20
PLACENTAL SITE AND EPITHELIOID TROPHOBLASTIC TUMOURS

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(Original chapter by Alan M Gillespie)

20.1 BACKGROUND

Placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT) are the rarest subtypes of GTD and are relatively chemoresistant compared to invasive mole and gestational choriocarcinoma. PSTTs accounted for 0.17% of GTD cases referred to specialist treatment centres in the United Kingdom [1]. Several, mostly small, case series have been reported internationally - the incidence in these series has varied from <1% to 7% of all GTN patients.

PSTTs and ETTs can occur months to years after the index pregnancy event and may develop after any type of antecedent pregnancy [1,2,5-7]. Typically, patients are premenopausal and present with localised uterine disease after term pregnancy [5,6,8]. However, ETTs can present with primary disease in the cervix (31%) and/or at extrauterine sites, most commonly in the lung (19%)[5]. Furthermore, there have been reports of extrauterine disease in the broad ligament, small bowel, gall bladder, ovary and vagina [3,9-12].

PSTT and ETT are generally slow growing tumours that can metastasise months or years after the initial primary has developed. At diagnosis, metastases were found in 16-54% of cases with PSTT and 25-35% of cases with ETT [1,2,5-7, 13]. The most common site of distant metastases for both PSTT and ETT is the lungs; other reported metastatic sites for PSTT include the liver, bowel, local and distant lymph nodes, vagina, brain, kidney and spleen [1,5]. Lymphatic spread can occur in both PSTT and ETT. 17 of 286 (5.9%) patients with PSTT were reported to have lymph node metastases in one literature review, with pelvic (5) and para aortic (7) lymph nodes most frequently affected [14].

Over the last few decades the establishment of National and Regional Centres for screening and treatment of trophoblastic diseases has led to the centralisation of care and development of expertise in the management of most forms of GTD. However, PSTT and ETT are so rare that even those centres treating large numbers of patients with GTD will infrequently manage patients with this condition. Therefore, these tumours present a challenge to clinicians managing GTD due to their rarity and varied biological behaviour. Currently, there is no consensus on optimal treatment strategies.

In fact few large series describing the clinical experience of a single group of investigators with the diagnosis and treatment of these

tumours have been reported. In the entire UK experience a total of 62 cases were evaluated [1]. Other smaller series have also been published (Table 20.1). Baergan et al [4] reported 55 cases and reviewed the literature emphasising factors of prognostic significance.

As a clinical and pathological entity PSTT was first described in 1976 [15] when the term 'trophoblastic pseudotumour' was adopted to characterise a tumour that followed a benign clinical course. In the following years it was shown that the cases in the original report were not fully representative of the entire disease spectrum and that this tumour did in fact have a malignant potential [16]. The current nomenclature was proposed in 1981 [17] in response to this new understanding of the tumour's biological behaviour. ETT was initially described as a rare variant of PSTT. However, since the mid-1990s this has been recognised as a separate disorder[2]. Over 100 cases of ETT are described in the literature compared to over 300 cases for PSTT. It is critical to make the distinction between these and other more common forms of GTN as they are less chemo-sensitive and adverse outcomes are more common.

Both PSTT and ETT have been described as developing following a normal pregnancy, abortion or molar pregnancy. Confirmation that PSTT can arise following molar or non-molar conceptions is provided by genetic analysis [18]. There is some data to suggest that not only is a female conception a common antecedent pregnancy [19] but also an independent poor prognostic variable [20]. These findings have not been confirmed by other investigators. Human chorionic gondotrophin – free beta-subunit may prove to be useful in the diagnosis of PSTT [21].

20.2 PATHOLOGY (see also chapter 4)

Histologically PSTT arises from the intermediate trophoblastic cell population and has a pattern of invasion similar to that of the normal intermediate trophoblast. Typically a poorly circumscribed mass infiltrates between muscle fibres and along vessel walls at the site of implantation. In comparison, ETT develops from chorionic type intermediate trophoblastic cells to form nests or solid masses in a nodular pattern. PSTT and ETT are two of four trophoblastic lesions that may arise from the intermediate trophoblast – the others being the exaggerated placental site and placental site nodule (PSN). The latter whether typical or atypical may be found mixed with PSTT/ETT and there is now literature to suggested that up to 15% of atypical PSN may be associated with PSTT/ETT [22].This suggests that APSN and possibly PSN cannot be regarded as completely benign lesions and close surveillance of such patients might be warranted.

Both gynecologists and pathologists should be alert to the potential misdiagnosis of squamous cell carcinoma when ETT is present in the lower uterus/cervix. The distinction between these entities can be made through comparative genetic analysis using microsatellite polymorphisms. A genuine ETT will contain paternally derived genes from the patient's partner whilst cervical carcinoma will only have

genetic material from the patient herself.

20.3 CLINICAL AND PROGNOSTIC FEATURES (Table 20.1)

The interval between antecedent pregnancy and the clinical presentation and subsequent diagnosis of PSTT/ETT is variable. A number of reports suggest that a prolonged interval between the antecedent pregnancy and the development of a PSTT is a poor prognostic feature The most common presenting feature of PSTT and ETT reported by a number of authors is that of irregular bleeding per vaginum sometimes following amenorrhoea.

It would be tempting but incorrect to interpret this as evidence of a biologically indolent tumour; however, a significant number of patients present with tumour beyond the genital tract at the time of diagnosis and a wide range of other presenting symptoms have been reported with PSTT including galactorrhoea, virilization [23] nephrotic syndrome [24], polycythaemia [25] and cutaneous metastases [26]. Moreover, the primary site either within the uterus or an ectopic pregnancy may no longer be present.

Also, clinical and pathological diagnosis can be difficult – for PSTT incorrect diagnosis may be made in a third of patients [27]. It can therefore make interpretation of studies quite difficult especially where there has not been centralised pathological review and/or genetics to confirm the gestational nature of the tumour.

Table 20.2 Some clinical features of PSTT

Authors	Number of Patients	Metastases at presentation	Unfavourable prognostic markers	Survivors
Feltmate et al [2001] [6]	13	33%	↑Mitotic index	62%

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Kim [2003] [28]	9	0%	AP >2y Stage III/IV	89%
Hoekstra et al [2004] [29]	7	43%	Stage >2 Mitotic count >2	57%
Bonazzi et al [2004] [30]	15	7%	> time since AP	93%
Baergen et al [2006] [5]	55	14%	Stage IV Clear cytoplasm	87%
Piura et al [2007] [9]	4	25%	> Stage II > time since AP	75%
Schmid et al [2009] [1]	62	34%	AP >4y	77%
Lan et al [2010] [14]	5	20%	Lymph node +ve	60%
Chen et al [2011] [31]	17	12%	_	100%
Hyman et al [2013] [13]	17	53%	Stage IV	65%
Moutte et al [2013] [27]	15*	13%	Stage IV AP >4y	100%
Van Trommel et al [2013] [32]	13	8%	_	100%

AP, antecedent pregnancy; * includes ETTs

PSTT characteristically show a high proportion of cells positive for human placental lactogen (hPL) on immunohistochemical staining with a relatively small proportion of the tumour cell population staining positive for human chorionic gonadotrophin (hCG). This staining pattern reflects the cellular origin of this tumour type – intermediate trophoblast cells produce large quantities of hPL and little hCG. It should however be noted that in some PSTT more of the cells stain for hCG than hPL [33,34]. Another immunohistochemical marker evaluated in

the assessment of PSTT is pregnancy associated major basic protein (pMBP). This protein is a marker for intermediate trophoblast and has been shown to stain positively for cells in a high proportion of exaggerated placental sites and PSTTs [35].

It is unfortunate that mitotic counts are inconsistent histological predictors of the biological behaviour of PSTTs. In our original series those patients with poor outcomes had tumours with high mitotic counts (a finding also reported by Feltmate and colleagues [6]) – but tumours with low mitotic counts also demonstrated the ability to metastasise. Others have shown that sampling variability within this tumour makes biopsy specimens unreliable in predicting tumour behaviour [36,37].

Baergen et al [4] retrospectively examined 55 patients from their pathology files (together with 180 cases from the literature) and analysed the effect of pathological and clinical features on survival. From their own patients, significant adverse factors were age >35 years, interval since last pregnancy of over 2 years, deep myometrial invasion, stage III or IV, maximum hCG level >1,000iu/L, extensive coagulative necrosis, high mitotic rate, and the presence of cells with clear cytoplasm. Only stage and clear cytoplasm were independent predictors of overall survival while stage and age were the independent predictors of time to recurrence or disease free survival. From the literature stage, interval from preceding pregnancy >2 years, previous term pregnancy, high mitotic rate and high hCG level were associated with worse survival.

In the UK clinical series of 62 patients [1] whilst several factors appeared significant on univariate analysis, multivariate analysis revealed that only disease onset >4 years from the causative/last known pregnancy was strongly prognostic of poor outcome. Indeed, all 13 patients presenting more than 4 yrs from their last known pregnancy eventually died even if their disease initially appeared localised to the uterus. In contrast, 48 of 49 patients (98%) became long-term survivors if they presented within 4 yrs and many had metastatic disease. This suggests that there is some sort of biological switch that may occur in those tumours presenting more than 4 years out. If the data were re-assessed excluding the time interval from the last known pregnancy then multivariate analysis was also able to show the potential importance of FIGO stage, number and site of metastasis, hCG level and mitotic index. We recognised from this work that more cases would be needed to help refine prognostic variables and improve management outcomes. Therefore, an international relational database has been established under the auspices of the International Society for the Study of Trophoblastic Diseases. A preliminary analysis of 210 patients from six countries, including 173 PSTTs, 17 ETTs and 15 mixed tumours (most often PSTT/choriocarcinoma), presented at the XVIIth ISSTD World Congress in 2013, confirmed many of the adverse prognostic factors reported from case series and that lympho-vascular invasion and/or spread outside the uterus were very unfavourable features. Overall mortality was 13%, being best (4%) for those who had surgery alone for Stage I disease and worst (33%) for those patients, with advanced disease, who were only suitable for chemotherapy. The multivariate analysis of the data, on 326 patients, was presented at the XVIIIth

ISSTD Congress in 2015. Stage VI disease and more the 4 years since the antecedent pregnancy were statistically significantly unfavourable factors. Data collection and follow-up will continue.

20.3 INVESTIGATION

Conventional FIGO scoring criteria for gestational trophoblastic neoplasia do not correlate well with outcome in PSTT/ETT. HCG is the tumour marker of choice in evaluating follow-up and treatment of patients with trophoblastic tumours and choriocarcinoma. In these tumours hCG correlates well with tumour bulk and persistence of disease – hCG evaluation is therefore integral to treatment protocols and management strategies. Unfortunately hCG, although it may be helpful in diagnosis, is not an accurate marker of PSTT/ETT disease activity. As with immunohistochemical staining this is a reflection of the intermediate trophoblast cell population from which they originate – this cell type produces little hCG but large quantities of hPL. This ability of the intermediate trophoblast cell population to produce hPL does not however mean that hPL is a useful tumour marker for PSTT. In our experience [19], and anecdotally that of others, serum hPL levels were not useful markers of disease activity and did not assist in guiding treatment decisions. Part of the problem with hPL may reside in those assays, used to measure this marker, which are not sufficiently sensitive or reproducible.

Imaging of PSTT/ETT is an inexact science. Investigators have reported on both the ultrasonographic [38,39] and magnetic resonance [40] imaging findings in this tumour. The findings are non-specific. Even with increasing sophistication of imaging technologies, given the rarity of these tumours it is unlikely that at any institution enough expertise will be gathered to characterise these tumours with pre-operative imaging investigations. In the UK our standard practice is to perform MRI head and pelvis, a CT chest and abdomen all with contrast and to do a Doppler ultrasound of the pelvis. We have noticed that the information derived from ultrasound and MRI may be non-overlapping and complementary. The value of FDG-PET in initial staging is unclear and we currently reserve this for selected cases where we are unsure about the significance of lesions seen on other imaging modalities or where we are trying to decide which lesion(s) to resect. Given the unreliability of hCG monitoring, it is realistic to expect that imaging will be a useful tool for monitoring treatment and subsequent surveillance of patients with histologically proven PSTT/ETT.

20.4 TREATMENT

The biological behaviour of PSTT/ETT is highly variable and difficult to predict using currently available strategies. The first diagnostic and therapeutic intervention is usually surgical. A variety of surgical approaches to the patient have been suggested. Conservative surgical

management has been suggested by those who have demonstrated PSTT regression after uterine curettage [16] or localised tumour excision at hysterotomy [41]. However it could be argued that this management should only be advocated in women who wish to retain their childbearing capacity. For other women with tumour confined to the uterus a hysterectomy (with or without oophorectomy based on a risk /benefit analysis depending on the patient's age and family history of ovarian/breast cancer) is a more appropriate surgical procedure for a tumour with unpredictable behaviour. Hysterectomy alone may be a curative procedure for women with PSTT located only in the uterus at the time of presentation. This especially seems to be the case, if the disease is diagnosed within 4 years of the last known and/or causative pregnancy.

Women with metastatic PSTT/ETT at the time of diagnosis cannot be cured by surgery alone and treatment with multi-agent systemic chemotherapy is required. Initially there were fears that PSTT was unresponsive to chemotherapy. However there have now been a number of reports demonstrating success of various different multi-agent chemotherapeutic regimens in treating metastatic – particularly pulmonary metastases – PSTT [1,42-46]. The therapeutic regimens used with most success are detailed in Table 20.2. Increasing experience with metastatic ETT suggests that this tumour may be relatively more chemo-resistant.

The pharmacotherapy of PSTT/ETT has recently been reviewed [47]. Radiation therapy has been used to good effect in the palliative setting [20,33], though the tumour response is inconsistent [19].

Unlike other forms of GTN, surgical resection should be considered for residual localised disease after apparently successful chemotherapy. Whilst many cases will only have dead/necrotic tumour present the concern about chemo efficacy has driven this clinical practice. Moreover, like other GTN, once the disease is refractory or relapsed, and is located in an accessible area, surgery may still be curative.

Gathering experience would suggest that metastatic ETT should be treated in a similar manner to PSTT.

Table 20.2 Metastatic PSTT chemotherapy regimens

Chemotherapy regimens used successfully in PSTT		Reference
EP-EMA	etoposide/cisplatin alternating with etoposide, methotrexate and dactinomycin (Actinomycin D)	[44]
EMA-CO	etoposide, methotrexate, dactinomycin alternating with cyclophosphamide and vincristine (Oncovin)	[42]
M-EA	methotrexate alternating with etoposide and dactinomycin	[19]
TP/TE	paclitaxel and cisplatin alternating with paclitaxel and etoposide	[48]

In patients with disease refractory to EP/EMA or TP/TE, the use of high dose chemotherapy is advocated, followed by stem cell transplantation, in patients with PSTT that are chemo responsive, though reports for the benefit of high dose chemotherapy and autologous stem cell transplant (HDSCT) are sparse [49]

The question arises with regards to how one should treat patients whose disease presents more than 4 years from the last known pregnancy. In the UK, given our findings of an extremely poor outcome even in patients whose disease appeared localised to the uterus we have abandoned surveillance or limited adjuvant chemotherapy. Instead, we now offer such Stage I patients EP/EMA for 8-12 weeks according to tolerability and then progress to stem cell mobilisation followed by tandem high dose chemotherapy with autologous stem cell transplant support. We have several cases managed in this new way who are currently in remission. Whilst this may be promising, until follow-up is sufficient, the value of this approach must be viewed cautiously.

20.5 PROGNOSIS

PSTT and ETT differ from other forms of GTN because serum hCG levels and FIGO/WHO scores [50] are not reliable prognostic indicators. Both subtypes typically secrete low levels of serum hCG (<1000 IU/L), which are not indicative of disease burden [6,7,13]. Nonetheless, a rise or plateau of serum hCG is still a marker of refractory or relapsed disease and serum/urine hCGs are monitored in follow up [6,7].

In the UK, there are two tertiary referral and treatment centres for GTD leading to expertise in management as well as accurate long term follow up data. These UK centres reported the outcomes of 62 patients with PSTT, which is the largest retrospective case series to date [1]. The 10-year survival was 90% (range 77-100%) for patients with stage I disease treated with surgery alone. In contrast,

the 10 year survival rates were 52% for patients with stage II and 49% for patients with stage III or IV who were treated with surgery and chemotherapy. In comparison, the overall survival for 196 patients with other types of high risk GTN at the UK centres was 94% with a median follow up of nearly 5 years [51].

Twelve of 56 (21%) patients with PSTT developed recurrence less than 5 years from diagnosis with a median interval of 13 months. Outcomes for patients with relapsed disease were poor with only 33% achieving long-term remission [1]. In comparison, 19 of 62 (30%) patients with ETT had relapse or metastases with a median follow up of 22 months (range 1-192 months) [3] However, the true figure is likely to be smaller because the numbers of patients that relapsed after hCG normalisation were not reported in this review.

In a worldwide survey of physicians known to treat GTN, the death rate for PSTT was higher than for other subtypes of GTN: 16.1% for PSTT compared to 6.5% for postmolar GTN and 13.4% for choriocarcinoma [52] .The death rates for ETT have been reported to be 13% with follow up ranging from 1-39 months [5] Another literature review, reported the death rate to be 24% (15 of 62 patients) with a median follow up time of 22 months (range 1-192 months) [3]. The authors in this study acknowledged the problem of reporting bias as 28 of 78 cases were from individual case reports. In Sheffield UK, multi-drug resistant PSTT is the single most important cause of disease-related death in GTN [53].

20.5 SUMMARY AND CONCLUSIONS

PSTT/ETT are rare forms of GTD with unpredictable biological behaviour. These tumours must be considered potentially curable – though prognosis is worse than with other forms of GTD. Clinically the diagnosis should be suspected when the hCG tumour marker levels are low relative to the tumour burden. Surgery has a crucial role with localised disease, but is useful in all stages. Hysterectomy is curative in early stage disease, though the role of neo adjuvant or adjuvant chemotherapy is unclear. Fertility conserving surgery should only be contemplated in exceptional cases. Metastasectomy may be considered for isolated distant disease. Chemotherapy (with or without surgery) is indicated in advanced disease. Due to the rarity of these conditions, no randomized controlled trials have been (nor are likely to be) done. A variety of combination regimens have been used and patients may require multiple lines of treatment including high dose chemotherapy. EMA/CO, EP/EMA, TP/TE are reported as efficacious first line regimens, but the consensus is that cisplatin containing regimens are best.

Based on data presented at the VIIIth ISSTD Congress (2015) a reasonable initial approach would be the following stage-adapted therapy:

1) Stage 1 with no adverse other factors – surgery alone
2) Stage 1 with adverse factors – surgery with adjuvant chemotherapy

3) All others – intensive chemotherapy with or without surgery.

All patients with PSTT or ETT should be managed at a centre with specialised histopathology and clinical expertise, since the recognition and separation of PSTT and ETT from other forms of GTN, and non-trophoblastic neoplasms, is essential to their effective management. International collaboration is vital to enhance understanding of treatment related outcomes in order to define optimal management and improve patient morbidity and mortality.

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