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A Case of Rapid Transformation from Hydatidiform Mole to Invasive Mole: The Importance of β-hCG (Human Chorionic Gonadotropin) Serum Levels in Follow-Up Evaluation

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 46-year-old
Final Diagnosis: Invasive mole
Symptoms: Bleeding • vaginal bleeding
Medication: —
Clinical Procedure: Curettage • hysterectomy
Specialty: Obstetrics and Gynecology • Oncology

Objective: Rare disease

Background: Gestational trophoblastic disease (GTD) is a spectrum of disorders consisting of premalignant (ie, complete [CHM] and partial hydatidiform moles [PHM]) and malignant conditions (ie, invasive moles, choriocarcinoma, placental site trophoblastic tumors, and epithelioid trophoblastic tumor). If GTD persists after initial treatment and has persistent elevated beta human chorionic gonadotropin (β-hCG), it is referred to as post-molar gestational trophoblastic neoplasia (pGTN). To date, there is no detailed information regarding how fast invasive moles can develop from CHM. However, the risk of developing any pGTN from CHM is rare within 1 month and is greatest in the first 12 months after evacuation, with most cases presenting within 6 months.

Case Report: We present a case of a 46-year-old primigravida woman with rapid transformation of an invasive mole. In the beginning, the patient had a chief concern of a uterus size greater than the gestational dates. Laboratory evaluation showed high β-hCG serum level (>300 000 mIU/mL), and ultrasonography evaluation revealed a hydatidiform mole. Suction evacuation and curettage procedures were then performed. Pathology evaluation afterwards revealed a complete hydatidiform mole without any sign of malignancy. Twenty-two days afterwards, the patient came to the emergency room with vaginal bleeding. β-hCG serum level was high (53 969 mIU/mL), and ultrasonography examination showed the presence of fluid filling the uterine cavity. The patient was then diagnosed with GTN, and hysterectomy was chosen as the treatment of choice. After the surgery, her β-hCG serum level gradually reverted back to normal.

Conclusions: Invasive moles can develop less than 1 month after suction evacuation and curettage procedure for CHM. Serial β-hCG serum level evaluation according to the guideline should be performed to prevent late diagnosis, which could lead to the development of metastasis and worsen the prognosis.

Keywords: Gestational Trophoblastic Disease • Hydatidiform Mole • Hydatidiform Mole, Invasive

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Background

Gestational trophoblastic disease (GTD) is a spectrum of disorders consisting of premalignant (ie, complete [CHM] and partial hydatidiform mole [PHM]) and malignant conditions (ie, invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor). If GTD persists after initial treatment and has persistent elevated beta human chorionic gonadotropin (β-hCG), it is referred to as post-molar gestational trophoblastic neoplasia (pGTN) [1]. Studies showed that the incidence of PHM is higher than that of CHM, but CHM has a more than 7 times higher risk of developing pGTN [2,3]. About 10-17% will develop into an invasive mole, which is a benign tumor that arises from myometrial invasion via direct extension through tissue or venous channels. Although it is a benign tumor, the mortality rate is 15% [4].

To date, there is no detailed information regarding how fast an invasive mole can develop from CHM. However, the risk of developing any invasive mole from CHM is low within 1 month and is greatest in the first 12 months after evacuation, with most cases presenting within 6 months [3,5]. In this case report, we present a rare case of an invasive mole that developed 22 days after the evacuation of CHM. This case report highlights the importance of serial β-hCG follow-up evaluation, as recommended in the guidelines [6].

Case Report

A 46-year-old primigravida woman was referred to our outpatient clinic in October 2020 with a chief concern of a uterus size greater than the gestational dates. Her last date of menstruation was 8 weeks ago, and the pregnancy test showed a positive result. The patient never had a miscarriage or underwent an abortion. Vital signs were unremarkable. Physical evaluation revealed an enlarged uterus proportional to 16 weeks of pregnancy. Laboratory evaluation showed elevated β-hCG serum level (>300 000 mIU/mL), while other parameters were within normal ranges. Ultrasonography (USG) evaluation revealed a hydatidiform mole (**Figure 1**); therefore, suction evacuation and curettage were performed. After the procedures, USG re-evaluation showed that the hydatidiform mole was completely removed (**Figure 2**). The samples were sent to the pathology anatomy lab for macroscopic and microscopic evaluation, which later revealed a complete hydatidiform mole without any sign of malignancy (**Figures 3, 4**).

The patient was scheduled for follow-up β-hCG serum level evaluation on the 7th, 14th, and 21st days after the procedure. However, the patient did not comply with the follow-up schedule. The patient came on the 9th day after the procedure, where follow-up evaluation showed that β-hCG serum levels fell to 9838 mIU/mL. Because of the significant reduction of the β-hCG serum levels, the patient decided to skip the evaluation on the 14th day. On the 22nd day, the patient came to the emergency room with severe vaginal bleeding. The USG examination showed the presence of fluid in the uterine cavity (**Figure 5**). The hemoglobin level had fallen to 6 mg/dL, and the β-hCG serum level drastically increased to 53 969 mIU/mL. The patient was then diagnosed with GTN. The chest X-ray evaluation showed no sign of distant metastases.

Based on several considerations and discussion with the patient, hysterectomy was chosen as the treatment of choice. Hysterectomy was performed 2 days later, after the hemoglobin level was increased to 8 mg/dL. The specimen was then sent to the pathology anatomy lab for evaluation, which later established the diagnosis of an invasive mole (**Figures 6, 7**). After the surgery, the patient was scheduled for serial β-hCG serum level evaluation. The β-hCG serum level were 355 mIU/mL on the 7th day, 115 mIU/mL on the 14th day, and 62 mIU/mL on the 21st day.

Discussion

Molar pregnancy and gestational trophoblastic neoplasm disorders originate from placental trophoblasts. Normal trophoblastic cells consist of cytotrophoblasts, syncytiotrophoblasts, and intermediate trophoblastic cells. If these 3 cells continue to proliferate, it will become gestational trophoblastic disease. The presence of hydropic degeneration of the chorionic villi with the proliferation of trophoblastic cells can cause death of the embryo. Invasive mole is a GTD spectrum that can still maintain the chorionic villi tissue (benign form) but has the ability to invade. Therefore, some studies classify invasive moles as gestational trophoblastic neoplasia because of its ability to penetrate molar tissue to other organs through the tissue or venous system [4].

In this case report, we presented a rapid transformation of an invasive mole within 22 days after curettage. We found only 2 previous publications that report a rapid transformation of an invasive mole in less than 1 month after curettage [7,8]. In previous reports, the patients were multiparous, while our patient was nulliparous. Distant metastases were present in the previous reports, while invasive utery was present in our case. The detailed differences between our report and previous reports are presented in **Table 1**.

The known risk factors for CHM are: 1) extreme maternal age (<20 or >40); 2) previous history of complete mole; 3) history of spontaneous abortion; 4) dietary deficiency of B-carotene and animal fats; 5) ovulation induction; and 6) certain ethnicities [9]. In our case, the patient was 46 years old and was

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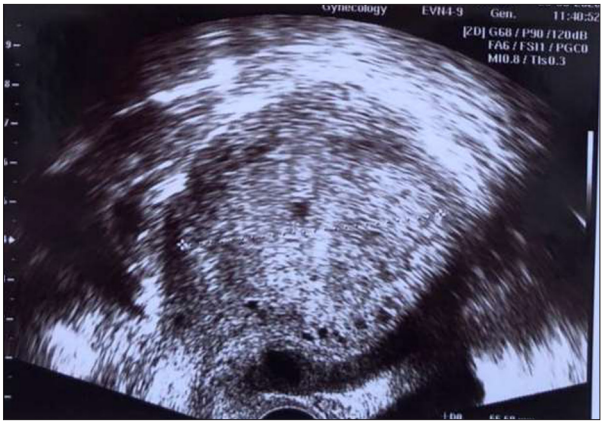

Figure 1. The USG Examination before curettage.

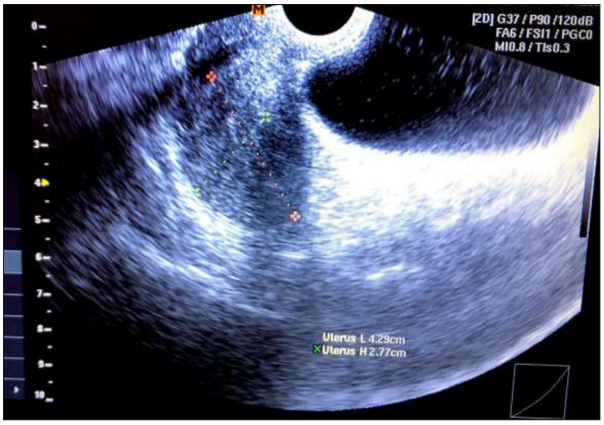

Figure 2. The USG Examination after curettage.

Asian ethnicity. Compared to women aged 21-35 years old, women aged >40 years old have a 7.5 times higher risk of developing CHM [4]. The incidence of CHM is higher in Asian populations compared to non-Asian populations [10]. Data on B-carotene level and animal fats consumption were not available in our patient.

Serial β-hCG evaluation is important in establishing the diagnosis of pGTN because pGTN is usually asymptomatic; therefore, the diagnosis relies on β-hCG surveillance. The monitoring evaluation is recommended to be done every 1-2 weeks after HM evacuation. The patient will be diagnosed with pGTN if the β-hCG serum level does not decline over the period of 3 weeks or if the β-hCG serum level is elevated for 2 consecutive weeks after HM evacuation [6]. In our case, the β-hCG serum level had not yet returned to normal and there was a significant serum level increase on the 22nd day after the HM evacuation. Thus, we decided not to wait for the rise in β-hCG until 3 consecutive weekly measurements, as mentioned in the guidelines, since we were concerned about metastasis. A previous report showed that a lung metastasis can be present on the 7th day after curettage [8]. Histology evaluation later supported the diagnosis of invasive mole in our patient.

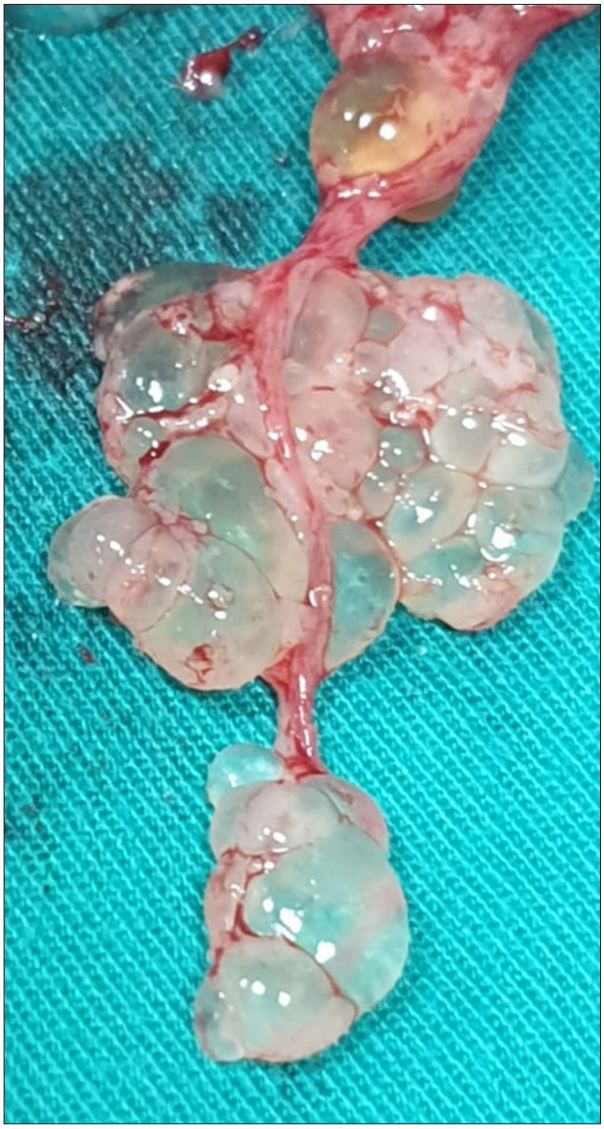

Figure 3. Macroscopic picture of complete hydatidiform mole suction evacuation and curettage procedures showed mole bubbles.

Prophylactic chemotherapy after suction curettage was not given to our patient because our center does not recommend giving that for patient with hydatidiform mole. A previous systematic review concluded that there is currently insufficient evidence to support the use of prophylactic chemotherapy to prevent GTN. Moreover, the chemotherapy regimens are too toxic for routine use, they can delay the time to GTN diagnosis, and can lead to subsequent drug resistance [11].

Hysterectomy is the first-line treatment in placental site trophoblastic tumors and epithelioid trophoblastic tumors since those diseases are less chemosensitive. The primary mode of treatment for invasive moles is chemotherapy [6]. However, hysterectomy was chosen as the treatment of choice for our

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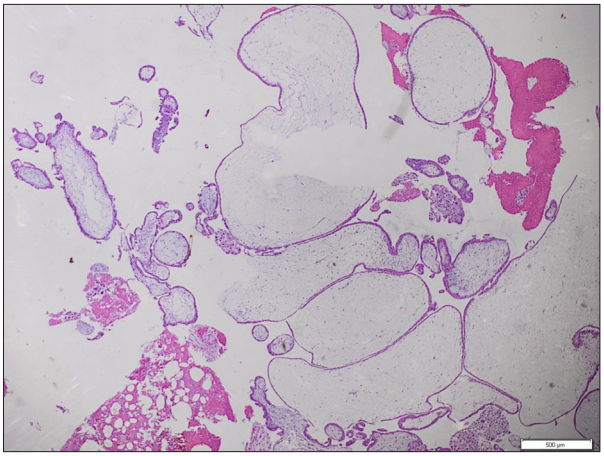

Figure 4. Microscopic image of complete hydatidiform mole showing chorialis villi experiencing hydrophilic degeneration of avascular scalloped form and accompanied by the formation of cisterns lined with proliferative cytotrophoblast cells.

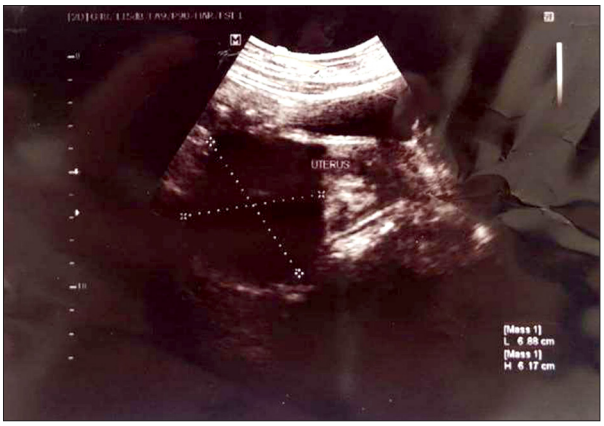

Figure 5. The USG Examination after recurrence.

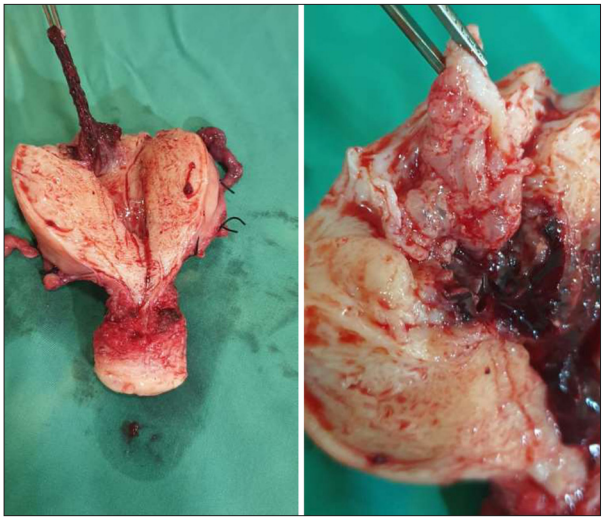

Figure 6. Macroscopic image of uterus with invasive mole in the fundus.

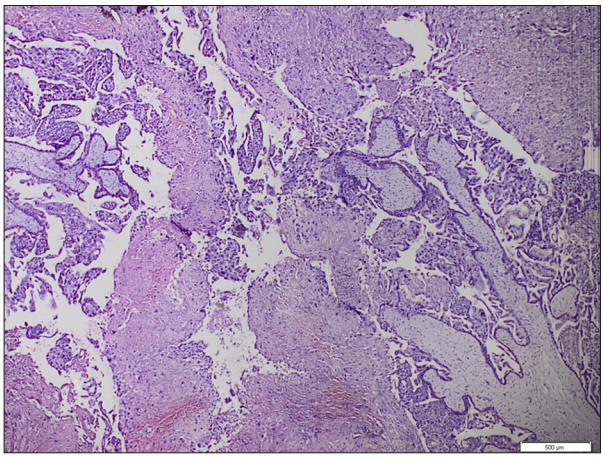

Figure 7. Microscopic image of invasive mole showing chorialis villi that are lined with hyperplastic trophoblast cells and have invaded the myometrium. The villous fibrovascular stroma is partly hydrophilic, with avascular degeneration.

patient based on several considerations: 1) extreme age of the patient [4]; 2) risk of recurrent GTD [12]; 3) patient fear of chemotherapy; 4) patient difficulties complying with the scheduled treatment and follow-up evaluation. The patient was included in the discussion to choose the best treatment option and made the final decision.

Several factors that are known to influence the development of GTN from hydatidiform mole are age, uterine size, parity, and pre-evacuation β-hCG levels [13,14]. In addition, there are 2 genes that are correlated with trophoblastic form: H19 and IGF2. The expression of the H19 gene is increased in complete hydatidiform mole and molar malignancy compared to normal trophoblast in the placenta, whereas IGF2 expression is decreased in complete hydatidiform moles and molar malignancy [15]. Many studies have revealed possible biomarkers that play a role in the transformation of hydatidiform moles to invasive moles [16-22] (**Table 2**). However, there is no clear theory that explains the pathological mechanism of the transformation. Moreover, the factors that contribute to the rapidity of this transformation are also still unknown.

Study limitations

The patient did not comply with the follow-up schedule for serial β-hCG serum level evaluation. Therefore, we cannot provide data on exactly when the β-hCG level started to rise again.

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Table 1. Reported cases of invasive mole rapid transformation after curettage procedure.

Case	Patient's age	Obstetric history	Current pregancy	Initial β-hCG level	Type of hydatidiform mole	Time to transform to invasive mole	Site of metastases	Treatment for invasive mole
Zou et al, 2012 [7]	34	1 pregnancy	16 weeks	800 842 mIU/mL	Partial	3 weeks	Lung	3 cycles of chemotherapy (fluorouracil + dactinomycin)
Martinez Leocadio et al, 2019 [8]	53	7 preganancies	–	684 180 mIU/mL	Complete	1 week	Lung and vagina	Hysterectomy → 3 cycles of chemotherapy (Etoposide + Methotrexate + Actinomycin-Oncovin + Cyclophosphamide)
Current case	46	0 pregnancy	8 weeks	>300 000 mIU/mL	Complete	Less than 22 days	Invasive Utery	Hysterectomy

Table 2. Biomarkers that have been suggested to plays a role in the transformation from hydatidiform mole to invasive mole.

Name of biomarker	Function	Normal placenta	Complete Hydatidiform Mole	Invasive Mole	Molar Malignancies
p57KIP2 [16,23,24]	Cyclin-dependent kinase (CDK) inhibitor in the G1/S phase cycle	Increased	Decreased/ absent	Decreased/ absent	Absent
P53 tumor suppresor [17,25]	Inhibiting the progression of the cell cycle in the G1→S phase/proapoptotic agent	Decreased	Increased	Higly increased	Higly increased
GTPase-activating proteins [18]	Inhibiting the throphoblast proliferation	Highly increased	Increased	Unknown	Absent
protein c-erbB2 [19,25]	Overexpression of the protein c-erb-B-2 was significantly more substantial in the complete hydatidiform mole and choriocarcinoma than in normal placenta and partial mole. This overexpression is due to the extravillous invasion of complete hydatidiform mole and choriocarcinoma. Overexpression of c-erb-B-2 may be associated with high proliferation and aggressive behavior of complete hydatidiform mole and choriocarcinoma	Decreased	Increased	Highly increased	Highly increased
Bcl-2 [20]	Antiapoptotic agent	Highly increased	Decreased	Decreased	Absent
Bax [21]	proapoptotic agent	Decreased/ absent	Increased	Unknown	Highly increased
MMPs [22,26]	Matrix metalloproteinases (MMPs) are a involved in the degradation of the protein matrix to allow trophoblastic invasion of maternal tissue	Decreased/ absent	Increased	Increased	Highly increased
TIMPs [22,26]	Tissue inhibitors of metalloproteinases (TIMPs) have an ability to inhibit MMP activity related to tumor growth and metastasis	Increased	Decreased	Decreased	Decreased

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Conclusions

Invasive moles can develop in less than 1 month after suction evacuation and curettage procedures for CHM. Serial β-hCG serum level evaluation according to the latest guidelines should be performed to prevent late diagnosis, which could lead to the development of metastasis and worsen the prognosis. Further research is needed to understand the pathological mechanism of the transformation and factors that contribute to the rapidity of the transformation.

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Department and Institution where work was done

Department of Obstetrics and Gynecology, Hasan Sadikin Hospital, Bandung, Indonesia.

Conflicts of Interest

None.

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