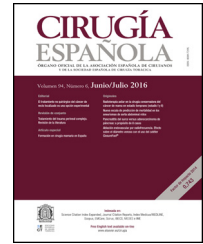




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



## Scientific letters

## Concomitant aortic, inferior mesenteric artery thrombosis and sigmoid colon perforation in severe COVID-19 disease



### Trombosis concomitante de la aorta, arteria mesentérica inferior y perforación del colon sigmoide en enfermedad COVID-19 severa

One of the most striking features of infection by SARS-CoV-2 – unlike other Beta-coronavirus (CoVs, SARS, MERS-coV) – is the development of thromboembolic complications<sup>1</sup>

The gastrointestinal thromboembolic complications of SARS-CoV-2 are associated with high mortality (32%–86%). We present the case of a patient with severe COVID-19 who developed infrarenal thrombosis and perforation of the colon.

A 79-year-old male was transferred to our center with severe bilateral pneumonia due to SARS-CoV-2 (COVID-19) and required mechanical ventilations. He had a history of acute myocardial infarction, hypertension, obesity (BMI 28), dyslipidemia and chronic obstructive pulmonary disease. On admission his ASA (American Society of Anesthesiology) score was IV. Blood analyses revealed hemoglobin 11.7 g/dL (Reference Range 13.6–17.0), leucocytes  $16.9 \times 10^9/L$  (RR 6–10) with 91% neutrophils, platelets  $251 \times 10^9/L$  (RR 150–450), D-dimer 1250 ng/ml (RR 150–500), C reactive protein 4.6 ng/dL (RR 0.0–0.50), ferritin 1171.1  $\mu\text{g/L}$  (RR < 500  $\mu\text{g/L}$ ), lactic acid 2.14 (RR < 2).

He was on antithrombotic prophylaxis with low molecular weight heparin (LMWH), 5000 UI/1xd.

Given the deterioration in his neurological state on admission (delirium, mental confusion), cranial and pulmonary computed tomographic angiography (CTA) was performed which revealed bilateral pneumonia (Fig. 1A) and pneumoperitoneum as a result of which an abdominal CTA was performed which showed pneumoperitoneum, mural thrombosis of the inferior mesenteric artery (IMA) and infrarenal aorta respectively (Fig. 1B, Fig. 2A and B).

The patient underwent surgery and perforation of the sigmoid colon with purulent peritonitis was identified and a Hartmann's procedure was performed. The patient progressed favorably after days in intensive care.

The histologic analysis revealed perforation of the colon associated with diverticulosis and a marked inflammatory reaction. A real time reverse-transcription polymerase chain

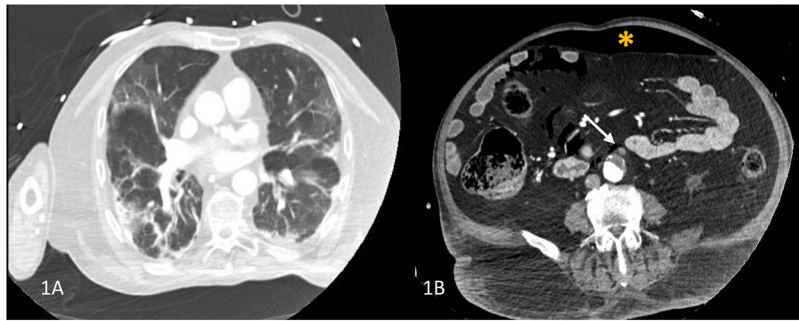
reaction (qRT-PCR) of the RNA extracted from the formalin-fixed, paraffin embedded tissue confirmed the presence of RNA from SARS-CoV-2, N gene, generic N:30,71 in the wall of the colon.

The patient signed the informed consent for the publication of his clinical information and images.

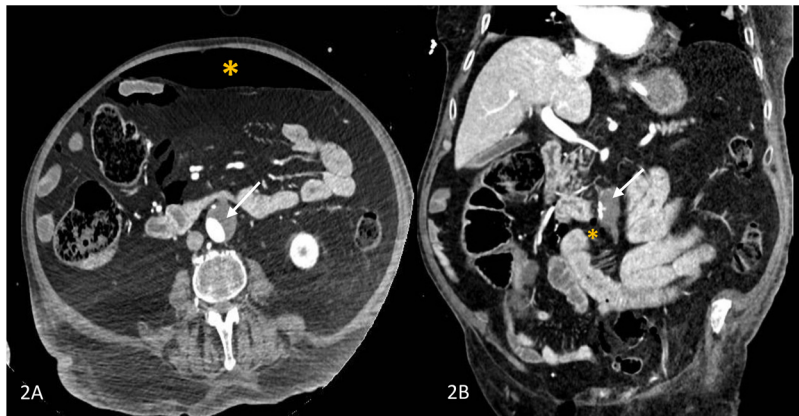
One of the most striking phenomena in severe COVID-19 is the high incidence of venous and arterial thromboembolic complications in multiple locations, even when prophylactic doses of low molecular weight heparin (LMWH) have been administered, a phenomenon which has recently been termed “COVID-19-associated coagulopathy” (CAC).<sup>1</sup> This abnormality is characterized by increases in D-dimer, fibrinogen, von Willebrand factor (VWF) and factor VIII with normal platelet levels, prothrombin time (PT) and activated partial thromboplastin time (aPTT) respectively.<sup>1</sup>

Recent studies have reported thromboembolic complications in 31% and 49% of COVID-19 patients admitted to intensive care in spite of antithrombotic prophylaxis.<sup>2,3</sup> In our case, thrombosis of the aorta and IMA was associated with perforation of the sigmoid colon with the presence of SARS-CoV-2 in the colon wall.

Several pathogenic mechanisms associated with thromboembolic complications and intestinal ischemia have been proposed. Firstly, vascular thrombosis would be due to the endothelial damage caused by SARS-CoV-2, thanks to the presence in the endothelium of angiotensin-converting enzyme 2 (ACE2) receptors and of type II transmembrane serine proteases (TMPRSS-2) which facilitate the binding of SARS-CoV-2 to the membrane of the cell endothelium a phenomenon known as immune-thrombosis or thromboinflammation.<sup>1,4</sup> Apart from the binding of viral proteins to the heparan sulfate, the endothelium loses its antithrombotic properties, a reduction in the synthesis of nitric oxide (NO) and an increase in angiotensin-II, which leads to procoagulant abnormalities.<sup>1,5</sup>



**Fig. 1 – (A) Computed tomographic angiography (CTA) of the chest showing bilateral ground-glass opacities and bibasilar areas of consolidation. (B) CT-angiographic image showing a large mural thrombus extending from the infrarenal aorta into the inferior mesenteric artery (arrow) and pneumoperitoneum (asterisk).**



**Fig. 2 – (A) CT-angiography image showing large mural thrombus of the infrarenal aorta (arrow) and pneumoperitoneum (asterisk). (B) Coronal CT-angiography depicting thrombus of the aorta (arrow) and pneumoperitoneum (asterisk).**

Secondly, direct injury of the mucosa of the intestine and colon has been reported by SARS-CoV-2, which is facilitated by the presence of abundant ACE2 and TMPRSS-2 membrane receptors in the intestine and colon.<sup>6,7</sup> The cell damage and necrosis would induce the innate immune response (the so-called “cytokine storm”) secondary to the release of damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), thus causing the synthesis of proinflammatory and prothrombotic cytokines.<sup>1,5,8</sup>

Finally, it cannot be ruled out that the perforation of the sigmoid colon might be due to the perforation of a diverticulum secondary to occlusive intestinal ischemia or non-occlusive ischemia resulting from abnormalities in perfusion.<sup>9</sup>

In spite of antithrombotic prophylaxis with LMWH and the recommendations of more than 70 scientific societies on antithrombotic prevention, in severe COVID-19 very often oligo-symptomatic (pauci-symptomatic) thromboembolic complications occur which require early diagnosis and treatment given their high morbidity and mortality.<sup>10</sup>

## Funding

None declared.

## Author contributions

Study concept and design (AA, JAC, JB,), data collection and analysis (AA, JAC), manuscript preparation (AA, JAC), manuscript review (AA, VV, JAC, FR). All authors reviewed and approved the final draft.

## Conflict of interest

All authors have no relevant conflicts of interest to report.

## REFERENCES

1. Iba T, Connors JM, Levy JH. The coagulopathy, endotheliopathy, and vasculitis of COVID-19. *Inflamm Res.* 2020;69:1181–9.
2. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020;191:145–7.

3. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost.* 2020;18:1023-6.
4. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet (London England).* 2020;395:1417-8.
5. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol.* 2020;20:363-74.
6. Mönkemüller K, Fry LC, Rickes S. COVID-19, coronavirus, SARS-CoV-2 and the small bowel. *Rev Espan Enferm Dig.* 2020;112:383-8.
7. Lamers MM, Beumer J, Van Der Vaart J, Knoops K, Puschhof J, Breugem TI, et al. SARS-CoV-2 productively infects human gut enterocytes. *Science.* 2020;369:50-4.
8. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. *Nat Med.* 2020;26:1017-32.
9. Peoc'h K, Nuzzo A, Guedj K, Paugam C, Corcos O. Diagnosis biomarkers in acute intestinal ischemic injury: So close, yet so far. *Clin Chem Lab Med.* 2018;56:373-85.
10. Wichmann D, Sperhake J-P, Lütgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. *Ann Intern Med.* 2020;173:268-78.

Ana Almeida<sup>a</sup>, Jorge Baixauli<sup>ab</sup>, Javier A. Cienfuegos<sup>abc</sup>, Víctor Valenti<sup>abc</sup>, Fernando Rotellar<sup>abc</sup>

<sup>a</sup>Department of General Surgery, Clínica Universidad de Navarra, School of Medicine, University of Navarra, Pamplona, Spain

<sup>b</sup>Institute of Health Research of Navarra (IdisNA), Pamplona, Spain

<sup>c</sup>CIBER Fisiopatología de la Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III, 31008 Pamplona, Spain

\*Corresponding author.

E-mail address: [fjacion@unav.es](mailto:fjacion@unav.es) (J. A. Cienfuegos).

<https://doi.org/10.1016/j.ciresp.2021.09.013>

0009-739X/© 2021 AEC. Published by Elsevier España, S.L.U. All rights reserved.

## Adenoma del colédoco: un reto diagnóstico y terapéutico



### Common bile duct adenomas: A diagnostic and therapeutic challenge

Los adenomas pueden aparecer en cualquier parte de la vía biliar, siendo la vesícula biliar el sitio más común y los del colédoco muy infrecuentes<sup>1</sup>. Hasta la fecha, existen descritos en la literatura científica solamente 39 casos<sup>2</sup>; no obstante, a pesar de su escasa prevalencia representan una patología de riesgo, dado el alto porcentaje de evolución a colangiocarcinoma. Se ha demostrado una secuencia evolutiva clara desde neoplasias de bajo grado, hasta convertirse en carcinomas invasivos, por activación de vías oncogénicas comunes como mutación de KRAS y sobre-expresión de p53<sup>3,4</sup>. Dada la escasez

de su presentación, no existen estrategias claras para su tratamiento. En términos globales existen dos tipos de posibles pólipos, los adenomatosos, que tienen comportamiento hostil, precisando un tratamiento igualmente agresivo y precoz; y por otro lado los hiperplásicos que virtualmente no tienen riesgo de malignización y se relacionan con inflamación crónica<sup>5,6</sup>. El tratamiento de los adenomas del colédoco es todo un reto para el cirujano que se enfrenta a la difícil decisión de resección ampliada de la vía biliar vs. una resección local del adenoma, sobre todo si, como en el caso



**Figura 1** – Figura 1(a). Colangio -RMN que muestra vacío nodular de señal en colédoco medio (flecha azul), compatible con adenoma. (b) Imagen del pólipo en el tercio medio del colédoco durante su resección laparoscópica. (c) Estudio anatomopatológico que muestra glándulas de tipo biliar rodeadas de estroma fibroso y con leve inflamación asociada.