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High-Risk Gestational Trophoblastic Neoplasia from a Homozygous NLRP7 Mutation

Zachary A. Kopelman *, Erica R. Hope

Department of Obstetrics and Gynecology, Brooke Army Medical Center, 3551 Roger Brooke Drive, Fort Sam Houston, TX 78234, USA

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1. Introduction

Gestational trophoblastic disease (GTD) is a collection of both benign and malignant conditions that develop from placental tissue. Hydatidiform mole (HM) represents approximately 80% of GTD and is considered a benign disease comprised of two types of pre-malignant moles: partial and complete molar gestation (Abu-Rustum et al., 2019). Partial molar gestations comprise 20% of HM and complete moles, which are more likely to precede malignancy, encompass the remainder at 80%. Both partial and complete moles may precede malignant sequelae, known as gestational trophoblastic neoplasia (GTN), at 1–5% and 15–20% respectively (Abu-Rustum et al., 2019). Differing from other gynecologic cancers, GTN develops from an abnormal proliferation of placental trophoblastic tissue and includes invasive moles, placental site trophoblastic tumors, choriocarcinomas, and epithelioid tumors. Invasive moles account for approximately 15% of all GTD with the remaining forms of GTN comprising approximately 5% (Abu-Rustum et al., 2019). While GTN can be aggressive, invading the uterus or rapidly metastasizing to distant sites such as the lungs, it is also exquisitely chemosensitive. Cure rates approach 100% for low risk disease (Abu-Rustum et al., 2019).

Risk of recurrent GTD is low after a single molar gestation, approximately 1–2%, but this rate increases significantly with each additional molar pregnancy a patient experiences (Abu-Rustum et al., 2019; Seckl et al., 2010; Altieri et al., 2003). Recurrent hydatidiform mole (RHM) has been reported as high as 15–25% in women with more than one previous molar gestation (Seckl et al., 2010; Altieri et al., 2003). Patients with germline genetic mutations are at significantly higher risk of recurrence, as high as 10–80% depending on the mutation (Moein-Vaziri et al., 2018). One such gene, the NLR family pyrin domain containing 7 (NLRP7) gene, contributes to the activation of the immune response to various microbials as well as normal oocyte and embryonic development by assisting with the control of trophoblastic differentiation (Alici-Garipcan et al., 2020; Slim and Wallace, 2013). The inheritance pattern is autosomal recessive and mutations in either the compound heterozygous or homozygous forms have been reported with RHM in nearly 130 cases (Alici-Garipcan et al., 2020; Soellner et al., 2017). Alternatively, the heterozygous NLRP7 variant (which is unique from the compound heterozygous or homozygous forms) is rare and to date only single cases have been reported, though they do support an association between the heterozygous NLRP7 form and RHM (Soellner et al., 2017). These mutations have been shown to enhance proliferation of trophoblastic tissue as well as decrease the immune cytokine release. The failure of immune response decreases the success in eliminating abnormal pregnancies and both of these factors can lead to the following outcome: abnormal human pregnancies with no embryo, excessive trophoblastic proliferation, and hydropic degeneration of the chorionic villi (Slim and Wallace, 2013; Nguyen and Slim, 2014). Additionally, genetic mutations of NLRP7 are well described in the literature for maternal imprinting defects which are also believed to increase the risk of recurrent GTD (Moein-Vaziri et al., 2018).

NLRP7 mutation can impact future fertility and is of specific

* Corresponding author.
E-mail address: zachary.a.kopelman.mil@mail.mil (Z.A. Kopelman).

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importance to the reproductive endocrinology community (Kalogiannidis et al., 2018). At this time there are no reported successful reproductive outcomes in patients who are homozygous (bi-parental autosomal recessive inheritance) for the NLRP7 gene mutation and the recommended option for successful pregnancy is donor oocytes (Williams et al., 2010; Cozette et al., 2020). To our knowledge, while NLRP7 mutation increases the risk of recurrent GTD, there are no described cases of an NLRP7 mutation resulting in high risk GTN. We present the first reported case of a patient with an NLRP7 mutation who subsequently developed high risk GTN.

2. Case presentation

A 36-year-old female gravida 3 para 0–0-2–0 with a history of two prior molar pregnancies presented to the emergency room (ER) while overseas with heavy vaginal bleeding. She had a known personal history of two prior molar pregnancies both of which were treated with a suction dilation and curettage (D&C) with no malignant sequelae. She reported no family history of molar pregnancy or early pregnancy loss. Pathology from her first molar pregnancy favored a complete mole, karyotype 46XX, and the pathology from her second molar pregnancy is unknown. During her ER course she had a transvaginal ultrasound performed which identified a suspected complete molar pregnancy. She was discharged home with close follow-up for a suction D&C; however, prior to her procedure she had spontaneous passage of tissue at home and on subsequent exam had no visible retained products in the uterus. At that time she was diagnosed with a completed abortion. No pathology was able to be obtained for analysis.

One month later she re-presented to the ER for new-onset severe abdominal pain and dyspnea. Laboratory evaluation noted a beta human chorionic gonadotropin (hCG) level $>$ 250,000 mIU/mL and a pelvic ultrasound demonstrated a cystic endometrium with an ill-defined mass and enlarged uterus. These findings were concerning for recurrent GTD in the setting of her history of molar pregnancies. She was taken to the operating room (OR) where she underwent an emergent suction D&C and chest x-ray revealing numerous pulmonary nodules suspicious for metastatic GTN. Surgical pathology from the suction D&C confirmed a complete mole with the karyotype 46XX and she received the clinical diagnosis of FIGO Stage III GTN given her lung involvement.

The patient was immediately transferred to the United States for further evaluation and management by a gynecologic oncologist. She received single agent chemotherapy with weekly methotrexate 30 mg/m^2 after World Health Organization (WHO) scoring was calculated as 5 (low-risk). The remainder of her initial evaluation revealed no brain metastasis and a significant reduction in the uterine burden of disease. After one month of weekly single agent treatment, rising beta hCG levels from 4,834 mIU/mL to 5,866 mIU/mL required transitioning to an alternate single agent, pulsed actinomycin D 1.25 mg/m^2 every 14 days. Repeat imaging for re-calculation of WHO score was obtained and remained low-risk (no WHO score or imaging available for review from the previous physician). She had an adequate initial response to this treatment and continued on actinomycin D for a total of three cycles. During this time her care was transferred to our facility in San Antonio, Texas.

Ahead of the fourth cycle of actinomycin D, her weekly beta hCG levels plateaued at 2374 mIU/mL (previously at 2,182 mIU/mL) and then started to rise to 9036 mIU/mL. Imaging revealed an intrauterine tumor burden at 7.1 $\times$ 5.4 cm with an increasing number of lung nodules, though the maximum size of these nodules remained stable at 1.2 cm (Figs. 1 and 2). Having failed both single agent therapies, recalculation of her WHO score was determined to be 12, high risk. The recommendation was made to transition to multi-agent chemotherapy with Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide, and Vincristine (EMA-CO) and undergo a uterine artery embolization followed by a repeat suction D&C for reduction in tumor burden. The patient strongly desired future fertility and declined a hysterectomy. Her

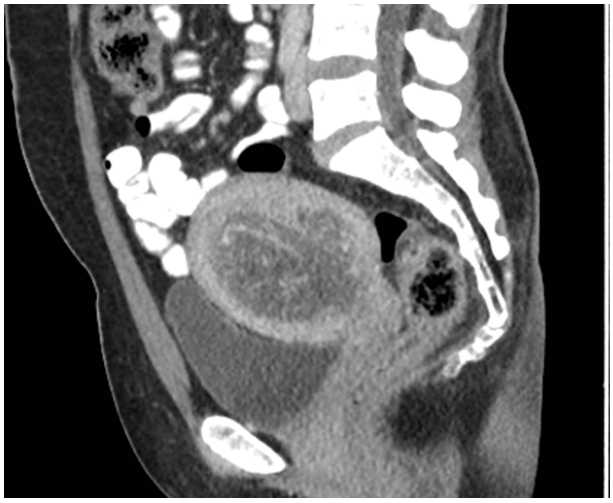

Fig. 1. Sagittal CT Abdomen/Pelvis demonstrating an enlarged heterogeneous mass within the endometrium.

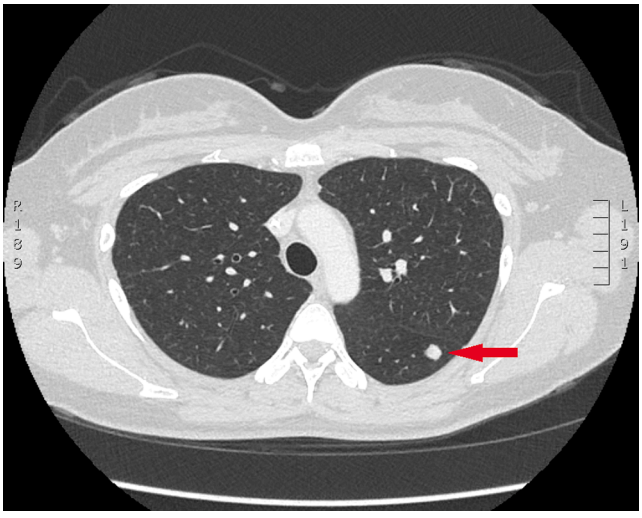

Fig. 2. Axial CT Chest performed after rising hCGs with pulsed Actinomycin-D. Representative pulmonary nodule shown (red arrow) and multiple others existed at various levels of the CT scan. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

beta hCG normalized after the first EMA-CO cycle and she completed three additional cycles for a total of four cycles. PCR amplification of the coding region on genomic DNA and bi-directional Sanger sequencing was performed and identified a pathogenic NLRP7, homozygous, autosomal recessive mutation.

At the completion of her treatment she was referred to reproductive endocrinology and maternal fetal medicine for a discussion of future fertility desires. She was counseled that reproductive outcomes are poor and given the homozygosity of her mutation, the recommendation to avoid future molar gestations would be in vitro fertilization (IVF) utilizing a donor oocyte. She underwent 12 months of close surveillance with undetectable beta hCG on continuous oral contraceptive pills. She is now more than one year out from completion of treatment with no evidence of disease recurrence.

3. Discussion

Recurrent hydatidiform mole is a rare phenomenon and is

specifically defined as at least two moles in the same female (Fallahi et al., 2019; Nguyen and Slim, 2014; Kalogiannidis et al., 2018). In most cases, GTD is sporadic occurring in 0.1% of pregnancies; however, some patients may have a genetic mutation which increases their risk of developing RHM (Abu-Rustum et al., 2019; Moein-Vaziri et al., 2018). These patients often have recurrent GTD and although they can have a subsequent normal pregnancy, the likelihood has been described as low as 1.8% (Cozette et al., 2020). These mutations are inherited in an autosomal recessive pattern and at this time three genes associated with RHM have been described in the reproductive endocrinology literature: NLRP7, KHDC3L, and PADI6 (Fallahi et al., 2019).

NLRP7 has been identified in the vast majority of RHM cases, nearly 48–80%, while KHDC3L has been identified in approximately 10–14% of cases (Fallahi et al., 2019). Neither KHDC3L nor PADI6 have ever been described in association with GTN and, until now, malignant sequelae from NLRP7 mutation has never been reported (Landolsi et al., 2011; Buyukkurt et al., 2010). On thorough literature review, a single case report published in 2018 of familial GTN was identified. In this case, two sisters developed GTN following molar pregnancies and a genetic factor was suspected to have predisposed these sisters to GTN. Unfortunately, no genetic analysis was performed during the evaluation and it remains unknown if NLRP7 existed within the family (Mu et al., 2018).

GTN aggressively invades the uterus with rapid metastases to distant sites such as the lungs; however, it is most often chemosensitive with cure rates approaching 100% for low risk disease (Abu-Rustum et al., 2019). Appropriate initial treatment of GTN following National Comprehensive Cancer Network (NCCN) guidelines for chemotherapy is fundamental in preventing advancement to high risk disease. Rather than receiving a five day 0.4 mg/kg/day methotrexate regimen, our patient received weekly methotrexate injections 30 mg/m^2 which is no longer recommended as a preferred initial systemic therapy by the NCCN due to lesser efficacy (Abu-Rustum et al., 2019). After inadequate response to methotrexate she was transitioned to pulsed actinomycin-D which is also not a recommended systemic therapy by the NCCN for methotrexate resistant disease (Abu-Rustum et al., 2019). It is possible that the initial approach to her treatment may have contributed to her development of high-risk GTN.

Due to the recurrent nature of her disease, our patient opted for germline testing and was found to be homozygous for an NLRP7 mutation. NLRP7 is known to be a maternal effect gene expressed in the oocyte during oogenesis and is essential for normal embryo development (Moein-Vaziri et al., 2018; Alici-Garipcan et al., 2020; Slim and Wallace, 2013). According to the genetics laboratory that performed the testing, our patient had an NLRP7 variant (p.Leu750Val) of which there are no homozygous controls and has been observed with a frequency of 0.05%. A mutation in NLRP7 is associated with RHM and patients have repetitive poor reproductive outcomes, often needing oocyte or embryo donation to successfully carry a gestation to term (Fallahi et al., 2019). Upon review of the reproductive endocrinology literature, there are no reported successful pregnancy outcomes in patients who are homozygous for NLRP7. For our patient, it is likely that a donor oocyte or embryo with IVF would provide the best opportunity to carry a successful pregnancy (Williams et al., 2010; Fallahi et al., 2019).

4. Conclusion

We report the first case of a patient with homozygous NLRP7 mutation with subsequent high risk GTN. This case highlights the need for awareness that GTN can arise from RHM and specifically a germline mutation in NLRP7. This case also identifies an opportunity to increase genetic testing for those individuals diagnosed with recurrent GTD or GTN. Further research is needed in these rare cases regarding GTN recurrence and reproductive outcomes.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author Contribution

- Zachary Kopelman drafted the paper and is the lead author.
- Erica Hope contributed to critical revision of the paper.

Suggested reviewers

- Chad Hamilton: chad.a.hamilton@gmail.com
- Jubilee Brown: jubilee.brown@atriumhealth.org

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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