

# Challenges in the Management of Placental Site Trophoblastic Tumor

Fereshteh Fakor, Hadi Hajizadeh Falah<sup>1</sup>, Sina Khajeh Jahromi<sup>2</sup>, Parham Porteghali<sup>2</sup>

Reproductive Health Research Center, Alzahra Hospital Guilan University of Medical Sciences, <sup>1</sup>Department of Pathology, Poursina Hospital, Guilan University of Medical Sciences, <sup>2</sup>Medical Student, Student Research Committee of Guilan University of Medical Sciences, Rasht, Iran

## ABSTRACT

Placental site trophoblastic tumor (PSTT) is a rare neoplasm of intermediate trophoblastic cells of the placenta. Two cases of PSTT are presented. A 24-year-old G2P2 female presented with a flat vaginal ulcerative lesion diagnosed as PTSS 2 years after a term pregnancy. Beta human chorionic gonadotropin ( $\beta$ -HCG) level was 110 mIU/mL and uterus was diffusely enlarged. Total abdominal hysterectomy was performed and on follow up, her serum  $\beta$ -HCG level was undetectable. The second case is a 33-year-old female with a history of vaginal bleeding referred to hospital. She had myomectomy and the pathology was reported as leiomyosarcoma. We doubted the pathology result. By further pathological investigations and increase in  $\beta$ -HCG consistent with PSTT, the diagnosis was made. The patient had hysterectomy. For both cases no adjuvant therapy was done and there has not been any sign of recurrence in them. It is thus concluded that complete resection in PSTT, could achieve long-term remission.

**KEY WORDS:** Case report, placental site trophoblastic, tumor

## INTRODUCTION

A unique group of human cancers derived from fetal tissue are trophoblastic tumors.<sup>[1]</sup> Trophoblastic tumors show variety of forms such as hydatidiform mole (partial and complete), invasive mole, gestational choriocarcinoma, and placental site trophoblastic tumors (PSTTs).<sup>[2]</sup> PSTT is rare tumor of young women<sup>[3]</sup> from intermediate type trophoblast, which secretes two substances, namely human placental lactogen (HPL) and human chorionic gonadotropin (HCG). PSTT has a spectrum of characteristics from benign lesion within uterus to highly malignant features, with wide spread metastasis.<sup>[3]</sup>

PSTT can develop following all kinds of pregnancy. Approximately 50% of PSTT cases occur after normal pregnancy and other cases follow: Miscarriage, termination of pregnancy, ectopic pregnancy, and molar pregnancy.<sup>[4]</sup>

The most common clinical findings are irregular bleeding associated with uterine subinvolution; hence any case of unusual bleeding should be investigated with dilatation and curettage (histopathological finding) and HCG level. With the exception of PSTT, HCG is specific and sensitive marker

for detecting and monitoring gestational trophoblastic disease (GTD).<sup>[5]</sup>

The patients can also present with symptoms like vaginal bleeding, amenorrhea, nephritic syndrome, abdominal pain, galactorrhea, and hemoptysis.<sup>[4]</sup>

As shown histopathologically, PSTT has proliferation of intermediate trophoblastic cells and absence of villi.<sup>[6]</sup> It shows less invasion of vascular tissue. Using immunohistochemistry (IHC) revealed that PSTT cells express (HPL) more than  $\beta$ -HCG. Also it is important to note that the level of serum  $\beta$ -HCG does not correlate with the amount of tumor present.<sup>[4]</sup>

Although the majority of patients with nonmetastatic PSTT are cured by hysterectomy but in metastatic cases, it requires aggressive treatment with chemotherapy and radiation.<sup>[7]</sup> In the present article, we report two cases of PSTT.

## CASE REPORTS

### Case 1

A 26-year-old G2P2 female, presented with the complaint of prolonged vaginal spotting for 2 months after 2 years amenorrhea.

#### Address for correspondence

Dr. Fereshteh Fakor,  
Reproductive Health Research Center, Azzahra Hospital,  
Guilan University of Medical Sciences, Namjo Street, Rasht, Guilan, Iran.  
E-mail: fereshtehfakor@yahoo.com

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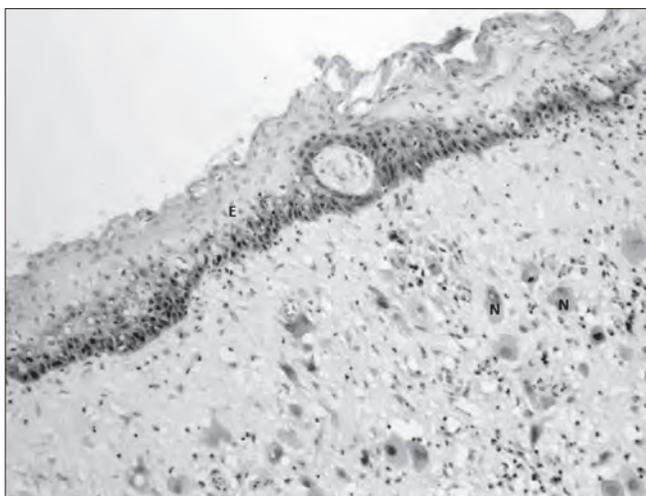
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Her antecedent pregnancy had been uncomplicated and had resulted in the normal vaginal delivery of a term male fetus 4 years prior to this presentation. Speculum examination showed a flat infiltrative ulcer in mid posterior vaginal wall that involved rectovaginal septum. Ultrasonography showed a diffusely enlarged uterus with no evidence of intrauterine pregnancy.  $\beta$ -HCG level was 110 mIU/mL. An impression of an incomplete abortion was made and dilatation and curettage was done. An excisional biopsy of the ulcer was undertaken. Histological study showed infiltrating neoplastic tissue, which was composed of highly pleomorphic giant cells with well-defined cytoplasmic membrane, eosinophilic cytoplasm, and hyper chromatic nuclei. Most tumoral cells have one nucleus but some of them are multinucleated. Foci of necrosis and hemorrhagic areas are present. PSTT was diagnosed [Figure 1].

Computed tomography (CT) of the brain, pelvic, and abdomen showed no evidence of metastasis, chest X-ray was normal. After 3 weeks, a new site of vaginal metastases in anterior and posterior walls of vagina presented. Patient was referred to our hospital and total abdominal hysterectomy and complete excision of sites of new metastases in vagina was done.

After hysterectomy, histology revealed a tumoral mass with above morphological description. The tumoral cells are identified between myometrium and extended to uterus serosa. Left ovary exhibits tumoral metastasis.

Patient refused any course of chemotherapy and she was in remission at her last follow up 4 years after surgery and  $\beta$ -HCG level is lesser than 10 mIU/mL. Physical examination work up showed no sign of metastases in any site of body and there was no sign of recurrence 5 years after operation.



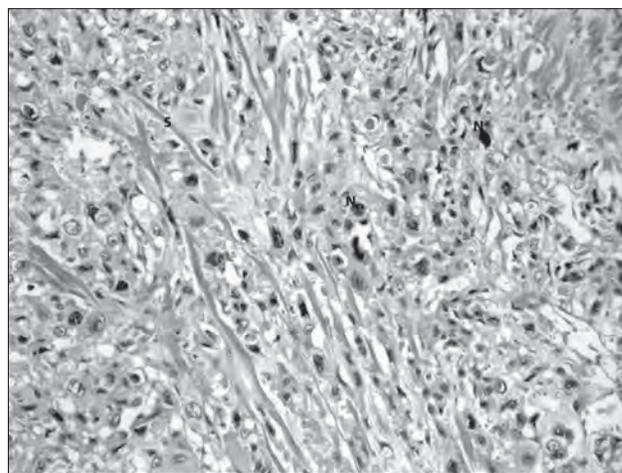
**Figure 1:** Vaginal mucosa biopsy reveals presence tumoral cells on underlying stroma (E: Vaginal epithelium, N: Neoplastic cell-  $\times 100$ )

## Case 2

A 33-year-old female who had a cesarean delivery of a term male fetus, 7 months after delivery, complained from on and off vaginal bleeding. Sonography was done for her, which revealed three intramural submucosal myoma of size  $3 \times 2$ ,  $2 \times 5$ , and  $3 \times 3$  cm. She had myomectomy at her local hospital and the pathology was reported as poorly differentiated sarcoma more compatible with leiomyosarcoma (high grade sarcoma). Then for follow up, she was referred to our hospital. Since the patient was young we doubted the results of the pathology. The paraffin blocks were taken and sent to other pathologists. They checked the  $\beta$ -HCG, which was more than 200 (more than 25 mIU/mL). Sections of myometrium reveal infiltration of well-defined neoplastic tissue composed of polyhedral or rounded mononucleated cells with marked pleomorphism and nuclei hyperchromasia. Some tumoral cells are binucleated or multinucleated extensive area of eosinophilic fibrinoid materials is present between tumoral cells [Figure 2]. In addition, we have done IHC staining for desmin and smooth muscle actin, which was negative. By the morphological features, IHC result, history of recent labor, and increase in  $\beta$ -HCG, PSTT was diagnosed. CT scan of brain, pelvic, and abdomen had normal finding. Vaginal bleeding was massive and her hemoglobin level was 6 and the  $\beta$ -HCG level was 250 mIU/mL. Hysterectomy was done, and Pathology showed no residual tumor. Patient was in remission at her last follow up, 3 years after surgery.

## DISCUSSION

PSTT is a rare form of GTD. The pathologic entity known as PSTT shows an absence of the characteristic dimorphic population of cytotrophoblast and syncytiotrophoblast.<sup>[8]</sup>



**Figure 2:** Sheets of tumoral cells, invade between bundles of myometrial smooth muscle (S: Smooth muscle bundle of myometrium, N: Neoplastic cell-  $\times 400$ )

Kurman and colleagues concluded that, although this lesion histologically appeared malignant, its clinical behavior was benign compared with other gestational trophoblastic neoplasm, however, these tumors are relatively insensitive to chemotherapy and subsequent experience has shown that patient with histologically indistinguishable tumor can have clinically aggressive, metastatic disease.<sup>[9]</sup> Additionally, 10% of patients have metastatic disease at the time of presentation and will require combination chemotherapy.<sup>[10]</sup>

Previous reports have described a relative chemoresistance in patient with PSTT to chemotherapy agents commonly used in the treatment of GTD.<sup>[11]</sup>

Chang *et al.* proposed a tentative treatment guideline that includes excision of all removable lesions and close follow up after surgery in early stage patients or EMA-CO (Etoposide, MTX, ActD, cyclophosphamide, and vincristine) regimen in patients with advanced stages (FIGO stage III-IV). The addition of adjuvant chemotherapy to patients with early stage disease or neoadjuvant therapy before surgery may be optionally used, but their roles have not yet been established.<sup>[12]</sup>

In few cases of progressive disease, chemotherapy and radiotherapy are ineffective. Long-term follow up is essential as PSTT may progress after years of remission. Serum HCG levels are the best available marker of disease, but the disease may still progress even if HCG levels are not raised.<sup>[13]</sup>

PSTT tends to invade locally, and prognosis is variable. Experience in Charing Cross Hospital showed that 90% of PSTT limited to the pelvis treated by surgery and chemotherapy had complete remission. Conversely, only 43% with metastasis survived.<sup>[14]</sup>

Women with metastatic PSTT at the time of diagnosis cannot be cured by surgery alone and patients with metastatic disease have responded to chemotherapy and are now free of the disease. The most recent data from Charing Cross Hospital and other centers suggest that EP/EMA chemotherapy is an effective regimen for metastatic and relapsing PSTT.<sup>[15-17]</sup>

Metastatic disease is not necessarily a contraindication to surgery. In fact, aggressive surgical management of chemoresistant metastatic disease may be appropriate for those young patients with an otherwise poor prognosis.<sup>[18]</sup>

Conservative therapy by combination chemotherapy without hysterectomy may be an alternative for patients desiring future fertility.<sup>[19]</sup> Bonnazzi *et al.* reported that one of their patients, treated medically only with EMA-CO, had complete recovery.<sup>[20]</sup> Nam *et al.* reported two cases of PSTT

treated successfully by chemotherapy followed by curettage without definite surgery.<sup>[21]</sup>

Our patients had complete response to surgical treatment with early stage PSTT without any adjuvant chemotherapy. While the management of clinical localized PSTT should generally include hysterectomy and for patients with primary metastatic PSTT, surgical removal of the metastatic tumor is the appropriate management.<sup>[7]</sup>

In addition, malignant trophoblastic tumors of the intermediate – cell type such as PSTT are rare and often difficult to diagnose accurately. New methods of immunohistochemical staining are providing a better understanding of their composition and origin. Even when properly diagnosed, these tumors do not respond well to chemotherapy, and hysterectomy is an important part of initial treatment.

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