BANTAO Journal 2021; 19(1): 20-22

BJ

BANTAO Journal

Case report

Reactive CMV Colitis in Multimorbidity Patient with Ganciclovir Resistance- Post-COVID-19: A Case Report

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Abstract

COVID-19 disease mainly causes mild upper respiratory diseases in infected people, with possible development of complications in 20% of the cases. The virus's predominance for bronchial epithelial tissue and reactive immune response to the virus can result in an overall immune reaction that can trigger latent infections such as cytomegalovirus (CMV) infection or cause bacterial, fungal, or viral coinfections. CMV infection can predispose to other viral respiratory infections, and chronic CMV infection state has been associated with impaired humoral immune response. An abundance of CMV IgG antibodies rate has even been correlated with a higher mortality rate. This state can occur due to underlying immunocompromised status (e.g., undergone transplantation or autoimmune disease) or comorbidity-relations susceptible to the development of complications (such as greater age and underlying chronic diseases), even in a post-COVID-19 state.

Keywords: CMV colitis, ganciclovir, kidney transplant, hypercoagulability, post-COVID-19

Introduction

COVID-19 causes predominately acute respiratory distress with a high possibility of complications and death outcomes in high-risk groups [1]. SARS-CoV-2 has a high affinity for angiotensin-converting enzyme 2 receptors (ACE2), mainly expressed on the epithelial cells lining the bronchial alveoli, what may explain the etiology of respiratory symptoms [2]. Infected patients usually have a mild disease. However, 20% will develop complications due to their predispositions such as age, sex, comorbidities, and overall immune competence [3]. The immunomodulatory effects of COVID-19 on humans have several pathways. The immune system reacts in a defense-based protective way but also exhibits a reaction to the inflammation-driven damaging phase of infection. Immune response takes toll due to various pathophysiologic reactions, such as affection of secondary lymphoid organs, mononuclear cell infiltration, elevation of inflammatory cells, B and T cell lines exposure, high cytokine production, altered coagulation pathways with elevated d-dimers, and many more [2, 4]. This overall reaction to the pathogen can also trigger some latent infections, such as cytomegalovirus (CMV) infection, which can cause colitis with ischemic and inflammatory lesions, which is the case we present in this report. This extensive and complex reaction to the virus brings into question the possibility of immune interference that could explain the age and comorbidity-relations in susceptibility to developing complications and possible concurrent coinfections or reactivations, even in a post-COVID state [5,6].

Case report

We present a case of a 59-year-old woman with many comorbidities, a plentiful medical history, and several prior hospitalizations. Since 1990 she was suffering from recurrent urinary tract infections (UTIs). In 2005, she was diagnosed with polycystic kidney disease and was started on hemodialysis. She received a renal allograft from a deceased donor in 2005 and was maintained on cyclosporine, mycophenolate mofetil and prednisone. Several months after transplantation, the patient had developed iatrogenic diabetes mellitus and massive bilateral pulmonary embolism (PE). She had a prior history of positive serological findings for CMV, for which she has been prescribed a prophylactic dose of valganciclovir. Since 2014, renal allograft function showed signs of impairment with recurrent UTIs, fever, elevated creatinine, and supraventricular tachycardia. Cardiologic workup showed no signs of peripheral arterial disease, ischemia, or myocardial scarring. However, kidney biopsy showed signs of secondary focal segmental glomerulosclerosis (FSGS). Other comorbidities are metabolic syndrome, post PE status (for which she was given low-molecular weight heparin), and subtotal parathyroidectomy. During her frequent relapses of UTI (most common pathogens: Pseudomonas a. or Klebsiella

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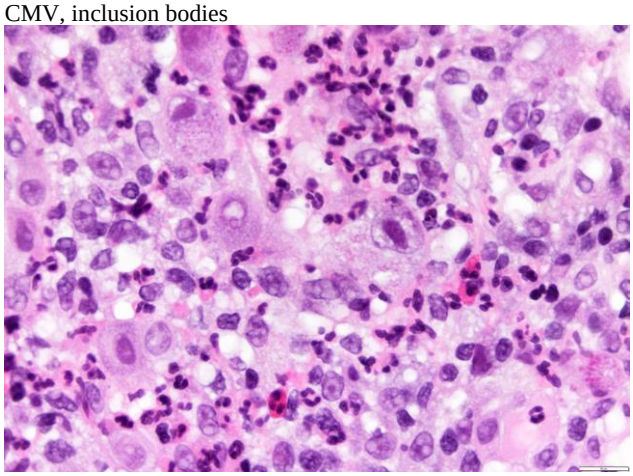
p.), she developed resistance to ciprofloxacin. In 2019, laboratory examination showed detectable quantitative CMV DNA in her blood (1170 IU/mL), so a valganciclovir was introduced to the therapy. Due to her repetitive UTIs, reduced renal allograft function, and CMV reactivation, our patient eventually received ganciclovir, ceftolazane + tazobactam (for UTI), and anti-CMV immunoglobulin (for CMV reactivation). The therapy was working well- the patient's urine was sterile and laboratory results showed normalization of inflammatory parameters and serum creatinine, together with a drop in copies of CMV DNA (<137 IU/mL).

In November 2020, the patient tested positive for SARS-CoV-2. She was hospitalized with the mild form of disease and did not require oxygen therapy.

At the outpatient visit in March 2021, a drop in serum hemoglobin was recorded (from 98 g/L to 56 g/L) with a history of gastrointestinal bleeding. She received a blood transfusion and had undergone esophagogastroduodenoscopy and colonoscopy. The procedure results showed segmental transversal colitis with ulcerations, changes in the mucosa, and diverticula. It also implied possible diverticular or angiodysplastic sources of bleeding. Histologic findings confirmed CMV infection in ulcer tissue. Regular workup revealed normocytic anemia and a new rise in CMV copies to 40100, so ganciclovir and anti-CMV immunoglobulin were prescribed, unfortunately, without therapeutic effect on high CMV reactivation. Drug resistance testing proved resistance to ganciclovir, so foscarnet was introduced to therapy. The new therapy reacted well to high CMV-DNA levels; however, the patient had developed neurologic side effects such as dizziness, headache, disorientation, and hallucinations. The symptoms receded after withdrawal of the drug. The patient is doing well now and was successfully released from the hospital. Letermovir was introduced as a secondary prophylaxis of CMV infection.

A. Hematoxylin eosin staining. Arrows point to specific findings in CMV, inclusion bodies



B. Immunohistochemistry staining for CMV. Arrows point to CMV-specific antigen-stained cells

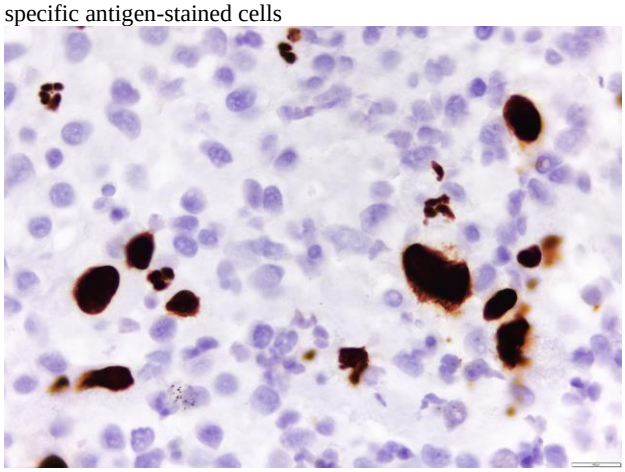


Fig. 1. Pathohistological findings in colon tissue after intestinal biopsy

Discussion

This complex case of reinfection with latent CMV in older, immunocompromised patient brings into question the immunomodulatory ways of the SARS-CoV-2 virus and possible previous infections and the way they could affect each other. Our patient had a previous immunocompromised state due to an allograft kidney transplant in 2005. Since then, she was on immunosuppressants. She suffered from relapsing UTIs that disturbed her urinary bacterial flora and CMV reactivations, both of which worsened her overall immunocompetence. Most prominent CMV reactivation had developed clinical signs of gastrointestinal bleeding. That was the reason for extensive workup with colonoscopy and colon tissue biopsy. Examination revealed ulcerations, edema, and friability of the mucosa. CMV colitis has been reported in several entities, from thickening of the bowel wall to different etiological states as ischemic, infectious, and inflammatory presentation [5,7].

The immune response to COVID-19 is an acute and dynamic reaction with pro-inflammatory increased cytokine expression, especially in severe cases. It was observed that COVID-19 infection leads to subsequent apoptosis of T lymphocytes, along with loss of $CD4^+$ and $CD8^+$ lymphocytes due to tissue sequestration and excessive production of pro-inflammatory cytokines. All of mentioned could result in the impaired immunological response to pathogen and possible reactivation of latent viruses. Increased vulnerability to targeted organs in COVID-19 could also be explained by the fact that a higher concentration of ACE-2 receptors can be found in the colon, kidneys, liver, vascular endothelium, and others [4,6]. CMV infection could also predispose to respiratory viral infections. Chronic CMV infection has been associated with impaired humoral response, and high CMV IgG antibodies were, in some cases, correlated with higher mortality [8]. Notably, reported cases of concomitant CMV reactivation and COVID-19 infections were all described in patients with turbulent COVID-19 symptoms. However, due to the severe immunocompromised patient in our case,

we conclude that even a mild form of COVID-19 infection can potentially cause reinfections with inflammatory clinical manifestations.

Conclusion

COVID-19 affects predominately upper and lower airway trucks; however, it can also infect other organ systems, including the gastrointestinal tract. This immune disturbance can sometimes, especially in elderly and immunocompromised patients, cause coinfections or reinfections that could further deteriorate the clinical state. Cases of SARS-CoV-2 and CMV coinfections have been reported several times [6,8]. This challenging and extensive case we have presented makes diagnostic and therapy decisions challenging to handle due to several comorbidities, resistance to antiviral drugs, and complex regular therapy as a consequence of the patient's chronic diagnoses and transplant status.

Conflict of interest statement. None declared.

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