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Case Report

Co-Occurrence of Chronic Histiocytic Intervillositis, Trophoblast Villi Necrosis and Polymerase Chain Reaction Prove Placental and Fetal/Neonatal Infection by SARS-Cov-2: A Case Series

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Abstract

COVID-19 infection began as an epidemic in China and has rapidly spread to a wide number of nations, with the number of infected people increasing every day. Pregnant women are susceptible to a more severe course of pneumonia because of physiologic maternal adaptations to pregnancy, with increased morbidity and death as a result.

Placental pathology in maternal infection settings by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) remains a topic of great interest. It is known that direct involvement of the placenta by SARS-CoV-2 is a rare event even using an immunohistochemical study, also the placental lesions in this context are heterogeneous and complex with a pathophysiology not yet fully understood.

We herein report three cases of uncommon co-occurrence of placental phenotypes related to maternal SARS-CoV-2 infection, one of them associated with neonatal death at day 9 of life, due to cardiac tamponade. SARS-CoV-2 infection was confirmed by polymerase chain reaction (PCR) in the placenta and in the lungs and heart of the neonate.

While our cases demonstrate an uncommon placental phenotype related to SARS-CoV-2 infection, the significance of these findings is by itself nonspecific requiring additional molecular studies to prove the meaning and consequence of different placental histopathological features.

Keywords: Atypical Red Blood Cells; Chronic Histiocytic Intervillositis; Polymerase Chain Reaction; Placental Lesions; Pregnancy SARS-Cov-2 Infection; Trophoblast Cell Necrosis

Introduction

The placenta plays a crucial role in maintaining an optimal environment for fetal development throughout pregnancy until birth [1,2]. This shared, highly perfused organ, separates the maternal and fetal circulation and offers a protective barrier that prevent the fetus to become exposed to maternal infections [3]. Despite this, microorganisms of the TORCH group (Toxoplasma gondii, other, Rubella virus, Cytomegalovirus, Herpes simplex virus) have been associated with the development of congenital diseases [4]. These infectious agents have evolved important mechanisms to bypass the microbial defenses of the placenta and its ability in restricting vertical transmission [4]. Therefore, understanding the complex mechanisms of pathogenesis underlying the interactions between the pathogen and maternal and/or fetal hosts during the context of pregnancy is crucial to manage the outcome of these infections.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel beta coronavirus that causes coronavirus disease 2019 (COVID-19), a severe infectious respiratory disease. Evidence from other coronavirus infections, such as SARS-CoV or MERS-CoV, suggests that infected pregnant women might be more susceptible to adverse outcomes, including intubation, admission to the intensive care unit (ICU), renal failure and death [5]. However, there is currently insufficient data regarding the impact of SARS-CoV-2 infection on pregnant women, specifically in pregnancy outcomes and the prevalence of perinatal complications. In this regard, recent data shown that infections by SARS-CoV-2 can affect the placenta, causing well-documented microscopic changes [6-10]. Indeed, several studies have evidenced fetal or maternal vascular malperfusion (or both), inflammatory lesions, including chronic histiocytic intervillositis, chronic non-specific villitis, funisitis, and acute or chronic chorioamnionitis [10-14]. Furthermore, SARS-CoV-2 infection has also been shown to increase placental inflammatory and oxidative stress, compromising fetal development and pregnancy outcome [15]. It is therefore not surprising that maternal SARS-CoV-2 infection can increase the risk of miscarriage, preterm birth, pre-eclampsia and till birth [6,7,10,12,13]. Crucially, these conditions can have long-term negative consequences, including the development of cardiovascular or metabolic diseases in adult life [16]. Therefore, proper management of these pregnancies requires that we understand the in utero impact of SARS-CoV-2 infections in the placenta to anticipate and minimize the disease [13,14]. This knowledge will improve our understanding on the placenta in maternal-fetal infection with SARS-CoV-2, and may help to evaluate placental risk factors for developing intrauterine transplacental fetal or neonatal infection [12-14,17].

In this work, we identified a distinctive placental inflammatory profile associated with the presence of active viral infection of the placenta. This inflammatory profile is characterized by chronic histiocytic intervillositis, hyaline necrosis of trophoblastic cell and basal membrane of chorionic villi associated with the presence of active viral infection of the placentas. We support our observations with potential interpretations of the effect of SARS-CoV-2 infection on the placenta and the pathophysiology of maternal-fetal and neonatal infection [10-14,18].

Cases Presentation

We herein report three cases of maternal SARS-CoV-2 infection diagnosed in the context of the universal testing that was implemented for all obstetrical patients admitted for surveillance due to intrauterine growth restriction and olygoamnio (case 1), or premature labor and delivery (case 2 and 3). Two of the cases (cases 1 and 2) were of singleton gestations and one (case 3) a twin bichorionic gestation. All cases had received a maternal laboratory-confirmed diagnosis of SARS-CoV-2 infection on the third trimester of pregnancy using a qualitative real-time polymerase chain reaction (RT-PCR) from a nasopharyngeal swab specimen. Preterm delivery occurred in all the cases. The newborns of case 1 and 2 tested negative for SARS-Cov-2 infection while both twins (case 3) tested positive.

Placental formalin fixation, sampling and lesions' classification were performed according to the Amsterdam Placental Workshop Group Consensus [14]. Placental percentiles and phenotypes were evaluated (Table 1) and classified [1,2,19-21] Molecular analysis for the presence of viral nucleic acids was performed in tissues collected from paraffin blocks using RT-PCR. A late neonatal death associated to a cardiac tamponade occurred in case 1 and the autopsy was requested and performed.

	GA (weeks)	CHI	HNTC	FVM	FD	MVM	Other	PWP*	FPR*	NND	GEN
Case 1	29	+	+	+	massive	+	-	P50-90	3,8 (P3)	+	+
Case 2	32	+	+	+	focal	+	-	P50	N/A	-	+
Case 3 (both twin)	34	+	+	+	focal	+	+	N/A	N/A	-	+

Legend: GA, gestational age; CHI, chronic histiocytic intervillositis; HNTC, hyaline necrosis of the trophoblastic cells and basal membrane; FVM, fetal vascular malperfusion; FD, fibrin deposition; MVM, maternal vascular malperfusion with distal villous hypoplasia in case 3; Other, Other non-specific lesions; PWP, placental weight percentile; FPR, fetal-placental ratio; NND, neonatal death; GEN, SARS-Cov-2 genome analysis; N/A, not available. *J Clin Anat Pathol 2019, Nogueira R

Table 1: Placental spectrum lesions and percentiles.

The ethic board committee approved this study as minimal-risk research using data collected for routine clinical and pathological practice and waived the requirement for informed consent.

Case 1

Clinical data: A 35-year old multiparous (IIIG, IIP) submitted to an emergency cesarean at 29 weeks plus 6 days of gestation, due to fetal bradycardia. She presented with pruritus, thrombocytopenia and mild liver dysfunction. The pregnancy had been uneventful up to that point, except for fetal growth restriction and olygoamnios. The newborn weighted 1,120g at birth and neonatal death ensued at day 9 of life from cardiac tamponade.

Placental and autopsy pathological study: The placental dimensions (15x14x2.5cm) and weight (293g) were on percentile 50-90. Histopathological analysis revealed the co-occurrence of chronic histiocytic intervillositis, and hyaline necrosis of the trophoblastic cells and basal membrane of villi (Figure 1). In addition, features such as fetal and maternal vascular malperfusion and acute subchorionic hematoma and massive transmural fibrin deposition (Katzman type) were documented [21]. Fetal autopsy documented a chylous pericardial effusion associated with lymphocytic pericarditis of non-specific type, also individual cardiac myocyte necrosis and lung endothelial injury without hyaline membrane disease, giant cells or eosinophils (Figure 1) were identified.

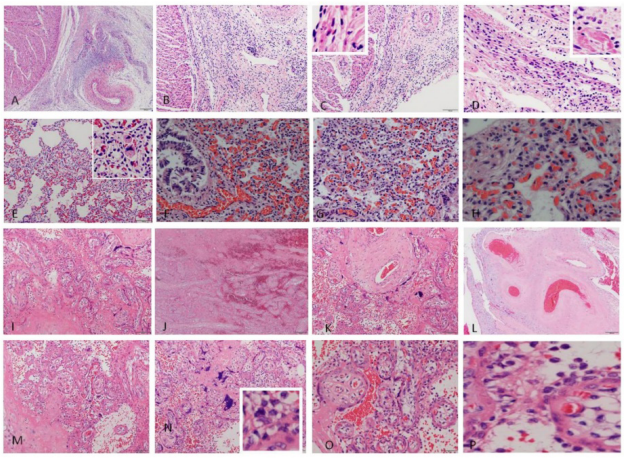

Figure 1: Case 1, Fetal and Placental Microscopy. Fetal heart: A, B, lymphocytic pericarditis of non-specific type [H&Ex100; C,D, individual cardiac myocyte necrosis (inset) [H&E x100 (C), x200(D)]. E-H, Fetal lung: E-H, cell injury with atypical features (inset) without hyaline membrane disease, [H&Ex200]. Placenta: I,J, extensive perivillous fibrin deposition with chorionic infarct [H&Ex100]; K,L, fetal obliterative vessel lesion [H&Ex100]; M,N, chronic inflammatory infiltrates in the maternal space (chronic histiocytic intervillositis) (inset) [H&Ex40]; O,P, hyaline necrosis of the chorionic trophoblastic cells and basal membrane subtrophoblastic layer of villi fetal-maternal interface [H&E x100 (O), x200 (P)].

Polymerase chain reaction study: SARS-CoV-2 genetic material was detected in the placenta (S gene Ct 3.248.151, ORF1ab positive, N gene positive, S gene positive), and in the lung, and heart of the newborn (Lung-ORF1ab Ct 3.248.151, ORF1ab positive, N gene positive, S gene Negative; ORF1ab 2.564.185 S gene Ct 2.881.335, ORF1ab positive, N gene positive, S gene Positive; Heart-S gene Ct 3.248.151, ORF1ab positive, N gene positive, S gene Negative; S gene Ct 2.533.126 ORF1ab positive, N gene positive, S gene Positive).

Case 2

Clinical data: A 34-year old primigravida with singleton pregnancy at 32 weeks plus 5 days of gestation. Asymptomatic, and carrier of the TTRMet30 mutation, she was hospitalized and submitted to an emergency cesarean due to severe thrombocytopenia (medicated with dexamethasone) and pathological cardiotocography (fetal bradycardia). The neonate had a favorable outcome and did not develop clinical features of COVID-19.

Placental pathological study: The placental dimensions (14x13x3cm) and weight (331g) were on percentile ≥P50. The umbilical cord had a marginal insertion, measuring 29cm of length. Histopathological analysis revealed the co-occurrence of chronic histiocytic intervillositis mixed with atypical red blood cells and hyaline necrosis of the chorionic trophoblastic cells and basal membrane subtrophoblastic layer of villi fetal-maternal interface (Figure 2). Fetal and maternal vascular malperfusion associated with fibrin deposition was also present.

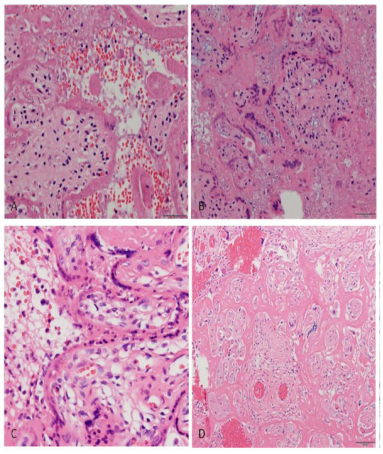

Figure 2: Case 2, Placenta Microscopy: A-D, mild inflammatory infiltrates in intervillous space mixed with cell debris and fibrin deposition; hyaline necrosis of the chorionic trophoblastic cells and basal membrane subtrophoblastic layer of villi fetal-maternal interface [H&E x100 (A,B), x200 (C,D)].

Polymerase chain reaction study: Analysis of SARS-CoV-2 genetic material detected placental infection (N gene Ct 9.739.334, ORF1ab positive, N gene positive, S gene Negative).

Case 3

Clinical data: A 39-year old primigravida with a bichorionic pregnancy, complicated by gestational diabetes and placenta previa. SARS-CoV-2 RT-PCR test was negative. Four days after admission she was diagnosed with COVID-19 after started coughing, and presented anosmia and dysgeusia. At 34 weeks of gestation, she presented with severe vaginal bleeding and an emergency cesarean section was performed. Both neonates were male; their weights and Apgar scores were 2300g and 5/7/9, and 2000g and 6/8/9, respectively.

Nasopharyngeal swab of the neonates collected at birth were positive for SARS-CoV-2 infection. The positive result was confirmed at the 4th day of live. The neonates never developed clinical features of COVID-19, and both displayed vital parameters in the normal range with favorable outcomes.

Placental pathological study: Confirmed a dichorionic twin placenta with 14x13x3cm, 860g of weight, and symmetric shared compartments. Umbilical cord length was of 30cm and 29cm in the first and second fetus, respectively, the latter with a velamentous insertion associated with acute retro membranous hemorrhage. Histopathological analysis revealed a distal villous hypoplasia and co-occurrence of chronic histiocytic intervillositis mixed with atypical red blood cells and hyaline necrosis of the trophoblastic cells and basal membrane of villi in both compartments (Figure 3).

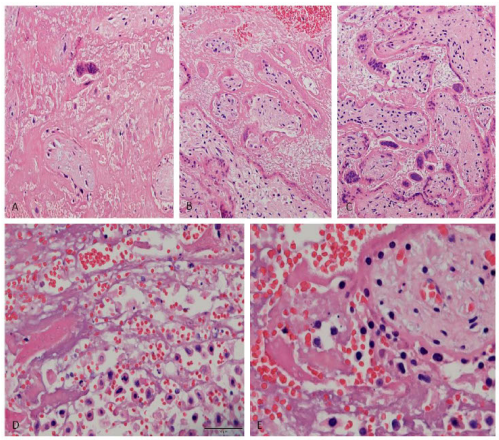

Figure 3: Case 3, Placenta Microscopy: A, fibrin deposition [H&Ex100]; B, C, hyaline necrosis of the chorionic trophoblastic cells and basal membrane sub-trophoblastic layer of villi fetal-maternal interface [H&Ex100]; D, E, chronic inflammatory infiltrates in intervillous space mixed with fibrinoid [H&E x100 (D), x200 (E)].

Polymerase chain reaction study: Placental and umbilical cord were positive for SARS-CoV-2. Twin 1-S gene Ct 2.136.129 ORF1ab positive, N gene positive, S gene Positive; 1.976.302 ORF1ab positive, N gene positive, S gene Positive. Twin 2-N gene Ct 1.231.384 ORF1ab positive, N gene positive, S gene Positive.

Discussion

Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was declared a global pandemic in March 2020. There is currently a worldwide effort to understand the long-term impacts of this disease, particularly on pregnant women and their fetus [22]. Accordingly, recent data suggest that the prognosis of SARS-CoV-2 infection could be more severe in pregnant women [7,11,13,17-19]. Indeed, maternal physiological adaptations to pregnancy have been shown to increase the risk of developing severe illness in response to viral infections [23-34]. Therefore, it is critical to define the impact of SARS-CoV-2 infection in pregnant women and their fetus.

Several studies have identified SARS-CoV-2 in the placentas of women who have tested positive for COVID-19 at, or prior to, delivery [7,35]. Importantly, in some cases the placenta displayed distinctive signs of inflammation with infiltration of maternal immune cells and increased vascular malperfusion, which is indicative of thrombi in fetal vessels [6,8-10,17]. Despite the significant variability in placental lesions of pregnant women with COVID-19, with or without fetal and neonatal infection, our cases document a recurrent phenotype (Table 1). Indeed, our pathological study identified a distinctive placental inflammatory profile associated with the presence of active viral infection of the placenta, characterized by chronic histiocytic intervillositis together with hyaline necrosis of trophoblastic cell and basal membrane of chorionic villi. These data are in line with recent reports (Schwartz) suggesting that the co-occurrence of chronic histiocytic intervillositis and trophoblastic necrosis are important risk factors for placental infection with SARS-CoV-2 as well as for maternal-fetal viral transmission. Indeed, chronic histiocytic intervillositis and trophoblastic necrosis are frequently associated with fetal and neonatal SARS-CoV-2 infection [12-14,24,27]. Therefore, it is tempting to speculate that these overlapping phenotypes are potential mechanisms by which SARS-CoV-2 breaches the maternal-fetal interface and causes miscarriage or neonatal disease with variable symptoms [23,24,27-29].

In addition, we also documented non-specific lesions, including distal villous hypoplasia, maternal vascular malperfusion (deciduous arteriopathy), fetal vascular malperfusion, and massive fibrin deposition, a type of lesion associated with high recurrence risk and perinatal adverse outcome (Case 1). These data taken together support the hypothesis that in utero SARS-CoV-2 vertical transmission is possible [12,23,24,27,36], and reinforces the association between the preterm delivery and the co-occurrence of two distinct histological phenotypes with and without fetal or neonatal SARS-CoV-2 infection [13,14,28,29,36].

The occurrence of massive fibrin deposition observed in case 1 could increase the risk of fatal neonatal disease. However, the lymphocytic inflammatory infiltrates found in the heart tissue (pericarditis of non-specific type), are associated with pericardial chylous effusion and cardiac myocytes necrosis-a characteristic histology finding of a recent myocardial infarction-are better explained by an infectious disease that was confirmed by molecular analysis of complement deposition of viral RNA in lung and heart tissues, despite the mild lung endothelial lesion with inconspicuous atypical cells (Figure 1). On the other hand, the fact that molecular analysis documented placental SARS-CoV-2 infection in cases 2 and 3, with neonatal infection in both twin of the case 3, the neonates never developed clinical features of COVID-19 and their vital parameters were always normal with favorable outcome.

As SARS-CoV-2 genome was detected in all samples analyzed our data show that molecular diagnose of SARS-CoV-2 infection is feasible from material extracted from formalin-fixed paraffin embedded tissues. Overall, our data demonstrate the possibility of detecting SARS-CoV-2 genome in material collected from formalin-fixed and paraffin-embedded samples, and support an associated characteristic phenotype characterized by the co-occurrence of chronic histiocytic intervillitis and trophoblastic and basal membrane villi necrosis, with or without fetal or neonatal infection [13,14].

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Ethics approval and consent to participate: Not applicable.

Consent for publication: Institutional consent form will be provided if required.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the

corresponding author on reasonable request. The datasets generated and/or analyzed during the current study are not publicly available due [to protect the anonymate] but are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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