Case series

Placental site trophoblastic tumor: Successful treatment of 13 cases[☆]

Amy L. Alexander[a], Anna E. Strohl[a,*], Kruti P. Maniar[b], John R. Lurain[a]

[a] John I. Brewer Trophoblastic Disease Center, Division of Gynecologic Oncology, Department of Obstetrics & Gynecology, Northwestern University Feinberg School of Medicine Chicago, IL, USA
[b] John I. Brewer Trophoblastic Disease Center, Division of Surgical Pathology, Department of Pathology, Northwestern University Feinberg School of Medicine Chicago, IL, USA

A B S T R A C T

Placental site trophoblastic tumor (PSTT) is a rare variant of gestational trophoblastic neoplasia (GTN) that is characterized by slow growth resulting in mostly uterine-confined disease, low human chorionic gonadotropin (hCG) levels, and resistance to chemotherapy.

Our objective was to update our center's experience with PSTT with respect to presentation, prognostic factors, treatment, and outcomes from 2003 to 2019.

Thirteen women with PSTT were identified. Mean age was 32 years. The most frequent presenting symptom was abnormal uterine bleeding (69%). A uterine mass was noted in 62%. The diagnosis was usually established by endometrial biopsy or curettage (62%). Nonmolar pregnancy was the preceding gestation in 85%. Median time from last pregnancy to diagnosis was 13 months (range 0–240 months). Serum hCG levels at diagnosis ranged from 1 to 2606 mIU/mL (median 98 mIU/mL). Three women (23%) presented with metastatic disease. All 13 women underwent surgery: 12 had a hysterectomy, 1 had a fertility-sparing hysteroscopic resection, and 2 underwent pulmonary metastatectomy. Nine women (69%) also received chemotherapy for persistently elevated hCG levels after hysterectomy (2), high-risk factors (4), or metastatic disease (3). Overall survival was 100% with a median survival of 65 months (range 30–167 months).

Survival for PSTT increased from 57% to 100%, including from 33% to 100% for metastatic disease, at our center from 1982 to 2003 to 2003–2017. Surgery is the most important component in the treatment of women with PSTT. Multidrug platinum/etoposide- chemotherapy should be used in women with metastatic disease and considered in women with nonmetastatic disease with high-risk features.

1. Introduction

Placental-site trophoblastic tumor (PSTT) is a rare variant of gestational trophoblastic neoplasia (GTN) that develops from the placental implantation site. Pathologically, PSTT consists of mononuclear intermediate trophoblast without chorionic villi infiltration and is associated with less vascular invasion, necrosis, and hemorrhage when compared to choriocarcinoma. Immunohistochemical (IHC) staining reveals diffuse presence of cytokeratin and human placental lactogen (hPL), whereas human chorionic gonadotropin (hCG) is only focally positive. Clinically, PSTT most often follows nonmolar pregnancies, presents with abnormal uterine bleeding, has disease localized within the uterus, is associated with low or normal hCG levels, and has a propensity for lymphatic metastasis. It is relatively resistant to chemotherapy, making surgery the mainstay of treatment. (Lurain, 2011; Froeling and Seckl, 2014; Horowitz et al., 2017)

In 2004, we reported on seven cases of PSTT treated at the Brewer Trophoblastic Disease Center between 1982 and 2003. (Hoekstra et al., 2004) Overall survival was 57%: 75% for the four patients with stage I disease and 33% for the three patients with stage IV disease. We found that presence of metastatic disease, interval from last known pregnancy

to diagnosis > 2 years, and high mitotic count were adverse prognostic indicators for survival. Our objective was to update our experience with PSTT at the Brewer Center with respect to clinical presentation, treatment, prognostic factors, and outcomes.

2. Materials and methods

A retrospective review of the clinical experience at the John I. Brewer Trophoblastic Disease Center of Northwestern University from 2003 to 2017 identified 13 women with PSTT referred for consultation and/or treatment. Medical records were abstracted for demographic data, clinical presentation, hCG levels, prior pregnancy information, disease sites, treatment with surgery and chemotherapy, and outcomes. Pathology was reviewed by a gynecologic pathologist with respect to diagnosis, tumor size, myometrial invasion, necrosis, mitotic count, and immunohistochemical features. The study was approved by the Institutional Review Board of Northwestern University.

3. Results

Table 1 summarizes the clinical features of the 13 patients with

Table 1
Clinical Characteristics of 13 patients with PSTT.

Clinical Characteristic (N = 13)	No./Mean (Range)
Age	32 (22–46) years
Presenting symptom/sign	
• Abnormal vaginal bleeding	9 (69%)
• Uterine mass	8 (62%)
• Positive urine pregnancy test	6 (46%)
• Amenorrhea	2 (15%)
Method of diagnosis	
• Endometrial biopsy or curettage	8
• Hysterectomy	4
• Ultrasound	1
Antecedent pregnancy	
• Normal term delivery	7 (54%)
• Third trimester pregnancy loss	1 (8%)
• Abortion (elective or spontaneous)	3 (23%)
• Hydatidiform mole (complete)	2 (15%)
Interval from antecedent pregnancy to diagnosis	12 (0–240) months
Serum hCG level at diagnosis	90 (1–2606) mIU/mL
Extent of disease (stage)	10 non-metastatic (I)
	3 pulmonary metastases (III)

PSTT. Patient age at diagnosis ranged from 22 to 46 years (mean 32 years). The most frequent presenting symptom was abnormal vaginal bleeding in 69%. A uterine mass was seen on imaging in 8 patients (62%). The diagnosis was usually made by endometrial biopsy or curettage (62%). The type of antecedent pregnancy was normal term pregnancy in 7 (54%), elective or spontaneous abortion in 3 (23%), molar pregnancy in 2 (15%), and third trimester loss in 1 (8%). The median time from last pregnancy to diagnosis was 13 months (range 0–240 months). Serum hCG levels at the time of diagnosis ranged from 1 to 2606 mIU/mL (median 98mIU/mL). Ten patients (77%) presented with International Federation of Gynecology and Obstetrics (FIGO) stage I disease (nonmetastatic), and 3 patients (23%) had stage III disease (pulmonary metastasis) at diagnosis.

Pathologic features of the cases are listed in Table 2. Of the 13 patients, 8 (62%) had a tumor size ≥ 3 cm, 6 (46%) had outer one half myometrial invasion, 6 (46%) had extensive necrosis, and 7 (54%) had a mitotic index > 5/10 high power fields (hpfs). Eleven patients (85%) had ≥1 of these features, and 8 patients (62%) had ≥ 2 high-risk pathologic features, including all 3 patients who had metastatic disease.

Treatment characteristics are listed in Table 3. All patients underwent surgery: 1 had fertility sparing hysteroscopic resection; 12 underwent hysterectomy, including 4 who also underwent pelvic lymph node dissection; and 2 had video-assisted thoracoscopic surgery (VATS) for pulmonary metastasis. Nine patients (69%) received chemotherapy: 2 for persistently elevated hCG levels after hysterectomy, 4 for high-risk pathologic features noted in Table 2 and/or interval from index pregnancy ≥2 years, and 3 for metastatic disease. The EMA/EP (etoposide, methotrexate, actinomycin D, etoposide, cisplatin) regimen was employed primarily in 8 of the patients receiving chemotherapy, while 3 patients received the TP/TE (paclitaxel-cisplatin/paclitaxel-etoposide) regimen as secondary chemotherapy.

Overall survival was 100%. No patient recurred after completing

Table 2
Pathologic features in 13 cases of PSTT.

Feature	No.
Tumor size ≥3 cm	8 (62%)
Depth of myometrial invasion > 50%	6 (46%)
Necrosis	6 (46%)
Mitotic rate > 5/10 HPFs	7 (54%)
≥1 high-risk feature	11 (85%)
≥2 high-risk feature	8 (62%)*

HPFs, high power fields.
* All 3 cases of metastatic PSTT.

Table 3
Treatment Characteristics of 13 patients with PSTT.

Treatment	No.
Surgery	13 (100%)
• Hysterectomy	12 (92%)
o BSO	1
o PLND	4
• Hysteroscopic resection	1 (8%)
• VATS	2 (15%)
Chemotherapy	9 (69%)
• Indication	
o Persistently elevated HCG	2
o High-risk features*	4
o Metastatic disease	3
• Type	
o EMA/EP	8
o TP/TE	3 (1 primary, 2 secondary)

BSO, bilateral salpingo-oophorectomy; PLND, pelvic lymph node dissection; VATS, video-assisted thoracoscopic surgery; hCG, human chorionic gonadotropin; EMA/EP, etoposide, methotrexate, actinomycin D, etoposide, cisplatin; TP/TE, paclitaxel-cisplatin/paclitaxel-etoposide
* High-risk features: Interval from index pregnancy ≥ 2 years, deep myometrial invasion, necrosis, mitotic count > 5/10 hpfs

initial treatment. Median survival was 65 months (range 30–167 months) at last contact.

4. Discussion

PSTT is such an uncommon form of GTN that only 13 cases were treated at the Brewer Trophoblastic Disease Center between 2003 and 2017, accounting for approximately 5% of all cases treated at our GTN referral center. It is clear that the most common clinical features of PSTT are abnormal vaginal bleeding, associated with the finding of an enlarged uterus, and relatively low hCG levels usually presenting distant from a preceding nonmolar pregnancy. The diagnosis of PSTT is usually made by curettage, although occasionally the diagnosis is not established until histologic examination of hysterectomy specimens. (Lathrop et al., 1988; How et al., 1995; Chang et al., 1999; Feltmate et al., 2002; Papadopoulos et al., 2002; Hassadia et al., 2005; Hyman et al., 2013; Schmid et al., 2009; Zhao et al., 2016).

Extent of disease (stage) is the most important predictor of prognosis. (Hoekstra et al., 2004; Froeling et al., 2019; Chang et al., 1999; Feltmate et al., 2002; Papadopoulos et al., 2002; Hassadia et al., 2005). Although most patients present with nonmetastatic (stage I) disease and have > 90% survival, the cure rate for patients with metastatic disease is much lower, between 50 and 60%. Metastatic disease is present in up to one third of patients with PSTT at diagnosis, with an equal number developing recurrence of disease. Common sites of metastases are the lungs, pelvis, vagina, and lymph nodes, with metastases to abdominal organs and the brain occurring less frequently. In our initial report on 7 patients treated for PSTT at our center before 2004, 3 of 4 patients who presented with stage IV disease and 1 of 2 patients who recurred after hysterectomy for presumed stage I disease died (Hoekstra et al., 2004). In our current series, all 13 patients, including 3 patients with metastatic disease, were cured, probably as a result of a more aggressive therapeutic approach employing both surgery and multiagent cisplatin/etoposide-based chemotherapy.

Prolonged interval from antecedent pregnancy to the diagnosis of PSTT is an important adverse prognostic indicator. Papadopoulos et al (Papadopoulos et al., 2002) reported that none of their patients with an interval of ≤2 years from last known pregnancy died, while those with an interval > 2 years had a 64% death rates. Similarly, Lathrop et al (Lathrop et al., 1988) noted in a literature review of 43 patients that all 10 fatalities occurred when the interval from antecedent pregnancy to diagnosis of PSTT was > 2 years. In a review by Chang et al (Chang et al., 1999), the median time from last pregnancy to diagnosis was

12 months in patients with nonmetastatic disease as compared to 24 months in patients with metastatic disease. More recently, Zhao et al (Zhao et al., 2016) and Schmid et al (Schmid et al., 2009) found that intervals between antecedent pregnancy and onset of PSTT of 36 months and 48 months, respectively, were more discriminatory for poorer outcomes. The negative impact of prolonged interval from prior pregnancy of > 48 months was confirmed in two database analyses. (Hancock et al., 2015) In our previous report the mean interval from last known pregnancy to diagnosis of PSTT for our patients surviving without disease was 9 months as compared to 59 months for our patients who were dead or had progressive disease. (Hoekstra et al., 2004) In our current report, mean interval from antecedent pregnancy to diagnosis of PSTT was 113 months (2 > 48 months) for the 3 patients who presented with metastatic disease versus 12.6 months (none > 24 months) for the 10 patients who presented with nonmetastatic disease.

Pathologic features of PSTT associated with adverse outcomes have been identified (Table 2). These are deep myometrical invasion, extensive necrosis, and high mitotic rate. (Zhao et al., 2016; Hancock et al., 2015; Baergen et al., 2006). Baergen et al noted that all tumors confined to the inner one third of the myometrium were associated with a favorable outcome, whereas recurrence or metastasis developed in 15% of cases when tumors involved the outer one half of the myometrium and 50% of cases with serosal involvement by tumor were fatal. These authors also found that survival was 94% in cases with no or minimal necrosis compared to 64% in cases with more extensive necrosis, and that the presence of tumor cells with clear cytoplasm was also associated with poor survival. (Baergen et al., 2006) Mitotic count has also been determined to be a strong prognostic indicator. (Hoekstra et al., 2004; Feltmate et al., 2002; Schmid et al., 2009; Froeling et al., 2019; Baergen et al., 2006) In a study by Feltmate et al, mitotic index > 5 mitoses per 10 high power fields (hpfs) significantly increased the risk of recurrent disease. (Feltmate et al., 2002) Hoekstra et al subsequently reported that none of the patients with mitotic counts ≤5 mitoses per 10 hpfs developed recurrent disease, while all patients with mitotic counts > 5 mitoses/10 hpfs experienced recurrence (Hoekstra et al., 2004). The Charing Cross-London group originally reported that the mortality rate was 18.7% in 16 patients with a mitotic rate ≤5 mitoses/10 hpfs as compared to 36.4% in 11 patients with a mitotic rate > 5 mitoses/10 hpfs. (Papadopoulos et al., 2002) Follow-up studies from the UK noted that the mitotic index was significantly associated with survival on univariate analysis. (Schmid et al., 2009; Froeling et al., 2019) Baergen et al also found that mitotic count was a strong predictor of survival with 88% of patients surviving who had mitotic counts < 2.5/10 hpfs versus 48% survival in patients with mitotic counts > 6/10 hpfs. Higher mitotic counts also correlated with advanced stage and development of recurrent or metastatic disease. (Baergen et al., 2006) In our series, 8 (62%) of the 13 patients had two or more of these high-risk pathologic features, including all 3 patients with metastatic disease. Postoperative use of adjuvant chemotherapy in our patients with nonmetastatic disease who had any high-risk features may have contributed to their excellent outcomes. While these pathologic factors all seem to be important prognostic factors for recurrence and survival, on univariate analysis in multiple reports, Zhao et al. (2016), Schmid et al. (2009), and Froeling et al. (2019) found that stage and time interval from antecedent pregnancy, were the only factors that affected survival on multivariate analysis.

Surgery is the mainstay of treatment for patients with PSTT (Hyman et al., 2013; Schmid et al., 2009; Zhao et al., 2016; Chang et al., 1999; Feltmate et al., 2002; Papadopoulos et al., 2002). Patients with disease apparently localized to the uterus or with minimal metastatic disease should undergo hysterectomy because of the relative resistance of PSTT to chemotherapy. Fertility sparing surgery, such as hysteroscopic resection or transperitoneal local uterine excision, may be offered to patients with nonmetastatic disease who are very motivated (Zhao et al., 2016; Chiofalo et al., 2017). One patient in out series was successfully treated with hysteroscopic resection, while another patient failed an attempt at local uterine excision prior to undergoing hysterectomy for residual disease. Resection of metastatic disease, especially from the vagina, lungs and lymph nodes, may make an important contribution in secondary treatment of persistent or recurrent disease (Hoekstra et al., 2004; Schmid et al., 2009; Zhao et al., 2016). In our initial report on PSTT, excision of multiple vaginal metastases that developed after hysterectomy in addition to chemotherapy resulted in cure of the patient. (Hoekstra et al., 2004) In our current report, two patients with solitary, chemotherapy-resistant lung nodules who underwent VATS excision were cured.

Chemotherapy should be given to all patients with metastatic PSTT and should be considered in patients with nonmetastatic disease who have high-risk factors (Froeling and Seckl, 2014; Feltmate et al., 2002; Schmid et al., 2009; Taylor and Hancock, 2015). Although the optimal chemotherapy regimen for PSTT remains to be defined, the current clinical impression is that a platinum/etoposide-containing regimen, such as EMA/EP or TP/TE, is the treatment of choice (Horowitz et al., 2017; Chiofalo et al., 2017). In our report, 6 of 10 patients with nonmetastatic disease received adjuvant EMA/EP chemotherapy for persistently elevated hCG levels after hysterectomy (2) or high-risk factors (4) and none developed recurrence, although one required additional TP/TE chemotherapy to enter hCG remission. The three patients with lung metastases in our series all received multiagent platinum-based chemotherapy. The one patient with multiple pulmonary nodules had a complete response to EMA/EP. A patient with an isolated growing pulmonary nodule while on EMA/EP, had VATS and then TP/TE chemotherapy. The third patient with metastatic pulmonary disease had received multiple courses of single-agent and multiagent chemotherapy prior to transfer to our center; she underwent VATS and received TP/TE chemotherapy postoperatively. These last two patients had histologically proven residual PSTT in the lung resection specimens.

5. Conclusion

Surgery, including hysterectomy and resection of metastatic disease, is the most important component in the treatment of PSTT. Multidrug platinum/etoposide-containing chemotherapy, most commonly EMA/EP or TP/TE, should be used in the presence of metastatic disease and considered in nonmetastatic disease with any high-risk clinicopathologic features, such as interval from last known pregnancy to diagnosis > 2 years, deep myometrial invasion, tumor necrosis, and mitotic count > 5/10 high power fields. All 13 patients in this report, including the 3 with metastatic disease, were cured using this therapeutic approach.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Baergen, R.N., Rutgers, J.L., Young, R.H., et al., 2006. Placental site trophoblastic tumor: a study of 55 cases and review of the literature emphasizing factors of prognostic significance. Gynecol. Oncol. 100, 511–520.

Chang, Y.-L., Chang, T.-C., Hsueh, S., et al., 1999. Prognostic factors and treatment for placental site trophoblastic tumor: report of 3 cases and analysis of 88 cases. Gynecol. Oncol. 73, 216–222.

Chiofalo, B., Palmara, C., Lagana, A.S., et al., 2017. Fertility sparing strategies in patients affected by placental site trophoblastic tumor. Curr. Treat. Options in Oncol. 18 (10). https://doi.org/10.1007/s11864-017-0502-0.

Feltmate, C.M., Genest, D.R., Goldstein, D.P., Berkowitz, R.S., 2002. Advances in the understanding of placental site trophoblastic tumor. J. Reprod. Med. 47, 337–341.

Froeling, F.E.M., Ramaswami, R., Papanastasopoulos, P., et al., 2019. Intensified therapies improve survival and identification of novel prognostic factors for placental-site and epithelioid trophoblastic tumors. Br. J. Cancer 120, 587–594.

Froeling, F.E.M., Seckl, M.J., 2014. Gestational trophoblastic tumours: an update for

2014. Curr. Oncol. Rep. 16, 408–417.

Hancock B, Froeling F, Ramaswami R, et al. The ISSTD global placental site and epithelioid trophoblastic tumor (PSTT/ETT) database-an analysis of 326 patients. Abstract #12. ISSTD XVIII World Congress on Gestational Trophoblastic Disease. Bali, Indonesia, September 15-18, 2015.

Hassadia, A., Gillespie, A., Tidy, J., et al., 2005. Placental site trophoblastic tumor: clinical features and management. Gynecol. Oncol. 99, 603–607.

Hoekstra, A.V., Keh, P., Lurain, J.R., 2004. Placental site trophoblastic tumor: a review of 7 cases and their implications for prognosis and treatment. J. Reprod. Med. 49, 447–452.

Horowitz, N.S., Goldstein, D.P., Berkowitz, R.S., 2017. Placental site trophoblastic tumors and epithelioid trophoblastic tumors: biology, natural history, and treatment modalities. Gynecol. Oncol. 144, 208–214.

How, J., Scurry, J., Grant, P., et al., 1995. Placental site trophoblastic tumor: report of 3 cases and review of the literature. Int. J. Gynecol. Cancer 5, 241–249.

Hyman, D.M., Bakios, L., Gualtiere, G., et al., 2013. Placental site trophoblastic tumor:

analysis of presentation, treatment, and outcome. Gynecol. Oncol. 129, 58–62.

Lathrop, J., Lauchlan, S., Noyak, R., et al., 1988. Clinical characteristics of placental site trophoblastic tumor (PSTT). Gynecol. Oncol. 31, 32–42.

Lurain, J.R., 2011. Gestational trophoblastic disease. II: classification and management of gestational trophoblastic neoplasia. Am. J. Obset. Gynecol 204, 11–18.

Papadopoulos, A.J., Foskett, M., Seckl, M.J., et al., 2002. Twenty-five years clinical experience with placental site trophoblastic tumors. J. Reprod. Med. 47, 460–464.

Schmid, P., Nagai, Y., Agarwal, R., et al., 2009. Prognostic markers and long-term outcome of placental-site trophoblastic tumors: a retrospective observational study. Lancet 374, 48–55.

Taylor, F., Hancock, B.W., 2015. Pharmacotherapy of placental site and epithelioid trophoblastic tumors. Exp Opin Orphan Drugs. 3, 75–85.

Zhao, J., Lv, W.G., Feng, F.Z., et al., 2016. Placental site trophoblastic tumor: a review of 108 cases and their implications for prognosis and treatment. Gynecol. Oncol. 142, 102–108.