Case Reports and Reviews

Case Report

Disseminated Intravascular Coagulation Associated With SARS-COV-2 Infection: A Post-Mortem Case Study

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Abstract

The mechanisms of coagulation disorder in COVID-19 are complex. However, it is already postulated that endotheliopathy and platelet activation may be important factors, causing direct damage to endothelial cells and the imbalance of inflammatory response, manifesting by venous arterial or microvascular thrombosis. The present study aims to describe a clinical case of an 8-year-old female patient with disseminated intravascular coagulation due to sepsis of viral etiology.

Introduction

Pneumonia caused by SARS-CoV-2 can present several complications, from severe pulmonary manifestations such as severe respiratory distress syndrome and pulmonary thromboembolism to coagulopathies, the latter being more associated with a poor prognosis [1]. The mechanisms of coagulation disorder are complex, postulating that endotheliopathy and platelet activation may be important factors, causing direct damage to endothelial cells and an imbalance in the inflammatory response, manifesting as venous, arterial, or microvascular thrombosis [2,3].

Pediatric patients, in contrast to adults, have a lower incidence of SARS-CoV-2 infection and, when infected, have much milder clinical manifestations of the disease. Reports from the United States point out that among the 149,082 confirmed cases as of April 2, 2020, only 73% of children had a fever, cough, or dyspnea, compared with 93% of adults, and only three deaths occurred in pediatric patients in this analysis [4]. In addition, studies conducted in China with 44,672 confirmed cases of COVID-19 up to February 2020 had only one death in children aged 10 to 19 years and none in the age group 0 to 9 years [5]

The pathogenesis of thrombotic complications in COVID-19 patients remains unclear [6]. However, vascular endothelium injury, platelet activation, and pro-inflammatory cytokine release appear to play some role in this process [7]. Patients with coronavirus who develop the severe type of disease have hemostatic abnormalities that resemble disseminated intravascular coagulopathy along with sepsis, with the difference that the presence of the coronavirus increases the chance of thrombosis rather than bleeding [6]. The inflammatory response and the hypercoagulable state cause a thromboinflammatory obstructive syndrome in the pulmonary, cardiac, and renal microvasculature with clots formed by neutrophils, platelets, and fibrins, evidenced in post-mortem studies and initiated through an intravascular aggregation of extracellular neutrophils, causing thrombi in the microcirculation and damaging organs [8,9]..

Among the most reported complications related to high mortality in those infected with COVID-19 there is coagulopathy, which is characterized by the activation and support of the coagulation cascade, which plays an important role in the aggravation of the disease, especially in patients with critical condition. The present study aims to describe a clinical case of an 8-year-old female patient with a condition of disseminated intravascular coagulation due to sepsis of viral etiology.

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Case report

Child, female, 8 years old, previously healthy, who had presented fever (not measured) starting two days before death, accompanied by vomiting after food, mild sore throat, mild dry cough, and some headache. Initially, family members medicated her with amoxicillin. Afterward, she was taken to medical attention, when she would have been advised to discontinue the antibiotic. Symptomatic drugs were prescribed and tests were requested that were not performed before death. At home, the day before her death, her father noticed her pale and cold skin. There were no reports of skin changes, sputum, runny nose, sneezing, neck pain, nuchal rigidity, or diarrhea.

About two weeks before the symptoms, the child had a boil on the skin of one of the lower limbs, which drained spontaneously. There was no history of trauma, comorbidities, or continuous use of medication. The child attended classes online, without any curricular or extracurricular face-to-face activities. The parents were diagnosed with COVID19 in June 2020, but the other family members did not undergo diagnostic tests at the time, as they did not have similar symptoms.

The child was taken to the emergency department feeling unwell, with severe shortness of breath and hyperextension movements of the upper limbs, whose description resembled a decerebration posture. During care, the patient had a cardiorespiratory arrest, with inaudible blood pressure, cold skin, and mydriasis. The heart rate was asystole. The body was sent to the Death Verification Service (*Serviço de Verificação de Óbito* - SVO) of Barbalha – CE, Brazil.

Autopsy presentation

The necroscopic examination revealed the body of a female child, with brown skin, brown eyes, black hair. He had signs of puberty (telarche, pubarche). Absence of trauma and signs of violence. Immunochromatographic (serological) tests were performed for HIV, Syphilis, COVID-19, Hepatitis B and C. All results were non-reactive.

On examination of the skull, it was found that the scalp and skullcap were congested. The meninges were also congested, without exudate. Heavy, swollen, and congested brain. Liquor with hemorrhagic aspect, resembling foci of subarachnoid hemorrhage (Figure 1). There were no other prominent macroscopic changes in the cut surface of the cerebrum, cerebellum, and brainstem.

Upon examination of the thoracic cavity, it was found that the pericardial fluid had a slightly increased volume, with a citrine appearance. The thymus had an area of hemorrhagic suffusion. The heart on the sections showed sparse dark mottiling reas in the left ventricular myocardium and dilatation of the right ventricular cavity, which showed recent blood thrombi adhered (Figure 2). Heart valves without abnormalities. There were no pleural effusions. The lungs were armed, with increased consistency, with ecchymotic foci in the visceral pleura. There were bilateral foci of red hepatization on sections (Figure 3).

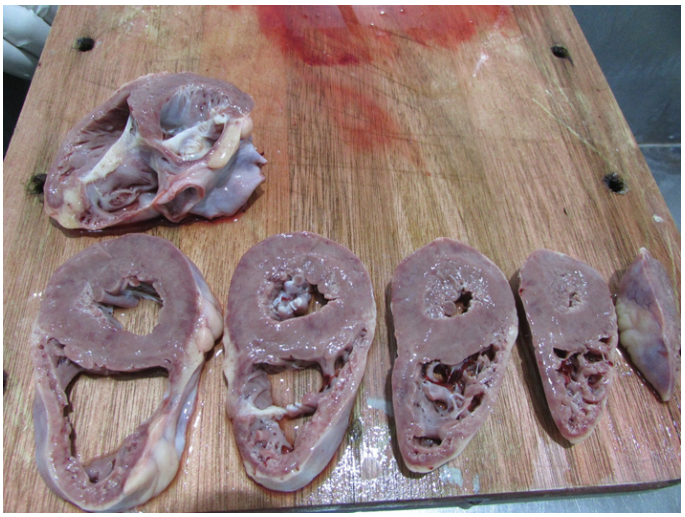

Figure 2. *Sections of the heart showing right ventricular dilatation and foci of hyperemia in all the walls of the left ventricle*

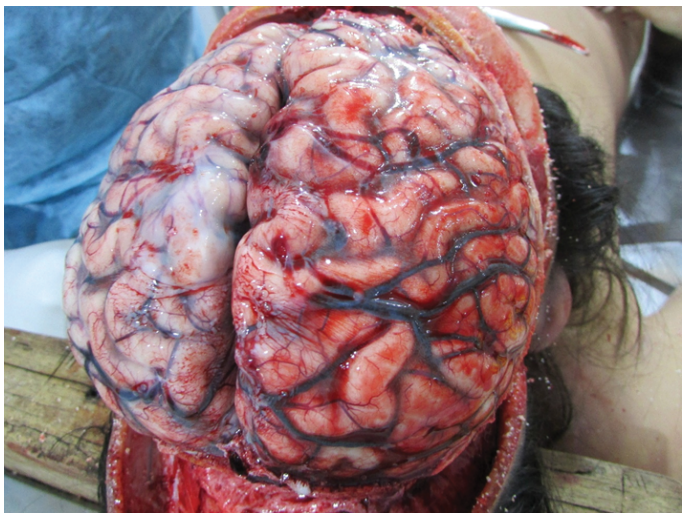

Figure 1. *External surface of the congested cerebral cortex, covered by hemorrhagic cerebrospinal fluid*

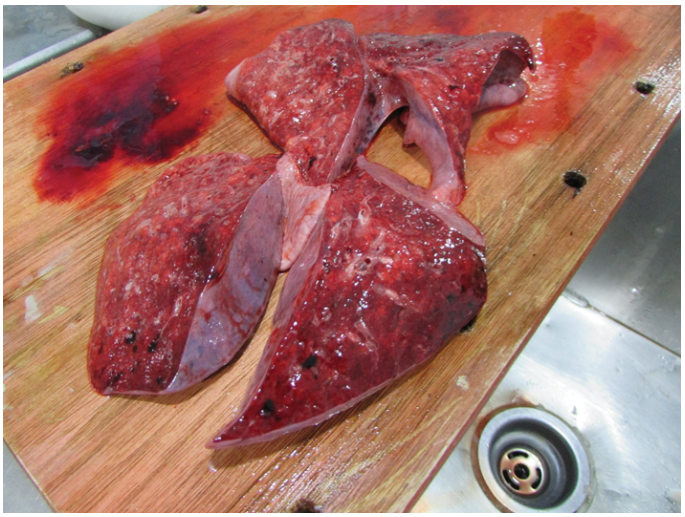

Figure 3. *Pulmonary cut surface with a hyperemic and compact appearance, as seen in infectious processes*

In the abdominal cavity, it was observed that the liver showed moderate steatosis. There was splenomegaly with a compact reddish cut surface and the presence of an accessory spleen. The kidneys were pale, with an appearance of shock. The pancreas, adrenals, intestinal loops, and cecal appendix had no prominent changes.

In the pelvic cavity, the ascitic fluid was more concentrated, with agglomerates with a fibrinous appearance. The urinary bladder was empty, with reddened mucosa. The uterus and annexes showed age-compatible morphology. Blood, cerebrospinal fluid, nasopharyngeal swab, and tissue fragments were submitted to serological, microbiological, and molecular analysis, considering that the doctors who attended the patient in the hospital emergency suggested the hypotheses of Meningitis or Heart Failure.

The histopathological examination revealed a swollen brain with discrete meningeal mononuclear inflammatory infiltrate and accentuated mononuclear inflammatory infiltrate affecting large areas of the myocardium. Congested lungs, with septal mononuclear inflammatory, infiltrate, sparing alveolar spaces, which were de-epithelialized, sometimes fused and forming pseudocysts. The liver with macro and microgoticular steatosis, presence of inflammatory cells in the sinusoids, and reactive aspect hepatocytes. The bladder had a mild mononuclear inflammatory infiltrate. In general, there were no granulomas, parasites, or malignancy.

A liquor bacterioscopy, by Gram stain, did not visualize microorganisms. One culture, also from the liquor, did not obtain microbial growth. Still, in the same sample, research was carried out for 27 microorganisms, using the Polymerase Chain Reaction (PCR) method. The results were negative for all pathogens surveyed: *Enterococcus spp., Staphylococcus aureus, Streptococcus (S. agalactiae; S.pneumoniae; S.pyogenes), Listeria monocytogenes, Acinetobacter baumannii, Pseudomonas aeruginosa, Haemophilus influenzae, Neisseria meningitidis, Enterobacteriaceae (Enterobacter cloacae complex; Escherichia coli; Klebsiella oxytoca; K.pneumoniae; Proteus spp.; Serratia marcescens.), Candida albicans, C. glabrata, C. krusei, C.parapsilosis, C.tropicalis*

Using blood samples, the test for Covid-19 was performed using the Chemiluminescence Microparticle Immunoassay method. The test revealed a result with a value equal to 60.2 (Non-Reagent: < 12.0; Inconclusive: >=12.0 and < 15.0; Reagent: >= 15.0) indicating reagent IgG for infection by Sars-Cov-2. The IgM test was non-reactive (result: 0.476; reference: Reagent: ≥ 1.00 AU/mL). RT-PCR for COVID-19 was not detectable in the sample collected through nasopharyngeal swab, investigating E, RdP, N, and IC genes. IgM serology for Zika Virus and Chikungunya in blood and liquor were negative, however IgM for dengue, both in blood and serum, was inconclusive. The search for NS1 antigen (Dengue) in the blood and the liquor was negative.

The autopsy findings, associated with laboratory tests and clinical history suggest the diagnosis of disseminated intravascular coagulation due to sepsis of viral etiology, with the main organs affected being the heart and lungs (myocarditis + bilateral pneumonitis).

Discussion

Children and adolescents constitute a smaller proportion of Covid-19 cases, generally developing more mildly, being mostly oligosymptomatic [10]. However, multiple organic inflammatory syndromes have been presenting more frequently in this age group than in adults and the elderly, characterizing a condition known as Pediatric Multisystem Inflammatory Syndrome (MIS-C) [11]. Despite being recognized mainly for promoting respiratory signs and symptoms, the multisystem inflammatory response caused by the SARS-Cov-2 infection is receiving greater emphasis, as it promotes an evident systemic dysfunction that affects several systems of the human body, including the cardiovascular, promoting an imbalance of homeostasis with increased inflammatory state and consequent development of coagulopathies [12].

SARS-Cov-2-induced coagulopathy presents mostly with consumption characteristics, similar to Disseminated Intravascular Coagulation (DIC), with thrombotic and hemorrhagic events being common as clinical manifestations of the clotting dysfunction generated by the virus [13]. The mechanism of this aggression is marked by the viral invasion of endothelial cells and its binding to the ACE-2 receptor, promoting direct cell damage and high release of cytokines, such as IL-1, IL-6, and TNF-α, occurring what is called of "cytokine storm", the main pathophysiological factor that leads patients to multiple organ failure (MOF) and even death [14]. Such cytokines act by attracting macrophages to different sites, which contribute to organic damage through phagocytosis of tissue structures, as in endothelial cells, releasing free radicals and increasing endothelial damage [14]. In our case report, this fact can be exemplified by observing in autopsy an abundant mononuclear inflammatory infiltrate in a large part of the myocardium, in addition to the lungs, brain, liver, and bladder.

In fact, the histopathological findings of lungs of increased consistency and ecchymotic foci in visceral pleura can be explained by the coagulopathy developed as a result of the coronavirus infection. This is characterized by an increase in the incidence of both thrombotic and hemorrhagic events, very similar to disseminated intravascular coagulation and quite marked in sepsis states. In the laboratory, this clotting disorder presents with an increase in thrombin synthesis, a drop in fibrinogen, an increase in D-dimer, and a prolongation of the prothrombin time, tending to a hypercoagulable state with a marked presence of microthrombi in the pulmonary circulation, which contributes to for this patient's respiratory and hemodynamic failure [15].

It is worth noting that the spectrum of manifestations of MIS-C, the probable post-infectious origin of these lesions, resulting from a systemic inflammatory process in response to infection, is usually observed at a time when, many times, the tests themselves for the direct identification of the viruses are negative, such as nasopharyngeal swab RT-PCR, while antibody serological tests are usually positive. On the other hand, in a US study of 100 hospitalized children with a clinical picture compatible with Kawasaki Disease or shock, ages ranging from 1 to 21 years, only 10% were not positive in the research tests for COVID-19, either for identification of the antigen, either to identify the antibody, and the majority progressed from the

baseline infectious condition to a more severe one weeks after the onset of the disease, which would point to a late worsening with a disproportionate immune response to the infection [16].

In addition, the systemic vascular injury promoted by the virus causes marked neurological aggression. This involvement can be observed by the presence of diffuse hypodense foci identified on MRI of the skull at an early stage of infection, and such foci represent accumulations of hemosiderin secondary to microhemorrhages in the central nervous system (CNS), as demonstrated by Regev et al. [17]. Comparing with our case report, we identified histopathological findings compatible with vascular congestion and hemorrhages, which corroborates the assumption of DIC promoted by Sars-Cov-2, in a post mortem brain piece with a scalp, skullcap, meninges, and brain congested and without exudate, which could indicate an inflammatory and non-infectious etiology of these findings, in addition to the hemorrhagic liquor, resembling foci of subarachnoid hemorrhage.

The study carried out by Larovere et al. [18], who collected data from 61 American hospitals, identified 15 cases of severe neurological impairment in patients younger than 21 years, of which eitght presented with acute CNS infection, either during the course of the disease or after. Among these infections, encephalitis and aseptic meningitis stood out. In cases of meningitis, developed as a result of direct viral infection, it was possible to identify particles of the virus or its RNA in the liquor in vivo or post-mortem. However, most cases did not develop meningoencephalitis due to direct viral infection, given the negativity for the presence of viral particles in the CSF, suggesting an immune-mediated lesion, which responded positively to plasmapheresis. MRI findings identified diffuse T2 hyperintensities and diffusion limitation involving white matter and corpus callosum, in addition to a diffuse demyelinating lesion, consistent with changes already reported in COVID-19 cases [19]. In our report, the clinical presence of headache and vomiting associated with a position similar to that of decerebrate led us to raise the diagnostic hypothesis of meningitis of infectious cause secondary to the virus, but the absence of other clinical findings such as nuchal rigidity and negative liquor serology ruled out this hypothesis. Furthermore, the same patient presented positive IgG serology for Sars-Cov-2 and negative IgM, reinforcing the theory of a post-infectious involvement explained by the diffuse endothelial lesion caused by the cytokine storm with the formation of microthrombi in the circulation. This fact justifies the ischemia present mainly in the microcirculation, such as the one that irrigates the meninges, causing tissue inflammation.

Finally, another relatively common finding among COVID-19 cases aggravated by MIS-C is cardiac involvement, presenting with left ventricular (LV) dysfunction evidenced on echocardiographic examination in approximately 62% of children admitted to hospitals in England, and who had criteria for MISC-C temporally associated with SarsCov-2, including signs and symptoms such as persistent fever for more than three days associated with clinical markers (such as shock, hypotension, skin rash, bilateral non-purulent conjunctivitis), laboratory (such as increased procalcitonin), absence of other possible diagnoses, and positivity for some diagnostic test for Covid-19 [20]. This fact can be evidenced in the report we present from the finding of dark mottiling reas in the LV myocardium, suggestive of ischemic involvement.

Conclusion

The case report presents a diagnosis suggestive of disseminated intravascular coagulation due to sepsis of viral etiology, evidencing a picture of myocarditis and bilateral pneumonitis. The histopathological findings of lungs with increased consistency and ecchymotic foci in visceral pleura can be explained by the coagulopathy developed as a result of the coronavirus infection.

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