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The Rare of the Rarest: Placental Site Trophoblastic Tumor, Epithelioid Trophoblastic Tumor, Atypical Placental Site Nodule

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Keywords
Epithelioid trophoblastic tumor · Placental site trophoblastic tumor · Atypical placental site nodule · Gestational trophoblastic disease · Gestational trophoblastic neoplasia · Rare diseases

Abstract
Background: ETT and PSTT are two of the rarest GTNs that share certain features at diagnosis and management. APSN is a relatively new entity considered as a premalignant lesion. ***Objectives and Methods:*** The aim of this review was to summarize the main characteristics of each of these entities, their diagnostic features, and their treatment's standard of care including fertility-sparing treatments. ***Outcome:*** This study provides a thorough review of ETT, PSTT, and APSN. ***Conclusions:*** The reader will gain an insight view of these rare tumors arising from the intermediate trophoblast.

Introduction

Epithelioid trophoblastic tumor (ETT) and placental site trophoblastic tumor (PSTT) are the rarest gestational trophoblastic neoplasia (GTN), which share some of their general features such as frequency, presentation, and treatment. Both are considered less chemo sensitive than choriocarcinoma, that is why immunotherapy arises as a promising treatment. Atypical placental site nodule (APSN) is a relatively new term that is considered a precursor lesion of PSTT and, when detected, implications on management must be discussed with the patient. In this article, we will review the special features of each of these rare lesions arising from intermediate trophoblast.

Placental Site Trophoblastic Tumor

Epidemiology and Pathogenesis

PSTT is one of the rarest placental tumors, primarily evolved from intermediate trophoblast. The incidence of PSTT ranges from 1% to approximately 3% of all GTN cases, which can be estimated as 1–100,000 pregnancies

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[1, 2]. During a process of implantation, cytotrophoblast cells proliferate forming villi and invading the decidua and uterine vessels. A process of differentiation of trophoblast allows to distinguish three different phenotypes, i.e., cytotrophoblast, intermediate trophoblast, and syncytiotrophoblast. Intermediate trophoblast, which shares both features of cyto- and syncytiotrophoblast, can be divided into sub-types, based on its location. Implantation site intermediate trophoblast (extra villous) gives rise to PSTT [3].

Pathological Features

PSTT can vary in size, ranging from small 1-2-cm tumors to a large mass covering the whole lining of the uterine cavity. PSTT can grow like fibroids; however, myometrial invasion and a perforation of the uterus in some cases can be a hint. On a microscopic examination, PSTT is composed of intermediate trophoblastic cells, mostly mononuclear with eosinophilic cytoplasm, which split myometrial fibers and invade uterine vessels with a deposition of fibrinoid debris. The mitotic rate is low (2–4 10/HPFs) in contrast with choriocarcinoma but with atypical figures [4]. Most cells are positive for cytokeratin AE1/3, cytokeratin 18, CD10, HLA-G and GATA-3, human placental lactogen (hPL), MUC-4, and Mel-CAM (CD146). The positive expression of hCG and inhibin is observed only within rare multinucleated cells, which resemble syncytiotrophoblast. Contrary to choriocarcinoma, PSTT is negative for SALL4 protein as it is a more differentiated form of trophoblastic neoplasm than choriocarcinoma [5]. Also, the Ki-67 index is lower in PSTT, which in choriocarcinoma usually extends to 40%. PSTT should be also differentially diagnosed from exaggerated placental site, ETT, epithelioid smooth muscle tumors, metastatic melanomas, and poorly differentiated carcinomas. The characteristics of exaggerated placental site and ETT are given in other parts of this manuscript. The characteristic pattern of invasion, namely, vascular invasion, cannot be seen in abovementioned tumors. Positive staining for cytokeratin 18, hPL, HSD3B1, and HMB-45 can be useful in differentiating from these tumors [4]. PSTT can be seen as a mixed lesion with choriocarcinoma and/or ETT.

Clinical Presentation

The majority of PSTT cases are diagnosed in reproductive age; however, early menopause and postmenopausal diagnoses have also been described. Abnormal vaginal bleeding, followed by amenorrhea, together with slightly elevated hCG after exclusion of pregnancy is the most common presentation [6]. The most common clinical features of PSTT are shown in Table 1. A paraneoplastic syndrome can occur with PSTT, and the following symptoms have been described: lupus-like syndrome, galactorrhea, virilization, and polycythemia [7–9]. Some presentations of PSTT can mimic other obstetrical and gynecological disorders and they are mentioned in Table 2. PSTT usually develops after a term pregnancy, even up to few years after the pregnancy is finished. Most cases are confined to the uterus; however, distant metastases, mostly to the lungs, can be found in up to 30% of cases at the time of diagnosis. PSTT can also spread to other organs like brain, vagina, skin, etc., and quite exclusively for GTN to pelvic and para-aortic lymph nodes [10]. hCG serum level is helpful in diagnosis; however, it does not reflect the full tumor activity as many of the tumor cells are abundant in hCG secretion. Usual hCG levels range between 10^2 mIU/mL and 10^4 mIU/mL and very rarely exceed 10^5 mIU/mL [11]. Even though tumor cells can produce large quantities of hPL, it is not a useful marker for PSTT in guiding clinical decisions, partly due to uncertain specificity of hPL assays [12]. While considering the rarity and different clinical presentations, it is easy to understand that significant number of PSTTs is not diagnosed, including the wrong histopathological diagnosis [13]. The conventional FIGO 2000 risk score for post-molar GTN and choriocarcinoma is not applicable in PSTT as it is a GTN per se. I–IV FIGO staging system is used to assess the extension of the tumor (Table 3).

Imaging

Due to aforementioned reasons, imaging is crucial for staging PSTT. For the local assessment, a transvaginal sonography and pelvic magnetic resonance imaging (MRI) are both useful and providing complementary data, although some authors find MRI superior to ultrasound (US) in low-vascularized cases [29]. Zhou at el. [30] describe three US patterns of PSTT according to the location and vascularity of the lesions. Type 1 is a tumor located inside the uterine cavity regardless of myometrium infiltration with minimal to moderate vascularization on color Doppler, type 2 is a solid mass in the myometrium, possible with a protrusion to uterine cavity and regardless of vascularization, and type 3 is a lacunar-like lesion with cystic areas within the myometrium with high vascularity that represents arteriovenous shunt. MRI features can be described as two different patterns. Type 1 is a hypervascularized tumor, which has no other specific features to differentiate from other GTN tumors, and type 2 is a hypovascularized tumor, isointense on T1 images when compared to myometrium and iso- to hyperintense

Table 1. Most common clinical features of patients diagnosed with PSTT

		Reference
Symptoms		
Abnormal vaginal bleeding	31.3–79.4%	[14]
Amenorrhea	11.7–43.2%	[13, 14]
Age	Median 35; range 20–54	[13]
Antecedent pregnancy (n = 439), n (%)		[1], [10–13], [15], [16–20]
Miscarriage	85 (19.4)	
Hydatiform mole	44 (10)	
Term pregnancy	331 (75.4)	
Time from antecedent pregnancy, %		[13]
<48 months	93	
≥ 48 months	7	
hCG level, mIU/mL	Median 205; range <4–15,648	[13]
Stage at presentation, %		[1], [11, 12], [15], [18], [20]
FIGO I	41–88	
II	1.8–8	
III	5.4–29.4	
IV	1.9–35.3	

Table 2. Examples of different clinical presentations of PSST, which were initially misdiagnosed

	Initial diagnosis	G/P	Age	hCG level, mIU/mL	Management	Ref
1	Intramural pregnancy	4/1	35	1,092	Conservative surgery	[22]
2	Arteriovenous malformation	2/2	39	23.55	Uterine arteries embolization	[23]
3	Adenomyosis	4/2	28	1,983	Hysterectomy	[24]
4	Endometrial polyp	4/2	51	19	Hysteroscopic excision	[25]
5	Tubal mass	2/0	26	2,075	Salpingectomy	[26]
6	Submucosal leiomyoma	3/2	40	na	Hysterectomy	[27]
7	Arteriovenous malformation	2/2	33	27.6	Hysterectomy	[28]

G/P, gravida/para.

Table 3. FIGO anatomical staging [30]

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus but is limited to the genital structures (adnexa, vagina, broad ligament)
Stage III	GTN extends to the lungs, with or without known genital tract involvement
Stage IV	All other metastatic sites

on T2-weighed images. After the administration of the gadolinium, some areas lacking enhancement in the center of the tumor may be observed [31].

Staging and Risk Factors

To describe the extent of the disease, the anatomic FIGO staging is used. The risk score assessment, however, useful in persistent gestational trophoblastic disease (GTD) and choriocarcinoma is not applicable in PSTT (Table 3). There are no consistent data on the most important histological risk factors. The poor outcome is

characteristic for tumors with high mitotic count; however, some tumors with low mitotic count have metastatic potential and poor outcome as well. Moreover, the variability of mitotic count within a tumor is too large to give a reliable result in pathological assessment [32]. In the large UK database analysis, two factors were significant in multivariable analysis: stage and interval from the last known pregnancy. The risk was greatest for stage IV and the interval ≥48 months [33]. The probability of survival at 5 and 10 years after treatment was 80% and 75%, respectively, in this cohort; however for stage I, a 10-year survival was 90%.

Treatment

The treatment of PSTT depends on stage. In stage I, a surgical treatment is recommended. If a patient has no further reproductive plans, a total hysterectomy is recommended; there is no oncological indication to remove the ovaries that can be preserved at least for premenopausal patients. The issue about pelvic lymph node sampling is not the subject of a consensus. Based on the 10–15% of lymph node metastasis, lymph node staging can be considered [34].

A conservative approach has been described as case series; however, it should be reserved for women with clear desire for preserving the fertility, informed about the high risk of treatment failure and the need of adjuvant therapy [35].

Adjuvant therapy after hysterectomy has no proven benefit and can be omitted in confirmed stage I disease if the causative pregnancy occurred no earlier than 4 years before the diagnosis [33]. Advanced stages cannot be treated with surgery alone and chemotherapy is required. The European Organization for the Treatment of Trophoblastic Diseases (EOTTD) currently recommends a platinum/etoposide-containing regimen such as etoposide, cisplatin/etoposide, methotrexate, dactinomycin (EP/EMA), or paclitaxel, cisplatin/paclitaxel, and etoposide (TP/TE).

Resection of persistent metastatic lesions is recommended as may be curative in cases of refractory or relapsed disease. Stage IV with more than 4 years period from the causative pregnancy has a very poor prognosis and should be treated with ultra-intense or novel therapies like pembrolizumab [36]. High-dose chemotherapy with autologous stem cell transplant is an option for refractory or relapsed disease. Prognosis for PSTT is worse than for other types of GTN and about 20% develop recurrence within 5 years of follow-up and only 33% of them have a chance for a long-time survival [15].

All patients with PSTT should be referred to GTD centers due to a need for expertise histopathology and clinical experience. International cooperation can ease understanding of treatment-related outcomes and defining of optimal management. The international database achievable at the address http://stdc.group.shef.ac.uk/psttuhr/ can be helpful in collecting data of this unique condition.

Epithelioid Trophoblastic Tumor

Epidemiology and Pathogenesis

ETT is the rarest type of GTN [14]. It accounts with features resembling a carcinoma, reason for which it was originally termed "atypical choriocarcinoma" [37, 38]. The trophoblastic nature of this entity was confirmed through molecular approaches [39]. This entity appears to develop from neoplastic transformation of cytotrophoblast cells that differentiate toward chorionic-type intermediate trophoblastic cells [37, 40].

Pathological Features

ETT is commonly found in the lower uterine segment or in the uterine corpus [4]. ETT size could range from 5 mm to 14.8 cm [4, 41–43]. Microscopically, ETTs are generally nodular and circumscribed, but infiltrative features at the periphery can be present. Mononucleate trophoblastic cells are arranged in nest and cords associated with an eosinophilic, fibrillar, hyaline-like material and necrosis debris. Necrosis can be present [4, 43]. The eosinophilic material may resemble keratin, that is why ETT could be confused with an epithelial malignant tumor such as squamous cell carcinoma [4, 41, 42, 44]. The mitotic count ranges from 0 to 12 mitoses/10 HPF, correlating to Ki-67 value generally low, but it can range from 3 to 77% [4, 37, 41].

At immunohistochemistry, hPL and CD146 (MelCAM) are only focally expressed, in contrast with PSTT in which both are diffusely expressed. Of note, inhibin-α and cytokeratin 18 should be expressed in ETT but not in squamous cell carcinoma and this immunohistochemistry could assist in the differential diagnosis [37, 41]. p63 is reliably positive in ETT and is useful for differential diagnosis. ETT can be seen in association with choriocarcinoma or PSTT [3, 4].

Clinical Presentation

Age at diagnosis ranges between 33 and 40 years in most series [41–43, 45–49] but can also be diagnosed during menopause. ETT can develop from 2 to

300 months from antecedent pregnancy. This tumor can develop after term delivery (43% of the cases), molar pregnancy (39%), or abortion (18%) [14, 41].

ETT symptoms at diagnosis are like other GTN entities such as PSTT with 57–67% of the patients presenting abnormal vaginal bleeding at diagnosis [41, 47, 50]. Other symptoms at diagnosis could include amenorrhea, abdominal pain, or abdominal bloating [14].

ETT typically produces much less hCG than GTN arising from villous trophoblasts; therefore, hCG levels at diagnosis are <1,000 mlU/mL, but higher levels have also been reported [41].

The majority of ETT are diagnosed at an early stage as an isolated uterine (40%) or cervical mass (31%). Some are metastatic at diagnosis presenting as isolated extrauterine disease (lung, small bowel, vagina, fallopian tube, broad ligament, gallbladder, etc.), or as primary uterine tumor associated with metastatic disease [41, 50].

Imaging

ETT presents with specific US features that assist on differential diagnosis from other GTN. A total of 100% of ETT are seen with a well-circumscribed border with hypoechogenic halo in the grayscale. Of note, this imaging has also been reported in PSTT and choriocarcinoma but only in around 5% of these malignancies. Doppler US could be helpful in the suspicion of ETT as, in contrast with other tumors, vascularization is more visible at the periphery of the tumor than the intratumoral area [51].

MRI is part of GTN workout imaging along with computerized tomography scan. On MRI, ETT is displayed as a well-circumscribed mass hyperintense on T2-weighted images, isointense on T1-weighted images, and with a heterogeneous distribution of gadolinium contrast [41].

Staging and Risk Factors

ETT risk of metastasis at diagnosis is 25% and the overall risk of death is 10–24% [37, 52]. Interval from antecedent pregnancy of over 2 years (48 months) and prior term pregnancy are associated with worse survival [6, 53]. Multifocal lesions, myometrial invasion, and serosal involvement are other described unfavorable factors in ETT [54].

Treatment

Hysterectomy is considered the first approach for stage I disease. Some reports have indicated, unlike choriocarcinoma, ETT/PSTT could spread to pelvic nodes. The incidence of pelvic lymph node metastasis is approximately 5–15% in clinical stage I tumors [34]. Lymph node dissection is not a generally accepted approach unless there are bulky lymph nodes visible on pre-operative imaging or in those large or deeply invasive ETTs [34].

For advanced disease, a multimodal approach is key. Hysterectomy, resection of metastatic sites, and multiagent chemotherapy depending on the FIGO scoring risk system with treatments such as EMA-CO, EP-EMA, or TP-TE are usually recommended. Unlike choriocarcinoma, ETT could partially respond to polychemotherapy. Data on immunotherapy for these rare GTN entities have been published with high response rates and long-lasting responses and a far more bearable toxicity profile than combination chemotherapy or high-dose chemotherapy regimens. A summary of the publications of pembrolizumab, a check-point inhibitor of programmed cell death protein 1 (PD1) receptor [55–58], is shown in Table 4. ETT patients should be referred to GTD centers for a proper management.

Data on fertility-sparing approaches are anecdotical in the literature and should be discussed in an expert multidisciplinary tumor board. EURACAN multidisciplinary tumors gynecological rare malignancies (G2 domain) meet monthly for discussing the management of patients diagnosed with rare gynecological malignancies, including rare GTNs such as ETT. The main features to differentiate between ETT and PSTT are shown in Table 5.

Atypical Placental Site Nodule

APSN is a recently described entity that shows features somewhere between typical PSN and ETT. It is an uncommon lesion that only represents about 0.5% of the cases referred to a referent national trophoblastic disease center [60]. APSN is most of the time incidentally described in endometrial biopsies sampled in women in their reproductive age. So far, little is known about its epidemiology, etiology, and natural history.

APSN arises from intermediate trophoblast of chorion laeve type [54] forming well-delimitated nodules of mononuclear cells with uniform small nuclei and eosinophilic abundant cytoplasm [61]. Albeit unanimous diagnostic criteria have not been firmly established, the following criteria have been proposed to distinguish APSN from PSN: larger nodule size (5–10 mm), increased cellularity, marked nuclear atypia, increased mitotic activity with a Ki-67 proliferation index superior to 5%. Diagnosis is difficult and should be submitted to pathology review by referent pathologist [4, 60, 62].

Table 4. Pembrolizumab in ETT and PSTT

Author	Tumor type (number of cases)	PDL1 expression, %	Number of cycles to hCG normalization	Disease response/ progression
Ghorani et al. [55] (2017)	Choriocarcinoma (2)	90–100	2–4	CR
	PSTT/ETT (1)		5	Progression
	PSTT (1)		8	CR
Choi et al. [56] (2019)	PSTT (1)	50–100	1	CR
	ETT (1)		11	PR
Pisani et al. [57] (2021)	ETT (1)	Not evaluated	Not declared	CR
Bell et al. [58] (2021)	ETT (1)	>5	Ongoing	PR

Adapted from [59].

Table 5. Main features to differentiate between ETT and PSTT

Characteristics	ETT	PSTT
Antecedent pregnancy	Majority term pregnancy	Majority term pregnancy
hCG level	<1,000 mIU/mL	Slight elevation (<105 mIU/mL)
Uterine location	Lower uterine segment/uterine corpus	Uterine corpus
Size	5 mm to 14.8 cm	From 1 to 2 cm to large mass
Necrosis	Extensive	Usually absent
Hysterectomy recommended	Yes	Yes
Consideration of pelvic lymph node sampling	Yes	Yes

In a series of 21 cases, Kaur et al. [60] reported that around 10–15% of histologically confirmed APSNs were associated with malignant GTD, such as PSTT and ETT, either concurrently with the APSN diagnosis or subsequently. In this series, the interval between diagnosis of APSN and diagnosis of malignant GTD (2 cases) was 6–16 months. To date, it remains unclear whether the malignant lesions were concomitant to APSN, meaning that the specimen leading to the APSN diagnosis might represent a sub-diagnostic partial sampling of a more significant associated lesion or represent a subsequent malignant transformation of APSN to PSTT/ETT. Recent case report has supported the putative link between APSN and ETT/PSTT [63, 64].

Once the diagnosis of APSN has been made, hysteroscopic exploration together with pelvic imaging (US or MRI) is encouraged to exclude an underlying malignant lesion. Serum hCG does not appear to be a reliable marker for early detection of development of GTN in patients with APSN. When desire to retain fertility is not a concern, total hysterectomy with ovarian preservation is recommended due to the 10–15% rate of associated PSTT/ETT.

In case of fertility preservation and if an invasive lesion has been ruled out, close surveillance may be considered. However, data on APSN are limited and surveillance is thought due to lack of reliable tumor markers. Therefore, the optimal surveillance program remains to be defined. Nevertheless, hCG monitoring and pelvic imaging are advised.

According to the available data, hysterectomy should be proposed when the fertility desire has been fulfilled. Considering the limited data available, further studies are eagerly awaited to define natural history and the proper management of this entity.

Conclusion

ETT and PSTT are the rarest GTN entities. Clinicians should be aware of referring patients with these diagnoses to GTD referral centers for a proper management. APSN is a relatively new term, considered a pre-malignant lesion that could derive on ETT. Further studies are necessary for determining the proper management of APSN.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

Gloria Marquina, Grzegorz Szewczyk, and Frederic Goffin contributed to the conception and design of the review, drafting the article, and the final approval of the version to be submitted.

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References

1 Zhao J, Lv WG, Feng FZ, Wan XR, Liu JH, Yi XF, et al. Placental site trophoblastic tumor: a review of 108 cases and their implications for prognosis and treatment. Gynecol Oncol. 2016;142(1):102–8.
2 Liu W, Zhao W, Huang X. Outcomes and prognostic factors of placental-site trophoblastic tumor: a retrospective study of 58 cases. Arch Gynecol Obstet. 2022;306(5):1633–41.
3 Burkett WC, Soper JT. A review of current management of placental site trophoblastic tumor and epithelioid trophoblastic tumor. Obstet Gynecol Surv. 2022;77(2):101–10.
4 Kaur B. Pathology of gestational trophoblastic disease (GTD). Best Pract Res Clin Obstet Gynaecol. 2021;74:3–28.
5 Stichelbout M, Devisme L, Franquet-Ansart H, Massardier J, Vinatier D, Renaud F, et al. SALL4 expression in gestational trophoblastic tumors: a useful tool to distinguish choriocarcinoma from placental site trophoblastic tumor and epithelioid trophoblastic tumor. Hum Pathol. 2016;54:121–6.
6 Hancock BW, Tidy J. Placental site trophoblastic tumour and epithelioid trophoblastic tumour. Best Pract Res Clin Obstet Gynaecol. 2021;74:131–48.
7 van der Lely SJ, Boorsma J, Hilhorst M, Kers J, Roelofs J, Jakulj L, et al. "It's not lupus." A placental site trophoblastic tumor presenting as a lupus-like paraneoplastic syndrome. A grand round case. Lupus. 2021;30(3):495–501.
8 Brewer CA, Adelson MD, Elder RC. Erythrocytosis associated with a placental-site trophoblastic tumor. Obstet Gynecol. 1992;79(5(Pt 2):846–9.
9 Nagamani M, Kaspar HG, Van Dinh T, Hannigan EV, Smith E. Hyperthecosis of the ovaries in a woman with a placental site trophoblastic tumor. Obstet Gynecol. 1990;76(5):931–5.
10 Lan C, Li Y, He J, Liu J. Placental site trophoblastic tumor: lymphatic spread and possible target markers. Gynecol Oncol. 2010;116(3):430–7.
11 Baergen RN, Rutgers JL, Young RH, Osann K, Scully RE. Placental site trophoblastic tumor: a study of 55 cases and review of the literature emphasizing factors of prognostic significance. Gynecol Oncol. 2006;100(3):511–20.
12 Hassadia A, Gillespie A, Tidy J, Everard R G N J, Wells M, Coleman R, et al. Placental site trophoblastic tumour: clinical features and management. Gynecol Oncol. 2005;99(3):603–7.
13 Moutte A, Doret M, Hajri T, Peyron N, Chateau F, Massardier J, et al. Placental site and epithelioid trophoblastic tumours: diagnostic pitfalls. Gynecol Oncol. 2013;128(3):568–72.
14 Gadducci A, Carinelli S, Guerrieri ME, Aletti GD. Placental site trophoblastic tumor and epithelioid trophoblastic tumor: clinical and pathological features, prognostic variables, and treatment strategy. Gynecol Oncol. 2019;153(3):684–93.
15 Schmid P, Nagai Y, Agarwal R, Hancock B, Savage PM, Sebire NJ, et al. Prognostic markers and long-term outcome of placental-site trophoblastic tumours: a retrospective observational study. Lancet. 2009;374(9683):48–55.
16 Choi MC, Jung SG, Park H, Joo WD, Lee C, Lee JH, et al. Placental site trophoblastic tumors: analysis of the clinicopathologic characteristics of 20 cases in Korea. Int J Gynecol Cancer. 2016;26(8):1515–20.
17 Papadopoulos AJ, Foskett M, Seckl MJ, McNeish I, Paradinas FJ, Rees H, et al. Twenty-five years' clinical experience with placental site trophoblastic tumors. J Reprod Med. 2002;47(6):460–4.
18 Hyman DM, Bakios L, Gualtiere G, Carr C, Grisham RN, Makker V, et al. Placental site trophoblastic tumor: analysis of presentation, treatment, and outcome. Gynecol Oncol. 2013;129(1):58–62.
19 Lee HJ, Shin W, Jang YJ, Choi CH, Lee JW, Bae DS, et al. Clinical characteristics and outcomes of placental site trophoblastic tumor: experience of single institution in Korea. Obstet Gynecol Sci. 2018;61(3):319–27.
20 Chen Y, Zhang X, Xie X. Clinical features of 17 cases of placental site trophoblastic tumor. Int J Gynaecol Obstet. 2011;115(2):204–5.
21 Ngan HYS, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK, et al. Diagnosis and management of gestational trophoblastic disease: 2021 update. Int J Gynaecol Obstet. 2021;155(Suppl 1):86–93.
22 Yordanov A, Strateva D, Kostov S, Kornovski Y, Slavchev S, Ivanova Y, et al. Placental site trophoblastic tumour mimicking an intramural pregnancy: a case report and review of the literature. Prz Menopauzalny. 2022;21(2):142–7.
23 Khoiwal K, Gill P, Chawla L, Agrawal S, Chaturvedi J. Placental site trophoblastic tumor masquerading as post-molar uterine arteriovenous malformation. J Turk Ger Gynecol Assoc. 2022.
24 Zhao CF, Du ZQ, Li N, Wang Y, Zhao SF. CARE-Placental site trophoblastic tumor presenting with thrombotic microangiopathy: a case report. Medicine. 2018;97(43):e12698.
25 Patacchiola F, Di Stefano L, Di Febbo G, D'Alfonso A, Di Fonso A, Carta G. Placental site trophoblastic tumor on endometrial polyp: a case report. Eur J Gynaecol Oncol. 2014;35(1):87–90.
26 Gupta N, Mittal S, Misra R, Vimala N, Das AK. Placental site trophoblastic tumor originating in a tubal ectopic pregnancy. Eur J Obstet Gynecol Reprod Biol. 2006;129(1):92–4.
27 Sakhel K, Khalil A, Kaspar H, Azar G, Mansour A, Nassar A. Placental site trophoblastic tumor in a patient with secondary infertility and radiological findings consistent with a leiomyoma: a case report. Int J Gynecol Cancer. 2004;14(4):694–6.
28 Ichikawa Y, Nakauchi T, Sato T, Oki A, Tsunoda H, Yoshikawa H. Ultrasound diagnosis of uterine arteriovenous fistula associated with placental site trophoblastic tumor. Ultrasound Obstet Gynecol. 2003;21(6):606–8.
29 Shaaban AM, Rezvani M, Haroun RR, Kennedy AM, Elsayes KM, Olpin JD, et al. Gestational trophoblastic disease: clinical and imaging features. Radiographics. 2017;37(2):681–700.
30 Zhou Y, Lu H, Yu C, Tian Q, Lu W. Sonographic characteristics of placental site trophoblastic tumor. Ultrasound Obstet Gynecol. 2013;41(6):679–84.
31 Brandt KR, Coakley KJ. MR appearance of placental site trophoblastic tumor: a report of three cases. AJR Am J Roentgenol. 1998;170(2):485–7.

32 Feltmate CM, Genest DR, Wise L, Bernstein MR, Goldstein DP, Berkowitz RS. Placental site trophoblastic tumor: a 17-year experience at the New England Trophoblastic Disease Center. Gynecol Oncol. 2001;82(3):415–9.
33 Froeling FEM, Ramaswami R, Papanastasopoulos P, Kaur B, Sebire NJ, Short D, et al. Intensified therapies improve survival and identification of novel prognostic factors for placental-site and epithelioid trophoblastic tumours. Br J Cancer. 2019;120(6):587–94.
34 Ngu SF, Ngan HYS. Surgery including fertility-sparing treatment of GTD. Best Pract Res Clin Obstet Gynaecol. 2021;74:97–108.
35 Chiofalo B, Palmara V, Laganà AS, Triolo O, Vitale SG, Conway F, et al. Fertility sparing strategies in patients affected by placental site trophoblastic tumor. Curr Treat Options Oncol. 2017;18(10):58.
36 Porter A, Barcelon JM, Budker RL, Marsh L, Moriarty JM, Aguiar X, et al. Treatment of metastatic placental site trophoblastic tumor with surgery, chemotherapy, immunotherapy and coil embolization of multiple pulmonary arteriovenous fistulate. Gynecol Oncol Rep. 2021;36:100782.
37 Shih IM, Ronnett BM, Mazur M, Kurman. Gestational Trophoblastic Tumors and related tumorlike lesions. In: Kurman RJ, editor. Blaustein's pathology of the female genital tract. New York: Springer; 2002. p. 1307–76.
38 Shih IM, Kurman RJ. Epithelioid trophoblastic tumor: a neoplasm distinct from choriocarcinoma and placental site trophoblastic tumor simulating carcinoma. Am J Surg Pathol. 1998;22(11):1393–403.
39 Oldt RJ 3rd, Kurman RJ, Shih IM. Molecular genetic analysis of placental site trophoblastic tumors and epithelioid trophoblastic tumors confirms their trophoblastic origin. Am J Pathol. 2002;161(3):1033–7.
40 Shih IM. Gestational trophoblastic neoplasia: pathogenesis and potential therapeutic targets. Lancet Oncol. 2007;8(7):642–50.
41 Horowitz NS, Goldstein DP, Berkowitz RS. Placental site trophoblastic tumors and epithelioid trophoblastic tumors: biology, natural history, and treatment modalities. Gynecol Oncol. 2017;144(1):208–14.
42 Zhang X, Lü W, Lü B. Epithelioid trophoblastic tumor: an outcome-based literature review of 78 reported cases. Int J Gynecol Cancer. 2013;23(7):1334–8.
43 Davis MR, Howitt BE, Quade BJ, Crum CP, Horowitz NS, Goldstein DP, et al. Epithelioid trophoblastic tumor: a single institution case series at the New England Trophoblastic Disease Center. Gynecol Oncol. 2015;137(3):456–61.
44 Narita F, Takeuchi K, Hamana S, Ohbayashi C, Ayata M, Maruo T. Epithelioid trophoblastic tumor (ETT) initially interpreted as cervical cancer. Int J Gynecol Cancer. 2003;13(4):551–4.
45 Zhang X, Shi H, Chen X. Epithelioid trophoblastic tumor after induced abortion with previous broad choriocarcinoma: a case report and review of literature. Int J Clin Exp Pathol. 2014;7(11):8245–50.
46 Rodríguez-Trujillo A, Martínez-Serrano MJ, Saco A, Torné A. Two cases of epithelioid trophoblastic tumors in postmenopausal women. Menopause. 2017;24(11):1304–8.
47 Ohya A, Higuchi K, Shimojo H, Fujinaga Y, Kadoya M, Shiohara S. Epithelioid trophoblastic tumor of the uterus: a case report with radiologic-pathologic correlation. J Obstet Gynaecol Res. 2017;43(8):1360–5.
48 Tse KY, Chiu KWH, Chan KKL, Chu MMY, Ngu SF, Cheung ANY, et al. A case series of five patients with pure or mixed gestational epithelioid trophoblastic tumors and a literature review on mixed tumors. Am J Clin Pathol. 2018;150(4):318–32.
49 Lei W, Zhang F, Zheng C, Zhao C, Tu S, Bao Y. Metastatic epithelioid trophoblastic tumor of the lung: a case report. Medicine. 2018;97(16):e0306.
50 Scott EM, Smith AL, Desouki MM, Olawaiye AB. Epithelioid trophoblastic tumor: a case report and review of the literature. Case Rep Obstet Gynecol. 2012;2012:862472.
51 Qin J, Ying W, Cheng X, Wu X, Lu B, Liang Y, et al. A well-circumscribed border with peripheral Doppler signal in sonographic image distinguishes epithelioid trophoblastic tumor from other gestational trophoblastic neoplasms. PLoS One. 2014;9(11):e112618.
52 Palmer JE, Macdonald M, Wells M, Hancock BW, Tidy JA. Epithelioid trophoblastic tumor: a review of the literature. J Reprod Med. 2008;53(7):465–75.
53 Frijstein MM, Lok CAR, van Trommel NE, Ten Kate-Booij MJ, Massuger LFAG, van Werkhoven E, et al. Management and prognostic factors of epithelioid trophoblastic tumors: results from the international society for the study of trophoblastic diseases database. Gynecol Oncol. 2019;152(2):361–7.
54 Shen X, Xiang Y, Guo L, Ren T, Feng F, Wan X, et al. Analysis of clinicopathologic prognostic factors in 9 patients with epithelioid trophoblastic tumor. Int J Gynecol Cancer. 2011;21(6):1124–30.
55 Ghorani E, Kaur B, Fisher RA, Short D, Joneborg U, Carlson JW, et al. Pembrolizumab is effective for drug-resistant gestational trophoblastic neoplasia. Lancet. 2017;390(10110):2343–5.
56 Choi MC, Oh J, Lee C. Effective anti-programmed cell death 1 treatment for chemoresistant gestational trophoblastic neoplasia. Eur J Cancer. 2019;121:94–7.
57 Pisani D, Calleja-Agius J, Di Fiore R, O'Leary JJ, Beirne JP, O'Toole SA, et al. Epithelioid trophoblastic tumour: a case with genetic linkage to a child born over seventeen years prior, successfully treated with surgery and pembrolizumab. Curr Oncol. 2021;28(6):5346–55.
58 Bell SG, Uppal S, Sakala MD, Sciallis AP, Rolston A. An extrauterine extensively metastatic epithelioid trophoblastic tumor responsive to pembrolizumab. Gynecol Oncol Rep. 2021;37:100819.
59 Mangili G, Sabetta G, Cioffi R, Rabaiotti E, Candotti G, Pella F, et al. Current evidence on immunotherapy for gestational trophoblastic neoplasia (GTN). Cancers. 2022;14(11):2782.
60 Kaur B, Short D, Fisher RA, Savage PM, Seckl MJ, Sebire NJ. Atypical placental site nodule (APSN) and association with malignant gestational trophoblastic disease; a clinicopathologic study of 21 cases. Int J Gynecol Pathol. 2015;34(2):152–8.
61 International Agency for Research on Cancer. WHO classification of female genital tumours. 5th ed. Iarc:France: WHO 2020; 2020; p. 309e22.
62 Shih IM, Kurman RJ. The pathology of intermediate trophoblastic tumors and tumor-like lesions. Int J Gynecol Pathol. 2001;20(1):31–47.
63 Dholakia J, Chen W, O'Malley DM, Ronnett BM. A rare case of atypical placental site nodule with an emerging intermediate trophoblastic tumor. Int J Gynecol Pathol. 2020;39(3):238–46.
64 Aiob A, Cohen HI, Naskovica K, Tendler R, Sharon A, Bornstein J. Coexisting epithelioid trophoblastic tumor and placental site trophoblastic tumor during asymptomatic relapse: a case report and literature review. Int J Gynecol Pathol. 2022;41(4):423–30.