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A Rare Case of Early Transformation of Gestational Trophoblastic Neoplasia Following Molar Pregnancy

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 19-year-old
Final Diagnosis: Gestational thropoblastic neoplasia
Symptoms: Bleeding
Medication: —
Clinical Procedure: Curettage
Specialty: Obstetrics and Gynecology • Oncology

Objective: Rare disease

Background: Gestational trophoblastic disease (GTD) encompasses a group of disorders that arise from abnormal growth of trophoblastic tissue. The spectrum of GTD includes 2 major groups: benign and malignant. The benign form is a hydatidiform mole, either complete or partial; the malignant forms, referred to as gestational trophoblastic neoplasia (GTN), consist of invasive moles, choriocarcinomas, placental site trophoblastic tumors, and epithelioid trophoblastic tumors. Most patients who undergo evacuation of a hydatidiform mole by curettage have a disease-free period before a new tumor develops that can be considered malignant. In rare cases, metastasis occurs rapidly and manifests coincidentally before the hydatidiform mole can be evacuated.

Case Report: A 19-year-old woman in Bandung City, West Java, Indonesia, was diagnosed with a molar pregnancy with early evidence of a mass in her vagina that was suspicious for stage II GTN. The early emergence of a vaginal mass was a rare case of early transformation of a molar pregnancy into GTN.

Conclusions: Careful evaluation is warranted of patients with characteristics typical of an intrauterine molar pregnancy who have an early presentation of a vaginal mass because of the possibility that the diagnosis could be GTN.

Keywords: Gestational Trophoblastic Disease • Hydatidiform Mole • Vaginal Neoplasms

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/930789

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Background

Gestational trophoblastic disease (GTD) encompasses a group of disorders that arise from abnormal growth of trophoblastic tissue. GTD is divided into 2 major groups: benign, of complete or partial hydatidiform moles, and malignant, referred to as gestational trophoblastic neoplasia (GTN), which consists of invasive moles, choriocarcinomas, placental site trophoblastic tumors (PSTTs), and epithelioid trophoblastic tumors (ETTs) [1,2]. Here, we describe a rare case of early transformation of a molar pregnancy to GTN.

Case Report

A 19-year-old woman in Bandung City, West Java, Indonesia, was diagnosed with a hydatidiform mole. The patient initially had presented to Obstetrics at 4 months of pregnancy with vaginal bleeding. The bleeding had started 9 days before she was admitted to the hospital and appeared to be fresh blood and clots. It soaked 1 sanitary pad daily and was not associated with abdominal pain. Vesicle-like tissue had been present along with the blood since the day before the patient's admission.

Four years previously, the patient had married. Two years previously, she had a spontaneous, full-term, singleton birth with no significant complications. She came to our outpatient clinic for her fourth antenatal visit. She had seen a midwife in Primary Care for 2 previous antenatal visits. Because of vaginal bleeding, she was then referred to an obstetrician for her first ultrasound screening, which was suspicious for a molar pregnancy. Then, she was referred to our hospital for curettage.

At her first presentation to our Outpatient Obstetrics Clinic, her vital signs were normal. Physical examination showed a 22- to 22-week-sized uterus. A speculum examination showed insignificant bleeding, and no mass infiltration in the vagina or in any other area.

Laboratory results revealed anemia (hemoglobin 8.1 g/dL and hematocrit 23.8%), leukocytes 9630/uL, platelets 396 000/µL, and a quantitative beta human chorionic gonadotropin (β-hCG) level of 1000×10^3 mIU/mL. The patient's thyroid function was within normal limits: triiodothyronine 1.6 mg/dL, free T4 1.5 mg/dL, and a slight decrease in thyroid stimulating hormone (<0.02 mIU/L). Her chest X-rays showed no abnormalities (**Figure 1A**). An ultrasound scan showed an enlarged uterus; the uterine cavity had a vesicular appearance that resembled a snowstorm (**Figure 1B**). We suspected a molar pregnancy and the plan for initial management, after blood transfusion, was to perform vacuum curettage.

On the 5th day of the patient's hospital admission, an external examination revealed a mass on her left labia minora that measured 3×3×2 cm (**Figure 2A**) and felt like a cyst. We had no reason to believe that the mass was an early metastasis of the molar mass and diagnosed it as a suspected hematoma. Vacuum curettage of molar tissue was performed, with blood loss ±3000 cc. After additional sharp curettage, the mass in the patient's uterine cavity had been completely removed. Conservative management initially was chosen because the hematoma was not enlarged.

During 4 hours of observation in the Recovery Room, the patient reported having pain in her genital area. She was still conscious but her vital signs deteriorated and she went into shock (blood pressure 90/60 mmHg, pulse 130 bpm). Physical examination revealed a vulvar mass measuring 6×5×4 cm with a perforation that measured 0.5×0.5 cm and active bleeding. We suspected that ongoing bleeding had caused enlargement of the hematoma and decided to perform emergency evacuation of it.

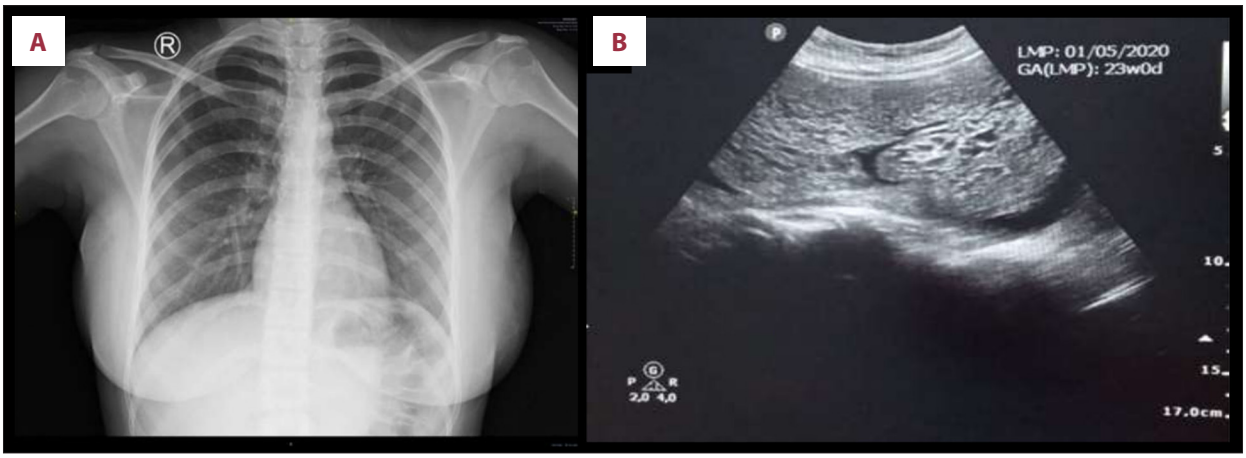

Figure 1. (**A**) Normal chest X-ray. (**B**) Abdominal ultrasound showing snowstorm appearance.

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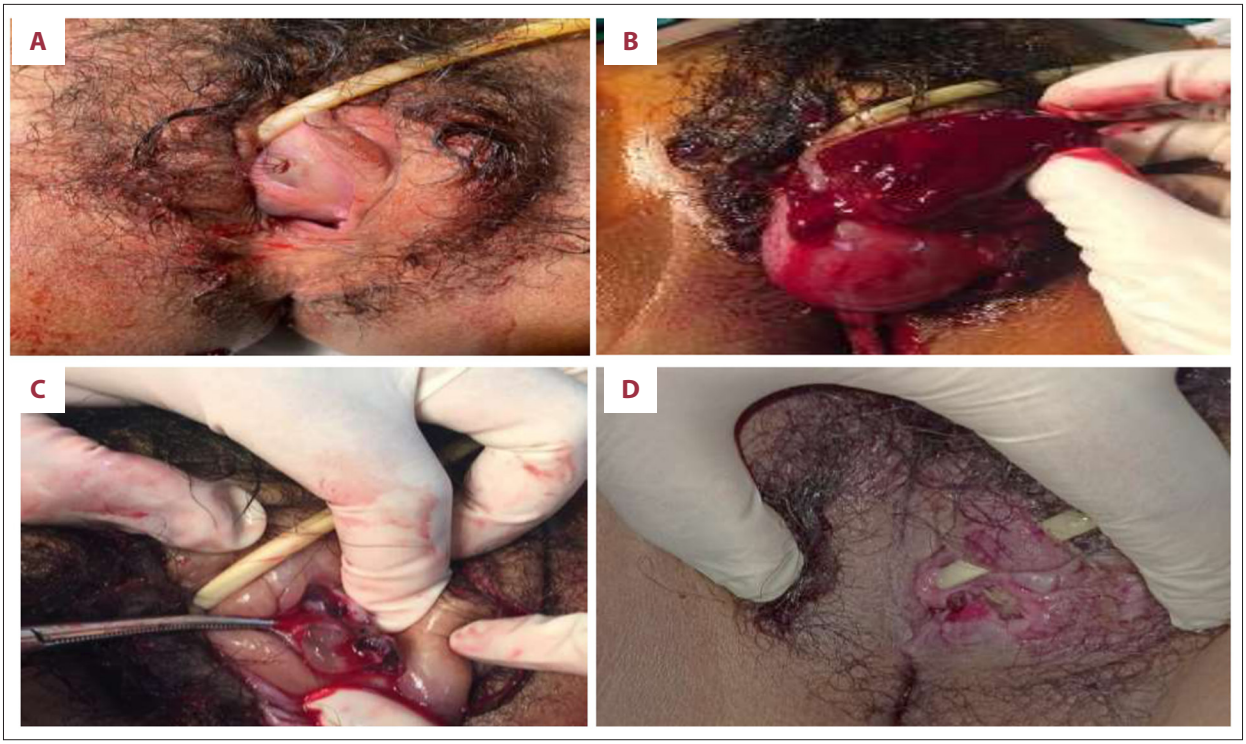

Figure 2. (**A**) The vaginal mass before perforation. (**B**) Incision and evacuation of the vaginal mass. (**C**) Presence of vesicular-like tissue inside the vaginal mass. (**D**) Appearance after evacuation of the vaginal mass.

The hematoma was incised and blood and a blood clot were evacuated from it (**Figure 2B**). We also found vesicle-like tissue in the mass (**Figure 2C**). At the base of the hematoma, we found fragile tissue that was actively bleeding. The bleeding was successfully controlled with placement of horizontal mattress and interrupted sutures (**Figure 2D**). The final diagnosis was suspected stage II GTN.

Histopathological examination was carried out on tissue specimens from the labial mass and from the sharp and vacuum curettage. They contained chronic villi with cystic dilatation, which had hydrophilic avascular degeneration, and were covered with cytotrophoblasts and syncytiotrophoblasts that exhibited excessive proliferation. The nuclei of the cells were within normal limits. A blood clot was present in the decidua. No malignant tumor cells were found. The final histopathologic diagnosis was complete mole with excessive trophoblastic cell proliferation (**Figure 3**).

Because the clinical presentation of the patient was suspected stage II GTN, the histopathologic examination was reevaluated. The determination for the vaginal mass was partial hydatidiform mole in the vagina due to suspected embolism (**Figure 4A**). The pathological result for the specimen from the uterine curettage was partial hydatidiform mole with excessive proliferation of trophoblastic cells (**Figure 4B**). An immunohistochemical examination showed that 20% of the cells were positive for p53 (**Figure 4C**).

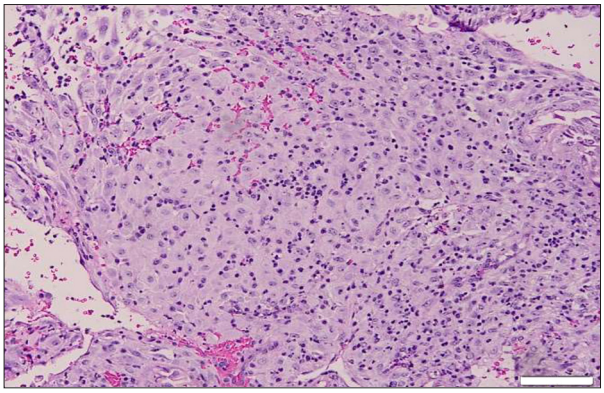

Figure 3. Histopathology of complete mole. Scale bar=100 µm.

Based on the anesthesiologist's recommendation, the patient was transferred from the operating room to the Intensive Care Unit (ICU) while still intubated. Her oxygen saturation level was 80%. During observation in the ICU, the patient's condition never improved and she never gain consciousness. Therefore, she experienced prolonged intubation, which could have led to hypoxia because of massive blood loss during surgery. Postoperatively, the patient's hemoglobin level was 2.3 g/dL, and after transfusion, it increased to 9 g/dL. The massive blood loss during surgery could have compromised the patient's general condition, and she went on to develop bilateral pneumonia on postoperative day 2 (**Figure 5A**), leukocytosis (18 460/µL), and then sepsis. She was treated with

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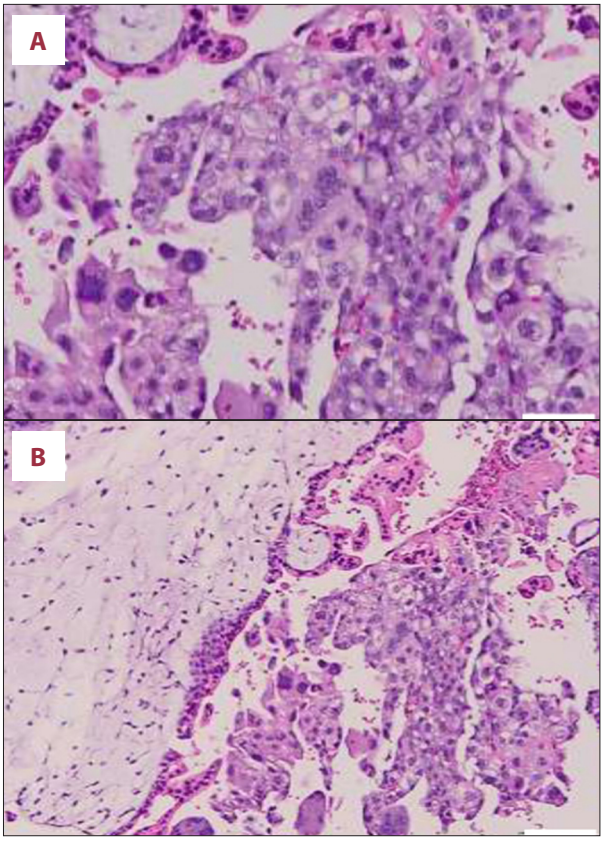

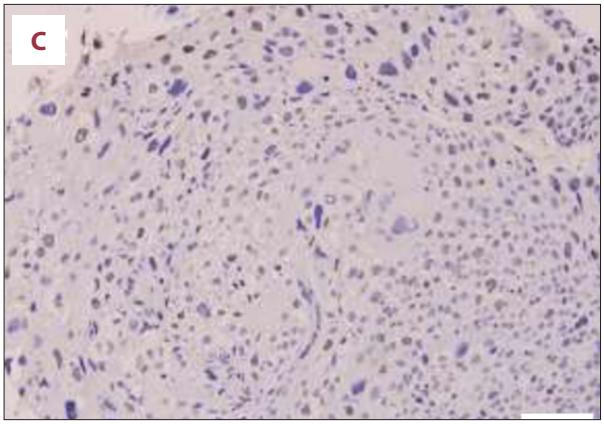

Figure 4. (**A**) Histopathologic reevaluation of the vaginal mass. (**B**) Histopathologic reevaluation of the uterine mass. (**C**) p53 immunohistochemistry of the molar mass. Scale bars=100 µm.

antibiotics according to our protocol for pneumonia. On postoperative day 4, the patient developed pulmonary edema due to a secondary infection in her lungs (**Figure 5B**) and then metabolic encephalopathy occurred. The patient died due to sepsis on postoperative day 22.

Discussion

The most common form of GTD is a hydatidiform mole, which is characterized by abnormal proliferation of trophoblastic tissue. Trophoblast is a tissue that first undergoes differentiation in the early embryonic period and then develops into extraembryonic tissue and forms the placenta. GTD includes a wide spectrum of diseases. The benign form is a hydatidiform mole (complete and partial), whereas the malignant form includes invasive moles, choriocarcinomas, PSTTs, and ETTs [3,4].

According to the World Health Organization, GTD is divided into neoplasms, molar pregnancy, non-neoplastic lesions, an exaggerated placental site, placental site nodule and plaque,

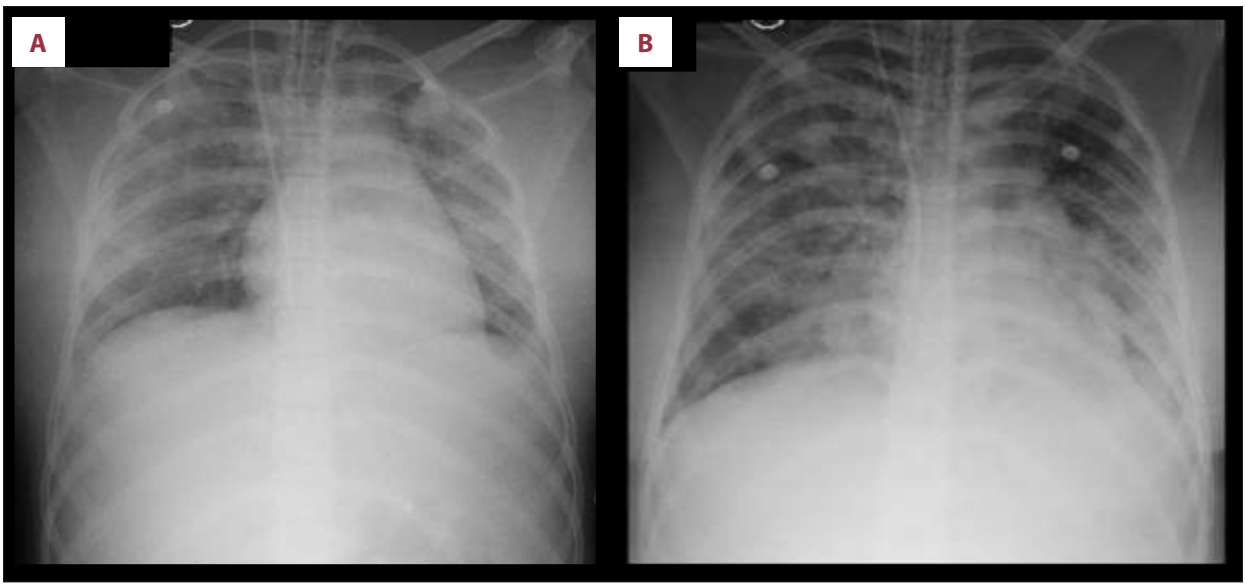

Figure 5. (**A**) X-ray taken on postoperative day 2 showing bilateral pneumonia. (**B**) X-ray taken on postoperative day 4 showing pulmonary edema.

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Table 1. Diagnostic features of GTN [6].

Diagnostic feature	Choriocarcinoma	PSTT	ETT
Age	Reproductive years (average 29 to 31 years)	20 to 63 years (average 30 to 32 years)	15 to 48 years (average 36 years)
Antecedent pregnancy	Term pregnancy, complete hydatidiform mole	Term pregnancy	Term pregnancy
Interval from index gestation	A few months to 14 months (average 2 months after term pregnancy and 13 months after complete mole)	2 weeks to 17 years (median 12 to 18 months)	1 to 25 years (average 6.2 years)
Clinical presentation	Vaginal bleeding, persistent GTD	Missed abortion, amenorrhea	Vaginal bleeding
Pretreatment hCG (mIU/mL)	$>100\times10^3$	$<1\times10^3$	$<3\times10^3$
Gross appearance	Circumscribed or invasive hemorrhagic masses	Expansive to infiltrative solid mass	Expansive solid mass
Tumor location	Corpus	Corpus	Cervix, lower uterine segment, corpus
Tumor border	Infiltrative	Infiltrative	Pushing
Tumor growth pattern	Trimorphic pattern consisting of all 3 types of trophoblast, extensive hemorrhage and necrosis	Large masses of tumor cells replacing vascular wall. Tumor cells split myometrial smooth muscle fibers at tumor periphery	Sheets, nests, and cords, geographic necrosis, deposition of hyaline-like material, colonizing mucosal surface epithelium
Tumor cells	Villous intermediate trophoblasts, syncytiotrophoblasts, and cytotrophoblasts	Implantation site-type intermediate trophoblast	Chronic-type intermediate trophoblast
Cytological atypia	Marked	Moderate to marked	Mild to moderate
Stroma	No intrinsic tumor stroma or vasculature, Ki-67 labeling index >90%	Intimately infiltrates myometrial muscle fibers	Presence of nearby decidualized stromal cells
Immunohistochemistry	Diffuse positivity for hCG, hPl, and HSD3B1 in syncytiotrophoblasts	Diffuse positivity for hPL and Mel-CAM, scattered multinuclear cells positive for hCG, Ki-67 labeling index 5% to 10%	Diffuse positivity for p63, rare individual cells positive for hPL and Mel-CAM, Ki-67 labeling index >10%

ETT – epithelioid trophoblast tumor; GTD – gestational trophoblastic disease; hCG – human chorionic gonadotropin; hPL – human placental lactogen; PSTT – placental site trophoblast tumor.

and abnormal villi lesions [5]. **Table 1** lists the diagnostic features of choriocarcinomas, PSTTs, and ETTs [6].

GTN should be suspected if a patient's β-hCG levels increase or remain high for several weeks after mole evacuation. The post-molar diagnosis of GTN can be made based on criteria from the International Federation of Gynecology and Obstetrics (FIGO) [4]:

1. A β-hCG level that does not change (±10% of the previous result) on 4 measurements made over ≥3 weeks.
2. A β-hCG level that increases by more than 10% on 3 consecutive weekly measurements made over ≥2 weeks.
3. Persistence of β-hCG in the serum for >6 months after mole evacuation.

Our case was a rare presentation of a clinical manifestation of a molar pregnancy with early evidence of a mass in the vagina, which could have been a stage II GTN. **Table 2** shows the differences in GTN staging by the The American Joint Committee on Cancer, with the TNM system, and by FIGO [7]. The early evidence of a vaginal mass in our patient raises the question of whether her stage II GTN followed her previous normal term pregnancy rather than representing early transformation into GTN of her current molar pregnancy.

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Table 2. Staging of GTN [7].

AJCC	Staging	FIGO	Description
I	T1, M0	I	Cancer in the uterus (T1). Tumor cells have not spread to the lungs or other distant organs (M0)
II	T2, M0	II	Cancer has developed outside of the uterus on other genital structures (such as the vagina or ovaries) (T2). Tumor cells have not spread beyond the pelvis to the lungs or to other distant organs (M0)
III	T any, M1a	III	The tumor has spread to the lungs (M1a). It may also involve genital structures, such as the vagina or vulva (any T)
IV	T any, M1b	IV	Cancer has spread to distant organs such as the brain, liver, kidney, spleen and/or gastrointestinal tract (M1b) [9]. It may also involve genital structures such as the vagina or vulva (any T)

AJCC – American Joint Committee on Cancer; FIGO – International Federation of Gynecology and Obstetrics; GTN – gestational trophoblastic neoplasia.

According to FIGO risk-factor scoring, the antecedent pregnancy of GTN can arise from a molar pregnancy, abortion, or a normal pregnancy [8]. The interval from a molar pregnancy to transformation into a GTN is reported to be as short as a few weeks [4,7]. Therefore, ours was a rare case with even earlier interval transformation of molar pregnancy to GTN.

Our patient initially was diagnosed with a hydatidiform mole because the clinical appearance and imaging results were characteristic of that condition. The histopathology results from the uterine curettage and the labial mass also were in accordance with a hydatidiform mole.

Unfortunately, massive bleeding during surgery resulted in a postoperative hemoglobin level of 3 g/dL in our patient. We managed to stabilize her vital signs with a blood transfusion and fluid resuscitation in the ICU. Postoperative observation of the patient on a daily basis showed that her average hemoglobin level was 9 g/dL. However, the patient continued to require intubation and never regained consciousness.

Identifying the cause of death in our patient would have required extensive exploration. She may have experienced hypovolemic shock after prolonged intubation. Given her condition, she also was prone to developing an infection; when sepsis occurred, she did not survive this condition. Another possibility is that the patient developed emboli due to a hydatidiform mole. No cause of death was definitively determined because the patient's family refused an autopsy, mainly for religious reasons.

The present case underscores the need for careful evaluation and management of patients with molar pregnancy. Our patient had a presentation typical of hydatidiform mole, but during observation, she developed a new mass in another area, which increased suspicion for GTN. In a patient with GTN, evacuation of the mass is associated with increased risk of morbidity and mortality. Therefore, the primary therapy should be chemotherapy. Suspected vaginal metastatic lesions of GTD are prone to massive bleeding. Experts recommend avoiding biopsy, excision, or other surgery involving such lesions [10,11]. In our case, surgery was performed on the vaginal mass only to control the bleeding from suspected fragile tumor tissue, which had caused the hematoma.

Clinicians also should be aware of high-risk factors for hydatidiform mole: age >40 years, multiparity, uterus size >20 weeks of pregnancy, β-hCG $>10\times10^3$ mIU/mL, lutein cyst on ultrasound, and histopathology that shows excessive trophoblastic proliferation [8,9,12]. In the present case, that patient had a uterus size that was approximately 20 to 22 weeks of pregnancy and her β-hCG level was 1000×10^3 mIU/mL. Therefore, careful evaluation was required before performing curettage.

Analysis of the histopathologic examination in the present case proved interesting. At first, the uterine mass was described as a complete mole, while the vaginal mass was described as a partial mole. Because of the rarity of the condition, the tissue was reevaluated by our anatomical pathologists, who concluded that it was a partial mole from the uterus and vagina. The differences between complete, very early complete, and partial hydatidiform moles are listed in **Table 3** [13]. In a complete mole, the trophoblast proliferation is diffuse, whereas with a partial mole, it is focal [14]. The anatomical pathologist's subjective assessment and the way the samples were cut could be another reason for the difference in the assessments. A karyotype examination was needed to diagnose the patient definitively, but unfortunately, it could not be done because of her condition. Our facility is not equipped to do p57 immunostaining. Even so, there would have been no significant change in how the patient was handled, whether it was found on histopathology to be a complete or partial mole.

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Table 3. Diagnostic features of hydatidiform mole [13].

Diagnostic feature	CHM	VECHM	PHM
Clinical presentation	Vaginal bleeding in second trimester (average 16 weeks). Excessive uterine size, hyperemesis, toxemia, preeclampsia or hyperthyroidism	Missed Abortion (6.5 to 12 weeks of gestation)	Vaginal bleeding, missed or incomplete abortion in late first or early second trimester
Pretreatment hCG (mIU/mL)	Elevated (>100×10^3) in >43% of cases	Normal or elevated (<100×10^3)	Normal or elevated (<100×10^3 in >93% of cases)
Ultrasound	Snowstorm pattern without fetus formation	–	Focal cystic change with fetus formation
Chorionic villi	Diffuse enlargement, round to oval shapes	Normal size, polypoid or cauliflower shapes	Mild, with syncytiotrophoblast knuckles
Trophoblastic hyperplasia	Marked, often circumferential with intervillous trophoblast bridging	Mild, often on villous tips	Mild, with syncytiotrophoblast knuckles
Cytological atypia	Marked	Mild to moderate	Limited to mild
Villous stroma	Marked edema with frequent cistern formation and trophoblastic inclusions. Absence of vasculature and nucleated RBCs	Cellular and myxoid with prominent karyorrhexis fetal capillaries may be present	Occasional cistern formation Round to oval trophoblastic pseudo-inclusion Presence of vasculature and nucleated RBCs (not always evident)
p57 Immunostain	Absence of nuclear staining in cytotrophoblast and villous stromal cells	Absence of nuclear staining in cytotrophoblast and villous stromal cells	Presence of nuclear staining in cytotrophoblast and villous stromal cells
DNA genotyping	Diploid diandric (paternal-only) genome	Diploid diandric (paternal-only) genome	Triploid diandric-monogynic genome

CHM – complete hydatidiform mole; VECHM – very early complete hydatidiform mole; PHM – partial hydatidiform mole; RBC – red blood cell.

Although the findings support the final conclusion of hydatidiform mole, the embolic phenomenon that was described is characteristic of choriocarcinoma. To support this, reports by Schmorl published in 1904 and 1905 state that in normal pregnancies, trophoblasts with or without chorionic villi can spread to sites such as the lungs, vulva, and vagina via the hematological route [15]. Certain distinguishing features can be found on histological examination. Blood from our patient's excess nodules showed no traces of trophoblasts or even villi. The presence of chorionic villi in nodules is generally accepted and serves to refute a diagnosis of choriocarcinoma, although it does not completely rule it out [16].

It has been suggested that vaginal lumps seen during pregnancy may arise from benign or relatively malignant lesions. Such masses must be meticulously explored to determine their nature. In most cases, this can be done with histological examination. Furthermore, it has been shown that nodules composed of syncytiotrophoblasts can appear suddenly, and macroscopically, as the dreaded metastases of choriocarcinoma. A brief review described vaginal nodules coincident with normal pregnancy, hydatidiform moles, and choriocarcinoma [12,17].

Two cases of metastatic choriocarcinoma that presented as vulvovaginal swelling were described in a report by Bhattacharyya et al. Choriocarcinoma is a highly vascular tumor of the trophoblast with immense potential for metastasis to the lung, liver, brain, or vulva. Thirty percent of such metastases are vulvovaginal [18] and their initial appearance often is misleading. The sole clinical presentation of onset of vulvovaginal swelling can confuse clinicians. Both cases that have previously been described were initially misdiagnosed. Unresponsiveness to treatment led clinicians to perform further examination [18,19].

We did not believe that the mass in our patient's vagina was a metastasis or an invasive mole because of the short interval during which it developed. Therefore, the present case likely was a rare occurrence of a molar pregnancy that metastasized rapidly outside of the uterus (stage II GTN) or possibly a rare case of invasive mole.

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Conclusions

Patients with a typical presentation for intrauterine molar pregnancy should undergo careful examination for the condition. If they are found to have a vaginal mass, an additional, cautious exploration should be undertaken for possible GTN.

Acknowledgments

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Conflict of Interest

None.

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