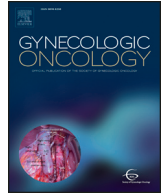




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Review Article

Placental site trophoblastic tumors and epithelioid trophoblastic tumors: Biology, natural history, and treatment modalities

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HIGHLIGHTS

- PSTT and ETT are rare types of GTN that arise from intermediate trophoblast.
- Time from antecedent pregnancy >4 years and advanced stage are poor prognostic factors.
- Hysterectomy is the primary treatment for stage I disease.
- Stage I disease with high-risk features and all advanced stage disease require chemotherapy.
- EMA-EP and TP/TE are the chemotherapy regimens recommended for treatment of PSTT and ETT.

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ABSTRACT

Placental site (PSTT) and epithelioid trophoblastic tumor (ETT) are rare types of gestational trophoblastic neoplasia (GTN) that arise from intermediate trophoblast. Given that this cell of origin is different from other forms of GTN, it is not surprising that the clinical presentation, tumor marker profile, and treatment paradigm for PSTT and ETT are quite different as well. The mainstay for therapy for stage I PSTT and ETT is hysterectomy with adjuvant chemotherapy reserved for those presenting greater than four years from the antecedent pregnancy. Surgery is also important for metastatic disease. There is no standardized chemotherapy regimen for advanced stage disease but often consists of a platinum-containing combination therapy, usually EMA-EP or TE/TP. Despite its rarity, PSTT and ETT account for a disproportionate percentage of mortality from GTN likely resulting from their relative chemotherapy resistance. Novel therapeutic modalities therefore are needed to improve the outcomes of women with advanced stage or resistant PSTT and ETT.

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1. Introduction

Gestational trophoblastic neoplasia (GTN) is a group of malignant lesions that arise from placental villous and extravillous trophoblasts. GTN can arise after both molar and non-molar pregnancy events and are comprised of 4 distinct histologic subtypes; invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT). While invasive mole and choriocarcinoma comprise the majority of GTN cases, PSTT and ETT are rare but important forms of GTN with unique pathology, natural history, and treatment paradigms [1–4]. Given the rarity of PSTT and ETT, our knowledge about these histologies has been based generally on case reports and small, single institution case series. However, there have been two, relatively large series from the United Kingdom and China which have further advanced our understanding [5,6] (Table 1). Ultimately the limitations of small sample size will be overcome when data from the International Society for the Study of Trophoblastic Disease Placental Site and Epithelioid Trophoblastic Tumor Database (<http://pstt.shef.ac.uk/>) mature. Until then, the goal of this review will be to summarize the existing data regarding the epidemiology, pathology, presentation, evaluation, and treatment of PSTT and ETT and provide a framework for future investigations into these diseases.

2. Historical perspective

Both PSTT and ETT are relatively newly recognized disease entities. In 1976 Kurman, Scully, and Norris presented a series of 12 cases

describing a lesion, previously not well characterized, as “trophoblastic pseudotumor of the uterus” [7]. Previous reports of similar lesions described them as an unusual type of sarcoma associated with pregnancy. In that initial series all but 1 patient was alive and well so it was thought to be a benign neoplasm. After a report by Twiggs et al. [8] revealed its malignant behavior, it was renamed “placental site trophoblastic tumor” by Scully and Young who confirmed its malignant potential in an updated review [9]. Approximately 20 years later, in 1998, ETT was described by Shih and Kurman [10]. Although having the same cell of origin, intermediate trophoblast, ETT was distinct from PSTT and had morphologic features similar to squamous cell carcinoma making the diagnosis more challenging [10]. Since their initial descriptions, cumulatively the world’s literature consists of reports on <500 cases of PSTT and approximately 110 cases of ETT.

3. Pathology

Trophoblastic stem cells develop along two lines of differentiation, villous and extravillous. Molar pregnancies and choriocarcinoma are derived from villous trophoblasts which are composed mostly of cytotrophoblast (CT) and syncytiotrophoblast (ST). PSTT and ETT are derived from extra villous trophoblast and are composed almost exclusively of intermediate trophoblast [11]. PSTT arises from intermediate trophoblast and has a growth pattern of invasion similar to that of normal intermediate trophoblast. In contrast, ETT develops from chorionic-type intermediate trophoblast present in other parts of the placenta (i.e. chorionic plate, fetal membranes, cell islands, etc.) [12,

Table 1
Summary of the largest published series on PSTT.

Authors (Reference)	Pts	Reported risk factors	hCG (median)	Chemotherapy regimens	Survival
Zhao et al. [6]	108	Stage* Time from AP (>36 mo)	154 IU/L	FAV FAEV EMA-CO	Stage I 94% Stage III/IV 88%
Schmid et al. [5]	62	Prognostic score Necrosis Deep invasion (>50%) Time from AP (>48 mo)*	<1000 IU/L	EMA-CO EMA-EP MAE	Stage I 93% Stage III/IV 49%
Baergen et al. [22]	55	Mitotic index Stage FIGO score hCG Age Number of mets Age (>35 yo)* FIGO Stage (III/IV)* Clear cytoplasm* Time from AP (>24 mo) Deep invasion (>33%) Mitotic rate Term AP	691 IU/L	ICE EMA-CO	Stage I 92% Stage III/IV 0%
Hyman et al. [21]	17	hCG FIGO Stage Time from AP (>12 mo) Term AP hCG	132 IU/L	EMA-EP EMA-CO BEP	Stage I 88% Stage III/IV 55%
Moutte et al. [30]	15	Age (>40 yo) NR	205 IU/L	MTX BEP	NR
Bonazzi et al. [55]	15	NR	110 IU/L	EMA-CO	Stage I 94% Stage III 100%
Feltmate et al. [23]	13	Mitotic index Tumor volume (>1 cm ³)	<500 IU/L	MAC EMA EMA-CO EMA-EP	NR

FAV – floxuridine, actinomycin-D, vincristine; FAEV – floxuridine, actinomycin-D, etoposide, vincristine; EMA-CO – etoposide, methotrexate, actinomycin-D, cyclophosphamide, vincristine; EMA-EP – etoposide, methotrexate, actinomycin-D, cisplatin; BEP – bleomycin, etoposide, cisplatin; ICE – ifosfamide, carboplatin, etoposide; MTX – methotrexate; MAC – methotrexate, actinomycin-D, cyclophosphamide; MAE – methotrexate, actinomycin-D, etoposide.

Pts = patients; hCG = human chorionic gonadotropin; AP = antecedent pregnancy; NR = not reported; mo = month; FIGO = International Federation of Gynecology and Obstetrics; yo = years old.

* Statistically significant risk factor ($p < 0.05$) on multivariate analysis.

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