



Letter to Editor

Duodenal bleeding in a patient with Covid-19-Related Acute Respiratory Distress Syndrome

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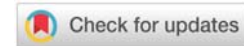
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Dear Editor,

High incidence of thrombotic complications was observed in patients with Acute Respiratory Distress Syndrome (ARDS) related to Coronavirus Disease 2019 (COVID-19) [1]. The pathophysiology seems related to systemic thrombophilia by hyper-immune reaction, inducing a “cytokine storm” [1].

Yet, gastrointestinal bleeding occurs in 2-3% of ARDS patients. Splanchnic hypo-perfusion is a major cause, due to increased plasma-renin-angiotensin-aldosterone activity, circulating catecholamines levels, and elevated Positive End Expiratory Pressure (PEEP) generally used in ARDS [2].

We propose the present case to reflect on the delicate balance between thrombosis and bleeding risk in patients affected by ARDS associated with COVID-19, especially when older, with multiple comorbidities, and undergoing treatments without the support of evidence-based medicine. Indeed, wanting to do “something” for COVID-19 critical patients, many doctors are utilizing treatments with unknown efficacy/safety profile, or never properly studied in critically ill patients: steroids and heparin at dosages higher than prophylactic ones, among others.

A 71-year-old man presented to the emergency department of our hospital on March 27, 2020, for acute respiratory failure. Upon arrival, he was alert, vital signs as follow: blood pressure 104/73 mmHg, heart rate 76 beats/minute, respiratory rate 40 breaths/minute, SpO₂ 70% in ambient air, body temperature 37.4 °C. Medical history was significant for arterial hypertension,

type II diabetes, and previous ischemic stroke. BMI was 31. He was discharged on March 21 from another hospital with diagnosis of COVID-19-related pneumonia without respiratory failure. Home therapy consisted of atenolol, valsartan, hydrochlorothiazide, pravastatin, ticlopidine.

At arrival arterial blood gas analysis at a FIO₂ of 0.5 showed: pH 7.51; PaCO₂ 27.1 mm Hg; PaO₂ 35.8 mm Hg with a PaO₂/FiO₂ of 71.6; bicarbonate 27.1 mEq/l; lactate 2.8 mmol/l, arterial O₂ saturation 84%. Abnormal laboratory data were: leucocytosis (13.28 k/μl) with lymphopenia (0.860 k/μl); normal haemoglobin (13.3 g/dl); D-dimer (2390 ng/ml); creatinine 1.34 mg/dl; LDH 922 UI/L; C reactive protein 140 mg/l. ECG was substantially normal. Chest Computed Tomography (CT) showed findings of COVID-19-related ARDS. Nasopharyngeal swab confirmed positivity for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

The patient was started on Non-Invasive Ventilation (NIV) in Pressure Support Ventilation (PSV) modality (pressure support, PS 12 cmH₂O; PEEP 8 cmH₂O; fO₂ 50%). After 1 hour, tachypnea ameliorated (28 breaths per minute), pO₂/FiO₂ increased (128), and blood pressure remained stable. The intensivist did not consider the patient suited for invasive mechanical ventilation suggesting to continue NIV.

In the following days, PS was progressively reduced to 6 cm H₂O and PEEP increased to 12 cm H₂O. The respiratory distress improved (pO₂/FiO₂ > 150 mmHg at subsequent checks). Pharmacological treatment consisted of fluids, piperacillin/tazobactam, azithromycin, omeprazole, methylprednisolone

(1 mg/kg qd) IV; ritonavir, darunavir, hydroxychloroquine, atenolol, valsartan (PO); enoxaparin (1 mg/kg qd SC, sub-therapeutic dosage).

During the night of day 3, the patient reported diffuse abdominal pain, without haemodynamic instability. Urgent blood count showed significant decrease of haemoglobin (9.1 g/dl), low RBC (3.020 mil/ μ l) and haematocrit (26.7%), normal platelets, persistent mild leucocytosis. Contrast-enhanced abdominal CT revealed duodenal perforation (as demonstrated by a small amount of extra-luminal free air in front of the liver) associated with evident arterial blushing (Figure 1).

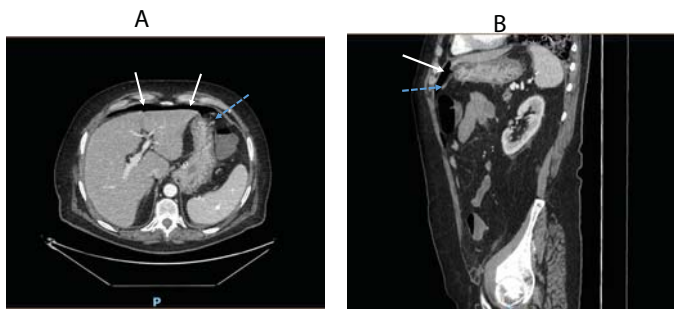


Figure 1A,B: Abdominal CT scan showing a duodenal perforation with arterial blushing. **1a:** axial section of the portal phase; **1b:** sagittal section of the portal phase; continuous arrows indicating extra-luminal free air in front of the liver; dashed arrow indicating arterial blushing.

Angiography, performed a few hours later, showed stop of the bleeding, therefore excluding the need for artery embolization. After intubation, a small perforation of the anterior surface of the duodenum was identified and sutured during laparotomy surgery. In addition, laparotomy confirmed the absence of active duodenal bleeding, in the presence of abundant amount of corpuscular material in the abdominal cavity, as for recent digestive haemorrhage. After surgery, the patient remained intubated, so still on invasive ventilation. Heparin was restarted in 24 hours, but at prophylactic dosage. No re-bleeding was documented, with stable values at serial blood count checks. After initial clinical improvement, he died of suppurative peritonitis few days later.

The haemorrhagic complication of our patient could be due to interaction among three main factors: NIV, steroids, heparin. Guidelines consistently suggest that patients with ARDS and $PO_2/FiO_2 < 150$ should promptly start on invasive mechanic ventilation, since delays increase mortality. High PEEP and low tidal volumes are suggested [3]. Yet, older patients are at higher risk of complications and of not being extubated following invasive ventilation: CPAP or NIV could, indeed, play a role in this population. However, it is important to remember that administering high pressures during Continuous Positive Airway Pressure (CPAP) or NIV is associated to barotrauma, including gastrointestinal perforation. A “more gentle” ventilation, with low tidal volume, possible only during invasive ventilation, could have prevented duodenal perforation in our patient.

Concerning steroids, there is no clear evidence of their efficacy in SARS-CoV-2-related ARDS [4]. On the other hand, it is well-known that they may give several side-effects, gastrointestinal bleeding or perforation among others. Least but not last the “heparin question”. Many colleagues are using intermediate or therapeutic doses in severe COVID-19 patients, due to reporting of increased risk of venous and arterial thrombosis. Yet, besides case reports and series, the only available (retrospective) study is on 449 Chinese patients with severe COVID-19. No difference was observed in 28-day mortality between patients treated with prophylactic-dose heparin and non-users. The mortality of heparin users was significantly lower only in patients with SIC score ≥ 4 , but in our patient SIC score was 2 [5-7]. For this reason, COVID-19-related ARDS should be currently treated with heparin at standard prophylactic dosage.

Finally, the disproportion between the amount of gastrointestinal bleeding and perforation observed in our patient may not have a pure iatrogenic basis. Researches on coagulation pattern of more severe forms of COVID-19 showed that these patients are at higher risk of developing not only thrombotic but also bleeding complications. This is true already within the principal target organ, the lungs: in an autopsy study, pulmonary thrombosis and hemorrhagic lesions were contemporary present in patients with COVID-19. Bleeding could be due to an imbalance in platelets production and disruption, prolonged PT and disseminated intravascular coagulation. Such heterogenous abnormalities of the coagulation system need to be better clarified, in particular to try to understand which patients are more at risk of thrombotic or bleeding complications.

Conclusion

A combination of therapeutic choices, widely used at present in the medical community without solid evidences, possibly both with a peculiar coagulation pattern, may have contributed to death of our patient affected by SARSCoV-2-related ARDS, not due to respiratory failure or thrombotic complications, but to significant gastrointestinal bleeding associated with duodenal perforation.

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