

CASE REPORT

Cytomegalovirus haemorrhagic colitis complicating COVID-19 in an immunocompetent critically ill patient: A case report

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Abstract

Suspicion threshold for opportunistic coinfections should be lowered in severe COVID-19. Serum CMV polymerase chain reaction and colonoscopy should be discussed in presence of persistent digestive disturbances.

KEYWORDS

coronavirus, COVID-19, critically ill, cytomegalovirus, immunodepression, lymphopenia

1 | INTRODUCTION

In severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19), lymphopenia has been established as a typical feature and a marker of poor prognosis.¹ Deep immune imbalance and depleted T cells have been reported in severely ill patients.²⁻⁵

Concerns are rising about COVID-19 associated immunodepression, as series of invasive aspergillosis (IA)⁶⁻⁹ have been reported. In one of these reports, up to 35% of critically ill SARS-CoV-2-infected patients had suspected IA (later either histologically proven or underpinned by bronchoalveolar fluid or serum positive galactomannan),⁶ whereas the usual

overall incidence of IA in the intensive care unit (ICU) is around 1%.¹⁰

Herein, we report a case of complicated cytomegalovirus (CMV) and COVID-19 coinfection, in a formally immunocompetent host.

2 | CASE PRESENTATION

By end of March 2020, a 71-year-old man was admitted to the ICU for acute respiratory distress syndrome (ARDS). Admission PaO₂/FiO₂ ratio was 165 mm Hg and Simplified Acute Physiology Score III was 61 (predicted mortality of

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38%). Real-time polymerase chain reaction for SARS-CoV-2 on nasopharyngeal swab was positive.

His medical history was characterized a post-tuberculosis aspergilloma known since 2016. There was no current medication. His nutritional state was normal.

Chest CT-scan displayed ground glass opacities involving over 65% of the right lung and cavitary tuberculosis sequelae in the left superior lobe with aspergilloma. A bronchoalveolar lavage fluid analysis revealed a positive galactomannan (GM) test (value 1.51). Serum GM was negative. Voriconazole was started on day 5 after admission. The patient also received hydrocortisone at the dose of 200 mg q.d., from day 6 to 10.

On day 16, ileus was noticed. Abdominal CT-scan showed a right-sided colitis and ileal distension without obstacle. Persistent anemia prompted endoscopic investigations. The colonoscopy performed on day 28 revealed a right-sided colitis with multiples ulcers. CMV colitis was confirmed by immunoperoxidase staining on colon biopsy. Ganciclovir was initiated on day 30. Significant rectal bleeding led to cecal artery embolization.

Serologic tests were positive for past CMV infection and negative for Human Immunodeficiency Virus.

Lymphopenia was present on admission and lasted 3 days, with a nadir of total absolute lymphocytes at $0.5 \times 10^3/\mu\text{L}$. Absolute CD4 cells count was 1368/ μL on day 42, with a CD4/CD8 ratio of 0.5 and normal values for immunoglobulins and complement. The first measured serum CMV load was 1173 UI/mL after 13 days of ganciclovir treatment.

The patient required 27 days of invasive mechanical ventilation and 9 days of continuous veno-venous hemofiltration. He was discharged from the ICU on day 32. A control colonoscopy on day 44 showed persisting signs of right-sided colitis. Ganciclovir was discontinued on day 59.

3 | DISCUSSION

To our knowledge, this is the first description of a CMV end-organ infection complicating COVID-19 disease in a previously formally immunocompetent host.

The first CMV and SARS-CoV-2 coinfection was reported in a 92-year-old Italian woman with diabetes mellitus and hypertension.¹¹ There was, however, no evidence of any end-organ CMV disease. She died 6 days after admission due to ARDS.

In a systematic review on coinfections among hospitalized COVID-19 patients, viruses were accountable for 3% of the coinfections.¹² CMV was the least frequently encountered virus. CMV infection diagnosis methods were not reported, nor were severity or end-organ lesions.

Cytomegalovirus colitis is rarely described among immunocompetent patients. Among 1061 colon biopsies in symptomatic patients, CMV polymerase chain reaction (PCR) was

positive in 185 samples. Of those, 15 samples belonged to 13 immunocompetent hosts and only one of them had compatible histological findings.¹³

Cytomegalovirus is less rare in the ICU. In a meta-analysis involving 2398 patients, CMV infection or reactivation was found in, respectively, 27% and 31% of the patients.¹⁴ The odds ratio for all-cause mortality among patients with CMV infection was 2.16 compared to control. Interestingly, patients with sepsis have the highest incidence of CMV infection.¹⁵ As the inhibition of CMV reactivation requires 10% of all peripheral CD4⁺ and CD8⁺ T cells,¹⁶ it is plausible that the immune dysregulation and the cytokine storm accompanying COVID-19 disease might participate to an increased risk of CMV end-organ disease.

Among severe COVID-19 cases, most had immune dysregulation dominated by low expression of HLA-DR on CD14 monocytes,¹⁷ triggered a.o. by excessive release of IL-6 and profound lymphopenia. That pattern was however distinct from the immunoparalysis state reported in bacterial sepsis or H1N1 influenza severe respiratory failure. Within 15 peripheral blood smears from COVID-19 patients admitted in ICU, cytological signals of Th2 immune response were found.¹⁸

Several immunoassays studies have demonstrated significantly lower CD3+, CD4+, and CD8⁺ counts among severe COVID-19 patients.²⁻⁴ In one of them,² median values for CD3, CD4, and CD8 counts among severe patients were, respectively: 305, 184, and 121/ μL , suggesting a deep disturbance of cell-mediated immunity. CD4/CD8 ratio was however not altered,^{2,3} unlike in other viral infections such as HIV or CMV.

B and NK cells counts were significantly lower among severely ill patients in two studies,^{2,3} yet not in another.⁵

A longitudinal study of 40 COVID-19 patients⁵ showed a significant decrease in lymphocytes count from day 7 to 15 after disease onset, in severe vs mild patients. The lowest CD3+, CD4+, and CD8⁺ counts were observed at day 4-6.

Reviews have suggested a link between CMV-related immune senescence and the poor outcome of COVID-19 among older persons.^{19,20} It has been proposed that COVID-19 cytokine storms might be promoted by CMV.²⁰ A relationship has also been suggested between the CMV seroprevalence in some areas such as northern Italy and the higher rates of COVID-19 mortality in those populations.¹⁹ Those links remain to be demonstrated.

Ultimately, we consider that our patient's CMV colitis was likely triggered by his immune dysregulation due to severe COVID-19.

4 | CONCLUSION

To our knowledge, this is the first described case of CMV end-organ disease concomitant to COVID-19 in an immunocompetent host.

Studies show that critically ill COVID-19 patients have an imbalanced immune response with deep T lymphopenia that may render them more susceptible to various infections.

Opportunistic infections are not systematically sought for in immunocompetent people. A part of the high mortality related to COVID-19 might be imputable to such undiagnosed diseases. Evidence is growing for IA coinfections, but other diseases might be underestimated, such as CMV reactivations.

Suspicion threshold for opportunistic diseases should be lowered when managing critically ill COVID-19 cases. Serum CMV PCR and endoscopic exploration with biopsy should be discussed in presence of persistent and unexplained digestive disturbances.

Further large-scale studies are warranted to investigate whether severe COVID-19 patients are prone to opportunistic infections.

ACKNOWLEDGMENTS

We are especially grateful to Dr Leila Mekkaoui and Dr Bhavna Mahadeb, who have made some retrospective laboratory analysis requests possible. Published with written consent of the patient.

CONFLICT OF INTEREST

The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

SL: summarized the data, reviewed the literature, wrote this manuscript and included the remarks and corrections of the other authors. EM: contributed to the interpretation of the data, reviewed the literature and revised the manuscript. HVN: contributed to the interpretation of the data and revised the manuscript. LODS: contributed to the acquisition of data and their interpretation. LML: contributed to the acquisition of data and their interpretation. PK: contributed to the acquisition of data and their interpretation and revised the manuscript. AG: contributed to the acquisition of data and their interpretation. PC: contributed to the interpretation of the data, reviewed the literature and revised the manuscript.

ETHICAL APPROVAL

The authors confirm that the patient signed an informed consent document before the submission of this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this case report are available from the corresponding author upon reasonable request.

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How to cite this article: Leemans S, Maillart E, Van Noten H, et al. Cytomegalovirus haemorrhagic colitis complicating COVID-19 in an immunocompetent critically ill patient: A case report. *Clin Case Rep*. 2021;9:e03600. <https://doi.org/10.1002/ccr3.3600>