Vaso-occlusive crisis in a patient with sickle cell trait and COVID-19

Sickle cell trait (SCT) is a benign condition that only rarely, under hypoxic conditions, may result in microvascular complications that are normally seen only in homozygous patients. In COVID-19, diffuse alveolar damage and endothelial activation contribute to tissue hypoxia. Studies comparing COVID-19 outcomes in patients with HbAS and normal haemoglobin have shown no differences between groups or greater mortality rate in the former group.1,2 Here, we present a case of a 63-year-old man, mixed-race, married, resident of Salvador, Bahia-Brazil. He presented at a reference infectious disease hospital with flu-like symptoms, fever, odynophagia and fatigue that started seven days prior to admission and worsened over the previous 24 h, in association with lipothymia and dyspnoea. The patient had a history of arterial hypertension and used losartan. RT-PCR was positive for SARS-CoV-2. Chest radiographs, on the 2nd and 4th days following hospitalization, revealed ground-glass opacities predominantly in the lower lung segments that evolved to consolidations. As the patient required mechanical ventilation, he was transferred to the intensive care unit and orotracheally intubated due to severe hypoxemia, gas exchange PaO$_2$/FiO$_2$ < 100 mm Hg, and acid-base and electrolyte disturbances. Sedation was optimized, and the patient was treated with dexamethasone, omeprazole 40 mg/day (intravenously, 24 h), and Ceftriaxone and Azithromycin.

The lungs showed lesions characteristic of an acute exudative phase of diffuse alveolar damage in all examined sections. Hypertrophic and hyperplastic type II pneumocytes were shed to the alveolar lumen and, in many sections, were mixed with hyaline membranes. Sickled red blood cells were observed in the lumen of congested alveolar capillaries (Figure 1E), as well as in foci of intra-alveolar haemorrhage. The liver presented an overall preserved hepatic architecture. Areas of hepatic infarction characterized by extensive zone 3 coagulative bridging necrosis were observed (Figure 1A and B). In these necrotic areas, as well as in more preserved liver tissue, congested sinusoids containing clumps of sickled red blood cells were noted (Figure 1A and B). Canaliculus biliary cholestasis was observed. No inflammation was detected in the portal tracts, nor in the parenchyma. All spleen histological sections showed extensive coagulative necrosis associated with blood vessel occlusion due to fibrinous thrombi in the arterial vessels and venules (Figure 1C and D). The splenic red pulp was suffused with sickled red blood cells. The white pulp was effaced.

A minimally invasive ultrasound-guided autopsy was performed, and tissue samples were collected from the heart, lungs, liver, spleen, kidney, skeletal muscle of the brachial biceps and skin. Tissue fragments were fixed in paraformaldehyde and processed for histological analysis.

The most relevant findings in the present case, in addition to diffuse alveolar damage characteristic of severe COVID-19, were liver and splenic infarcts. The occurrence of splenic infarcts has been associated with a state of hypercoagulability in patients with...
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COVID. Liver infarctions associated with COVID-19 seem to be uncommon, as a search of the literature returned only a few cases of extensive liver infarcts.\textsuperscript{4,5} The liver is an organ with dual circulation, in which venous blood from the portal vein primarily contributes to liver perfusion; additionally, venous blood mixes with arterial blood from the hepatic artery. Coagulative necrosis (ischaemic) in the liver occurs in zones 3 of the hepatic acini (perivenular) in cases of severe hypoxia. This is associated with severe congestive heart failure, sinusoidal occlusion syndrome, or sickle cell disease due to sinusoidal occlusion and hypoxemia. In the present case, while the patient did not have a reported history of sickle cell disease, the occurrence of liver and splenic infarcts associated with intense vascular congestion and clumps of sickled red blood cells in the absence of a previous history of haematological or vascular occlusive events

TABLE 1 Clinical pathology data

| Test                 | Day of hospitalization |
|----------------------|------------------------|
|                      | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th |
| Haemoglobin (g/dl)   | 11.7| 11.2| 10.2| 10.4| 10  | 9.1 | 8.2 |
| WBC ($\times 10^9$/L)| 17,240\textsuperscript{a}| 23,680\textsuperscript{a} | 47,030\textsuperscript{a} | 57,190\textsuperscript{a} | 66,470\textsuperscript{a} | 64,830\textsuperscript{a} | 49,919\textsuperscript{a} |
| Serum albumin (mg/dl)| 3.0 | 2.8 | 2.2 | 2.2 | 2.1 | 2.0 |
| AST (U/L)            | 237 | 3,252| 6,244| 2,425| 1,111| 653 | 852 |
| ALT (U/L)            | 95  | 1,562| 2,615| 1,491| 1,046| 680 | 523 |
| GGT (U/L)            | 67  | 67  | 100 | 108 | 105 | 114 | 147 |
| AP (U/L)             | 296 | 341 | 657 | 753 | 639 | 711 | 798 |
| CPK (U/L)            | 425 | 5,095| 28,023| 32,347|
| CPKMB (U/L)          | 135 | 211 | 635 | 497 |
| TB (mg/dl)           | 0.97| 2.30| 2.06| 4.57| 5.58| 5.82| 6.47|
| DB (mg/dl)           | 0.10| 1.39| 1.40| 3.22| 3.94| 4.04| 4.52|

Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatases; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CPKMB, CPK myocardial band; DB, direct bilirubin; GGT, gamma glutamyl transferase; TB, total bilirubin; WBC, White blood cells.

\textsuperscript{a}leukocytosis with left shift.

FIGURE 1 Vaso-occlusive crisis in a patient with sickle cell trait and COVID-19: A - liver with large areas of coagulative necrosis (white arrows) with hepatocyte eosinophilia and nuclear loss (karyolysis, B). C - Splenic arterial thrombosis with fibrin and incipient peripheral organization. D - Spleen coagulative necrosis with arteriolar thrombosis. E - Lung capillary packed with sickled red blood cell (sRBC) containing parallel filaments in the cytoplasm and rare normal red blood cells (nRBC) with smooth cytoplasm. Focal fibrin aggregates (white arrow) are present in the capillary lumen.

COVID.\textsuperscript{3} Liver infarctions associated with COVID-19 seem to be uncommon, as a search of the literature returned only a few cases of extensive liver infarcts.\textsuperscript{4,5} The liver is an organ with dual circulation, in which venous blood from the portal vein primarily contributes to liver perfusion; additionally, venous blood mixes with arterial blood from the hepatic artery. Coagulative necrosis (ischaemic) in the liver occurs in zones 3 of the hepatic acini (perivenular) in cases
raised the suspicion that the patient might have had undetected sickle cell disease or SCT. DNA extracted from liver fragments and molecular analysis at the sixth position of the beta globin chain revealed both GAG and GTG codons, thus confirming the suspicion of SCT. In contrast to the patients studied by Resurrection et al. (2021) and Singh et al. (2021), prior knowledge of SCT had been obtained, which may have had a favourable impact on the course of disease. Thus, the present findings, together with observations in the literature, suggest that the potential contribution of the genetic background of specific communities should be considered when treating patients with COVID-19.

KEYWORDS
COVID-19, sickle cell crisis, sickle cell trait, splenic infarction, thrombosis

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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