**Maternal SARS-CoV-2 infection associated to systemic inflammatory response and pericardial effusion in the newborn: a Case-Report**

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## Introduction

The emergence and rapidly spread of the new coronavirus SARS-CoV-2 has become a worldwide public health problem. On March 2020, the "Coronavirus Disease-2019" (COVID-19) was classified as a pandemic. Transmission of SARS-CoV-2 mostly occurs between people through either respiratory droplets, although alternative routes have also been suggested[1].

Pregnant women and newborns are considered groups of greater attention in viral epidemic situations. Recently, a case of transplacental transmission of SARS-CoV-2 with neurological manifestations in the neonate was reported, confirming the potential for vertical transmission route [2].

This report, briefly, informs about the case of a 27-year-old woman admitted to the hospital at 32 weeks of gestation with SARS-CoV-2 infection. We describe for the first time in the literature a case of fetal pericarditis due to SARS-CoV-2 maternal transmission, accompanied by systemic inflammatory profile.

## Case report

Mother: 27 years old, second pregnancy, blood group O, Rh positive, without comorbidities, performed prenatal care with no complications, negative serologies, sterile urine culture and without changes in morphological ultrasound and nuchal translucency. She presented with flu-like symptoms in the 29$^{th}$ week of gestation, during the SARS-CoV-2 pandemic, and received symptomatic treatment. At 32 weeks and 4 days, the fetal echocardiogram performed routinely in the prenatal period revealed significant pericardial effusion with dilation of the vena cava, which demonstrates an overload in the cardiovascular system. Thus, interruption of pregnancy was recommended. During the hospitalization, the mother underwent corticosteroid therapy to prevent hyaline membrane disease in the baby

after birth. Maternal blood was negative for a panel of agents that may cause fetal pericardial effusion, such as Parvovirus, Epstein-Barr virus, Adenovirus, Influenza A and B, while a rapid serological test for SARS-CoV-2 showed both reagent IgM and IgG. The fetal echocardiogram was repeated after six days and an increase in the volume of the pericardial effusion was observed, suggesting a risk of fetal death from cardiac tamponade (Figure 1A).

An emergency cesarean section was performed at 33 weeks in an isolated operating room. The mother wore an N95 mask and immediate clamping of the umbilical cord was performed. The newborn had no contact with the mother at birth, being immediately taken to a radiant heat unit. The newborn, a female, was premature at 33 weeks and 4 days by the New Ballard Score and weighed 2400 grams, which is suitable for gestational age. She presented with apnea and bradycardia at birth, requiring neonatal resuscitation according to international guidelines. She responded well after a mask-bag ventilation cycle, with Apgar scores at 7 and 9 in the first and fifth minutes, respectively, maintaining a satisfactory respiratory drive. She was immediately transferred to a neonatal intensive care unit using a transport incubator, where a bedside echocardiogram was performed, confirming the pericardial effusion. No signs of cardiac tamponade were observed at that time (Figure 1B-C).

During first hour of life, the newborn was cleaned and blood samples were obtained. Results of blood tests collected were satisfactory and biochemical parameters were also considered normal (Table S1). Nasal and oropharynx swabs were also collected, and RT-PCR tests for SARS-CoV-2 were positive. A rapid serological test of cord blood and peripheral blood of the newborn was performed, and results were non-reactive for anti SARS-CoV-2 IgM and reactive for IgG, as expected in the case of maternal infection. Blood culture and serology for toxoplasmosis, cytomegalovirus, rubella, herpes, hepatitis A, B and C, anti-HIV and VDRL were negative, as well as a complementary viral panel. Amniotic fluid and

maternal blood samples were negative for SARS-CoV-2. Results of RT-PCR and serology tests are summarized in Table S2.

Fragments from different placental regions were negative for SARS-CoV-2, while data obtained from chorion were inconclusive, with amplification of a single target (Table S2). Histopathological analysis of the placenta showed mild and nonspecific circulatory changes, with varying sizes of chorionic villi, intervening space with foci of calcification and hemorrhage, deciduous with slight deposition of fibrin and fibrinoid necrosis in the wall vessels.

Two-hour-old patient was transferred to a referral service in pediatric cardiology for follow-up, and tests for cardiac enzymes and inflammatory markers such as D-dimer, ferritin, and serum transaminases were found altered (Table S1). The *electrocardiogram* showed *sinus rhythm.* On the first day of life, RT-PCR tests for SARS-CoV-2 on peripheral blood were also positive.

Although the chest X-ray did not show clinical expression, computed tomography scan showed an inflammatory ground glass pattern affecting less than 25% of the lung parenchyma, remaining under clinical surveillance (Figure 1D-F).

On the third day of life, the newborn evolved with hemodynamic instability, bradycardia, respiratory discomfort and apnea associated with metabolic acidosis (pH = 7.12, $pCO_2$=45, $pO_2$=107, $HCO_3$=15, BE=13.7, $O_2$ saturation=96%, lactate=12.4). After sedation, orotracheal intubation combined with invasive mechanical ventilation support, pericardiocentesis, amine administration in continuous infusion were performed. Empirical antibiotic therapy with Ampicillin and Gentamicin was also started. Twenty-eight milliliters of pericardial fluid were drained, and it showed cloudy aspect, cytology content of 350 cells (11% polymorphonuclear and 89% mononuclear cells) and 8,900 red blood cells. Biochemistry analysis of the fluid revealed glucose dosage of 118 mg/dL, 3.2 protein mg/dL,

530 LDH and negative bacterioscopy. RT-PCR for SARS-CoV-2 and viral panel were negative.

The pericardial drain was removed after 24 hours, along with sedation, and a new echocardiogram showed resolution of pericardial effusion. The newborn was transferred to the Neonatal Unit at the place of birth when she was five days old, still under invasive mechanical ventilation. Nasal and oropharyngeal swabs and blood samples remained positive for SARS-CoV-2 at that time (Table S2). Results of a cytokine panel indicated increased plasma levels of proinflammatory cytokines such as IL-1β, INF-γ, IL-6, and TNFα in the newborn's sample when compared to the mother. High levels of IFN-γ and IL-6 were observed in pericardial fluid (Table S3). In brief, the patient presented changes in cardiac enzymes, D-dimer, ferritin and serum transaminases, in addition to pro-inflammatory cytokines that, associated with the clinical picture and the presence of pericardial effusion, showed a systemic inflammatory response.

SARS-CoV-2 RNA obtained from the newborn oropharyngeal sample collected 1h after birth was sequenced using Illumina Platform, and 88% of viral genome was covered. The consensus sequence was aligned to reference genome NC_045512.2 and classified as lineage B. The mutation Asp614Gly was identified in the region of the S gene. Phylogenetic analysis revealed that the sequenced genome falls within one of the Brazilian transmission clusters (Figure S1).

At five days of life, the patient presented generalized hypotonia, even without sedation and a worsening of the infection associated with the use of invasive devices such as pericardial drain and deep venipuncture. Therefore, antibiotic therapy was modified to Cefepime and Vancomycin after the collection of a new blood culture. Thyroid hormone tests were conducted on the newborn and showed to be within normal limits (Table S1). Neonatal screening test was performed (heel prick test) and, shortly thereafter, patient received red

blood cell concentrate due to low hematimetric levels. After two days, on the seventh day of life, she was already more active and programmed extubation was performed. Patient was coupled to non-invasive ventilation, evolving from respiratory weaning to nasal CPAP and ambient air. Transfontanellar and total abdominal ultrasounds were performed, in addition to a new echocardiogram, and normal patterns were observed. Sucking was stimulated and the mother's breast was allowed with hygiene measures and use of a mask by the mother. Nasal and oropharyngeal swabs collected from newborn on the thirteenth and fourteenth days of life were negative for SARS-CoV-2 (Table S2), and contact isolation was suspended. Patient was discharged at 22 days of life, weighing 2405 grams.

**Discussion**

Vertical transmission of SARS-CoV-2 has been investigated in case reports and case series studies and the transplacental transmission route has recently been confirmed [2]. Nevertheless, literature data regarding clinical consequences of SARS-CoV-2 infection for the fetus and newborn are still limited. Mild symptoms are usually observed, although cases of pneumonia, respiratory distress, abnormal liver function and even death have also been reported [3]. Recently, a single case of neurologic damage after intrauterine infection by SARS-CoV-2 was also described [2]. In this study, we report a case of vertical transmission confirmed by the detection of the SARS-CoV-2 RNA in the newborn’s nasal cavity, oropharynx and blood shortly after birth. Unlike other studies, the symptoms of the newborn were critical, with severe inflammatory response evidenced by the presence of pericardial effusion. The virus was not detected in the pericardial fluid, suggesting that tissue damage results from inflammatory response. Pulmonary involvement was detected by tomography, which showed signs a ground-glass aspect. The mother presented positive serology and signs of controlled inflammatory response.

A phylogenetic analyses showed that the SARS-CoV-2 genome sequence obtained falls within one of the Brazilian transmission clusters [4]. The substitution detected at S protein is commonly observed in sequences from European countries and Brazil. Although residue 614 does not directly interact with SARS-CoV-2 receptor ACE2 or cellular proteases, a possible role on protein S stability cannot be ruled out[5].

Herein we report the first case of neonatal pericarditis and systemic inflammatory response after maternal infection with SARS-CoV-2. The lack of significant variations in SARS-CoV-2 genome suggests that clinical complications are probably attributed to host-related factors.

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**Conflicts of Interest**

The authors declare no competing interests.

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**Figure titles and legends**

**Figure 1: Fetal and post-natal echocardiogram and image exams.**

Legend: A: Fetal echocardiogram at 32 weeks and 4 days. B-C: post-natal echocardiogram showing no signs of cardiac tamponade. D-E: Sagittal chest tomography images showing the "ground-glass pattern" of inflammatory infiltrate in lungs (E) and pericardial effusion at mediastinal region (E). F: Chest X-ray showing well expanded pulmonary parenchyma, without infiltrate. Tomography and X-ray images were obtained 2 hours after birth. The arrows indicate pericardial effusion.

Figure 1