Case Report

Decoding the Genetics of Recurrent Molar Pregnancy

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Abstract

Hydatidiform mole is a condition characterised by abnormal trophoblastic hyperplasia and failure of embryonic tissue development. The risk of recurrence is seen to be associated with biallelic maternal mutations in *NLRP7, KHDC3 L* and *PAD16* genes. Women with such mutations have a major risk of reproductive failure and normal pregnancy is seen in only 1.8%. We report the case of a 31-year-old woman with previous three molar pregnancies who on genetic testing was found to be compound heterozygous for pathogenic variants in the *NLRP7* gene (c.2738A>G and c.2078G>C). Accordingly, the woman was counselled regarding assisted reproduction with oocyte donation for a normal pregnancy outcome. At present, the patient has an ongoing 5-month pregnancy through oocyte donation.

Keywords: *Familial recurrent hydatidiform mole, genomic imprinting, hydatidiform mole, NLRP7, recurrent molar, trophoblastic diseases*

Introduction

Hydatidiform mole (H. mole) is the part of a spectrum of gestational trophoblastic diseases characterised by abnormal trophoblastic proliferation and maturation; complete and partial molar pregnancy being at the benign end and invasive mole, choriocarcinoma and placental site trophoblastic tumour being the malignant forms. Fifteen percent of complete molar pregnancies and around 5% of partial moles undergo malignant transformation. Recurrent molar pregnancy is extremely rare with the risk of repeat molar pregnancy after one complete H. mole to be 1.5% which increases to 25% after two molar pregnancies.[1] Recurrent complete molar pregnancies are extremely rare occurrences; they can be sporadic or be associated with a family history, with only 30 such families being reported in the literature. Women with such mutations have a major risk of reproductive failure and normal pregnancy is seen in only 1.8%.[2] Recurrent molar pregnancies have a genetic basis and pathogenic variants in *NLRP7, KHDC3 L* and *PADI6* genes are responsible for most of the cases with mutations in the *NLRP7* gene seen in 48%–80% of cases.[3] Oocyte donation is the best option for a successful pregnancy in these women and proper genetic counselling is of paramount importance to correctly guide the couple for a successful obstetric outcome.

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Case Report

Mrs X, 31 years old with a history of recurrent molar pregnancies in the past 5 years attended the outpatient department for prenatal counselling. The age of her partner was 34 years and it was a non-consanguineous marriage. The first pregnancy was diagnosed as complete H. mole on ultrasound at 7 weeks and was also confirmed on histopathological examination of products of conception[Figure 1]. The second pregnancy a year later was diagnosed with a partial H. mole on sonogram which was evacuated and confirmed to be a complete mole histopathologically. The last molar pregnancy was 1 year back and the patient had now come for prenatal counselling. All her molar pregnancies had been followed up with serial beta human chorionic gonadotropin levels and chemotherapy was not required after any molar pregnancy. There was no history of recurrent molar pregnancies in the family. She is the only

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child of non-consanguineous parents. The karyotype of the patient and her husband was normal. Genetic testing was done and clinical exome sequencing of the patient showed her to be a carrier of compound heterozygous pathogenic variants in the *NLRP7* gene (c.2738A>G and c.2078G>C) [Figure 2]. The results of genetic testing were explained to the couple, but parental segregation of the index case could not be done due to lack of consent. The likely presence of biallelic pathogenic variants implies reproductive failure with self-ovum and thus assisted reproduction with oocyte donation was offered. The patient underwent *in vitro* fertilisation using donor oocyte resulting in a successful pregnancy and she is currently in her 5th month of pregnancy.

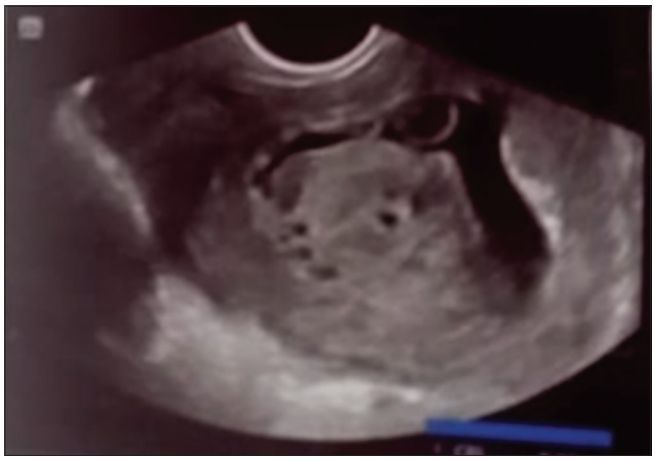

Figure 1: Sonogram showing complete hydatidiform mole

Discussion

H. mole is characterised by trophoblastic hyperplasia, hydropic swelling of placental villi and absent or abnormal foetal development. There are two types of H. mole-partial and complete; A complete mole has an absence of any foetal parts and is androgenetic while a partial mole with the presence of some foetal tissue is mainly triploid. The incidence of molar pregnancy varies according to a geographical area with incidence ranging from 1 to 160 pregnancies in India and the Middle East and 1 in 1500 pregnancies in the Western world.[1]

The risk of having a repeat molar pregnancy after one complete H. mole is about 1.5% increasing to 25% after 2 molar pregnancies. Recurrent molar pregnancies are not only associated with poor reproductive outcomes for the woman but also carry the risk of malignant transformation. They can either be sporadic or associated with a family history of molar pregnancies. Patients with a personal history of recurrent complete molar pregnancies but no family history of recurrent are generally genetic while the ones with a family history are diploid and biparental.[3] Women with familial recurrent hydatidiform mole (FRHM) are developmentally normal themselves but a genome-wide failure to correctly

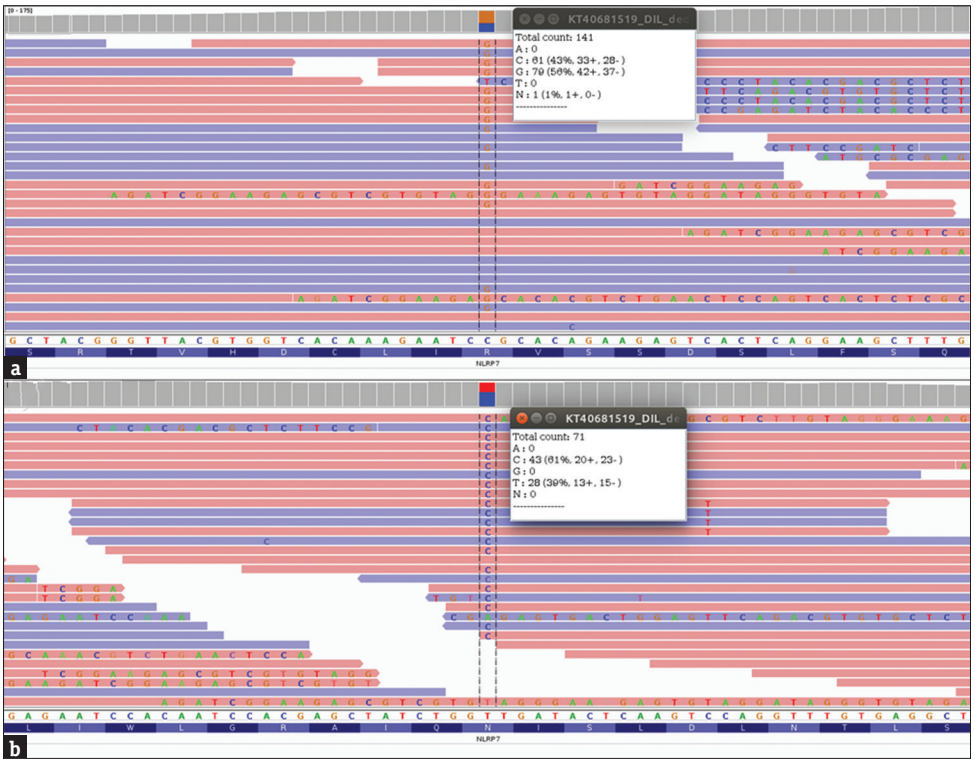

Figure 2: Integrated genome viewer images from next-generation sequencing-based exome sequencing showing *NLRP7* gene variants identified in compound heterozygous state, (a): exon 5:c.2078G>C; (b): exon 9:c. c.2738A>G

maintain a maternal epigenotype at imprinted loci leads to repeated pregnancy loss in them.[4]

Three genes *NLRP7, KHDC3 L* and *PADI6* are known to be implicated in the pathogenesis of FRHM with mutations in the *NLRP7* gene accounting for most of such cases; they have also been implicated in causing spontaneous abortions, stillbirths and foetal growth restriction. The mechanisms by which these mutations lead to molar pregnancies are still not clear. *NLRP7* codes for a cytoplasmic protein, which takes part in inflammasome formation and pro-inflammatory cytokine release and thus this gene plays an important role in innate human immunity. In addition, it is a member of the reproduction-associated human gene cluster, a group of genes highly expressed in the reproductive organs. Women who harbour a biallelic pathogenic variant in *NLRP7* have normal methylation patterns in somatic cells, however, their germ cells have faulty imprinting.[5] During gametogenesis, the gametes undergo a remarkable shift in their epigenotype pattern which is orchestrated by various proteins, one of which is the *NLRP7* protein. *NLRP7* protein is involved in rewriting the methylation pattern during oogenesis at the germline differentially methylated regions, establishing normal maternal methylation patterns.[6] This is the normal maternal imprint. This event occurs just after the primordial germ cells migrate to the primitive gonads. At least one normal copy of the *NLRP7* gene is necessary for the establishment of a normal epigenotype or maternal imprint. However, in the presence of two mutated copies, or the absence of at least one normal copy of the *NLRP7* gene, the methylation pattern in the ovum becomes aberrant. Consequently, after fertilisation, the conceptus shows marked trophoblastic proliferation. The absence of normal maternal imprint is also the reason for the development of trophoblastic proliferation in a diploid, 'paternal only' genome seen in complete molar pregnancies.

Sharlene Murdoch *et al*. reported five mutations in the *NALP7* gene in women with FRHM and recurrent HMs.[7] Ulker *et al*. have reported a novel *NLRP7* mutation in two large Turkish families with recurring molar pregnancies; one family had a homozygous single nucleotide insertion causing a frameshift while a heterozygous 60-kb deletion of the *NLRP2* and *NLRP7* was found in the other family.[8] Rezaei *et al*. have described mutations in the *KHDC3 L* gene instead of *NLRP7* in two Asian patients with FRHM; two protein-truncating mutations (homozygous) in an Iranian patient and a splice mutation in an Indian patient.[9] Nguyen *et al*. conducted a comprehensive genetic analysis of 113 patients with recurrent HM and found that all HM from patients with biallelic *NLRP7* or *KHDC3 L* mutations were biparental diploid while they were highly heterogeneous from women without mutations.[10] Our patient was also confirmed to harbour compound heterozygous mutations in the *NLRP7* gene, thus explaining her previous recurrent molar pregnancies. Decoding the genetics in this family helped the couple in their reproductive decision leading to a successful outcome.

Conclusion

Recurrent molar pregnancy is rare but is associated with significant psychological trauma to the patient and also has an increased risk of malignant transformation. Counselling for future pregnancies poses an obstetric dilemma in such cases. Genetic testing should be offered to all women with a history of recurrent molar pregnancies for a better understanding of their future obstetric course and effective and proper counselling.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Author's contribution

Conceptualization, manuscript drafting and revision was done by Sumita Mehta and Dr Sunita Bijarnia-Mahay. Data collection and analysis were done by Dr Abhishek Satapathy and Dr Kiran Arora. All authors have read and approved the final version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

Data will be available from corresponding author upon reasonable request.

References

1. Kumari S, Dhingra M, Ahmad SN, Singh A. Recurrent molar in five consecutive pregnancies – A case report. Int J Womens Health 2020;12:171-4.
2. Cozette C, Scheffler F, Lombart M, Massardier J, Bolze PA, Hajri T, *et al.* Pregnancy after oocyte donation in a patient with NLRP7 gene mutations and recurrent molar hydatidiform pregnancies. J Assist Reprod Genet 2020;37:2273-7.
3. Soper JT. Gestational trophoblastic disease: Current evaluation and management. Obstet Gynecol 2021;137:355-70.

4. Parry DA, Logan CV, Hayward BE, Shires M, Landolsi H, Diggle C, *et al*. Mutations causing familial biparental hydatidiform mole implicate c6orf221 as a possible regulator of genomic imprinting in the human oocyte. Am J Hum Genet 2011;89:451-8.
5. Sanchez-Delgado M, Martin-Trujillo A, Tayama C, Vidal E, Esteller M, Iglesias-Platas I, *et al*. Absence of maternal methylation in biparental hydatidiform moles from women with NLRP7 maternal-effect mutations reveals widespread placenta-specific imprinting. PLoS Genet 2015;11:e10056.
6. Mahadevan S, Wen S, Wan YW, Peng HH, Otta S, Liu Z, *et al*. NLRP7 affects trophoblast lineage differentiation, binds to overexpressed YY1 and alters CpG methylation. Hum Mol Genet 2014;23:706-16.
7. Murdoch S, Djuric U, Mazhar B, Seoud M, Khan R, Kuick R, *et al*. Mutations in NALP7 cause recurrent hydatidiform moles and reproductive wastage in humans. Nat Genet 2006;38:300-2.
8. Ulker BV, Gurkan H, Tozkir H, Karaman V, Ozgur H, Numanoglu C, *et al*. Novel NLRP7 mutations in familial recurrent hydatidiform mole: Are NLRP7 mutations a risk for recurrent reproductive wastage? Eur J Obstet Gynecol Reprod Biol 2013;170:188-92.
9. Rezaei M, Nguyen NM, Foroughinia L, Dash P, Ahmadpour F, Verma IC, *et al*. Two novel mutations in the KHDC3L gene in Asian patients with recurrent hydatidiform mole. Hum Genome Var 2016;3:16027.
10. Nguyen NM, Khawajkie Y, Mechtouf N, Rezaei M, Breguet M, Kurvinen E, *et al*. The genetics of recurrent hydatidiform moles: New insights and lessons from a comprehensive analysis of 113 patients. Mod Pathol 2018;31:1116-30.