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Placental Site Trophoblastic Tumor: A Report of Successful Management With Combination Chemotherapy, Subsequent Spontaneous Conception, and a Live Birth at Term

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ABSTRACT

Introduction: Placental site trophoblastic tumor (PSTT) is a rare form of gestational trophoblastic disease (GTD) that is typically associated with higher mortality compared to other subtypes due to its unpredictable biological behavior, lower responsiveness to chemotherapy, and poor prognosis.

Case Presentation: We present the case of a 27-year-old nulliparous woman who was referred to our center for recurrent vaginal bleeding following two evacuations for an incomplete spontaneous miscarriage after eight weeks of amenorrhea. Her assessment revealed low serum beta-human chorionic gonadotropin (βhCG) and elevated human placental lactogen (hPL) levels. Ultrasound and Doppler studies showed a highly vascular tumor infiltrating the myometrium. The patient strongly desired to preserve her fertility and was initially started on low-dose methotrexate, resulting in a marginal reduction in tumor volume but resistance to higher doses. She responded well to combination chemotherapy, and the tumor disappeared after the second course. She received three additional courses and was monitored with serial ultrasonography for one year. Subsequently, she conceived spontaneously and delivered a live, normal female baby at term via vaginal delivery.

Conclusion: Although hysterectomy combined with chemotherapy is the standard management for PSTT, and serum hPL is typically used as the tumor marker for follow-up, we present a case of successful treatment with combination chemotherapy alone. This approach resulted in subsequent cure, spontaneous conception, and the delivery of a live baby.

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Introduction

Placental site trophoblastic tumor (PSTT) is a rare form of gestational trophoblastic disease (GTD), accounting for 0.25-5% of all trophoblastic tumors. On a global scale, the disease-specific mortality rate for PSTT is higher than for other GTD subtypes (16.1% for PSTT, compared to 6.5% for hydatidiform mole and 13.4% for choriocarcinoma)(2). This higher mortality is attributed to the unpredictable biological behavior of PSTT, its lower responsiveness to chemotherapy, and its poor prognosis compared to other GTD subtypes (3,4). PSTT originates from the intermediate trophoblast at the placental implantation site after an abortion or normal intrauterine pregnancy(5). It primarily consists of mononuclear intermediate trophoblasts without chorionic villi and infiltrates the uterine wall in sheets or cords between myometrial fibers. Compared to choriocarcinoma, PSTT shows less vascular invasion, hemorrhage, and necrosis but carries a higher risk of lymphatic metastasis. βhCG production is focal, with relatively low serum

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levels, typically less than 1,000 mIU/ml. PSTT is typically diagnosed by elevated serum human placental lactogen (hPL) levels and confirmed immunohistochemically by staining for cytokeratin, hPL, inhibin, and Mel-CAM[5]. The Ki-67 labeling index is usually elevated (>10%) in neoplastic non-villous trophoblastic lesions[5, 6].

Total abdominal hysterectomy combined with combination chemotherapy is the recommended treatment modality for PSTT, given its unpredictable course and the high mortality associated with it. However, fertility preservation, recurrence, and chemotherapy resistance pose significant challenges in managing this condition(5-7).

We present the case of a 27-year-old nulliparous woman diagnosed with placental site trophoblastic tumor (PSTT) based on low levels of β-hCG, ultrasonography suggesting an endometrial tumor with myometrial invasion, and elevated serum hPL levels, following repeated evacuations for a presumed spontaneous incomplete miscarriage at a referral center. The standard treatment for PSTT typically involves a hysterectomy followed by chemotherapy, with serum hPL used for follow-up. However, due to her strong desire to preserve fertility, she was treated with combination chemotherapy alone, and her follow-up was monitored with ultrasonography, as serum hPL testing was prohibitively expensive. She responded well to treatment, with serial ultrasonography showing a gradual reduction in tumor volume until it wholly resolved. Ultrasonography continued to show no evidence of tumor recurrence throughout the follow-up period. The patient subsequently conceived spontaneously and delivered a healthy female baby at term.

Case report

A 27-year-old woman, Para 0+4, presented with recurrent vaginal spotting lasting two weeks following a second manual vacuum aspiration (MVA). Her last normal menstrual period was four months before presentation. Two months earlier, she had experienced a spontaneous incomplete miscarriage at eight weeks of pregnancy and underwent MVA to evacuate the retained products of conception. However, vaginal bleeding persisted, necessitating a second evacuation. The products of conception were not sent for histopathological examination after either evacuation. While the bleeding initially stopped, it resumed 17 days after the second evacuation, prompting her referral to our hospital. She had a history of three previous induced abortions, each without any post-abortal complications. General and systemic examinations were unremarkable. Examination of the vulva revealed altered blood, and a bimanual pelvic examination showed a slightly bulky uterus. Quantitative serum β-hCG was 41.51 mIU/ml, and transvaginal ultrasonography revealed obliteration of the myometrial-endometrial border, with heterogeneous Grade 4 myometrial infiltration extending 11 mm from the posterior uterine serosa and 12.4 mm from the fundus, approaching the anterior uterine serosa. The tumor volume was 17.6 cm^3 (7.7 cm x 3.2 cm x 2.8 cm), strongly suggesting gestational trophoblastic neoplasia (GTN). Endometrial biopsy could not be performed due to the risk of excessive hemorrhage. Based on the relatively low β-hCG and ultrasonographic findings, her serum human placental lactogen (hPL) was measured. The value of 0.81 mcg/ml, corresponding to 16-18 weeks of pregnancy, was considered elevated. Therefore, combining the low β-hCG, ultrasonographic evidence of an endometrial tumor with myometrial invasion, and the elevated hPL, a placental site trophoblastic tumor (PSTT) diagnosis was considered.

Due to the high cost and limited availability of serum hPL, ultrasonography was used for follow-up. The patient was initially started on low-dose methotrexate (50 mg/m^2) every two weeks. After the first course, the tumor volume decreased slightly from 15.6 cm^3 to 14.3 cm^3 (8.3% reduction). The methotrexate dose was subsequently increased to 300 mg/m^2, but a follow-up ultrasonography two weeks later showed no further decrease in tumor volume. A diagnosis of single-agent resistance was made, and the patient was switched to combination chemotherapy with etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMACO) every two weeks. After the first course of EMACO, the tumor volume reduced significantly from 14.3 cm^3 to 5.9 cm^3 (58.7% reduction), and her β-hCG concentration dropped to 6.6 mIU/ml. After the second course, the tumor completely disappeared, and her β-hCG concentration normalized. The patient developed oral mucositis while awaiting the third course, which was managed with parenteral cefuroxime, metronidazole, and antiseptic mouthwash, resulting in a good response. She received three more courses but could not complete the planned six courses due to financial constraints. She was followed up clinically and sonographically for one year while on combined oral contraceptives. Three

months after discontinuing contraception, she conceived spontaneously. An anomaly scan at 20 weeks of gestation showed a structurally normal fetus and no evidence of PSTT recurrence. She delivered a live female baby weighing 3.7 kg at term, and the placenta was histologically normal.

Discussion

Placental site trophoblastic tumor (PSTT) is a rare form of gestational neoplastic tumor and can follow any type of gestational event. In 66% of cases, it follows a full-term pregnancy, with a median latency of 12-18 months (ranging from a few months to 20 years)(3, 7). In approximately 10-50% of cases, it may follow spontaneous abortions or hydatidiform moles[7]. When the preceding event is a full-term delivery, patients typically present with a period of amenorrhea, abnormal uterine bleeding, and associated uterine enlargement[8]. In the present case, the patient had a history of spontaneous incomplete abortion after eight weeks of amenorrhea, followed by repeated uterine evacuation before referral to our center.

Persistent uterine bleeding after the evacuation of a missed or spontaneous abortion often raises suspicion of gestational trophoblastic disease (GTD). The diagnosis is typically made when there are persistently elevated or rising β-hCG levels. When abnormal uterine bleeding occurs after gestational events, accompanied by persistently elevated serum β-hCG levels but less than 1,000 mIU/ml, PSTT must be considered, as invasive mole and choriocarcinoma are usually associated with higher β-hCG levels. PSTT involves the proliferation of the intermediate trophoblast, which, unlike the syncytiotrophoblast, produces low to moderate quantities of β-hCG[3]. A closely related but distinct entity to PSTT is the epithelioid trophoblastic tumor (ETT). While PSTT arises from the intermediate trophoblast, ETT originates from chorionic-type intermediate trophoblast. Both tumors produce low levels of β-hCG, but ETT produces higher levels than PSTT. However, PSTT is characterized by high concentrations of human placental lactogen (hPL), a biomarker for this condition. ETT often exhibits positivity for p63 and cytokeratin, reflecting its epithelial characteristics (5, 9,10). In our patient, the low serum β-hCG and elevated hPL levels supported the diagnosis of PSTT. Unfortunately, due to the high cost and limited availability of the hPL assay locally, it could not be used for follow-up.

Ultrasonography is the first-line imaging method for diagnosing gestational trophoblastic neoplasia (GTN) in conjunction with clinical history and β-hCG levels due to its convenience and cost-effectiveness(11). It is particularly crucial in diagnosing placental site trophoblastic tumor (PSTT) because of the low β-hCG levels, which can complicate the diagnosis of GTN. Additionally, ultrasonography serves as a valuable adjunct for the follow-up of PSTT. Three types of PSTT are described based on transvaginal ultrasonography: type 1, where most of the tumor protrudes into the uterine cavity; type II, where the lesion is in both the uterine cavity and part of the myometrium; and type III, where the entire lesion is located in the myometrium (11, 12). The lesions are typically found in the uterine corpus and are rarely seen in the uterine cervix or pelvic wall, though lymphatic spread occurs frequently[13]. On ultrasonography, lesions can appear solid, cystic, or mixed with solid components. About half of the lesions appear hypoechoic or echogenic, with no clear boundary between the lesion and the surrounding tissue(11,12). Cystic and mixed cystic-solid lesions may be misdiagnosed as choriocarcinoma or hydatidiform mole(12). Based on hemodynamic parameters assessed through color Doppler interrogation, PSTT can be classified into two types: blood vessel-abundant and relatively low blood vessel types [12]. The present case was classified as ultrasound type II, blood vessel-abundant PSTT, as shown in Figure 2. Due to the limited availability and high cost of serum hPL in our setting, ultrasonography was used for tumor volume measurements and vascularity assessments while the patient underwent chemotherapy (Figures 1, 2, 3, and 4).

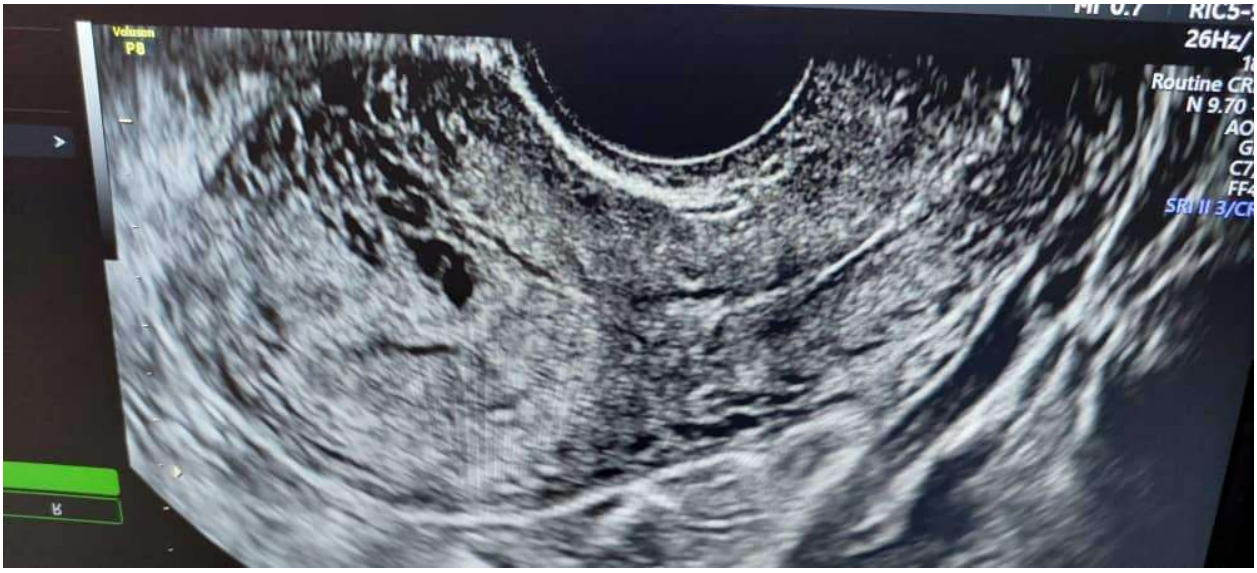

Fig 1. 2D image showing endometrial stripe replaced by heterogenous tissue. The endometrial-myometrial junction could not be delineated at the fundal region of the uterus.

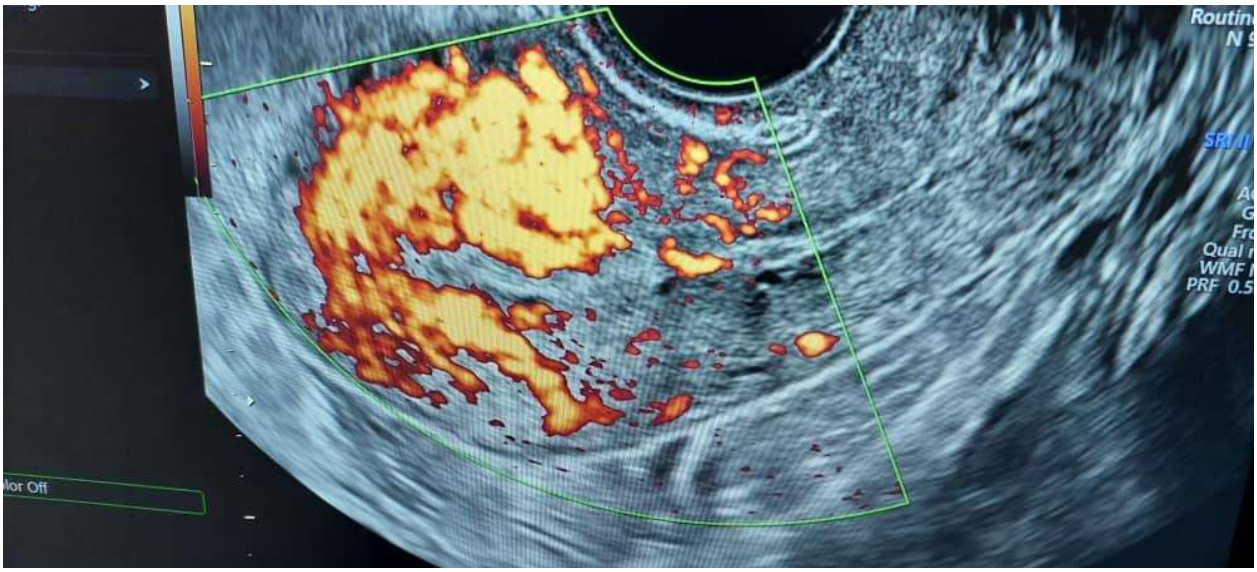

Fig 2. Doppler image showing myometrial infiltration by grade 4 hyper vascular tissue, 11 mm from the posterior uterine serosa, 12.4 mm from the fundus, but approaching the anterior uterine serosa.

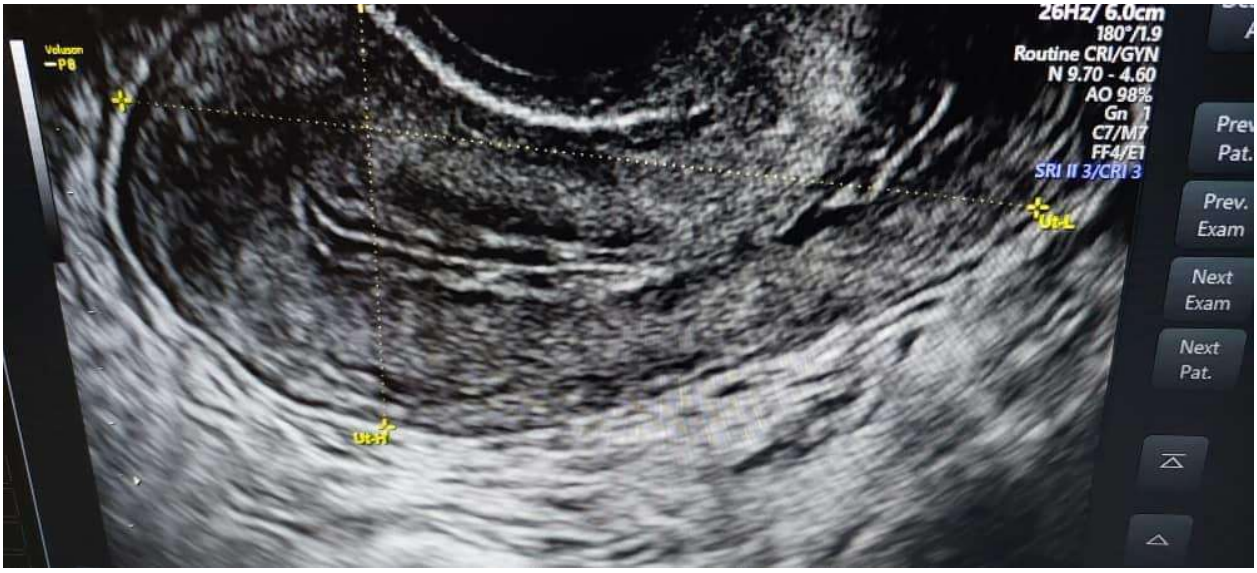

Fig 3. 2D image of tumour clearance after second course of EMACO

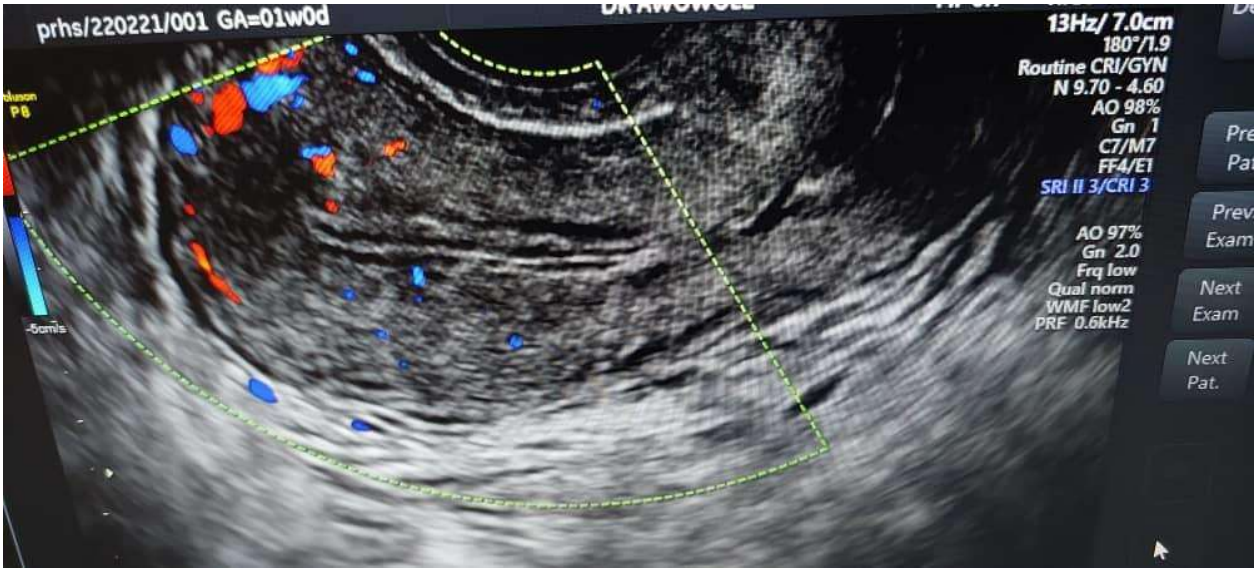

Fig 4. Doppler image of tumour clearance after second course of EMACO

Although most cases of placental site trophoblastic tumor (PSTT) present with FIGO stage 1 disease, hysterectomy remains the treatment of choice, as PSTT is relatively resistant to chemotherapy, unlike other forms of gestational trophoblastic neoplasia (GTN). However, in cases with evidence of metastasis or high-risk features, multi-agent adjuvant chemotherapy may be considered(14,15). Since PSTT predominantly affects women of childbearing age, who often desire fertility, fertility preservation should be the primary goal of management, mainly if the tumor is confined to the uterus. However, the literature on fertility-sparing treatment for PSTT and subsequent pregnancy outcomes is limited. Reported cases of fertility preservation have typically involved a combination of conservative surgery and chemotherapy, with favorable fertility outcomes(16,17).

This reported case, however, was managed with chemotherapy alone and followed up with ultrasonography. The patient conceived spontaneously, experienced no adverse events during pregnancy, and had a favorable pregnancy outcome. Histopathological evaluation of the placenta revealed no abnormalities. This case highlights the feasibility, efficacy, and potential for favorable pregnancy outcomes when chemotherapy alone is used for the management of

young patients with PSTT, particularly those with localized disease who wish to preserve their fertility. Given the higher likelihood of resistance to single-agent therapy, as observed in this patient, combination chemotherapy is considered the preferred treatment. This approach is associated with a high response rate and long-term remission, even in patients with recurrent or metastatic PSTT. However, only a few patients achieve a complete response(14,15). A prolonged interval from pregnancy to diagnosis is a poor prognostic indicator[15]. This interval was relatively short in the present case, and the patient responded well to EMACO alone. This regimen was chosen as the second-line combination chemotherapy after resistance developed to methotrexate due to its lower toxicity and relative efficacy. Another combination recommended as a neoadjuvant treatment is EMA/EP(15,18). Interestingly, the overall response rate to EMA/CO or EMA/EP is approximately 71%, with a complete response observed in 38% of patients(19). However, drug resistance can develop rapidly, leading to progression once recurrence or metastases occur. Therefore, multidrug-resistant metastatic PSTT remains the leading cause of death due to PSTT(18,19). The rate-limiting step in the use of EMACO and EMA/EP is often mucositis, a characteristic side effect of methotrexate[19]. This can occur even with prophylactic administration of folinic acid, as seen in this patient after the second course, which delayed the third course by a few days. Another limiting factor is bone marrow suppression, which may manifest as anemia, thrombocytopenia, or neutropenia, and requires correction before the next course can be administered(19).

Conclusion

Although hysterectomy combined with adjuvant multi-agent chemotherapy is the standard management for patients with placental site trophoblastic tumors, chemotherapy alone may be sufficient to achieve long-term remission and preserve fertility in selected patients. Additionally, ultrasonography can be helpful for treatment monitoring and follow-up, particularly in low-resource settings where serum hPL testing may not be readily available or is prohibitively expensive.

Declarations

Ethics approval and consent to participate: Ethical approval was obtained.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Availability of data and material: These are available.

Competing interests: We declare no conflict of interest.

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Authors' contributions: AC, EA and KO managed the patient, AC and EA drafted the initial manuscript, IO did all the ultrasonography. IO and KO reviewed the draft and all authors agreed to the final draft.

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