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Case Report

Cytomegalovirus-Induced Gastrointestinal Bleeding and Pancreatitis Complicating Severe Covid-19 Pneumonia: A Paradigmatic Case

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Abstract. COVID-19 is a new pandemic disease whose pathophysiology and clinical description are still not completely defined.
Besides respiratory symptoms and fever, gastrointestinal (GI) symptoms (including especially anorexia, diarrhea, and abdominal pain) represent the most frequent clinical manifestations.
Emerging data point out that severe SARS-CoV-2 infection causes an immune dysregulation, which in turn may favor other infections.
Here we describe a patient with severe COVID-19 pneumonia who developed in the resolving phase abdominal pain associated with cytomegalovirus (CMV)-induced duodenitis with bleeding and pancreatitis.
A high level of suspicion toward multiple infections, including CMV, should be maintained in COVID-19 patients with heterogeneous clinical manifestations.

Keywords: Cytomegalovirus, SARS-CaV-2.

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Case Report.

A 73-year-old man was referred to the Emergency Department of our University Hospital because of fever, dry cough, and worsening dyspnea after contacts with two sons recently diagnosed with COVID-19. No gastrointestinal (GI) symptoms were present. History revealed multimorbidity characterized by type 2 diabetes mellitus, hypertension, atrial fibrillation, multivessel coronary artery disease (requiring repeated percutaneous angioplasty with stenting two years before), and a recent diagnosis of primary cutaneous large B-cell lymphoma (PCLBCL) leg type, localized at the right leg without extra-nodal involvement, which was treated with local radiotherapy two months before.

The presenting clinical and imaging picture suggested a severe acute respiratory syndrome (SARS). The patient was severely hypoxemic (paO2/FiO2 less than 100), chest X-ray, and computerized tomography (CT) (**Figure 1a**) revealed bilateral interstitial pneumonia. SARS-CoV-2 infection was diagnosed through polymerase chain reaction on a nasopharyngeal swab, and the patient was admitted to a dedicated

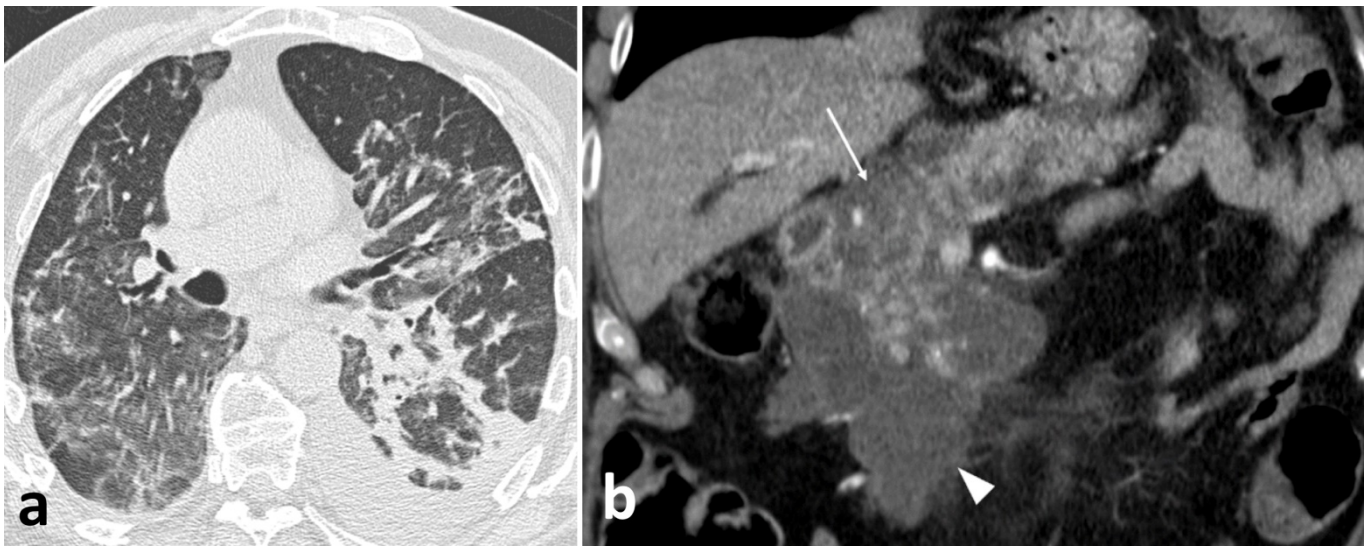

Figure 1. CT imaging. **a)** High resolution CT scan of the chest, showing extensive areas of ground-glass opacity, with strands of consolidation and left pleural effusion. **b)** Coronal arterial phase CT image shows areas of reduced parenchymal perfusion (arrow) and large peripancreatic collections (arrowhead).

COVID-19 area. High flows of oxygen and continuous positive airways pressure (CPAP) were started, and the patient was stimulated to pronation. Electrocardiogram confirmed atrial fibrillation with a normal QTc interval. Initial blood analysis showed C-reactive protein 263 mg/L, leukocytosis (16,610/mm^3) with neutrophilia (15,940/mm^3) and marked lymphocytopenia (260/mm^3), ferritin 487 mcg/L, D-dimer 719 mcg/L, fibrinogen 8.91 g/L, LDH 287 U/L, lactate 2.9 mmol/L. Hemoglobin, platelets, creatinine, and liver enzymes were in the normal range. Lymphocyte subpopulations analysis revealed a marked reduction of CD4+ T-cells (100/mm^3). Revision of previous records excluded any prior immunodeficiency. Empirical treatment was started with hydroxychloroquine 200 mg BID (after a loading dose of 400 mg BID for the first 24 hours), lopinavir/ritonavir 100/25 mg BID, methyl-prednisolone 80 mg OD (1 mg/kg) with subsequent tapering, and enoxaparin at therapeutic doses. Overall, the duration of the antiviral and methyl-prednisolone treatments was ten days. After an initial critical phase, the respiratory failure slowly improved so that the patient could be gradually weaned from CPAP from day 14 after admission.

However, on day 18, the patient developed epigastric pain, melena, hypotension, tachycardia, and a substantial drop of hemoglobin levels (from 14.5 to 10.6 g/dL). After hemodynamic stabilization with intravenous fluids and transfusion with two units of red blood cells, an upper endoscopy was performed, which showed multiple large and confluent ulcers in the first and second portions of the duodenum (**Figure 2a**), suggesting a Cytomegalovirus (CMV) duodenitis. The diagnosis was confirmed by the positivity of circulating CMV-DNA (6,080 IU/mL titer) and by duodenal histopathological findings (**Figure 2b,c,d**). CMV serologic test showed positive IgG (154 U/mL; positive ≥ 14 U/mL) and borderline IgM at diagnosis. Helicobacter pylori and Epstein-Barr encoded RNA were not found on the histologic specimens.

Enoxaparin was immediately stopped, and ganciclovir (5 mg/kg BID) was started. The patient also underwent a CT-scan of the abdomen, which showed pancreatitis with a non-homogeneous pattern of the pancreatic head and peripancreatic fluid collection (**Figure 1b**). Pancreatic amylases and lipases were only slightly increased (59 and 63 U/L, respectively). The clinical evolution was favorable, as abdominal pain disappeared, and pancreatic enzymes returned within the normal range in few days, allowing early enteral refeeding. The CMV-DNA titer dropped to 1,320 IU/mL after 12 days of treatment with ganciclovir. On day 43 from admission, the patient was successfully discharged by the COVID Unit.

Discussion. Gastrointestinal (GI) symptoms, including anorexia, diarrhea, and abdominal pain, have been observed in near one-fourth of COVID-19 patients.[1] They have been attributed to a direct injury by SARS-CoV-2 on enterocytes, which highly express the viral receptor angiotensin-converting enzyme 2 (ACE2),[2,3] although the direct contribution of the virus to this plethora of symptoms is uncertain. In small COVID-19 series, GI bleeding,4 and pancreatitis[5] have also been reported as possible complications of SARS-CoV-2 infection. Upper endoscopy has been performed rarely in COVID-19 patients, with some retrieving of SARS-CoV-2 genetic materials whose implications remain uncertain.[6] Nevertheless, defining the pathophysiology of GI clinical manifestations in COVID-19 is critical for appropriate treatment.

Here we describe a patient who developed a clinically relevant GI bleeding due to severe duodenitis with multiple ulcers and pancreatitis on day 18 of severe

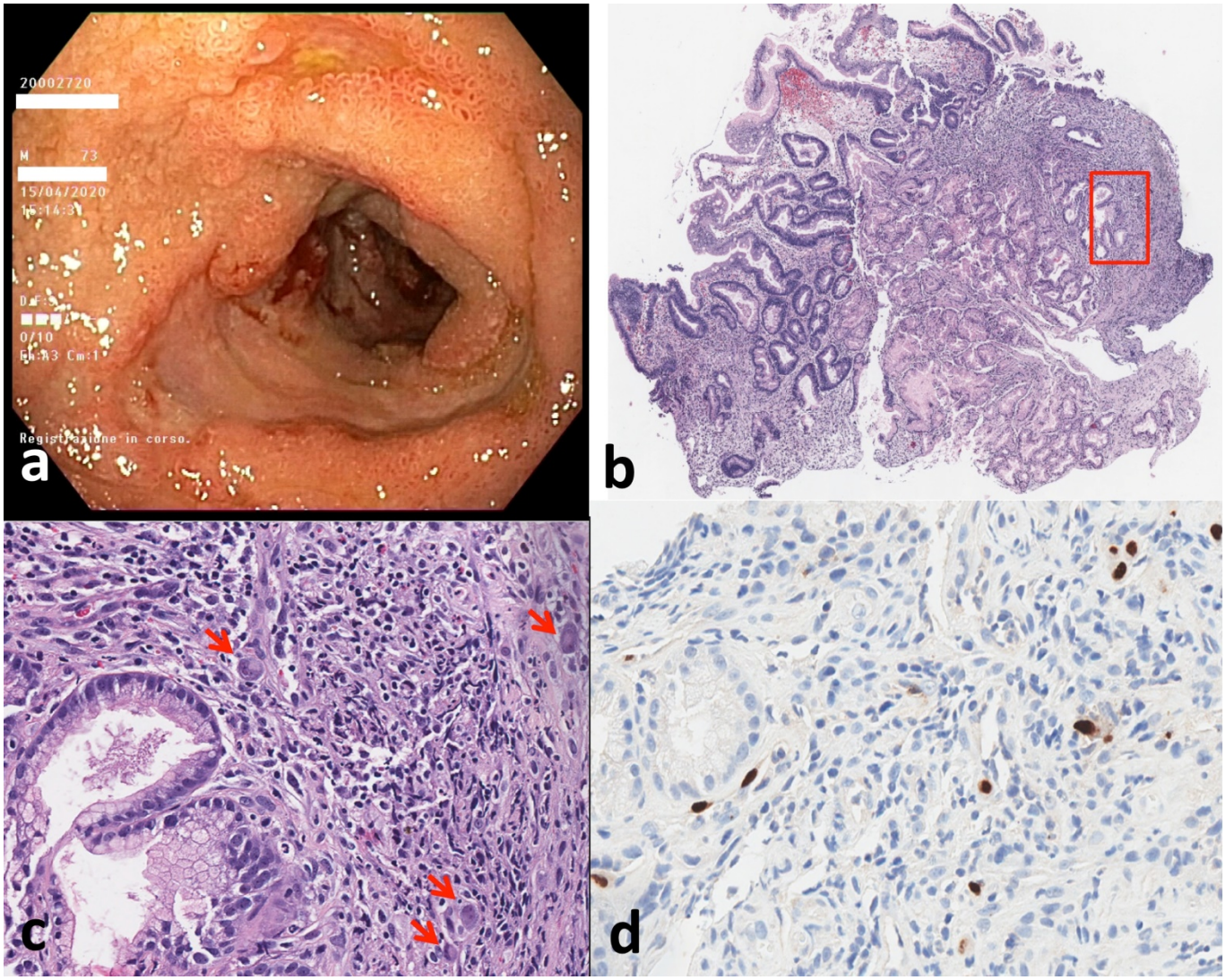

Figure 2. **a)** Upper endoscopy showing multiple large and confluent ulcers in the first and second portions of the duodenum with initial re-epithelialization and an ischemic-like pattern. **b)** Duodenal ulcer biopsy H&E staining. **c)** High power view of the area highlighted in «a» H&E: large basophilic CMV inclusions within endothelial cells in the granulation tissue (arrows). **d)** High power view Immunohistochemistry showing CMV-positive cells.

COVID-19 pneumonia. Both duodenitis and pancreatitis are known as possible complications of CMV infection/reactivation in the immunocompromised host.[7-11] We could demonstrate that duodenitis was due to CMV, while some uncertainty remains about the etiology of pancreatitis, as histology was not feasible. Nevertheless, no obvious causes of pancreatitis were evident, as CT did not reveal gallstones, triglycerides were in the normal range, and the patient had no history of alcohol abuse or recurrent pancreatitis. Considering the whole clinical picture, the probability of CMV-induced pancreatitis was quite high in our patient. An emerging feature of severe COVID-19 patients is represented by secondary immune dysregulation,[12] heralded by marked lymphocytopenia, which involves all the lymphocyte subtypes, and functional impairment of innate immunity.[13,14] Indeed, in our patient, we observed a marked reduction of lymphocytes, with a nadir of 260/mm^3, of which CD4+ T-cells were 100/mm^3, CD8+ T-cells were 39/mm^3, B-cells were 33/mm^3, and NK cells were 82/mm^3. Since the CMV IgG test was positive, a possible explanation is the reactivation of CMV in an immunocompromised host with severe COVID-19 pneumonia. Corticosteroid treatment may have further contributed to immunodepression, while it is unlikely that the localized PCLBCL with no signs of evolution at the moment played a role. Intriguingly, CMV, and SARS-CoV-2 infections may have potentiated each other, since they share some innate immunity pathways. For example, patients affected by COVID-19, besides having a reduced number of NK and CD8+ T cells, also show functional exhaustion of these cells, with an increased expression of the inhibitory receptor NKG2A.[15] NKG2A signal can suppress the cytotoxic activity of NK and CD8+ T cells, and promote viral spreading during a variety of chronic viral infections, including CMV.[14] Furthermore, CMV infection can also influence the expression of NKG2A,[16] and it has been linked to the pathogenesis of a number of disorders characterized by

immune dysregulation.[17,18]

In conclusion, to the best of our knowledge, this is the first description of CMV-associated severe GI complications in a patient with COVID-19 pneumonia. We hypothesize that CMV reactivation may be due to the marked immune dysregulation during severe COVID-19 pneumonia, which in turn may be further influenced by the use of immuno-regulatory drugs (e.g., glucocorticoids, tocilizumab, and others)[].[19] This complication, potentially treatable, may be overlooked in patients with COVID-19 and secondary immune dysfunction.

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