Case report

Primary cytomegalovirus infection with invasive disease in a patient with inflammatory bowel disease

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SUMMARY

A 37-year-old woman with a history of inflammatory bowel disease on mercaptopurine presented with a week of recurrent fever, headache, myalgias and mildly elevated serum transaminases and leucopenia. Her workup revealed primary cytomegalovirus (CMV) infection with atypical lymphocytosis, elevated viral load, positive IgM and negative IgG. Two weeks after her initial presentation, she developed odynophagia and diarrhoea prompting endoscopic evaluation with biopsies, which demonstrated CMV disease of the gastrointestinal tract. Her fever and systemic symptoms improved rapidly with initiation of intravenous ganciclovir. She was transitioned to and maintained on oral valganciclovir until two and half months after discharge when her symptoms and lab abnormalities had fully subsided.

BACKGROUND

Cytomegalovirus (CMV), a member of the beta group of human herpesviruses, is a double stranded DNA virus with high seroprevalence (>50%) in the USA.¹ CMV disease can be either due to reactivation of latent infection or acquisition of primary CMV. Primary infection with CMV in immunocompetent hosts can be asymptomatic or present with a mononucleosis syndrome (fever, lymphadenopathy, leucopenia with atypical lymphocytosis).² Only very rarely is CMV infection in immunocompetent hosts severe. While the relationship between CMV reactivation and inflammatory bowel disease have been extensively studied, there is a paucity of information on primary CMV infection in inflammatory bowel disease (IBD) patients.^{3 4}

CASE PRESENTATION

A 37-year-old woman with a history of inflammatory bowel disease on 100 mg mercaptopurine daily presented with a week of recurrent fever to 39°C, headache, retro-orbital pain and pressure, and myalgias. These symptoms led to four visits to the emergency department during that week.

Regarding her inflammatory bowel disease, her disease was most consistent with ulcerative colitis, with a normal terminal ileum, no known extra-intestinal manifestations, and predominantly left-sided disease over the years, without skip lesions. She was diagnosed about 10 years prior to this presentation when she presented with bloody stools and diarrhoea. She was initially on infliximab for about a year. She was then on adalimumab and 6-mercaptopurine for around 6 years and was

eventually weaned to mercaptopurine as monotherapy, which was her regimen for the 4 years preceding this presentation. She had never required bowel surgeries.

On her initial presentation, she had leucocyturia (>100+ white blood cells on urinalysis) and was prescribed a 5-day course of nitrofurantoin to empirically treat possible urinary tract infection. The urine culture remained no growth and her symptoms persisted, so she returned. At this point her labs were notable for mild leucopenia (leucocyte of 2.6K) as well as mildly elevated transaminases (aspartate aminotransferase (AST) 47, alanine aminotransferase (ALT) 56). A detailed travel history revealed that she had travelled to Maine for a picnic 2 weeks prior to presentation (in early July). She was started on doxycycline empirically given concern for an arthropod-borne illness. Lyme screen, *Ehrlichia/Anaplasma* PCR, *Babesia* PCR, *Babesia* blood smear were sent and she was discharged home. When her symptoms persisted despite doxycycline, she came back 2 days later and was admitted for persistent fever of unknown origin.

Her most notable symptoms on admission included headache, fever, chills and night sweats. She had no respiratory, urinary or abdominal symptoms, including no vomiting or diarrhoea. She had no rashes or joint pain. She was febrile to 39.5°C on admission, tachycardic to 113 beats/min, with other vital signs within normal limits. On examination, she was non-toxic appearing. She had no meningeal signs, no focal neurological signs, intact mental status, no lymphadenopathy, benign cardiac, pulmonary and abdominal exams, no notable joint effusions/tenderness or rashes.

INVESTIGATIONS

Her peripheral blood tick-borne illness workup returned negative, including for Lyme screen, *Ehrlichia/Anaplasma* PCR, and *Babesia* PCR and smear. Her blood work showed a leucocyte count of 4.53, AST/ALT 99/113, alkaline phosphatase 71, total bilirubin 1.8, direct bilirubin 0.4. Blood cultures had been repeatedly negative since her initial presentation. A CT abdomen/pelvis showed no evidence of active colitis, including normal bowel wall thickness. A lumbar puncture was performed on admission in light of her headache and fever (day 8 of her presentation). The

colony stimulating factor (CSF) cell counts and chemistries showed no nucleated cells, a normal glucose of 70 and a normal total protein of 28. CSF

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Table 1 Summary of key lab values during the patient's course

Day of presentation	1	5	8	9	10	12	14	15*	26	49
<i>Patient hospitalised</i>										
Maximum temperature (°C)	38.8	38.4	39.5	38.2	39.5	39.5	38.9	39.6	AF	AF
Leucocyte (normal 4–10x10 ⁹ /L)	3.60	2.62	4.53	3.33	3.43	5.18	5.75	5.70	4.62	3.71
Atypical lymphocytes (normal 0%)					4%	6%	15%	5%		
Haemoglobin (normal 115–164 g/L)	133	129	133	131	119	121	124	115	132	132
Platelets (normal 150–450x10 ⁹ /L)	249	185	204	204	185	222	296	293	368	328
AST (normal 10–50 U/L)	27	47	99	130	156	223	202	170	68	37
ALT (normal 10–50 U/L)	36	56	113	147	168	244	237	189	59	39
Alkaline phosphatase (normal 35–130 U/L)	44	54	71	59	55	70	95	97	78	58
Total bilirubin (normal 0.0–1.0 mg/dL)	1.2	1.6	1.8	1.1	0.8	0.9	0.8	0.8	0.5	1.5
Direct bilirubin (normal 0.0–0.3 mg/dL)	0.2	0.3	0.4	0.2	0.2	0.3	0.3	0.2		0.3
CMV viral load (IU/mL)				2291				23 847	502	UD†
Blood cultures	Neg (x2)	Neg (x2)	Neg (x2)			Neg (x2)				
Antibiotics	Nitrofurantoin (days 1–5)	Doxycycline (days 5–12)								

*Started on intravenous ganciclovir.

†Undetectable.

AF, afebrile; CMV, cytomegalovirus.

culture remained negative. Additional CSF studies for West Nile virus PCR and Lyme disease PCR were both negative.

Given her persistent fever with leucopenia and elevated transaminases, a viral work up was obtained that was notable for negative fourth generation HIV antibody/antigen test and negative EBV serum viral load, but elevated CMV serum viral load of 2291 IU/mL (hospital day 2). CMV serology subsequently

revealed a positive IgM and negative IgG, supporting a diagnosis of primary CMV infection. Her transaminases peaked at 244/223 for ALT/AST, respectively on day 5 of her hospital admission and she also developed atypical lymphocytosis that peaked at 15% on hospital day 7. [Table 1](#) provides detailed summary of key lab findings during her course. Of note, the source of the patient's CMV was unclear but she had two children (ages 5 and 9) who had not been sick prior to her presentation: the 9-year-old child had recently finished an academic year in elementary school and the 5-year-old child stayed at home and was not enrolled in preschool.

While in the hospital she also developed odynophagia and abdominal cramping with diarrhoea which prompted repeating CMV viral load and gastroenterology consult for endoscopic evaluations. CMV viral load was 23 847 IU/mL on hospital day 8 and she underwent oesophagogastroduodenoscopy and flexible sigmoidoscopy that day, too. She was found to have active oesophagitis with ulcerations involving at least 75% of oesophageal circumference with no bleeding, diffusely erythematous mucosa in the stomach and duodenal bulb and loss of vascularity and some ulcerations from rectum to descending colon (see [figure 1](#)). Biopsies showed severe CMV oesophagitis and colitis with ulcerations and intranuclear inclusions (see [figure 2](#)). Rare CMV infected cells were also seen in the duodenal bulb but not in the stomach. Immunohistochemical staining for *Helicobacter pylori* was negative. Her rectal biopsies showed moderate chronic active colitis. An ophthalmological examination revealed no signs of CMV retinitis.

Figure 1 . Photographs from endoscopic evaluation of patient. (1) Oesophageal ulcerations, (2) and (3) erythematous mucosa in gastric body and duodenal bulb, respectively, and (4) loss of normal vascularity and small ulcerations involving the rectum.

Figure 2 Severe cytomegalovirus (CMV) esophagitis and colitis. Luminal surface at top of image in (A), (C). Severe oesophagitis with ulceration involving surface of tissue fragment (A, asterisks), and CMV-infected cell (B, arrow). Severe colitis with ulceration (C, asterisks), and intranuclear inclusion (D, arrow). Magnification: 200× (A), (C); 1000× (B), (D).

TREATMENT

The patient's mercaptopurine was held from the day of admission. She was started on intravenous ganciclovir 5 mg/kg every 12 hours on hospital day 8 (following her endoscopic findings and increasing transaminases) and was transitioned to oral valganciclovir 900 mg two times per day when she was discharged on hospital day 12 (day 19 of presentation).

OUTCOME AND FOLLOW-UP

After starting CMV therapy her fever rapidly abated. Her CMV viral load returned at <137 IU/mL 2 weeks after her discharge and became undetectable the following week. Her AST and ALT were 41 and 56, respectively 3 weeks after her discharge. When she was seen in infectious diseases clinic a month after her discharge, she reported improved tolerance for oral intake and resolution of fever, headache and fatigue. A couple weeks later she developed increasing stool frequency with some blood and mucus along with new lower abdominal pain, resembling previous flares of her IBD. Since her recent endoscopic evaluation showed active colitis she did not undergo a repeat colonoscopy and was started back on mercaptopurine along with vedolizumab. This humanised monoclonal antibody is a relatively new agent for IBD that seems to act more specifically in the gut than some other biological agents used for IBD.⁵ There is emerging data on the relative risks of opportunistic infections associated with various immunosuppressive regimens used for IBD. Some but not all studies have suggested that vedolizumab as monotherapy may have lower rates of infectious complications compared with tumour necrosis factor (TNF) antagonists.^{6,7} In one study vedolizumab decreased response to an orally administered vaccine but not to an intramuscular vaccine.⁸ After additional consideration, her mercaptopurine was stopped since thiopurines confer an excess risk of opportunistic viral infections; at least one study showed this risk is higher with thiopurines compared with TNF antagonists.⁹ Steroids were considered but she responded quickly to her new regimen and by 4 weeks after initiation of her regimen she was having two-to-three loose, non-bloody stools each day. At 3 months after starting vedolizumab she was having

normal bowel movements. Her next colonoscopy was around 6 months later and showed just mild focal active colitis in her rectum. Her valganciclovir was stopped two and half months after discharge given the resolution of her symptoms and lab abnormalities.

DISCUSSION

We present a case of primary CMV infection in a patient with inflammatory bowel disease of the colon. CMV disease is most commonly described in heavily immunosuppressed patients including in patients with advanced AIDS or after stem cell or solid organ transplantation. CMV disease has occasionally been described in patients without known immunosuppression.^{10,11} The patient described here had a chronic inflammatory disease and was on modest immunosuppressive drugs that impaired her immune system function.

CMV infection in the IBD population has been studied in the setting of worsening colitis.^{4,12} The association between CMV infection and IBD continues to be explored; it has been estimated that between 4.5% and 16.6% of IBD patients have CMV reactivation in their colon.³ A cross-sectional, prospective study found that compared with non-IBD patients who underwent colonoscopy for non-inflammatory indications, patients with IBD had over a 20-fold increase in the probability of having CMV genome detected in their colon samples (32.9% vs 2.4%, OR 20.14, 95% CI 2.66 to 157.06, $p < 0.0001$).¹³ Mechanistically, it has been shown that CMV replication can be induced in allogeneically stimulated monocytes-derived macrophages, indicating the predilection for CMV disease to occur within inflamed tissues.¹⁴ The effect of CMV diagnosis on prognosis of IBD patients was explored in a retrospective study that compared IBD exacerbations in those with or without a diagnosis of CMV. Patients with CMV had a higher chance of undergoing colectomy as their treatment (29% vs 11.2%, $p = 0.007$); but there was no difference in overall mortality.¹⁵ In addition, a prospective study that included hospitalised ulcerative colitis patients requiring intravenous steroid treatment found that pretreatment CMV viral load on biopsy predicted resistance to immunosuppressive therapy.¹⁶ CMV detection in a colonic specimen does not necessarily indicate CMV disease and instead may only indicate shedding, especially in the absence of macroscopic ulcerations and consistent clinical symptoms.¹⁷ While there is no standard definition for classifying CMV disease in IBD patients, the definitions used in the transplant infectious diseases community can be helpful and include: (1) a clinical syndrome consistent with CMV; (2) macroscopic mucosal lesions (ulcerations); and (3) demonstration of CMV on pathology or culture of tissue.¹⁸ For IBD patients, gastrointestinal (GI) symptoms alone may be from IBD or CMV. The patient here had CMV viremia and CMV detected by immunohistochemical staining at multiple sites of her GI tract consistent with invasive disease, macroscopic ulcerations (including areas outside her IBD-affected left colon) and a syndrome consistent with CMV (including fever and leucopenia). She also had a positive CMV IgM antibody and a negative IgG antibody consistent with primary infection. Altogether we felt this fit the criteria for CMV disease.¹⁸

Primary CMV disease in patients with IBD is not widely described. A retrospective review by Rowan *et al* studied primary CMV in IBD patients.¹⁹ They identified eight patients who were all on a thiopurine immunomodulator. Presentations of the disease included neutropenia, abnormal liver function test and intestinal involvement. Consistent with this study, our patient had systemic involvement with liver, intestinal and blood count

abnormalities. Her initial presenting symptoms were constitutional, including fever and myalgias, instead of colonic. This case along with the aforementioned retrospective study points to the possibility that the frequency of primary CMV infection involving multiple organ systems in IBD patients on immunomodulators such as thiopurines may be currently under-recognised.

The possibility of antibiotic related fever and drug induced liver injury was considered in this patient. This was felt less likely since the fever and leucopenia were present on the patient's initial presentation (prior to administration of antibiotics) and since the fevers persisted after cessation of doxycycline (and until anti-CMV therapy was initiated).

Although this patient's initial presentation did not involve GI tract symptoms, during her admission she subsequently developed symptoms and was found to have tissue-invasive disease. CMV infection is commonly considered as a part of the differential diagnosis in patients presenting with IBD flare symptoms given its predilection for the colon.²⁰ Involvement of the oesophagus and duodenum, however, may be more unusual in this population, although CMV oesophagitis is not uncommon in patients with additional immunosuppression or immunodeficiency.^{21 22} The extensive involvement of the GI tract in this case despite a moderate level of immunosuppression and timely discontinuation of the immunosuppressive medication illustrates the potential for severe infection even in patients without severe immunodeficiency, particularly in those with IBD.

The complex immune dysregulation leading to IBD is continuing to be worked out, just as CMV's multifactorial effects on the immune system are still being described. Inflammation with upregulation of certain cytokines (TNF- α) and T cell depletion and dysregulation all promote to CMV reactivation.²³ Given the association between CMV and IBD, the immune pathogenesis of IBD may contribute to more severe CMV disease in this population. Severe primary CMV disease may therefore be more common in IBD patients than previously recognised, and providers should maintain a high suspicion for this syndrome in such patients and look for CMV early in the course when patients present with a consistent syndrome. Most CMV in immunocompetent patients is mild and does not require antiviral treatment, and patients return to their baseline without intervention. Antiviral treatment for CMV is itself not benign and a study in haematopoietic stem cell transplant recipients demonstrated that even short courses can induce neutropenia requiring granulocyte-colony stimulating factor (G-CSF) in >10% of patients.²⁴ Once severe disease is confirmed by evidence of end organ involvement, as was seen in this patient, treatment should be initiated. Treatment of severe disease should include (where possible) temporary discontinuation of immunomodulators and

initiation of anti-viral therapy. Although cases are few, prior reports of immunocompetent patients with severe CMV disease support initiation of anti-viral therapy.²⁵ In fact, the mortality rate of untreated severe primary CMV infection in immunocompetent individuals can be high.²⁵

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Learning points

- IBD patients on immunomodulators may be at elevated risk for severe primary cytomegalovirus (CMV) disease.
- Primary CMV in patients with IBD can present as tissue-invasive disease.
- Providers should have a high index of suspicion for invasive CMV disease in IBD patients.
- Primary CMV infection in immunocompetent patients is most often asymptomatic or mild and self-limited and usually does not require therapy. However, for patients with severe disease and end-organ involvement, anti-viral therapy should be initiated.

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