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Cytomegalovirus Colitis and Subsequent New Diagnosis of Inflammatory Bowel Disease in an Immunocompetent Host: A Case Study and Literature Review

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 40
Final Diagnosis: CMV colitis
Symptoms: Abdominal pain • diarrhea • jaundice
Medication: —
Clinical Procedure: Flexible sigmoidoscopy • colonoscopy
Specialty: Family Medicine

Objective: Rare co-existance of disease or pathology

Background: Infection with gastrointestinal cytomegalovirus in an immunocompetent host is a rather rare occurrence in the literature. There are a few reports of gastrointestinal infection in the immunocompetent who are then subsequently given a new diagnosis of inflammatory bowel disease. It is speculated that the initial cytomegalovirus colitis infection triggers the onset of inflammatory bowel disease.

Case Report: Herein we report a case of cytomegalovirus colitis and new diagnosis of inflammatory bowel disease identified in a 40-year-old immunocompetent adult man who presented with gastrointestinal symptoms and disseminated cytomegalovirus infection requiring anti-viral therapy, which successfully treated the episode of cytomegalovirus infection. He then went on to have persistent symptomatic inflammatory bowel disease confirmed by pathology.

Conclusions: In this paper we will review the literature and explore the rare case of cytomegalovirus colitis in the immunocompetent host and discuss the pathology, physiology, diagnosis, and treatment of cytomegalovirus colitis.

MeSH Keywords: Colitis • Cytomegalovirus Infections • Inflammatory Bowel Diseases

Abbreviations: **ED** – emergency department; **IBD** – inflammatory bowel disease; **GI** – gastrointestinal; **CMV** – cytomegalovirus; **IgG** – immunoglobulin, G type; **IgM** – immunoglobulin, M type; **EIA** – enzyme immunoassay; **ELISA** – enzyme linked immuno-sorbent assay; **O+P** – ova and parasites; **Ag** – antigen; **Ab** – antibody; **H&E** – hematoxylin and eosin

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/898005

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Background

Gastrointestinal (GI) Cytomegalovirus (CMV) colitis requiring hospitalization and anti-viral therapy is an infrequent but familiar diagnosis. However, CMV colitis in the immunocompetent host with a resulting new diagnosis of Inflammatory Bowel Disease (IBD) is a relatively rare finding. A literature review from 1960–2016 yielded approximately of 33 case reports. Herein we will describe a case of CMV colitis in an immunocompetent host with a resulting new diagnosis of IBD. This is a diagnosis admitting hospitalists, primary care providers, and emergency providers should be familiar with.

Case Report

A 40-year-old man with no relevant past medical history presented to the ED with a one-week history of diarrhea with fevers to 38.7 degrees Celsius, bright red blood per rectum, light headedness, and dizziness for the past eleven days. Patient had a similar episode about seven months prior which resolved spontaneously after three weeks. He denies recent foreign travel or exposure to sick contacts.

On admission his physical examination was benign other than diffuse abdominal tenderness, mild jaundice, and blood on digital rectal exam. Labs revealed a transaminitis but negative viral hepatitis (Table 1). Computed tomography of the abdomen with oral and intravenous contrast showed nonspecific colitis.

Table 1. Relevant laboratory findings.

Observations	Normal	Day 1	Day 3	Day 6	Day 11	Day 14	Day 16	Day 37
AST (units/L)	15–40	158						21
ALT (units/L)	10–64	289						27
Alkaline phosphatase (units/L)	36–122	245						118
Bilirubin, total (mg/dL)	0.2–1.3	0.9						0.8
Albumin (g/dL)	3.5–5.2	3.3						3.3
Monospot	Negative		Negative					
Hepatitis panel*		Negative						
HIV 1/2 Elisa	Negative		Negative					
Hematocrit (%)	38–50	40						31
C Reactive Protein (mg/L)	0.10			185.4				
IBD serology 7**	Negative						IBD and Crohn's Predicted	
Herpes Simplex/Varicella Zoster fluorescent antibody stain from colon biopsy				Not Detected				
CMV monoclonal Ab stain from colon biopsy				Detected				
CMV quantitative PCR from serum (copies/mL)					3200			
Serum CMV IgG EIA	Negative					Positive		
Serum CMV IgM EIA	Negative					Positive		

* Hepatitis Panel: Hep B surface Ag, Hep B surface Ab, Hep B core Ab, HepA Ab, Hep A Ig, Hep C Ab; ** IBD Serology 7 Normal values: ASCA IgA Elisa <20 EU/mL, ASCA IgG Elisa <40 EU/mL, Anti-OmpC IgA Elisa <16.5 EU/mL, Anti-CBir1 Elisa <21 EU/mL, PANCA AutoAb Elisa <12.1 EU/mL, IFA Perinuclear pattern not detected, NDAse Sensitivty Not detected. IBD Serology 7 measured values: ASCA IgA Elisa 14.9 (negative), ASCA IgG Elisa 25.8 (negative), Anti-OmpC IgA Elisa 6.0 (negative), Anti CBir1 Elisa 8.2 (negative), pANCA AutoAb Elisa 19.3 (Positive), IFA Perinuclear pattern not detected, DNAse sensitivity not detected. Details can be found at *http://www.prometheuspatients.com/Products_Diagnostics.asp*.

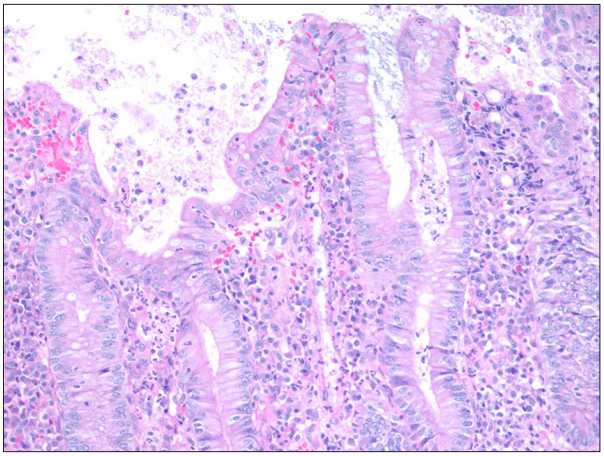

Figure 1. Medium power (100×) H&E: A representative medium power view demonstrating moderate mixed (acute and chronic) inflammatory infiltrate, acute cryptitis with crypt abscess formation, and crypt-architectural distortion.

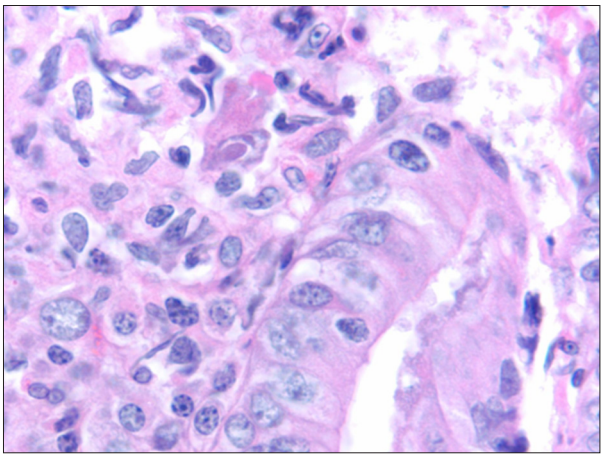

Figure 2. High power (400×) H&E: A representative high power view demonstrating typical intranuclear ("owl's eye") and intracytoplasmic (tiny eosinophillic globules) CMV inclusions.

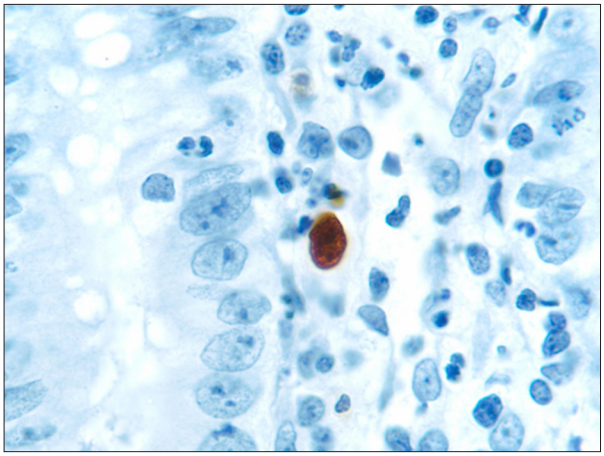

Figure 3. High power (400×) Immunohistochemical staining for CMV with hematoxylin counter-stain. A representative high power view demonstrating strong focal CMV immunoreactivity.

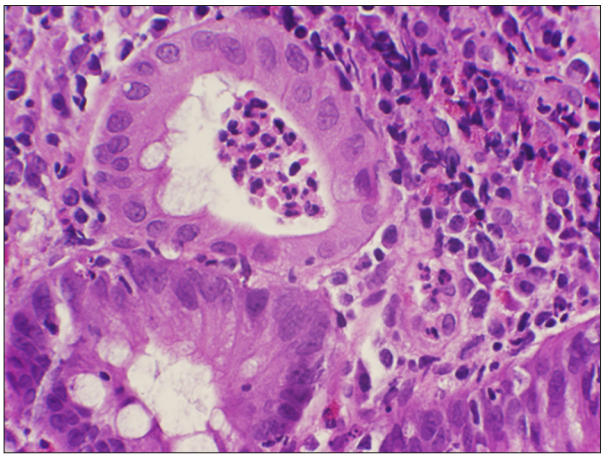

Figure 4. A representative image showing chronic active colitis with focal acute cryptitis, crypt abscess formation, reactive epithelial changes, and focal mild crypt architectural distortion consistent with inflammatory bowel disease (IBD).

He underwent a flexible sigmoidoscopy which showed diffuse inflammation and crypts along with gross blood. Given the clinical picture along with the findings on flexible sigmoidoscopy, CMV was suspected and pathology samples sent for testing. Once they returned positive, he was started on IV Ganciclovir.

Pathological samples from flexible sigmoidoscopy and colonoscopy demonstrated acute cryptitis with crypt abscess formation, characteristic of acute colitis. Some of the crypts were branched and others absent, evincing a previous bout of destruction and regeneration (crypt-architectural distortion). This finding is characteristic of idiopathic inflammatory bowel disease. Closer inspection of the lamina propria demonstrated the presence of characteristic intranuclear ("owl's eye") and intracytoplasmic (tiny eosinophillic globules) CMV inclusions. The presence of CMV inclusions was confirmed immunohistochemically (Figures 1–3).

Over the next few days the patient began to have a decrease in the frequency of bowel movements, remained afebrile, and was able to tolerate oral intake without nausea along with a positive trend in his labs, as seen in Table 1, and was thus discharged home. One month after discharge, a colonoscopy to assess bowel pathology demonstrated ongoing colitis from the rectum to the hepatic flexure and a normal appearing terminal ileum and ascending colon. Biopsies were consistent with Inflammatory Bowel Disease (Figure 4).

Discussion

CMV

Cytomegalovirus is a fairly ubiquitous virus with past exposure found in 40% to 100% of the general population per serology [1]. CMV is a member of the Herpesviridae family of DNA viruses which consist of the Epstein Barr virus (EBV), Herpes Simplex viruses 1–2, Human Herpes viruses 6–8, and Varicella Zoster. When replicating, the virus is shed and excreted in blood, saliva, respiratory secretions, semen, urine, and breast milk [2].

CMV can cause active disease and latent infection. CMV tends to remain dormant and non-replicative in endothelial cells, myeloid cells, and fibroblasts [3]. Studies of serology have shown a bimodal distribution of disease, with a peak in early childhood likely due to vertical transmission from the mother and horizontal transmission from daycares, and a peak in young adulthood likely from sexual and close contact and exchange of bodily fluids such as saliva and semen [1,4].

Active CMV infection (primary infection) is often asymptomatic but may present with an infectious mononucleosis-like syndrome based on the viral genotype [5,6]. Primary CMV infection often presents with fever, myalgia, mild transaminitis, cervical lymphadenopathy, and splenic enlargement, although the latter two are more common in EBV than CMV mononucleosis [1,7].

Symptomatic active CMV infection in adulthood is most often seen in the immunosuppressed (those on immune modulating drugs, immune modulating chemotherapy, AIDS, and transplant patients), and often has a poorer prognosis than infection at a younger age [8–10]. It is estimated that 40% of those with HIV/AIDS will eventually acquire life-threatening or ocular CMV if their CD4 counts drop below 50/μL [7]. Albeit rare, when CMV colitis affects immunocompetent hosts, it often presents with diarrhea, hematochezia, abdominal pain, tenesmus, fevers, anorexia, malaise, and weight loss [11].

Diagnosis of CMV colitis

The gold standard for diagnosing CMV colitis is the histological finding of large eosinophilic intranuclear inclusion bodies with surrounding halo and cytomegalic (enlarged) cells of 2–4× normal [1,12,13]. Up to 37.5% of patients have no histological findings [14]. If no findings are evident on H&E stain, immunohistological staining is suggested as it is more sensitive [1,15].

Endoscopic findings include patchy erythema, exudates, diffusely edematous mucosa with micro erosions and resulting deep ulcers [16]. Serum CMV DNA PCR has a quick turnaround time of 6–48 hours [3] with variable sensitivity alone, but greater than 80% concordance with antigen results as well [17,18]. Quantitative studies are more sensitive than qualitative studies [19]. IgM antibodies in the blood tend to have a sensitivity of 100% and specificity approaching 100% as well for active CMV infection [20]. IgM usually becomes positive one week after exposure and IgG 3-4 weeks after exposure [21]. Yet given the fact that up to 61% of individuals with CMV colitis may not have positive serologies [22], IgM and IgG must be analyzed along with the clinical situation.

CMV culture from blood was previously the gold standard for diagnosis but given a 1–3 week incubation time and sensitivities not nearly as high as PCR, it has lost popularity [20,23]. CMV stool DNA PCR may be more sensitive and organ specific, but at this point there are no specific studies to support its use [24].

CMV Colitis in the Immunocompetent Host

There have been few documented reports of CMV colitis in the immunocompetent and most clinician's knowledge is based on anecdotal experiences. Recently there was an excellent meta-analysis which reviewed the literature from 1983–2003 and found only 28 cases of CMV colitis in patients with no immune-modulating conditions [22]. Since this meta-analysis was published in 2005, there have been 5 reported cases (per search using Medline indexing keywords) of CMV colitis in immunocompetent hosts, most of which were in the elderly. The most recent case was published in 2012 [25–29].

In the meta-analysis it was found that amongst those with non-immune modulating comorbidities, the mean age was 70.2 years old, and most were women, with 55.6% of infections being community acquired and the remainder hospital acquired; 22.2% required colectomy and the group had a mortality rate of 22.2% (higher in men and mostly related to perioperative complications from their colectomies). In the group with no comorbidities, the mean age was a younger 37.4 years old and 100% community acquired. None had colectomies, and the mortality rate was 10%. None of the patients who died were below the age of 55 years [22].

CMV serology was available for only 38.6% of patients and only 13 were serum IgM positive. Thus, IgM alone is not a sensitive marker of active CMV colitis. Most cases were limited to the left colon hence making flexible sigmoidoscopy or complete colonoscopy appropriate diagnostic tools [22].

Most patients in the literature review were >55 years old with a mean age of 61.1years. Given the higher incidence of comorbidities in this age group and waning cellular and humoral immunity associated with age, the lack of mortalities in the <55 age group is understandable [22].

IBD and CMV

It is well known that individuals already possessing the diagnosis of IBD tend to have worsening of their disease when infected with CMV leading to colitis, as well as increasing the incidence of medication refractive IBD [30,31]. Interestingly, amongst the group <55 years of age, 41.7% (5) were subsequently given a new diagnosis of IBD after resolution of CMV colitis. Three were found to have ulcerative colitis, one Crohn's disease, and one indeterminate [22]. It is questionable whether CMV super infected already inflamed mucosa or if CMV infection triggered an immune hypersensitivity reaction leading to clinically and histopathologically evident IBD. CMV tends to avoid immune detection by blocking antigen presentation of MHC 1 and 2 proteins [32–34]. It is thought that MHC proteins (especially those of class 1) are up regulated and may thus lead to an autoimmune response causing subsequent IBD [11,35]. In this case, the patient was eventually also given a presumptive diagnosis of inflammatory bowel disease and was begun on appropriate management and therapy.

The authors of the meta-analysis thus concluded that CMV colitis resolved completely in those under 55. In the older groups, clinical variables such as comorbidities and severity of disease determined outcome [22]

Recommended treatment

For many, the infection may resolve on its own, thus the watch and wait strategy has been proposed as first line management in stable systemic CMV, with symptomatic management.

The currently agreed upon pharmacological treatment for systemic CMV is IV Ganciclovir, a nucleoside analog which is activated by the virus [3] It is begun at 5 mg/kg IV every 12 hours for two to three weeks, and up to four weeks in severe colitis. If patients are able to tolerate and absorb oral medications, IV is often changed to PO after five days [3]. Adverse effects to monitor for include myelotoxicity which occurs in up to 40% of the patients [1].

Case follow-up

The patient presented herein was unique in that he was immunocompetent without prior comorbidities or chemotherapy and was younger than the mean age of those similar cases described in the literature. It is likely that he had subclinical IBD and an initial flare 7 months ago. His subclinical IBD may have made him more susceptible to infection with CMV. A review of the initial pathology reveals that despite the presence of crypt abscesses and multiple inflammatory cells, there was a paucity of inclusion bodies, albeit present. If the CMV infection came prior to the IBD, the presence of inclusion bodies would have been more pronounced; that is, for CMV colitis to cause the symptoms described, the viral load would have likely been higher. Thus, the inflammation was likely due to IBD, with superimposed CMV systemic infection. Once the patient was treated with Ganciclovir the systemic CMV infection cleared but the patient remained symptomatic from his IBD. He was followed in clinic and, although his CMV colitis resolved, he continued to have symptomatic IBD over the next 6 months.

Conclusions

In sum, systemic CMV colitis most often affects the immunocompromised. It is rare in the immunocompetent but should be considered when more common etiologies have been ruled out. Isolated CMV colitis in the immunocompetent young patient tends to resolve with minimal complications and even spontaneous resolution in some cases; a few are left then with a diagnosis of IBD. There is an increased mortality in the elderly for numerous reasons including the higher prevalence of comorbidities. Therefore, it is crucial that CMV colitis be diagnosed in a timely manner to ensure adequate treatment and resolution of infection.

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Conflicts of interest

None.

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