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Original Article

Clinicopathologic characteristics of placental site trophoblastic tumors

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Abstract: Objective: This study was aimed at analyzing the clinicopathological features and treatment of patients with placental site trophoblastic tumor (PSTT) in Shanghai, China, and to investigate high-risk factors for metastasis and relapse. Methods: Thirteen patients with placental site trophoblastic tumors who received treatment in the Obstetrics and Gynecology Hospital Affiliated with Fudan University in Shanghai, China, between Jan 2002 and July 2014 were reviewed. The cases were divided into two groups: confined and non-confined (CG and NCG, respectively). CG included patients in stage I without evidence of recurrence during the follow-up, whereas NCG included advanced stage or stage I with recurrent lesions. The clinical data, treatment and prognosis were collected from medical records. Results: The median age of the patients with placental site trophoblastic tumors was approximately 30.1 years. Gravidity ranged from 1 to 4 pregnancies. Antecedent pregnancies included term deliveries, abortions and complete molar pregnancies. The average time interval from antecedent pregnancy was 7.7 months. Irregular vaginal bleeding was the most common presentation. Most patients had a plasma hCG level less than 500 mIU/ml. All patients received either laparoscopically assisted vaginal hysterectomy or total abdominal hysterectomy. Patients in the NCG group were treated with combined chemotherapy such as EMA-CO or EP-EMA to achieve remission. No difference was observed in the expression of hPL, inhibin-α, p53 or the Ki-67 labeling index between the CG and NCG groups. However, there were statistically significant differences of age (≥ 35 years), gravidity (> 2), tumor size (≥ 30 mm) and myometrial invasion depth (≥ 1/2) in the NCG group (*P = 0.002, 0.002, 0.015 and 0.024*, respectively). Conclusions: This study showed that patient age, gravidity, tumor size and myometrial invasion depth might be predictors for metastasis and recurrence of PSTT. Surgery and combined chemotherapy are suggested in patients with those high-risk factors.

Keywords: Placental site trophoblastic tumor, clinicopathologic feature, surgery, chemotherapy, prognostic factors

Introduction

Gestational trophoblastic disease (GTD) defines a heterogeneous group of interrelated lesions arising from abnormal proliferation of trophoblastic cells [1, 2]. Placental site trophoblastic tumor (PSTT) is a rare type of gestational trophoblastic disease that has the potential for local invasion and metastasis. The clinical and pathological features of PSTT were first described as trophoblastic pseudotumor, which was characterized as benign in nature in 1976 by Kurman and Scully [3]. In 1981, trophoblastic pseudotumor was reported as a malignant and fatal disease and named placental site trophoblastic tumor. In 1983, the World Health Organization (WHO) formally acknowledged the neoplastic nature of this disease and adopted the terminology of PSTT. Histologically, it originates from intermediate trophoblastic cells with occasional multinuclear giant cells in the site of placental implantation, with potential for local invasion and metastasis. Owing to its rare occurrence and untypical clinical presentation, the diagnosis and management of PSTT are still poorly understood. PSTT may occur months to years after pregnancy with any outcome, including normal term pregnancy, miscarriage or gestational trophoblastic disease [4]. Irregular vaginal bleeding with or without a preceding period

of amenorrhea has been reported as the most common presentation [4, 5]. In this study, we analyzed the clinicopathological features and management of patients with PSTT treated in the Obstetrics and Gynecology Hospital of Fudan University, Shanghai, PR of China. We aimed to find potential prognostic factors that could predict extra-uterine spread or relapse of PSTT.

Materials and methods

Patients

The present study was carried on according to a protocol approved by the ethics committee in the Obstetrics and Gynecology Hospital Affiliated with Fudan University, Shanghai, PR of China. In this study, we analyzed the clinical data from 13 patients who were diagnosed with PSTT and treated in our hospital during the years 2002 to 2014.

Clinical characteristics

Clinical data including age, date of initial diagnosis, presenting symptoms and signs, plasma human chorionic gonadotrophin level at diagnosis, type of surgery, stage at presentation, histological type, chemotherapy regimens, relapse details, and menstrual function of all patients were collected from patient medical records and reviewed retrospectively.

Immunohistochemical staining

Two experienced pathologists specialized in gynecologic oncology evaluated all pathology specimens randomly without awareness of the clinical course and outcome of each case. Immunohistochemical staining was performed with the following antibodies: human placental lactogen (hPL), inhibin-α, p53 and Ki67. The result was assessed by semi-quantitative evaluation of the number of positively stained cells as follows: -, no staining; + (weakly positive), 1~25% of cells stained; ++ (moderate positive), 26~50% of cells stained; +++ (strongly positive), 51~100% of cells stained. The Ki67 labeling index was determined by the percentage of positive nuclei stained with MIB-1 antibody.

Follow-up

All the patients in this study had been followed up since the day of surgery every three months. Routine clinical check-ups, including symptoms, pelvic examination, plasma hCG level and ultrasonic examination were performed and evaluated periodically.

Statistical analysis

Data were collected, and statistical analysis was performed using Student's t test and the x^2 test when appropriate by comparing values of CG with those of NCG. SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used to perform all statistical analyses. A *P*-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Thirteen patients diagnosed with placental site trophoblastic tumor were treated in our hospital between 2002 and 2014. All patients had staging examinations including abdominal and vaginal ultrasound scan, chest X-ray, biochemical tests and endocrine hormone test. Selected patients had MRI or PET-CT scans. The clinical features, treatment, and outcome of the 13 patients with PSTT are shown in **Table 1**. The average age at diagnosis was 30.1 years (range 22 to 41 years). Gravidity ranged from 1 to 4 pregnancies with a mean of 1.8 times. Nine of the 13 patients (69.2%) were diagnosed with PSTT following term deliveries. The remaining antecedent pregnancies included one therapeutic abortion, one spontaneous abortion, and two following a complete molar pregnancy. The mean time interval from the antecedent pregnancy was 7.7 months (range 2 to 21 months). All patients were symptomatic at presentation. Irregular vaginal bleeding was the most common complaint, happening in eleven of thirteen patients, while the other two patients presented with amenorrhea. Plasma hCG levels ranged from 1.92 to 1000 mIU/ml at presentation, while most patients (12/13) had hCG levels less than 500 mIU/ml. All patients were initially diagnosed by endometrial curettage, eight of which were through dilatation and curettage and five through hysteroscopy. One patient presented with vaginal metastasis, while three patients had lung metastasis at the time of diagnosis.

Surgery and chemotherapy

All patients received an operation, eight undergoing LAVH and five cases undergoing TAH.

Table 1. Clinical features, treatment, and outcome in 13 patients with PSTT

Case	Group	Age (years)	Gravidity	Antecedent pregnancy	Interval from AP (months)	Presenting symptom	hCG at diagnosis (IU/mL)	FIGO stage and extra-uterine lesion	Surgery	Chemotherapy	Current status/follow up period (months)	
										Before surgery	After surgery	
1	CG	27	1	TD	4	IVB	14	I	D&C, LAVH	MTX, EMA-CO, EP-EMA	EP-EMA	NED/8
2	CG	29	1	TD	10	Amenorrhea	147	I	Hysteroscopy, LAVH	/	/	NED/12
3	CG	32	2	TD	5	IVB	210.03	I	D&C, LAVH	MTX	/	NED/114
4	CG	25	1	TD	8	IVB	108.54	I	Hysteroscopy, LAVH	MTX, Mifepristone	EMA-CO	NED/27
5	CG	30	1	SAB	4	IVB	189.23	I	Hysteroscopy, TAH	MTX	EMA-CO	NED/38
6	CG	27	1	TD	7	IVB	69.59	I	D&C, LAVH	EMA-CO	EMA-CO	NED/82
7	CG	27	2	TD	2	IVB	24.47	I	D&C, TAH	MTX	/	NED/97
8	CG	25	1	TD	9	Amenorrhea	1.92	I	Hysteroscopy, LAVH	/	/	NED/34
9	NCG	41	3	TD	4	IVB	118.39	I/RE	D&C, LAVH	MTX, Mifepristone	EMA-CO, EP-EMA	DOD/38
10	NCG	35	3	TAB	3	IVB	1000	III/lung	D&C, TAH	/	EMA-CO	NED/123
11	NCG	36	4	MP	21	IVB	142	III/lung	D&C, TAH	/	EMA-CO	NED/123
12	NCG	22	1	TD	17	IVB	320	III/lung	Hysteroscopy, TAH	EMA-CO	EMA-CO,EP-EMA	NED/12
13	NCG	35	3	MP	6	IVB	58.09	II/vagina	D&C, LAVH	EP-EMA	EP-EMA	NED/48

Abbreviations: CG: confined group; NCG: non-confined group; AP: antecedent pregnancy; FIGO: International Federation of Gynecology and Obstetrics; TD: term delivery; SAB: spontaneous abortion; TAB: therapeutic abortion; MP: molar pregnancy; IVB: irregular vaginal bleeding; TAH: total abdominal hysterectomy; D&C: dilation and curettage; LAVH: laparoscopically assisted vaginal hysterectomy; EMA: etoposide, methotrexate, actinomycin; CO: cyclophosphamide, vincristine; EP, cisplatin; MTX, methotrexate; NED: no evidence of disease; DOD: died of disease; RE: recurrence.

Table 2. Histological features in 13 patients with PSTT

Case	Group	hPL	Inhibin-α	P53	Ki-67 labeling index (%)	Tumor size (mm)	Depth Involving the myometrium
1	CG	+	+	-	-	12	< 1/2
2	CG	+	+	+	15%	32	< 1/2
3	CG	-	+	-	< 5%	15	< 1/2
4	CG	++	+	-	10%	20	< 1/2
5	CG	+++	+	-	20%	20	0.5
6	CG	++	++	-	30%	15	0.5
7	CG	+	+	-	< 5%	25	< 1/2
8	CG	++	++	-	20%	20	0.5
9	NCG	+++	+	+	30%	55	0.5
10	NCG	++	++	-	10%	40	> 1/2
11	NCG	+++	++	-	< 5%	43	0.5
12	NCG	+++	+	++	80%	30	> 1/2
13	NCG	+	+	-	5%	20	> 1/2

Table 3. Clinical findings of two distinct groups

	CG (N = 8)	NCG (N = 5)	*P* value
Age (years)			
< 35	8 (100%)	1 (20%)	0.002**
≥ 35	0 (0)	4 (80%)	
Interval from AP (months)			
< 12	8 (100%)	3 (60%)	0.052
≥ 12	0 (0)	2 (40%)	
Initial hCG (mIU/ml)			
< 1000	8 (100%)	4 (80%)	0.188
≥ 1000	0 (0)	1 (20%)	
Gravidity			
≤ 2	8 (100%)	1 (20%)	0.002**
> 2	0 (0)	4 (80%)	
Antecedent pregnancy			
Term delivery	7	2	0.093
TAB	0	1	
Molar pregnancy	0	2	

**P < 0.01.

Because all patients were relatively young, no patient had ovaries or fallopian tubes removed. No patient underwent a lymphadenectomy. Two patients did not receive chemotherapy before or after surgery. Two patients received a single dose of methotrexate (MTX) before surgery and were observed only after surgery. Three patients received MTX with or without mifepristone before surgery but changed to etoposide/methotrexate/dactinomycin and vincristine/cyclophosphamide (EMA/CO) because of elevated plasma hCG after surgery. Two patients did not receive any chemotherapy before surgery but received EMA/CO because of continued elevated plasma hCG after surgery. Four patients had etoposide/cisplatin and etoposide/methotrexate/dactinomycin (EP-EMA) replaced by EMA/CO for persistent elevated plasma hCG. All patients had been followed up since the day of surgery every three months until Sep 2014. Twelve patients were alive at the last follow-up without evidence of relapse. One patient relapsed after 38 months of hysterectomy and chemotherapy and finally died of the disease.

Histological features

All cases showed similar histology, invasive proliferation of intermediate trophoblastic cells in the background of endometrial and myometrial tissues. The average tumor size was 26.7 mm, ranging from 12 to 55 mm. In terms of myometrium invasion, five cases had lesion extending less than 50% into the myometrium, five cases had lesion extending 50% into the myometrium, while three cases extended more than 50%. According to immunohistochemistry staining, the Ki-67 labeling index as determined by MIB-1 antibodies (%) was positive in twelve patients, mostly ≤ 50%, with only one case > 50%. hPL antibody was negative in one patient and positive in the remaining twelve patients. As for p53 antibody, most patients (10 of 13) were negative, while three patien-

Table 4. Histological findings of two distinct groups

	CG (N = 8)	NCG (N = 5)	*P* value
Tumor size (mm)			
< 30	1 (12.5%)	4 (80%)	0.015*
≥ 30	7 (87.5%)	1 (20%)	
Depth of invasion (% myometrial thickness)			
< 50%	3 (37.5%)	5 (100%)	0.024*
≥ 50%	5 (62.5%)	0 (0)	
hPL			
Positive	7 (87.5%)	5 (100%)	0.411
Negative	1 (12.5%)	0 (0)	
Inhibin-α			
Positive	8 (100%)	5 (100%)	> 0.05
Negative	0 (0)	0 (0)	
P53			
Positive	1 (12.5%)	2 (40%)	0.252
Negative	7 (87.5%)	3 (60%)	
Ki-67 labeling index			
< 50%	8 (100%)	4 (80%)	0.606
≥ 50%	0 (0)	1 (20%)	

*P < 0.05.

ts were positive. The results are shown in **Table 2**.

Difference between CG and NCG groups

All PSTT cases were divided into confined and non-confined groups based on the presence or absence of lesions beyond the uterine corpus or recurrence after hysterectomy. FIGO stage I with no recurrence or persistence was classified into the confined group (CG), while stage I lesions with recurrence or persistence as well as stage II/III/IV lesions belonged to the non-confined group (NCG). Stage I with persistence was defined as persistence of abnormal level of plasma hCG after hysterectomy but without a clear metastatic lesion. **Tables 3** and **4** summarize the clinical and pathological findings of the two distinct groups. Differences of age at diagnosis (≥ 35 years) and gravidity (> 2) were statistically significant (both $P = 0.002$), while other clinical features were not. As for histological features, differences of tumor size (≥ 30 mm) and myometrial invasion depth (≥ 1/2) were statistically significant ($P = 0.015$ and $P = 0.024$, separately). However, the expression of hPL, p53, inhibin-αrelated antigen, and Ki-67 labeling index did not differ between the CG and NCG groups.

Discussion

Placental site trophoblastic tumor is a rare form of gestational trophoblastic disease, accounting for 1~2% of trophoblastic tumors [6]. It was named less than 30 years ago [3, 7, 8]. It can occur following any type of pregnancy and mostly occurs after full-term normal delivery [4, 9, 10]. The incidence of PSTT in GTN was approximately 0.25% in the Obstetrics and Gynecology Hospital of Fudan University between 2002 and 2014.

The most common symptom of PSTT is irregular vaginal bleeding [4, 10]. At the time of diagnosis, the disease shows metastasis in 16~54% of patients [4, 10-12]. In our study, irregular vaginal bleeding was indeed the most common presentation in most cases, although a small number of patients presented with amenorrhea. Thirty-one percent (4 of 13) of the investigated patients had metastatic disease at the time of diagnosis, of whom three had lung metastasis, and the remaining had vaginal metastasis.

Surgery is considered the first-line treatment strategy in patients with PSTT because of its chemoresistance. Surgery is aimed to remove the tumor and related lesions, including total hysterectomy with or without bilateral salpingo-oophorectomy. Preservation of ovaries is recommended for young patients. It was reported recently that reproductive function could be preserved for selected patients with PSTT [13]. For patients with metastatic or recurrent PSTT, chemotherapy still plays an important role. A variety of regimens have been utilized, but EMA-CO and EMA-EP appear to give encouraging results for high risk patients. Patients with metastasis or recurrence may still achieve remission with intensive combination chemotherapy after surgical intervention [14, 15].

Predicting aggressive tumor behavior at initial diagnosis is important for doctors to decide on continued treatment. It has been reported that patient age, high plasma hCG levels, FIGO stage, the interval from AP, the depth of myo-

metrial invasion, the presence of extensive coagulation necrosis, the presence of tumor cells with clear cytoplasm, previous term pregnancy, high mitotic rate, and p53 positivity are important clinicopathological factors of patients with PSTT [11, 12, 16-18]. Many pathological molecules related to PSTT have been reported, such as Hpl [19, 20], inhibin-α [21], p53 [16] and Ki-67 [22]. To detect differences between early and advanced or recurrent PSTT, we investigated many related features and molecules. In the present study, age (≥ 35 years), gravidity (> 2), tumor size (≥ 30 mm) and myometrial invasion depth (≥ 1/2) were found to be high risk factors for discriminated confined and non-confined PSTT cases. Although it was a small-sample study, that result showed an impact on predicting extra-uterine spread and recurrence, as well as, possibly, on choice of chemotherapy regimen. When patients with PSTT have these risk factors, a powerful chemotherapeutic protocol should be considered, even if the patient is at stage I. However, in the present study, the interval from AP, plasma hCG level, p53 positive rate and the Ki-67 labeling index were indeed higher in NCG than in CG, but the differences were not statistically significant. The present study may suffer from some limitations, such as its small sample. Multicenter studies would allow us to strengthen the observed associations.

In conclusion, as a rare type of GTD, PSTT lacks a clear understanding of its diagnosis and treatment. Along with the reported data, our study showed that age ≥ 35 years, gravidity > 2, tumor size ≥ 30 mm and myometrial invasion depth ≥ 1/2 might be used as predictors for metastasis and recurrence. Total hysterectomy and excision of related lesions is recommended as the first-line treatment for PSTT. Combined chemotherapy such as EMA-CO and EP-EMA could play an important role in patients at high risk.

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Disclosure of conflict of interest

None.

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