Case report

Invasive Hydatidiform Mole Showing Resistance to Single Etoposide Chemotherapy

Satoru Takeuchi

Department of Gynecology and Obstetrics, Kochi Health Sciences Center, Kochi, Japan

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Introduction

Gestational trophoblastic disease (GTD) varies widely among various populations with figures as high as 1 in 120 pregnancies in some areas of Asia and South America compared with 0.6 – 1.1 per 1000 in the United States¹. Approximately 92% of hydatidiform moles resolve spontaneously after evacuation, and the majority of the rest can be successfully treated with a minimum of toxicity². However about 20% of cases become chemoresistant and require multi-agent chemotherapy such as MAC (MTX, Act-D, Cyclophosphamide) or MEA (MTX, etoposide, Act-D). In general, GTD is hypervascular, and transvaginal ultrasonography is useful for detection of blood flow in the tumor during treatment to assess its activity.

Case Presentation

A 28-year-old woman with no gravida visited a clinic because of genital bleeding. The patient had normal menstrual periods until November 2005. She was diagnosed as having a hydatidiform mole and underwent a dilatation and curettage. Histological examination revealed a total hydatidiform mole. About one month after the curettage, she had massive genital bleeding with a Hb of 5.9 g/dL. Before the curettage, the urine hCG level was 306,695 mIU/mL (Table 1). On day 13 after the curettage, the serum β -human chorionic gonadotropin (β -hCG) level was 18 ng/mL, and the level increased to 273 ng/mL at the time of massive bleeding. The patient was diagnosed as having an invasive hydatidiform mole by vaginal ultrasonography (US) and MRI. She was referred to our institution for treatment.

When she visited our institution, her serum hCG level was 53,572 mIU/mL. A vaginal US revealed a $2.8 \times 2.5 \times 4.3$ cm tumor with a cystic component in the uterine body in which blood flow was identified (Fig. 1). In enhanced images CT, an irregularly enhanced tumor was identified in the uterine body (Fig. 2). No tumor was identified in the abdomen or chest; a tumor was only identified in the uterine body. The patient was diagnosed as having a clinical invasive hydatidiform mole (WHO classification) in Stage Ib according to the FIGO Anatomical Staging. The disease was confined to the uterus. The patient's risk factor score was three (Modified WHO Prognostic Scoring System as Adapted by FIGO; Table 2). As the patient was in a low risk group (less than 7 points), a single etoposide treatment (100 mg/m² for 5 days iv with a three week interval) was adopted according to the General Rules for Clinical and Pathological Management of Trophoblastic Disease in Japan in 1995.

The level of serum hCG fell in good response until the 3rd course of single etoposide chemotherapy, but around the 4th course, it was elevated (Fig. 3). The patient was considered to have developed chemoresistance. A combination regimen of MAC was then performed instead of the single etoposide treatment. The serum hCG and β -hCG levels then began to decrease well and could not be detected after the first course of MAC therapy. The serum-hCG-CTP level could not be detected after the second course of MAC therapy. Another two courses of MAC were administered. After 4 courses of etoposide treatment, 2.7 cm tumor (max diameter) was identified by US and CT. After 2 courses of MAC therapy, the tumor could no longer be found and no blood flow was identified in the uterine muscle. Three months after the last chemotherapy, the basal body temperature was

Table 1. Transition of the hCG level

	Before curettage	Day 13	Day 19	After 6 weeks	At first visit
Urine hCG (mIU/mL)	306,695		388	12,807	16,404
Serum β -hCG (ng/mL)		18		273	267

Correspondence to: Satoru Takeuchi
Kochi Health Sciences Center, Gynecology and Obstetrics, Ike 2125-1,
Kochi City, Kochi 781-8555, Japan
E-mail: satoru_takeuchi@khsc.or.jp

Figure 1 Findings of ultrasonography on the first visit. a, b: A tumor of $2.8 \times 2.5 \times 4.3$ cm in diameter with cystic compartment in the uterine body. c: Blood flow was identified in the tumor.

Figure 2 Findings of enhanced CT on the first visit. An irregularly enhanced tumor was identified in the uterine body.

biphasic. The patient became pregnant six months after the last MAC therapy and gave birth to a healthy newborn via a smooth vaginal birth.

Discussion

The total number of GTD cases has dropped steadily from 1938 (1979–1981) to 483 (1999–2001)³. The exact reasons for this change are not apparent. Factors such as decreased parity and improved socioeconomic conditions in many countries may be responsible³.

In normal pregnancy, the serum β -hCG level reaches a peak of 50,000–100,000 mIU/mL at about 12 weeks of

gestation, decreases to 10,000–20,000 mIU/mL by 20 weeks and remains at that level until term⁴. Invading trophoblasts from hydatidiform moles and choriocarcinomas secrete higher amounts of hCG compared with trophoblasts in a normal pregnancy⁵. In GTD, higher levels of hCG may elicit stronger immunosuppression at the primary site, which allows malignant trophoblasts to escape from maternal immune system surveillance^{6, 7}.

The current classification scheme of the World Health Organization is based on histologic characteristics and lists the hydatidiform mole (complete or partial), invasive mole, choriocarcinoma, placental site trophoblastic tumor, miscellaneous trophoblastic tumor and unclassified

Table 2. Modified WHO prognostic scoring system adapted by FIGO

Score	0	1	2	4
Age	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval month from index pregnancy	<4	4–6	7–12	>12
Pretreatment serum hCG (iu/l)	<10 ³	10 ³ –10 ⁴	10 ⁴ –10 ⁵	>10 ⁵
Largest tumor size (cm; including uterus)	<3	3–4	≥5	–
Site of metastases	Lung	Spleen, Kidney	Gastro-intestinal	Liver, Brain
Number of metastases	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single drug	2 or more drugs

Stage I: 3 (low risk group).

Figure 3 Transition of serum hCG level.

trophoblastic lesions^{1, 3, 8–11}). Complete moles result from diandry (fertilization of an empty ovum), and partial moles result from diandric triploidy¹¹).

Persistent trophoblastic diseases develop in about 10–15 percent of patients after molar evacuation in Japan, and persistent trophoblastic diseases are classified into three groups: (1) post-molar persistent hCG; (2) invasive mole or metastatic moles; and (3) choriocarcinoma¹²). About 50% of choriocarcinoma originate from the normal pregnancies and the remaining 50% are transformed from invasive moles¹³).

GTD is rare in humans and is extremely responsive to chemotherapy even with metastatic forms¹⁴). The remarkable curability of GTDs with chemotherapy might reflect the great blood flow of the tumor and the underlying immune response of the host (the mother) to paternal antigens expressed on the surface of the trophoblastic

cells¹⁵). Doppler study of the myometrium in invasive gestational trophoblastic disease has proven to be a useful diagnostic tool¹⁶). A score of 6 or less indicates a low-risk disease treatable by single agent chemotherapy. A score of 7 or more indicates a high-risk disease requiring combination chemotherapy^{3, 8, 17}). Most invasive moles have been accompanied by low-risk factors¹⁸).

Chemotherapy is considered to be effective when the level of serum hCG after the chemotherapy decreases to one tenth of all observed pretreatment levels. A change of chemotherapy regimen is indicated in the following conditions: 1. the serum hCG level rises by more than 10% for two to three consecutive values within a 1- to 2-week interval; 2. the serum hCG level plateaus ($\pm 10\%$) for 2–3 weeks; 3. new metastases appear¹⁹). The serum hCG level of the present case dropped to 58 mIU/mL after the third

single etoposide chemotherapy. After that, it rose by more than 10% for two consecutive values within a 1- to 2-week interval. About 20% of cases become chemoresistant and require multi-agent chemotherapy. Chemotherapy with MAC is effective for many diseases when they show resistance to single agent chemotherapy¹⁹⁾.

After diagnosis of a molar pregnancy, follow-up is essential to detect patients who require chemotherapy²⁰⁾. Follow-up mainly relies on serial measurements of serum hCG levels for at least half a year after evacuation²¹⁾.

Patients treated for invasive hydatidiform mole seldom have problems involving post-treatment pregnancy or delivery²²⁾. However, in cases of pregnancy or abortion after treatment with multi-cancer agents, heart malformations are seen in some newborns, and preservation of egg cells may pose a problem at the time of anti-cancer agent administration²²⁾. A previous study followed up patients who conceived within one year after multi-agent chemotherapy and conducted an analysis to determine an abnormal pregnancy result²³⁾. The wastage rate of the patients who conceived in the first half of the year was higher than that of the patients who conceived in the latter half of the year²³⁾. Hydatidiform mole and post term choriocarcinoma have been reported in patients who conceived within 5 months after chemotherapy²³⁾. In the present case, the patient became pregnant six months after the last MAC therapy and gave birth to a healthy newborn via a smooth vaginal birth.

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