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CASE

Placental site trophoblastic tumor with multiple metastases and complete response to salvage BEP regimen: a case report and review of the literature

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Abstract Placental site trophoblastic tumor is a rare form of gestational trophoblastic disease, derived from invasive implantation site (intermediate) trophoblastic cells. It is frequently resistant to chemotherapy. Patients with metastases, however, frequently have progressive disease and die despite surgery and multiagent chemotherapy. In this case, a 24-year-old woman was referred because of intermittent vaginal bleeding episodes for 5 months following delivery. Multiple metastases in lungs, liver, kidneys, breast, pancreas, and adrenal and thyroid glands were detected. Combination therapy including surgery and multiagent chemotherapy was planned. Hysterectomy and pelvic lymph node dissection were performed. All metastatic lesions disappeared with EMA-CO treatment. However four courses of BEP regimen, salvage therapy, was performed for plateauing hCG level. Surgery and multiagent chemotherapy seem mainstay of treatment of cases having multiple metastases of PSTTs.

Keywords Placental site trophoblastic tumor · Metastases

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Introduction

Placental site trophoblastic tumor (PSTT) is a rare variant of gestational trophoblastic diseases. It is characterized by neoplastic transformation of intermediate throphoblastic cells. It may arise after term pregnancy, spontaneous abortion, elective termination of pregnancy, ectopic or molar pregnancy. It may be metastatic or nonmetastatic. In an analysis of 27 patients with metastatic PSTT, the lung was the most common site of metastasis (19 cases). Metastatic sites also included the vagina (8 cases), lymph nodes (6 cases), brain (4 cases), liver (4 cases), ovary (3 cases), pancreas (3 cases), and bladder (2 cases). It is usually resistant to chemotherapy and in most of the cases surgery is required. However in cases with multiple distant metastases chemotherapy is also required and frequently these patients show disease progression despite aggressive multiagent chemotherapy [1]. In this case report we present clinical management of a PSTT case with multiple metastases.

Case

A 24-year-old women gravida 2, parity 2 was referred to our hospital with initial diagnosis of gestational throphoblastic disease that differential diagnosis of PSTT or choricarcinoma could not be performed. Her complaint was intermittent vaginal bleeding episodes for 5 months following antecedent pregnancy and she had been tailored to diagnostic dilatation and curettage. In gynecological exam uterus had the enlargement of 8 weeks gestation. Transvaginal utrasonography revealed 4 × 4 × 5 cm mass with hypo-hyperechogenic areas in uterine wall. Multiple lesions in lung parenchyma and a lesion in thyroid gland both implementing metastases were detected in thorax CT

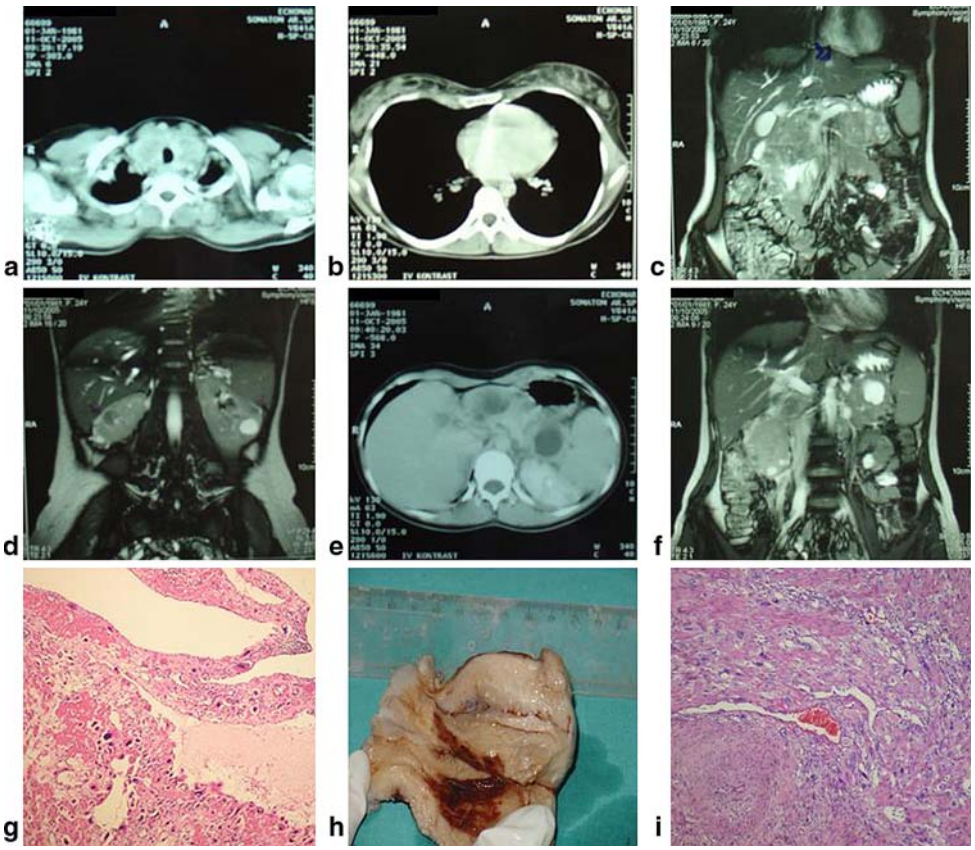

Fig. 1 A lesion in thyroid gland (**a**) and 1.5 cm lesion in lower external quadrant of left mammary gland was present (**b**) both implementing metastases were detected in thorax CT. (**c**–**g**) In abdominal MRI multiple metastatic cystic lesions were detected in liver (**c**) and an extensive lesion in head of pancreas (**d**) and in both of the kidneys (**e**) and in both of the adrenals (**f**). (**g**) Tumor cells replace the wall of a uterine blood vessels and fibrin. (**h**) The tumor is polypoid, projecting in to the uterin cavity and involving myometrium to some extend. There is no hemorrhage. (**i**) Tumor cells separate muscle bundles as they invade myometrium

(computed tomography). Also 1.5 cm lesion in lower external quadrant of left mammary gland was present (Fig. 1a, b). In abdominal MRI (Magnetic Resonance Imaging) multiple metastatic cystic lesions were detected in liver, and an extensive lesion in head of pancreas and in both of the kidneys and in both of the adrenals (Fig. 1c–f). In uterus the lesion was $4 \times 4 \times 5$ cm and had deep myometrial invasion in the left side of the corpus uteri. Initial serum hCG level was 23624 mIU/ml. In lomber puncture the ratio of hCG level in BOS to serum hCG level was found to be lower than 1/60, and cranial CT did not reveal any metastatic lesions. Dilatation and curettages were performed for two times. Firstly performed curettage specimen demonstrated necrotic material, fibrin, and a few couple of nests of atypical intermediate type trophoblasts and lack of chorionic villi. Atypical trophoblasts replaced the walls of arteries which was characteristic of intermediate type trophoblasts (Fig. 1g). The specimen lacked the dimorphic pattern of choriocarcinoma and there was no hemorrage. On immunostaining, 60% of the tumor cells were positive for human placental lactogen (HPL) and 10% of the cells were positive for human chorion gonadotropin (hCG). The Ki-67 labeling index exceeded 40%. Even all findings were consistent with PSTT, recurettage was requested because of the small amount of material and high level of serum hCG. Recurettage specimen revealed the same histopathologic and immunostaining pattern. As the patient had no desire of future fertility chemotherapy and laparotomy with hysterectomy and bilateral pelvic lymphadenectomy and omentectomy were planned and performed. In the first chemotherapy course the patient developed febrile neutropenia and total dose of etoposide was reduced by 50% (by omitting the day 2 doses of etoposide for all of the subsequent EMACO therapies) and prophylactic recombinant human granulocyte colony stimulating factor (G-CSF) was added. The initial hCG value decreased to the level of 4039 mIU/ml after third course of EMA/CO (etoposide 100 mg/m^2/day in day 1, methotrexate 300 mg/m^2/in day 1 (with intramuscular folinic acid 15 mg given at 24 h after commencing the methotrexate dose), actinomycin D 0.5 mg/day in days 1 and 2, cyclophosphamide 600 mg/m^2/day in day 8, oncovin (vincristine) 1 mg/m^2/day in day 8, of every 14 days) [2–4]. Grossly, on pathologic examination of specimens obtained by the operation performed at this stage, the uterus showed a 2 cm polypoid tumor, projecting into the cavity. On the sectioned surface, it was soft and tan, and invaded 1 cm thickness of the myometrium (Fig. 1h). Microscopically; the tumor was composed of large, polygonal implantation site intermediate trophoblastic cells with irregular, hyperchromatic nuclei and dense eosiofilic cytoplasm. At the periphery of the tumor, the atypical trophoblastic cells

invaded singly and in nests separating muscle fibers (Fig. 1i). Few mitosis (1–2/10 high power fields) and minimal necrosis were identified. Immunohistochemical stains revealed that tumor cells, were almost diffusely immunoreactive for cytokeratine, epithelial membrane antigen (EMA), and hPL (human placental lactogen) in 50–60% of cells; Mel-CAM (CD 146) in 60–70% of cells; PLAP (placenta-specific alkaline phosphatase) in 10–15% of cells, hCG in 10–15% of cells. Ki-67 was positive in 35–40% of tumor cells. Tumor cells were all negative for HMB-45. Omental tissue and pelvic lymph nodes were free of the tumor. After 6th courses of chemotherapy and the operation serum hCG value was 766 mIU/ml. Whole body PET (positron emission tomography) and CT imaging revealed no evidence of malignancy. BEP (bleomicin 30 mg/day in days 1, 7, and 15; etoposide 100 mg/m^2/day in days 1–5; and cisplatin 20 mg/m/day in days 1–5, of every 21 days) chemotherapy for four courses was initiated because of the still high serum hCG level [2, 5]. After four courses of chemotherapy hCG was below 1 mIU/ml. 12 months following the second line chemotherapy, patient was free of disease with hCG level of 1 mIU/ml.

Discussion

Baergen et al. reported that significant factors associated with adverse survival were: age over 35 years, interval since the last pregnancy of over 2 years, deep myometrial invasions, stage III and IV, maximum hCG level >1,000 mIU/ml, extensive coagulative necrosis, high mitotic rate, and the presence of cells with clear cytoplasm in their 55 cases. They stated that only stage and clear cytoplasm were independent predictors of overall survival, while stage and age were the only independent predictor of time to recurrence or disease-free survival. Also their review including 180 cases in literature revealed that stage, interval since the last pregnancy of over 2 years, previous term pregnancy, high mitotic rate, and high hCG level are the factors that are associated with survival. In this study, reported percentage of stage IV was 9% and Hassadia et al. reported the highest serum hCG level that is 107600 IU/l (range 6–107600 IU/l) [6, 7].

Our case was 24 years old. Interval since the last pregnancy which was term was 5 months. Tumor was stage IV according to FIGO (International Federation of Gynecology and Obstetrics) gestational trophoblast staging system [8]. Serum hCG level was 23,624 mIU/ml.

Favorable prognostic factor that our case possesses are the fact that the tumor was polypoid with 1 cm superficial invasion of myometrium, had minimal coagulative necrosis other than extensive, no cells with clear cytoplasm, low mitotic rate as 1–2/HPF. Also all of 11 lymph nodes from right and left pelvic regions showed reactive lymphoid hyperplastic changes.

As the current case had high initial level of serum hCG we rendered the literature from that point of view. In Baergen's article of review [6], there are four (7%) of 55 cases with serum hCG level above 3,000 mIU/ml. Also Seung Kim is mentioning that seldom hCG levels in PSTT can be as high as in choriocarcinoma [9]. Also, in advanced stages of the disease it could be very high (Table 1).

Paradinas is also mentioning that some aggressive PSTT might be change biological behavior in metastasis because of identifying reversal immunostaining pattern (more hCG than hPL positive cells [12]). These entities may be the explanation of the high level of hCG and fine response to chemotherapy in some of the PSTT. Also this could be a subject of further studies.

The reported most common metastatic sites were the lungs, liver, and vagina [6]. Our case had multiple metastases including lung, liver, thyroid, pancreas, breast, kidneys, and adrenals. To date our case is the first case with breast and thyroid metastasis. In medline search our case is third case with adrenal metastases and fifth tenth case with pancreas metastases [1, 6, 7, 13–15]. Surgery and chemotherapy combinations seem to be the commonest preferred option for the treatment of stage IV PSST cases. Metastatic disease is not an obstacle for surgery. Limited numbers of reported survival in stage IV vary between 1 and 12 years. Hysterectomy with or without oopherectomy and lymph node dissection is recommended as surgical options [2]. Because adnexal micrometastasis is infrequent (3%), preservation of the ovaries is recommended, especially since the majority of patients are supposed to be less than 40 years of age [1]. In the present case, we preserved the ovaries as she was 24 years old. However her FSH level was 51 IU/l following multiagent chemotherapy. She is in iatrogenic menopause. So bilateral oopherectomy decisions should be based on patients' fertility desire, spread of the disease, ovaries' condition during the operation, and informed patients' desire in such cases with many metastases. Multiple metastatic focuses may respond to chemotherapy, otherwise need surgery which is recommended [16, 17]. But initiation of treatment with chemotherapy may be an advantage in cases with multiple metastasis because number of surgery on metastatic sites can be reduced as it is in our case. Another controversial issue is lymphadenectomy. It may be considered in patients who lack poor prognostic characteristics and would not receive adjuvant chemotherapy [16]. Because we were encouraged by good response to initial EMACO treatment and expected good prognosis, we performed pelvic lymphadenectomy. Mostly recommended chemotherapy option for metastatic PSTT is multiagent chemotherapy, namely EMA/CO. The response rate has been reported to be 71%

Table 1 Summary of stage IV placental site trophoblastic tumor cases in the literature

References	Number of case	Age (years)	GPA	Last pregnancy (months) type	Metastases (site)	Stage	Serum hCG (IU/l)	Treatment	Follow-up (years)
[4]	1	32			Scalp	IV	158	H, EMA-CO+G-CSF, CE	1 AWD
[1]	11				Brain, liver, kidney pancreas, bladder, colon spleen, stomach, urethra, vagina, lymph node, ovary	IV		2 Chemo only, 4 Chemo then H 7 H then Chemo 1 BSO then Chemo	Survival for stege IV is 9% when reported
[10]	2				Brain, bowel	IV		Chemo/surgery/Chemo	
[7]	3	43	–	156	Lungs, vagina, liver, brain	IV	107600	MAE, CEC, IT, MTX, RT	2 DOD
	–	50	–	132	Lungs, spinal, kidneys, pancreas	IV	45690	EP/EMA, CP, MICE, RT MTX	12 DOD
	–	43	–	36	Lungs, liver	IV	111	EP/EMA, CP, CEC, HDC	1.25 AWD
[6]	5	44	G4P4	–	–	IV	26000	D and C/H/Chemo	DOD
	–	32	G2P2	24	–	IVB	1880	D and C/H/Chemo	1.6-DOD
	–	30	G3P1	13	–	IVB	90	D and C/H/Chemo	2.5-NED
	–	36	G3P3	108		IVB	5500	D and C/H/Chemo	4-DOD
	–	28	G4P3A1	18	–	IVB	22000	D and C/Chemo	1-DOD
[11]	1	25		–	Ovary, skin		8345	D and C/H/Chemo	2.2-DOD
Present case	1	24	G1P1	5	Liver, thyroid gland, pancreas mammary gland, kidneys, adrenals	IV	23624	EMA-CO/H + BSO+PL+O/ EMA-CO, BEP	1 NED

G = Gravidity; P = parity; A = abortion; hCG = human chorionic gonadotropin; D and C = dilatation and curettage; H = hysterectomy; BSO = bilateral salpingo-oophorectomy; PL = pelvic lymphadenectomy; O = Omentectomy; Chemo = chemotherapy; NED = no evidence of disease; DOD = died of disease; AWD = alive with disease; MAE = Methotrexate/dactinomycin, etoposide; CE = Etoposide/cisplatin; CEC = Cyclophosphamide/etoposide/cisplatin; IT = intrathecal; RT = Radiotherapy; EP/EMA = Etoposide, cisplatin/etoposide, methotrexate/dactinomycin; MICE = Methotrexate, ifosfamide, cisplatin, etoposide; MTX = Methotrexate; CP = Carboplatin, paclitaxel; HDC = High dose chemotherapy; EMA-CO = etoposide, methotrexate, actinomycin D, cyclophosphamide, oncovin; BEP = bleomycin, etoposide, cisplatin

with a complete response in 38% of patients [6]. Salvage treatment alternatives are EMA/EP (etoposide, methotrexate, actinomycin D, etoposide, and cisplatin), BEP (bleomycin, etoposide, and cisplatin) and VIP (etoposide, ifosfamide and cisplatin) [6]. As the number of cases with metastatic lesions are not sufficient to plan prospective randomized studies to determine the best regimen in management of metastatic placental site tumors and the data obtained by management of such cases will help to enlighten the ideal management strategy in this type of metastatic tumor.

Furthermore, because of high level of serum hCG and complete response to chemotherapy, it might be worth discussing about the diagnosis. Tumor mass is composed of large cells with pleiomorphic, abundant eosinophilic cytoplasm predominantly and scattered multinucleated giant cells. There is neither hemorrhage nor bilaminar pattern. Within the tumor mass, there are intact venouse sinuses and capillaries in many areas which is the major point of distinction of PSTT from choriocarcinoma. Beyond the histopathologic characteristic features, positive staining for hPL and MelCAM in majority of tumor cells and minor positivity for hCG and 35–40% positivity for Ki-67 supports the diagnosis of PSTT rather than choriocarcinoma, epithelioid trophoblastic tumor, and benign counterpart of intermediate type trophoblastic lesions. However the most important immunohistochemical reagent to indicate atypical trophoblast as intermediate type is HLA-G [18]. But it is not available at present in our country. “HLA-G” is not available at present in our country.

In this case, contrary to common belief that PSTT is resistant to chemotherapy metastatic lesions responded completely to EMA-CO regimen. However, after six courses of EMA/CO and total abdominal hysterectomy and pelvic lymph node dissection between third and fourth course of EMA/CO, hCG level decreased and plateaued at hCG level of 766 mIU/ml. BEP regimen had to be initiated as a salvage therapy. In conclusion, surgery and multiagent chemotherapy seem mainstay of treatment of cases having multiple metastases of PSTT’s. BEP seems to be a good alternative in patients who have persistent disease after treatment with non-platinum-containing regimens.

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