

Case Report

A rare case of choriocarcinoma admixed with placental site trophoblastic tumor

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Abstract: We report a rare case of choriocarcinoma admixed with placental site trophoblastic tumor (PSTT). The 36-year-old patient with persistent vaginal bleeding and elevated human chorionic gonadotropin (hCG) received three curettages and laparoscopic hysterectomy followed by five cycles of combination chemotherapy with EMA-CO. The serum hCG first decreased and then increased steadily accompanied by a possibly metastatic nodule in the lung even after hysterectomy, and the serum hCG decreased to normal level with no lesion in the lung after all interventions. The final diagnosis was choriocarcinoma of uterus (Stage 1, Score 7) admixed with PSTT (Stage 1, without risk factors). We conclude that choriocarcinoma admixed with PSTT, especially with extensive or metastatic disease is candidate for cytoreductive surgery and chemotherapy. Pneumoperitoneum-based surgery should be considered carefully and EMA-CO may be a best choice of chemotherapy.

Keywords: Case report, placental site trophoblastic tumor (PSTT), choriocarcinoma, mixed gestational trophoblastic neoplasms

Introduction

Gestational trophoblastic disease (GTD) is a group of disorders that arise from the placenta encompassing the premalignant complete and partial hydatidiform moles and the malignant invasive hydatidiform mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) [1]. The malignant forms of GTD are also collectively known as gestational trophoblastic tumors or neoplasia (GTN).

Choriocarcinoma is characterized by abnormal trophoblastic hyperplasia and anaplasia, absence of chorionic villi, hemorrhage, and necrosis, with direct invasion into the myometrium and vascular invasion resulting in spread to distant sites. Approximately 25% of cases follow abortion or tubal pregnancy, 25% are associated with term or preterm gestation, and 50% arise from hydatidiform moles, although only 2-3% of hydatidiform moles are estimated to progress to choriocarcinoma [1].

PSTT constitutes about 1-2% of GTN, arises from the placental implantation site and consists predominantly of mononuclear intermedi-

ate trophoblasts, which constitute a transitional form between cytotrophoblasts and syncytiotrophoblasts, without chorionic villi infiltrating in sheets or cords between myometrial fibers. It is associated with less vascular invasion, necrosis, and hemorrhage than choriocarcinoma, and it has a propensity for lymphatic metastasis [2].

Briefly, a choriocarcinoma consists of an admixture of syncytiotrophoblasts, cytotrophoblasts, and intermediate trophoblasts (ITs), whereas an ETT and PSTT respectively show differentiation of chorionic-type ITs and implantation-site ITs. Mixed gestational trophoblastic neoplasms of combinations of choriocarcinomas, ETTs, and/or PSTTs were also described [3-7]. To our knowledge, there are only 3 papers which mentioned 4 cases of choriocarcinoma admixed with PSTT in the literature, but the relevant data are not complete enough [3-5]. Here we report a rare case of choriocarcinoma admixed with PSTT in detail.

Case description

A 36-year-old lady gave birth to a boy by cesarean section in 2002. She also had 6 selected

Choriocarcinoma admixed with PSTT

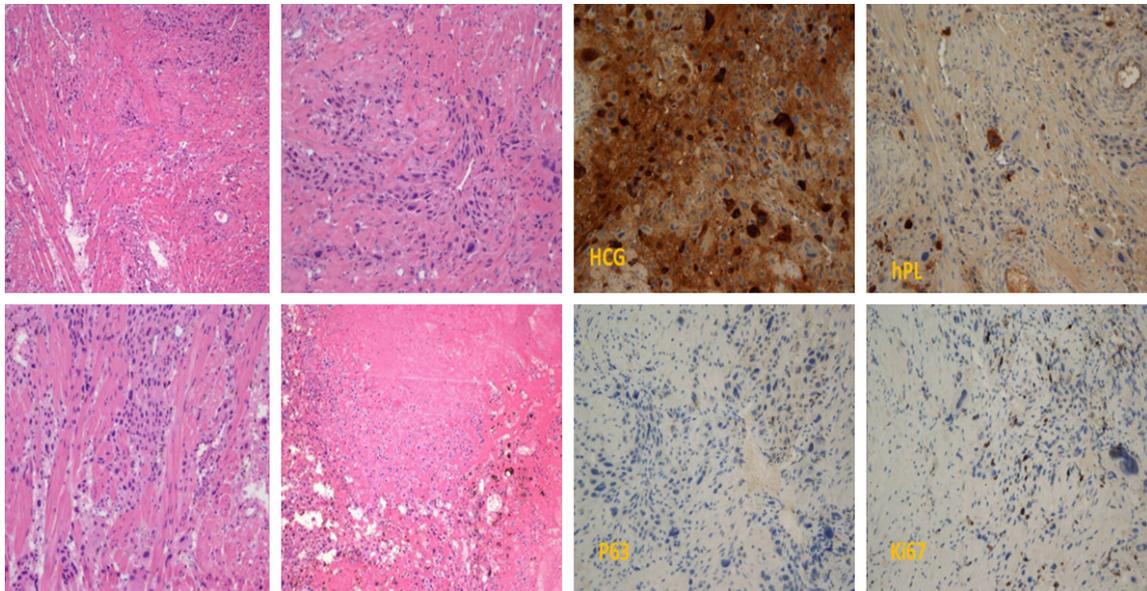


Figure 1. The pathological examination (12/26/2014, curettage) showed a strong likelihood of PSTT but still could not entirely exclude the possibility of choriocarcinoma, and part of hCG (+), part of P63 (+), part of hPL (+) and 40% Ki-67 (+).

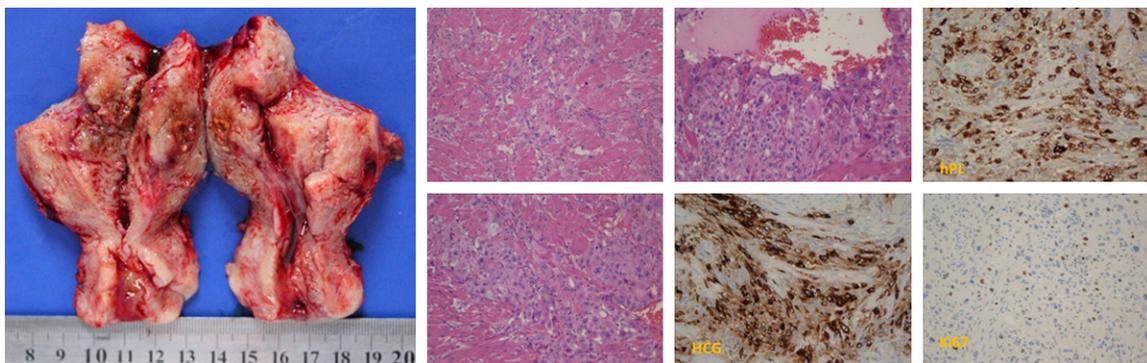


Figure 2. The pathological examination (01/19/2015, hysterectomy) showed choriocarcinoma admixed with PSTT, 3.0 cm in diameter, infiltrating into the deep layer of the uterus muscle without involving the cervical canal, and part of hPL (+), inhibin- α (+), part of hCG (+), PLAP (-), part of P53 (+), 20% Ki-67 (+), SMA (-) and AE1/AE3 (+).

medical abortions, and 3 times among these with subsequent complete curettage of uterine cavity. The patient had regular cycles and the last menstrual period (LMP) was 07/25/2014, and sonographic screening discovered abnormal hybrid echo-mass with honeycomb appearance in the uterine cavity on 09/29/2014 (65 days after the first day of LMP), which suggested hydatidiform mole. The patient received complete curettage of uterine cavity without pathological examination in a small hospital. One month later, 09/14/2014, the serum human chorionic gonadotropin (hCG) was 992.90 mIU/ml with hybrid echo-mass in the uterine cavity which looked like

coming from posterior uterine wall. The patient received second complete curettage of uterine cavity, and pathological examination showed PSTT. Four weeks after the second complete curettage (12/10/2014), the serum hCG was 954.93 mIU/ml, and sonographic screening discovered hybrid echo-mass with ill defined margin (35*41*44 mm³) in the posterior uterine wall. There is no identifiable information included in this case report.

On 12/19/2014, the patient came to our outpatient department because of persistent vaginal bleeding and elevated hCG after twice complete curettage of uterine cavity, and was hos-

Choriocarcinoma admixed with PSTT

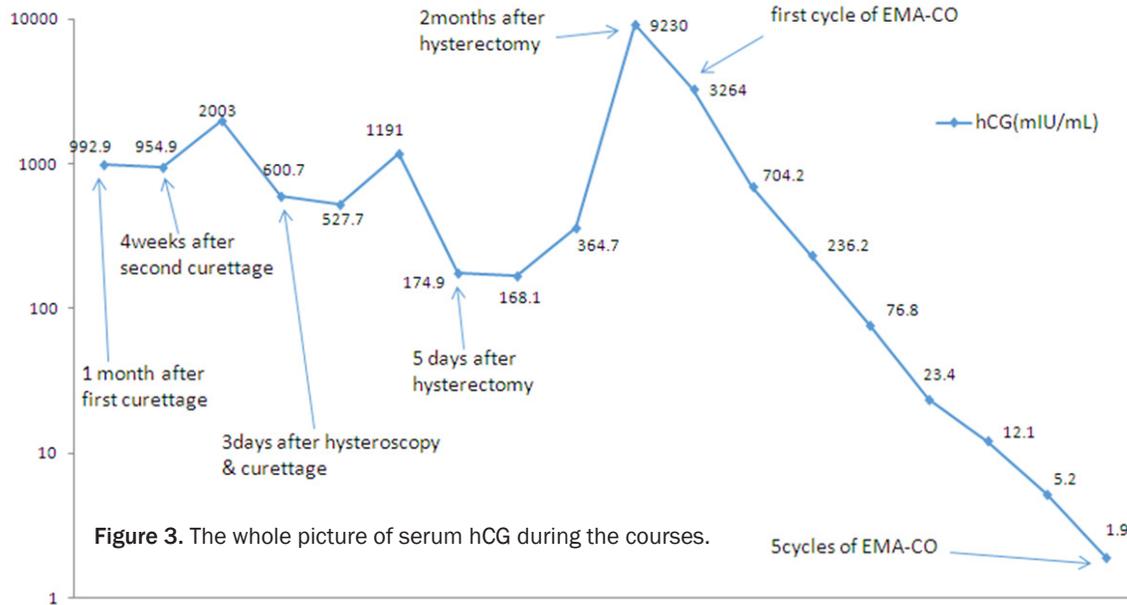


Figure 3. The whole picture of serum hCG during the courses.

pitalized. The serum hCG was 2,003 mIU/ml at that moment with sonographic screening discovering hybrid echo-mass with ill defined margin (38*39*35 mm³) in the posterior uterine wall, and we reexamined the pathological section of the second complete curettage (12/10/2014) and considered a strong likelihood of PSTT but still could not entirely exclude the possibility of choriocarcinoma, and immunohistochemical findings were AE1/AE3 (+), hCG (+), part of human placental lactogen (hPL) (+), part of P63 (+) and 20% Ki-67 (+). On 12/26/2014, the patient received hysteroscopy and curettage. The pathological examination showed proliferating trophoblasts with secretory endometrium, highly degenerated villus and placental site nodule (PSN), and immunohistochemical examination showed that proliferating trophoblasts was part of hCG (+), part of P63 (+), part of hPL (+) and 40% Ki-67 (+), so we considered a strong likelihood of PSTT but still could not entirely exclude the possibility of choriocarcinoma (**Figure 1**). The serum hCG was 600.65 mIU/ml three days after the surgery (12/29/2014), but elevated again to 1,191 mIU/ml two weeks later (01/13/2015) with MRI showing multiple small cysts in the right lobe of liver and abnormal lesion in the posterior uterine wall, and enhancement scanning showing mild heterogeneous enhancement. The patient received laparoscopic hysterectomy on 01/19/2015, her serum hCG was 174.9 mIU/ml four days later (01/23/2015), the pathological examination showed choriocarcinoma admixed with PSTT, 3.0 cm in diam-

eter, infiltrating into the deep layer of the uterus muscle without involving the cervical canal, and immunohistochemical examination showed part of hPL (+), inhibin- α (+), part of hCG (+), PLAP (-), part of P53 (+), 20% Ki-67 (+), SMA (-) and AE1/AE3 (+) (**Figure 2**). The patient could not come to our hospital because of family stuff until 03/17/2015, when she already had a bad cough with elevated serum hCG (9,230 mIU/ml) and CT scanning showing a possibly metastatic nodule in her left lung. Then the patient received five cycles of combination chemotherapy with EMA-CO (Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide and Vincristine). The serum hCG was 3,264 mIU/ml after the first cycle of chemotherapy and PET-CT scan showed that the lesion was confined to uterus with no evidence of metastasia. The serum hCG was normal and there was no lesion in her lungs after five cycles of chemotherapy. The whole picture of serum hCG during the courses was showed as **Figure 3**. The final diagnosis was choriocarcinoma of uterus (Stage 1, Score 7) admixed with PSTT (Stage 1, without risk factors). The patient receives no further therapy and is still on close follow-up.

Discussion

The clinical features and medical investigations of choriocarcinoma and PSTT

Patients with choriocarcinoma usually present with abnormal uterine bleeding and symptoms

Choriocarcinoma admixed with PSTT

consistent with pregnancy including bloating, nausea, vomiting, and a pelvic mass. The dominating clinical signs of PSTT are vaginal bleeding and enlargement of the uterus, while serum levels of hCG are elevated (average 691 mIU/ml) in 77% of the cases [4]. PSTT presents with metastases in about 10% of cases and develops in an additional 10% of patients during follow-up and the most common sites of metastasis are the lung and vagina [4]. The variable and often low level of hCG detected in these tumors reflects the lack of syncytiotrophoblast. Free beta hCG is a reliable marker for PSTT, especially in situations where there is uncertainty about whether the patient has choriocarcinoma (high proportion of hyperglycosylated hCG, hCG-H) or PSTT (high proportion of free beta hCG) [8]. Ultrasonography shows an echogenic mass that can involve endometrium and myometrium, and both solid intramural masses and cystic lesions are described [9]. CT scan may also delineate uterine mass and MRI shows myometrial masses that are isodense to healthy myometrium. Combined use of MRI, PET scan, sonohystrography and high-resolution digital hysteroscopy will help with the diagnosis [10].

In this case, it was persistent vaginal bleeding and elevated hCG that made the patient come to our department. MRI, CT, PET-CT, sonohystrography and hysteroscopy did help with the diagnosis. It should be noted that the serum hCG first decreased and then increased steadily from 174.9 to 9,230 mIU/ml accompanied by a possibly metastatic nodule in her left lung two months after hysterectomy without chemotherapy, which was also a strong indication of choriocarcinoma. How to explain this? Studies have shown that macrophages exposed to CO₂ produced less cytokines (IL-1, TNF- α and so on) with a substantial reduction in cytotoxic activity than cells that were not exposed. This effect of CO₂ on macrophages is presumed to be due to intracellular acidification and these findings suggest that pneumoperitoneum-based surgery may contribute to the spread of malignant tumors [11]. So we cannot completely exclude the effect of persistent pneumoperitoneum pressure during the course of laparoscopic hysterectomy, which took 105 minutes and maybe improve the cycle metastatic of tumor. Is it necessary to consider pneumoperitoneum-based surgery

thoroughly and carefully when it is supposed to treat tumors especially those with predominantly hematogenous metastasis? More researches are still needed.

The pathological features of choriocarcinoma and PSTT

Syncytiotrophoblast, cytotrophoblast, and intermediate trophoblast are the three major cell types found in choriocarcinomas, while intermediate trophoblasts represent the predominant cell type traditionally associated with PSTT. The mitotic rate is variable from less than 1 to greater than 30 mitoses per 10 HPF [12].

With immunohistochemical staining, 50-100% of intermediate trophoblasts show positivity for hPL and fewer than 10% of tumor cells stain for hCG. This can be valuable in diagnosis and in discriminating PSTT from carcinoma or sarcoma. Pregnancy-associated major basic protein (pMBP), a marker of intermediate trophoblast, presents in 78% of cases and is useful in distinguishing PSTT from other forms of trophoblastic tumor immunohistochemically [13]. In PSTT, mean Ki67 staining is 14% of total specimen area, when compared with 69% of total specimen area in choriocarcinoma. Immunohistochemical staining for P53 reveals intense nuclear labeling [14].

In this case of choriocarcinoma admixed with PSTT, the pathological examination showed intermediate trophoblast as well as varying degrees of syncytiotrophoblast and cytotrophoblast, and the immunohistochemical staining showed strong expression of hCG and hPL, and varying expression of Ki-67 and P63.

The treatment and outcome of choriocarcinoma and PSTT

GTN is the first cancer successfully cured with chemotherapy and remains the most curable gynecologic cancer. In the literature, factors associated with survival are stage, interval from preceding pregnancy of over 2 years, previous term pregnancy, high mitotic rate and high level of hCG [4]. In this case, the patient's tumor has components of a mixed PSTT and of histologically verified, classical choriocarcinoma. Patients with disease confined to genital tract (FIGO I and II) has 93.5% survival, which is higher than that of those with disease extend-

ed outside genital tract (FIGO III and IV, 33.3%). In patients with PSTT, the presence of non-pulmonary metastases (anatomic FIGO Stage IV disease) is a predictor of poor overall survival [15].

The development of cytotoxic chemotherapy has dramatically improved the prognosis of choriocarcinoma. The most widely accepted regimen is weekly cycles of EMA-CO. Choriocarcinomas respond well to chemotherapy and cure rates are greater than 90% [16]. PSTT may be less responsive to chemotherapy than choriocarcinoma does and is resistant to chemotherapeutic agents commonly used for chorionic tumor, such as Methotrexate and Actinomycin D, but combination chemotherapy such as EP-EM or EMA-CO has been reported to be highly effective [2].

The importance of surgery in the management of GTN should not be underestimated, and surgical intervention may be required to deal with bleeding complications, particularly where selective angiographic embolization is not possible or has failed [2]. Drug-resistant cases with a single or just 2 or 3 lesions can be surgically cured, and hysterectomy may also be useful to reduce the duration of chemotherapy in nonmetastatic patients who do not desire to preserve fertility [2].

In conclusion, choriocarcinoma admixed with PSTT is a rare case, whose diagnosis depends on curettage, biopsy and pathological examinations after surgery. Patients with extensive or metastatic disease are candidates for cytoreductive surgery and chemotherapy. Choriocarcinoma admixed with PSTT is not sensitive enough to chemotherapy and EMA-CO may be a best choice. It may be necessary to consider pneumoperitoneum-based surgery thoroughly and carefully in this situation.

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Disclosure of conflict of interest

None.

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