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Case Series

Placenta Site Trophoblastic Tumor and Choriocarcinoma from Previous Cesarean Section Scar: Case Reports

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Abstract

Choriocarcinoma and placental site trophoblastic tumor (PSTT) are rare varieties of gestational trophoblastic disease (GTD). PSTT alone constitutes about 1-2% of all trophoblastic tumors, which presents at early reproductive age and the serum beta-hCG level is much lower than choriocarcinoma. This tumor usually invades the myometrium and its depth of penetration is a prognostic factor**.** The first case report is regarding a 33-year-old woman with vaginal bleeding 3 months after abortion. The ultrasound exhibited heterogeneous and hypervascular mass related to previous cesarean scar. Serum beta-hCG level was 67 mIU/ml and chemotherapy was administered. However, due to severe vaginal bleeding and no regression in mass size, total abdominal hysterectomy was performed. Histopathological examination and IHC staining confirmed PSTT from previous cesarean section. The second case report is regarding a 33-year-old woman with cervicoisthmic choriocarcinoma, which was mistaken as cesarean scar pregnancy. The ultrasonography and elevated serum beta-hCG level suggested cesarean scar pregnancy. The patient was treated with methotrexate without any effect. Eventually, cervicoisthmic choriocarcinoma was detected after hysterectomy. A diagnostic error was made leading to possible uterus perforation along with incorrect chemotherapy that resulted in a life-threatening condition. It is concluded that PSTT and choriocarcinoma are the two important differential diagnoses of sustained elevated beta-hCG when imaging evidence is also suggestive. Although PSTT and cervicoisthmic choriocarcinoma are rare, they do exist and are on the rise.

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Keywords ● Trophoblastic neoplasms ● Cesarean scar ● pregnancy ● Trophoblastic tumor ● Placental site

What's Known

- Cesarean scar placental site trophoblastic tumor (PSTT) and cervicoisthmic choriocarcinoma are rare conditions.
- The exact diagnosis of such life-threatening condition is very difficult.

What's New

- A rare case of PSTT from previous cesarean scar is reported.
- It is strongly recommended to suspect cesarean scar placental site trophoblastic tumor and choriocarcinoma to avoid delays in an accurate treatment plan.

Introduction

Placental site trophoblastic tumor (PSTT) constitutes about 1-2% of all trophoblastic tumors. About 75% of the cases occur following a normal pregnancy, 17% following abortion, and only 5% of the cases occur following molar pregnancy.[1] It presents at early reproductive age and the serum beta-hCG level is much lower than choriocarcinoma.[2] This tumor usually invades the myometrium and its depth of penetration is a prognostic factor. PSTT is a very rare condition and a PSTT from previous cesarean scar has only been reported twice.[1,3] Herein, for the third time

ever, a case of PSTT from previous cesarean scar is reported (first patient).

Choriocarcinoma is another rare variety of gestational trophoblastic disease. Most choriocarcinomas are preceded by a complete mole that occurs in about 1-2% of complete moles. Other cases of choriocarcinoma occur following partial mole (a very unusual occurrence), ectopic pregnancy, non-molar abortion, or term pregnancy.[4] Extrauterine choriocarcinoma has been reported rarely and the most common location is in the uterine cervix.[5] Untreated choriocarcinoma is a life-threatening condition; however, it is often chemo-sensitive. Nevertheless, incorrect chemotherapy and insufficient treatment may lead to cure delay and metastasize. When choriocarcinoma is located extrauterine, its exact diagnosis is very difficult. As part of the second case report, we present a cervicoisthmic choriocarcinoma, which was mistaken as cesarean scar pregnancy.

The patients described in this case report referred to Vali-Asr Hospital, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.

Case Report

First Patient

A 33-year-old woman referred to the emergency ward of Vali-Asr Hospital with complaints of amenorrhea and irregular spotting. Her past medical history was unremarkable. The patient had one cesarean delivery and one spontaneous abortion 3- and 1-year ago, respectively. She was at 7 weeks of gestation with last menstrual period date. Her pregnancy was spontaneous and twins. A recent transvaginal ultrasound revealed dichorionic diamniotic twin pregnancy with normal fetal heart rate. She experienced a sudden vaginal bleeding and one fetus was aborted.

Vaginal ultrasound was performed and the demised fetus was detected in the lower segment of the uterus with a subchorionic hematoma. Uterine curettage revealed products of conception. She had amenorrhea for 3 months after curettage, but irregular spotting occurred and continued for 1 month. Consequently, the patient was referred to Vali-Asr Hospital. On admission, there was no significant abnormality on her physical examination and vital signs were stable. Only spotting from closed cervix was detected on speculum examination. The laboratory results were as follows: Hemoglobin 11/2 mg/dl (11-14), hematocrite 34/1 (34-38), and beta-hCG 67 mIU/ml.

A Doppler vaginal ultrasound showed that the uterus size was 35×49 mm and the endometrial thickness was 5 mm. There was a heteroechoic and hypervascular mass from previous cesarean section scar (figure 1). Serum beta-hCG level also raised to 93 mIU/ml one week later. There were several differential diagnoses, such as cesarean scar pregnancy, retention placenta accreta, and gestational trophoblastic disease. Actinomycine was prescribed to the patient because it was believed that the above-mentioned differential diagnoses were sensitive to chemotherapy. Four courses of actinomycine 2 mg were administered in consecutive 2 weeks. The patient had a strong desire to save her fertility and did not accept surgery. After three courses of actinomycine, the serum beta-hCG level returned to zero. Hence, the remaining course of chemotherapy was continued. Two weeks later, the patient presented severe vaginal bleeding. On admission, the blood pressure was 100/70 mm Hg, pulse rate 110 per minute, and the cervix was closed. However, there was severe vaginal bleeding on speculum examination. The uterus and adnexes appeared normal size. The laboratory tests were as follows: Hemoglobin 8/3 mg/dl, hematocrite 23/7, platelet count 153,000 and coagulation profile was normal, and beta-hCG was 0/7mU/ml.

The patient received 2000 cc normal saline infusion and 2 units packed red blood cells. Doppler ultrasound exhibited hypervascular heteroechoic mass 33×41 mm, similar to previous cesarean section scar. There was no evidence of regression in vascularity or size of the mass located in the cesarean section scar in comparison with the imaging before chemotherapy. Vascular resistance index (RI) was 0/37 and the sinologist suggested placental site trophoblastic tumor. There were no

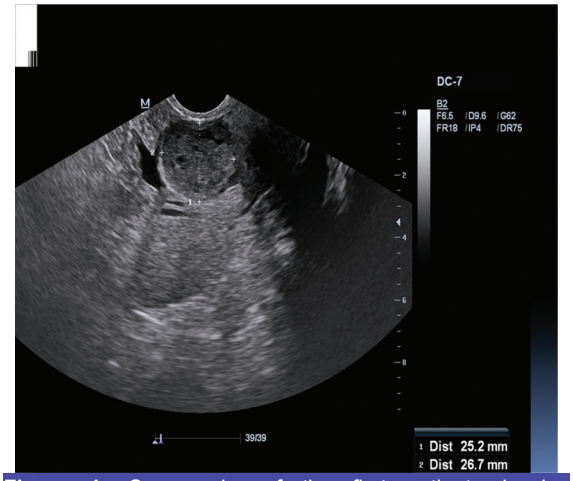

Figure 1: Sonography of the first patient showing heteroechoic mass from previous cesarean section scar.

metastatic lesions in other parts of the body, such as liver, lung, and brain. After consultation, the patient agreed with hysterectomy. Laparatomy was performed and no significant lesion in abdominopelvic exploration was observed. There was a normal size uterus with a regular surface, except for the previous cesarean section scar location, which was slightly enlarged and protruded. Total abdominal hysterectomy was performed and the ovaries were preserved to save the endocrine function. On the cut section of the specimen, a brownish irregular friable mass was detected (figure 2). The operation and the recovery period were uneventful and the patient was discharged after 4 days.

On microscopic examination, histopathological dominant pattern was the large trophoblastic cells with eosinophilic cytoplasm and pleomorphic nuclei that invaded the myometrium (interdigitating pattern of myometrial invasion) with strong immunoreactivity for human placental lactogen (HPL) and focal immunoreactivity for beta-hCG absence of immunoreactivity for p63 (a useful feature in the differential diagnosis with epithelioid trophoblastic tumor). The Ki67 (a proliferating marker) was up to 12%. The depth of invasion to myometrium was 85%. The mitotic rate was 7 per 10 high power fields. Finally, PSTT was confirmed (figure 3). Serum beta-hCG and HPL were checked consecutively for 8 months. All measurements were in the normal range and the patient is presently symptom-free without any evidence of the disease. Written informed consent was obtained from the patient.

Second Patient

A 33-year-old woman referred to Vali-Asr Hospital with complaints of irregular abnormal uterine bleeding. She had two pregnancies within 7 years. The first was a cesarean delivery due to malpresentation and the second (9 months before admission) was a miscarriage that led to curettage at 8 weeks of gestation. Her past medical history was unremarkable. On admission, the patient was stable and there were no significant issues in her routine examination. In vaginal speculum test, cervix was mid and closed with short spotting from it. The uterus and adenxes were not tender in deep bimanual palpation. The laboratory results were as follows: Hemoglobin 12/3 mg/dl, hematocrite 35/8, platelet count 143,000, and beta-hCG 3,664 mIU/ml.

Vaginal sonography revealed an empty uterus cavity with a closed cervix. Endometrial thickness was 12 mm. There were no abnormalities in the tubes or ovaries, but there was a focal heterogeneity 41×30 mm in the previous cesarean section scar that had a low resistance index (RI) in Doppler waves (RI: 0/29). Magnetic resonance imaging (MRI), with and without contrast, also confirmed the mass 40×30 mm in the previous cesarean section scar.

Based on laboratory tests and imaging evidence, cesarean scar pregnancy (CSP) was diagnosed. In the absence of CSP treatment, according to a standard protocol, chemotherapy was recommended. Beforehand, the patient was debriefed regarding the advantages and disadvantages of chemotherapy. Methotrexate 1 mg/kg (68 mg) was administered intravenously every 48 hours and the serum beta-hCG level was measured sequentially. On the first day of the chemotherapy, the serum beta-hCG level was 3,664 mIU/ml; however, it was reduced to 794 mIU/ml on the 8th day and was checked again a week later. Unfortunately, despite a good response to methotrexate along with 4 courses of chemotherapy, the serum beta-hCG level raised to 4,325 mIU/ml 7 days later. Ultrasonography was performed and there was no change in the

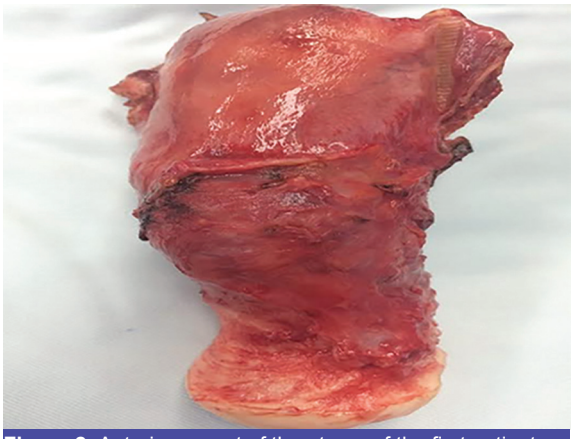

Figure 2: Anterior aspect of the uterus of the first patient.

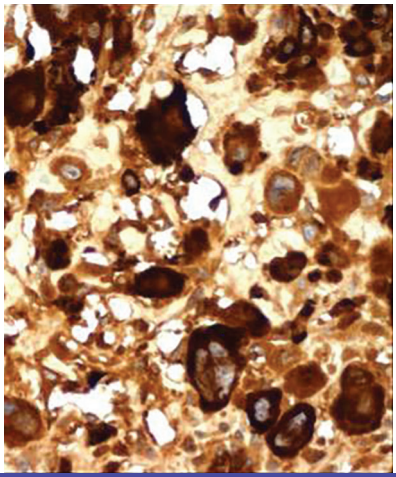

Figure 3: IHC staining of the first patient showing strong immunoreactivity for HPL and focal immunoreactivity for beta-hCG.

size of the mass and was still hypervascular. The distance to the serosal surface was 2 mm and deep penetration to myometrium was detected. Considering the ineffectiveness of chemotherapy, a surgery was planned for the definite treatment of CSP. The patient was consulted regarding the consequence; however, she had no desire to preserve her fertility and accepted the inevitability of hysterectomy during the operation. A midline incision was used to access the abdominal cavity. There were no abnormalities in the abdominopelvic exploration. The ovaries and tubes appeared normal and there was a bulged (largest size: 5 cm) in the anterior and inferior segments of the uterus just below the bladder reflection. The parametrium was fragile, particularly on the left side. The serosal surface was intact, but due to the location of the mass, uterus preservation seemed impossible. Consequently, total abdominal hysterectomy was performed. Considering the patient's age, the ovaries were saved to preserve endocrine function. The dissected uterus is shown in figure 4. The recovery period was uneventful and the patient was discharged 13 days after hospitalization. The serum beta-hCG level on the third day after hysterectomy was 30 mIU/ml.

Histopathological examination revealed soft, dark-red, and hemorrhagic mass invading the uterus cervix and lower segment measuring 4×5×3.5 cm. It filled the full thickness of the uterus cervix wall and parametrial tissue and all surgical margins were free. Microscopically, there was plexiform proliferation of cytotrophoblasts and cyncytiotrophoblasts with the frequent presence of hemorrhage and necrosis without any villi. On immunohistochemistry (IHC) staining, it was positive for the beta-hCG marker and Ki67 (a proliferation marker) was 85%. Hence, as shown in figure 5, cervicoisthmic choriocarcinoma was diagnosed.

Brain, lung, and liver cut scans were performed to detect metastatic lesions. Based on the international federation of gynecology and obstetrics (FIGO) staging system for GTD, the patient was in stage 1 and the score was 5 (low-risk). Therefore, single-agent chemotherapy was administered. After the first course of actinomycine, the serum beta-hCG level returned to zero and thus the chemotherapy was continued for 3 additional courses. Currently, the patient is asymptomatic and followed up by a monthly measure of the serum beta-hCG level. Written informed consent was obtained from the patient.

Figure 4: Cut of uterus specimen.

Discussion

Several conditions can lead to post-abortion hemorrhage and elevated serum beta-hCG levels, such as cesarean scar ectopic pregnancy (CSP), gestational trophoblastic disease (GTD), and retention placenta increta. CSP is the rarest subtypes of ectopic pregnancy, but nowadays the incidence of CSP is rising due to the increase of cesarean delivery in the world.[1,4] GTD is a group of trophoblastic tumors with malignant potential. PSTT constitutes about 1-2% of all trophoblastic tumors. About 75% of the cases occur following a normal pregnancy, 17% following abortion, and only 5% of the cases occur following molar pregnancy.[2] It presents at early reproductive age and the serum beta-hCG level is much lower than choriocarcinoma.[3,5]

PSTT typically composed of fewer extensive vascular patterns in comparison with choriocarcinoma.[6] The exact pathogenesis is unclear, but there is a concept that suggests chemo-resistance or chemo-sensitivity of this tumor is due to their cell types.[7,8] PSTT usually invades the myometrium and its depth of penetration is a prognostic factor. The use of immunohistochemistry (IHC) staining for definite diagnosis of GTN subtypes was initially described by Shih.[9] GTN staging, as described

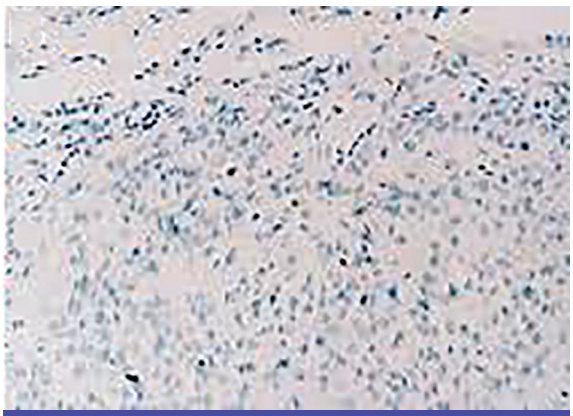

Figure 5: IHC staining is positive for beta-hCG marker and Ki67 (a proliferation marker) is 85%.

by the international federation of gynecology and obstetrics (*FIGO*), is not solely helpful for the prognosis of PSTT. As mentioned by Schmid,[10] there are several other factors which are important for prognosis, such as mitotic count rate, extensive coagulative necrosis, depth of myometrial invasion, serum beta-hCG level >1000 mIU/ml, age >35 years, and interval between antecedent pregnancy >2 years. Recently, a cut-off for the lengthened time of over 4 years since pregnancy has been reported.

The first patient in the present case report underwent curettage after embryonic demise; she had amenorrhea for 3 months and then presented with spotting. The first pathology report revealed products of conception without any evidence of PSTT. After 4 months, beta-hCG was 67 mIU/ml and there was a mass in the cesarean scar, which was hypervascular with RI=0/37 according to the Doppler ultrasound imaging. There were several differential diagnoses such as CSP, retention placenta increta, and GTD. In all these, the beta-hCG is higher than normal and imaging (e.g. ultrasound, Doppler, or MRI) is unspecific for a definite diagnosis. Pathological examination is mandatory for the confirmation of the exact disease. However, we administered actinomycine without histopathological confirmation. Since we believed that all differential diagnoses such as CSP, GTD, or increta are sensitive to chemotherapy, it was concluded that none would provide a satisfactory result. PSTT was not suspected as a differential diagnosis. PSTT is chemo-resistant, but in this case, the beta-hCG level responded positively to actinomycine. Low levels of beta-hCG may be responsible for its rapid decrease, but no regression in mass size and severe vaginal bleeding indicated a specific chemo-resistance condition. Therefore, PSTT was strongly suspected and total abdominal hysterectomy was performed. The fact that histopathological confirmation (e.g. transcervical ultrasound-guided biopsy) is mandatory for careful evaluation prior to hysterectomy was unknown to us. PSTT is a very rare condition and a PSTT from previous cesarean scar has only been reported twice.[1,3] Our encounter with PSTT is the third such case.

Further significant issue in our patient was an early proliferation of PSTT within 3 months after abortion. We stained slides with IHC markers. The beta-hCG showed scattered positivity and HPL was stained extensively. Taken together, the level of beta-hCG, chemo-sensitivity, histopathology, and finally IHC staining results were most consistent with PSTT. Considering the age of the patient, we managed to save the ovaries to preserve endocrine function. The PSTT was in stage 1 and confined to the uterus. Considering good prognosis after surgery without recurrence in other sites, it was treated by surgery. The 10-year survival rate for people with PSTT stage 1 is 90%. Chemotherapy and radiation are not recommended after surgery.

There are several differential diagnoses (e.g. cesareans scar pregnancy (CSP) and placenta increta) for patients with positive human chorionic gonadotropin (hCG) combined with imaging evidence such as a cervicoisthmic mass with empty uterus cavity. Nonetheless, without any response to chemotherapy alone, trophoblastic disease is possible. The exact diagnosis is essentially difficult.[10] The incidence of CSP is rising due to the increase of cesarean delivery and is reported as 1 per 2,216 pregnancies.[11] There is no specific and definite strategy to treat CSP and chemotherapy with methotrexate is one of the options. However, the critical issue at hand is the life-threatening condition due to unnoticed CSP and incorrect diagnosis. Surgery is mandatory in the absence of any response to the selected medical treatment. Dilatation and curettage after uterine artery embolization have been discussed to cure CSP.[12] In our patient, chemotherapy was chosen since we had no experience with uterine artery embolization in CSP. Prior to hysterectomy, our final diagnosis was GTD. It was only after the surgery that the exact diagnosis was revealed and subsequently the lungs, brain, and liver were evaluated to identify possible metastatic lesions.

GTD is composed of abnormal proliferation trophoblastic cells with malignant potential. Choriocarcinoma is a rare subtype of GTD and its incidence in Asia is high and reported as 1 per 500-1,000 pregnancies. About 25% of GTDs occur after abortion and often mistaken as CSP since the symptoms and imaging evidence are similar.[13] The pathogenesis of cervicoisthmic choriocarcinoma is controversial. It is suggested that malignant transformation of the remaining chorionic cells from the previous pregnancy is responsible for its formation. After confirmation, choriocarcinoma must be staged. Based on the international federation of gynecology and obstetrics (FIGO) staging system for GTD, our patient was in stage 1 and the score was 5 (low-risk). The FIGO point system is categorized as follows:

- Maternal age (year): 0 point
- Antecedent pregnancy: 1 point
- Interval of antecedent pregnancy to chemotherapy: 2 points
- Serum beta-hCG level: 1 point
- Number of metastases: 0 point
- Largest tumor size: 1 point

- Prior chemotherapy: 0 point

The patient presented in this case report had a score 5 and was a candidate for single agent chemotherapy after hysterectomy. Four courses of actinomycine 2 mg were used intravenously.

Conclusion

Although PSTT and cervicoisthmic choriocarcinoma are rare, they do exist and are on the rise. Specific focus should be placed on GTD even if other differential diagnoses are probable. If we had suspected cervicoisthmic choriocarcinoma, the hysterectomy of a 33-year-old woman (second patient in this case report) could have been avoided with accurate chemotherapy after a fine-needle aspiration biopsy confirmation. A diagnostic error was made leading to possible uterus perforation along with incorrect chemotherapy that resulted in a life-threatening condition.

PSTT grows very slowly and metastasize occurs after several years. Therefore, hysterectomy can prevent future spread of the disease. Despite choriocarcinoma, PSTT is less sensitive to chemo agents. Therefore, surgery is recommended even if serum beta-hCG level is normalized.

Conflict of Interest: None declared.

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