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Management of a complete mole and coexisting fetus in post-dobbs world

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ABSTRACT

BACKGROUND: Twin pregnancies consisting of a complete hydatidiform mole and a coexistent fetus (CMCF) are rare and associated with a high rate of maternal-fetal morbidity and mortality. Management of these pregnancies remains controversial and increasingly challenging following the *Dobbs versus Jackson Women's Health* decision given the viability of the coexisting twin fetus.

CASE: This case looks at the diagnosis, management, and maternal-fetal outcomes of a viable fetus coexisting molar pregnancy at a large academic center in an abortion-restricted state.

CONCLUSION: CMCF pregnancies are associated with a high risk of morbidity and mortality and are increasingly difficult to manage following the Dobbs decision. Testing platforms, which identify genetic abnormalities in the first trimester, are increasingly important as access to abortion care in the United States is restricted.

1. Introduction

Gestational trophoblastic disease (GTD) refers to a spectrum of both benign and malignant placental conditions including hydatidiform moles, which are premalignant lesions resulting from anomalous fertilization (Lurain, 2010). Molar pregnancies are suspected following identification of an abnormal placenta on ultrasound and elevated levels of human chorionic gonadotropin (hCG) but are confirmed pathologically following uterine evacuation (Lurain, 2010). Patients can present with abnormal vaginal bleeding, elevated hCG levels, early onset pregnancy induced hypertension, and theca lutein cysts (Soper, 2021; Wee and Jauniaux, 2005). Given the accessibility of early first trimester ultrasound, molar pregnancies are often diagnosed and evacuated prior to the development of symptoms (Soper, 2021).

A twin pregnancy consisting of a viable fetus and coexisting molar pregnancy is a rare obstetric phenomenon occurring 1 in 22,000 to 100,000 pregnancies and termed complete hydatidiform mole and a coexistent fetus (CMCF) (Vaisbuch, 2005; Sebire, 2002). This condition is suspected following ultrasound though is commonly diagnosed after 20 weeks gestation due to the need for additional diagnostics (Wee and Jauniaux, 2005; Vaisbuch, 2005; McNally, 2021; Braga, 2017). Serum cell free DNA (cfDNA) testing has been adopted widely in practice, and potentially represents a less invasive and earlier option for CMCF screening. A pathologist ultimately needs to evaluate the products of conception and perform DNA genotyping to diagnose CMCF, which will differentiate between CMCF and other conditions.

Management of CMCF pregnancies remain a challenge due to balancing the possibility of fetal survival with the maternal risks. Maternal risks include hyperemesis gravidarum, thyrotoxicosis, severe preeclampsia, HELLP syndrome, and progression to invasive gestational trophoblastic neoplasia (GTN) (Vaisbuch, 2005; Sebire, 2002). Original publications describing CMCF pregnancies recommended immediate pregnancy termination and uterine evacuation due to the maternal risks and low likelihood of live birth (Soper, 2021; Braga, 2017; Matsui, 2000). While the data remains sparse due to the rarity of this diagnosis, there have been studies outlining the role for expectant management in CMCF pregnancies for patients desiring pregnancy continuation. These studies demonstrate a live birth rate between 16 and 50 % with progression to GTN between 19 and 50 %, depending on the study (Wang, 2022). While there does not appear to be a difference in progression to GTN between those who elect for pregnancy termination compared to expectant management, over half of those who remain pregnant will go

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on to develop a life-threatening condition as defined by the World Health Organization including vaginal hemorrhage, preeclampsia, clinical hyperthyroidism, and respiratory distress. (Matsui, 2000; Wang, 2022). Sixteen to 32 % will require medically indicated termination (Sebire, 2002; Lin, 2017; Garbin, 1995). There does not appear to be a difference between risk of post-molar malignancy between cesarean section and vaginal delivery, though hysterectomy has been shown to reduce the risk of malignant conversion (3–5 %) compared to those undergoing uterine evacuation (15–20 %) in patients who do not desire future fertility (Soper, 2021).

The nuance of CMCF pregnancy management has become increasingly complicated following the overturning of *Roe versus Wade*. The *Dobbs versus Jackson Women's Health* decision reversed the U.S. federal protection of abortion as a fundamental right under the 14th Amendment of the U.S. Constitution. Following cessation of federal protection, abortion access and legislation is left to the discretion of the state. This has resulted in states enforcing a variety of pre-Roe bans or enacting post-Roe trigger bans which immediately took effect with the fall of federal protection. As of March 2024, there are 14 states in which abortion is illegal, criminalizing abortion care with limited exception, and many more states with extremely limited abortion care (Abortion Laws, 2023). Following the Dobbs decision, it is unclear if termination and uterine evacuation would even be an option for a patient diagnosed with a CMCF pregnancy given the co-existent viable fetus. There exists a large disparity in access to abortion care from state to state, and management of CMCF pregnancies poses a unique challenge for patients and providers. Below we will review a case of CMCF pregnancy diagnosed in a restrictive state, in part by cfDNA technology and expectantly managed until delivery at 31 weeks gestation with resultant invasive GTN on final pathology.

2. Case

Our patient is a 40-year-old P1332 who presented for prenatal care with dating ultrasound confirming viable intrauterine pregnancy at 6.5 weeks. Her medical history was notable for type 2 diabetes, chronic hypertension, severe preeclampsia, and intrauterine fetal demise in a previous pregnancy. She received routine prenatal care and was started on medication for her co-morbidities. First trimester cfDNA resulted "low risk" for fetal trisomies though was "no call," or unable to ascertain the risk for monosomy X or sex chromosome aneuploidy. Targeted anatomy ultrasound at 22 weeks revealed a singleton fetus with normal anatomy, a normal fetal echocardiogram, and a normal appearing anterior placenta. Additional images showed a 12 cm by 7 cm area of multi-cystic placental tissue in the uterine fundus concerning for possible molar tissue *versus* placental mesenchymal dysplasia.

Repeat cfDNA testing, using single nucleotide polymorphism-based next-generation sequencing, reported results consistent with a possible triploid, vanishing twin, or unrecognized multiple gestation. The report also noted suspected complete uniparental disomy, which is most consistent with a molar pregnancy. She received genetic counseling and declined amniocentesis for diagnostic testing.

She was asymptomatic and had normal vital signs. Labs were notable for a significantly elevated hCG over 250,000, subclinical hyperthyroidism, and normal hepatic function. Chest x-ray was negative for metastatic disease. She was counseled by a multidisciplinary team including Maternal Fetal Medicine (MFM) and Gynecologic Oncology regarding expectant management *versus* uterine evacuation. Despite the serious health risks posed by continuation of her pregnancy, pregnancy termination was not available in her state as her gestational age at the time of diagnosis was greater than the gestational age ban limit of 20 weeks post conception. Counseling did include the ability to explore termination care in other states with later gestational age limits, though given the legal restrictions in place she could not be directly referred or transferred if she desired termination care (Abortion Laws, 2023). Her options were further limited by the additional barriers of out-of-pocket costs for the procedure, travel, lodging, and childcare. She elected to proceed with expectant management and was co-managed by MFM and Gynecologic Oncology. Delivery was scheduled for no later than 32 weeks after consensus conference, but she ultimately developed severe preeclampsia at 31 weeks necessitating delivery. Following counseling, the patient desired to proceed with cesarean hysterectomy given she did not desire future fertility and she was counseled about a decreased risk of post-molar conversion to GTN following hysterectomy compared to uterine evacuation. Her case was uncomplicated with total EBL 1300 cc. Other than blood pressure elevations in the setting of severe preeclampsia, her post-operative course was uncomplicated and she discharged home on post-operative day four. APGARs were 1, 6, and 8, and the neonatal course was complicated by prematurity and respiratory distress requiring a 19-day NICU stay.

Histology revealed an intact unremarkable placental disc loosely adherent to the posterior uterine wall, together with a tan-pink, spongy cystic mass densely adherent to the right uterine wall measuring 13.5 cm by 7.7 cm by 2.6 cm (Fig. 1A). Sections of tissue demonstrate a tan friable cut surface with focal myometrial invasion (Fig. 1B). Hematoxylin and eosin slides show a complete hydatidiform mole displaying intrauterine implantation with focal extension of a molar villous into the superficial myometrium, which is diagnostic of invasive hydatidiform mole (Fig. 2A and 2B). There was complete absence of immunohistochemical staining for p57 in the molar villi and hyperplastic trophoblast, which confirmed the diagnosis of complete hydatidiform mole (Fig. 2C). Additionally, there is a distinct interface identified without invasion into the normal placental disc (Fig. 2D). Based on her WHO score and FIGO stage 1 disease she was low risk for recurrence or progression and was followed with serial hCGs. Her hCG nadir was 8.0 before rising two months after delivery, consistent with post-molar GTN. She has since finished 4 cycles of single agent Actinomycin D, receiving 3 cycles of chemotherapy past a negative hCG. She is now 8 months from treatment with no evidence of disease by exam and serially negative hCG testing.

3. Discussion

CMCF pregnancies are undoubtedly high-risk. Nineteen to 50 % of CMCF pregnancies will progress to GTN, and approximately 56 % of people with CMCF pregnancies will develop a life-threatening condition. Additionally, CMCF pregnancies present diagnostic challenges and are often diagnosed at a later gestation and are associated with a greater tendency to progress towards GTN compared to singleton molar pregnancies (Vaisbuch, 2005; Sebire, 2002). CMCF pregnancies are frequently not detected in the first trimester because of the concomitant normal appearing fetus and may not be suspected until detailed fetal anatomy scan. Subsequent necessary diagnostic testing can delay treatment options while the normal fetus approaches viability.

This case highlights the challenges associated with a CMCF pregnancy. Despite having national experts involved in her care at a large academic referral center, diagnosis was not identified until 22 weeks. Following the Dobbs decision, early diagnosis of a CMCF pregnancy is critical for patients to have access to all treatment options. Since the overturning of *Roe v. Wade*, there are 14 states where abortion is illegal to varying degrees, and many states which do provide abortion care do so with gestational age limits. Alabama House Bill 314 makes "abortion and attempted abortion felony offenses except in cases where abortion is necessary to prevent a serious health risk to the unborn child's mother." While clauses like these do provide protection for medically indicated termination, the definition of a "serious health risk" remains purposefully ambiguous, which leaves providers uncertain if their patient's diagnosis is precarious enough to permit termination. At our institution, the designation of "serious health risk" is decided via expert consensus. This requires physicians to predict the risk of morbidity for each patient, which may not be corroborated by a court if charges were brought putting the physicians at risk of being charged with a felony. While limited in exception, some states do not provide even this protection.

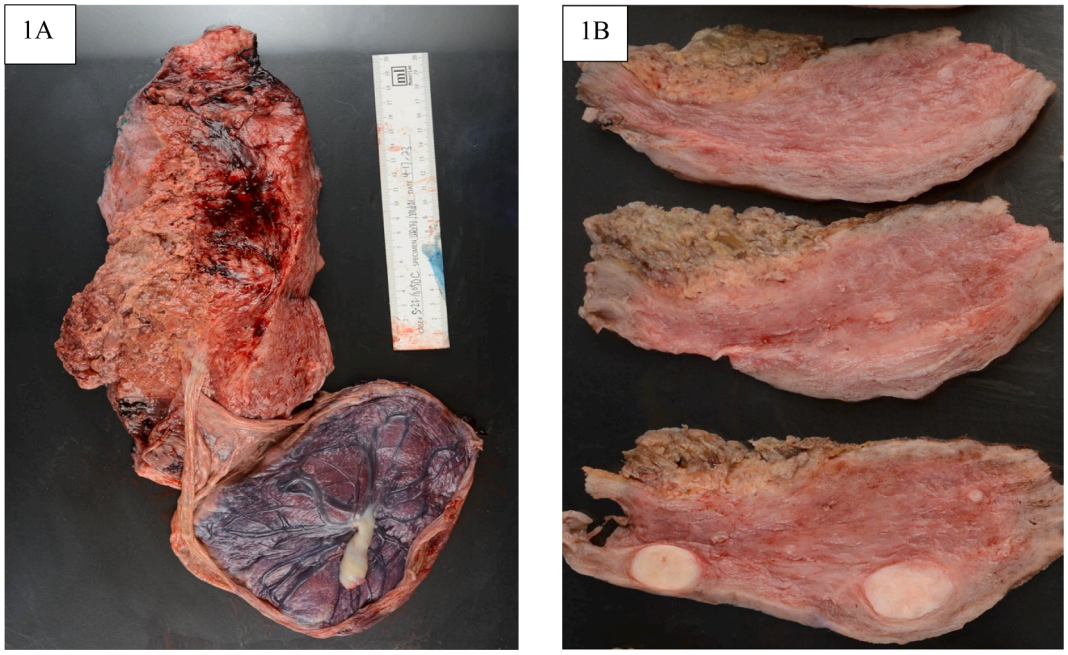

Fig. 1. Gross photo of the opened uterus with a loosely attached intact placental disc and a densely attached spongy cystic mass to uterine wall (1A). Sections of tissue shows the mass focally invading superficial myometrium (1B).

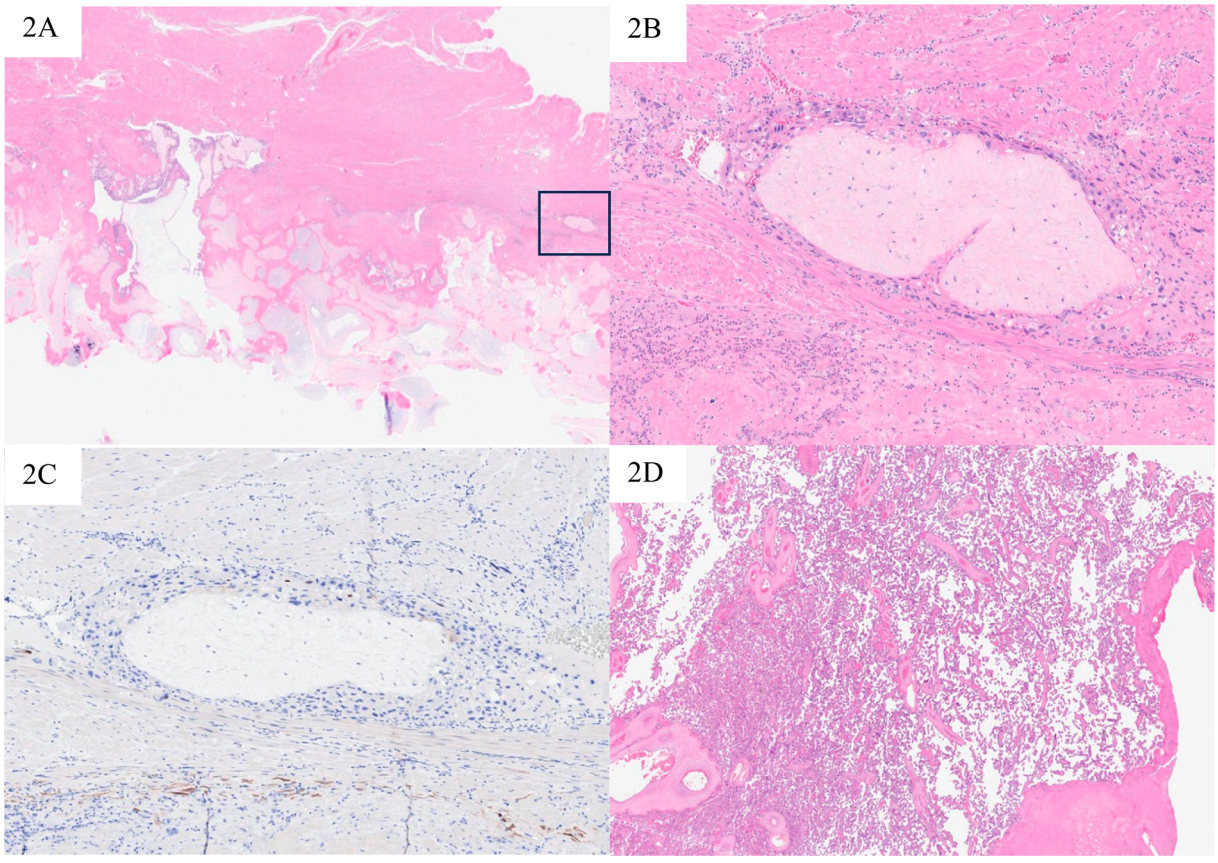

Fig. 2. Complete hydatidiform mole displaying intrauterine implantation (2A 20 x), with focal invasive hydatidiform mole myometrium involvement (2B 100 x). P57 immunostaining in complete absent in molar villi and hyperplastic trophoblast (2C 100 x). No invasion into the normal placental disc is found (2D 20 x).

Given an increasing lack of access to abortion care nationally, the role of testing platforms like cfDNA, which can identify uniparental disomy in the first trimester could prompt for earlier evaluation and diagnosis, which is essential in times of limited abortion access. While growing in popularity, these tests remain cost prohibitive to many patients as coverage varies widely and patients can incur substantial out of pocket

costs depending on the insurer. Additionally, while there are published case reports of how these tests can identify genetic abnormalities other than fetal aneuploidy, they are not FDA approved for this indication and the rarity of such diagnoses make it difficult to validate (Gabra, 2020). While the future of noninvasive testing platforms remains an important diagnostic tool, the current reality is many of these pregnancies are diagnosed well into the second trimester, which may limit treatment options for patients residing in restrictive states.

It should be noted for those proceeding with expectant management CMCF pregnancies are not only associated with a risk of progression to GTN, development of life-threatening conditions, and a low live birth rate, but between 16 and 32 % of those expectantly managed will go on to require medically indicated termination due to development of severe maternal complications, such as severe preeclampsia (Wang, 2022; Hajri, 2023). This point is especially pertinent for patients who live in states with complete abortion bans, which would necessitate transfer out of state for life saving care. It is also important to note states with the strictest abortion bans may also have criminal laws in place which prohibit the referral or transfer of patients to obtain termination care (Abortion Laws, 2023). In addition to this, many patients do not have the means to travel out of state to receive this medical care. This leaves patients vulnerable to serious risk, and physicians unable to deliver adequate reproductive care. CMCF pregnancies demonstrate how clinical decisions are complex and multifaceted, and how delivery of care has been impacted by the current legal landscape. Earlier diagnosis of abnormal pregnancies using noninvasive prenatal tests like cfDNA may offer additional opportunities for patients to have access to the full spectrum of reproductive healthcare.

4. Consent statement

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

CRediT authorship contribution statement

Jordan Barton Garcia: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Angela R. Seasely:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Damien Roland:** Writing – original draft. **Hua Guo:** Writing – review & editing, Writing – original draft, Visualization, Data curation. **Margaret Boozer:** Writing – review & editing. **Gabriella Cozzi:** Writing – review & editing. **Michael D. Toboni:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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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