Tocilizumab-induced Cytomegalovirus Colitis in a Patient with COVID-19

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Abstract

Cytomegalovirus (CMV) infection exists in 50-80% of the world's population in clinically undetected form due to their immunocompetent status. Here we report a case of a 42-year-old COVID-19 patient with no past medical history, who received tocilizumab, which led to a massive lower gastrointestinal bleeding not responded to medical management.

Key Clinical Message

The authors urge clinicians to observe the early signs of lower gastrointestinal bleeding and perforation associated with tocilizumab treatment in patients with COVID-19. On-time recognition and performance of exploratory laparotomy with double-barrel colostomy are effective life-saving measures.

Background

Cytomegalovirus (CMV) is a double-stranded deoxyribonucleic acid virus belonging to the Herpesviridae family. [1] It is more commonly seen in individuals with immunosuppressive diseases, including inflammatory bowel disease (IBD), hematological malignancy, organ transplantation, acquired immunodeficiency syndrome (AIDS), or therapies such as cancer, and corticosteroids. [2] However, most of the CMV-related infections in immunocompetent individuals go undetected, [3] and presented as fever, sometimes with pancytopenia. Diarrhea (watery and bloody in severe cases) may begin to develop as an inflammatory response. Ulcerative changes can be seen when the colon tissue affected by CMV.

Subsequently, inflammatory polyps may develop, which, rarely, may cause colon obstruction. Severe inflammation and vasculitis may lead to bowel perforation and peritonitis due to ischemia and transmural necrosis. [4] We describe a case of COVID-19 pneumonia on immunosuppressive treatment presenting with lower gastrointestinal bleeding due to CMV colitis confirmed by histopathology.

Case Report

A 42-year-old gentleman with no past medical history admitted to our intensive care unit (ICU) with a laboratory-confirmed case of COVID-19, requiring non-invasive ventilation (NIV). He developed spontaneous pneumothorax, for which chest drain placed. One day after his admission he was intubated and pronned for deterioration of his oxygen levels and PaO2/FiO2 ratios (*Figure 1*). For possible cytokine storm in view of high ferritin levels and persistent fever patient received IL-6 inhibitor (Tocilizumab 400 mg Once) 3 days after admission to ICU.

His course was complicated by upper gastrointestinal bleeding (melena) with a drop in hemoglobin by one gram on day nine, Gastroenterology team managed him conservatively, as the melena subsided. Almost 22 days after admission, he re-developed bleeding per rectum again (hematochezia), with a drop in hemoglobin

from 9 gm/dl to 6 gm/dl, this time he was hemodynamically unstable, requiring nor adrenaline vasopressor support and multiple blood product transfusions. Esophagogastroduodenoscopy did not show active bleeding or altered blood from upper esophageal sphincter to level-D3 part of the duodenum, and only clear biliary secretions were found.

Colonoscopy performed with a difficulty till the splenic flexure, the colon was filled with blood clots and fresh bleed was noted around the colon circumferentially and the scope could not be passed further due to poor visibility due to blood clots, the procedure was abandoned, hemostasis not achieved due to not identifiable active bleeder.

A computed tomography (CT) angiogram was done for identifying the cause of bleeding and for possible angioembolization. No bleeder could be identified, and the only positive finding was mural thickening with intramural axial hemorrhage involving the splenic flexure and proximal part of the descending colon (*Figure 2*). In view of hemodynamical instability, a team of multi-disciplinary surgeons decided to take him for lifesaving emergency laparotomy.

A small bowel enterotomy was done at the suspicious site of bleeding; GI team passed the colonoscope to locate bleeding; no evidence of bleed found up to three meters of small bowel and enterotomy closed. Left hemicolectomy was done in view of the high suspicious site of bleeding at the splenic flexure, both the loops of large bowel brought out as functional transverse colon and descending mucous fistula as double-barrel stoma performed. Histopathology report confirmed CMV colitis with colonic perforation, for which he was started on Ganciclovir therapy 220 mg once daily for 4 days. Intime recognition and timely performance of life-saving surgery helped our patient survival; we continued for ganciclovir 440 mg every 12 hours for a total of 3 weeks, the patient has been tracheostomized and stepped down to the inpatient ward with a functional colostomy.

Discussion

CMV infections are becoming more prevalent in immunocompetent patients.[5] Recently, with the outbreak of Coronavirus disease (COVID-19), many studies have suggested that COVID-19 may activate dysregulated host immune responses, where interleukin-6 (IL-6) levels are elevated in cases of severe COVID-19, so the anti-IL-6 such as tocilizumab may be beneficial. [6] however, the available evidence still not conclusive that tocilizumab is beneficial to patients with severe COVID-19 and not yet recommended for routine clinical guidelines.

Al-Omari et al. noted that the risk factors such as the immunocompromised, mechanical ventilation, sepsis were found to be strongly associated with CMV. In contrast, the use of corticosteroids, blood transfusion and stress were weakly associated. They found no association with risk factors such as age, gender, disease severity scores, and active malignancy. [7]

It demonstrates an organ-specific tropism within the body affecting mainly hemopoietic stem cells and parenchymal connective tissue. As per the systemic review done by Rafailidis et al., in immunosuppressed patients with tissue-invasive (TI) CMV, the gastrointestinal tract is the most commonly affected and comprises almost 30% of the disease.[5] CMV lesions may be present throughout the gastrointestinal tract, from the oral cavity to the rectum. However, colon involvement is the most common, comprising up to 94% of cases.[8-10] For viral reactivation in the immunocompetent, critical illness is a major predisposing factor for developing TI-CMV disease. [11]

Endoscopic findings of CMV colitis, like ulcers and inflammation, are similar to UC exacerbation. Biopsies that reveal CMV inclusion bodies in the pathological specimen may be the only way to distinguish between IBD and CMV. The presence of CMV infection in our patient was diagnosed only based on the presence of inclusion bodies. Biopsy with Immunohistochemistry using monoclonal antibodies against CMV antigens is now considered the gold standard. [12] The characteristic Owl's eye inclusion bodies are highly specific for CMV.[13] CMV colitis and IBD closely mimics each other in their clinical, endoscopic and histological appearance. Therefore, it is crucial to avoid misdiagnosis and mismanagement, keeping in mind the high

morbidity associated with it.

Conclusion

This case highlights the importance of keeping a high suspicion and diagnosing the pathology at the earliest to treat and control the disease in these critically ill patients. Though they may be immunocompetent and with no risk factors prior to admission to the ICU, they become vulnerable and the risk of developing primary/latent CMV infection is high. A timely diagnosis can prevent prolonged ICU and hospital stay. It also warrants judicious use of corticosteroids and other immunomodulatory drugs like tocilizumab in critically ill patients. In the present Scenario, while treating patients with COVID-19 with the use of immunosuppressive therapy should be justified while being alert for signs and symptoms of CMV reactivation. Early recognition of CMV infection and initiation of early treatment will prevent life-threatening bleeding and mortality.

Abbreviations

CMV: Cytomegalovirus

COVID-19: Coronavirus disease

IBD: Inflammatory bowel disease

AIDS: Acquired immunodeficiency syndrome

ICU: Intensive care unit

IL-6: Interleukin 6

Declarations

Ethics approval and consent to participate

The article describes a case report. Therefore, no additional permission from our Ethics Committee was required.

Consent for publication

The consent for publication was obtained.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MYK, KSS, AAA, MAA, AJN, ASM: Data Collection, Literature Search, Manuscript Preparation

All authors read and approved the final manuscript

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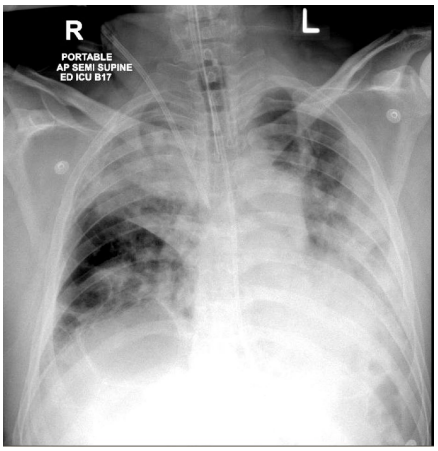
Figure 1 : Shows bilateral consolidation of lung, Endotracheal tube, Nasogastric tube (NG Tube) right IJV (Internal jugular vein) Central venous catheter.

Figure 2 : Mural thickening with intramural axial hemorrhage involving the splenic flexure of the colon.



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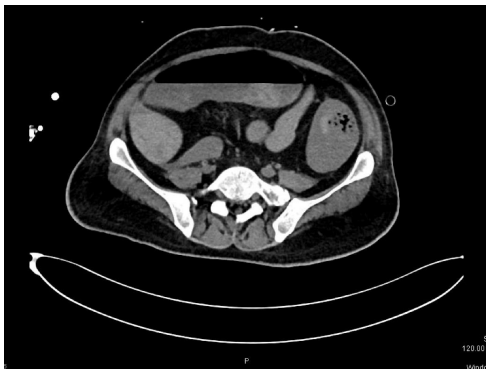

Figure 2: Mural thickening with intra mural axial hemorrhage involving the splenic flexure of colon.

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