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Case Report

Recurrent hydatidiform moles: detection of a new mutation in the NLRP7 gene in the family

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ABSTRACT

Hydatidiform moles are the most common type of gestational trophoblastic neoplasia. Hyperproliferative vesicular trophoblasts and imperfect fetal development are abnormal pregnancies, and recurrent hydatidiform moles are rare. Mutations in NLRP7 are responsible for recurrent hydatidiform mole. Genetic heterogeneity has been demonstrated in patients with the NLRP7 mutation. This study presents our case with gravida 11, parity 0, histopathologically diagnosed with six hydatidiform moles and five missed abortion histories at age 35. Karyotype analyses of the unrelated couple were normal. A genetic examination revealed a novel mutation of the NLRP7 gene in the patient, his brother, and his parents. Detecting a new NLRP7 mutation in recurrent hydatidiform moles cases provides further evidence for the predetermined role of NLRP7 mutations in the pathophysiology of recurrent moles hydatidiform. Based on our findings, we hope to contribute to the literature by expanding the spectrum of recurrent pregnancy loss associated with NLRP7 mutations in patients.

Keywords: Recurrent hydatidiform moles, NLRP7, Mutation

INTRODUCTION

Hydatidiform moles are an abnormal concept characterized by atypical hyperplastic trophoblasts and hydropic viruses, but it is the most common type of gestational trophoblastic disease.[1] Moles are classified as complete or partial according to their basic morphology, histopathology, and karyotype. Complete moles are diploids. Diffuse trophoblastic hyperplasia is defined by diffuse swelling of chorionic villas and the absence of embryonic tissue. The partial hydatidiform moles are triploids. Focal trophoblastic hyperplasia is characterized by focal swelling of chorionic villas and triploid embryonic tissue.[2] The genetic material in the complete hydatidiform moles is entirely paternal. There is no maternal genetic contribution. The entire paternal source-derived genome is called the androgenetic complex hydatidiform mole.[3] It has been determined that the recurrent hydatidiform mole, which is pathologically indistinguishable from the androgenetic complete hydatidiform mole, has a two-parent genotype.[4] This unusual picture is often associated with families with a hereditary predisposition to molar pregnancies.[5] Genetic studies on these families have identified the basic maternal recessive locus for familial recurrent hydatidiform moles and the gene NALP7 that causes it in 19 q13.4. The gene that causes it encodes the protein NLRP7 which is reportedly implicated in the inflammatory and apoptotic pathways.[6]

The prevalence is about one pregnancy in a thousand. The risk of recurrent hydatidiform moles is about 1.5% after a molar pregnancy, while the risk is about 25% after two molar pregnancies. Genetic mutations significantly

increase the risk in more than two molar pregnancies.[7] The histopathological type of molar pregnancy in recurrent cases is often the same as the type of earlier molar pregnancies in the patient.[8] Recurring hydatidiform moles are usually sporadic.[9] Three maternal genes (NLRP7, KHDC3L, and PADI6) are responsible for recurrent molar pregnancies. It has been suggested that these three genes regulate the process of genomic imprinting.[10]

NLRP7 mutations are reported in 48-80% of recurrent molar pregnancy cases, while mutations in KHDC3L are reported in only 10-14% of these patients who do not have the NLRP7 mutation. In most affected women, homozygous or compound heterozygous mutations of these three genes are observed.[11] In parents with the NLRP7 or KHDC3L mutation, defective genome imprinting blocks embryo development by silencing maternal gene expression and causes defective trophoblast proliferation. It has been confirmed that these genes are the main cause of recurrent moles hydatidiform.[12]

CASE REPORT

The patient, a 35-year-old gravida 11, parity 0, with six times pathologically proven hydatidiform moles, 5 missed abortus history, and no living children, has no known additional systemic disease and the habit of smoking and alcohol use without regular medication. There is no history of moles in the patient's family. Two sisters and one brother have living children. In vitro fertilization has been tried in the patient, but a healthy pregnancy has not succeeded because the continuity of the oocytes fertilized by intracytoplasmic sperm injection cannot be achieved.

The patient applied to the clinic in November 2021 with a period delay and suspicion of pregnancy. In the transvaginal ultrasound, the area compatible with molar pregnancy was monitored in the intrauterine cavity with dimensions of 45 x 28 mm. The beta hCG value was 115000 mlU/ml; on the same day, the beta hCG level was 120383 mlU/ml. No pathological findings were detected on the patient's lung scan and in laboratory values. Thyroid function values were within the normal range. The patient, whose general condition is stable, was hospitalized, and a revision curettage was performed. The patient, who was followed for four days in our hospital, was released after the follow-up and the treatment process was finished. In the laboratory tests that were retaken during the patient's stay in the hospital, thyroid, liver and kidney function tests were within normal limits. ANA, AM ASMA, beta-2 microglobulin, anti-t, and anti-m values taken in the previous molar pregnancy were within normal limits. Histopathological assessment of the pathological material was identified as a partial hydatidiform mole. The patient was followed up with beta hCG follow-up with serial b-hCG levels, according to the standard Royal College of Obstetricians and Gynaecologists (RCOG) guideline, until the beta hCG value was 0 mlU/ml. The patient who was being monitored did not develop any complications. After discharge, she was consulted by the medical genetics department.

After genetic counseling, a mutation scan was planned with a multi-gene panel of 4 genes in the phenotypic series "Hydatidiform mole, recurrent" (OMIM: PS231090) from the individual with a history of recurrent moles (Table 1).

Table 1: Transcripts/locus/phenotype names and numbers of the genes examined.

Name of gene	Transcript	Locus	Name of phenotype	Phenotype OMIM number
C11orf80	ENST00000360962	11q13.2	Hydatidiform mole, recurrent, 4	618432
KHDC3L	ENST00000370367	6q13	Hydatidiform mole, recurrent, 2	614293
MEI1	ENST00000401548	22q13.2	Hydatidiform mole, recurrent, 3	618431
NLRP7	ENST00000588756	19q13.42	Hydatidiform mole, recurrent, 1	231090

C11orf80: Chromosome 11 Open Reading Frame 80, KHDC3L: KH Domain Containing 3 Like, MEI1: Meiotic Double-Stranded Break Formation Protein 1, NLRP7: NLR Family Pyrin Domain Containing 7.

Following genomic DNA isolation from peripheral blood samples from the patient and her partner, library preparation was made with the target-based capture kit. The indexed samples were combined into a single tube at the appropriate concentration and loaded into the NGS device (IlluminaMiSeq) cartridge. The sequence data from the device as "FASTQ" was evaluated in an online bioinformatics program (SEQ, Genomize). After the bioinformatics analysis, the 20X reading depth coverage of the coding regions in all the genes examined was 100%. The resulting variants were exonic (exon-intron junction points, 3' and 5' UTR regions were included), and allele frequency <5% filters were applied to population studies. After filtering, homozygous change was detected in the NLRP7 (NM_001127255.1) gene, c.3024_3025 INSC (p.Glu1009ArgfsTer13). The change was considered a highly likely cause of disease based on the ACMG criteria, with evidence of PM2 and PVS1. No records were found in previous databases for reporting this change. Counseling was given on the variants and clinical expectations detected in the case, and a segregation analysis was planned for her family.

For this reason, sequence analysis was performed by the Sanger method using the primers of the variant region from peripheral blood samples taken from the mother, father, and brother, who are accessible family members. Heterozygous alteration of c.3024_001127255 INSC (p.Glu1009ArgfsTer13) was detected in the NLRP7 (NM_3025.1) gene in all three individuals. The findings were consistent with the autosomal recessive inheritance pattern. PVS1 and PM2 were evaluated as highly likely

pathogenic according to the American College of Medical Genetics and Genomics (ACMG) criteria. The pathological result was not determined in the karyotype analysis performed on the patient and her partner. In the advanced genetic examination, sequence analysis was performed by the Sanger method using the primers of the variant region from peripheral blood samples taken from the mother, father, and brother. Heterozygous alteration of c.3024_001127255 INSC (p.Glu1009ArgfsTer13) was detected in the NLRP7 (NM_3025.1) gene in all three individuals. The findings were consistent with the autosomal recessive inheritance pattern. PVS1 and PM2 were evaluated as highly likely pathogenic according to the ACMG criteria with evidence codes.

DISCUSSION

This report presents a patient with six recurrent molar pregnancies and a new mutation in the NLRP7 gene. Even though the patient has eleven pregnancies, she has no living child.

The prevalence is about 1 in 1000 pregnancies. The risk of recurrent hydatidiform moles is about 1.5% after a molar pregnancy and about 25% after two molar pregnancies. Genetic mutations significantly increase the risk in more than two molar pregnancies.[7] Six repetitive molar pregnancies are quite rare. Familial and sporadic recurrent moles have been reported in the literature.[12,13] NLRP7 mutations are reported in 48-80% of recurrent molar pregnancy cases, while mutations in KHDC3L are reported in only 10-14% of these patients who do not have the NLRP7 mutation. In most affected women, homozygous or compound heterozygous mutations of these three genes are observed. It has been confirmed that these genes are the main cause of recurrent moles hydatidiform.[12]

Genetic analysis showed heterozygous alteration in the NLRP7 gene in the patient and her partner's genetic parents and siblings in c.3024_3025 INSC (p. Glu1009ArgfsTer13). In the patient, this change was identified as homozygous. This mutation in the NLRP7 gene is not found in the data banks and is considered a new mutation.

Passed hydatidiform moles increase the risk of recurrent molar pregnancies after pregnancies. Several case reports of recurrent hydatidiform moles have revealed that the likelihood of achieving a normal pregnancy after relapse is reduced. The risk of malignancy after repeated molar pregnancies is unknown. Federschneider et al have reported four cases of invasive moles that develop after a recurrent history of hydatidiform.[13] Saleem and Masoom have also reported a case of a woman who has seven molar pregnancies in a row and then has been diagnosed with choriocarcinoma in a hysterectomy.[14]

The first live birth after oocyte donation among recurrent molar pregnancy cases was reported in 2011 by a 29-year-old woman.[15] Successful pregnancies following oocyte donation have also been reported in two women of Indian descent who have a heterozygous mutation in the NLRP7 gene and have previously had one miscarriage and three full molar pregnancies. The first patient (at age 27, carrying a homozygous NLRP7 mutation) became pregnant with twins after three embryo transfers. 16 The second patient (at age 26, carrying two heterozygous NLRP7 mutations) had a singular pregnancy. The gestational course was normal in both cases, resulting in healthy live births. Recently, an Iranian research team detected a new homozygous NLRP7 mutation in a woman who had five molar pregnancies in her past, in which oocyte donation allowed for a successful pregnancy.[11]

Based on these data, considering that a pregnancy that may occur in our patient is likely to be molar pregnancy again and that it may be possible to turn into an invasive mole, the patient was presented with an oocyte donation or adoption option.

CONCLUSION

Our report reiterates the importance of NLRP7 mutations in the pathophysiology of recurrent moles with the detection of a new NLRP7 mutation in the case of recurrent moles. Since the case has a homozygous mutation, only oocyte donation from existing treatment methods is considered an option for live birth.

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