A case report on a possible link between SARS-CoV-2 infection and gastric pathology onset

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Abstract

Many organs have been described as involved in long-COVID processes. Concerning the stomach, few cases have been reported and discussed. Particularly, we have very few information about the potential direct damage to the gastric mucosa caused by SARS-CoV-2. We report the case of a 45-year-old Italian woman with no known chronic diseases or food intolerances who developed severe gastrointestinal manifestations as long COVID-19 manifestation following a SARS-CoV-2 infection. During the acute phase of COVID-19, she exhibited, among other symptoms including respiratory ones, an intense vasculitis affecting the superficial veins of the lower limbs and near-total desquamation of the lingual epithelium. Treatment with corticosteroids (betamethasone) led to complete remission in a few days. However, after recovery, she suddenly developed worsening heartburn and esophageal reflux. A year later, she was diagnosed with severe gastritis and mild dysplasia of the gastric body. Anamnesis revealed new-onset food intolerances to gluten-containing food and dairy foods. Histological examination showed *Helicobacter pylori* (HP) infection. After eradication therapy and dietary modifications, her gastric inflammation regressed, and dysplasia resolved. We hypothesize that SARS-CoV-2 may have triggered disruption of the gastric mucosa homeostasis, in turn leading to both food intolerances and HP proliferation. This case raises the question of whether SARS-CoV-2-induced molecular mimicry mechanisms may have long-term consequences on the gastric muco-microbiotic layer and in turn on the whole gastric homeostasis.

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Patient consent for publication: the patient gave her written consent to use her personal data for the publication of this case report and any accompanying images.

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Introduction

Since the onset of the COVID-19 pandemic, multiple extra-pulmonary manifestations of SARS-CoV-2 infection have been reported, including gastrointestinal involvement.[1] Although much attention has been given to antibiotics and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) overuse as risk factors for *Helicobacter pylori* (HP)-induced gastritis, in which are involved both innate and adaptive immune response,[2,3] little is known about the potential direct damage to the gastric mucosa caused by SARS-CoV-2.[4] This case report presents an unusual clinical case and its course, exploring the possible pathophysiological links between SARS-CoV-2 infection and alteration of gastric muco-microbiotic layer homeostasis.

Case Report

A 45-year-old woman, previously healthy and without obesity, hypertension, or any other chronic conditions, contracted SARS-

CoV-2 infection – diagnosed by molecular swab test – during the first wave of the COVID-19 pandemic in Italy, in June 2020. Apart from fever and respiratory distress, she developed an aggressive vasculitis affecting the superficial veins of her lower limbs (Figure 1a) as well as experienced the near-total desquamation of the lingual epithelium (not shown) referred to by the patient as "desquamation" of the tongue. Her physician, suspecting she was developing an autoimmune endothelial and epithelial injury triggered by molecular mimicry mechanisms, treated her with a one-week course of oral betamethasone, without NSAIDs or antibiotics, leading to complete resolution of symptoms. Unfortunately, neither blood examination nor occult fecal blood or fecal calprotectin research were performed at that time.

After recovery, she noticed novel symptoms after eating gluten-containing foods and dairy products, experiencing constipation rather than diarrhea, as well as severe facial rashes (Figure 1b) after consuming these foods. Approximately one year later, since the symptoms were progressively worsening, she underwent gastroenterological examination for severe gastritis symptoms, including gastroesophageal reflux, which she had never experienced before. Upper gastrointestinal endoscopy with biopsy revealed severe gastritis with mild dysplasia of the gastric body but no Barrett's esophagus or duodenal villous atrophy. HP infection was diagnosed histologically. In particular, the histological evaluation of the gastric body region, performed with hematoxylin and eosin staining, revealed moderate to severe chronic

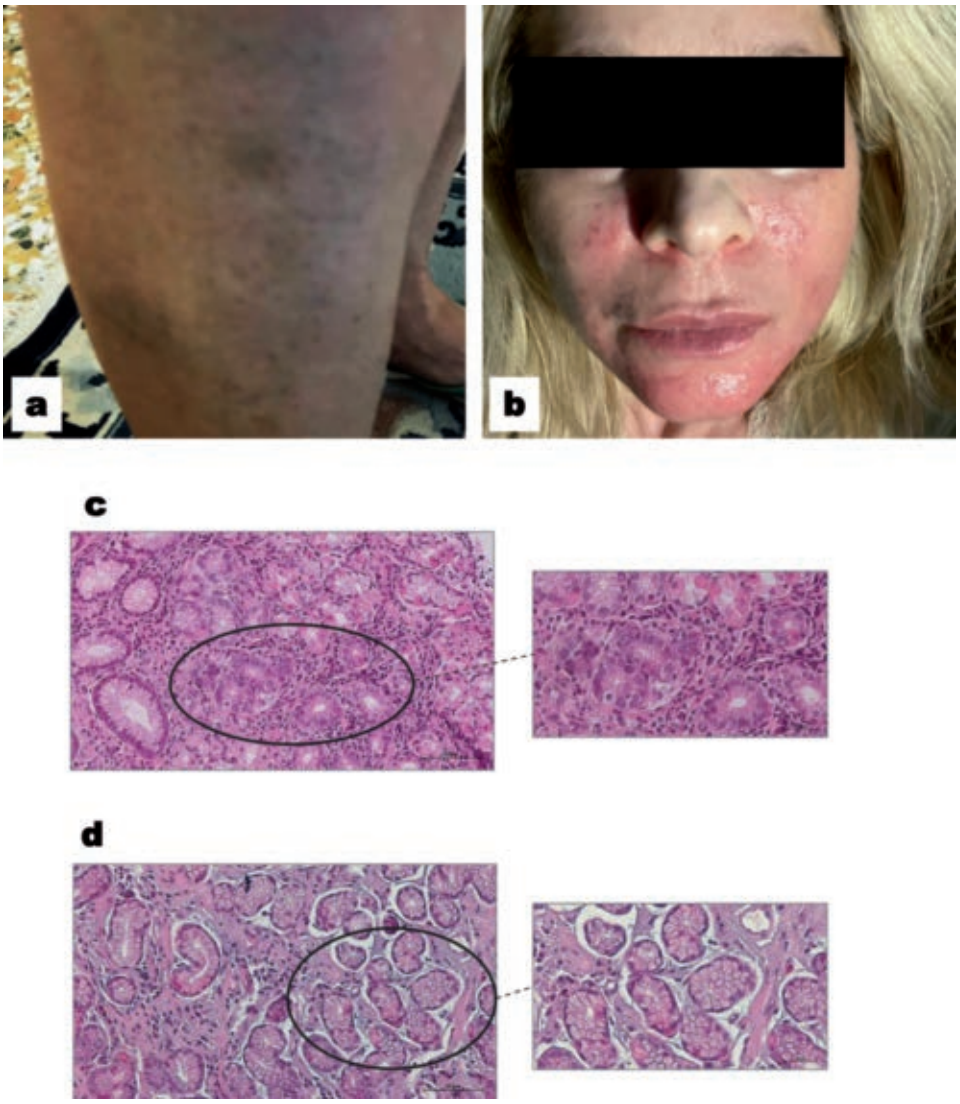

Figure 1. Representative images from our patient of (a) vascular lesions at the superficial veins of the lower limbs resembling vasculitis during acute COVID-19 symptoms and (b) the severe facial rashes experienced after consuming gluten-containing food and/or dairy foods during long-COVID-19. See text for more clinical details. Representative images of gastric body sections stained with Haematoxilin & Eosin. Magnification 200×, scale bar 50 µm, on the left; magnification 400×, scale bar 20 µm, on the right (*i.e.*, magnification of the area circled in the left microphotograph). Particularly, in (c) the presence of dysplastic glandular structures is evident, showing morphological alterations of the cellular elements and nuclear architecture. Several inflammatory cells are also present in the lamina propria. *Vice versa*, in (d) the lamina propria presents sparse foci of inflammatory cells and the glandular architecture does not show any significant morphological alterations. See text for more information about correlation between histopathology and clinical signs and symptoms.

gastritis and moderate-grade dysplastic changes affecting some glandular elements, which showed epithelial lining with enlarged, irregular, and pleomorphic nuclei (Figure 1c).

Hence, she underwent HP eradication therapy (bismuth-based quadruple therapy), along with a gluten- and lactose-free diet. Proton Pump Inhibitors (PPIs) and prokinetics were prescribed as needed. Three months later, HP eradication was confirmed via stool analysis. A maintenance regimen of PPI cycles, probiotics (*Limosilactobacillus reuteri*) and prokinetics was initiated.

At the 12-month follow-up, endoscopic evaluation confirmed HP negativity, complete resolution of dysplasia, and mild residual gastric inflammation. The histological evaluation at that time revealed a significant reduction in the inflammatory component present in the lamina propria and the complete absence of dysplastic changes in the glandular epithelial elements (Figure 1d). After an additional six months of clinical monitoring, she discontinued PPIs while continuing probiotics and occasional prokinetic therapy. However, the intolerances to gluten-containing and dairy foods remained and, to date, her diet excludes gluten- and dairy-containing products in order to keep symptoms under control.

Discussion

COVID-19 has significantly impacted the use of antibiotics, NSAIDs, and corticosteroids leading to increased HP-related gastritis cases. However, little is known about the direct effects of SARS-CoV-2 on the gastric mucosa.[4] This patient had no history of antibiotic or NSAID use, and she was treated only with corticosteroids during the acute phase of COVID-19 due to clinical signs of autoimmunity.

Psychological stress during the pandemic has been associated with gastrointestinal symptoms,[5] but it is unlikely that stress alone could explain the rapid onset of HP-positive severe gastritis with dysplasia and concurrent food intolerances described in this case. Alternative hypotheses must be explored.

Molecular mimicry is primarily driven by the adaptive immune response, though it is initiated by innate immunity through antigen presentation, leading to cross-reactivity when pathogen-derived epitopes resemble self-antigens and trigger autoreactive T or B cells. Molecular mimicry damage during COVID-19 has been well-documented by our group,[6-9] particularly affecting endothelial cells in multiple organs, including the lungs, heart, vessels, kidneys, bowel, and nervous system. Molecular mimicry is known to contribute to severe complications such as disseminated intravascular coagulation and multiorgan failure, as well as long-COVID neurological and cardiovascular damage.[10,11] However, little is known about its potential effects on the stomach during acute as well as long-term COVID-19.

The impairment of the muco-microbiotic layer in the stomach has already been postulated as a predisposing factor to develop and maintain HP infection.[12] We can hypothesize that gastric muco-microbiotic layer could be susceptible to SARS-CoV-2 infection, including molecular mimicry-induced damages (as already postulated by an independent group),[13] that could lead in turn to: i) alteration of microbiota homeostasis, allowing HP proliferation from a previously subclinical state, and ii) modification in biochemical/physiological tolerance to gluten and/or dairy products, triggering intolerance towards these aliments and chronic inflammation of gastric mucosa. However, we lack molecular confirmation for these hypotheses.

Conclusions

In conclusion, there is currently no clear answer to whether SARS-CoV-2 can directly induce alterations in gastric tissue homeostasis and/or HP proliferation and/or food intolerances in predisposed individuals. May SARS-CoV-2 infection play a role in the onset of functional disorders of the gastrointestinal tract? And among these, could celiac gluten sensitivity and other food intolerances be included?

The case reported in this work could not be an isolated one, but, to the best of our knowledge, we lack observational studies and translational research on *in vivo* and *ex vivo* models to explore the long-term gastrointestinal effects of COVID-19. Further investigation, including molecular mimicry pathogenetic phenomena, could improve our understanding of post-COVID gastrointestinal complications and guide future therapeutic strategies.

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