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Sudden fetal death with placental mesenchymal dysplasia complicated by placenta previa

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Running title: Placental mesenchymal dysplasia

Abstract

Placental mesenchymal dysplasia (PMD) is a rare placental abnormality that is closely related to severe pregnancy complications.

A 27-year-old woman with fetal growth restriction and placenta previa was referred to a university hospital at 22 gestational weeks (GW). She was suspected of having a twin pregnancy with a complete or partial hydatidiform mole and coexisting normal live fetus, because two separate placentas, an enlarged one with multiple cystic lesions and a normal one, were shown on ultrasound examinations.

At 27 GW, she experienced a sudden intrauterine fetal death (IUFD) after bleeding due to placenta previa, despite confirmation of fetal well-being at 2 hours before bleeding. After delivery, histopathological examination confirmed the diagnosis of PMD.

This is the first documented case of a woman with PMD and placenta previa who had a sudden IUFD after bleeding. Patients with both PMD and placenta previa should be considered at an extremely high risk for IUFD.

Key words:

Fetal growth restriction, hydatidiform mole, intrauterine fetal death, placental mesenchymal dysplasia, placenta previa

Introduction

First described in 1991, placental mesenchymal dysplasia (PMD) is a rare placental abnormality characterized by mesenchymal stem villous hyperplasia.[1] The prevalence of PMD is estimated to be 0.002%–0.02% of all pregnancies.[2, 3]

PMD is closely associated with pregnancy complications, including preterm delivery, fetal growth restriction (FGR), intrauterine fetal death (IUFD), and hypertensive disorders of pregnancy (HDP).[4, 5] A previous study has shown that stillbirths in pregnancies with PMD usually occurred following non-reassuring fetal status (NRFS).[6] Therefore, early hospitalization is recommended for patients with PMD in order to monitor fetal well-being closely.[6]

To the best of our knowledge, there are three English literatures on pregnancies with PMD and placenta previa.[7-9] This report is the first to describe a pregnant woman with PMD, FGR, and placenta previa, who had IUFD after bleeding, despite an extended hospital stay and confirmation of fetal well-being at 2 hours before bleeding.

Case report

This case report followed the principles of the Declaration of Helsinki, and a written informed consent was obtained from the patient. A 27-year-old pregnant woman, gravida 2, para 1, was diagnosed as having FGR and placenta previa in another hospital at 21+2/7 gestational weeks (GW) and was referred to Kobe University Hospital at 22+5/7 GW. An ultrasound examination during the first visit to our hospital demonstrated severe FGR (estimated fetal body weight [EFBW] 328g and the mean -2.5 standard deviation [SD] for GW) without morphological abnormalities. Laboratory tests showed that she was negative for Toxoplasma immunoglobulin M (IgM), cytomegalovirus IgM, and herpes

simplex virus IgM, and also negative for antiphospholipid antibodies. In addition, the ultrasound examination showed that the pregnant woman had placenta previa (Figure 1-A), and seemed to have two separate placentas, one of which was an enlarged placenta with multiple vesicular lesions and another was a placenta appearing normal (Figure 1-B). A Doppler study showed no flow within cysts or abnormal vascularization in the placenta (Figure 1-B). Magnetic resonance imaging (MRI) showed similar findings as those identified on ultrasound examination (Figure 1-C and D). The serum level of human chorionic gonadotropin (hCG) at the first visit was 30069.0 mIU/mL. Because the pregnant woman seemed to have two separate placentas, a partial mole pregnancy or a twin pregnancy with a complete or partial hydatidiform mole and coexisting normal live fetus were suspected. The pregnant woman and her husband refused chromosome analysis following amniocentesis.

She was admitted to the university hospital at 23+2/7 GW. She was closely monitored for fetal well-being using ultrasonography and cardiotocogram (CTG); she was also monitored for lung metastasis using chest X-ray. The fetus had grown while maintaining the mean -2.2 SD of EFBW for GW without abnormal findings in the fetal Doppler studies, and no lung metastasis was observed. The maximum serum level of hCG during her pregnancy (35461.0 mIU/mL) was observed at 26+2/7 GW.

At 27+6/7 GW, the pregnant woman had massive bleeding and was diagnosed with IUFD, although reassuring fetal status was confirmed through CTG at 2 hours before bleeding. Because the patient had placenta previa and active bleeding, she delivered a dead 830 g (-1.63SD) female infant and a single placenta by cesarean section. The placenta weighed 540 g, which was greater than the 95th percentile for GW[10] (Figure 2). Gross examination of the fetal surface of the placenta showed dilated and tortuous vessels

(Figure 2-A). The maternal surface of the placenta consisted of grossly normal area and abnormal area, including multiple grape-like vesicles (Figure 2-B, C).

On histological examination, we observed enlarged stem villi with various degrees of edema (Figure 3-A), absence of trophoblastic proliferation around the periphery of the hydropic stem villi with avascular stroma (Figure 3-B), and hydropic stem villi with chorangioma-like vascular proliferations (Figure 3-C). Using immunohistochemical staining for $p57^{Kip2}$ (clone 57P06, Neomarker, Fremont, CA), which was previously reported to be useful for distinguishing PMD from molar pregnancies,[11] we observed nuclear staining in the villous cytotrophoblasts, but not in the villous stroma (Figure 3-D). Histopathological examination confirmed the diagnosis of PMD.

Neither autopsy nor karyotype analysis of the stillborn infant was performed, because the patient and her husband refused them.

The patient was discharged without any troubles and additional treatments on postoperative day 6.

Discussion

PMD is a rare placental abnormality and its prevalence is estimated to be 0.002%–0.02% of all pregnancies.[2, 3] In this case, because the patient seemed to have two separate placentas on the US and MRI findings, we suspected a pregnant woman of having a twin pregnancy with a complete or partial hydatidiform mole and coexisting normal live fetus before delivery; however, she was diagnosed with PMD on histological examination after delivery. A previous study reported that stillbirths in pregnancies with PMD usually occur following NRFS.[6] Our case experienced sudden fetal death following massive bleeding

caused by placenta previa, despite receiving close fetal monitoring during the hospital stay and confirming the reassuring fetal status at 2 hours before bleeding. To date, there were three English literatures on pregnancies with both PMD and placenta previa.[7-9] To the best of our knowledge, this is the first report of a pregnant woman with PMD and placenta previa who had a sudden IUFD after bleeding.

It is important to distinguish between PMD and molar pregnancies, i.e., a partial mole pregnancy or a twin pregnancy with a complete hydatidiform mole and coexisting normal live fetus, because a complete mole can metastasize to the maternal lung, whereas a partial mole is associated with triploidy. However, differential diagnosis is often difficult because the imaging findings of PMD resemble those of molar pregnancies.[12] A systematic review demonstrated that the most common ultrasound findings of PMD were cystic placenta with hypoechoic areas, enlarged/thickened placenta, dilated chorionic vessels, and fetal abnormalities associated with Beckwith–Wiedemann syndrome (BWS), 17–23 % of which is associated with PMD,[5, 13] (i.e., large-for-gestational age, omphalocele, and hepatomegaly).[4] Other investigators have suggested that the presence of blood flow in placental cyst helps distinguish PMD from molar pregnancies.[14] In contrast, it was reported that MRI might be useful for diagnosing PMD as MRI findings suggestive of PMD display an enlarged placenta with heterogeneous signals and dilated placental vessels.[15] In our ultrasound and MRI findings, the pregnant woman had an enlarged placenta with multiple cystic lesions, but she seemed to have two separate placentas, one of which appeared normal and had no placental cyst including blood flow. In addition, no fetal morphological abnormalities associated with BWS were observed. Therefore, we suspected her of having a twin pregnancy with a complete hydatidiform mole and coexisting normal live fetus or twin pregnancy consisting of a partial

hydatidiform mole where a triploid fetus died and coexisting normal live fetus before delivery. Based on the ultrasound and MRI findings, the patient seemed to have two separate placentas. Indeed, maternal surface of the delivered placenta seemed to consist of grossly normal area and abnormal area. Kodera et al. suggested that even specimens obtained from a grossly normal area in a placenta with PMD included PMD lesions histopathologically. [5] Clinicians should be aware that a placenta with PMD can appear two separate placentas due to the uneven distribution of edematous stem villi in the placenta.

It is reported that chromosome analysis following amniocentesis is useful for prenatal diagnosis of partial molar pregnancies because it demonstrates triploidy. However, this patient and her family refused amniocentesis. We did not think that chromosome analysis was essential for prenatal diagnosis in this case; we hypothesized that one sac included normal placenta and fetus with FGR and the other sac had a complete hydatidiform mole or a fetus who died during the early stage of pregnancy and a partial hydatidiform mole.

A previous study suggested that elevated serum hCG and alpha-fetoprotein (AFP) levels can be observed in patients with PMD.[16] Another previous study found that 83.3% (15/18) of patients with PMD had elevated serum AFP levels, and that 17.8% (5/28) of them had transient elevations in serum hCG levels. [5] In the present case, even the maximum serum hCG level during her pregnancy (35461.0 mIU/mL) was within normal range; the absence of hCG elevation might not exclude the diagnosis of PMD. Conversely, when the cases with enlarged and multiple cystic placentas have no elevations of serum hCG levels, not molar pregnancy but pregnancy with PMD should be suspected. Unfortunately, we did not measure the serum AFP levels.

A previous study reported that the most prevalent pregnancy complications among pregnant women with PMD were preterm delivery (52%), FGR (33%), IUFD (13%), and hypertensive disorders of pregnancy (9%).[4] Some investigators speculated that FGR and IUFD in pregnancies with PMD may be caused by vascular thrombosis and decreased maternal–fetal gas exchange.[17] Although a previous study showed that 7 of the 8 PMD case with IUFD had no abnormal findings preceding IUFD, [5] it is generally believed that stillbirths in patients with PMD occur following NRFS.[6] A systematic review of 109 pregnancies with PMD, including 32 stillbirths, found that only two stillbirths occurred during the hospital stay; therefore, the authors recommended early hospitalization for patients with PMD to closely monitor fetal well-being.[6] However, despite staying in the hospital until 23 GW and receiving close fetal monitoring, our patient had sudden fetal death following bleeding caused by placenta previa. Because autopsy of the stillborn infant was not performed, the true cause of death in the fetus was unclear. However, it is speculated that massive bleeding may exacerbate fetal hypoxia, which was caused by impaired maternal–fetal gas exchange due to PMD. Thus, her fetus had sudden death at 2 hours after the confirmation of fetal well-being. This outcome indicates that patients with both PMD and placenta previa should be considered at an extremely high risk for IUFD.

This first report on PMD and placenta previa leading to sudden IUFD provides useful information to clinical practitioners in perinatal medicine for managing such cases in future.

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Disclosure

The authors state that they have no conflict of interest.

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Figure legends

Figure 1. Ultrasound and magnetic resonance imaging findings

(A, B) Ultrasound findings at 22+5/7 gestational weeks. (A) Transvaginal sonogram showed that a placenta with multiple cysts covered the uterine cervix. (B) Abdominal sonogram demonstrated two placentas, one was an enlarged placenta with multiple vesicular lesions without blood flow (arrows) and another was a placenta appearing normal (asterisk). (C, D) Magnetic resonance imaging (MRI) findings at 23+4/7 gestational weeks. (C) Sagittal, T2-weighted MRI showed an enlarged placenta with multiple cysts. (D) Transverse, T2-weighted MRI indicated the presence of a normal placenta (sharp sign) and an abnormal one (arrowheads).

Figure 2. Gross appearance of the placenta

(A) The fetal surface of the placenta. Dilated and tortuous vessels were observed (arrows).

(B) The maternal surface of the placenta consisted of grossly normal area (arrow heads) and grossly abnormal area.

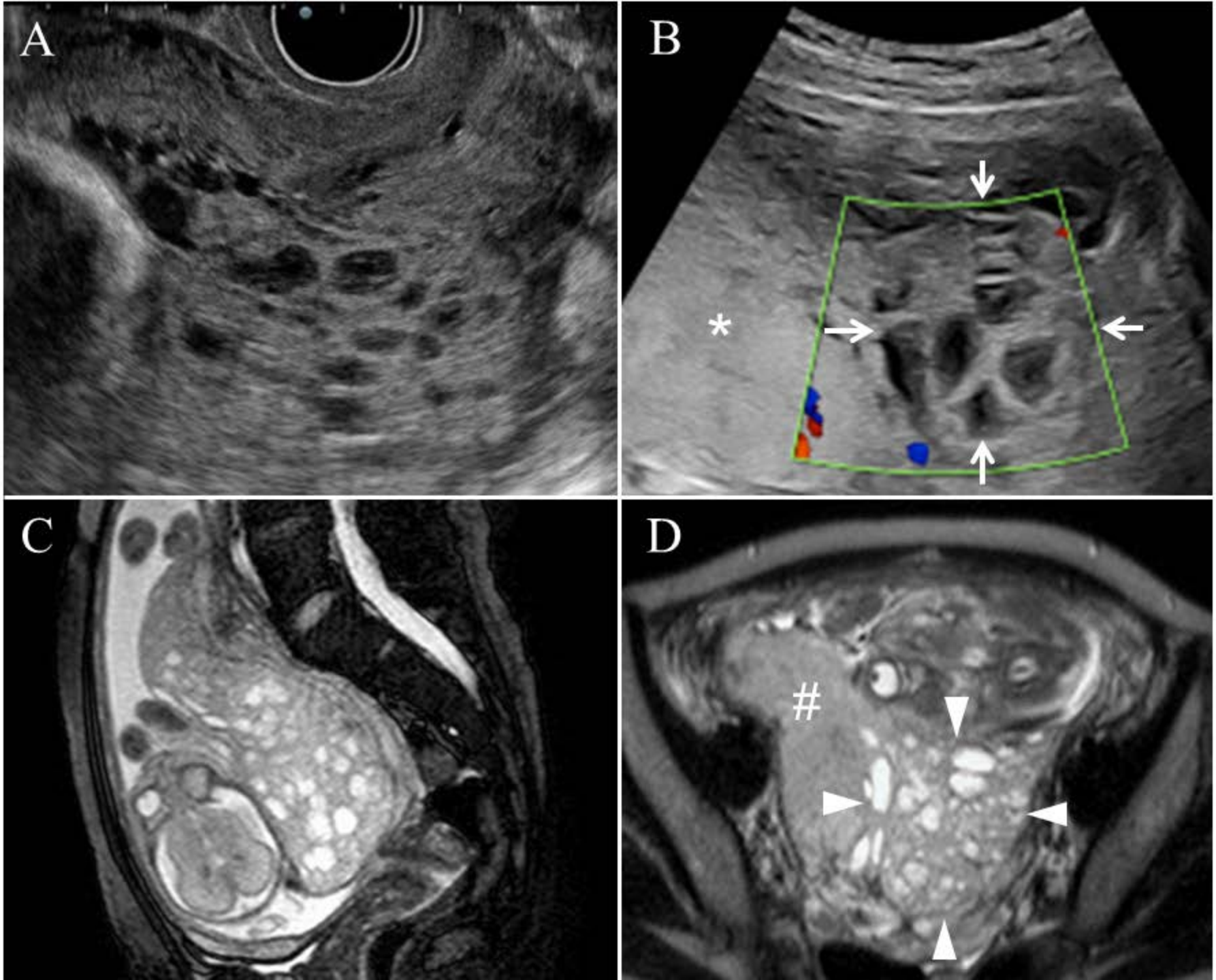
(C) The maternal surface of the placenta. Multiple grape-like vesicles were observed.

Figure 3. Pathological findings of the placenta

(A, B, and C) Hematoxylin and eosin stain; original magnification, 100x objective. (D) Immunohistochemical staining for $p57^{Kip2}$; original magnification, 400x objective.

(A) Enlarged hydropic stem villi, (B) no trophoblastic proliferation around the hydropic stem villi with avascular stroma, and (C) hydropic stem villi with chorangioma-like vascular proliferations were observed. (D) In immunohistochemical staining for $p57^{Kip2}$, positive staining in the villous cytotrophoblasts and no staining in the villous stroma were

observed.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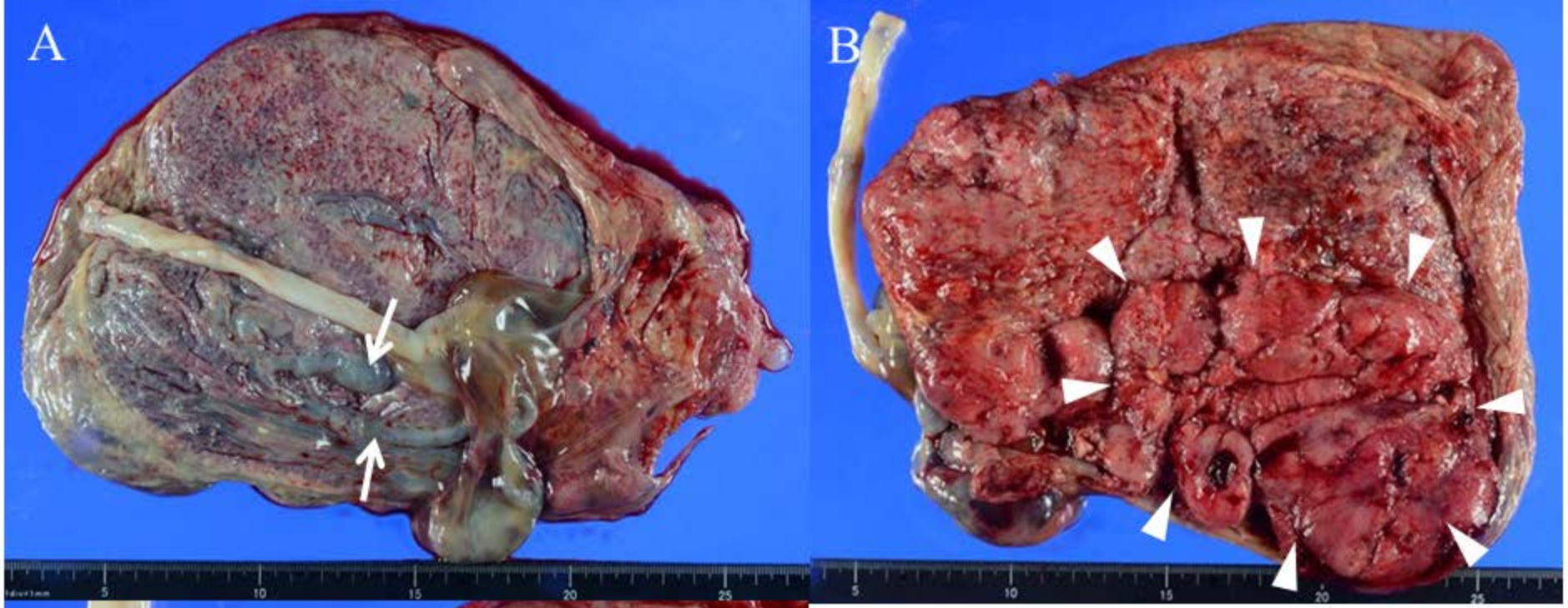
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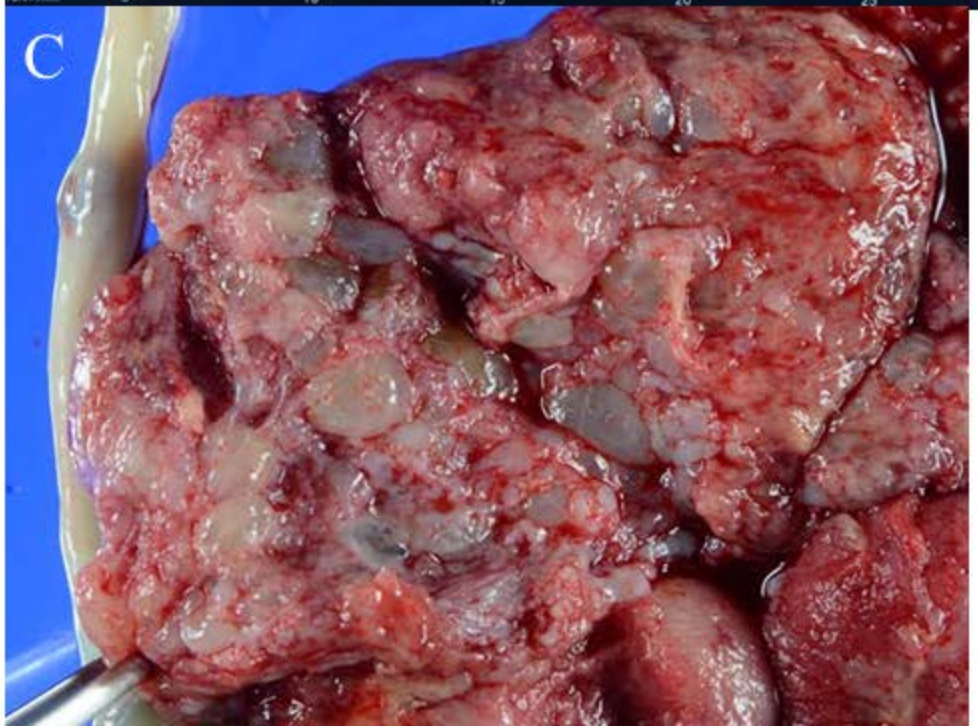
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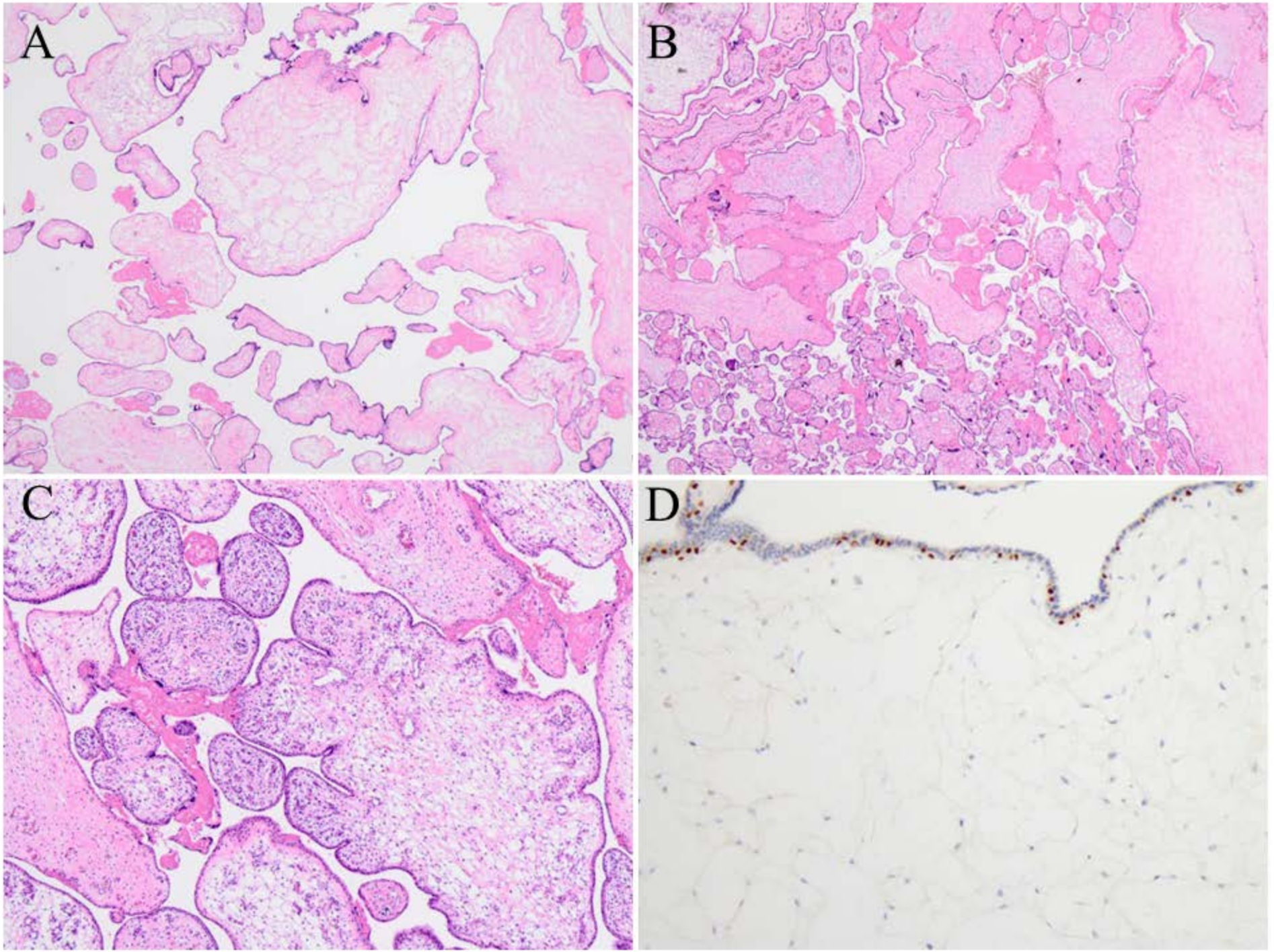
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