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Placental site trophoblastic tumour: Clinical features and management

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Abstract

Objective. To describe the clinical features, treatment and outcome of all consecutive patients with placental site trophoblastic tumour (PSTT) treated at the Sheffield Trophoblast Centre and to compare these findings to other reports.

Method. All cases of PSTT on the Sheffield Trophoblastic Tumour Centre database from 1984 to 2004 were reviewed. Data obtained included age at diagnosis, antecedent pregnancy (AP), interval from antecedent pregnancy until diagnosis, presenting features, presenting serum human chorionic gonadotrophin hormone (hCG) level, number and sites of metastases, treatment received, outcome and follow-up.

Results. Seventeen patients with PSTT were identified from the database which incorporates a total of 7489 cases of trophoblastic disease. Fourteen (70.6%) were more than 30 years old at presentation; 5 were over 40. The median interval from pregnancy to diagnosis was 18 months (range 6 months to 22 years). The outcome of antecedent pregnancy was a female in 11 out of the 13 patients where the sex was known. Eleven (70.6%) of patients presented with irregular vaginal bleeding, with or without a preceding period of amenorrhoea. All 8 patients with non-metastatic (Stage I) disease were alive and well after hysterectomy (6), chemotherapy alone (1) or hysterectomy and chemotherapy (1) whereas only 4 of 9 patients with metastatic (Stage III/IV) disease were alive and well after treatment with chemotherapy and hysterectomy.

Conclusion. PSTT is rare and accounts for 0.23% cases of gestational trophoblastic disease referred to this centre. It has a variety of presenting features and its course is unpredictable. Metastatic involvement and antecedent pregnancy interval greater than 4 years are poor prognostic factors. Hysterectomy is the primary mode of treatment in the majority of cases. However, chemotherapy can still play a major role when curative surgery is not feasible.

Keywords: Placental site trophoblastic tumour; Features

Background

Placental site trophoblastic tumour (PSTT) is a rare form of gestational trophoblastic disease (GTD). The first observations were made in 1895 and 1910 by Merchand and Ewing, respectively, and the clinical and pathological characteristics of PSTT were described in 1976 by Kurman and Scully when the term 'trophoblastic pseudotumour' was adopted to characterise the apparently benign nature of the disease [1]. Subsequent case reports described evidence of a sometimes aggressive, malignant and fatal course of the disease and the nomenclature was changed to placental site trophoblastic tumour in 1981 [1,2]. Histopathologically, it is characterised by a neoplastic monomorphic population of implantation-like intermediate trophoblastic cells, often as sheets of polyhedral, rounded or occasionally spindle-shaped cells extensively infiltrating the myometrium. Due to the rarity of this type of tumour, there is little information about its epidemiology and aetiology and few large series on diagnosis and treatment have been published [3]. It is seen

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mostly in patients of reproductive age and can follow a normal pregnancy, miscarriage or gestational trophoblastic disease [4–7]. Irregular vaginal bleeding has been the most commonly reported presenting feature, but a wide range of other symptoms have also been reported including galactorrhoea, virilization [8], nephrotic syndrome [9,10] and polycythaemia [11]. In view of the scarcity of PSTT, we have reviewed the clinical features and management of consecutive patients presenting to the Sheffield Trophoblastic Tumour Centre.

Method

All UK patients with GTD are consented and registered with one of three Trophoblast Centres. During the period of study (1984–2004), 7489 were registered at the Sheffield Centre. In those with PSTT data obtained included patient age at diagnosis, antecedent pregnancy (AP), interval from antecedent pregnancy until diagnosis, presenting features, presenting serum β human chorionic gonadotrophin (hCG) levels, metastases (number and sites), new FIGO [12] stage and score, treatment received, outcome and follow-up.

Results

Seventeen patients with PSTT were identified. In all cases, the pathology specimen was centrally reviewed. In 12 cases, PSTT had been suspected locally and was confirmed on central review. In 5 cases, the diagnosis made locally was changed to PSTT on central review.

Clinical features

The median age of patients at presentation was 35 years (range 26–52), 14 patients were over 30 years of age; 5 were over 40. Previous pregnancy was recorded in 16 patients; the antecedent pregnancy was normal term delivery in 13 cases resulting in 11 females and 2 male offspring, miscarriage in 2 cases, elective termination in 1 case and unknown in 1 case. The median interval from pregnancy to diagnosis was 18 months (range 6 months–22 years). All the patients in this series were symptomatic at presentation. Irregular vaginal bleeding was the most common presenting feature occurs in 8 (47%) of 17 patients. Other presentations included (in order of decreasing frequency) amenorrhoea (4 cases), ruptured uterus (2 cases), abdominal pain (2 cases), post menopausal bleeding (1 case) and an enlarged neck node (1 case).

Extent of disease

Eight patients had widely metastatic disease at presentation and one patient had regional disease. Eight patients had negative staging investigations including abdominal ultrasound scan, CT scan of the head, abdomen and pelvis, chest X-ray, clinical chemistry and haematology and MRI scan in selected patients. The lungs were the most common site of metastases in this series. In fact, all patients who presented with distant metastases had pulmonary deposits. Other sites of metastases included liver (3 cases), vagina (2 cases), brain (1 case), pancreas (1 case) and kidneys (1 case). The median serum ßhCG at diagnosis was 13,923 iu/l (range 6–107,600 iu/l), but 10/17 had levels of less than 500 iu/l. A breakdown of various clinical factors thought to be of prognostic import is given in Table 1.

Treatment and outcome

All patients are summarised in Table 2. Eight patients presented with disease confined to the uterus at diagnosis. Total abdominal hysterectomy was the primary treatment in 6/8 patients with ovarian conservation in 5/6. All six patients are well and alive with no evidence of disease (follow up 0.25–11 years). Two patients were initially treated with methotrexate. One, treated with 'low risk' methotrexate (methotrexate 50 mg im on alternate days ×4; folinic acid 7.5 mg oral 24 h after MTX; 7 days between cycles), is disease free at 5 years. The other was initially treated with methotrexate after presenting with a suspected ectopic pregnancy. However, her hCG levels remained high so she underwent total abdominal hysterectomy with subsequent normalisation of her beta hCG levels. She is currently free of the disease with 8 years follow up.

Nine patients had metastatic disease at the time of presentation; four patients have died of their disease and one is alive but with active disease. Four patients are alive and well (follow up 2.5–11 years). Two were treated with 'low risk' methotrexate and both needed treatment with second line chemotherapy. One patient received dactinomycin and

Table 1
Patient groups according to risk factors

		Dead	Alive
Risk score	Low (13)	1	12
	High (4)	3	1
Stage	I (8)	0	8
	II (1)	0	1
	III (5)	1	4
	IV(3)	2	(1)
HCG (iu/L)	Low <500 (10)	1	8 (1)
	Medium (3)	0	3
	High >10 k (4)	3	1
Interval to antecedent pregnancy (months)	≤6 (4)	0	4
	≤24 (6)	1	5
	≤48 (2)	0	1 (1)
	>48 (5)	3	2
Age (years)	≤39 (12)	1	11
	≥40 (5)	3	1 (1)
Outcome of AP	Term (13)	4	8 (1)
	Unknown (1)	0	1
	Miscarriage (2)	0	2
	Termination (1)	0	1

Table 2
Clinical summaries of all patients

Patient number	Age (years)	Antecedent pregnancy (AP)	Interval to AP (months)	Presenting features	Presenting hCG iu/l	Metastases (number)	Metastases (site)	FIGO stage	WHO score	Treatment	Outcome	Follow-up (years)
1	37	Female FTND	30	Amenorrhoea	10	0	–	I	2	TAH	AW NED	10
2	26	Female twins	14	Ruptured uterus	6	0	–	I	6	TAH	AW NED	11
3	52	None known	–	Amenorrhoea	107	0	–	I	2	TAH	AW NED	10
4	35	Miscarriage	6	Ruptured uterus	74	0	–	I	3	TAH	AW NED	9
5	24	Miscarriage	6	Amenorrhoea	7,561	0	–	I	4	MTX	AW NED	5
6	38	Female FTND	18	Abdominal pain	68	0	–	I	7	MTX, TAH	AW NED	8
7	28	Termination	2	IVB	22	0	–	I	1	TAH	AW NED	0.25
8	23		18	IVB	34	0	–	I	6	TAH	AW NED	1.5
9	38	Female ND	12	IVB	314	1	Vagina	II	6	TAH, RT, MTX, Et, Met, MAE, MTX	DOD	20
10	34	Female FTND	132	Amenorrhoea	2,525	Multiple	Lungs	III	9	MAE, TAH, CEC	AW NED	13
11	27	Male FTND	18	IVB	1,575	Multiple	Lungs	III	5	MTX, CEC	AW NED	10
12	52	Female FTND	264	Post-menopausal bleed	56,766	Multiple	Lungs	III	6	MAE, TAH, EP/EMA, Met, CP, HDC, MTX	DOD	3
13	30	Female FTND	6	IVB	36,819	Multiple	Lungs	III	7	MAE	AW NED	3.5
14	34	Female FTND	13	IVB	300	Multiple	Lungs, vagina	III	7	TAH, MAE, CEC	AW NED	2.5
15	43	Female FTND	156	IVB	107,600	Multiple	Lungs, vagina liver/brain	IV	15	MAE, CEC, IT, MTX, RT	DOD	2
16	50	Male FTND	132	Enlarged neck node	45,690	Multiple	Lungs, liver, spinal, kidneys, pancreas	IV	14	EP/EMA,CP, MICE, RT, MTX	DOD	12
17	43	Female FTND	36	Abdominal pain	111	Multiple	Lungs, liver	IV	11	EP/EMA, CP, CEC, HDC	AWD	1.25

AE, Actinomycin, etoposide; AP, Antecedent pregnancy; AW NED, alive and well no evidence of the disease; AWD, alive with the disease; CEC, Cyclophosphamide/etoposide/cisplatin; CP, Carboplatin, paclitaxel; DOD, Died of disease; Et, Etoposide; EP/EMA, Etoposide, cisplatin/etoposide, methotrexate, dactinomycin; FTND, Full-term normal delivery; hCG, Human chorionic gonadotrophin; HDC, High dose chemotherapy; IT, intrathecal; IVB, Irregular vaginal bleeding; MAE, Methotrexate/dactinomycin, etoposide; Met, Metastatectomy; MICE; Methotrexate, ifosfamide, cisplatin, etoposide; MTX, Methotrexate; ND, Normal delivery; RT, Radiotherapy; TAH, Total abdominal hysterectomy.

etoposide, underwent hysterectomy and subsequently died of her disease. The second patient received CEC (cisplatin 25 mg m^2 intravenously daily ×3, etoposide 100 mg m^2 daily ×3, cyclophosphamide 600 mg m^2 intravenously day 1; 7–10 days between cycles) and is alive and well. Five patients were treated with MAE (methotrexate 300 mg m2 intravenous; folinic acid 15 mg 6 h × 8 starting 24 h after methotrexate, alternating with dactinomycin 0.5 mg daily intravenous ×3 and etoposide 100 mg m^2 intravenous daily ×3; 7 days between cycles). Three underwent hysterectomy; in one case, the surgery was part of her initial management and in two cases, it was performed for the treatment of drug resistant PSTT. Three women required second line chemotherapy with either CEC or EP/EMA (etoposide 150 mg/m^2 intravenous, cisplatin 25 mg m^2 intravenous ×3, alternating with etoposide 100 mg m^2 intravenous, methotrexate 300 mg m^2 intravenous and dactinomycin 0.5 mg intravenous; folinic acid 15 mg 12 hourly ×4 starting 24 h after methotrexate; 7 days between cycles); and subsequently, one underwent high dose chemotherapy with stem cell transplantation. Two of these women died of their disease. Two patients were treated with EP/EMA; both required second line chemotherapy with cisplatin and paclitaxel and one underwent high dose chemotherapy with stem cell transplantation. Both also received radiotherapy. One patient has died of her disease and the other patient is alive with active disease.

Discussion

The establishment of centres for screening and treatment of gestational trophoblastic diseases has improved the care provided to patients and led to more research. However, placental site trophoblastic tumour is rare compared to other forms of GTD, so much so that only 17 cases were identified among 7489 cases registered as GTD at our Centre. In this study, we have reviewed the literature and interpreted our findings in the context of other large studies [13–16]. We have previously reported 7 cases [17]; the current paper expands the number of cases to 17 and provides the second largest series in the literature. Consecutive patients seen at the Sheffield Centre and managed according to agreed clinical protocols are reported.

The histology of all cases of persistent GTD referred to the centre was reviewed by an experienced gynaecological pathologist. The working diagnosis reached by the referring hospital was changed in a number of cases. In the majority choriocarcinoma was changed to PSTT, thus emphasising the importance of expert histopathological review. In many cases, clinical suspicion had also been aroused by sub-optimal response to chemotherapy.

It was not possible to do a valid statistical analysis because of the small numbers. However, certain clinical factors were associated with bad prognosis (death or multi resistant disease). These were FIGO stage IV and high-risk score, high (>10,000 iu/L) hCG, time from antecedent diagnosis ≥48 months and age ≥40 years. Individual FIGO scores were not a reliable predictor for most patients since the range was narrow and clustered around the low/high risk (≤6, ≥7) cut off. Indeed, it is now recommended that scores should not be used to guide treatment in PSTT [12].

Although the disease is seen mostly in women of reproductive age, a few cases have been reported in post-menopausal women [13,18,19]. In this series, the median age of patients at presentation was 35 years (range 26–52). Three presented after menopause, all with metastatic disease. Two of these patients died of disease and the third is alive and well.

A prolonged interval between the antecedent pregnancy and the development of PSTT is considered as a poor prognostic factor in a number of studies [9,20,21]. In this series, the interval from antecedent pregnancy to diagnosis varied, with a range of 6 months to 22 years and a median of 18 months. A recent study by Papadopoulos et al. [14] mentioned "risk factors for death include pulmonary metastatic involvement and antecedent pregnancy interval equal to or greater than 4 years". Three of the four of our patients who presented more than 4 years after an antecedent pregnancy have died of the disease. In addition, Newlands et al, in an earlier study, concluded that an interval of less than 2 years from antecedent pregnancy to initiation of treatment was the most significant prognostic factor [22]. In their study four out of five patients who were treated more than 2 years following the antecedent pregnancy died of the disease. In our series, 3 of 5 patients with an interval from antecedent pregnancy of more than 2 years died of disease.

In most large series, as many as 30% of patients presented with metastatic disease. Approximately half of our patients (53%) presented with metastases at the time of diagnosis. All but one had pulmonary metastases. The occurrence of CNS metastasis is considered to be a poor prognostic factor [23]. Indeed, of three patients in this series who developed cranial or spinal metastasis, two have died of their disease and one is alive but with active disease.

β hCG is an excellent marker in evaluating and monitoring choriocarcinoma and molar pregnancies. However, serum β hCG levels in PSTT correlate neither with the burden nor with malignant behaviour and thus appear to have no predictive value. In our series the median β hCG at diagnosis was 13,923 iu/l (range 6–107,600 iu/l) with no direct correlation between tumour burden and hCG value. Significantly, 10 patients had hCG levels of less than 500 iu/l. This is consistent with the findings of other studies.

There is conflicting data as to whether high tumour mitotic count is a significant adverse prognostic factor for survival [13,24,25]. We have not yet evaluated this relationship.

Surgery remains the primary mode of therapy in patients presenting with disease limited to the uterus. Remission rates of up to 100% have been reported [24]. Since adenexal micrometastasis is uncommon (3%) [26], preservation of the ovaries is reasonable. Eight patients (47.1% of our group) presented with disease confined to the uterus. Six were cured by hysterectomy, with ovarian preservation in 4 patients. Overall, 64.7% (11/17) of all patients underwent hysterectomy at some stage of their treatment. The other six patients either refused to undergo hysterectomy in order to preserve their fertility, or presented with widespread metastasis.

Women with metastatic PSTT at the time of diagnosis cannot be cured by surgery alone and treatment with combination chemotherapy is required. Four patients with metastatic disease have responded to chemotherapy and are now free of the disease. The most recent data from Charing Cross Hospital and other centres suggest that EP/EMA chemotherapy is an effective regimen for metastatic and relapsing PSTT [14,15,22,26]. In our series, both patients treated with this regimen developed drug resistant disease and required salvage. We treated five cases with MAE as first line treatment and in two cases no further chemotherapy was required; both patients are alive and well. Three of these cases developed drug resistant disease and were treated with a variety of regimens. CEC salvaged one of these cases. Two early cases in this series were initially treated with 'low dose' methotrexate but both required multiagent chemotherapy for drug-resistant disease; one was salvaged using the CEC regimen.

The ideal chemotherapy regimen for metastatic PSTT has yet to be described but our series demonstrates that MAE as a first line treatment is active against this disease and the CEC regimen may have a place in the treatment of drug resistant disease.

Metastatic disease is not necessarily a contraindication to surgery. In fact, aggressive surgical management of chemo-resistant metastasic disease may be appropriate for those young patients with an otherwise poor prognosis [27]. Radiation therapy has been used to good effect in the palliative setting but is not a primary modality of treatment.

Conclusion

PSTT is rare. It has varied presenting features and its course is unpredictable. Total abdominal hysterectomy is

the primary mode of treatment for localised disease. However, chemotherapy can play an important role when surgery is not feasible. We have confirmed that a metastatic involvement and delay between the pregnancy event and diagnosis of 4 years or longer are adverse prognostic factors.

References

[1] Kurman RJ. The morphology, biology, and pathology of intermediate trophoblast: a look back to the present. Hum Pathol 1991;22:847–55.

[2] Twiggs LB, Okagaki T, Phillips GL, Stroemer JR, Adcock LL. Trophoblastic pseudotumour—evidence of malignant disease potential. Gynecol Oncol 1981;12:238–48.

[3] Gillespie AM, Hancock BW. Placental site trophoblastic tumour. In: Hancock BW, Newlands ES, Berkowitz RS, Cole LA, editors. Gestational Trophoblastic Disease, 2nd ed, p. 329–36 [www.isstd.org/gtd/index.html].

[4] Schneider D, Halperin R, Segal M, Bukovsky I. Case report: placental-site trophoblastic tumor following metastatic gestational trophoblastic neoplasia. Gynecol Oncol 1996;63:267–9.

[5] Fisher RA, Paradinas FJ, Newlands ES, Boxer GM. Genetic evidence that placental site trophoblastic tumours can originate from a hydatidiform mole or a normal conceptus. Br J Cancer 1992;65:355–8.

[6] Oldt III RJ, Kurman RJ, Shih LeM. Molecular genetics analysis of trophoblastic tumours and epithelioid trophoblastic tumours confirms their trophoblastic origin. Am J Pathol 2002;161:1033–7.

[7] Rutgers JL, Baergen RN, Young RH, Scully RE. Placental site trophoblastic tumour: clinicopathologic study of 64 cases. Mod Pathol 1995;8:96A.

[8] Nagelberg SB, Rosen SW. Clinical and laboratory investigation of a virilized woman with placental trophoblastic tumour. Obstet Gynecol 1985;65:527–34.

[9] Bower M, Paradinas FJ, Fisher RA, Nicholson S, Rustin GJS, Begent RH, et al. Placental site trophoblastic tumour: molecular analysis and clinical experience. Clin Cancer Res 1996;2:897–902.

[10] Young RH, Scully RE, McCluskey RT. A distinctive glomerular lesion complicating placental site trophoblastic tumour. Hum Pathol 1995;16:36–42.

[11] Brewer CA, Adelson MD, Elser RC. Erythrocytosis associated with placental site trophoblastic tumour. Obstet Gynecol 1992;79:846–9.

[12] FIGO Oncology Committee. FIGO staging for gestational trophoblastic neoplasia. Int J Obstet Gynecol 2002;77:285–7.

[13] Feltmate CM, Genest DR, Wise L, Bernstein MR, Goldstein DP, Berkowitz RS. Placental site trophoblastic tumour: a 17-year experience at the New England Trophoblastic Disease Centre. Gynecol Oncol 2001;82:415–9.

[14] Papadopoulos AJ, Fosket M, Seckl MJ, McNeish I, Paradinas FJ, Rees H, et al. Twenty five years' clinical experience with placental site trophoblastic tumours. J Reprod Med 2002;47:460–4.

[15] Hoekstra AV, Keh P, Lurain JR. Placental site trophoblastic tumor: a review of 7 cases and their implications for prognosis and treatment. J Reprod Med 2004;49:447–52.

[16] Bonazzi C, Urso M, Dell'Anna T, Sacco S, Buda A, Cantu MG. Placental site trophoblastic tumor: an overview. J Reprod Med 2004;49:585–8.

[17] Gillespie AM, Liyim D, Goepel JR, Coleman RE, Hancock BW. Placental site trophoblastic tumour: a rare but potentially curable cancer. B J Cancer 2000;82:1186–90.

[18] Newlands ES. The management of recurrent and drug resistant gestational trophoblastic neoplasia (GTN). Best Pract Res Clin Obstet Gynecol 2003;17:905–23.

[19] Sonu N, Niti S, Sajeev Kumar J, Divye C, Usha M. Placental site trophoblastic tumour in a postmenopausal female. Case report. Gynecol Oncol 2004;93:550–3.

[20] Finkler NJ, Berkowitz RS, Driscoll SG, Goldstein DP, Bernstein MR. Clinical experience with placental site tophoblastic tumours at the New England Trophoblastic Disease Centre. Obstet Gynecol 1988;71:854–7.

[21] How J, Scurry J, Grant P, Sapountzis K, Östor A, Fortune O, et al. Placental site trophoblastic tumour. Report of three cases and review of the literature. Int J Gynecol Cancer 1995;5:241–9.

[22] Newlands ES, Bower M, Fisher RA, Paradinas FJ. Management of placental site trophoblastic tumour. J Reprod Med 1998;7:854–7.

[23] Guvendag Guven ES, Guven S, Esinler I, Ayhan A, Kucukali T, Usubutun A. Placental site trophoblastic tumour in a patient with brain metastases. Int J Gynecol Cancer 2004;14:558–63.

[24] Kim SJ. Placental site trophoblastic tumour. Best Prac Res Clin Obstet Gynecol 2003;17:969–84.

[25] Chang YL, Chang TC, Hsueh S, Huang KG, Wang PN, Liu HP, et al. Prognostic factors and treatment for placental site trophoblastic tumour—Report of 3 cases and analysis of 88 cases. Gynecol Oncol 1999;73:216–22.

[26] Machtinger R, Gotleib WH, Korach J, Fridman E, Apter S, Goldenberg M, et al. Placental site trophoblastic tumor: outcome of five cases including fertility preserving management. Gynecol Oncol 2005;96:56–61.

[27] Dainty LA, Winter III WE, Maxwell GL. The clinical behaviour of placental site trophoblastic tumor and contemporary methods of management. Clin Obstet Gynecol 2003;46:607–11.