Cytomegalovirus Colitis in Recent COVID-19 Infection: A Case Report

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Abstract

Human cytomegalovirus (CMV) is a double-stranded DNA virus with high seroprevalence and is common in developing countries. The ability to cause a lifelong latent infection is established, and it can be reactivated later in life in both immunocompetent and especially in immunosuppressed carriers. We report a case of CMV colitis in a gentleman who was initially admitted for COVID-19 pneumonia.

Keywords
CMV colitis, COVID-19, human cytomegalovirus, immunosuppressed, reactivation.
Introduction
Cytophagalovirus is a herpesvirus, found across the world and causing a broad spectrum of clinical syndrome such as congenital infection, infectious mononucleosis, and infecting people with reduced immune systems such as patients with AIDS and the one undergoing immunosuppressive therapy.

Coronavirus disease (COVID-19) on the other hand, is an infectious disease caused by the novel coronavirus SARS-CoV-2 virus that caused a world pandemic recently, was discovered in late 2019 and had been known to cause mainly respiratory symptoms. We report a case of a patient that was initially admitted for COVID-19 infection but later acquiring CMV colitis during hospitalization, possibly reactivation of latent CMV that was reactivated due to his illness and the usage of steroids causng immunosuppression.

History
A 58-year-old Chinese gentleman with underlying hypertension presented with history of fever, dry cough, and myalgia for six days duration to a private medical centre. His chest radiograph was suggestive of pneumonic changes and nasopharyngeal swab was positive for SARS-CoV-2 RNA virus. His condition worsened, required intubation and the clinical impression at that time was COVID-19 pneumonia category 5. He was admitted to intensive care unit (ICU) and was treated with intravenous (IV) hydrocortisone. Due to financial constraints, he was then transferred to ICU in a government hospital on the fourteenth day of admission for further management.

On the day of admission to the government hospital, he was afebrile and haemodynamically stable. He was extubated and put on a high flow nasal cannula and allowed to drink fluids. On the next day, the patient was transferred to the common ward with oxygen support 3L/min via nasal prong and oral prednisolone was given instead of IV hydrocortisone and started on subcutaneous clexane for deep vein thrombosis (DVT) prophylaxis.

Two days later, patient started vomiting a large amount of coffee ground vomitus. About 1 litre of coffee ground aspirates was drained through Ryle's tube. He also had few episodes of constipation which was resolved after administration of syrup lactulose. Abdomen examination revealed sluggish bowel sound and per rectal examination was unremarkable. Subcutaneous clexane and prednisolone were put on hold. Intravenous infusion pantoprazole, a proton pump inhibitor, was prescribed instead to decrease the amount of acid produced in the stomach.

His total white cell count was slightly increased while the liver functions test remains unremarkable since admission. An abdominal-Xray performed on the following day showed dilatation of his small bowel which was confirmed by computed tomography (CT) abdomen (Figure 1, label A). Abdominal CT scan showed dilatation and collapse of ileum with minimal ileal wall thickening, ascending colon diverticula and mild ascites and required colonoscopy intervention, suggestive of paralytic ileus secondary to sepsis. Serial measurement of abdominal girth showed an increased trend in the circumference. He was kept nil by mouth for elective decompression colonoscopy to achieve plateau level of the abdominal circumference measurement.
Figure 1: A) The initial abdominal CT scan done showed dilatation and collapse of ileum with minimal ileal wall thickening, ascending colon diverticula and mild ascites. B) The repeated abdominal CT scan after the completion of 28 days of IV ganciclovir, showing resolved small bowel dilatation and normal thickness of bowel wall. However, the large bowel dilatation is still apparent.

A well-defined punched out rectal ulcer was found about 10 cm from anal verge during colonoscopy procedure. Tuberculosis or cytomegalovirus (CMV) colitis were suspected. Colonoscopy biopsies were sent for culture and sensitivity, and polymerase chain reaction (PCR) for *Mycobacterium tuberculosis*, however the results came back as no growth and not detected respectively.

The biopsied tissue was also sent for histopathological examination. Histopathological findings of the biopsies showed areas of ulceration (Figure 2). High power view of the ulcerated area showed granulation tissue formation with acute and chronic inflammatory cell formation (Figure 3). Immunohistochemistry (IHC) for CMV antigen revealed one single possible positive cell and many cells with intracytoplasmic low positivity (Figure 4). Both CMV IgM and IgG antibodies were detected. The serology result was confirmed with detection of 340.4 IU/mL CMV DNA by PCR, and he was started on IV ganciclovir 5mg/kg (total 300mg) twice a day for 3 weeks.
Figure 2: Low power view showing two pieces of colorectal mucosa biopsy with areas of ulceration (arrows) [H&E, 4x].

Figure 3: High power view of the ulcerated area showing granulation tissue formation with acute and chronic inflammatory cell formation. Viral cytopathic effects could not be easily appreciated, although there is a suggestive affected cell (arrow) [H&E, 40x].
After 28 days of treatment, CMV DNA by PCR was no longer detected. Follow up colonoscopy showed significant improvement with no recurrent or persistent ulcers. Repeated CT abdomen showed resolved small bowel dilatation, and normal thickness of bowel wall. However, the large bowel still showed generalised dilatation with no other underlying causes and no perforation seen (Figure 1, label B).

Patient was discharged after 96 days of admission. He had two subsequent follow up after discharge and was generally well except for some occasional loose stools. Abdominal X Ray indicated no recurrent bowel dilatation. Repeated colonoscopy was scheduled for him in the next three months.

**Discussion**

When COVID-19 pandemic was declared by the World Health Organization in early 2020, it shook the world and healthcare system especially by surprise [9]. Together with the chaos it brought, COVID-19 also has changed the medicine we know when it became a risk factor to worsen the condition of some other diseases due to its ability to cause immunosuppression in people infected with it. Amongst these diseases, human cytomegalovirus (CMV) is one of them.

Known for its ability to stay latent, reactivation of CMV may occur at any time, but is more common in the immunosuppressed group [2]. Infection also could be caused by primary infection, or patients have risk of getting it via transplantation or blood transfusion [3]. Few case reports have shown the association between SARS-CoV-2 and CMV co-infection. Risk factors to have this co-infection would include the patient’s critical condition and the usage of glucocorticoids used amongst COVID-19 patients, which is a known risk factor for CMV reactivation [4]. Al-Omari et al reported that risk factors for CMV infection could be divided into 2 groups: strong association would be being immunocompromised, mechanical ventilation and sepsis, whilst history of blood transfusion, usage of steroids, and stress are weakly associated with it. However, there was no correlation found between other risk factors such as age, gender, active malignancy and disease severity scores[5]. Another factor to consider is, due to pathophysiology of the SARS-CoV-2 infection causing chronic stimulation of adaptive immune cells, resulting in a cytokine storm and exhaustive T-cells, the body defence system is weakened causing them to be susceptible to reactivation of CMV infection[6].
Usually associated with inflammatory bowel disease, our patient’s presentation started with an episode of coffee ground vomitus, and later slowly developed episodes of abdominal distension, with occasional constipation. In this case, gastrointestinal bleeding must be suspected too, in view of patient was started on low molecular weight heparin during his admission. Serial abdominal x-ray showed persistent small bowel dilatation, which was confirmed by CT abdomen. These symptoms appeared at day 14 of admission, and the patient was initially treated as COVID-19 pneumonia stage 5 and was started on steroids therapy. Pedro Amaral et al described a similar finding in their case report where the patient started to have the symptoms after almost 1 month of admission to the hospital[7]. In severe cases, tissue necrosis that leads to bowel wall perforation could occur, but it is rare in primary clinical presentation. In view of its ability to mimic many other diseases like inflammatory bowel disease and ischemic colitis, unexplained prolonged diarrhoea in immunocompetent patients warrants investigation for CMV disease[6].

Most patients that are presented with CMV colitis usually have well-defined and punched out appearance during colonoscopic evaluation, however some minority cases could present with irregularly and cobblestone-like appearance ulcers too[2]. Pathogenesis wise, it is thought that once HCMV infects the host cell, it causes lytic infections that lead to ulcer formation. These ulcers, which are later sent for histopathological examination, will show the presence of cytomegalic cells. Typically, infected cells would show increase in size and have this owl’s eye appearance due to cytomegalic inclusion, which is the gold standard for diagnosing CMV infection in each organ. The usage of CMV-specific immunoperoxidase or immunohistochemistry (IHC) will increase the sensitivity of CMV detection in tissue specimens [9,10].

The presence of CMV infection in this patient was diagnosed based on the positive CMV serology, CMV PCR and taking into consideration of the tissue histopathological examination findings. This patient possibly has previous latent CMV infection based on IgG seroconversion. The presence of IgM, together with positive PCR is suggestive of reactivation. The presence of suggestive affected cell showing possible viral cytopathic effects, with immunohistochemistry for CMV antigen showing only one single possible positive cells and many cells with intracytoplasmic low positivity however makes it hard to decide whether it was a true positive CMV infection, because both nucleus and cytoplasmic activity seen in immunohistochemistry is considered to be the gold standard [11,12], together with appearance of a haemorrhagic mucosa, is highly suggestive of CMV infection.

Apart from colitis, CMV coinfection in COVID-19 patients had been reported to occur in other end organs. Moniz,J et al reported a case series of SARS-CoV-2 and CMV coinfections, where 5 patients ended up in intensive care unit requiring invasive mechanical ventilation and the diagnosis were confirmed using CMV PCR (using plasma or bronchoalveolar lavage sample)[13]. All patients were in immunocompromised state, either from having immunodeficiency virus (HIV) infection, diabetes mellitus, systemic lupus erythematosus or history of heart transplant on immunosuppressive medications. They were all intubated and was admitted to intensive care unit at one point during their admission[13]. Aldehaim et al reported a case of concurrent CMV pneumonitis that was admitted and treated for severe coronavirus disease 2019 pneumonia, requiring ICU care. The patient had underlying systemic lupus erythematosus which could have worsened the condition to begin with [14].

Ganciclovir is the considered drug of choice for CMV infection (in colitis and other organs) and the duration is depending on the organs involved. 21-42 days is the suggested duration for CMV colitis, depending on the symptoms of the patients[15]. Our patient responded well after 28 days of Ganciclovir, as per evidenced by resolution of symptoms, negative CMV PCR, improvements on repeat colonoscopy and CT abdomen.

Conclusion
This case highlights the importance of having a high index of suspicion for CMV infection or reactivation especially during this pandemic caused by SARS-CoV-2. Patients who are previously well with no obvious
risk factors can become vulnerable if they are infected with COVID-19, especially if such a patient is admitted to an intensive care unit, has undergone prolonged mechanical ventilation support, received steroids and is severely ill. Making diagnosis of this condition is also a challenge to the clinicians, especially if the findings of the histopathological examinations are not straightforward, like in this case, hence other supplementary tests and findings must be taken into consideration before making a diagnosis, because early initiation of CMV antiviral treatment would reduce the incidence CMV viraemia and further unwanted complications.

References