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Case report

Hydrops fetalis associated with SARS-CoV-2 placentitis and de novo CDK13 mutation: An integrated genetic and histological analysis

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Abstract. We present a case of a 33-year-old woman with a diagnosis of hydrops fetalis at 33 weeks' gestation. The histopathological examination of the placenta deposes for SARS-CoV-2 placentitis and genetic analysis reveals evidence of a de novo heterozygous mutation of the CDK13 mutation gene in the newborn. This report presents a case of COVID-19 during pregnancy associated with SARS-CoV-2 placentitis and highlights the characteristic histopathology of this recently described condition, which can lead to hydrops. On the other hand, this is the first reported case of hydrops fetalis in a fetus carrier of a pathogenic CDK13 gene variant. Moreover, since the reported patients with CDK13 mutations and prenatal complications we cannot exclude the causality or at least the contribution of this variant in generating the hydrops. (www.actabiomedica.it)

Key words: hydrops fetalis, pregnancy complications, SARS-CoV-2, CDK13 mutation, placenta diseases

Introduction

Nonimmune hydrops is characterized by abnormal fetal fluid collection in two or more compartments of the fetal body (peritoneal cavity, pleura, and pericardium) without red cell alloimmunization. If the condition progresses other frequent sonographic findings include edema, placental thickening and polyhydramnios. The most common etiologies include cardiovascular, chromosomal, lymphatic and hematologic abnormalities, followed by infections, structural fetal anomalies, metabolic diseases, complications of monochorionic twinning, tumors, urinary causes, and placental abnormalities. The prevalence of non-immune hydrops fetalis (NIHF) ranges from 1 in 1500 to 1 in 4000 births. Hydrops fetalis is typically an unexpected discovery during standard prenatal examination. The root cause significantly impacts symptom, progression and outlook (1). Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, has rapidly spread throughout the world evolving into a global pandemic. Scientific evidence on manifestations and potential impact of the virus on pregnancy is still limited. The following adverse outcomes have been documented in pregnant women who have contracted SARS-CoV-2: serious maternal illness, maternal death, fetal growth restriction, intrauterine death and preterm birth, but the majority of patients report a mild illness without pregnancy complications. A real-time reverse transcription polymerase chain reaction (RT-PCR) test is considered the benchmark for diagnosis. Pulmonary ultrasonography has also been proposed for a quick pneumonia diagnosis in expectant mothers. With regard to medical treatments, there are currently no approved treatments for COVID-19, although several agents are being

evaluated, including chloroquine and remdesivir (2). Our understanding of the impact of COVID-19 on pregnancy is currently derived from individual case reports and small cohorts, highlighting the need for additional research to comprehensively ascertain its true effects. SARS-Co-V-2 placentitis is an uncommon but easily identifiable complication of maternal SARS-CoV-2 infection. It may serve as an indicator of potential vertical transmission and that may have the capacity to cause fetal compromise via direct harm to the placenta. The three histological features associated with SARS-CoV-2 placentitis are chronic histiocytic intervillositis, villous trophoblast necrosis, and intervillous fibrin deposition (3). CDK13-related disorder is a recently described genetic condition characterized by developmental delay/intellectual disability, neonatal hypotonia, facial dysmorphisms, behavioral problems, feeding difficulties, congenital heart disease, brain defects and seizures. CDKs are proteins that regulate cell cycle and transcription in higher eukaryotes. In particular, the protein encoded by CDK13 gene is a member of the cyclin-dependent serine/threonine protein kinase family, it plays a role in mRNA processing and may be involved in the regulation of hematopoiesis (4). Several case reports have been described in the literature but only a case of neonatal CDK13 mutation was reported for a cystic hygroma discovered during the pregnancy (5). This paper presents a case study involving a pregnancy in the third trimester complicated by hydrops fetalis resulting in emergency Caesarean delivery with two possible determining causes: a demonstrable placentitis caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and a heterozygous *de novo* pathogenic variant in the *CDK13* gene detected by a trio-based Whole-Exome Sequencing analysis (WES).

Case presentation

A 33-year-old nulliparous woman was admitted at 33 weeks' gestation to the Obstetric Emergency Room in Udine due to uterine contractile activity. Ultrasound examination showed a cervical shortening with a cervical length of 15-20 mm and an increased amniotic fluid. The obstetric history of the patient was negative, ultrasonographies of the 13th, 20th, and 30th gestational weeks documented an appropriate fetal growth without malformations. She was tested with an antigenic nasopharyngeal swab for SARS-CoV-2 RT-PCR that resulted negative and during pregnancy she had minor cold episodes never tested for Covid infection. The patient was not vaccinated for SARS-CoV-2. She was admitted to the obstetrics ward and tocolytic therapy with Atosiban and corticosteroid prophylaxis were started. On the second day of hospitalization, a variable deceleration appeared on cardiotocographic monitoring due to uterine hypertone (Figure 1).

The obstetric ultrasound examination indicated the presence of hydrops fetalis characterized by skin

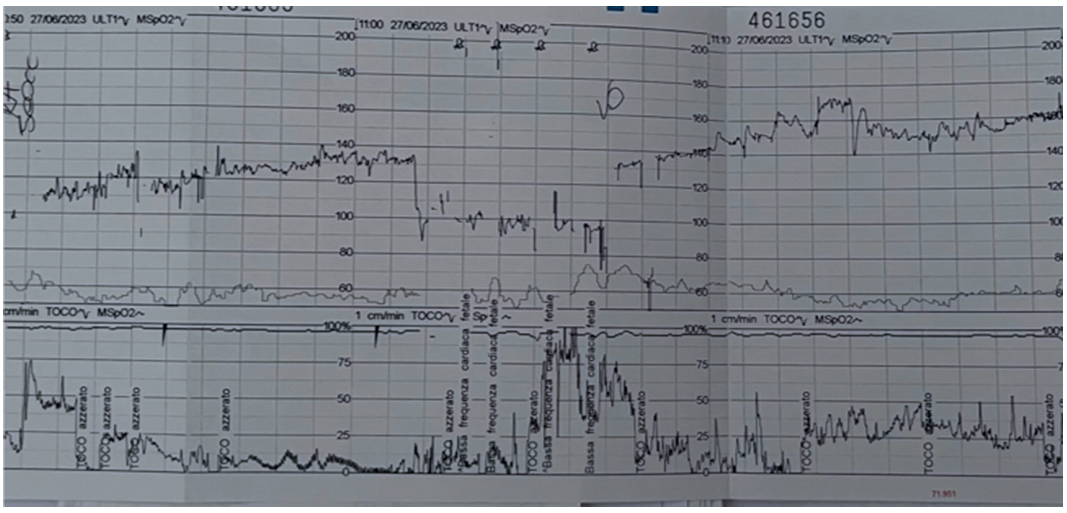

Figure 1. Variable deceleration due to uterine hypertone.

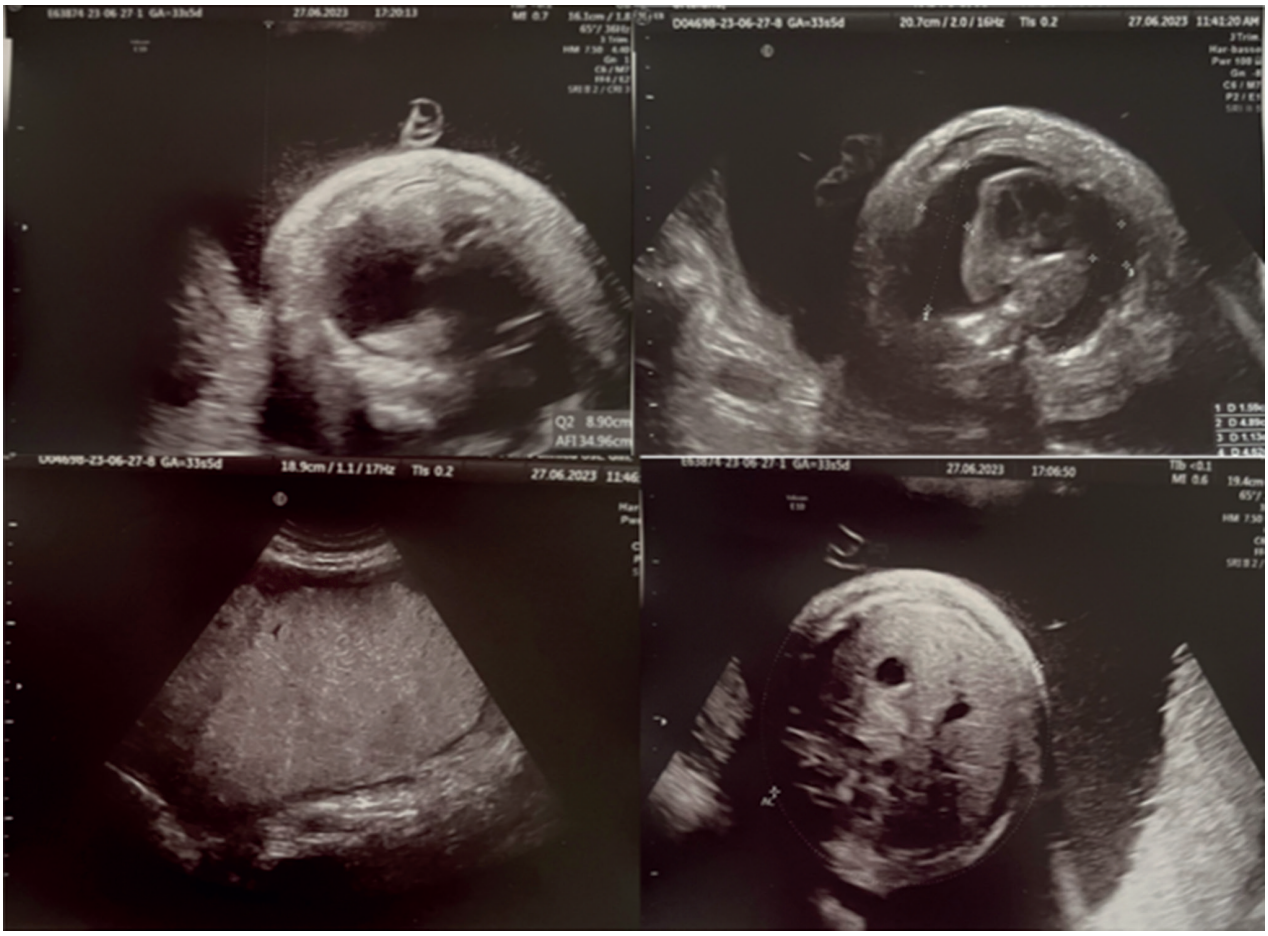

Figure 2. Ultrasound evaluation revealing polyhydramnios, thoracic effusion, placental thickening and skin edema.

edema, polyhydramnios, severe thoracic effusion and placental thickening (Figure 2).

Few hours later a worsening fetal hydrops with pericardial effusion, pathological umbilical artery Doppler and absence of active fetal movements were detected. Consanguinity was denied. The TORCH screening yielded negative results, indicating the absence of Toxoplasmosis, Other (syphilis, varicella-zoster virus, parvovirus B19), Rubella, Cytomegalovirus, and Herpes simplex virus infections. Additionally, thrombophilia tests were also negative. During the pregnancy she received a dose of Anti-D immunoglobulin due to her RhD-negative status and her husband's RhD-positive status, despite her having negative anti-RH antibodies. No anemia was identified throughout the pregnancy. Considering the clinical worsening a cesarean section (CS) was performed. A female newborn was delivered by CS at 33+5 weeks' gestation with a birth weight of 2266 g. Apgar scores were 1 and 6 at 1st and 5th minute of life, respectively. The newborn presented severe diffuse skin edema, cyanosis and apnea with a heart rate < 100 bpm. She required endotracheal intubation, bilateral pleural drainage and conventional ventilation. Bilateral chest tubes were placed on the 1st day of life for persistent hydrothorax. Pleural fluid was citrine, and its chemical examinations rule out a chylothorax; cell count showed a lymphocyte prevalence. For hypoalbuminemia she received plasma transfusion. Cardiac ultrasound showed normal morphology and function. Antibiotic therapy (ampicillin and netilmicin) was administered from birth to the 5th day of life. Blood and pleural fluid cultures were negative. Nasal swab was

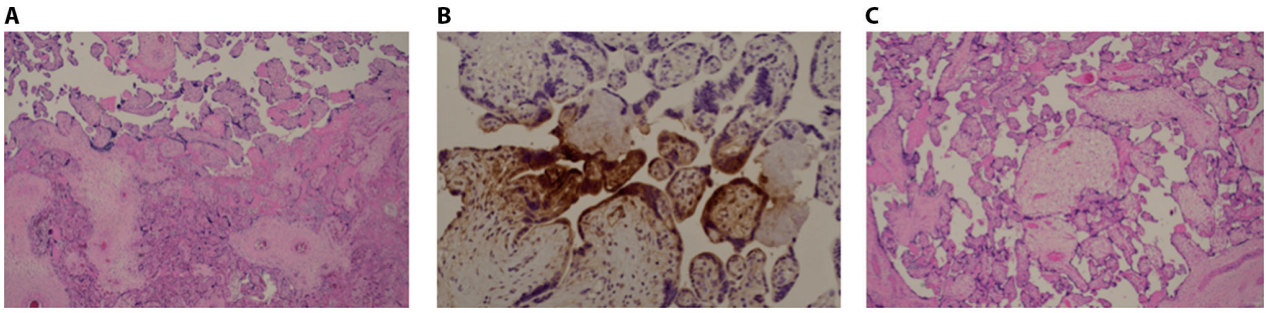

Figure 3. a) Placental parenchyma showed accelerated villous maturation (presence of small or short hypermature villi for gestational period, accompanied by an increase in syncytial knots), multiple foci of increased intervillous fibrin deposition adherent to trophoblast that showed area of necrosis and associated with presence of histiocytes, alternating with areas of villous paucity. (H&E 10x) b) Immunostaining for SARS-CoV2 spike protein showed multiple foci of villar trophoblast positivity. (SARS-CoV2 spike protein, 20x). c) Placenta with edematous large villi. (H&E 10x)

negative for SARS-CoV-2. Cytomegalovirus-PCR in urine and enterovirus-PCR in blood were negative. Hydrothorax resolved on the 4th day of life and chest tubes were removed. On the same day the baby was extubated and received non-invasive ventilation. Oxygen supplementation was definitively discontinued on the 42nd day of life. Cerebral ultrasound showed a simplified gyral pattern confirmed by a brain magnetic resonance. Eye examination was normal. Abdominal ultrasound detected a pelvicalyceal dilatation on the left kidney and antibiotic prophylaxis was started. The baby was discharged in good condition at 41 weeks of post-conceptional age. Considering the complex clinical picture a trio-based WES was started finally identifying the c.2887G>T; p.Glu963Ter heterozygous *de novo* variant in the *CDK13* (NM_003718.5) gene. Mother and father were negative for all analyzed mutations. The placenta underwent a pathological examination, revealing the following findings: Macroscopic examination indicated a placental weight of 309 grams. The placental disc measured 16 cm in its longest dimension, with thickness ranging from 0.5 cm to 2 cm. The umbilical cord had an average diameter of 0.8 cm and showed marginal insertion. No macroscopic anomalies were observed in the membranes. Microscopic examination revealed meconium-laden and hemosiderin-laden macrophages in the amniotic membranes. Within the placental parenchyma, accelerated villous maturation was noted, characterized by the presence of small or short hypermature villi for the gestational period, accompanied by an increase in syncytial knots. Multiple areas of increased intervillous fibrin deposition were found, adherent to trophoblasts, some of which showed areas of necrosis. These areas were associated with the presence of CD68-positive histiocytes and alternated with regions of villous paucity (Figure 3a). Spiral artery remodeling was absent, and focal retroplacental hemorrhage was observed, causing compression of the overlying intervillous space. This resulted in villous crowding, congestion, and intravillous hemorrhage. Additionally, some edematous large villi were identified (Figure 3c). Based on clinical suspicion of a viral infection, other potential causes of hydrops fetalis were ruled out. Molecular analysis on the tissues employing a reverse trascriptase, one step real time PCR for the detection of SARS-CoV-2 Envelop viral protein confirmed a high level of SARS-CoV-2 in the placental tissue. Immunostaining for the SARS-CoV-2 spike protein was performed, revealing multiple areas of villar trophoblast positivity (Figure 3b).

In summary, the anatomopathological diagnosis demonstrated maternal vascular malperfusion and features of COVID-19 placentitis, without morphological aspects of Parvovirus or CMV infection (6,7). In this light, research for SARS-CoV-2 DNA on sputum, urine, feces, gastric aspirate and eye swab were done on the newborn. All these investigations were negative; however, these results could be due to the fact that they were performed at 40 days of life.

Discussion

We report an in-depth analysis of two potentially determining causes of hydrops fetalis, whose pathogenesis is not fully known. It has not yet been demonstrated the possible correlation between SARS-CoV-2 infection and non-immune hydrops fetalis. However, the occurrence of fetal hydrops associated with a confirmed SARS-CoV-2 placentitis, in the absence of any other notable clinical or obstetric disorders, suggests a possible link between the hydrops and the SARS-CoV-2 infection. Importantly, the risk of adverse fetal outcomes appears independent of the clinical SARS-CoV-2 infection. Therefore, even asymptomatic pregnant women may not be exempt from such adverse outcomes (8), as illustrated by our case. In recent research by Bernier et al. immune and inflammatory profiles of placenta and blood samples from pregnant women exposed to the pandemic were compared to that of unexposed women. They reported a pro-inflammatory bias in the circulation of pregnant women exposed to SARS-CoV-2 pandemic (9). Furthermore, literature documents few cases of COVID-19 infection complicated by hydrops fetalis. For instance, Popescu et al. recently reported a case of pregnancy complicated by hydrops fetalis that emerged 7 weeks following recovery from a mild SARS-CoV-2 infection, ultimately resulting in the intrauterine demise of the fetus. They identified evidence of SARS-CoV-2 placentitis through the presence of viral particles in the placenta, as confirmed by immunohistochemistry. As well as in our case, all potential etiological factors for non-immunologic hydrops fetalis were excluded, suggesting a plausible association between fetal outcomes and vertical transmission of SARS-CoV-2 virus (10). Gubbari et al documented a case of nonimmune hydrops secondary to fetal COVID-19 myocarditis in a COVID-19 positive pregnant woman at 34 weeks of gestation; obstetric scan revealed absent diastolic flow in umbilical arteries along with fetal right ventricular dilation, fluid collection in peritoneal, and bilateral pleural cavities suggestive of hydrops fetalis (11). Krasniqi et al reported another case of non-immune hydrops fetalis diagnosed intra-uterine three weeks after recovery from COVID-19 (12). Garcia-Manau et al. described two instances of fetal transient skin edema observed in pregnant women diagnosed with COVID-19 during their second trimester. In both cases, fetal skin edema manifested concurrently with positive maternal COVID-19 test results and resolved following subsequent negative results on maternal SARS-COV-2 RT-PCR test (13). Additionally, Martinez-Varea et al reported a transient fetal skin edema linked with polyhydramnios in a pregnant patient with COVID-19 after a negative RT-PCR for Sars-CoV-2. The fetal findings presented a spontaneous resolution in utero, and abnormal findings were not found in the newborn (14). Shende et al. documented a case involving a pregnant woman in the first trimester who tested positive for SARS-CoV-2 at 8 weeks of gestation, despite experiencing no symptoms. By the 13th week of gestation, her throat swab returned negative for SARS-CoV-2, but viral RNA was detected in the placenta. Immunolocalization revealed Spike (S) proteins (S1 and S2) in cytotrophoblast and syncytiotrophoblast cells of the placental villi. Ultrasonography showed extensive subcutaneous edema with pleural effusion, indicative of hydrops fetalis, and the absence of cardiac activity confirmed fetal demise. This led to the conclusion that hydrops fetalis and intrauterine fetal demise resulted from congenital transmission of COVID-19 (15). These findings are similar to that reported in our case, where evidence of SARS-CoV-2 placentitis was established by the presence of S-proteins in the placenta. Following the exclusion of all potential etiological factors for non-immunologic hydrops fetalis, it is reasonable to surmise that the fetal outcomes described in our case may, at least in part, be linked to vertical transmission of the COVID-19 virus. In our scenario, the two most prevalent patterns observed among the three histological features associated with SARS-CoV-2 placentitis (namely, chronic histiocytic intervillositis, villous trophoblast necrosis, and intervillous fibrin deposition) were villous trophoblast necrosis and intervillous fibrin deposition. These particular elements have the potential to result in impaired placental perfusion. It's worth noting that these two types of lesions have also been frequently documented in cases of infections. For instance, in TORCH infections, the histological pattern may exhibit a diffuse histiocytic infiltrate accompanied by villous edema and occasional lymphocytes (16). In our

case, there were also instances of edematous large villi, a characteristic commonly observed in infections and in cases of hydrops fetalis. On the other hand, it is possible that the variant detected in the *CDK13* gene is responsible or partially contributes to determining the clinical phenotype of the hydrops fetalis. The protein encoded by this is a member of the cyclin-dependent serine/threonine protein kinase family. Members of this family are well known for their essential roles as master switches in cell cycle control. The exact function of the protein encoded by the *CDK13* gene has not yet been determined, but it may play a role in mRNA processing and may be involved in the regulation of hematopoiesis. The c.2887G>T variant is considered as high impact since it is: a) classified as pathogenic according to the American College of Medical Genetics (ACMG) guidelines; b) extremely rare variant in the control population (17) although it is not reported in the gene mutations databases (HGMD professional or ClinVar). Moreover, the major series reported from Rouxel et al. described 18 patients and 29,4% (5/17) of them showed pregnancy complications (18). Unfortunately, there are no detailed data on prenatal problems.

Conclusions

Our case is emblematic as there are two potentially determining causes of hydrops fetalis, which pathogenesis is not fully known. This report presents a case of COVID-19 during pregnancy associated with SARS-CoV-2 placentitis and highlights the characteristic histopathology of this recently described condition, which can lead to hydrops. The risk of hydrops is not contingent upon the clinical presentation of SARS-CoV-2 maternal symptoms, therefore also an asymptomatic woman can have such adverse outcomes, as shown in our case without documented COVID-19 infection during pregnancy. Is it essential to test women for SARS-CoV-2 periodically during pregnancy to perform a closer follow up in those who have tested positive? To answer this question, additional studies are required to elucidate the mechanism of vertical transmission and effects of SARS-CoV2 infection on both pregnant women and their fetuses.

On the other hand, this is the first reported case of hydrops in a fetus carrier of a pathogenic *CDK13* gene variant. Moreover, since the reported patients with *CDK13* mutations and prenatal complications we cannot exclude the causality or at least the contribution of this variant in generating the hydrops.

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Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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