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Three Consecutive Complete Hydatidiform Moles: A Rare and Challenging Pattern of Gestational Trophoblastic Disease

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ABSTRACT

Introduction Recurrent hydatidiform mole is an uncommon gestational trophoblastic disease but is clinically important. Although a single molar pregnancy is generally well understood, consecutive recurrences remain rare and raise concerns regarding the underlying genetic predisposition, with implications for malignant progression and future reproductive outcomes.

Case Illustration A 26-year-old woman presented with one month of vaginal bleeding with clots, lower abdominal pain, severe nausea, dizziness, and weakness. She had undergone three prior curettages (one miscarriage and two molar pregnancies). Inspection detected anemia, uterine enlargement, lower abdominal tenderness and visible tissue on the cervix. Ultrasound revealed a classic "snowstorm" pattern. Transfusion stabilized the patient, who had evacuation curretage. The patient was then referred to a tertiary care center for genetic identification and serial β-hCG surveillance.

Discussion The risk of hydatidiform mole in subsequent pregnancies is known to increase in cases of previous hydatidiform mole. Recurrences occur in 1.3%-2% of women who have had hydatidiform mole and rise to 15% in women who have had two consecutive hydatidiform mole. It is more common in those of reproductive age (15-45 years) and in multiparous. Approximately 10% of all cases are prone to malignant transformation.

Conclusion This case underscores the importance of considering recurrent cases of hydatidiform mole in woman with early pregnancy bleeding and prior molar history. Early ultrasonographic evaluation, histopathological confirmation, and prompt evacuation are essential to reduce morbidity. Careful postevacuation surveillance is critical to detect persistent trophoblastic disease and prevent malignant progression.

Key Words: Complete hydatidiform mole; Gestational trophoblastic disease; β-hCG monitoring

INTRODUCTION

Gestational trophoblastic diseases (GTDs) involve trophoblasts abnormal proliferation, the predominant constituent of the placenta. Hydatidiform mole (HM) is the most common forms.[1] HM is an abnormal pathognomonic gestational condition, characterized by excessive proliferation of trophoblastic cells/villous edema and the absence or inconstant fetal development. Histologically, GTD includes a spectrum of premalignant lesions such as partial molars and complete hydatidiform moles, as well as malignant entities, as invasive moles, choriocarcinoma, and placental site trophoblastic tumors (PSTTs). These malignancies are referred to as gestational trophoblastic neoplasia (GTN) and may occur after a gestational events. Complete moles are often diploid with absence of fetal tissue and markedly elevated serum beta human chorionic gonadotropin (β-hCG) levels, whereas partial moles tend to be triploid with presence of fetal components accompanied by proper or low β-hCG levels for gestational age.[2] Hydatidiform mole is more common in Asians than in Westerns with approximately 1 per 120 pregnancies.[3] There is geographic variation in the incidence of hydatidiform mole; rates among live births have been reported as 1 in 1000–1500 (USA), 1 in 538 (Japan) and 1 in 357 (Malaysia). Indonesia, however, has a greater prevalence with an estimated 1 in 100–141 pregnancies.[4] A history of a previous molar gestation is now proven to be a strong risk factor for complete hydatidiform mole, with an approximately tenfold increased risk of carrying a prior complete molar pregnancy.[5]

Recurrent hydatidiform moles are characterized by two or more occurrences of molar gestations in the same woman. Recessive pathogenic variants in NLRP7 account for approximately 55% of cases. KHDC3L, which is the second most common cause, affects approximately 5% of affected individuals.[6]

This report aims to describe a case of consecutive recurrent complete hydatidiform mole and to discuss its clinical significance, including recurrence risk, appropriate follow-up strategies, and the role of genetic evaluation.

CASE ILLUSTRATION

A 26-year-old woman presented with vaginal bleeding that had persisted for one month, which was suddenly aggravated during the last three hours. The bleeding was red in color with tissue-like clots, accompanied by lower abdominal pain radiating to the back, with her abdomen had increased in size. She also reported dizziness, frequent nausea and vomiting (more than six times daily) and weakness. Patient's obstetric history revealed that the patient had given birth with a full-term spontaneous vaginal delivery in 2022. The second pregnancy in 2023 ended in abortion and was managed with curettage. The third pregnancy in 2024 was complicated with complete hydatidiform moles and curettage was performed, as was the fourth pregnancy in early 2025. The fifth pregnancy is the current pregnancy. The patient reported she had not yet attended any antenatal care visits for the current pregnancy.

Examination revealed a blood pressure of 97/58 mmHg, and generalized bilateral conjunctival pallor was observed with pallor of the lips and skin. On obstetric examination, inspection revealed a convex abdomen with a surgical scar. The uterine fundus was palpable two fingerbreadths below the umbilicus. No fetal heart sounds were detected. Speculum examination revealed bleeding from the cervix, opening of the external uterine ostium (OUE) and tissue in the vaginal canal. The laboratory findings were notable for severe anemia (hemoglobin 5.9 g/dL). Ultrasound examination revealed a "snowstorm" pattern.

She was given crystalloids for initial hemodynamic stabilization and oxygen through a nasal cannula. The patient received tranexamic acid 1 g intravenously**,** metoclopramide 10 mg IV every 8 hours, and ranitidine 50 mg IV twice daily**.** Packed red cell (PRC) transfusion was administered for anemia. Once her condition improved favorably, curettage was planned. Uterotonics, antibiotics, analgesia and antifibrinolytics were then administered postcurettage. No intraoperative complications or unexpected adverse events were observed. Histopathologic analysis of the evacuated tissue was consistent with hydatidiform mole. The patient's condition gradually improved and the patient was discharged with outpatient follow-up (Table 1).

Table 1. Inpatient and outpatient clinical data

Date (2025) & Time (WITA)	Setting	Key Clinical Findings & Investigations	Management
Nov 29 00:13	Emergency Department	One-month intermittent vaginal bleeding with clots (worsened), weakness, severe nausea/vomiting, lower abdominal pain. Anemia +/+, lower abdominal tenderness (+).	Crystalloids, O_2 4 L/min via nasal cannula, IV H2 receptor, antiemetic, antifibrinolytic, planned ultrasound
Nov 29 03:47	Ward	Heavy clots, worsening pain, dizziness, FHR (-), Hb 5.9 g/dL, OUE open	Continued previous management with planned 3 PRCs
Nov 29 09:42	Ward	Reduced bleeding; Hb 5.9 g/dL; Ultrasound: snowstorm pattern	Continued therapy
Nov 30 06:56	Ward	Heavy clots (2x), Hb 7.8 g/dL post-2 PRC, WBC 13.7	Monitoring q3h; planned curettage; 2 PRCs prepared
Nov 30 11:45	Ward → OR	Persistent heavy bleeding	oxytocin infusion; transfer to OR
Nov 30 18:16	Postcurettage	Postoperative pain; OUE was opened	Same above with IV antibiotics and NSAID, Hb recheck, histopathology planned
Nov 30 20:34	Laboratory	WBC 14.2, RBC 4.26, Hb 10.5, HCT 34.6%, Platelets 138	—
Dec 1 06:57	Postcurettage	Postoperative pain; urine output 1100 mL/20 hours	IV antibiotics, uterotonics, antifibrinolytic, iron
Dec 2	Postcurettage	Pain reduced; ultrasound: anteflexed	Oral therapy; discharge

15:58		uterus 8.9×6.8 cm, no intrauterine mix-echoic mass, clot (+)	
Dec 7	Histo-pathology	Hydropic chorionic villi, trophoblastic proliferation, hemorrhage	—
Dec 9–24	Outpatient	Intermittent spotting, occasional pain	Antibiotics, iron, vaginal toilet, referral to tertiary gynecologic oncology for β-hCG surveillance

DISCUSSION

The present case illustrates a clinically significant example of a recurrent hydatidiform mole, a condition that remains relatively uncommon but has substantial reproductive and oncologic implications.[1] The patient was a 26-year-old woman with a history of two prior molar pregnancies, fulfilling the definition of recurrent hydatidiform mole, which is defined as the occurrence of two or more molar gestations in the same individual. Although extreme maternal age (40 years old) is a recognized risk factor, this case highlights that recurrent disease may also occur in women of reproductive age, particularly in those with a prior history of molar pregnancy.[5,7]

Clinically, the patient presented with prolonged vaginal bleeding, excessive nausea and vomiting, progressive uterine enlargement, and severe anemia. These findings are typical manifestations of hydatidiform mole and are largely attributable to markedly elevated β-hCG levels, which promote exaggerated trophoblastic proliferation and systemic symptoms.[8,9,10] The discrepancy between gestational age and uterine size, combined with the absence of fetal heart activity and the classic "snowstorm" appearance on ultrasonography, strongly supports the diagnosis of a complete hydatidiform mole.[8]

The patient's obstetric history is particularly noteworthy, as her previous pregnancies included two documented molar gestations managed by curettage. Recurrent hydatidiform moles

are often associated with underlying genetic abnormalities. Although genetic testing was not performed in this case, the repeated occurrence of molar pregnancies raises suspicion of a possible genetic cause.[11] The majority of CHMs are diploid in karyotype and arise from the fertilization of an empty ovum by one sperm, resulting in a 46, XX character. More rarely, fertilization of an oocyte by two spermatozoa (di-spermic fertilization) can cause a 46, XY karyotype. In both cases, the situation is abnormal and leads to a genome that is purely paternal in origin. This is characterized by aberrant proliferation of cytotrophoblasts and syncytiotrophoblasts associated with marked hydropic degeneration of the chorionic villi. From a clinical perspective, affected patients frequently have prominent serum β-hCG elevations that can exceed 100,000 IU/L and unlike the partial moles, complete hydatidiform moles are associated with an increased risk for persistent trophoblastic disease and malignant transformation. Partial hydatidiform moles result from abnormal fertilization with two sperm fertilizing a normal ovum, producing a triploid karyotype (69, XXY or 69, XYY most often; also less commonly 69, XXX). In such cases, the hydropic villi are not as widely proliferated and are interspersed with normal chorionic villi. β-hCG values in partial mole pregnancies are usually within the reference range for a normal pregnancy.[12]

From a management perspective, suction curettage remains the standard initial treatment for hydatidiform mole in women who desire future fertility. In this case, the patient was appropriately stabilized prior to surgical evacuation. Management involves rapid hemodynamic stabilization, continuous monitoring of vital signs, establishment of large-bore intravenous access, fluid resuscitation with crystalloids, and blood transfusion when needed.[13] The use of uterotonics, antifibrinolytics, and blood transfusions was consistent with current management principles for molar pregnancy complicated by significant bleeding.[2] Meticulous postevacuation follow-up with serial serum monitoring is essential to detect persistent trophoblastic disease at an early stage. Unfortunately, the absence of antenatal care during the current pregnancy may have contributed to delayed diagnosis and worsening of the clinical condition of this patient.

On the basis of this theory, this case can be categorized as a condition associated with a substantial risk of persistent trophoblastic activity and possible malignant transformation. Variants

in NLRP7 are considered as the leading genetic contributors in most recurrent cases. Nevertheless, in routine practice, genetic evaluation is frequently postponed until repeated recurrences occur, delaying definitive diagnosis and individualized care. Increasing evidence supports the initiation of genetic counseling and molecular testing after a second histologically confirmed complete mole to enable earlier recognition of inherited susceptibility and to inform personalized reproductive planning. Studies have demonstrated that NLRP7 alterations are linked to recurrent molar pregnancies and a greater likelihood of developing gestational trophoblastic neoplasia, underscoring the importance of timely genetic risk assessment.[14]

Early integration of genetic referrals into clinical pathways may refine surveillance strategies, enhance counseling on reproductive options—including the potential role of oocyte donation—and address psychosocial concerns. Moving from a reactive approach to a proactive, individualized model allows more effective management of recurrent gestational trophoblastic disease while reducing the cumulative morbidity associated with repeated molar gestations. This perspective highlights the interplay between genetic background and reproductive outcomes and aligns with the precision-medicine framework increasingly applied in reproductive endocrinology and trophoblastic disease management. Furthermore, serial β-hCG follow-up is essential for early detection of the risk of malignant transformation. In this case, β-hCG follow-up and genetic identification were performed at the tertiary health facility.

CONCLUSION

Recurrent hydatidiform mole constitutes a clinically significant variant of gestational trophoblastic disease, with important consequences for the probability of recurrence, malignant transformation, and subsequent reproductive potential. This report underscores a previous molar gestation as the most robust risk factor for recurrence and highlights that repeated molar pregnancies can occur in women of childbearing age. The occurrence of multiple episodes warrants consideration of an underlying genetic susceptibility, most frequently associated with pathogenic variants in oocyte-specific genes, including NLRP7 and KHDC3L. Timely uterine evacuation,

followed by meticulous posttreatment surveillance via serial serum β-hCG monitoring, remains critical for the early identification of persistent trophoblastic disease. Heightened clinical vigilance, prompt diagnosis, and structured long-term follow-up are essential to minimize morbidity and improve reproductive outcomes.

ABBREVIATIONS

GTD: Gestational trophoblastic disease

HM: Hydatidiform mole

GTN: Gestational trophoblastic neoplasia

β-hCG: beta human chorionic gonadotropin (Used in text/table)

PRC: Packed red cell (Used in text/table)

WITA: Central Indonesia Time (Used in table)

OUE: External uterine ostium (Used in text/table)

OUI: Internal uterine ostium (Used in table)

IV: intravenous (Used in table)

FHR: Fetal heart rate (Used in table)

WBC: White blood cell (Used in table)

RBC: Red blood cell (Used in table)

HCT: Hematocrit (Used in table)

q3h: every 3 hours (Used in table)

OR: Operating room (Used in table)

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