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Finding of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) within Placental Tissue 11 Weeks after Maternal Infection

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Running title: long persistence of the SARS-CoV-2 virus in human placenta

Dear Editor:

We read with particular attention the article of Schwartz *et al*. recently published in your journal [1].

Here we want to discuss a case of long persistence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus in placental specimens, associated with histiocytic intervillositis, marked increase in perivillous fibrin deposition and chronic high-grade villitis. The mother was previously hospitalized for a symptomatic SARS-Cov-2 infection at 26th week of gestation (GW), while spontaneous delivery occurs at 37th GW. The reverse transcription polymerase chain reaction (RT-PCR) of the nasopharyngeal swab taken at delivery was negative, in both mother and child. Placental weight was under the 3rd centile for gestational age, no IUGR (intrauterine growth restriction) was recorded during pregnancy; the neonatal outcome was unremarkable.

Here we show a pattern of histiocytic intervillositis associated with the immunohistochemical permanence of SARS-Cov-2 in Hofbauer cells and in the walls of intravillous fetal vessel, not in trophoblastic cells. The clone used to identify the virus (anti-nucleocapsid GTX135361, GeneTex) was previously tested for this purpose[2]. Besides, we find another hallmark of chronic persisting damage such as a marked increase in perivillous fibrin deposition, chronic high-grade villitis, and chronic deciduitis (Fig 1A, B, C, D).

Viruses can be vertically transmitted from mother to infant through intrauterine (hematogenous or ascending paths), intrapartum, and postpartum routes. Even though a large majority of infants born to pregnant women with coronavirus disease 2019 (COVID-19) have been uninfected, new evidence shows that vertical transmission can occur. A recent analysis reveals that nearly 70% of SARS-CoV-2 positive neonates have acquired the infection through postpartum transmission, while the remaining 30% through intrauterine or intrapartum mechanisms. Among all (122), 5.7% were stated to have confirmed congenital infection [3].

It has been reported that, once the transmission has taken place, its effect on the fetus and the newborn can be relevant, leading to preterm delivery, admission to neonatal intensive care, or even stillbirth. A review of literature has shown only a case of persistence of the virus associated with placental lesions suggestive of inflammation, after a previous SARS-CoV-2 infection. However, in this case, the infection occurs at 8th GW, leading to a spontaneous abortion at 13th GW [4].

While the placental lesions previously described in the work of Schwartz et al[1] were related to an acute, symptomatic infection, here we demonstrate a histiocytic intervillositis with the specific viral persistence, even after 11 weeks from the previous maternal symptomatic infection, in otherwise healthy mother and newborn.

All these findings may be the consequence of an immune-mediated persistent injury to the maternal-fetal interface. Trophoblast destruction may act as a potential mechanism to allow the virus to penetrate the chorionic villi and, once reached the fetal vessels, to widespread in the fetal circulation, persisting in fetal vessels and macrophages, as shown (Fig 1 D).

Besides confirming the pathogenesis of damage previously hypothesized, our findings add new relevant information about how long SARS-CoV-2 can survive in human placentas. This may be crucial for clarifying the viral mechanism of persistence in all the tissue involved after primary infection, not only in trophoblastic derived cells.

Figure legend:

Figure 1. A) histiocytic intervillositis (hematoxylin and eosin stain [H&E]; magnification 20X); B) perivillous fibrin deposition and high-grade chronic villitis (H&E; magnification 25X); C) histiocytic intervillositis confirmed by CD 68 staining (PGM1 ready to use DAKO; magnification 25X); D) permanence of severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) in Hofbauer cells and in the walls of intravillous fetal vessels (anti-nucleocapsid; magnification 40X).

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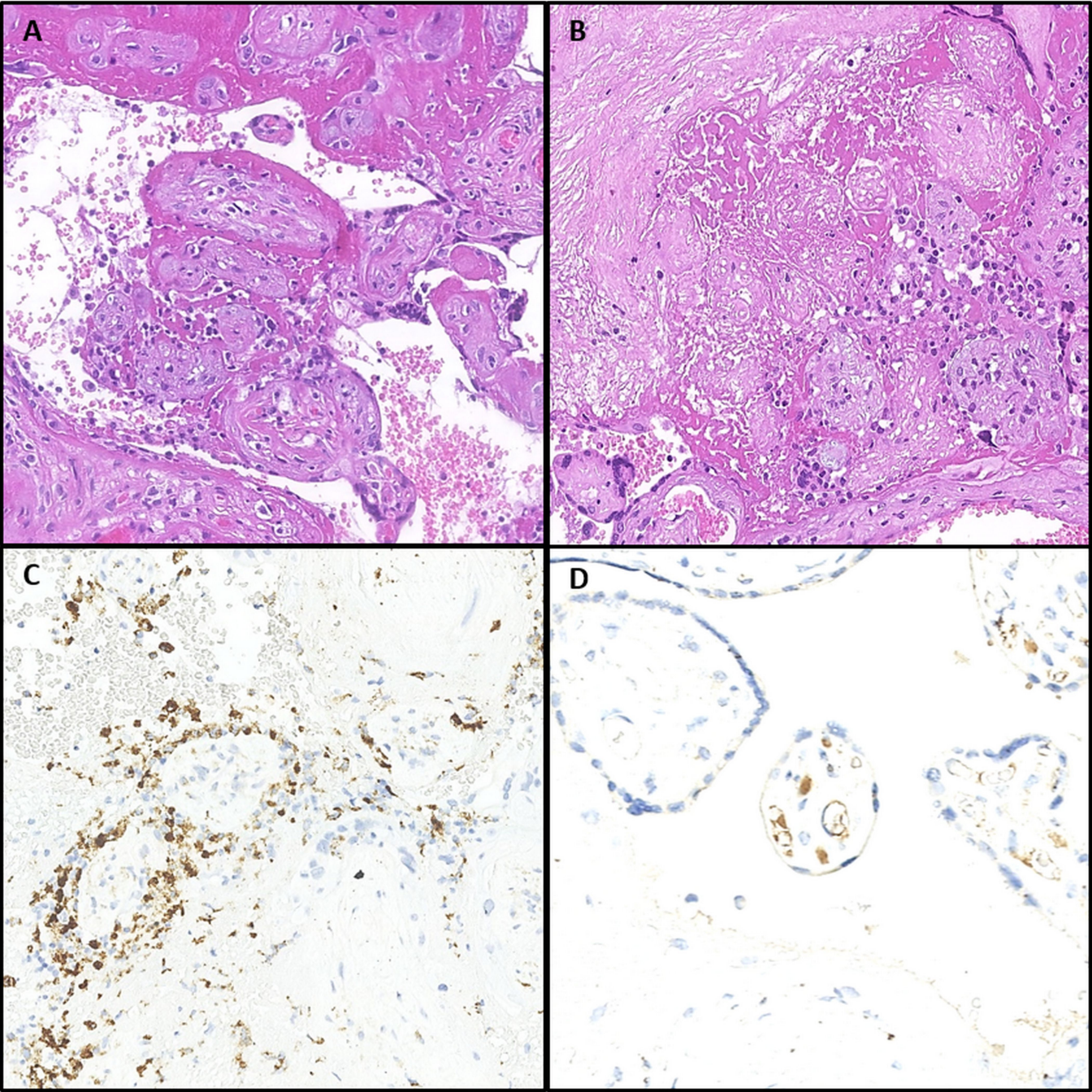
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