

# A diagnostic challenge: extrauterine placental site trophoblastic tumors

Ibrahim Gulhan<sup>1,\*</sup>, Alper Ileri<sup>2</sup><sup>1</sup>Department of Gynecologic Oncology, Izmir Tepecik Education and Research Hospital, 35120 Izmir, Turkey<sup>2</sup>Department of Gynecology and Obstetrics, Izmir Tepecik Education and Research Hospital, 35120 Izmir, Turkey\*Correspondence: [drigulhan@yahoo.com](mailto:drigulhan@yahoo.com) (Ibrahim Gulhan)DOI: [10.31083/j.ejgo.2021.02.2280](https://doi.org/10.31083/j.ejgo.2021.02.2280)This is an open access article under the CC BY 4.0 license (<https://creativecommons.org/licenses/by/4.0/>).

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**Objectives:** Extrauterine placental site trophoblastic tumors (PSTT) are very rare and have diagnostic difficulties. We aimed to investigate distinctive clinical and pathological features of extrauterine PSTT. **Methods:** A literature search was conducted. **Results:** In total, 13 cases of extrauterine PSTT were identified. Of 13 cases, 4 cases originated from fallopian tubes, 3 from ovary, 2 from vagina, 2 from cervix, 1 from pelvic wall and 1 case from ectopic pregnancy. The mean age of the patients was 33.2 (25--46) years and the mean human chorionic gonadotropin level was 992.16 mIU/mL. In 11 patients, the previous pregnancy history was known and 5 of 11 (45%) had term deliveries, 6 of 11 (55%) had other pregnancy events (3 ectopic pregnancies, 2 abortions, 1 abortion or ectopic pregnancy). In 10 patients main presenting symptoms were available and of 10 patients, 4 (40%) had acute abdominal pain, 3 (30%) had vaginal bleeding, 2 had amenorrhea and 1 had painless swelling. In 10 of 13 patients' data about tumor spread were available. While no patient had distant metastasis, 3 patients had local spread. Ki-67 proliferation index was performed in 5 patients and mean Ki-67 index was 59.7% (22.8--80). **Conclusion:** Extrauterine PSTT occur mostly after ectopic pregnancy or abortion with different presenting symptoms than intrauterine PSTT such as acute abdominal pain or painless lesions. It may have higher human chorionic gonadotropin level and Ki-67 index. It tends to stay localized.

## Keywords

Extrauterine placental site trophoblastic tumor; Ectopic pregnancy; Ki-67

## 1. Introduction

Placental site trophoblastic tumors (PSTTs) originate from the intermediate trophoblastic cells at the implantation site in the uterine corpus and accounts for 1--2% of gestational trophoblastic neoplasms. They generally affect women during their reproductive years and occur most commonly after a normal pregnancy with a variable interval. PSTTs most often present with amenorrhea or abnormal bleeding with or without uterine enlargement. Although PSTTs tend to stay initially in the uterus, up to 30% of patients have metastatic lesions to sites such as the lungs, peritoneum, liver and/or brain at presentation. Hysterectomy is the preferred treatment for women with early-stage disease and the outcome is usually favorable. For advanced-stage diseases, a combination of surgery and chemotherapy is the choice of treatment

[1--3].

While PSTT primarily occurs in the uterine cavity, there are primary lesions of PSTT occurring at extrauterine sites such as vagina, fallopian tube, ovary, pouch of Douglas, and the pelvic wall. We assume that primary cervical PSTTs should be considered in this category, as the cervix is a different part of uterus, like fallopian tubes and placentation at these sites is not normal.

Extrauterine PSTTs are extremely rare and difficult to diagnose. In this study, we aimed to investigate the clinical and pathological features of extrauterine PSTT.

## 2. Methods

We conducted a literature search in PubMed Central with the terms 'extrauterine placental site trophoblastic tumors', 'placental site trophoblastic tumors outside the uterine cavity', 'cervical placental site trophoblastic tumors', 'tubal placental site trophoblastic tumors' and 'vaginal placental site trophoblastic tumors' (<https://www.ncbi.nlm.nih.gov/pmc/>).

Age, antecedent pregnancy, symptoms, primary site of the tumor, distant or local metastasis, human chorionic gonadotrophin level, pathology (macroscopy, microscopy and immunohistochemical staining) and treatment of the cases were noted. The extent of immunohistochemical staining was graded as negative, weakly and/or focally positive, positive, or strongly positive (0 to 3+), and the percentage of positively staining cells was estimated.

## 3. Results

We identified 15 cases mentioned as extrauterine PSTT or PSTT outside the uterine cavity [4--14]. However, 2 of 15 cases were excluded. One of these cases is not a PSTT case [15]. In this case report, Kjer described a 53-years-old patient with choriocarcinoma in the left fallopian tube. The other case report presented primary ovarian PSTT in a 30-month-old girl with isosexual precocious puberty of one month of duration. Childhood cancers may have some other etiology than adult cancers thus we did not include this case in our group [16].

**Table 1. Clinical features of the cases.**

Case	Age (yrs)	PP	Primer site and/spreading	of tumor (IU/L)	hCG level	Treatment	Final pathology of uterine corpus
1. Su, 1999 [4]	37	TD	Right fallopian tube/+			cesarean section + tah + bso + omentectomy	NED
2. El Hag, 2002 [5]	35	EP	Ectopic pregnancy located in Douglas pouch/+	< 5		Lithopedion was removed, involved colon, rectum, and small intestine were resected and permanent colostomy was done	Uterus was not removed
3. Baergen, 2003, 1 [6]	42	Unknown	Right fallopian tube/?	-		Tah + right salpingo-oophorectomy	NED
4. Baergen, 2003, 2 [6]	25	Unknown	Right fallopian tube/?	-		Biopsies	?
5. Baergen, 2003, 3 [6]	27	EP	Right ovary/?	581		Tah + bso + chemotherapy	NED
6. Condous, 2003 [7]	33	TD	Right ovary/+	112		Right salpingo-oophorectomy + chemotherapy	Uterus was not removed
7. Soma, 2004 [8]	43	A or EP	Cervix/-	4000		Resection of the cervical polyp + hysterectomy + left salpingo-oophorectomy + chemotherapy	NED
8. Palmieri, 2005 [9]	33	TD	Right ovary/-	104		1st op: right salpingo-oophorectomy. 2nd op: left oophorectomy	Uterus was not removed
9. Gupta, 2006 [10]	26	EP	Right fallopian tube/-	2075		Right salpingectomy	Uterus was not removed
10. Wang, 2010 [11]	27	A	Cervix/-	1900		Hysterectomy + chemotherapy	NED
11. Tang, 2013 [12]	29	A	Right pelvic Wall/-	984.5 (1722)	(247-	Tumor excision + chemotherapy	Uterus was not removed
12. Rauw, 2013 [13]	46	TD	Vaginal vault/-	41		Tumor excision + bilateral salpingo-oophorectomy and pelvic lymphadenectomy	NED (Uterus was removed 4 years ago before presentation)
13. Gupta, 2017 [14]	29	TD	Vagina/-	124.1		Chemotherapy	NED, Uterus was not removed but an endometrial biopsy was performed

PP, previous pregnancy; TD, term delivery; EP, ectopic pregnancy; NPP, no previous pregnancy; A, abortion; tah, total abdominal hysterectomy; bso, bilateral salpingo-oophorectomy; NED, no evidence of disease; hCG, human chorionic gonadotropin.

In total, we evaluated the clinical and pathological features of 13 cases (Tables 1,2,3).

The mean age of the patients was 33.2 (25–46) years and the mean human chorionic gonadotropin level was 992.16 mIU/mL. In 11 patients the antecedent pregnancies were known; 5 of 11 (45%) had term delivery, 6 of 11 (55%) had other pregnancy events (3 ectopic pregnancies, 2 abortions, 1 abortion or ectopic pregnancy). Two of 13 patients were clinically misdiagnosed with and treated for ovarian ectopic pregnancy and 4 of 13 patients were pathologically misdiagnosed with carcinoma.

In 10 patients the main presenting symptoms were noted. Four (40%) of these patients had acute abdominal pain, 3 (30%) had vaginal bleeding, 2 had amenorrhea and 1 had painless swelling.

Primary tumor sites were right fallopian tube in 4 cases, right ovary in 3 cases, vagina in 2 cases, cervix in 2 cases, right pelvic wall in 1 case and ectopic pregnancy remnant in 1 case. The uterus was removed in 6 patients (1 of them had a hysterectomy 4 years before the clinical presentation) and was not removed in other 6 patients. One patient had no data about the treatment. The pathology reports of 6 patients

who underwent hysterectomy showed that they had no evidence of PSTT in the uterine corpus. One of 6 patients without uterine removal had uterine biopsy, which did not show PSTT.

In 10 of 13 patients data about tumor spread were available. No patient had distant metastasis, 7 patients had no local metastasis and 3 patients had local metastasis. However, 1 patient with no evidence of local spread at the the initial time of diagnosis, had recurrent disease in her left ovary 2 years later.

The size of primary tumor was between 2–6 cm and the common gross pathological finding was the yellow color of the tumor. Gross pathological findings are shown in Table 2.

Large polygonal cells were the common cell type. In 6 patients, different levels of mitoses were seen but generally not higher than 5 mitoses per 10 high-power fields. In one patient, no mitotic activity was detected. In 5 patients there was necrosis of different degrees. Vascular invasion was observed in 5 patients. Microscopic pathological findings are also summarized in the Table 2.

Staining data for human chorionic gonadotropin were available in 9 patients. 6 of 9 (66.6%) were focally positive, 1 was positive and 2 were negative. Human placental lacto-

**Table 2. Pathological findings of the cases.**

	Macroscopy	Microscopy
1. Su, 1999 [4]	Fragile, yellowish tissues	Hyperchromatic polygonal cells arranged in nests, with focal multinucleated cells and occasional vacuolated cytoplasm. Invasion of the vascular wall with deposition of fibrinoid material was found. Necrosis and mitotic activity were easily identified.
2. El Hag, 2002 [5]	Irregular yellowish tumour nodule of 20 mm size	A central area of necrosis surrounded by viable large sized tumour cells with abundant eosinophilic cytoplasm, well-defined cell membrane, hyperchromatic and pleomorphic nuclei exhibiting high mitotic rate which included atypical mitoses. Few multinucleated tumor giant cells were seen but they were not of syncytiotrophoblastic type.
3. Baergen, 2003, 1,2,3 [6]		In one tumor, large multinucleated cells containing many irregular, hyperchromatic nuclei were present. Mitotic activity including abnormal forms was easily appreciated. The cells had a tendency to infiltrate into vessel walls with a characteristic deposition of fibrinoid material. Focal necrosis and hemorrhage were noted.
4. Condous, 2003 [7]	A yellow plaque of tissue	
5. Soma, 2004 [8]	Soft thumb-sized cervical polyp	A few syncytiotrophoblasts and abundant cytotrophoblasts resembling intermediate trophoblasts with relatively larger nuclei and clear cytoplasm, as well as rare mitoses in the removed polypoid tissue.
6. Palmieri, 2005 [9]		Mononuclear cells, with vacuolated or eosinophilic cytoplasm. Focal hyperchromatic nuclei and multinucleate cells were present. Focal regions of necrosis and stromal hyalinisation.
7. Gupta, 2006 [10]		Cytotrophoblasts and intermediate trophoblasts and few giant cells with areas of haemorrhage and necrosis. No mitotic figures.
8. Wang, 2010 [11]	A 6 cm soft autolysing mass in the cervical canal	Rounded-to-polygonal intermediate trophoblastic cells with relatively large nuclei and clear cytoplasm.
9. Tang, 2013 [12]	A 4.0 × 3.5 × 4.0 cm mass in the right pelvic wall, yellow fleshy cut surface, accompanied by foci of hemorrhage and necrosis	Large and polygonal tumor cells, hyperchromatic with vesicular nuclei and abundant eosinophilic cytoplasm. Obvious vascular invasion and severe nuclear atypia. The mean mitotic count was five mitoses per 10 high-power fields.
10. Rauw, 2013 [13]	Nodular growth measuring 3.5 × 3.5 × 3.8 cm. The mass is pearly white color with areas of hemorrhage	Pleomorphic population of polygonal intermediate trophoblast cells with amphiphilic to clear cytoplasm. These cells have often a single irregular highly atypical nucleus with focally prominent nucleoli, but some are multinucleate, resembling to syncytiotrophoblastic giant cells. Mitotic figures 2/10 per high power field, extensive necrosis, hemorrhage and vascular invasion.
11. Gupta, 2017 [14]	A 2 × 1.5 cm suburethral nodule	Large polygonal cells displaying large convoluted hyperchromatic nuclei, distinct nucleoli, and abundant eosinophilic cytoplasm. Deposition of fibrinoid material was seen in a vessel with infiltration of its wall by tumor cells. Occasional mitotic figures were evident.

gen staining was performed in 8 patients. In 6 of 8 (75%) patients it was diffusely positive, in 2 patients it was focally positive. Ki-67 proliferation index was performed in 5 patients (in one case it was not quantitated). Mean Ki-67 index was 59.7 (22.8–80). Five patients had cytokeratin staining. It was diffusely positive in 4 patients and it was positive in 1 patient. Inhibin staining was performed only in 3 patients and all were focally positive. The only patient who had CD 146 staining, had diffusely positive staining. All immunohistochemical patterns of the cases are shown in Table 3.

#### 4. Discussion

PSTT is a rare variant of gestational trophoblastic neoplasia that develops from the placental implantation site in the uterine cavity. Clinically, PSTTs often follow term pregnancies, presents with abnormal uterine bleeding, have dis-

ease localized within the uterus and are associated with low or normal human chorionic gonadotropin levels [1–3].

However, PSTTs outside the uterine cavity are very rare. We have identified 13 cases in the literature. Primary tumor sites were right fallopian tube in 4 cases, right ovary in 3 cases, vagina in 2 cases, cervix in 2 cases, right pelvic wall in 1 case and ectopic pregnancy remnant in 1 case. Interestingly all ovarian and tubal cases were on the right side.

The pathological evaluation of uterus is the main step of definitive diagnosis of extrauterine PSTT from intrauterine PSTT. In 7 patients in our group, primary extrauterine PSTT was confirmed by uterine evaluation. The pathology reports of 6 patients who underwent hysterectomy and 1 patient with uterine biopsy showed that they had no evidence of PSTT in the uterine corpus. Uterine evaluation was

**Table 3. Immunohistochemical pattern of the cases.**

	hCG	hPL	PLAP	Inhibin	Mel-CAM	Ki-67 index (%)	CK
1. Su, 1999 [4]	+	+++					++
2. El Hag, 2002 [5]	-	+					+++
3. Baergen, 2003, 1 [6]							
4. Baergen, 2003, 2 [6]							
5. Baergen, 2003, 3 [6]							
6. Condous, 2003 [7]							
7. Soma, 2004 [8]	+	+++		+		28.8 ± 7.35	+++
8. Palmieri, 2005 [9]	+	+++	+				
9. Gupta, 2006 [10]	++						
10. Wang, 2010 [11]	+	+++				+	
11. Tang, 2013 [12]	+	+++	+++	+	+++	80	+++
12. Rauw, 2013 [13]	+	+	++	+		65 (60–70)	
13. Gupta, 2017 [14]	-	+++				65 (60–70)	+++

hCG, human chorionic gonadotropin; hPL, human placental lactogen; PLAP, placental alkaline phosphatase; Mel-CAM, melanoma cell adhesion molecule or CD146; CK, Cytokeratin.

made by transvaginal ultrasound, computerized tomography, hysteroscopy, exploratory laparotomy and laparoscopy in the other 6 patients. None of the patients had evidence of uterine disease and 5 out of 6 patients had no recurrence within the uterus during the follow-up period. One patient was lost to follow-up.

PSTT is generally seen in women of childbearing age. We found the mean age of the patients with extrauterine PSTT to be 33.2 (25–46) years. Zhao *et al.* (108 cases), Baergen *et al.* (55 cases), Choi *et al.* (20 cases) and Chen *et al.* (17 cases) found similar mean age in their uterine PSTT case series (31.8, 32, 32, 32 ± 4 respectively) [17–20].

The mean human chorionic gonadotropin level of patients with extrauterine PSTT is 992.16 mIU/mL, which is higher than the level reported in women with uterine PSTT. Chen *et al.* and Baergen *et al.* reported hCG levels of 556.7 and 691 mIU/mL, respectively in women with uterine PSTT [9, 18]; while Alexander *et al.* reported a much lower mean serum human chorionic gonadotropin level of 90 (1–2606) mIU/mL in their series consisted of 13 cases [3].

Generally antecedent pregnancy event, instead of causative pregnancy event, was stated in the studies focused on PSTT. However, known antecedent pregnancy is not always the pregnancy responsible for the tumor. This should be clarified by genetic testing which is also required for confirmation of gestational origin of these tumors. Chen *et al.* found that among 20 patients with PSTT the antecedent pregnancy was a delivery at term in 88.2% and 1 abortion and 1 hydatidiform mole [20]. In Zhao's series the most common antecedent pregnancy of PSTT was also a normal pregnancy (n = 67, 62%) [17]. Similarly, Baergen *et al.* reported an antecedent normal pregnancy rate of 57%, an abortion rate of 17% and 26% hydatidiform mole [18]. Unfortunately, we cannot confirm the causative pregnancy events in our series. On the other hand, we found a higher abnormal antecedent pregnancy events rate. In our study

45% of patients had an antecedent term delivery and 55% had abnormal pregnancy events (ectopic pregnancy, abortion). This may be related to mechanism of extrauterine PSTT. The placenta of ectopic pregnancy in the tubes, ovaries or other sites and the migration of intermediate cells in the abortion process may have a predisposition to develop extrauterine PSTT. Because placental site intermediate trophoblasts, which refer to the cells at the distal villus that attach to the endometrium, become dispersed and independent cell lines, and then acquire the abilities of proliferation and migration. In normal pregnancy, those cells migrate away from placenta and invade the decidual artery and uterine spiral artery to remodel the blood vessels [2].

The most common clinical manifestations of PSTTs are abnormal vaginal bleeding and/or amenorrhea. In Choi's study 95% of patients presented with abnormal vaginal bleeding or amenorrhea [19]. Similarly, in the Zhao's series vaginal bleeding and amenorrhea were the most common presenting symptoms [17]. Contrary to these findings, we found that half of the patients had vaginal bleeding or amenorrhea as the presenting symptom and the other half had different symptoms such as acute abdominal pain or painless swelling. The different presenting symptoms such as acute abdominal pain may lead to misdiagnosis as 2 of patients in our group were clinically misdiagnosed with and treated for ovarian ectopic pregnancy.

PSTTs metastasise mostly to the lungs and genital organs. In a series of 62 patients, Schmid found that 39 (63%) patients had local disease, and 23 (37%) patients had distant metastasis of the lung (n = 21 patients), liver (n = 3), bowel (n = 2), retroperitoneal lymph nodes (n = 2), brain (n = 2), and kidney or spleen (n = 1) [1]. In Zhao's series 71 (65.7%) patients were at stage I, 4 (3.7%) patients were at stage II, 31 (28.7%) patients were at stage III and 2 (1.9%) patients were at stage IV [17]. In Baergen's study 84% of patients were stage I, 2% stage II, 5% stage III, and 9% stage IV [18]. None of the patients in

our study had distant metastasis, but a few has spread to adjacent tissues. Interestingly, one patient without evidence of spread at the time of diagnosis, had recurrent disease in the contralateral ovary 2 years later.

Considering gross pathological results Beargen *et al.* mentioned the yellow color of the tumor tissue similar to our findings. In their study the tumors were on average 5 cm in greatest dimension close to the mean size of the the extrauterine PSTT we identified [18].

Regarding histological appearance, PSTTs consist of mononuclear intermediate trophoblasts without chorionic villi, are associated with less vascular invasion, necrosis, and hemorrhage when compared to choriocarcinoma. Monomorphic population of large polyhedral tumor cells with irregular hyperchromatic nuclei, which is at the different stages of mitosis and eosinophilic or transparent substance in the cytoplasm that could be large amount of fibrin, are among the histopathological features of PSTT [2]. We found that there were similar microscopic pathological findings in our patients with extrauterine PSTT. Large polygonal cells, hyperchromatic nucleus and eosinophilic cytoplasm were also the common microscopic findings in most of the patients in our study. However, 2 cervical cases had clear cytoplasm. Our patients' results varied widely from different levels of mitosis to necrosis. In Baergen's study, fibrinoid material was found within blood vessel walls and surrounding groups of cells in 90% of cases [18]. They concluded that this finding was particularly characteristic of this tumor. Similarly, in our group there were 2 patients who had deposition of fibrinoid material in blood vessels.

Immunohistochemical staining is essential for diagnosis of PSTTs, focally staining for human chorionic gonadotropin and diffusely staining for human placental lactogen, placental alkaline phosphatase, cytokeratine and CD 146 is well known [2]. Most of our immunohistochemical staining results reinforced the current data of PSTT. Although most of our patients were focally positive, interestingly 2 patients were negative for human chorionic gonadotropin. Human placental lactogen staining was 75% diffusely and 25% focally positive in our study. In our study, almost half of the patients had cytokeratin staining, mostly diffuse. Only patient who had CD 146 staining, had diffusely positive staining. Inhibin staining was performed only in few patients and all were focally positive as in PSTT. In uterine PSTTs, Ki-67 positivity is found in approximately 15 of cells [2]. In contrast, we observed a higher Ki-67 index. Although it was performed in a limited number of patients, it should be taken into account in future cases.

Generally, the patients with FIGO stage I PSTT can be cured by simple hysterectomy with or without pelvic lymph node biopsy and patients with stage II to IV PSTT, lymph node biopsy should be added to provide guidance of whether to perform lymphadenectomy. The management of metastatic lymphatic lesions is crucial to decrease the recurrence rate. The retroperitoneal lymph nodes, especially the

paraortic lymph nodes, are the most frequent sites of lymphatic metastasis [2].

Oophorectomy remains controversial and chemotherapy is considered according to risk factors after the surgery such as interval between antecedent pregnancy, deep infiltration, necrosis and mitotic index. The 10-years survival rate can be as high as 100% for patients with stage I PSTT, 52% for the stage II patients, 49% for stage III and IV patients [2]. However, there is no standardized treatment for extrauterine PSTT and treatment options vary according to tumor site. The patients we report were treated with tumor excision and hysterectomy (alone or with bilateral or unilateral salpingo-oophorectomy) with or without chemotherapy. However, one patient with vaginal disease received only chemotherapy. Twelve of 13 patients were followed for up to 12 years, one patient had recurrent disease and no patient died due to PSTT. The main questions in the treatment of extrauterine PSTT are: is hysterectomy and chemotherapy needed after tumor excision and what are the major prognostic factors.

Although limited by the small number of cases and incomplete data we believe that reviewing and summarizing these cases provides some insight on the presentation and treatment alternatives of extrauterine PSTT. A significant piece of information that is not available in the cases we reviewed is the interval between antecedent pregnancy and PSTT diagnosis.

In conclusion, extrauterine PSTTs occur mostly after ectopic pregnancy or abortion with presenting symptoms such as acute abdominal pain or painless lesions somewhat different than the symptomatology of patients with uterine PSTT. The differential diagnosis of uterine PSTT includes intrauterine non-neoplastic intermediate trophoblastic proliferation such as exaggerated placental site reaction, placental site nodule and other malignant tumours such as choriocarcinoma. Particularly when the location of a pregnancy cannot be identified by ultrasound and the serum human chorionic gonadotropin levels have reached a plateau or when an ectopic pregnancy with a relatively low level of human chorionic gonadotropin which doesn't respond to the medical treatment, a diagnosis of extrauterine PSTT should be considered. Extrauterine PSTT may have higher human chorionic gonadotropin levels and Ki-67 index than uterine PSTT. However, further studies are needed to confirm these findings.

### Author contributions

IG contributed to the design and implementation of the research, literature review, the analysis of the results and to the writing of the manuscript. AI took responsibility in necessary literature review and the writing of the manuscript.

### Ethics approval and consent to participate

Not applicable.

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## Conflict of interest

The authors declare no conflict of interest.

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