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Case Report

Recurrent hydatidiform mole: a case report highlighting NLRP7 gene mutations and genetic imprinting

Riya Sudev*, Jyoti Ramesh Chandran, Santhosh Kuriakose

Department of Obstetrics and Gynaecology, Government Medical College, Kozhikode, Kerala, India

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***Correspondence:**
Dr. Riya Sudev,
E-mail: riyasudev@gmail.com

ABSTRACT

Recurrent hydatidiform mole (RHM) is a rare form of gestational trophoblastic disease and is frequently associated with mutations in maternal-effect genes, particularly NLRP7, which play a critical role in early embryonic development and genomic imprinting. We report the case of a 26-year-old woman (G7P0) who presented at 9 weeks' gestation with features suggestive of a complete molar pregnancy. Ultrasonography demonstrated a heteroechoic intrauterine mass, and serum β-human chorionic gonadotropin levels were markedly elevated at 272,600 IU/l. Her obstetric history was significant for 6 prior molar pregnancies, highlighting the recurrent nature of the condition; one of these pregnancies progressed to low-risk gestational trophoblastic neoplasia with pulmonary metastases, which was successfully managed with multiagent chemotherapy and close follow-up. In view of the recurrent disease, genetic evaluation was undertaken and revealed compound heterozygous pathogenic variants in the NLRP7 gene, including an exon 3 deletion and an exon 4 truncation. The patient received comprehensive counseling regarding the genetic etiology of her condition, its oncologic implications, and future reproductive options. Biallelic NLRP7 mutations result in abnormal oocyte development and impaired genomic imprinting, leading to recurrent molar gestations and a significantly reduced likelihood of achieving a viable pregnancy with autologous oocytes. Ovum donation remains the most viable reproductive option for affected women. This case underscores the importance of early genetic evaluation in women with recurrent molar pregnancies to guide individualized management, surveillance, and reproductive counseling.

Keywords: Recurrent hydatidiform mole, NLRP7 gene mutation, Gestational trophoblastic disease, Genomic imprinting, Biparental mole

INTRODUCTION

Hydatidiform mole is a form of gestational trophoblastic disease characterized by abnormal trophoblastic proliferation and hydropic degeneration of chorionic villi. Incidence varies geographically, occurring in approximately 1 in 1,000 pregnancies in Western countries and up to 1 in 500 pregnancies in Asian populations, including India.[1] Although most cases are sporadic, risk of recurrence after a single molar pregnancy is about 1-2%.[2]

RHM, defined as two or more molar pregnancies in the same woman, is extremely rare, with an estimated incidence of approximately 1 in 100,000 pregnancies.[3] The risk of recurrence increases substantially with each subsequent mole and may exceed 15-20% after two molar pregnancies, suggesting an underlying genetic cause.[4]

Recent studies have identified maternal-effect gene mutations as the principal etiology of RHM, particularly mutations in the NLRP7 gene located on chromosome 19q13.42. NLRP7 mutations account for nearly 50-80% of familial and recurrent complete hydatidiform moles.[5] These mutations impair normal genomic imprinting during oogenesis, leading to abnormal embryonic development despite biparental fertilization.

Women with NLRP7 mutations frequently experience repeated complete moles and are at increased risk of developing gestational trophoblastic neoplasia (GTN), reported in 15-25% of affected pregnancies.[6] The present case describes a young woman with seven consecutive molar pregnancies, two episodes of GTN with pulmonary metastases, and confirmed compound heterozygous pathogenic variants in the NLRP7 gene, highlighting the aggressive clinical course and the importance of early genetic evaluation in recurrent mole.

CASE REPORT

A 26-year-old woman, gravida 7, presented at 9 weeks and 1 day of amenorrhea with symptoms suggestive of early pregnancy. Transvaginal ultrasonography revealed a 5×5×4 cm heteroechoic mass containing multiple small cystic spaces within the endometrial cavity, with increased internal vascularity.

Serum β-human chorionic gonadotropin (β-hCG) level was markedly elevated at 272,600 IU/l, suggestive of molar pregnancy.

Her obstetric history was significant for six previous molar pregnancies; all managed with suction and evacuation followed by complete β-hCG surveillance until normalization. During her sixth pregnancy, she developed low-risk gestational trophoblastic neoplasia with radiological evidence of pulmonary metastases. She initially received six cycles of methotrexate with leucovorin rescue but failed to achieve remission. Subsequently, she was treated with multiagent chemotherapy using the EMA-CO regimen, following which complete clinical and biochemical remission was documented.

At the present admission, the patient was hemodynamically stable.

Abdominal and pelvic examination revealed a bulky uterus with no adnexal masses. Suction evacuation was performed. Histopathological examination confirmed a complete hydatidiform mole. Post-evacuation serum β-hCG level declined to 104,791 IU/l.

However, serial β-hCG monitoring showed persistent elevation. Contrast-enhanced computed tomography (CECT) of the thorax demonstrated pulmonary metastases, confirming the diagnosis of low-risk GTN. She was treated with three cycles of actinomycin D followed by three consolidation cycles.

Following treatment, β-hCG levels normalized, and the patient has remained disease-free on follow-up for one year.

In view of repeated molar pregnancies, genetic counseling was offered. Molecular genetic analysis of maternal blood revealed compound heterozygous pathogenic variants in the NLRP7 gene, including a deletion of exon 3 and a truncating mutation in exon 4, consistent with autosomal recessive inheritance. The patient was counseled regarding the very high risk of recurrence in future pregnancies and advised about alternative reproductive options, including oocyte donation. She is currently asymptomatic and has not attempted conception since.

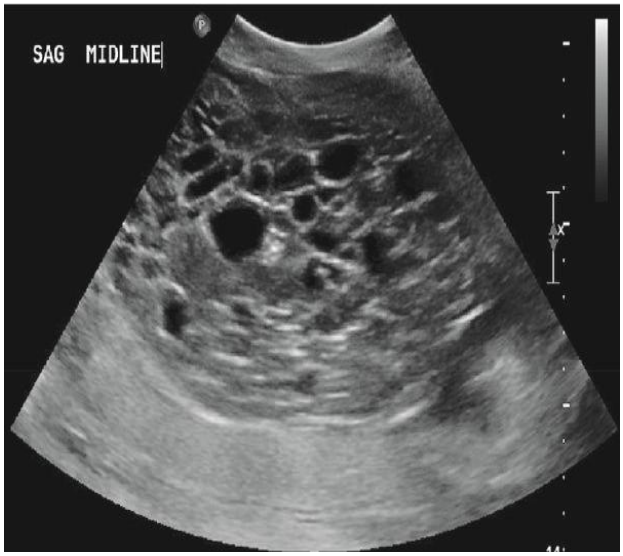

Figure 1: Ultrasonographic image of heteroechoic intrauterine mass with multiple cystic spaces suggestive of complete hydatidiform mole at 9 weeks gestation.

Table 1: Serial serum β-hCG trend during diagnosis, treatment and follow up.

Dates	β-hCG
14 June 2024	727260
16 June 2024	104791
23 June 2024	3054
30 June 2024	780
07 July 2024	601
14 July 2024	948
31 July 2024	193
14 August 2024	17
28 August 2024	2.2
11 September 2024	0.1
24 September 2024	0.1
13 October 2024	2.4
24 November 2024	0.24
05 January 2025	0.15
09 February 2025	0.06
16 March 2025	0.36
20 April 2025	0.4
25 May 2025	0.5
01 July 2025	0.33
05 August 2025	0.2
09 September 2025	0.23
10 October 2025	0.16

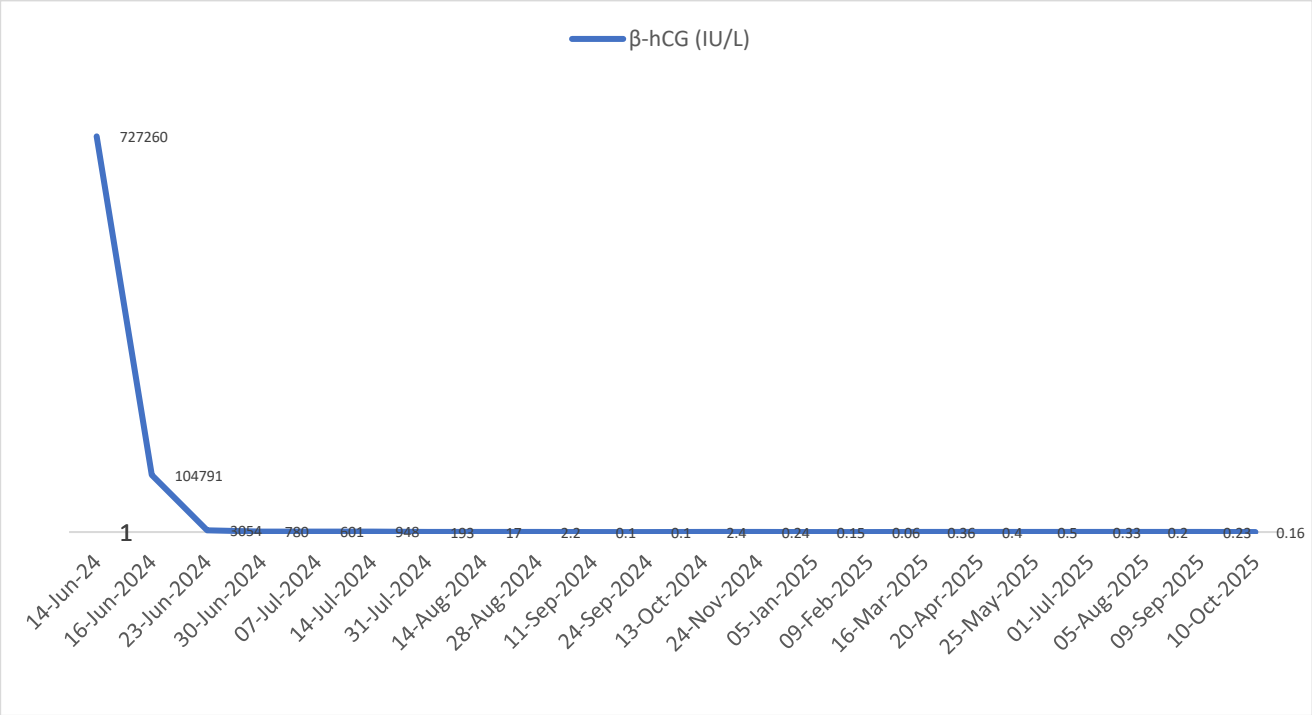

Figure 2: Serial serum β-human chorionic gonadotropin trend during diagnosis, treatment, and follow-up.

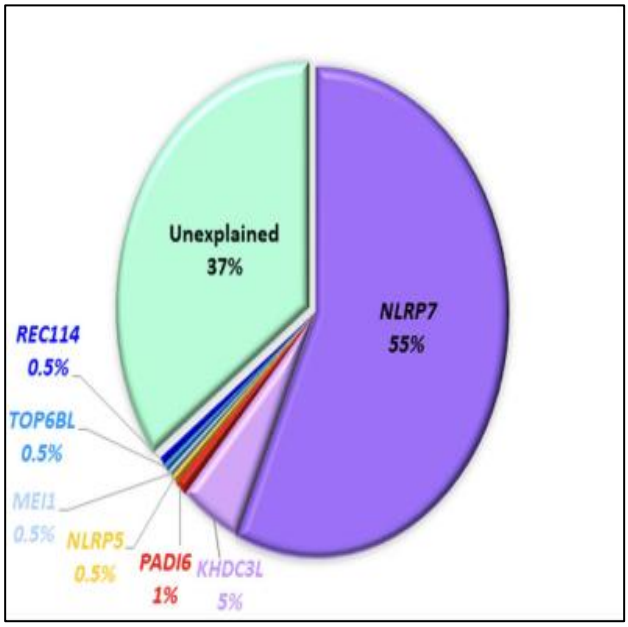

Figure 3: Genes associated with RHM.

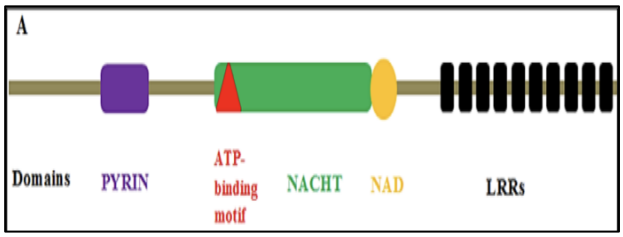

Figure 4: Structure and functional domains of the NLRP7 gene.

DISCUSSION

RHM represents a rare and distinct subtype of gestational trophoblastic disease with a strong genetic basis. Unlike sporadic complete moles, which are typically androgenetic, recurrent moles associated with maternal-effect gene mutations are usually biparental in origin due to abnormal genomic imprinting. The two principal genes implicated in this condition are NLRP7 and KHDC3L.[5,6]

The NLRP7 gene, located on chromosome 19q13.42, is responsible for approximately 50-80% of cases of recurrent complete hydatidiform mole.[5] It plays a critical role in oocyte maturation, inflammasome regulation, and establishment of maternal methylation marks during oogenesis. Loss-of-function mutations result in defective imprinting, abnormal trophoblastic proliferation, and early embryonic arrest. In the present case, compound heterozygous pathogenic variants involving deletion of exon 3 and a truncating mutation in exon 4 of the NLRP7 gene were identified, confirming an autosomal recessive inheritance pattern.

The KHDC3L gene (also referred to as C6orf221), located on chromosome 6q13, is another important maternal-effect gene implicated in RHM, accounting for approximately 10-14% of genetically confirmed cases.[6,7] The KHDC3L protein interacts functionally with NLRP7 and is essential for early embryonic development and maintenance of genomic imprinting. Mutations in KHDC3L lead to a clinical phenotype indistinguishable from NLRP7-related disease, including recurrent complete moles and very poor reproductive outcomes.

Both NLRP7 and KHDC3L mutations are inherited in an autosomal recessive manner, and women affected by these mutations typically develop molar pregnancies regardless of paternal genotype. Consequently, changing partners does not reduce recurrence risk, and spontaneous normal pregnancy is extremely uncommon.[6,8]

The risk of progression from complete mole to gestational trophoblastic neoplasia is approximately 15-20%, compared with 1-5% following partial mole.[9] Women with recurrent molar pregnancies may have a higher cumulative risk of GTN due to repeated trophoblastic exposure. In the present case, the patient developed GTN on two occasions, both with pulmonary metastases, underscoring the malignant potential associated with genetically determined molar disease.

Low-risk GTN is highly chemosensitive. Single-agent chemotherapy with methotrexate or actinomycin D achieves remission rates of 70-90%.[10] However, resistance occurs in nearly 20-30% of patients, necessitating escalation to multiagent regimens such as EMA-CO, which offer cure rates exceeding 95%.[11] This therapeutic pattern was reflected in our patient, who required multiagent chemotherapy following methotrexate failure and subsequently responded well to actinomycin D during recurrence.

Reproductive prognosis in women with NLRP7 or KHDC3L mutations is poor, with reported live birth rates of less than 5% using autologous oocytes.[5,6] In contrast, pregnancies achieved through oocyte donation bypass the defective maternal imprinting process and have been associated with successful term outcomes.[12] Therefore, early genetic diagnosis is crucial to guide counseling and prevent repeated physical and psychological morbidity.

This case highlights the importance of considering maternal-effect gene mutations, particularly NLRP7 and KHDC3L, in women presenting with RHM and emphasizes the role of genetic counseling and assisted reproductive options in long-term management.

Genetic analysis results

Genetic analysis revealed compound heterozygous pathogenic variants in the NLRP7 gene, comprising an exon 3 deletion and a truncating mutation in exon 4 (p.Glu580Ter), consistent with autosomal recessive RHM.

Test details

This test analyzed the NLRP7 and KHDC3L genes associated with RHM.

In addition, pathogenic (disease-causing) and likely pathogenic (likely disease-causing) variants in other well-covered genes included in the Strand Clinical Exome Test were evaluated for secondary findings.

Table 2: Genetic analysis.

Genes	Variation	Zygosity	Inheritance	Clinical significance
NLRP7	chr19:55452299_55452373+?del c.(277+1_278−1)_(352+1_353−1)del (Exon 3 deletion)	Heterozygous	Recessive	Pathogenic
NLRP7	chr19:55450449C>A c.1738G>T p.Glu580Ter	Heterozygous	Recessive	Pathogenic

CONCLUSION

RHM should raise strong suspicion for an underlying genetic etiology, particularly in women with multiple complete moles and absence of viable pregnancies. This case underscores the clinical and genetic complexity of RHM associated with compound heterozygous NLRP7 mutations. Establishing a molecular diagnosis is crucial, as it confirms the etiology, facilitates accurate risk stratification, and enables individualized reproductive counseling. Assisted reproductive technologies, especially the use of donor oocytes, represent a promising option for achieving successful pregnancy in women with confirmed maternal-effect gene mutations.

Early recognition and genetic evaluation are essential to prevent repeated morbidity and to guide long-term management in this rare condition.

Recommendations

Early genetic evaluation should be considered in women with two or more molar pregnancies to identify underlying maternal-effect gene mutations such as NLRP7 and KHDC3L. Comprehensive genetic counseling is essential to explain the autosomal recessive inheritance pattern, the extremely high recurrence risk, and the poor reproductive prognosis associated with the use of autologous oocytes. Strict post-evacuation serum β-human chorionic gonadotropin surveillance should be maintained in recurrent molar pregnancies due to the increased cumulative risk of gestational trophoblastic neoplasia. Prompt evaluation for gestational trophoblastic neoplasia, including appropriate imaging, is recommended in cases of plateauing or rising β-hCG levels to ensure early initiation of chemotherapy. Multidisciplinary management involving obstetricians, gynecologic oncologists, geneticists, and fertility specialists is crucial for optimal

long-term care. Assisted reproductive techniques using donor oocytes should be discussed as the most reliable option for achieving a successful pregnancy in women with confirmed NLRP7 or KHDC3L mutations. In addition, psychological support and long-term follow-up should be offered, given the significant emotional burden associated with recurrent pregnancy loss and repeated oncologic treatment.

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