16
PLACENTAL SITE TROPHOBLASTIC TUMOUR

Alan M. Gillespie and Barry W. Hancock

16.1 Background

Placental site trophoblastic tumour (PSTT) is an uncommon form of gestational trophoblastic disease (GTD). 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 is so rare that even those centres treating large numbers of patients with GTD will infrequently manage patients with this condition. PSTT presents a challenge to clinicians managing GTD due to its rarity and varied biological behaviour – there is no consensus on optimal treatment strategies.

In fact few large series describing the experience of a single group of investigators with the diagnosis and treatment of these tumours have been reported with the exception of recent studies from the Trophoblastic Disease Centres at Charing Cross Hospital - 17 patients (recently updated to 34 [1]), New England [2] - 13 patients and Sheffield [3] - 7, updated to 15 in this chapter (Table 16.1).

As a clinical and pathological entity PSTT was first described in 1976 [4] 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 [5]. The current nomenclature was proposed in 1981 [6] in response to this new understanding of the tumour's biological behaviour. It is critical to make the distinction between this and other more common forms of GTD, as the PSTT is less chemo-sensitive and adverse outcomes are more common.

PSTT has been described 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 [7]. There is some data to suggest that not only is a female conception a common antecedent pregnancy [3] but also an independent poor prognostic variable [8]. These findings have not been confirmed by other investigators.

Table 16.1 Features of patients with PSTT managed in sheffield

Patient reference	Age (years)	Antecedent pregnancy (AP)	Interval to AP (months)	Presenting features	Presenting hCG iul^{-1}	Metastases (no.)	Metastases (sites)	Treatment	Outcome	Follow-up (years)
1	37	Female FTND	30	Amenorrhoea	10	0	-	TAH	AW NED	10
2	26	Female twins	14	Ruptured uterus	6	0	-	TAH	AW NED	11
3	38	Female ND	12	IBPV	314	1	Vagina	TAH,RT, MTX,etoposide, surgery,MAE,MTX	DOD	20
4	43	Female FTND	156	IBPV	107,600	Multiple	Lungs,vagina liver,brain	D/C,MAE,CEC, ITMTX, cranial RT	DOD	2
5	34	Female FTND	132	Amenorrhoea	2,525	Multiple	Lungs	D/C, MAE, TAH BSO	AW NED	7
6	52	None known	-	Amenorrhoea	107	0	-	TAH BSO	AW NED	4
7	27	Male FTND	18	IBPV	1,575	Multiple	Lungs	D/C x2, MTX, CEC	AW NED	4
8	52	Female FTND	264	Post-menopausal bleed	56,766	Multiple	Lungs	MEA, EP/EMA, TAH, CT, HDC, MTX	DOD	3
9	50	Male FTND	132	Enlarged neck node	45,690	Multiple	Lungs,liver, kidneys, pancreas	EP/EMA, CT, MICE, spinal RT,MTX	DOD	12
10	35	Miscarriage	6	Ruptured uterus	74	0	-	TAH	AW NED	4
11	24	Miscarriage	6	Amenorrhoea, IBPV	7,561	0	-	MTX	AW NED	3
12	38	Female FTND	18	Abdominal pain, IBPV	68	0	-	MTX TAH	AW NED	3
13	30	Female FTND	6	IBPV	36,819	Multiple	Lungs	MAE	AW NED	0.5
14	23	Female FTND	18	IBPV	34	0	-	TAH	AW NED	0.5
15	27	Male FTND	18	IBPV	1,575	0	-	MTX CEC	AW NED	9

AP, Antecedent pregnancy; AW, Alive and well; BSO, Bilateral salpingo-oopherectomy; CEC, Cyclophosphamide/etoposide/cisplatin; CNS, Central nervous system; CT, Carboplatin/Taxol; D/C, Dilatation and curettage; DOD, Died of disease; EP/EMA, Etoposide, cisplatin/etoposide, methotrexate, dactinomycin; FTND, Full-term normal delivery; hCG, Human chorionic gonadotrophin; HDC, High dose chemotherapy; hpf, High power field; hPL, Human placental lactogen; IBPV, Irregular bleeding per vaginum; IT, Intrathecal; MAE, Methotrexate/dactinomycin/etoposide; MICE, Methotrexate, ifosfamide, cisplatin, etoposide; MTX, Methotrexate; ND, Normal delivery; NED, No evidence of disease; RT, Radiotherapy; TAH, Total abdominal hysterectomy.

16.2 Clinical features (Table 16.2)

The interval between antecedent pregnancy and the clinical presentation and subsequent diagnosis of PSTT 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 [1,9,10,11]. The most common presenting feature of PSTT reported by a number of authors is that of irregular bleeding per vaginum sometimes following a time period of amenorrhoea [3,8,11].

Table 16.2 Some clinical features of PSTT

Authors	Number of Patients	Metastases at presentation	Favourable prognostic markers	Survivors
Feltmate et al [3]	13	4 (33%)	↓ Mitotic index	27 (62%)
Papadopoulos et al [1]	34	19 (56%)	AP < 4y No metastases	8 (79%)
Gillespie and Hancock [vide infra]	15	7 (47%)	Short time since AP No metastases	11 (73%)
All patients	62	30 (48%)	Localised disease	46 (74%)

AP, Antecedent pregnancy

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 including galactorrhoea, virilization [12], nephrotic syndrome [11,13], polycythaemia [14] and cutaneous metastases [15].

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. PSTT is one of four trophoblastic lesions that may arise from the intermediate trophoblast – the others being the exaggerated placental site, placental site nodule and epithelioid trophoblastic tumour [16] (see also chapter 4).

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 [11,17]. 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 PSTT [18].

It is unfortunate that mitotic counts are poor histological predictors of PSTT biological behaviour. In our original series those patients with poor outcomes had tumours with high mitotic counts (a finding also reported by Feltmate and colleagues [2]) – but tumours with low mitotic counts also demonstrated the ability to metastasise [3]. Others have shown that sampling variability within this tumour makes biopsy specimens unreliable in predicting tumour behaviour [9,19,20].

16.3 Investigation

Conventional scanning and staging criteria for gestaional trophoblastic neoplasia do not correlate with outcome in PSTT as its behaviour is variable. 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 disease activity. As with immunohistochemical staining this is a reflection of the intermediate trophoblast cell population from which the PSTT originates – 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 [3] and anecdotally that of others serum hPL levels were not useful markers of disease activity and did not assist in guiding treatment decisions.

Imaging of PSTT is an inexact science. Investigators have reported on both the ultrasonographic [21,22] and magnetic resonance [23] imaging findings in this tumour. The findings are non-specific. Given the rarity of PSTT it is unlikely that at any institution enough expertise will be gathered to characterise these tumours with pre-operative imaging investigations. It is however realistic to expect that at Treatment Centres imaging will be a useful tool for monitoring treatment of patients with histologically proven PSTT.

16.4 Treatment

The biological behaviour of PSTT 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 with a PSTT have been suggested. Conservative surgical management has been recommended by those who have demonstrated PSTT regression after uterine curettage [4,24] or localised tumour excision at hysterotomy. 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) is a more appropriate surgical procedure for a tumour with unpredictable behaviour. Hysterectomy may be a curative procedure for women with PSTT located only in the uterus at the time of presentation.

Women with metastatic PSTT 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 [20]. However more recently there have been a number of reports demonstrating success of various different multi-agent chemotherapeutic regimens in treating metastatic – particularly pulmonary metastases – PSTT [3,25,26,27,28,29]. The therapeutic regimens used with most success are detailed in Table 16.3. Radiation therapy has been used to good effect in the palliative setting [9,11,30], though the tumour response is inconsistent [3].

Table 16.3 Metastatic PSTT chemotherapy regimens

Chemotherapy regimens used successfully in PSTT		Reference
EP-EMA	etoposide/cisplatin alternating with etoposide, methotrexate and dactinomycin (Actinomycin D)	[27]
EMA-CO	etoposide, methotrexate, dactinomycin alternating with cyclophosphamide and vincristine (Oncovin)	[25]
M-EA	methotrexate alternating with etoposide and dactinomycin	[3]
CEC	cyclophosphamide, etoposide and cisplatin	[3]

16.5 Conclusion

PSTT is a rare form of GTD with unpredictable biological behaviour. This tumour 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 is the mainstay of management but experience has shown that systemic multi-agent chemotherapy can be successfully employed in the management of those with metastatic

disease. Patients with PSTT should be managed in Trophoblastic Disease Centres to optimise patient outcomes by concentrating clinical and pathological expertise.

REFERENCES

1. Papadopoulos AJ, Foskett M, Seckl MJ, McNeish I, Paradinas FJ, Rees H, Newlands ES (2002). Twenty-five years' clinical experience with placental site trophoblastic tumors. *J Reprod Med* **47**: 460-4
2. Feltmate CM, Genest DR, Wise L, Bernstein MR, Goldstein DP and Berkowitz RS (2001). Placental site trophoblastic tumor: A 17 year experience at the New England Trophoblastic Disease Centre. *Gynecol Oncol* **82**:415-419
3. Gillespie AM, Liyim D, Goepel JR, Coleman RE and Hancock BW (2000) Placental site trophoblastic tumour: a rare but potentially curable cancer. *Br J Cancer* **82**: 1186-1190
4. Kurman RJ, Scully RE and Norris HJ (1976) Trophoblastic pseudo-tumour of the uterus. *Cancer* **38**: 1214-1226
5. Twiggs LB, Okagaki T, Philips GL, Stroemer JR and Adcock LL (1981) Trophoblastic pseudotumour – evidence of malignant disease potential. *Gynecol Oncol* **12**: 238-248
6. Scully RE and Young RH (1981) Trophoblastic pseudotumour: a re-appraisal. *Am J Surg Pathol* **5**: 75-76
7. Fisher RA, Paradinas FJ, Newlands ES and Boxer GM (1992) Genetic evidence that placental site trophoblastic tumours can originate from a Hydatidiform mole or a normal conceptus. *Br J Cancer* **65**: 355-358
8. Finkler NJ (1991) Placental site trophoblastic tumor: diagnosis, clinical behaviour and treatment. *J Reprod Med* **36**: 27-30
9. Finkler NJ, Berkowitz RS, Driscoll SG, Goldstein DP and Bernstein MR (1988) Clinical experience with placental site trophoblastic tumors at the New England Trophoblastic Disease Centre. *Obstet Gynecol* **71**: 854-857
10. How J, Scurry J, Grant P, Sapountzis K, Oster A, Fortune O and Armes J (1995) Placental site trophoblastic tumour. Report of three cases and review of the literature. *Int J Gynecol Cancer* **5**: 241-249
11. Bower M, Paradinas FJ, Fisher RA, Nicholson S, Rustin GJS, Begent RH, Bagshawe KD, Newlands ES (1996) Placental site trophoblastic tumour: molecular analysis and clinical experience. *Clin Cancer Res* **2**: 897-902
12. Nagelberg SB and Rosen SW (1985) Clinical and laboratory investigation of a virilized woman with placental site trophoblastic tumour. *Obstet Gynecol* **65**: 527-534

13. Young RH, Scully RE and McCluskey RT (1995) A distinctive glomerular lesion complicating placental site trophoblastic tumour. *Hum Pathol* **16**: 35-42
14. Brewer CA, Adelson MD and Elder RC (1992) Erythrocytosis associated with a placental site trophoblastic tumour. *Obstet Gynecol* **79**: 846-849
15. YuenYF, Lewis EJ, Larson JT, Wilke MS, Rest EB and Zachary CB (1998) Scalp metastases mimicking aloplecia areata. First case report of placental site trophoblastic tumour presenting as cutaneous metastasis. *Dermatol Surg* **24**: 587-591
16. Shih IM and Kurman RJ (2001) The pathology of intermediate trophoblastic tumors and tumor-like lesions. *Int J Gynecol Pathol* **20**: 31-47
17. Kurman RJ, Young RH, Norris HJ, Main CS, Lawrence WD and Scully RE (1984) Immunocytochemical localization of placental lactogen and chorionic gonadotrophin in normal placenta and trophoblastic tumours, with emphasis on the intermediate trophoblast and placental site trophoblastic tumour. *Int J Gynecol Pathol* **3**: 101-121
18. Rhoton-Vlasak A, Wagner J, Rutgers JL, Baergen RN, Young RH, Roche PC, Plummer TB and Gleich GJ (1998) Placental site trophoblastic tumor: human placental lactogen and pregnancy-associated major basic protein as immunohistological markers. *Hum Pathol* **29**: 280-288
19. Hopkins M, Nunez C, Murphy JR, and Wertz WB (1985) Malignant placental site trophoblastic tumor. *Obstet Gynecol* **66**: 95S-100S
20. Lathrop JC, Lauchlan S, Ramakrishna N and Ambler M (1988) Clinical characteristics of placental site trophoblastic tumour (PSTT). *Gynecol Oncol* **31**: 32-42
21. Bettencourt E, Pinto E, Abraul E, Dinis M and De Oliveira CF (1997) Placental site trophoblastic tumour: the value of transvaginal colour and pulsed Doppler sonography in its diagnosis: case report. *Eur J Gynaecol Oncol* **18**: 461-464
22. Sumi Y, Ozaki Y, Shindoh N and Katayama H (1999) Placental site trophoblastic tumor: imaging findings. *Radiat Med* **17**: 427-430
23. Brandt KR and Coakley KJ (1998) MR appearance of placental site trophoblastic tumor: a report of three cases. *Am J Roentgenol* **170**: 485-487
24. Driscoll SG (1984) Placental site chorioma: the neoplasm of the implantation site trophoblast. *J Reprod Med* **29**: 821
25. Dessau R, Rustin GJS, Dent J, Paradinas FJ and Bagshawe KD (1990) Surgery and chemotherapy in the management of placental site tumour. *Gynecol Oncol* **39**: 56-59
26. King L, Okagaki T and Twiggs LB (1992) Resolution of pulmonary metastases with chemotherapy in a patient with placental site trophoblastic tumour. *Int J Gynecol Cancer* **2**: 328-331

27. Newlands ES, Mulholland PJ, Holden L, Seckl M and Rustin GJ (2000) Etoposide and cisplatin/ etoposide, methotrexate, and actinomycin D (EMA) chemotherapy for patients with high-risk gestational trophoblastic tumors refractory to EMA/cyclophosphamide and vincristine chemotherapy and patients presenting with metastatic placental site trophoblastic tumors. *J Clin Oncol* **18**; 854-859
28. Randall TC, Coukos G, Wheeler JE and Rubin SC (2000) Prolonged remission of recurrent, metastatic placental site trophoblastic tumor after chemotherapy. *Gynecol Oncol* **76**: 115-117
29. Mangili G, Garavaglia E, De Marzi P, Zanetto F and Taccagni G (2001) Metastatic placental site trophoblastic tumor. Report of a case with complete response to chemotherapy. *J Reprod Med* **46**: 259-262
30. Wain GV, Friedlander M, Jensen D and Truskett P (1993) Placental site trophoblastic tumour (PSTT) – an enigmatic disease: two case reports. *Int J Gynecol Cancer* **3**: 47