found to have: ulcers (including deep, superficial and serpiginous), erosions, erythema, colitis (including pseudomembranous) and mass-like lesions [19-22, 24, 26].

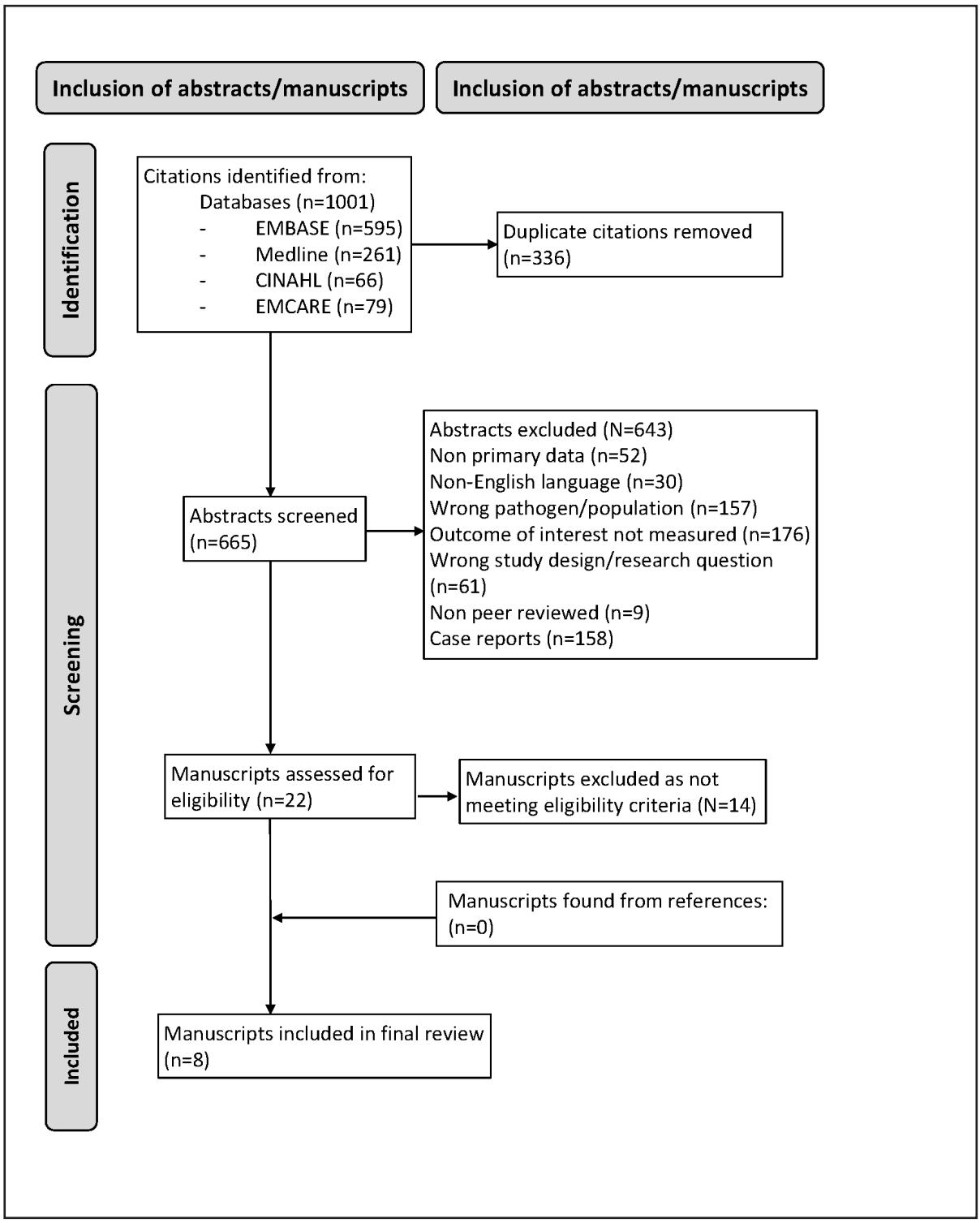

Figure 1. Flow chart of study selection for inclusion in the systematic review.

Table 1. Study design and risk factors associated with CMV procto-colitis in immunocompetent adults.

Manuscript	Study characteristics		Population	CMV testing	Factors associated with CMV in immunocompetent adults
Surawicz et al 1988, USA.[20]	Case series	Reported cases of CMV-procto-colitis	n=3 Aged 37 (female), 25 (male) and 71 (female)	Histology	**Behaviour:** receptive anal sexual intercourse Factors: erythema nodosum, urinary tract infection **Symptoms:** diarrhoea, rectal bleeding, constipation, fever **Endoscopy:** friable mucosa, mucosal erosion, serpiginous ulceration, cobble-stoning
Ng et al., 1999, China.[22]	Case series	CMV procto-colitis cases from 2 hospital pathology databases	n=10, Median age 70	Histology	**Factors:** *Shigella* dysentery, acute myocardial infarction, Psuedomonas/enterococcus pyelonephritis, gastric ulcer, HSV oesophagitis, cerebral infarction, hyperosmolar diabetic coma **Symptoms:** rectal bleeding, fever, diarrhoea, constipation **Endoscopy:** ulcers, erosion, polyp/growth, erythema
Klauber et al., 1998, USA.[21]	Case series	Reported cases of CMV procto-colitis	n=2 Aged 85 and 67 (male)	Histology	**Factors:** respiratory disease, sepsis **Symptoms:** diarrhoea, fever, rectal bleeding, abdominal pain, bloating **Endoscopy:** ulcer, erosions, erythema
Seo et al., 2012, Korea.[23]	Case series	Reported cases of CMV procto-colitis	n=12, Median age 66	Histology	**Factors:** diabetes mellitus, chronic renal failure, ischaemic heart disease. **Symptoms:** had GI bleeding, diarrhoea **Endoscopy:** ulcers
Siciliano et al., 2014, Brazil.[24]	Case series	Reported cases of CMV procto-colitis admitted to an intensive care unit	n=14, Median age 64	Histology	**Factors:** Hypertension, cardiomyopathy, congestive heart failure, pulmonary hypertension, chronic renal failure, diabetes mellitus, hepatitis C, autoimmune disease, chronic obstructive pulmonary disease, septic or cardiogenic shock, mechanical ventilation, vasoactive drugs, pneumonia, *Clostridium* colitis, acute renal injury, urinary tract infection **Symptoms:** rectal bleeding, diarrhoea, fever, nausea/vomiting, meleana, abdominal distension
Ko et al., 2015, Korea.[25]	Case control	Immunocompetent adults presenting with CMV procto-colitis and non CMV procto-colitis.	51 CMV-colitis patients, matched with 102 non-CMV-colitis. Mean age of cases =65 years	Histology & PCR	**Factors:** lower body mass index (p=0.45), requiring ICU care (p<0.001) renal disease (p=0.037), renal disease or hemodialysis (p=0.003), neurological disease (p=0.013), rheumatologic disease (p=0.021), antibiotic use (p<0.01), H2/PPI use (p<0.001). **Symptoms:** diarrhoea (45%), rectal bleeding (51%), fever (16%), abdominal pain (16%), melaena (8%), nausea/vomiting (6%) **Endoscopy:** ulcer (88%), erosion (37%), mass-like lesion (4%)

Le et al., 2017, Taiwan.[26]	Cross-sectional	immunocompetent and immunodeficiency cases of CMV procto-colitis from a pathology database.	69 CMV-colitis patients, 42 (61%) immunocompetent (mean age 64 years) and 27 (40%) immunocompromised	Histology	**Factors:** (compared with immunosuppressed patients with CMV colitis) age (older) (p=0.009), requiring ICU care (p=0.023), longer (days of) hospital stay (0.023), coronary artery disease (p=0.019), hypertension (p=0.01), **Symptoms:** melaena (52%), diarrhoea (36%), pain (29%), fever (41%).
Verma et al., 2022, India.[27]	Case series	Reported cases of CMV procto-colitis	n=4, Median age 54	Histology	**Factors:** diabetes mellitus, hypertension, COVID-19 **Symptoms:** diarrhoea (including bloody), abdominal pain **Endoscopy:** multiple ulcers (superficial and deep)

Table 2. Risk factors associated with CMV procto-colitis in immunocompetent adults

Demographic & behavioural factors	Older age Low body mass index Receptive anal sex
Infection factors	Urinary tract infection (including pyelonephritis) Shigellosis Hepatitis C COVID-19 Antimicrobial use Sepsis
Medical conditions	Cardiovascular (including coronary disease, cardiomyopathy, cerebrovascular disease and hypertension) Respiratory disease (including pneumonia, COPD, pulmonary hypertension) Renal disease (including acute/chronic renal impairment and dialysis) Autoimmune disease (including rheumatological) Diabetes Mellitus
Hospitalistation factors	Require intensive care unit admission Longer length of hospital stay (compared with immunosuppressed patients)
Presenting symptoms	Rectal bleeding Diarrhoea and melaena Fever Nausea/vomiting Abdominal pain/bloating Constipation
Endoscopy findings	Ulcer Erosion Erythema Polyp/mass

Hospitalisation Factors

We found that patients in our review with CMV procto-colitis frequently required intensive care unit admission and experienced longer length of stay in hospital (compared with immunosuppressed patients with CMV procto-colitis) [24, 25].

Although we were unable to estimate the pooled prevalence of factors in this review due to the nature of the manuscripts, broadly the prevalence of cardiovascular disease (excluding hypertension) was 22%, renal disease 28%, hypertension 29% and diabetes mellitus 28%. We were unable to establish the number of individuals with CMV proctocolitis in this review without risk factors.

DISCUSSION

Although it is well established that immunocompromised hosts can experience severe CMV disease including procto-colitis, the effects of CMV in immunocompetent patients is less understood. Characterizing the predisposing factors, presenting symptoms and endoscopic findings may improve the diagnosis, clinical guidelines and provide focus for future research. In this review, we have CMV procto-colitis in immunocompetent adults is associated with demographic and behavioural factors (including older age and lower BMI, receptive anal sexual intercourse), infection factors (including urinary tract infection, shigellosis, hepatitis C, COVID-19, sepsis and antibiotic use), medical conditions (including cardiovascular, respiratory, renal disease, autoimmune disease and diabetes) and hospitalisation factors (including requiring intensive care unit admission and increased hospital length of stay). We have also demonstrated that patients with CMV procto-colitis present with rectal bleeding, diarrhoea and melaena, fever, nausea/vomiting, abdominal pain/bloating and constipation. Colonoscopy findings describe ulcers, non-specific erosions, erythaema and polyp/mass like lesions.

We have shown that increasing age and having a low BMI is associated with CMV procto-colitis in immunocompetent adults: extremes of BMI and increasing age are well recognised to be associated with an increased risk of infection [27, 28]. It is interesting that immunocompetent individuals with CMV procto-colitis experience longer hospital length of stay and are more likely to require an ICU admission including compared with patients with immunodeficiency [24, 25]. There are several possible explanations for this including the presence of co-morbidity in immunocompetent people described in this review, compared to those with immunodeficiency, and selection bias for people with severe immunodeficiency where ICU may not be appropriate. This finding may also represent delays in diagnosis of CMV proctocolitis in immunocompetent patients. Sexual transmission of CMV is less well understood compared to other herpes viruses [29]. Although this review considers CMV procto-colitis to be a predominantly reactivation phenomenon, it may be that some cases are due to acute infection in the colon/rectum from sexual transmission. We were unable to explore this further in this review as no studies considered serological markers of CMV in their cases to delineate acute infection from reactivation. Mono and multiple infections of Herpes simplex viruses, *Treponema pallidum, Chlamydia trachomatis, Neisseria gonorrhoeae* and more recently Mpox are well described causes of an acute proctitis, mainly amongst men who have sex with men [30-32].

The colon is the most frequently affected end organ in CMV in immunocompetent adults and co-involvement with other organ systems (e.g. haematological) is rare [17]. The mortality of gastrointestinal CMV in immunocompetent adults is higher in those with diabetes and other medical conditions affecting immune responses (diabetes mellitus, renal disease, pregnancy and non haematological malignancy) [17]. TNF-α, IL-6 and INF-γ are increased in patients with acute and chronic inflammatory conditions for example: inflammatory bowel disease, renal disease, rheumatological disease, cardiovascular disease, respiratory disease, liver disease and infection including sepsis [33]. An increase in cytokines has been shown to promote the reactivation of CMV [17]. We suggest that the findings of this review provide further evidence that immunocompetent patients with acute or chronic inflammatory disease, including cardiovascular disease and renal disease are at risk of (reactivated) CMV procto-colitis.

Patients presenting with rectal and bowel symptoms including change of bowel habit, bleeding, unexplained diarrhoea, abdominal discomfort, and mass lesions require investigation for malignancy or inflammatory bowel disease. This review suggests that patients with the described risk factors of inflammatory disease should also be investigated for CMV procto-colitis even in the absence of immunodeficiency. In this review we have described the findings of lower bowel endoscopy namely ulcers, erosions, erythema, colitis and mass-like lesions which although may have a wide differential diagnosis, should further prompt clinicians to investigate CMV disease.

Limitations

There are several limitations to this review including having a small number of manuscripts and a small overall number of participants from mostly high-income settings. Although we decided a-priori to exclude case reports this review consisted of relative low-quality case series and a medium quality cross-sectional study and case control study making overall interpretation of the results challenging. There is likely to be significant reporting bias due to the complex nature of diagnostics required for CMV procto-colitis and many patients may experience missed opportunities for diagnosis. It is also likely that some important factors, presenting characteristics (including immunosuppressive states or treatment including corticosteroids) and endoscopic features were not reported accurately due to the nature of the manuscripts included in this review. This review focused on CMV procto-colitis, and manuscripts exploring CMV of the whole gastrointestinal tract where sufficient information about CMV procto-colitis could not be extracted were not included. Most manuscripts in this review used histology for the diagnosis of CMV procto-colitis (H&E staining or immunohistochemistry staining) which has limitations.

CONCLUSIONS

In summary, CMV procto-colitis presents some important diagnostic challenges and requires a high index of suspicion particularly in immunocompetent patients. Beyond traditional medical conditions known to cause immunodeficiency (e.g. advanced HIV), this review highlights the importance of considering pre-disposing pro-inflammatory medical conditions which may increase the susceptibility of immunocompetent patients to CMV disease and CMV procto-colitis. In any patient presenting with clinical deterioration and procto-colitis symptoms, it is important to ensure CMV is carefully considered during assessment. Further research exploring pro-inflammatory causes of reactivation of CMV in the rectum and colon of immunocompetent adults is needed.

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Supplementary material 1. Eligibility, quality and Risk of bias assessment

Authors	Year	Decision	Reason excluded	Risk of bias
Surawicz et al.	1988	Include		High
Cheung et al.	1993	Exclude	Case series of entire gastrointestinal tract	-
Klauber et al	1998	Include		High
Ng et al	1999	Include		Low
Crowley et al.	2002	Exclude	Case series included immunocompromised patients	-
Ng et al.	2003	Exclude	Case series included immunocompromised patients	-
Maiorana et al.	2003	Exclude	Case series of entire gastrointestinal tract	-
Chae et al	2010	Exclude	Case series of entire gastrointestinal tract	-
Agaimy et al	2011	Exclude	Case series included immunocompromised patients	-
Momin et al.	2011	Exclude	Case series where diagnosis was not confirmed with histology	-
Seo et al	2012	Include		Low
Siciliano et al.	2013	Include		Moderate
Ko et al.	2015	Include		Low
Ranjan et al	2015	Exclude	Case series included immunocompromised patients	-
Bernard et al.	2015	Exclude	Case series of entire gastrointestinal tract	-
Le et al.	2017	Include		Low
Kang et al	2018	Exclude	Cross sectional study of IBD patients	-
Chaemsupaphan et al.	2019	Exclude	Cohort study of entire gastrointestinal tract	-
Verma et al	2021	Include		High
Yoon et al.	2021	Exclude	Cross sectional study of entire gastrointestinal tract	-
Luangsirithanya et al.	2021	Exclude	Case series of entire gastrointestinal tract	-
Yeh et al.	2022	Exclude	Cross sectional study of entire gastrointestinal tract	-