

# Placental site trophoblastic tumor: A case report and literature review

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## Summary

Here, we report a case of a placental site trophoblastic tumor (PSTT) in a 36-year-old Chinese woman 10 months after a normal pregnancy. Two months postpartum, the woman presented with abnormal vaginal discharge and her condition was overlooked by her local hospital. The woman did not receive further attention until a mass with a heterogeneous echo was found in an ultrasound examination eight months postpartum. The final diagnosis was confirmed by histological examinations in conjunction with immunohistochemical studies. Since the patient had potential risk factors, she was successfully treated with a hysterectomy and peri- and post-operative chemotherapy. The latest follow-up (16 months after diagnosis) was uneventful, and the patient exhibited no signs of recurrence or metastasis.

**Keywords:** Placental site trophoblastic tumor (PSTT), intermediate trophoblast (IT), diagnosis, treatment

## 1. Introduction

A placental site trophoblastic tumor (PSTT), originating from intermediate trophoblasts (ITs), refers to a special and rare type of gestational trophoblastic disease (GTD). In 1976, Kurman first described PSTT as syncytial endometritis and designated it a trophoblastic pseudotumor (1). In 1981, its malignant characteristics garnered attention when Twiggs reported a patient that died from the condition (2). At the same time, Scully reappraised the morphological aspects and malignant potential of the condition, designating it PSTT (3). In 1983, the World Health Organization (WHO) formally acknowledged the neoplastic nature of this lesion and adopted the terminology PSTT. PSTT has since become the third most common gestational trophoblastic neoplasm (GTN), second to invasive moles (IMs) and choriocarcinoma (CC). The incidence of PSTT is approximately 1/100,000 of all pregnancies and roughly

1-2% of all GTNs, while its mortality is 25% (4). To date, almost 300 cases of PSTT have been reported around the world (5). Its low mobility, uncharacteristic clinical presentation, and non-specific auxiliary examinations pose a substantial challenge to clinicians, leading to a low preoperative rate of diagnosis. In December 2013, the current authors encountered a case of PSTT, and this was the first such case seen at this hospital. This case is reported here and its clinical and pathological features have been analyzed based on the literature with the goal of enhancing the understanding of this disease.

## 2. Case presentation

A 36-year-old Chinese woman, gestation 2, miscarriage 1, underwent a cesarean section because of fetal distress and gave birth to a healthy full-term girl in February 2013. There was no postpartum hemorrhaging or puerperal fever during her postpartum course. The woman had no previous medical history and no personal or family history of GTD.

Two months postpartum, the woman visited her local hospital for abnormal vaginal discharge. The woman's condition was thought to be endometritis, and she was given antibiotic prophylaxis and medication to promote uterine contractions. Unfortunately, this treatment

Released online in J-STAGE as advance publication June 23, 2015.

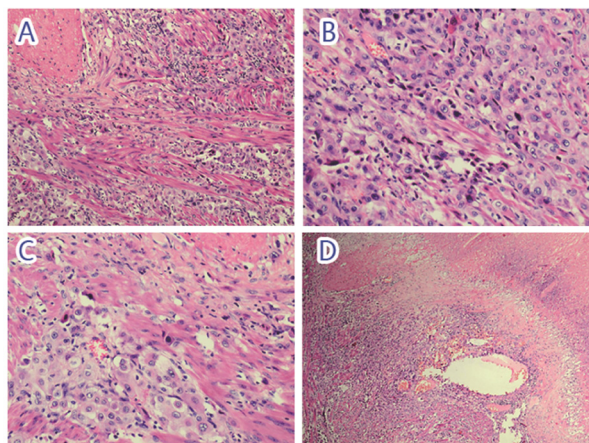
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was ineffective. The patient subsequently made repeated visits and was intermittently treated with anti-inflammatory therapy, but the therapy was ineffective. Eight months postpartum, a pelvic color Doppler ultrasound indicated a heterogeneous echo 17 mm × 10 mm in size in the uterine cavity, but no treatment was recommended except for monitoring by her doctor. Nine months postpartum, a second pelvic color Doppler ultrasound indicated that the heterogeneous echo was 56 mm × 20 mm in size, and the patient's serum beta human chorionic gonadotropin ( $\beta$ -hCG) level was 54.60 mIU/mL, compared to a normal level of lower than 5.4 mIU/mL. The patient subsequently underwent a hysteroscopy, and a pathological examination of endometrial curettage specimens suggested PSTT. Thus, the patient was referred to this hospital, a tertiary care center, for further management.

On admission, a physical examination revealed no abnormalities in the heart, lungs, or extremities. A gynecological examination revealed a normal vulva, little vaginal bleeding, no pain in the cervix upon lifting or manipulation, and an enlarged uterus about the size of that during the 8th week of pregnancy. In addition, the uterus was soft on palpation, and there was mild tenderness in the adnexa. The patient's  $\beta$ -hCG level was 66.14 mIU/mL. A pelvic color Doppler ultrasound indicated a region 12 mm × 10 mm in size with an abundant blood flow, and the patient's vascular resistance index (RI) was 0.41. Pelvic magnetic resonance imaging (MRI) indicated that the right posterior wall of the uterus was irregular, consistent with malignant changes.



**Figure 1. Microscopic findings.** (A) The PSTT had monomorphic intermediate trophoblastic cells extensively infiltrating the myometrium, partly in nests and cords, separating myometrial muscle fibers, both individually and in groups. (B) These tumor cells were usually large and polygonal with irregular vesicular nuclei and displayed an abundance of dense eosinophilic to amphophilic cytoplasm. Abundant extracellular fibrinoid material was seen on occasion. (C) Multinucleated tumor giant cells are evident in places, but no syncytiotrophoblastic cells are evident. (D) Lesional cells displayed characteristic vascular invasion, replacing vessel walls, and tumor cells have vast areas of necrosis (hematoxylin and eosin staining, original magnification 100 $\times$ , 200 $\times$ , 200 $\times$ , and 40 $\times$ ).

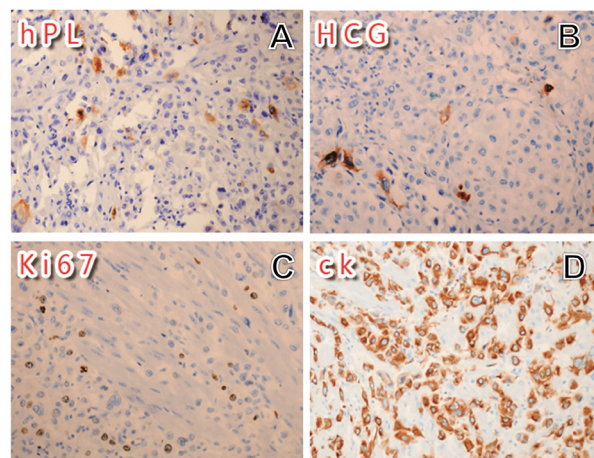
Pathological slides obtained from the referring hospital were viewed at this hospital. Ultimately, pathologists diagnosed the mass as a PSTT.

The mildly elevated level of serum  $\beta$ -hCG and pathological findings strongly suggested PSTT. The patient was treated with 5-fluorouracil, methotrexate, and etoposide (5-Fu, MTX, Vp16) for two days, followed by a total abdominal hysterectomy (TAH) with sparing of the ovaries. She finished the five-day chemotherapy regimen the day after surgery. Gross examination revealed an irregular mass, almost 1 cm × 1 cm in size, protruding from the uterine isthmus. Pathological examination of hysterectomy specimens (Figure 1) revealed a PSTT, along with extensive surface necrosis and vascular invasion, infiltrating the shallow muscle layer. Moreover, the tumor cells also displayed nuclear atypia, while chorionic villi and cytotrophoblasts were not evident. In order to confirm the diagnosis, pathologists were asked to perform immunohistochemical (IHC) studies (Table 1 and Figure 2), which indicated that the tumor cells

**Table 1. Immunohistochemical results for the PSTT**

Antigen	P(+)/N(-)
CK	+++
hPL	+++
Ki67	++
P53	++
P63	++
Calponin	++
HCG	+
PLAP	+
Vim	+
SMA	+
S-100	+
Inhibin	-

PLAP, placental alkaline phosphatase; hPL, human placental lactogen; SMA, smooth muscle actin; +++, strongly positive; ++, positive; +, focally positive; -, negative.



**Figure 2. Immunohistochemical findings (200 $\times$ )** (A) Tumor cells were diffusely positive for hPL; (B) Tumor cells were focally positive for hCG; (C) About 10% of the tumor cells were slightly positive for ki67; (D) Tumor cells were strongly positive for CK.

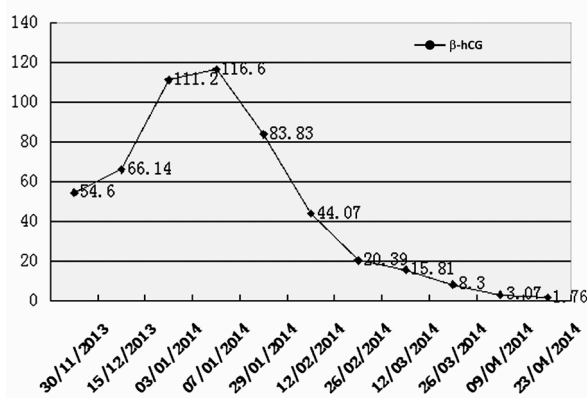


Figure 3. Changes in  $\beta$ -hCG levels (mIU/mL) during the treatment period.

were strongly positive for CK and human placental lactogen (hPL), positive for ki67, p53, p63, and calponin, and focally positive for HCG, placental alkaline phosphatase (PLAP), Vim, smooth muscle actin (SMA), and S-100. On the 10<sup>th</sup> day after surgery, the patient's serum  $\beta$ -hCG level was 111.20 mIU/mL, and that level rose to 116.60 mIU/mL on the 14<sup>th</sup> day after surgery. The presence of vast areas of necrosis and vascular invasion, together with a term pregnancy, all indicated that this PSTT possessed high-grade histological features that were suggestive of a poor prognosis. The patient subsequently underwent adjuvant chemotherapy. After the second cycle of the triple drug chemotherapy regimen (5-Fu, MTX, and Vp16), the patient's serum  $\beta$ -hCG level was 83.83 mIU/mL. Given the slow decline in the  $\beta$ -hCG level, treatment was changed to five cycles of the EMA-CO chemotherapy regimen (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine). During chemotherapy, the patient displayed obvious mouth ulcers and bone marrow suppression. When the level of  $\beta$ -hCG was under the measurable limit, two courses of consolidation chemotherapy were given. Changes in  $\beta$ -hCG levels during the treatment period were evident (Figure 3). At the latest follow-up (16 months after diagnosis), the patient's course was satisfactory, and she exhibited no signs of tumor recurrence or metastasis.

### 3. Discussion

PSTT frequently develops in women of reproductive age. The interval from prior pregnancy to tumor development is usually less than 2 years. PSTT is typically secondary to varieties of pregnancies and often follows a term labor for a female infant or after an abortion, molar pregnancy, or ectopic pregnancy (6). PSTT has also been reported in conjunction with a live twin pregnancy and was successfully resected during a caesarean section (7). Interestingly, PSTT can also develop in patients with no history of pregnancy, and PSTT has been noted in the ovary of a young child with

isosexual precocious puberty (8) and in men (9).

The clinical presentation of PSTT is nonspecific and uncharacteristic. Patients usually present with amenorrhea or irregular vaginal bleeding. Gynecological examination reveals that the uterus is uniformly or irregularly enlarged. The overwhelming majority of PSTTs manifest as benign lesions and most frequently develop within the uterus. About 10%-15% of patients present with metastatic disease. However, several studies have suggested that metastases develop in over 30% of PSTTs upon presentation (32% according to Feltmate *et al.*, 53% according to Newland *et al.*, and 31% according to Chang *et al.*) (10-12). Recurrence occurs in over 30% of cases. Metastasis in the lungs, liver, kidneys, brain, abdomen, pelvic lymph nodes, or vagina is common. Based on 10 years of experience in dealing with PSTT, Schmid *et al.* noted that the probability of overall survival for patients with PSTT was 70% and the recurrence-free survival rate was 73% (13).

Unlike other GTNs (IM and CC), the level of serum  $\beta$ -hCG in PSTT is usually under the measurable limit or slightly elevated. The level of serum  $\beta$ -hCG in 79% of patients at Charing Cross Hospital was below 1000 mIU/mL (14), and the level was below 400 mIU/mL in 97% of the patients at the New England GTD Center (15). The level of serum  $\beta$ -hCG seldom reaches that noted in a CC is not proportional to the tumor load (16). In addition, the level of serum  $\beta$ -hCG is not associated with malignant behavior (10). Therefore, the level of serum  $\beta$ -hCG cannot accurately reflect the tumor burden and is of little value in assessing prognosis. However, a study found that hyperglycosylated hCG testing was more sensitive at detecting recurrent or persistent disease (17). A pelvic B ultrasound can display the signal of the tumor's blood flow. MRI has the advantage of displaying soft tissue in sharp contrast and allowing multi-aspect imaging, so it can be used to accurately determine the depth of myometrial invasion.

A macroscopic examination reveals that the tumors are localized nodules or polypoid tumors protruding into the uterine cavity. They may also present as masses infiltrating the myometrium with indistinct margins. Small bleeding foci may also be evident. Serosal infiltration may cause spontaneous perforation. A pathological examination reveals that the tumor only contains one form of trophoblastic cell that is either polygonal or circular. Spindle-shaped cells may be evident in some instances. Cells have a clear cell membrane and abundant cytoplasm that is eosinophilic or amphophilic. The nucleus is circular or ovoid and a few cells also have a macronucleus or multiple nuclei. A characteristic of tumor growth is diffuse infiltration. Bundles or clumps of tumor cells may invade muscle fibers. Histological findings from a PSTT are specific, but they are unable to distinguish the benign or malignant characteristics of a PSTT. A high mitotic rate of more than 5/10 HPF (and especially one more than 10/10

HPF) and substantial hemorrhaging and necrosis within the tumor are certainly suggestive of malignancy.

IHC is currently considered to be the "golden standard" for diagnosis of PSTT (18). On examination, tumor cells usually have a high level of Ki-67 expression (about 10%-15%). Inhibin is highly expressed by a PSTT. hPL, hCG, and PLAP are all secreted by syncytiotrophoblast cells, and these markers are rarely evident or even absent in a PSTT. In the current case, however, the tumor cells were positive for hPL and PLAP and slightly positive or negative for hCG. Accordingly, an IHC examination has distinct value in diagnosing a PSTT.

Tumor cells cannot be effectively removed through curettage because they invade uterine muscle fibers. In addition, they tend to spread through lymphatic pathways, resulting in relative resistance to chemotherapy (19). Thus, TAH is recommended for women if fertility need not be preserved, provided that the disease is localized to the uterus. Additionally, ovarian metastases are uncommon and an oophorectomy cannot prevent postoperative extrauterine metastasis or improve prognosis. Thus, ovaries and even fertility can be preserved in young women without ovarian metastasis (20,21). In contrast to other GTNs, the prevailing FIGO score as is routinely used to guide treatment for IM and CC is not valid for PSTT, so the choice of therapy should be made on grounds of possible related risk factors. Patients with low risk usually have a good prognosis after undergoing lesion resection. Patients with high risk may have a poor prognosis, so a hysterectomy along with chemotherapy is recommended. The risk factors associated with prognosis are: *i*) metastases from the uterus (22), *ii*) an interval from the preceding pregnancy of more than 4 years (13), *iii*) being over 40 years of age (13), *iv*) evidence of high-grade histological features such as deep myometrial invasion ( $> 1/2$ ), a high mitotic figure ( $> 5$  per 10 HPF), cells with a clear cytoplasm, coagulative necrosis, involvement of the vascular space, and a prior term pregnancy (12,14,23). The most critical of these risk factors is metastasis from the uterus. A patient with a PSTT has a good prognosis if lesions are limited to the uterus, but the mortality rate can reach as high as 25%. Chemotherapy is much more effective for cells that are positive for hCG than for cells that are positive for hPL. Therefore, several chemotherapy regimens have been found to successfully treat IM and CC, but which regimen is optimal for PSTT is still unknown. Single-agent chemotherapy and combination chemotherapy that are suitable for other GTNs with low-to-moderate risk only achieve partial remission of a PSTT or may fail to achieve any response at all. Chemotherapy has made a breakthrough with EMA/CO or EMA/EP regimens (etoposide, methotrexate, dactinomycin, and cisplatin). The two regimens are now mostly used

as adjuvant therapy, and they play a significant role in the treatment of postoperative recurrence, residual tumors, and distant metastasis. Fortunately, the overall response rate to EMA/CO or EMA/EP is reported to be 71%, with a complete response in 38% of patients (24). Cytoreductive surgery combined with chemotherapy has become the standard treatment for metastatic PSTT. Recurrent PSTT after chemotherapy with EMA/CO or EMA/EP retreated with EMA/EP can still result in long-term complete remission. Therefore, the importance of using cisplatin to treat PSTT should be emphasized. Most researchers believe that EMA/EP has a definite effect on EMA/CO resistance, post-chemotherapy recurrence, and metastatic PSTT and should thus be used as the chemotherapy regimen of choice. For recurrent or progressive PSTT, the alternative second-line treatments are BEP (bleomycin, etoposide, and cisplatin) and VIP (etoposide, ifosfamide, and cisplatin) protocols (24). In addition, Feltmate *et al.* (10) noted that radiation may be effective in controlling local lesions and could be considered individually for recurrent disease. In general, the disease readily results in drug resistance and progresses rapidly once recurrence occurs or metastases develop, so metastatic multidrug-resistant PSTT was and still is the single leading cause of death due to PSTT (25).

In the current case, the patient was younger than 40 and she exhibited no evidence of extrauterine metastases, but the tumor developed after a term delivery of a female neonate. As Hassadia *et al.* (15) noted, the antecedent pregnancy resulted in a girl for 11 of 13 patients, and they also noted that 3 of 4 deaths occurred following a term delivery of a girl. This result is similar to the findings in the current case. Thus, full-term delivery of a girl is potentially linked to an adverse prognosis. Furthermore, the tumor in the current case displayed coagulation necrosis and vascular invasion. Therefore, the patient underwent TAH and was concurrently treated with peri- and post-chemotherapy, initially in a triple-drug regimen and then with EMA-CO, which further verified EMA-CO was the optimal regimen. The patient's ovaries were spared and displayed no signs of recurrence after more than 16 months of follow-up. The patient's  $\beta$ -hCG level was higher after surgery than before. This phenomenon is supposedly associated with the beta-subunit variant and excessive production of the beta-subunit as a result of the stimulation from surgery. However, literature focusing on this point has yet to be found.

In conclusion, PSTT is usually difficult to diagnose and routinely requires a combination of serum  $\beta$ -hCG testing, a radiological examination, a pathological examination, and IHC staining due to the heterogeneity of clinical manifestations. PSTT is potentially highly curable provided that the disease is confined to the uterus and that the disease is treated appropriately and regularly. Until recently, surgery has been the primary

treatment option. However, chemotherapy has also played an equally important role in cases of high risk. A close follow-up with serial serum  $\beta$ -hCG levels, a pelvic examination, and radiologic imaging such as MRI is suggested.

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(Received April 14, 2015; Revised May 27, 2015; Accepted May 28, 2015)