Case report

Placental site trophoblastic tumor with sole metastasis to breast: A case report

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\textbf{ABSTRACT}

Placental site trophoblastic tumor (PSTT) is a rare form of gestational trophoblastic neoplasia (GTN). It most commonly occurs after a delivery but may arise after any type of pregnancy. PSTT arises after neoplastic transformation of intermediate trophoblastic cells. The most commonly reported symptoms are abnormal bleeding or amenorrhea. Due to the rarity of this disease, evidence on prognostic factors as well as optimal treatment is limited. While treatment for early-stage disease is usually limited to surgery, multimodal treatment with chemotherapy and surgery may be important for metastatic disease. Metastatic disease may be associated with minimal elevations of human chorionic gonadotropin (hCG). Here we present an unusual case of a patient with PSTT and an isolated breast metastasis who was successfully treated with surgical resection and single-agent chemotherapy.

\section{1. Introduction}

PSTT represents a rare form of GTN. It is characterized by neoplastic transformation of intermediate trophoblastic cells. PSTT most commonly develops after a delivery but may arise after any type of pregnancy (Baergen and Rutgers, 1997; Feltmate et al., 2001; Papadopoulos et al., 2002; Baergen et al., 2006; Hyman et al., 2013; Zhao et al., 2016). The most common presenting symptoms of PSTT are abnormal bleeding or amenorrhea, associated with elevated levels of hCG (Feltmate et al., 2001; Papadopoulos et al., 2002; Hyman et al., 2013). Treatment for early stage disease is primarily hysterectomy, however metastatic or recurrent disease often requires a multifaceted approach with chemotherapy and/or surgery (Horowitz et al., 2017; Schmid et al., 2009). The most common sites of metastases are lung, vagina, and central nervous system (Horowitz et al., 2017). We present the first reported case of a patient treated for PSTT, who subsequently developed an isolated breast metastasis.

\section{2. Case report}

A 44-year-old gravida 7 para 3 abortion 3, presented for surgical management of a missed abortion diagnosed by ultrasound at 6 weeks gestational age. An intrauterine pregnancy was noted on ultrasound, with no fetal cardiac activity. Serial quantitative serum hCG measurements had been performed, and the trend was not consistent with a viable early pregnancy. The patient's last known term delivery had occurred 13 years previously. In the interim, she had a spontaneous abortion and a termination of pregnancy, but the patient could not recall the dates.

She underwent an uncomplicated dilation and curettage for a presumed missed abortion at an outside institution; however, no chorionic villi or fetal tissue were identified on pathologic examination. After the procedure, the serum hCG rose from 900 mIU/mL to 2600 mIU/mL, and pelvic ultrasound showed a possible 1 cm left adnexal mass. The patient received a single dose of methotrexate for presumed ectopic pregnancy, but the hCG level increased. A repeat pelvic ultrasound showed increased flow to the endometrial cavity with a 3–4 cm mass. As a result, the patient received a second dose of methotrexate 1 week
later. The hCG level decreased slightly but not appropriately 1 week post-treatment. The patient then underwent a third dose of methotrexate, causing the hCG to decrease initially, but then plateau at 1300–1400 mIU/mL. She subsequently underwent a second dilation and curettage, with microscopy showing an intermediate trophoblastic tumor. Chest radiography was negative for pulmonary metastasis. One month later, the patient underwent an uncomplicated total abdominal hysterectomy with left salpingo-oophorectomy (LSO) by a gynecologic oncologist. LSO was performed because of a benign left ovarian cyst. Gross inspection of the surgical specimen showed a 2.9 × 2.3 cm soft, rubbery, tan-yellow mass located in the body and fundus, confined to the uterus (Fig. 1a). Microscopic examination demonstrated myometrial invasion by individual cells and sheets of extravillous (intermediate) trophoblasts infiltrating and separating muscle fibers (Fig. 1b). The tumor cells characteristically invaded the walls of blood vessels (Fig. 1c). Mitotic figures were abundant, including atypical

Fig. 1. Uterine PSTT a) Gross photo showing 2.9 cm tan-yellow mass located in body and fundus. b) Myometrial invasion by extravillous (intermediate) trophoblasts of PSTT (H + E, 200 ×). c) Characteristic tumor invasion of blood vessel walls (H + E, 200 ×). d) Atypical mitotic forms (H + E, 400 ×). e, f, g, h) Positive cytokeratin 8/18, hPL, hCG, and alpha inhibin stains (400 ×). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
forms (Fig. 1d). Immunohistochemical staining was positive for cytokeratin 8/18 (Fig. 1e), human placental lactogen (hPL) (Fig. 1f), hCG (Fig. 1g), and alpha inhibin (Fig. 1h). Staining was negative with p63, and the MIB-1/K-67 stain showed a moderate (30–40%) proliferative index. These histologic findings were consistent with a diagnosis of PSTT. Serum hCG was 1236 mIU/mL preoperatively and decreased to 359 mIU/mL on postoperative day 1.

Two months after hysterectomy, the patient had a palpable left breast mass. One year prior to her PSTT diagnosis, she had a negative screening mammogram. Diagnostic mammography performed after discovery of the breast mass failed to demonstrate the lesion. However, breast ultrasound showed a solid mass measuring 6 × 4 × 6 mm with microlobulated margins and mild hypervascularity on Doppler (Fig. 2a). Serum hCG collected 11 days after breast imaging was 3 mIU/mL. The patient underwent an excisional breast biopsy approximately 2 weeks later, which showed a 1.0 × 0.5 cm tan-pink, well-
circumscribed mass containing hemorrhagic foci (Fig. 2b). Microscopic examination again revealed sheets of extravillous trophoblasts typically infiltrating vascular walls (Fig. 2c,d). Positive immunohistochemical staining for cytokeratin 8/18 (Fig. 2e), hPL (Fig. 2f), hCG (Fig. 2g), and alpha inhibin (Fig. 2h) confirmed the diagnosis of metastatic PSTT. Computed tomography (CT) of the brain, chest, abdomen and pelvis showed no other sites of metastasis. A repeat serum hCG post-procedure was undetectable. The patient then received treatment with actinomycin-D 0.5 mg daily for 5 consecutive days, administered at 2-week intervals for a total of 2 months. Thereafter, she underwent surveillance for recurrent disease. Serum hCG was monitored monthly for 1 year then every 2–4 months; serum hPL levels were also followed. CT was performed every 6 months for the first year then annually. Surveillance was continued for 4 years after initial diagnosis. Eight years post-operatively, the patient is alive and well with no evidence of disease recurrence.

3. Discussion

PSTT is a rare form of gestational trophoblastic disease, accounting for < 0.25% of cases in some series (Hyman et al., 2013). Worldwide there are < 500 cases reported (Horowitz et al., 2017). The age of presentation varies greatly from the 2nd to 7th decade, with mean and median ages at presentation of 30–33 (Baergen and Rutgers, 1997; Feltmate et al., 2001; Papadopoulos et al., 2002; Baergen et al., 2006; Zhao et al., 2016) and 31–33 (Baergen et al., 2006; Hyman et al., 2013), respectively. The majority (53%–62%) of PSTT are preceded by a prior full or preterm pregnancy (Baergen and Rutgers, 1997; Feltmate et al., 2001; Papadopoulos et al., 2002; Baergen et al., 2006; Hyman et al., 2013; Zhao et al., 2016). However, therapeutic abortions (20–23%), missed or spontaneous abortions (8–41%), and even hydatidiform moles (5–26%) (Baergen and Rutgers, 1997; Feltmate et al., 2001; Papadopoulos et al., 2002; Baergen et al., 2006; Zhao et al., 2016) may predate PSTT. Tumor diagnosis usually occurs between 16 months and 3 years following the last known prior pregnancy, but this interval may vary widely from 0 to 33 years (Baergen and Rutgers, 1997; Feltmate et al., 2001; Papadopoulos et al., 2002; Baergen et al., 2006; Hyman et al., 2013; Zhao et al., 2016). The most common presenting symptoms are abnormal bleeding (59–79%); Feltmate et al., 2001; Papadopoulos et al., 2002; Hyman et al., 2013) and amenorrhea (12–30%; Feltmate et al., 2001; Hyman et al., 2013). hCG levels are elevated in most (75–90%) cases but are usually lower than that commonly observed with choriocarcinoma (< 500–691 mIU/mL; Feltmate et al., 2001; Baergen et al., 2006). Diagnosis is often made with ultrasound, and findings include a solid or cystic uterine mass with or without vascularity on color Doppler (Horowitz et al., 2017).

In PSTT, the tumors are primarily located in the endometrium and vary widely in size. They may be microscopic or polypoid nodular masses as large as 10 cm (Baergen and Rutgers, 1997; Papadopoulos et al., 2002; Baergen et al., 2006). Sectioning reveals a solid, tan-yellow, soft, fleshy tumor with foci of hemorrhage and necrosis (Baergen and Rutgers, 1997; Baergen et al., 2006). Often the tumors are deeply myoinvasive with 10% extending to the uterine serosa (Baergen et al., 2006; Shih and Kurman, 2001). Microscopic examination demonstrates solid sheets of large polygonal cells with moderately abundant cytoplasm, characteristic of extravillous (intermediate) trophoblasts (Baergen and Rutgers, 1997; Feltmate et al., 2001; Baergen et al., 2006; Ayas et al., 2009). These trophoblasts are typically highly infiltrative, readily separating smooth muscle fibers and invading blood vessel walls (Baergen and Rutgers, 1997; Baergen et al., 2006). Atypical mitotic figures may be seen in up to 90% of PSTT (Baergen and Rutgers, 1997; Baergen et al., 2006; Shih and Kurman, 2001) but are not normally present amidst non-neoplastic intermediate trophoblasts within an implantation site. Similarly, MIB-1/Ki-67 labeling is absent in these non-tumoral intermediate trophoblasts, and therefore positive staining is indicative of PSTT (Shih and Kurman, 2001). Immunohistochemical staining of PSTT is also positive with cytokeratin (Baergen et al., 2006; Ayas et al., 2009), hPL (Baergen and Rutgers, 1997; Papadopoulos et al., 2002; Baergen et al., 2006; Zhao et al., 2016; Ayas et al., 2009), hCG (Baergen and Rutgers, 1997; Papadopoulos et al., 2002; Baergen et al., 2006; Zhao et al., 2016), and alpha inhibin (Shih and Kurman, 1999).

Evidence on the optimal treatment and prognostic factors in PSTT is limited due to rarity of the disease. Treatment for early-stage PSTT is primarily surgical. The ovaries may be preserved in premenopausal patients unless there is evidence of pelvic pathology. A retrospective study of 108 patients with PSTT showed that the overall survival rate was 93.5%, with survival rates up to 87.9% for stage III and IV disease (Zhao et al., 2016). Adjuvant chemotherapy did not lead to improved outcomes for Stage I disease. Stage appears to be the most important prognostic factor for survival in PSTT. Other reported poor prognostic factors include interval since last pregnancy > 2 years; age > 35 years; deep myometrial involvement; maximum hCG level > 1000 mIU/mL; tumor necrosis; high mitotic rate; and the presence of cells with clear cytoplasm (Baergen et al., 2006; Hyman et al., 2013; Horowitz et al., 2017). Although some authors recommend adjuvant chemotherapy for stage I patients with an interval of > 4 years since the antecedent pregnancy, evidence to indicate an improved outcome is lacking (Horowitz et al., 2017).

The recurrence rate ranges from 21% to up to 43% (Feltmate et al., 2001; Schmid et al., 2009). The incidence of metastatic disease ranges from 16% to 56% (Papadopoulos et al., 2002; Baergen et al., 2006). Common sites of metastases include lung, brain, and vagina (Baergen and Rutgers, 1997; Papadopoulos et al., 2002; Baergen et al., 2006; Hyman et al., 2013; Zhao et al., 2016; Ayas et al., 2009). Additional reported metastatic sites are the liver, gastrointestinal tract, bladder, ovary, omentum, diaphragm, spleen, pancreas, lymph nodes, bone marrow, and spine (Baergen and Rutgers, 1997; Feltmate et al., 2001; Papadopoulos et al., 2002; Baergen et al., 2006; Zhao et al., 2016). Most authors recommend multi-agent chemotherapy for metastatic disease, however PSTT is relatively insensitive to chemotherapy compared to other gestational trophoblastic neoplasms. The most common chemotherapy regimen used for metastatic PSTT is EMA/CO (etoposide, methotrexate, leucovorin, actinomycin-D and vincristine, cyclophosphamide; the reported response rate to EMA/CO is 71%, with complete response in 38% of patients (Ajithkumar et al., 2003). Therefore, surgical resection of metastatic lesions should also be considered an important component of treatment (Horowitz et al., 2017; Schmid et al., 2009).

In 2009, Ayas et al. reported a case of a 24-year-old woman who presented with intermittent vaginal bleeding 5 months after delivery (Ayas et al., 2009). Metastatic PSTT was discovered in the patient's lungs, liver, and pancreas. There was also widely disseminated tumor in numerous other organs, including the breast. To date, this is the only previously reported case of PSTT with breast metastases. Unlike their patient with disseminated PSTT, the breast was the sole site of metastasis in our patient, as no other loci of tumor dissemination were identified. Our patient was treated with surgical excision and single-agent actinomycin-D. The successful outcome in this case suggests that surgical excision and single-agent chemotherapy may be considered for patients with potentially resectable metastatic PSTT.

Conflict of interest statement

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