Recurrent familial hydatidiform mole - a rare clinical problem

Rekürren ailesel hidatidiform mol - nadir bir klinik problem

Lavanya Rai, Hebbar Shripad, Shyamala Guruvayare, Adiga Prashant, Anjali Sunil

Department of Gynaecology and Obstetrics, Kasturba Medical College, Manipal University, Manipal, India

Abstract

Familial recurrent hydatidiform mole is a rare event; here we report an unusual case of a gravida 5 aged 29 years, with five recurrent hydatidiform moles and no normal pregnancy. After the fourth molar pregnancy, she developed persistent trophoblastic disease that required 7 cycles of single agent chemotherapy. Two years after the treatment, she presented with her fifth molar pregnancy. Her elder sister had seven hydatidiform moles from two different unrelated male partners. As this is familial, and recurrent, with no viable conceptions in both the sisters, it is likely to be biparental in origin. Unlike androgenetic moles, biparental moles arise due to a global inherited failure of maternal imprinting. It is an autosomal recessive defect in the female germ line. Genetic analysis is essential, although it is not available in all centers. Donor Oocyte IVF is the only option for women with biparental moles to have normal offspring.

(J Turkish-German Gynecol Assoc 2012; 13: 284-6)

Key words: Recurrent hydatidiform mole, persistent trophoblastic disease, familial mole, donor oocyte invitro fertilisation, preimplantation genetic diagnosis.

Received: 12 December 2011 **Accepted:** 14 April 2012

Özet

Ailesel rekürren hidatidiform mol nadir bir olaydır; biz burada beş rekürren hidatidiform molü olan ve normal gebeliği olmayan gravidası 5, yaşı 29 olan olağan dışı bir olgu bildiriyoruz. Dördüncü molar gebelikten sonra hasta tekli ajan ile 7 döngü kemoterapi gerektiren persistan trofoblastik hastalık geliştirdi. Tedaviden iki yıl sonra hasta beşinci molar gebelik ile başvurdu. Hastanın ablasında birbiri ile ilişkisiz iki farklı erkek eşten toplam yedi hidatidiform mol gebelik olmuştu. Bu durumun ailesel ve rekürren olması ve her iki kız kardeşte de canlı konsepsiyonun olmaması nedeniyle biparental orijinli olması muhtemeldir. Androjenik mollerin aksine biparental moller, global kalıtsal maternal imprinting yetmezliğinden kaynaklanmaktadır. Bu, dişi germ hattında otozomal resesif bir defekttir. Tüm merkezlerde ulaşılabilir olmamasına rağmen genetik analiz zorunludur. Biparental molü olan kadınların normal çocuğa sahip olması için tek seçenek donör oosit IVF'dir.

(J Turkish-German Gynecol Assoc 2012; 13: 284-6)

Anahtar kelimeler: Rekürren hidatidiform mol, persistan trofoblastik hastalık, ailesel mol, donör oosit in vitro fertilizasyon, preimplantasyon genetik tanı

Geliş Tarihi: 12 Aralık 2011 **Kabul Tarihi:** 14 Nisan 2012

Introduction

Hydatidiform mole is the result of abnormal fertilization and is most often a sporadic event. Recurrent moles account for 2% of all hydatidiform moles (1). Some of these recurrent moles are familial, with more than one member of the family having hydatidiform moles and often from different partners (2). The genetic origin of these moles is biparental (BiCHM) and is different from the androgenetic (AnCHM) origin of the usual hydatidiform mole. Besides the risks of persistent trophoblastic disease (PTD), women with recurrent biparental moles are unable to have normal pregnancies.

Case Report

Our index case was a gravida 5, para 0, muslim lady aged 29 years, with 4 previous hydatidiform moles who presented at 8 weeks of gestation with a diagnosis of a 5th hydatidiform mole for termination. Her scan showed typical anechoic spaces suggestive of hydatidiform mole. Ovaries did not show any theca lutein cysts. Her blood group was B positive. Her liver, renal function tests and chest X-ray were normal. Preevacuation serum beta hCG (β hCG) was 113527mLU/mL. Histopathology following suction evacuation revealed a complete hydatidiform mole (CHM). Post evacuation serum β hCG regressed in 6 weeks and at present she is under postmolar survelliance.

Her previous 4 molar pregnancies occurred at intervals of 2 years. They were evacuated elsewhere and were reported as CHM. Following the 4th molar evacuation, PTD was diagnosed with a rising trend of serum β hCG after 2 months of evacuation. She received chemotherapy consisting of methotrexate with folinic acid rescue for low risk PTD (WHO score 4). Serum β hCG had become normal after the 5th cycle and 2 more cycles of chemotherapy were given for residual disease. Her husband is not related to her. The karyotype of the couple is normal.

Address for Correspondence: *Lavanya Rai, Department of Gynaecology and Obstetrics, Kasturba Medical College, Manipal University, 576104 Manipal, India*
Phone: 0850 29622176 e.mail: lavanya.rai@manipal.edu - railalavanya@yahoo.com

doi:10.5152/jtgga.2012.48

Her elder sister had 7 consecutive hydatidiform moles with no normal pregnancy. Four hydatidiform moles occurred with her first husband after which she was divorced. She had 3 more molar pregnancies from her second husband. The pedigree chart of this family is depicted in Figure 1. There is no relevant past or family history of genetic disease.

Due to the familial, recurrent nature of these moles with no viable conceptions in both the sisters, it is likely to be biparental in origin. As molecular techniques to detect the origin of these moles was not feasible in our set up, we advised donor oocyte in-vitro fertilization (IVF). Adoption was also suggested as an alternative option

Discussion

The majority of CHMs (80%) have a diploid set of paternal chromosomes due to fertilization of an anucleate oocyte by sperms, leading to reduplication of the paternal haploid set of chromosomes (1). This is termed as Androgenetic (AnCHM) origin. Recurrent moles may be sporadic, occurring in a single individual in a family or may be familial as in biparental moles (3). Biparental moles have both a maternal and a paternal component. These are due to an autosomal recessive defect in the female germ line (4).

The hydatidiform moles in our case occurred in sisters married to unrelated men. Their parents are 3° descendents from common parents as depicted in the pedigree chart (Figure 1). BiCHM are seen in families where ≥2 individuals have recurrent molar pregnancies (4). Since the women themselves are affected with the autosomal recessive mutation, paternal genotype does not contribute to the pathogenesis. Dysregulation of imprinting occurs due to the methylation defect during oogenesis in the female germ line (2, 4). This is believed to be a global methylation defect leading to a switch from maternal to paternal methylation pattern, resulting in BiCHM (5). Women with this methylation defect in the germline are unable to establish a normal female imprinting pattern. Initially, Mogalbey et al. (6) mapped this maternal recessive locus to chromosome 19 q13.4. This defect is now seen in several genes in different chromosomes (5). However, recent literature suggests mutation of NLRP7 gene as a major contributor to familial biparental moles (7).

NALP7 gene has a role in cytokine secretion, particularly interleukin 1B (IL-1B), which is necessary for inflammation and apoptosis. This is also essential for folliculogenesis, ovulation, decidualization and trophoblast invasion. Mutation in this gene is said to cause biparental moles and other forms of reproductive loss (1, 7).

AnCHM can also recur more than twice when there are consanguinous marriages in families. However, the risk of recurrence is much lower than BiCHM and they have some chance of having normal pregnancy, unlike BiCHM, and hence it is suggested that genetic analysis should be done after 2 or more moles (3). Anucleate oocytes caused by defective meiosis are the result of extrusion of the maternal nuclear genome into one of the polar bodies leaving an anucleate ovum. Another hypothesis for post zygotic diploidisation (PDT) has been postulated for recurrent moles because triploid conceptions occur far more frequently than anucleate oocytes (3) According to this concept, all non BiCHM moles can be the result of dispermic fertilization. These triploid conceptions are unstable at first mitosis and give rise to daughter cells that could develop AnCHM.

The risk of PTD is higher (50%) in recurrent molar pregnancy. Histology and degree of invasiveness also increases in successive molar pregnancies (8). Although in our index case, PTD developed after 4 moles, her sister with 7 moles did not have this problem. Incidence of recurrent mole was 0.7% in the Sheffield Trophoblastic centre. They noted that the Asian women, particularly of Indian/ Pakistan origin, and those with blood group B had a higher incidence (9). Our patient also had the same blood group.

The majority of recurrent moles are reported from Muslim countries such as Egypt, Lebanon etc (2). Our patient also was a Muslim. Seoud et al. (10) reported familial recurrent moles in a family with extensive intermarriage.

Molar tissue should be genotyped with polymorphic DNA markers to determine the parental origin as this helps to plan therapeutic options. If it is BiCHM, conception with a donor oocyte is the only option. Tuncer et al. (11) have reported a successful pregnancy through ovum donation in a lady with 3 recurrent molar pregnancies with 2 different partners. The report is not clear whether it was a biparental mole.

Sensi et al. (12) attempted a pregnancy with ovum donation which failed, as the repeat molar pregnancy showed it was established by fertilization of the maternal ovum. It is also believed that, despite fertilization with ovum donation, implantation may fail due to an abnormal inflammatory response in the endometrium as result of mutation of the NLRP7 gene (7) (Figure 2).

If the origin of a recurrent mole is heterozygous androgenetic, then Intracytoplasmic Sperm injection (ICSI)/preimplantation diagnosis (PGD) with Fluorescent in situ hybridization (FISH) is appropriate (3). ICSI ensures monospermic fertilization. FISH for male preselection of embryo, ensures that fertilization occurs with a Y chromosome so that androgenesis with X sperms is avoided. If a female embryo is required, preimplantation determination of parental origin by DNA typing is required (8). Standard IVF procedure and transfer of an embryo presumed to be normal can still result in an hydatidiform mole. As women with BiCHM cannot have their own genetic offspring, counseling has an important role.

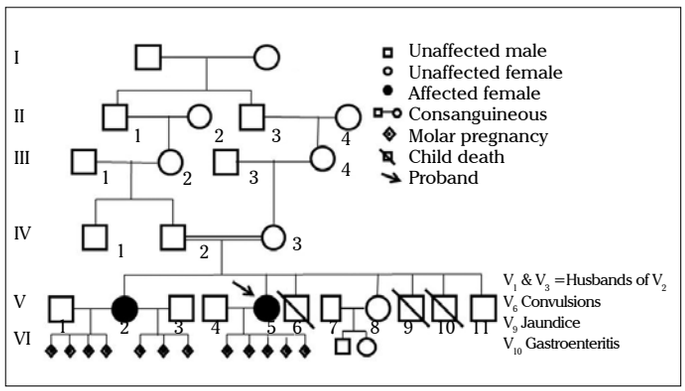

Figure 1. Pedigree Chart of Mrs S

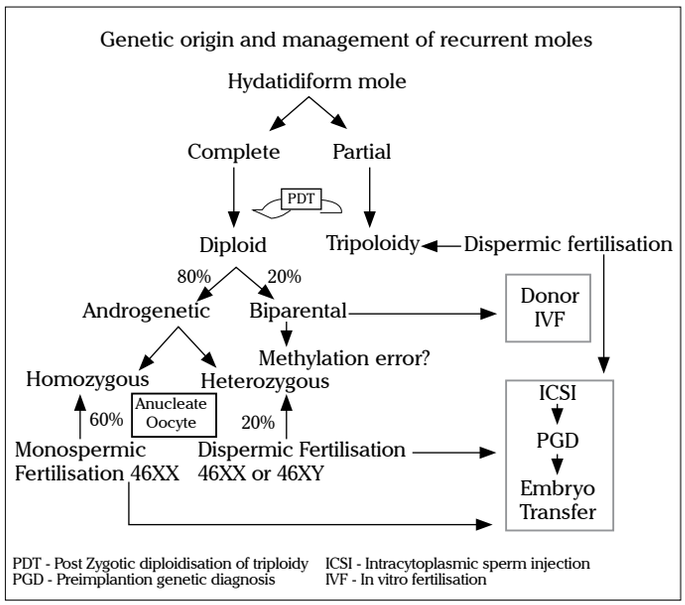

Figure 2. Flow Chart

Conflict of interest

No conflict of interest was declared by the authors.

References

1. Slim R, Mehio A. The genetics of hydatidiform moles: new lights on an ancient disease. Clin Genet 2007; 71: 25-34. [ ]
2. Al-Hussaini TK, Abd el-Aal DM, Van den Veyver IB. Recurrent pregnancy loss due to familial and non-familial habitual molar pregnancy. Int J Gynaecol Obstet 2003; 83: 179-86. [CrossRef]
3. van der Smagt JJ, Scheenjes E, Kremer JA, Hennekam FA, Fisher RA. Heterogeneity in the origin of recurrent complete hydatidiform moles: not all women with multiple molar pregnancies have biparental moles. BJOG 2006; 113: 725-8. [CrossRef]
4. Fisher RA, Hodges MD, Newlands ES. Familial recurrent hydatidiform mole: a review. J Reprod Med 2004; 49: 595-601.
5. Devriendt K. Hydatidiform mole and triploidy: the role of genomic imprinting in placental development. Hum Reprod Update 2005; 11: 137-42. [CrossRef]
6. Moglabey YB, Kircheisen R, Seoud M, El Mogharbel N, Van den Veyver I, Slim R. Genetic mapping of a maternal locus responsible for familial hydatidiform moles. Hum Mol Genet 1999; 8: 667-71. [CrossRef]
7. Williams D, Hodgetts V, Gupta J. Recurrent hydatidiform moles. Eur J Obstet Gynecol Reprod Biol 2010; 150: 3-7. [CrossRef]
8. Reubinoff BE, Lewin A, Verner M, Safran A, Schenker JG, Abeliovich D. Intracytoplasmic sperm injection combined with preimplantation genetic diagnosis for the prevention of recurrent gestational trophoblastic disease. Hum Reprod 1997; 12: 805-8. [CrossRef]
9. Lorigan PC, Sharma S, Bright N, Coleman RE, Hancock BW. Characteristics of women with recurrent molar pregnancies. Gynecol Oncol 2000; 78: 288-92. [CrossRef]
10. Seoud M, Khalil A, Frangieh A, Zahed L, Azar G, Nuwayri-Salti N. Recurrent molar pregnancies in a family with extensive intermarriage: report of a family and review of the literature. Obstet Gynecol 1995; 86: 692-5. [CrossRef]
11. Tuncer SZ, Bernstein MR, Wang J, Goldstein DP, Berkowitz RS. Repetitive Hydatidiform Mole with different male partners Gynecol Oncology 1999; 75: 224-6. [CrossRef]
12. Sensi A, Gualandi F, Pittalis MC, Calabrese O, Falciano F, Maestri I, et al. Mole maker phenotype: possible narrowing of the candidate region. Eur J Hum Genet 2000; 8: 641-4. [CrossRef]