

IBD LIVE Case Series—Case 5: The Many Faces of Cytomegalovirus in Inflammatory Bowel Disease

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LEARNING OBJECTIVES

After completing this IBD LIVE-CME activity, physicians should be better able to

1. Identify the signs and symptoms of systemic and localized CMV infection in patients with IBD.
2. Outline the virulence of CMV and the molecular pathophysiology of CMV infection.
3. Be aware of which type of patients are at highest risk of CMV infection or reactivation.
4. Identify which medications may contribute to the risk of CMV infection or reactivation.
5. Identify when CMV requires treatment in patients with IBD.
6. Identify which IBD medications may be safest to use concomitantly with treatment for CMV.

HISTORY

This is a 39-year-old white female with Crohn's disease (CD) presenting with bloody diarrhea and a recent history of cytomegalovirus (CMV) infection. She was diagnosed with CD in 2003 and has no other illnesses. She has a negative surgical history and is married, living with her husband and 3 children. She is a nonsmoker

who does not use recreational drugs or drink alcohol. She has no known allergies to medications. She reports a second and/or third degree history of inflammatory bowel disease (IBD), with a great aunt having CD and a grandmother having "colitis." No other gastrointestinal diseases run in her family. Her medications include mesalamine 400 mg TID, 6-mercaptopurine (6-MP) 1.5 mg/kg/day, prednisone 30 mg/day (tapered dose), omeprazole 20 mg/day, and an oral contraceptive pill. She denies a history of nonsteroidal anti-inflammatory drug use.

The patient first presented in 2003 with bloody diarrhea. Colonoscopy showed mild ileal and rectosigmoid inflammation consistent with CD. At that time, she began mesalamine 400 mg TID that provided minimal clinical improvement. Subsequently, she was started on 6-MP 1.5 mg/kg/day in 2005, and maintained clinical and endoscopic remission. In February of 2014, the patient's colon and ileum appeared normal on colonoscopy. Random biopsies taken during colonoscopy were also normal. In February of 2015, she experienced a recurrence of bloody diarrhea. Colonoscopy performed in March 2015 showed proctitis, and biopsies were consistent with active colitis and cryptitis. She was treated for recurrent CD flares during this period with

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prednisone tapers followed by extended-release budesonide. Upon taking high doses of steroids, her symptoms improved, but did not resolve. As the prednisone was tapered, her bleeding and diarrhea returned, which prompted an esophagogastroduodenoscopy (EGD) in August of 2015. Esophagogastroduodenoscopy showed mild erosive duodenitis, and histopathology revealed minimally increased lymphocytes and was negative for *Helicobacter pylori*. Flexible sigmoidoscopy, also performed in August 2015, demonstrated severe left-sided colitis with ulcers, and biopsies noted chronic active colitis. She was continued on mesalamine and 6-MP, and was placed on another steroid taper. In early September 2015, outpatient labs were notable for pancytopenia. Her providers attributed the low cell counts to the antibiotic sulfamethoxazole/trimethoprim that she had been taking for a urinary tract infection. Her immunosuppressant 6-MP was held.

In late September 2015, the patient was readmitted to the hospital with fever, altered mental status, and continued pancytopenia. A computed tomography scan of the abdomen was performed which indicated the presence of severe pancolitis without evidence of abscess or perforation. A subsequent flexible sigmoidoscopy was performed which demonstrated severe diffuse colitis with ulcerations (Figs. 1 and 2). Biopsies performed at this time were consistent with severe Crohn's colitis without notable CMV inclusions; however, the immunostained histologic specimens taken at biopsy were positive for CMV. She was started on intravenous (IV) ganciclovir for approximately 1 week and then was switched to oral form to complete 14 days of treatment. She was discharged on oral steroids and mesalamine. Polymerase chain reaction (PCR) for CMV at the outside institution was negative. At this point, the patient continued to complain of bloody diarrhea and lethargy. She was referred to us at the University of Pittsburgh Medical Center and was admitted to our hospital on October 31, 2015 for IV hydration and further workup by specialists in Gastroenterology and Infectious Disease.



FIGURE 1. Endoscopic image of sigmoid colon showing an ulceration with colitis.

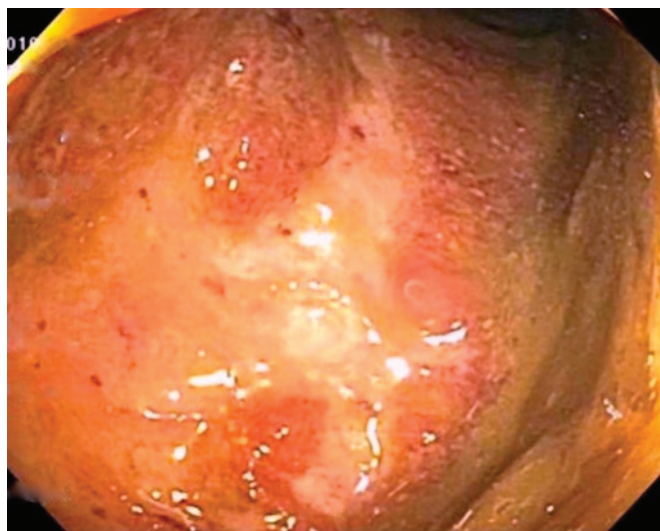


FIGURE 2. Endoscopic image of rectosigmoid colon demonstrating ulcerations, and inflamed, granular, and erythematous mucosa consistent with severe colitis.

Review of systems was notable for fatigue, bloody diarrhea, 20-pound weight loss over 2 months, fevers to 101°F, and mild abdominal pain. On physical exam, she was hemodynamically stable and afebrile. Her abdomen was soft, but she had mild left-sided tenderness. Active medications at admission included prednisone 40 mg and mesalamine. Initial laboratory studies were conducted. The patient had a normal chemistry 9 panel, negative celiac antibodies, normal thyroid stimulating hormone, normal cortisol, and her stool tested negative for *Clostridium difficile*. She was no longer leukopenic, with a white blood cell count of 5700/mm³ and her platelets were normal at 203,000 per μ L. However, she remained anemic with hemoglobin of 10 g/dL (normal 12–15 g/dL). She had an erythrocyte sedimentation rate of 100 (normal 1–25 mm/h), and her previously normal C-reactive protein was elevated to 5.3 (normal <3.0 mg/dL). CMV immunoglobulin G was positive but CMV immunoglobulin M was negative. CMV PCR was positive with 30,882 CMV copies per milliliters.

An unprepped colonoscopy was performed at admission which demonstrated ulcerations and moderately active chronic colitis.

Dr. Taher Reza Kermanshahi

There is distinct evidence of colonic ulceration with distortion in the normal cellular architecture and some cryptitis. In this photograph, an immunostain for CMV shows dark brown intranuclear and intracytoplasmic inclusions in both stromal and endothelial cells, consistent with CMV (Fig. 3). Some of the colonic biopsies show normal endothelial cells and some enlarged cells in the stroma, and endothelial cells that may be consistent with CMV. In this last image, 1 or 2 stromal or endothelial cells contain cherry red inclusions consistent with CMV (Fig. 4). Notably, this last biopsy would not be diagnostic of CMV unless immunostaining was positive, because there are no great morphological changes to these cells other than the ulceration.

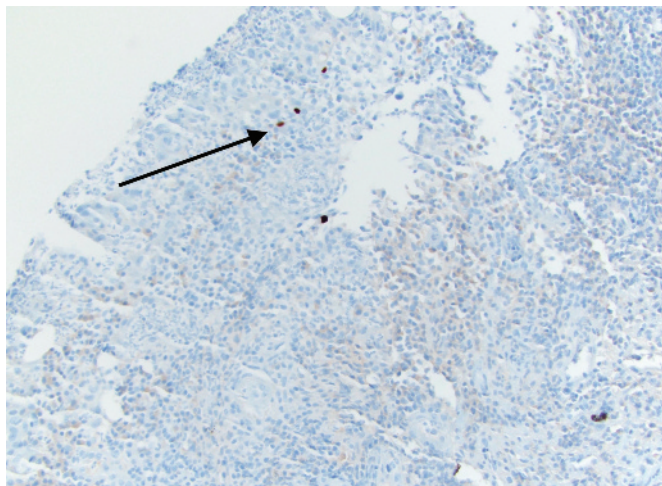


FIGURE 3. CMV IHC staining of colonic biopsy shows viral cytoplasmic and intranuclear inclusions (brown arrow) in stromal and endothelial cells.

Dr. Miguel Regueiro

In summary, this is a 39-year-old woman with Crohn's ileocolitis who has been in long-term remission on 6-MP. Recently, she has had an exacerbation of her Crohn's with bloody diarrhea and weight loss despite prednisone and 6-MP. A colonoscopy shows severe colitis with CMV on biopsies and high copies of CMV from blood PCR. She is quite ill and failing medical therapy. The questions I pose to you are as follows:

1. What do you do with patients who have CMV in the setting of IBD? How do you treat them?

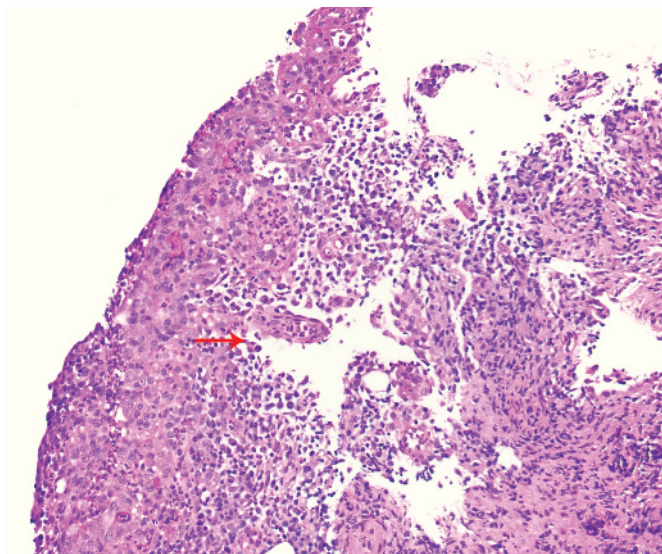


FIGURE 4. Biopsy from sigmoid colon with standard hematoxylin and eosin (H & E) stain is less diagnostic for CMV, showing few morphologic changes other than evidence of ulceration. The red arrow points to a CMV viral inclusion.

2. Do we have to stop immunosuppression or can we continue or even add biologics to treat the IBD?
3. What is the role of surgery in these patients?

Let us open this for discussion. What are your thoughts on this particular case, and how would you address CMV in somebody with IBD?

Dr. Manny Williams

From similar cases that we have treated previously, the first thing to do is to treat the CMV colitis. We would taper the steroids slowly as much as possible, and after we have completed the treatment course of her CMV colitis, we would follow the patient closely. In the past, I would be more prone to treat with anti-tumor necrosis factors (TNFs). In this patient, I am concerned about the pancytopenia that was noted repeatedly, which may have developed because of the immunosuppressive agents she was taking. I would try to get her off the steroids, treat the CMV colitis, and follow her. If her symptoms get significantly worse, she might need a colectomy.

Dr. Myron Brand

I think that the dilemma that we always face with these ill patients is whether the CMV is actually a pathogen exacerbating the IBD or is simply an innocent bystander. I agree that the immunosuppression is the major issue and if we are really concerned about the immunosuppression, then she is going to be headed towards colectomy.

Dr. Steve Bensen

Given how sick she is and how severe the colitis has become in the setting of CMV, I would be inclined to do a colectomy. The real challenge will be whether to leave her with a permanent ileostomy or whether we could consider an ileal pouch anal anastomosis. In the short term, I would suggest a colectomy, Hartman's pouch closure of the rectum, and an end ileostomy. We could make the decision about a J pouch at a later date.

Dr. Stefan Holubar

This patient is getting into a life-threatening situation from her Crohn's ileocolitis and is refractory to medical therapy. I would recommend proceeding with a laparoscopic subtotal colectomy with end-ileostomy. Given that she has Crohn's disease, a future pouch procedure is off the table in my opinion. Although one might consider a pouch for purely colonic Crohn's, and there is no history of perianal disease, she has had documented terminal ileitis that precludes a safe J-pouch construction. Regarding the surgical approach, this can be done completely laparoscopically and the ileostomy site can be used for specimen extraction. I would leave a rectal stump of 15 to 20 cm. The issue is balancing leaving a stump which can be used in the future for an ileo-proctostomy with leaving too long of a stump which then continues to fester as a source of inflammation that may develop into fulminant proctitis. Because she has responded to medical therapy in the past, and the rectum was relatively spared, I think an ileorectal anastomosis is definitely an option for her, once her malnutrition and CMV are resolved.

Regarding CMV superinfection in our acute colitis, my sense is that it is yet another marker of disease severity, and that by the time they develop CMV, they are usually already on near maximal medical therapy, and thus heading toward surgery. Practically speaking, we usually give the IV ganciclovir a try for less than 1 week, similar to what we do with toxic colitis and steroids or cyclosporine A, but the patient should be prepared for surgery including ostomy site marking and education.

Dr. David Keljo

I agree. I am also quite concerned about the pancytopenia. The steroids need to be discontinued and then I think you can see what happens when she is off the steroids and the ganciclovir has a chance to work. My suspicion is that she is probably going to wind up needing a colectomy.

Dr. David Binion

We lack definitive data regarding CMV superinfections in IBD and how to differentiate the coexisting viral activation from end-organ damage and disease. CMV is common and fairly ubiquitous; it is found in over one-half of 6 year olds; so, it is an infection that is often acquired early in life. As people grow older, they will frequently acquire the virus as a primary infection. About 90% of 80-year-olds in the United States are CMV-positive. For most healthy, immunocompetent people, a primary CMV infection in adulthood is not dangerous. But, this may not be the case in individuals who are ill with a coexisting acute and/or chronic illness.

The biggest challenge is the immunosuppressed individual such as the organ transplant patient who contracts a primary CMV infection or develops a reactivation infection. Back in the early days of organ transplantation, CMV would contribute to the deaths of one-quarter of kidney transplant recipients, most commonly due to reactivation infections. Transplant teams now often use pre-emptive therapy, surveying heavily immunosuppressed patients (i.e., those with a more significant human leukocyte antigen mismatch) monthly to see if there is any viral load emerging in the bloodstream, and if any CMV does show up, they immediately put the patient on an aggressive antiviral regimen.¹ This practice has significantly reduced mortality associated with CMV in the setting of long-term organ transplant immunosuppression. We do not routinely screen for CMV in our patients with IBD, because the level of immunosuppression we use does not warrant this practice. However, there are important scenarios to consider. Primary CMV infection in an immunosuppressed IBD patient can result in severe, intensive care unit (ICU) level illness. Many of us are familiar with a stable IBD patient on immunosuppression with purine analogs suddenly becoming severely ill, which is the classic presentation of primary CMV infection in IBD.

The more challenging situation is a reactivation CMV infection, where an IBD flare occurs alone or in association with infection with other pathogens such as *C. difficile*. The combination of an increase in steroid immunosuppression and infection is the perfect scenario for CMV to reactivate. Therefore, the sicker the patient, the more likely CMV will emerge and be contributing to the

severe colitis, which is why colonic biopsies for immunohistochemical (IHC) detection of CMV are essential in hospitalized colitic patients. One thing that is known from lab studies is that CMV replication increases in the presence of TNF- α .² So, when a patient with IBD becomes very ill and TNF starts to increase, it actually may serve as a growth factor for the virus. So if we think about attempting to use medical therapy to try to get this person under control, I completely agree with the recommendations to reduce steroids and to avoid immunosuppression with purine analogs, both of which will typically worsen CMV infections. However, if there is an attempt to salvage with medical therapy, maybe an anti-TNF agent could be considered once IV antiviral therapy is started, viral loads are dropping, and her health is improving.

Dr. Miguel Regueiro

I think about CMV in 3 general categories in our patients. Although there is overlap between categories, by and large, this is how I treat these patients.

1. Patients with primary infection with new CMV or a reactivation of CMV with viremia (systemic CMV infection)—if the patient has viremia, this is usually a sick patient similar to the one being presented, and we have to treat the CMV aggressively.
2. Patients who have deep punched out ulcers in the colon that are CMV-positive but do not have evidence of CMV in the blood.
3. Finally, the most common form of CMV is what Dr. Brand alluded to as “the innocent bystander.” In this case, CMV shows up on IHC stains and on biopsies of the colon in somebody with inflammation of the colon but without deep ulcers and without viremia. These patients are usually having an exacerbation of their colitis and we happen to find CMV on the biopsies.

My treatment of these 3 different CMV presentations in IBD is as follows: if it is CMV viremia, the patient is usually sick and I try to limit the steroids and stop the thiopurines. I think anti-TNFs may be ok, but I would treat the CMV first and once it clears from the bloodstream, if the patient’s IBD is active, then I would choose to treat the IBD with a biologic or even a colectomy. For the patient with deep ulcers in the colon from CMV, I think they also need CMV treatment followed by IBD treatment—either medication or surgery. For both of these types of patients, I think starting with IV treatment, e.g., ganciclovir, and then transitioning to an oral antiviral is reasonable. I should say that I would always do this in conjunction with an infectious disease specialist. The most common patient, the “innocent bystander” CMV-positive biopsy, is someone that probably does not warrant CMV treatment and I simply treat his or her IBD. Of course, if this patient’s condition were to worsen, I would keep in mind the CMV-positive biopsies. Despite this, I do think that the rare CMV-positive cells may be a harbinger of an ultimately more aggressive course of colitis. I have no evidence-based data to support this, but my experience with these patients would suggest this.

Dr. Heitham Abdul-Baki

To continue with our patient, the infectious disease team got involved and felt very strongly that we should not immunosuppress her anymore. She was started on IV ganciclovir, her prednisone was reduced to 10 mg per day, and she was started on sulfasalazine 4 g per day. She was discharged from the hospital. Her CMV load was undetectable after 1 week of ganciclovir and she was doing quite well. When she was tapered off of the prednisone, her diarrhea and bleeding returned. Her CMV by serology has remained negative. We initiated infliximab and azathioprine. She completed 1 month of IV ganciclovir and moved on to take oral valganciclovir hydrochloride. However, her symptoms did not resolve and she presented with another significant flare. A colectomy was recommended. In January of 2016, she underwent a total colectomy with end-ileostomy. Colectomy specimens demonstrate the extent and severity of disease (Figs. 5 and 6).

DISCUSSION

Our case describes a 39-year-old woman with CD who had fairly sudden onset of bloody diarrhea, followed by symptoms of a systemic infection and evidence of ulcerations of the entire colon on colonoscopy. Before her worsening symptoms, she had been in remission for close to 10 years on a regimen of 6-MP and mesalamine. A differential diagnosis for her symptoms would include entities such as *C. Difficile* infection, nonsteroidal anti-inflammatory drug use, viral or bacterial gastroenteritis, celiac disease, or the loss of response to immunomodulators. When a patient with IBD presents with an acute flare of colitis, it is also reasonable to investigate CMV as a possible cause.

According to the Centers for Disease Control, 50% to 80% of 40-year-olds are infected with CMV.³ Primary CMV infection frequently goes unnoticed, although some individuals experience flu-like symptoms including fever, lymphadenopathy, and malaise. CMV is more likely to act as an opportunistic infection in newborns,



FIGURE 5. Colectomy specimen shows severe colitis throughout most of the colon with distinct ulcerations in the sigmoid colon, and normal tissue in the ascending colon.

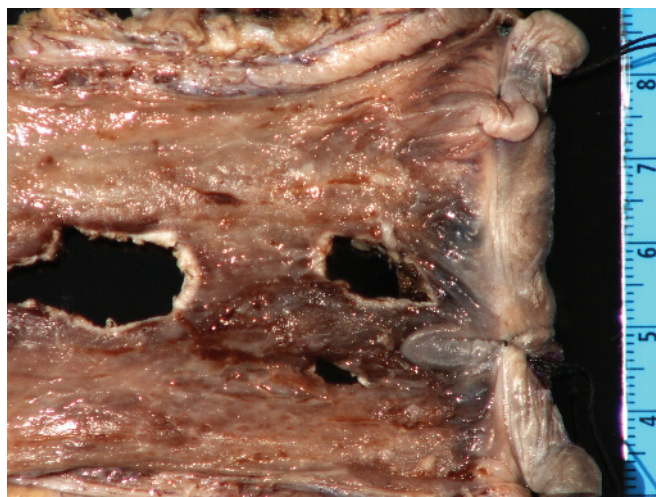


FIGURE 6. A section of the patient's sigmoid colon demonstrating severe colitis with punched out ulcers.

people who have decreased cellular immunity (e.g., HIV) and individuals who take immunosuppressive medications.⁴ CMV is a well-recognized pathogen affecting organ transplant patients, and this is especially true when a CMV-positive organ is transplanted into a CMV naive recipient.⁵ A case fatality rate of 11% was recently noted among renal transplant patients who had CMV.⁶

CMV is a member of the Herpesviridae family, along with herpes simplex 1 and 2, varicella zoster, and Epstein-Barr virus. CMV is a double-stranded DNA virus that replicates in the host cell's nucleus, manifesting histopathologically as large intranuclear inclusion bodies and smaller cytoplasmic inclusions.⁴ When CMV has infected cells in the bowel, these large "owl's eye" inclusion bodies are sometimes evident in intestinal endothelial and stromal cells on hematoxylin and eosin specimens. However, IHC staining is a more reliable way to determine the existence of CMV, because it uses monoclonal antibodies to identify the early CMV antigen.⁷ CMV may be found arbitrarily in IHC stains of colonic biopsies from patients with ulcerative colitis. Because CMV is tissue invasive and causes deep ulcerations of the bowel and erosion of blood vessels, the challenge is often to determine whether its presence reflects a systemic CMV infection or whether it is CMV that has reactivated in the colonic epithelium of patients with IBD, without viropathic or clinical consequences. A more accurate diagnosis of CMV can be made using a real-time PCR assay that detects and quantifies CMV-DNA.⁷

Studies evaluating CMV reactivation in the setting of the ICU may be relevant to patients with IBD. A 2009 study out of France prospectively surveyed 242 ICU patients who were mechanically ventilated for 2 or more days.⁸ Using routine pp65 antigenemia and serology to test for CMV at admission and weekly, they noted that about 16% of the patients became viremic with CMV. CMV also affected patient outcomes. Among those patients who developed CMV viremia, their chance for a successful wean from the ventilator in the next month was

12% versus greater than 50% for patients who were CMV-negative. In this particular study, factors that corresponded to CMV reactivation were a concurrent bacterial infection—whether it was a single or multiple microorganisms—steroid exposure, and blood transfusions. A separate study of immunocompetent critically ill patients found that CMV infection was most likely to occur 4 to 12 days after admission to the ICU and risk factors included sepsis, requirement of mechanical ventilation, and blood transfusions.⁹ Similar to the IBD patient on steroids and other immunosuppressants, reactivation of latent virus results in an opportunistic infection in certain higher risk patients.

The presence of CMV on biopsy does not necessarily indicate that the virus is the root cause of worsening disease in a given IBD patient. There is an ongoing debate concerning whether CMV intensifies inflammation in this cohort of patients or whether CMV functions as a surrogate marker of severe disease.⁴ Similar to other viral infections or reactivations, some patients will demonstrate fewer severe viral symptoms and may not require suspension of immunosuppressant treatment for their IBD. When patients with IBD exhibit severe viral symptoms or have sequelae due to CMV infection, discontinuation of thiopurine treatment is recommended. Treatment with cyclosporine and systemic corticosteroids has been shown to correspond to increased rates of CMV reactivation in patients with IBD.⁴ Anti-TNF agents, however, are not associated with CMV reactivation or viremia in patients with IBD, whereas the data for thiopurines have been inconsistent. Patients with severe or steroid-refractory ulcerative colitis are more likely to have CMV, with rate estimates of 21%–36%.¹⁰ CMV is less likely to be a pathogen that complicates CD.¹¹

Editor's Comment

CMV infection in patients with IBD can occur in at least 3 separate manners: (1) CMV infection with systemic symptoms and CMV viremia without gastrointestinal involvement, similar to an acute mononucleosis infection; (2) CMV disease involving the colon, with systemic and localized evidence of CMV infection by virologic testing; (3) colonic CMV infection as an incidental finding without systemic signs of disease, often picked up on IHC staining of colonic biopsies. If the patient does not have significant inflammation, specifically manifested as deep ulcers, and does not have CMV in the blood, we continue IBD treatment and do not treat the CMV. However, it has been our experience that the CMV may be a harbinger of a more aggressive course of

IBD. In general, antiviral therapy is indicated in patients with IBD with viremia or a primary CMV infection associated with an exacerbation of colitis. In patients with CMV viremia and/or severe colitis related to CMV, we recommend prescribing antiviral treatment, limiting corticosteroids, and stopping the thiopurines until colitis symptoms improve. In these cases, it has been our experience that the IBD may become quite active and we will use anti-TNFs without worsening the CMV colitis. We also have a low threshold for surgery and, as occurred in this case, a colectomy may be required. In general, any primary bowel infection in IBD, e.g., CMV and *C. difficile*, commonly leads to a more severe course of colitis that is refractory to medications.¹²

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CME EXAM—22.9
“IBD LIVE Case Series—Case 5: The Many Faces of Cytomegalovirus in Inflammatory Bowel Disease”

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LEARNING OBJECTIVES

After completing this IBD LIVE-CME activity, physicians should be better able to:

1. Identify the signs and symptoms of systemic and localized CMV infection in patients with IBD.
 2. Outline the virulence of CMV and the molecular pathophysiology of CMV infection.
 3. Be aware of which type of patients are at highest risk of CMV infection or reactivation.
 4. Identify which medications may contribute to the risk of CMV infection or reactivation.
 5. Identify when CMV requires treatment in patients with IBD.
 6. Identify which IBD medications may be safest to use concomitantly with treatment for CMV.
1. Which patient is most likely to have a diagnosis of a systemic CMV infection that also involves the colon?
 - (a) A Crohn's colitis patient whose disease is well controlled on infliximab, reporting 1–2 bowel movements per day
 - (b) A Crohn's colitis patient who is in clinical and endoscopic remission on azathioprine and adalimumab
 - (c) An ulcerative colitis patient on long-term 6-MP who presents with sudden onset, unexplained bloody diarrhea as well as chills and fever
 - (d) An ulcerative colitis patient taking infliximab who has recent onset of copious diarrhea and tests positive for *Clostridium difficile*

Please see the following references for further study:

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2. Your patient is an otherwise healthy 34-year-old woman with left-sided ulcerative colitis that is well controlled on 6-MP and sulfasalazine. Biopsies taken from normal appearing mucosa at routine colonoscopy demonstrate 2 CMV inclusions on IHC staining, although she has no systemic or localized (bowel) symptoms of CMV infection. A reasonable course of action for this patient would be to
- (a) Discontinue the 6-MP and add a steroid taper
 - (b) Discontinue the 6-MP and treat her CMV with IV ganciclovir followed by oral ganciclovir
 - (c) Continue her current IBD medications and treat the CMV only if she develops symptoms
 - (d) Do not treat the CMV but discontinue her current IBD medications

Please see the following references for further study:

1. Sager K, Alam S, Bond A, et al. Review article: cytomegalovirus and inflammatory bowel disease. *Aliment Pharmacol Ther.* 2015;41:725–733.
2. Garrido E, Carrera E, Manzano R, et al. Clinical significance of cytomegalovirus infection in patients with inflammatory bowel disease. *World J Gastroenterol.* 2013;19:17–25.
3. Lawlor G, Moss AC. Cytomegalovirus in inflammatory bowel disease: pathogen or innocent bystander? *Inflamm Bowel Dis.* 2010;16:1620–1627.

3. CMV could best be described as
- (a) A double-stranded DNA virus that presents mainly as an opportunistic infection
 - (b) A single-stranded RNA virus that causes significant symptoms in most individuals on primary infection
 - (c) A retrovirus that causes nausea and vomiting after primary infection, but is easily cleared by the host
 - (d) A double-stranded DNA virus that divides in the cytoplasm of infected cells

Please see the following references for further study:

1. Ali T, Yun L, Shapiro D, et al. Viral infections in patients with inflammatory bowel disease on immunosuppressants. *Am J Med Sci.* 2012;343:227–232.
2. CDC. About CMV; the Centers for Disease Control and Prevention. National Center for Immunization and Respiratory Diseases. 2009. Available at: <http://www.cdc.gov/cm/overview.html>. Accessed February 26, 2016.

4. Your symptomatic 42-year-old male ulcerative colitis patient has just been diagnosed with CMV viremia. On colonoscopy, he has evidence of significant inflammation and punched out ulcers in the sigmoid and rectum. His recent medications include azathioprine and 20-mg prednisone. Which of the following treatment options should be recommended for this patient?
- (a) Holding the azathioprine and tapering the prednisone and treating the CMV with IV ganciclovir followed by oral ganciclovir
 - (b) Discontinuing only the azathioprine and treating the CMV with IV ganciclovir followed by oral ganciclovir
 - (c) Discontinuing the azathioprine but increasing the dose of prednisone and treating the CMV with IV ganciclovir followed by oral ganciclovir
 - (d) Switching azathioprine to methotrexate, increasing the dose of prednisone, and treating the CMV with IV ganciclovir followed by oral ganciclovir

Please see the following references for further study:

1. Lawlor G, Moss AC. Cytomegalovirus in inflammatory bowel disease: pathogen or innocent bystander? *Inflamm Bowel Dis.* 2010;16:1620–1627.
2. Kandiel A, Lashner B. Cytomegalovirus colitis complicating inflammatory bowel disease. *Am J Gastroenterol.* 2006;101:2857–2865.
3. Takahashi Y, Tange T. Prevalence of cytomegalovirus infection in inflammatory bowel disease patients. *Dis Colon Rectum.* 2004;47:722–726.

5. It would be reasonable to add an anti-TNF medication to the treatment regimen for which of the following patients:
- (a) A patient with ulcerative proctitis using topical budesonide foam that has histologic evidence of CMV inclusions from endoscopic biopsy but is asymptomatic
 - (b) A patient with severe ulcerative pancolitis despite 7 days of IV/oral ganciclovir for CMV colitis

- (c) A patient with left-sided ulcerative colitis in remission on 6-MP, who has histologic evidence of CMV inclusions from endoscopic biopsy but is asymptomatic
- (d) An ulcerative colitis patient with a previous colectomy that has CMV viremia after liver transplant

Please see the following references for further study:

1. Lawlor G, Moss AC. Cytomegalovirus in inflammatory bowel disease: pathogen or innocent bystander? *Inflamm Bowel Dis*. 2010;16:1620–1627.
2. Kandiel A, Lashner B. Cytomegalovirus colitis complicating inflammatory bowel disease. *Am J Gastroenterol*. 2006;101:2857–2865.
3. Sager K, Alam S, Bond A, et al. Review article: cytomegalovirus and inflammatory bowel disease. *Aliment Pharmacol Ther*. 2015;41:725–733.

6. In the setting of CMV colitis, a characteristic inclusion might be found in
- (a) The cytoplasm of endothelial cells
 - (b) The nucleus of endothelial cells
 - (c) The nucleus of stromal cells
 - (d) Any of the above

Please see the following references for further study:

1. Langner C, Magro F, Driessen A, et al. The histopathological approach to Inflammatory bowel disease: a practice guide. *Virchows Archiv*. 2014;464:511–527.
2. Kandiel A, Lashner B. Cytomegalovirus colitis complicating inflammatory bowel disease. *Am J Gastroenterol*. 2006;101:2857–2865.
3. Lawlor G, Moss AC. Cytomegalovirus in inflammatory bowel disease: pathogen or innocent bystander? *Inflamm Bowel Dis*. 2010;16:1620–1627.

7. The best method of confirming a systemic CMV infection is by using:
- (a) Conventional culture of saliva
 - (b) Western blot of stool
 - (c) PCR of blood
 - (d) High-performance liquid chromatography (HPLC) of urine

Please see the following references for further study:

1. Zidar N, Ferkolj I, Tepes K, et al. Diagnosing cytomegalovirus in patients with inflammatory bowel disease—by immunohistochemistry or polymerase chain reaction? *Virchows Archiv*. 2015;466:533–539.
2. Yoshino T, Nakase H, Ueno S, et al. Usefulness of quantitative real-time PCR assay for early detection of cytomegalovirus infection in patients with ulcerative colitis refractory to immunosuppressive therapies. *Inflamm Bowel Dis*. 2007;13:1516–1521.
3. Sager K, Alam S, Bond A, et al. Review article: cytomegalovirus and inflammatory bowel disease. *Aliment Pharmacol Ther*. 2015;41:725–733.

8. The cellular inclusions that are pathognomonic for cytomegalovirus are often described with the term
- (a) Howell Jolly inclusion bodies
 - (b) Teardrop inclusion bodies
 - (c) Owl's eye inclusion bodies
 - (d) Kayser–Fleischer inclusion bodies

Please see the following references for further study:

1. Jones A, McCurdy JD, Loftus EV Jr, et al. Effects of antiviral therapy for patients with inflammatory bowel disease and a positive intestinal biopsy for cytomegalovirus. *Clin Gastroenterol Hepatol*. 2015;13:949–955.
2. Maconi G, Lombardini M, Furfaro F, et al. Long-term outcome of inflammatory bowel diseases with cytomegalovirus colitis: effect of antiviral treatment. *Eur J Gastroenterol Hepatol*. 2014;26:1146–1151.
3. Lawlor G, Moss AC. Cytomegalovirus in inflammatory bowel disease: pathogen or innocent bystander? *Inflamm Bowel Dis*. 2010;16:1620–1627.

9. Which of the following cohorts of the population is least susceptible to CMV infection?
- (a) People 20–30 years of age
 - (b) Newborns
 - (c) Transplant patients
 - (d) Individuals taking immunosuppressants

Please see the following references for further study:

1. Emery V. Investigation of CMV disease in immunocompromised patients. *J Clin Pathol.* 2001;54:84–88.
2. Peterson PK, Balfour HH Jr, Marker SC, et al. Cytomegalovirus disease in renal allograft recipients: a prospective study of the clinical features, risk factors and impact on renal transplantation. *Medicine.* 1980;59:283–300.
3. Osawa R, Singh N. Cytomegalovirus infection in critically ill patients: a systematic review. *Crit Care.* 2009;13:R68.
4. Ali T, Yun L, Shapiro D, et al. Viral infections in patients with inflammatory bowel disease on immunosuppressants. *Am J Med Sci.* 2012;343:227–232.