




A Case Series of Gestational Choriocarcinoma with Review of Literature

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Abstract

Choriocarcinoma can be gestational and nongestational. Gestational choriocarcinoma is rare with an incidence of 9.2 in 40,000 pregnancies in Asian population. They can occur following molar, partial molar pregnancy, abortion, or delivery. It is detected by elevated levels of serum beta-human chorionic gonadotropin (beta-hCG) and by imaging modality. The need for histopathological diagnosis for choriocarcinoma is debatable. Six cases of choriocarcinoma are described with variable presentations and outcomes. Out of six cases, three were following vaginal delivery, two were after abortion, and one case was perimenopausal with antecedent pregnancy 10 years ago, unclear whether it was the cause for choriocarcinoma. Brain and lung metastasis were seen in three cases each; one case, which had metastasis to all organs, had worse prognosis and succumbed to the disease. All belonged to high-risk group according to International Federation of Gynaecology and Obstetrics score (8–13). The prognosis is usually very good, provided that prompt diagnosis and treatment are initiated early. Long-term follow-up with beta-hCG levels needs to be done to detect recurrence but it did not act like a prognostic indicator in our case series.

Keywords

- ▶ choriocarcinoma
- ▶ gestational trophoblastic neoplasia
- ▶ metastasis

Introduction

Choriocarcinoma is a subtype of gestational trophoblastic neoplasia (GTN), an extremely malignant tumor. GTN also includes invasive mole, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). Choriocarcinoma and molar pregnancy arise from cytotrophoblasts and syncytiotrophoblasts, whereas PSTT and ETT arise from intermediate trophoblasts.¹ It produces human chorionic gonadotropin (hCG) and is highly vascular.² Gestational choriocarcinoma is a rare malignancy with an incidence of 9.2 in 40,000 pregnant women in southeast Asia.³ GTN can be distinguished into nonmetastatic and metastatic. Lesions that are limited to the uterus are termed nonmetastatic

GTN. Lesions outside the uterus that spread typically through hematogenous dissemination are termed metastatic GTN.⁴ Most common site of metastasis is lung, followed by vagina, brain, liver, and intestines.⁴ Early diagnosis of gestational choriocarcinoma is crucial as it is highly chemosensitive and has an excellent prognosis, even in advanced stages.³ This case series demonstrates different scenarios of choriocarcinoma. Here, we would like to share six cases of choriocarcinoma in the last 5 years in our hospital (▶ **Table 1**).

Case 1

A, P1L1A2, 24-year-old lady who had delivered 2 months back visited general hospital with postpartum persistent

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Table 1 Clinical presentations of the cases

No.	Age (y)	Clinical presentation	Antecedent pregnancy	Interval (mons)	Beta-hCG (mIU/mL)	Sites of metastasis	FIGO score	Treatment	Outcome
1	24	Postpartum persistent vaginal bleeding, altered sensorium, slurred speech	Vaginal delivery	2	1,08,000	Brain	12	6 cycles of EMACO Brain radiation	In remission; no relapse
2	32	Generalized weakness	Missed abortion (HPR-NA)	2	34,900	All organ metastasis	12	Ongoing 1st cycle of EMACO	Died
3	31	Lower abdominal pain	Incomplete abortion (HPR-NA)	3	5,872	Brain, lungs	12	2 cycles of EMACO; developed respiratory complication; discontinued treatment	Lost to follow-up
4	28	Pain abdomen, irregular vaginal bleeding	Vaginal delivery	13	68,000	Nil	8	6 cycles of EMACO	In remission; no relapse
5	52	Pain abdomen, generalized weakness	Vaginal delivery	120	2,26,150	Nil	13	6 cycles of EMACO followed by TAH + BSO	In remission; no relapse
6	32	Pain abdomen, amenorrhea	Vaginal delivery	18	8,49,850	Lungs	12	Still under treatment. Received 2nd cycle of EMACO	-

Abbreviations: Beta-hCG, beta-human chorionic gonadotropin; EMACO, etoposide, methotrexate, actinomycin-D, cyclophosphamide, oncovin; FIGO, International Federation of Gynaecology and Obstetrics; HPR, histopathology report; NA, not available.



Fig. 1 Computed tomography brain showing an intraparenchymal lesion in left frontoparietal region.

vaginal bleeding, for which she underwent dilatation and curettage. Histopathology report (HPR) showed features of choriocarcinoma (>5cm tissue). Her first pregnancy was partial molar pregnancy and second pregnancy was a missed abortion; HPR was not available. She came to our center with complaints of altered sensorium and slurred speech. At the time of presentation, her Glasgow Coma Scale was 12/15. Computed tomography (CT) brain (► **Fig. 1**) showed an intraparenchymal hematoma with perilesional edema in left frontoparietal region causing cerebrovascular attack with right hemiparesis and aphasia and a 5 mm mid-line shift. Chest X-ray was normal, and beta-hCG levels were 1,08,000-mIU/mL. Neurosurgery did not recommend any need for surgical intervention immediately as there was no active bleeding noted in brain parenchymal tissue and they advised to start chemotherapy.

Her International Federation of Gynaecology and Obstetrics (FIGO) score was 12 (high risk: <40 years old [24 = 0]), index pregnancy (vaginal delivery = 2), time since delivery (2 months = 0), beta-hCG (1,08,000mIU/mL = 4), size of tumor (>5cm = 2), metastasis (brain = 4), number of metastasis (two = 1), and previous failed chemotherapy drugs (no = 0).

She received six cycles of chemotherapy with etoposide, methotrexate, actinomycin-D, cyclophosphamide, oncovin (EMACO) followed by cranial radiation therapy of 20 fractions. Post-treatment beta-hCG dropped to 5.13mIU/mL. Presently she has minimal right upper limb weakness and is on follow-up for the last 4 years.

Case 2

A lady aged 32 years, P1L1A1, underwent suction and evacuation for missed abortion at outside hospital 2 months ago but HPR was not available. She came to our center with generalized weakness and bilateral lower limb pain. On evaluation, beta-hCG levels was 34,900 mIU/mL and contrast-enhanced computed tomography (CECT) abdomen

showed intrauterine mass of 4 × 4cm suggestive of gestational trophoblastic disease with hepatic, pancreatic, renal, adrenal, and bilateral lung lesions, suggestive of metastatic deposit. Magnetic resonance imaging (MRI) brain showed left parietal hemorrhagic dural metastasis.

Her FIGO score was 12 (high risk): less than 40 years old (32 = 0), index pregnancy (abortion = 1), time since abortion (2 months = 0), beta-hCG (34,900mIU/mL = 2), size of the tumor (4 cm = 1), metastasis (liver and brain = 4), number of metastasis (>8 = 4), and previously failed chemotherapy drugs (no = 0).

She was started on EMACO chemotherapy regimen. During first cycle chemotherapy patient desaturated and succumbed to the advanced disease.

Case 3

A 31-year-old lady, G3A2, had undergone suction evacuation for incomplete abortion 2 months ago outside hospital. HPR was not available. She came to our center with 2 months of amenorrhea, lower abdominal pain, and excessive vomiting. Her beta-hCG was 5,872mIU/mL. Ultrasound abdomen showed an enlarged uterus with a heterogenous mass (>5cm) lesion within the endometrial cavity, infiltrating the myometrium, suggestive of GTN. CECT chest was suggestive of lung metastasis. MRI head showed hemorrhagic vascular periventricular deposits in the right corona radiata involving the choroid plexus of the bilateral lateral ventricle, third and fourth ventricle (brain metastasis).

Her FIGO score was 12 (high risk): less than 40 years old (31 = 0), index pregnancy (abortion = 1), time since delivery (<4 months = 0), beta-hCG (5,872mIU/mL = 1), size of the tumor (5 cm = 2), metastasis (lungs and brain = 4), number of metastasis (>8 = 4), and previously failed chemotherapy drugs (no = 0).

She was planned for six cycles of EMACO regimen and cranial radiation. She received two cycles of chemotherapy; later she developed complaints of breathlessness, hypotension and was diagnosed to have pulmonary edema. The patient and family discontinued the treatment in view of financial constraints and were lost to follow-up.

Case 4

A multiparous (P5L5) lady of 28 years presented to a hospital outside with 2 months duration of pain abdomen and irregular heavy menstrual bleeding. All were normal vaginal deliveries; last childbirth was 1 year ago. After dilatation and curettage, medical management for abnormal uterine bleeding was tried, but her symptoms were not relieved. Finally, they did a total abdominal hysterectomy with bilateral salpingectomy in that hospital. HPR showed features of choriocarcinoma (<3 cm tissue). Serum beta-hCG was 68,000mIU/mL. She came to our center and we did CECT chest and MRI brain that showed no evidence of metastasis.

Her FIGO score was 8 (high risk): less than 40 years old (28 = 0), index pregnancy (term = 2), time since delivery (>12 months = 4), beta-hCG (68,000mIU/mL = 2), size of

the tumor (<3 cm = 0), metastasis (no = 0), and previously failed chemotherapy drugs (no = 0).

She received six cycles of chemotherapy with EMACO. Post-chemotherapy beta-hCG was 3.13mIU/mL. She is being followed up for the past 2 years and is doing fine.

Case 5

A 54-year-old perimenopausal woman, P6L6, presented to our hospital with lower abdominal pain. She had lost weight and experienced easy fatigability. Her last menstrual period was 6 months ago. Her previous cycles were normal. She had all vaginal deliveries, with no history of GTN and her last delivery was 10 years ago. On admission, she was pale and tachycardic, and systemic examination was normal. Uterine fundus was 12 weeks enlarged. Ultrasound abdomen revealed large hyperechoic heterogeneous lesion with cystic changes that measure 6.2 × 5.8cm, with no vascularity and no lesions in the liver and lungs. Beta-hCG was 2,26,150-mIU/mL. Chest X-ray and MRI brain were normal.

Her FIGO score was 13 (high risk): more than 40 years old (52 = 1), index pregnancy (term = 2), time since delivery (10 years = 4), beta-hCG (2,26,150mIU/mL = 4), size of the tumor (>5 cm = 2), metastasis (no = 0), and previously failed chemotherapy drugs (no = 0).

She received six cycles of chemotherapy with EMACO regimen. Beta-hCG levels dropped to 1.40 mIU/mL. She underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. The patient is in good health and is being followed up in our center for the last 4 years.

Case 6

A, P2L2A1, 32-year-old lady presented with complaints of pain abdomen and amenorrhea for 2 months. Scan abdomen showed uterine mass and serum beta-hCG was 8,49,850-mIU/mL. She had delivered her second child 1½ years ago by normal vaginal delivery. Prior to this she had a molar pregnancy that was evacuated and followed by beta-hCG levels. MRI abdomen and pelvis (→ Fig. 2) showed a well-defined multilobulated lesion measuring 10 × 10 × 12cms, arising from the fundus and posterior myometrium. CT chest showed multiple parenchymal lung nodular metastatic lesions. MRI brain was normal.

Her FIGO score was 12 (high risk): less than 40 years old (32 = 0), index pregnancy (term = 2), time since delivery (>12 months = 4), beta-hCG (8,49,850 mIU/mL = 4), size of the tumor (>5cm = 2), metastasis (lung = 0), and previously failed chemotherapy drugs (n = 0).

She is planned for six cycles of chemotherapy with EMACO. She has received two cycles of chemotherapy and currently under treatment.

Discussion

GTN is most commonly seen in reproductive age women. It is seen in 9.2 and 3.3 in 40,000 pregnant women in southeast Asia and Japan, respectively³ and much rarer, that is 1 in



Fig. 2 Magnetic resonance imaging of pelvis showing multilobulated lesion of $10 \times 10 \times 12$ cm arising from the fundus and posterior myometrium.

50,000 deliveries in United States of America.² It can occur after any antecedent pregnancy. It usually occurs 50% of cases after hydatidiform mole, 25% cases after spontaneous abortion, 22.5% after normal pregnancy, and 2.5% after ectopic gestation.⁵ In our case series, out of six cases, three cases were after vaginal delivery that is difficult to diagnose as they present with abnormal uterine bleeding (either amenorrhea, irregular vaginal bleeding or persistent vaginal bleeding) and present to the hospital late. Two cases were after abortion where products were not sent for HPR, so it might have been a type of molar pregnancy that needed follow-up. It is extremely important to send the products for HPR. The case in perimenopausal age was nearly 10 years after her last pregnancy, so one cannot be sure what triggered the choriocarcinoma, whether it was the antecedent pregnancy or did it happen de novo. In such cases, it is difficult to say whether the antecedent pregnancy led to choriocarcinoma.⁵

Choriocarcinoma after nonmolar pregnancy is associated with worse outcomes due to delay in diagnosis and widespread metastatic disease, increased interval between onset of disease, and previous pregnancy.⁶ In our case series, all were after nonmolar pregnancies and in that four had metastatic disease. So, high level of suspicion and prompt diagnosis and appropriate treatment with chemotherapy can save lives and will have very good prognosis. Choriocarcinoma can clinically present with abnormal uterine bleeding, acute pelvic pain, and metastatic symptoms such as chest pain, cough, hemoptysis, dyspnea, epigastric pain, neurological deficits secondary to brain hemorrhage. GTN is further classified into metastatic and nonmetastatic disease. Nonmetastatic disease occurs in 15% of cases and metastatic disease in 4% of cases after complete mole evacuation. Metastatic disease is more often seen after nonmolar gestation.⁷ Metastasis is most commonly to lungs 60 to 75%, vagina 40 to 50%, brain and liver 15 to 20%,

spleen, central nervous system and intestines 10%, very rarely manifests as cardiac metastasis. In 30% cases, by the time of final diagnosis, metastasis would have already occurred.⁵ In our case series, brain metastasis was seen in three cases, lung metastasis was seen in three cases, one case had multiorgan metastasis that had worse prognosis and succumbed to the disease, and two cases had no metastasis.

Initial diagnosis is made based on clinical features, serum beta-hCG, and pelvic imaging such as ultrasound and MRI. Beta-hCG is an excellent marker for diagnosis. First line of imaging is color Doppler USG, used to look for uterine cavity and vascularity. Choriocarcinoma is characterized by myometrial and vascular invasion.⁸ As diagnostic adjuvants, CT or MRI can be used to assess depth of myometrial invasion and extrauterine spread. Chest radiography, high-resolution CT chest, and MRI brain are used to stage the disease.⁵ Diagnosis is confirmed after histopathological examination of endometrial curetting or the placenta. The true incidence of choriocarcinoma may be higher than the reported data, likely due to missed cases as half of the cases are asymptomatic and routine pathological examination of placenta is not performed.⁸

The World Health Organization (WHO) prognostic scoring system is used for plan of management. If it is low risk (score < 6), single agent chemotherapy is given. If it is a high risk (score > 7), multidrug chemotherapy with or without surgery/ radiation therapy is the line of management. Beta-hCG is an excellent surveillance marker for choriocarcinoma but is not a prognostic indicator as in our series we found patients with low beta-hCG performed poorly. Five-year survival rate can be up to 90%.² GTN is a rare human tumor that can be cured even in the presence of widespread dissemination.⁷ In all our cases, FIGO score ranged from 8 to 13, belonged to high-risk group. EMACO was the first line of choice for multidrug chemotherapy in our cases. One patient died and one lost to follow-up, one patient is currently under treatment, and other cases are under remission. Our patients who completed the treatment achieved undetectable beta-hCG levels after four cycles and went on to receive two more cycles of consolidation chemotherapy. The need for increased methotrexate dose was not required in our case 1 who had brain metastasis as she responded well to regular EMACO regimen and she also received brain radiation. In patients with brain metastases, an increase in the methotrexate infusion to $1\text{g}/\text{m}^2$ will help the drug cross the blood-brain barrier better and is found to be beneficial. Some centers also use intrathecal methotrexate of 12.5 mg.⁹ This can be given at the time of CO when EMACO is used, or with the EP in the etoposide, methotrexate, actinomycin-D, etoposide, cisplatin (EMA/ EP) regimen. Some may give whole brain radiotherapy 3000 cGy in 200cGy daily fractions concurrent with chemotherapy or use stereotactic or gamma knife radiation to treat existing or residual brain metastases after chemotherapy.⁹

Recurrence rate of conventional low-risk GTN is 1.6 to 3.1% and high-risk is 6.9%.⁴ Even in cases of recurrence, a

good cure rate has been observed with the use of etoposide and platinum drugs, combined with surgical excision of drug-resistant lesions and radiation therapy. For patients failing to respond to regular EMACO regimen, multiple salvage therapies are also available. Other chemotherapy regimens include TP/TE (paclitaxel and cisplatin interchanged with paclitaxel and etoposide weekly), BEP (bleomycin, etoposide, cisplatin), VIP (etoposide, ifosfamide, cisplatin), and ICE (ifosfamide, carboplatin, etoposide). Role of peripheral blood stem cell support and high-dose chemotherapy is uncertain. Role of immunotherapy in the management needs further investigation. The fact that GTN strongly expresses Programmed Death - Ligand 1 (PD-L1) has led to checkpoint inhibitor use in GTN, a significant advance of immunotherapy in recent years. Pembrolizumab (anti-PD-L1) has effectively induced complete responses in 75 to 80% of unresectable, chemo-resistant GTN, including cases that had failed high dose chemotherapy.⁴

In a case series of six cases, patients displayed a variety of unusual clinical manifestation including suspected pulmonary tuberculosis, lung mass, pneumonia, heavy vaginal bleeding, pelvic mass, and peritonitis that highlighted the importance of having a high degree of clinical suspicion of choriocarcinoma in women of reproductive age.¹⁰ All their cases were with scores of 8 to 12, EMACO therapy and selective hysterectomy proved to be beneficial. Administering three cycles of consolidation chemotherapy after remission that is given every 15 days was their standard practice.

In a systematic review,¹¹ a total of 121 case reports pertaining to unusual clinical manifestations of gestational choriocarcinoma were analyzed. The age of patients reported ranged from 17 to 67 years, and the time period between the index pregnancy and development of choriocarcinoma varied from 4 weeks to as long as 25 years. This shows choriocarcinoma can occur in any age (even menopause) and several years after the antecedent pregnancy just like in our case 5 where diagnosing the disease becomes challenging. Cardiopulmonary complaints (20.66%) followed by gastrointestinal (18.43%) and central nervous system manifestations (17.67%) were found to be the most common.¹¹

Though hematogenous metastasis is well known in choriocarcinoma that spreads to lung initially and liver is the most common organ to metastasize in the abdomen, authors noted intestine metastasis in 5% cases in their case series.¹² They recommended a comprehensive evaluation including whole abdomen CT for all patients, not only those with pulmonary metastases. Intestinal metastasis has a poor prognosis.

For those patients with widespread metastasis, starting with standard chemotherapy may cause sudden tumor collapse with severe bleeding, metabolic acidosis, myelosuppression, septicemia, and multiple organ failure, any or all of which can result in early death that may have been the reason in our case 2 as she had extensive metastasis and succumbed to the disease during first cycle of EMACO regimen. To avoid this, the use of initial gentle rather than full-dose chemotherapy has

been suggested. Induction with etoposide 100 mg/m² and cisplatin 20 mg/m² on days 1 and 2, repeated weekly for 1 to 3 weeks, before starting normal chemotherapy appears to have eliminated early deaths in one series¹³ and similar promising results were reported by others too.¹⁴

Conclusion

Obstetricians and clinicians should have increased awareness of varied symptoms and presentations; a choriocarcinoma can present with and importance of early diagnosis. Delaying in diagnosis results in poor prognosis. So, high level suspicion and prompt diagnosis and treatment with chemotherapy can save lives. Serum beta-hCG is an excellent surveillance marker for choriocarcinoma and can be monitored to detect recurrence but prognosis does not depend on the levels.

Authors' Contributions

All authors have agreed for the manuscript description. AT contributed to data collection and manuscript preparation. VS contributed to concept design and clinical treatment. NN contributed to manuscript preparation and editing.

Patient's Consent

Informed consent was obtained from all individual participants included in the study.

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Conflict of Interest

None declared.

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