CASE OF THE MONTH Christian Rojas MD, Venkatesh Ariyamuthu MD & Naveen Rajpurohit MD

A 68 year old Caucasian male, with a past history of myasthenia gravis, peptic ulcer disease, vertebral compression fractures and hypertension, presented to University Hospital with a two month history of anorexia and diarrhea. The diarrhea was described as watery, greenish-brown stools occurring 4-5 times per day and during the night; no mucous or blood had been noted. He reported a weight loss of 67 pounds over the past year and had been constantly fatigued. He denied current fever, abdominal pain, nausea, vomiting, dysphagia or early satiety. He had no recent travel or sick contacts and denied use of alcohol or illicit drugs. The patient is a former smoker, with a 30 pack-year history of tobacco use.

Of note, three weeks prior to this admission, he was admitted to the hospital for evaluation of nausea, vomiting, diarrhea and melena. During that hospitalization, an EGD revealed a large ulcer at the GE junction, multiple gastric ulcers and some duodenal ulcerations; biopsies were negative for H. pylori and a fasting gastric level was normal. Clostridium difficile toxin and fecal leukocytes were positive and the patient was eventually discharged on a PPI and oral metronidazole. His nausea and vomiting resolved but the diarrhea did not improve.

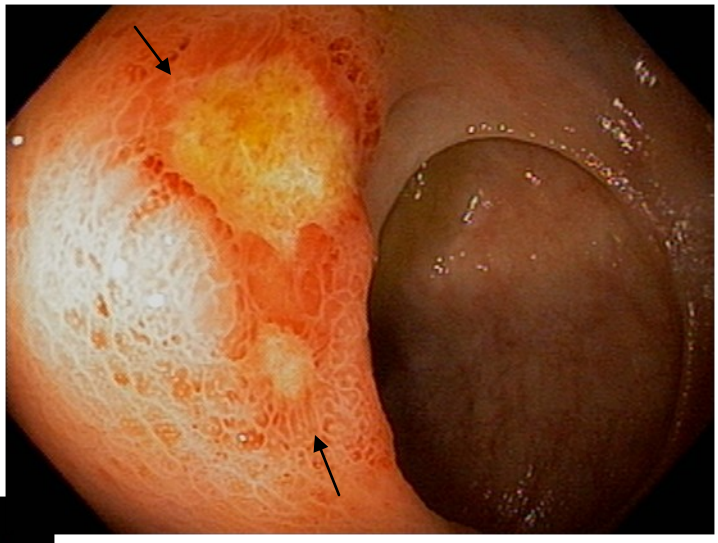
Myasthenia gravis had been diagnosed one year prior to admission, when he presented with muscular weakness and respiratory failure; he was discharged on prednisone 60 mg/day, pyridosigmine and monthly IVIG. The Neurology team added azathioprine seven months prior to the current admission and had been tapering his prednisone dose. At the time of admission, he was on prednisone 10 mg/day, azathioprine 150 mg/day, pyridostigmine 60 mg 5x/day and the monthly IVIG.

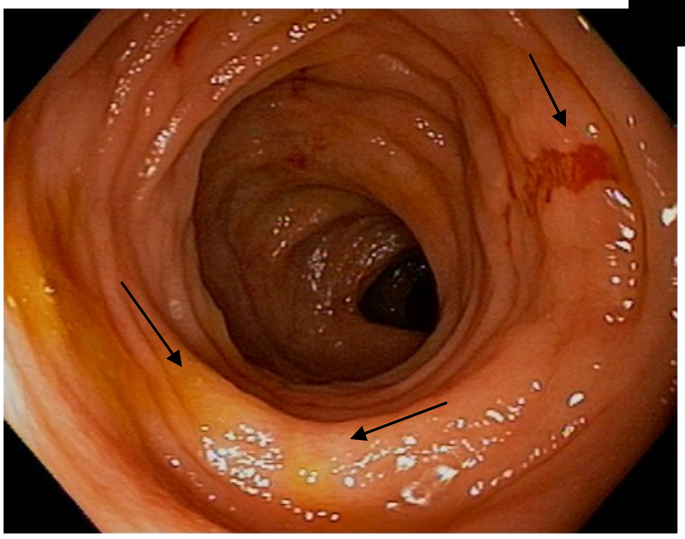
His physical exam on admission revealed normal vital signs; his oral mucosa was dry but he was in no acute distress. HEENT was otherwise clear. Neck was supple and nontender and there was no adenopathy or JVD. Scant crackles were noted at the right lung base. Cardiac exam was unremarkable, with no murmur, rub or gallop. Abdomen was soft, nontender and not distended; bowel sounds were normal and there was no mass or organomegaly; there was some mild tenderness in the left hypochondrium. Rectal exam was normal. Neuromuscular exam was unremarkable with no focal deficits and with normal mentation; there was no peripheral edema, clubbing or cyanosis.

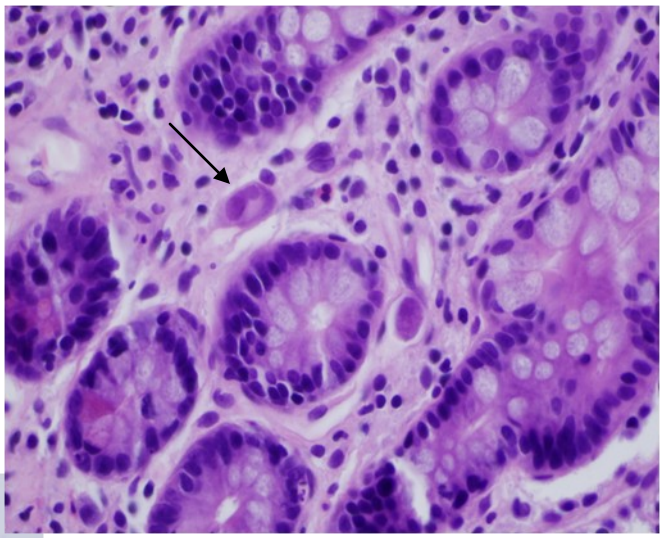
Admission labs revealed WBC 3.6 (86G, 6L, 6M, 1.5E, .5B), Hgb 11.8, MCV 111, Platelets 158, Na 132, K 3.1, Cl 91, HCO3 32, Gluc 98, BUN 19, Cr 0.8, TP 5.1, Alb 2.6, AP 48, AST 51, ALT 30, Amylase 136, Lipase 64. His UA was normal. HIV was negative. Stools revealed the presence of leukocytes but were negative for Clostridum difficile, giardia antigen, ova or parisites, AFB, routine culture, Microsporidia, Cryptosporidia, Cyclospora and Isospora. CMV IgG was positive but IgM was negative. A CT Abd/Pelvis revealed mild thickening of the wall of the cecum and terminal ileum, an enhancing mass in the periphery of the right hepatic lobe, a cyst in the inferior right hepatic lobe, sigmoid diverticulosis and multiple old thoracolumbar vertebral compression fractures.

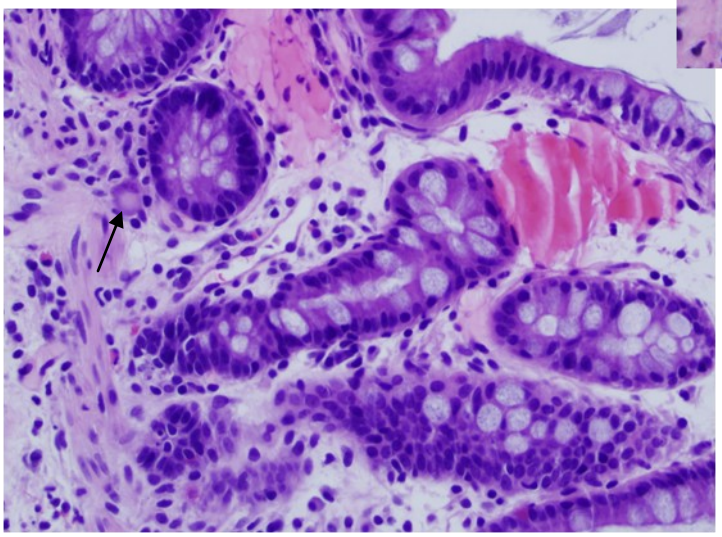
CMV DNA by PCR was ordered and GI was consulted for colonoscopy. The latter showed ulceration around the ileo-cecal valve and scattered serpiginous ulcerations of the transverse and descending colon (as shown in figures 1 &2; next page). Biopsies were taken and showed viral inclusions consistent with CMV (see figures 3&4 on next page) and the CMV immune stain was positive. The CMV DNA by PCR of the blood was also positive.

Figures 1 (right) and 2 (below) demonstrate serpiginous ulcerations seen on colonoscopy (arrows)









Figures 3 (above) and 4 (left) reveal the typical cytomegalic cells (arrows) indicating infection with CMV. The cells have a large, densely staining nucleus and abundant cytoplasm with intracytoplasmic inclusions.

DISCUSSION:

Cytomegalovirus (CMV) is a herpes virus that can cause a wide spectrum of disorders, ranging from subclinical infection to a disseminated disease in immunocompromised patients. The primary infection can be obtained through sexual contact, blood or tissue exposure and is generally asymptomatic or may present as a mononucleosis syndrome. CMV can damage many organs, including lung, retina, liver and gastrointestinal tract. Occasionally, primary CMV infection can lead to severe, organ-specific complications. Once the primary infection resolves, it enters a prolonged period of latency; latent infection is the presence of virus in tissue without secondary damage while CMV disease implies signs and symptoms of tissue injury. In patients with latent CMV infection, disease may develop by reactivation of the virus or by infection with a novel exogenous strain; those who experience reactivation have adequate anti-CMV antibodies but have defective cell-mediated immunity due to conditions such as AIDS, organ transplantation, chemotherapy or steroid therapy. Gastrointestinal CMV disease is usually cause by reactivation of latent infection.

A reasonable definition of **gastrointestinal CMV disease** is an erosive or ulcerative process in the wall of the GI tract in which the presence of CMV is demonstrated (by routine histologic examination, culture, antigen staining or DNA studies) and for which other causes have been excluded. Histologic examination will reveal the presence of large cytomegalic cells, characterized by basophilic intranuclear inclusions, surrounded by a clear halo (owl's eye), and clusters of intracytoplasmic inclusions.

CMV can involve any part of the GI tract. In the mouth, it may cause salivary gland infection or painful oral, pharyngeal or epiglottic ulcers. In the esophagus, CMV infection may produce odynophagia and substernal pain due to solitary ulcers or strictures. Gastric mucosal ulcerations may cause epigastric pain, nausea, vomiting or bleeding. In the small intestine, CMV infection can cause terminal ileum disease and, rarely, obstruction. The manifestations of colonic CMV disease are diarrhea, hematochezia, urgency, tenesmus, abdominal pain, fever, weight loss and, rarely, toxic megacolon (most often seen in AIDS patients).

Diagnostic testing may be positive in latent infection and a positive result does not always indicate the presence of active disease; furthermore, testing may be negative in cases of active CMV. **Serologic testing** includes the presence of IgM antibodies and/or a fourfold increase in IgG antiboidy titer (at least 2-4 weeks apart); the benefit of serologic testing is limited by the fact that IgM antibody can persist for several months (or may be negative in active disease) and that IgG testing cannot provide a timely diagnosis. **Antigen detection** includes early antigen in shell vial cultures and pp65 in peripheral blood leukocytes. The former requires 2-3 days for detection, using monoclonal antibodies on biopsy specimens (can be detected even before the cytopathic effects) while the latter requires 24 hours to yield results. Diagnosis by culture (of blood, urine, CSF, bronchial washings, oropharyngeal secretions or biopsy tissue) will take weeks for cytopathic changes to occur. The most sensitive way to detect CMV in blood or other fluids is by amplifying CMV DNA via the polymerase chain reaction (PCR) method. The gold standard for diagnosis is a **histopathologic examination** of biopsy tissue, demonstrating cytomegalic cells by H&E stain and the presence of CMV antigen with immunoperoxidase staining.

GI tract CMV infections are progressive and are associated with significant mortality if untreated. The current **treatment options** are: Ganciclovir 5mg/kg IV, BID; Valganciclovir 900mg/day PO; Foscarnet 90mg/kg IV BID; Cidofovir 5 mg/kg IV weekly; all of these drugs inhibit DNA polymerase. In addition, some reports have shown that octreotide may be effective for severe CMV colitis, although its mechanism of action remains unclear. By expert consensus, the duration of treatment is 3-6 weeks and discontinuation of therapy should be based on resolution of symptoms, disappearance of inclusion bodies and healing of ulcers (at 6 weeks). If Ganciclovir is used, the CBC should be monitored twice weekly due to the potential side effects of neutropenia and thrombocytopenia; if severe thrombocytopenia is present, Foscarnet therapy should be considered. However, Foscarnet can cause renal injury and hypocalcemia and labs should thus be monitored closely (twice weekly is recommended).

BACK TO OUR PATIENT:

This 68 year old male was an immunosuppressed host due to his chronic therapy with prednisone and azathioprine for myasthenia gravis. His positive IgG antibody for CMV indicates that he had a primary CMV infection in the past, which became latent. Reactivation occurred due to the medication-induced immunosuppression and caused gastrointestinal CMV disease, specifically CMV colitis. The patient was treated with Ganciclovir 5mg/kg IV BID and his azathioprine was held for the duration of his treatment in order to avoid additional bone marrow suppression. He started to feel better, his diarrhea improved significantly and he was discharged on oral Valganciclovir 900 mg qd for 3 weeks; he will be followed in ID Clinic and the GI team will investigate the liver nodule (found incidentally on CT) in their clinic.

REFERENCES:

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