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CASE REPORT

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Delayed diagnosis of intraplacental choriocarcinoma in a term healthy neonate—A case report and literature review

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Abstract

Gestational choriocarcinoma is rare. The intraplacental formation of choriocarcinoma is much rarer. We present a diagnosis of choriocarcinoma, 4 months postpartum, in a 28-year-old, presenting with vaginal bleeding. Three weeks after the last chemotherapy session, the patient's β-HCG titer was normal and did not require hysterectomy.

KEYWORDS

case reports, choriocarcinoma, placenta diseases, rare diseases, term pregnancy

1 | INTRODUCTION

Choriocarcinoma is a highly malignant tumor, a subtype of gestational trophoblastic disease (GTD), composed of two types of cells, syncytiotrophoblasts, and cytotrophoblasts (the differentiated hormone secreting component). Choriocarcinoma predominantly occurs in women; but can also occur in men, usually as part of a mixed germ cell tumor arising from the gonads.[1] A late diagnosis can be life-threatening because of the uncontrollable hemorrhage and metastasis.[2,3] Considering its rarity and difficulty in diagnosis, various incidence rates have been reported for choriocarcinoma in various parts of the world.[4]

The prognostic and therapeutic implications vary based on the origin of choriocarcinoma, gestational, or non-gestational. In women, most cases are intra-uterine and of gestational origin, resulting from the hyperplasic and anaplastic changes in the trophoblastic cells, most frequently within a year following a hydatidiform mole, normal pregnancy, or spontaneous abortion.[1] Late presentation in postmenopausal women is very rare.[5–7] The incidence of gestational choriocarcinoma is believed to be about 0.133 per 100,000 woman-years in the United States, with an age-adjusted ratio of one in 41,094 pregnancies.[8]

Postpartum gestational choriocarcinoma with a live birth is a highly complicated disease, with about one-third reported to develop metastatic disease.[3,9,10] Therefore,

reporting the disease course, complications, and response-to-treatment of these rare cases can help to provide a better perspective for researchers and physicians. Here, we present a diagnosis of choriocarcinoma 4 months after giving birth to a healthy neonate in a 28-year-old woman with a history of septate uterine and two abortions, presenting to us with prolonged postpartum vaginal bleeding.

2 | CASE PRESENTATION

A 28-year-old pregnant woman (G3A2L1) was referred to us with persistent vaginal bleeding after a cesarean section (C/S). Because of the septate uterus, her first pregnancy was aborted at 8 weeks of gestation (although the fetal heart was detected). The patient underwent hysteroscopic septolysis. After 6 months, her second pregnancy was a spontaneous abortion because of no fetal heart formation. In her last pregnancy (third), the fetus was normal; but she was advised to use progesterone suppositories from the first trimester (because of her history of abortions). Four months after giving birth to a normal neonate by C/S, she was referred to us with persistent vaginal bleeding. Serum tests yielded normal levels of blood urea nitrogen (17.1 mg/dL; normal range: 6.0.–20.0.), and creatinine (1.1 mg/dL; normal range: 0.6–1.2) with a blood urea nitrogen/creatinine ratio of 16. The complete blood count revealed a normal white blood cell count (6.10×10^3/μl; normal range: 4.5–10.5), a low level of red blood cell count (3.63×10^6/μl; normal range:4.0–6.0) and low hemoglobin (10.4 gr/dL; normal range:12.0–16.0); a near normal hematocrit (35%; normal range: 36%–48%), and normal platelet count (261×10^3/mm^3; normal range: 150–450). The chest radiography and computed tomography (CT) scan results were normal. Abdominal ultrasound examination showed normal liver, gall bladder, spleen, pancreas, kidneys, and ureters without free ascites fluid, collection, or para-aortic lymphadenopathy. Transvaginal ultrasound examination revealed the normal size of the uterus with a normal myometrial echo pattern with no sign of mass lesion. There was a heterogeneous lesion in the uterine cavity (40 × 34 mm), which suggested GTD or retained placental tissue. The patient was scheduled for hysteroscopic dilatation and curettage (D&C), during which the retained tissue was taken out, and the specimen from the uterine corpus was sent for pathological examination. During hysteroscopy, she received cefazolin, and she was discharged in good condition and prescribed to take 500 mg azithromycin and hematinic acid capsules (one daily). A macroscopic examination by the pathologist revealed multiple pieces of creamy brown soft tissue admixed with a few blood clots (5 × 4 × 2 cm). Multiple sections, 20% embedded, revealed proliferation of atypical cytotrophoblast and syncytiotrophoblast, high mitotic count, hemorrhage, and necrosis, in addition to the ghost of chorionic villi consistent with intraplacental choriocarcinoma (IC; Figure 1), immunohistochemistry study revealed positive CK, sall 4, high ki-67 (>90%), and negative p63 (Figure 2). The patient had persistent high β-human chorionic gonadotrophin (β-HCG) levels in different examinations: 33,609 mIU/ml on December 25, 2021, and 182,658 mIU/ml 7 days later (January 1, 2022) and dropped significantly after the surgery. The trend of changes in β-HCG levels is shown in Figure 3. In the final serum test, the β-HCG level of the patient was 47.50 mIU/ml (12th Feb 2022). Considering the size of the tumor (>3.5 cm), high β-HCG titer, and diagnosis 4 months after C/S, the patient was considered high risk and indicated for 6 courses of chemotherapy (EMA-CO). The chemotherapy regimen for each course was performed in 3 days, which included etoposide, actinomycine, and methotrexate on the first day; etoposide, actinomycine, and folinic acid on the next day; and cyclophosphamide and vincristine on Day 8. After the first course of EMA, the patient had severe bone marrow suppression; therefore, CO was administered with delay. Also, the second course could not be initiated at the routine interval of 15 days after the previous course and was initiated with delay. The subsequent courses were performed uneventfully. On the last follow-up visit (3 weeks after the last chemotherapy session), the patient's β-HCG titer was within the normal range. The patient was in good conditions and did not require additional chemotherapy or hysterectomy.

3 | DISCUSSION

In this case, the patient was diagnosed with an IC 4 months after a normal delivery through C/S, presenting prolonged postpartum vaginal bleeding. This is while the most common form of choriocarcinoma in women is postpartum (gestational), diagnosed within a year after delivery, and the most common site is intrauterine.[1] Thus, one of the distinctive features of our case was the presence of chorionic villi in choriocarcinoma, which was not diagnosed during pregnancy or delivery. Instead, the patient had a normal delivery with a full-term neonate in complete health. Previous reports have demonstrated that some of the neonates of mothers with gestational choriocarcinoma are born dead (stillbirth) or complicated with intrauterine death[11]; but most cases report live birth (like ours) with an incidence rate of 1:26,000 live births.

Generally, choriocarcinoma is a very rare disease, and the clinical presentations are unspecific, including abnormal vaginal bleeding (AUB), shock, and bleeding from metastatic sites.[10] Some unusual clinical presentations

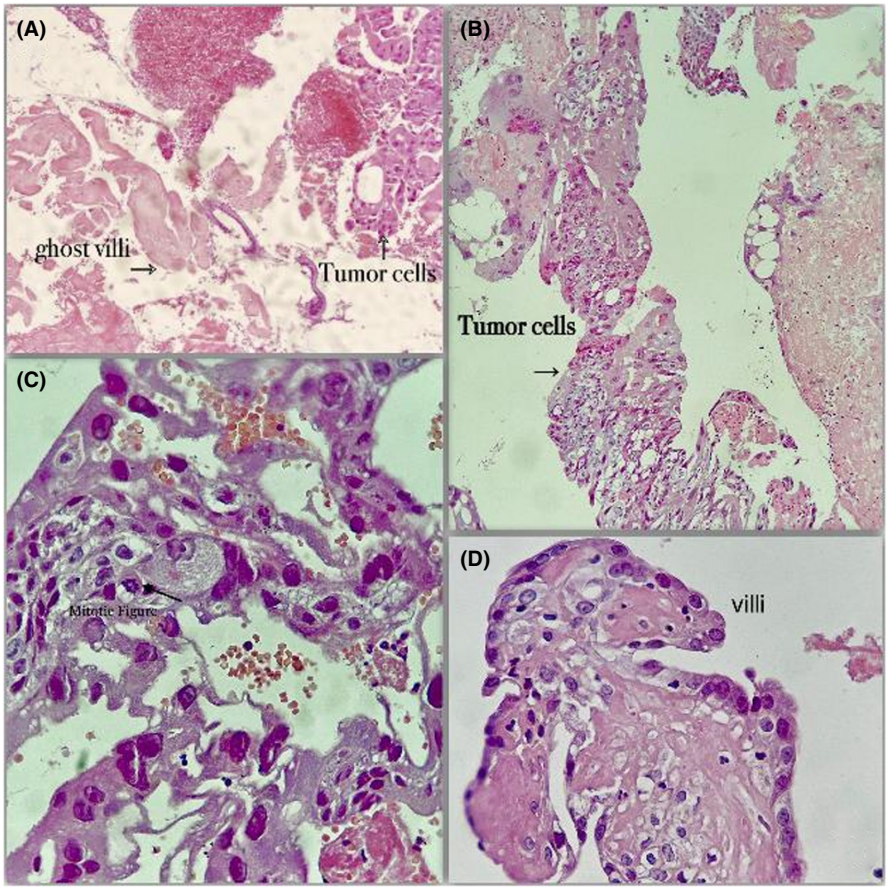

FIGURE 1 Light microscopic view (Hematoxylin and eosin), A: Proliferation of atypical cells with the ghost of mostly necrotic vili (x400), B: Cytotrophoblastic and syncytiotrophoblastic proliferation with marked pleomorphism (x100), C: Frequent mitosis (x400), D: Few mature placental vili (x400)

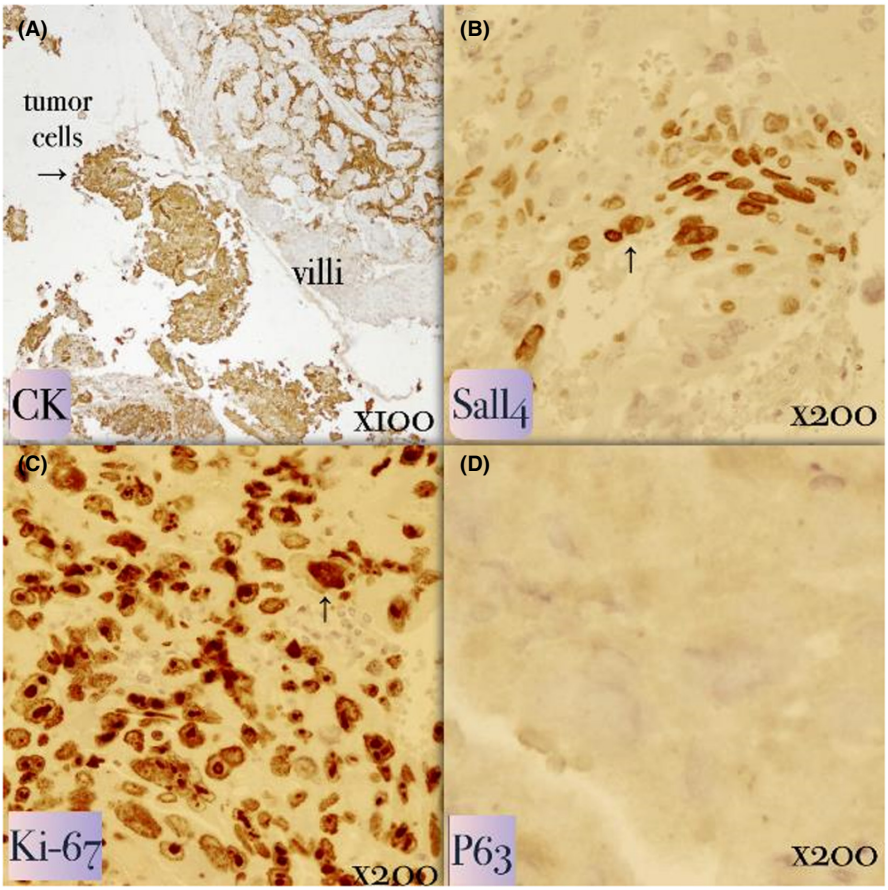

FIGURE 2 Immunohistochemistry findings, A: Positive CK (x100), B: Positive Sall4 (x200), C:Ki-67 (x200), D: Negative P63 (x200)

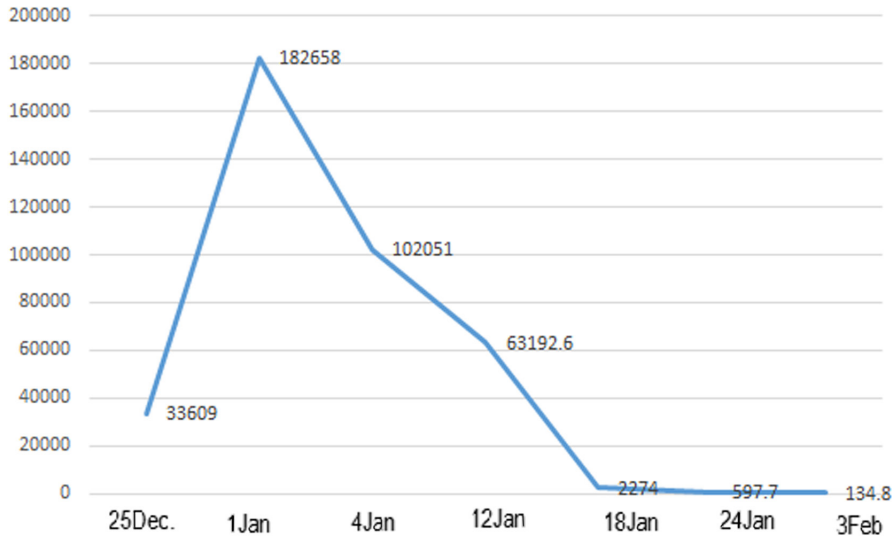

FIGURE 3 Trend of changes in B-HCG levels of the patient

have also been reported in the literature, such as cardiopulmonary, gastrointestinal, and central nervous system manifestations.[12] Therefore, it may be misdiagnosed as other conditions. In our case, the patient had no complaint other than AUB. Comparison of the presentations in recent years (1996–2011) with prior years (1964–1996) has also shown a lack of significant clinical presentations in more women recently, as well as later diagnosis (46.1 vs. 19.7 weeks),[13] which is consistent with the clinical presentation of our patient. In our patient, ultrasound examination detected an intra-uterine mass, considered as placental remnants. The diagnosis was made based on the increased serum levels of β-HCG and confirmed by the pathological report after D&C. Therefore, measurement of the serum values of β-HCG can be beneficial in the diagnosis of both the primary and gestational presentations and secondary/metastatic conditions; β-HCG can help determine the possibility of a germ cell or GTD origin of the tumor or rule out the differentiation of an epithelial tumor.[1] Furthermore, immunohistochemical analysis has revealed the presence of antibodies, such as Mel-CAM, HLA-G, MUC-4, and β-catenin in the specimens, which suggests the possible mechanisms of the development of choriocarcinoma.[14] Consistent with this notion, in our patient, an immunohistochemistry study revealed positive CK, Sall 4, high ki-67 (>90%), and negative p63.

Diagnosis is the major challenge of choriocarcinoma, as the late diagnosis can result in hypovolemic shock because of massive bleeding from the primary or metastatic sites.[2,3] About 10% of patients with gestational choriocarcinoma may end up in death, caused primarily by uncontrollable bleeding or secondarily by massive metastases.[8,13] Fortunately, our case did not have any signs of hypovolemic/hemorrhagic shock and no evidence of metastasis on chest X-ray examination and abdominopelvic ultrasound.

IC, a subtype of gestational choriocarcinoma, is rare, with few case reports published. Pathological examination of 11,223 cases with a possible diagnosis of GTD revealed IC only in four cases (suggesting a prevalence of 0.04% in suspected cases).[15] Extension of this research showed that among 27,101 women with GTD, eight had IC.[16] Referring to the literature shows that most cases of IC are diagnosed earlier than our case; most cases in the third trimester and a few cases in the first and second trimesters, and the whole placenta is examined both macroscopically and microscopically. The lesion is found on a small section of the placenta, while the rest of the placental tissue is normal.[15,16] About 30% of placenta have a normal macroscopic appearance.[16] In the case presented here, the obstetrician reported no abnormality in the gross appearance of the placenta at the time of delivery, and the pathological examination was performed (by us) only on the remnants of D&C (4 months after the delivery); fortunately, we did not miss the pathognomonic section. This suggests the significance of paying attention to the appearance of the placenta at the time of delivery for accurate and early diagnosis of IC by sending the placenta for pathological examination. A review of the reported cases suggests that about 50% of IC are asymptomatic, and most cases are diagnosed by incidental examination of the placenta. Metastasis is reported to be presented in 50%–60% of patients at the time of diagnosis, and fetal death is reported in 15%–30% of cases.[15,16] Very few cases with both maternal and infantile metastases have also been reported.[17] Similar to the overall frequencies reported, in our case, the mother had no symptoms during pregnancy and was diagnosed 4 months after the delivery of a normal healthy neonate and had no metastasis. Apart from diagnosis, a challenging issue in choriocarcinoma, treatment is another important issue in these cases. After detection of similar survival rates in

patients treated with fertility-preserving modalities versus hysterectomy, the trend of treatment has been changed to prevent hysterectomy as much as possible, although combined chemotherapy increased the risk of cardiac anomalies in the neonate.[18] As our case was diagnosed after delivery, these challenges were not met, but the important challenge in our case was the mother's response to treatment. A review of 31 cases with metastatic IC showed the highest long-term survival in the chemotherapy plus surgery or radiotherapy (RT; 86%), while surgery or RT alone resulted in 100% death.[16] In line with the results of this study, which reported early aggressive chemotherapy as the excellent choice in patients with rising β-HCG and considering the size of the tumor in this patient, we also chose chemotherapy for our patient, which resulted in a favorable therapeutic outcome (until the last follow-up visit). As there are few case reports in the literature on choriocarcinoma and especially very fewer cases reported with IC, the best treatment choice is still unknown and more studies are required in this regard.

4 | CONCLUSION

The case presented here is one of the rare cases diagnosed with IC. One of the distinctive points about this case, compared with the reported cases, was diagnosis 4 months after the delivery after a normal course of pregnancy, while most cases of IC are diagnosed during pregnancy. Most cases with IC are asymptomatic, and most cases are found incidentally; therefore, the actual frequency of IC might be much higher than that reported in the available literature. An effective strategy for increasing the chance of diagnosis can be the examination of the placenta in any suspected cases. More studies are required to determine the most appropriate diagnostic and therapeutic approach for such patients.

AUTHOR CONTRIBUTIONS

Mahdokht Azizi: Conceptualization; writing – original draft. **Mojgan Akbarzadeh Jahromi:** Supervision. **Parvin Ghaffari:** Data curation. **Mazaher Ramezani:** Writing – review and editing.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICAL APPROVAL

This case report is ethical according to the world medical association declaration of Helsinki.

CONSENT

Written informed consent is obtained from patients to publish this report.

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