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Gestational Ovarian Choriocarcinoma: A Review of the Literature and Presentation of a Perplexing Case

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Abstract: Gestational trophoblastic tumors are a heterogeneous and aggressive group of neoplasms. Choriocarcinoma, an extremely rare subset of gestational trophoblastic tumor, is often metastatic at diagnosis and typically follows a pregnancy that is either ectopic or molar. We present a critical review of choriocarcinomas with an emphasis on choriocarcinomas of ovarian origin which are even more uncommon with an incidence estimated at 1 per 369 million. This manuscript also includes a case of a woman with polycystic ovarian syndrome who required assisted conception to conceive her daughter and then developed a rare extrauterine gestational ovarian choriocarcinoma eighteen months following her antecedent healthy pregnancy with uncomplicated delivery. Many aspects of this presentation are unique, even for such an extraordinary tumor; some of these include the absence of vaginal bleeding, the presence of unilateral pulmonary metastases, and an overwhelmingly positive serum β-hCG with a negative urine β-hCG. While such a discrepancy in urine and serum β-hCG has been reported in gestational trophoblastic disease following molar pregnancies, to our knowledge it has not yet been reported in choriocarcinomas following a normal pregnancy.

Keywords: Gestational Trophoblastic Disease, Ovarian Choriocarcinoma, Beta-Human Chorionic Gonadotropin, Pulmonary Metastases

1. Case Report

A 33-year-old Caucasian woman with a past medical history significant for polycystic ovarian syndrome (PCOS), oligomenorrhea, and gestational hypothyroidism presented to the emergency department with a one-week history of epigastric and right upper quadrant abdominal pain associated with nausea and vomiting. Her last menstrual period was 3 months prior and she was sexually active. She had one pregnancy 18 months prior to presentation with a normal spontaneous vaginal delivery without any placental abnormalities. She had no history of abortions or ectopic pregnancies. To conceive her child, she used choriogonadotropin alfa and clomiphene. She breast-fed for a few months and then briefly used a combination estrogen and progestin oral contraceptives. Her only medication at the time of presentation was Zofran and she has had no prior surgeries. Family history was remarkable for a mother with hypertension and a father with Graves disease and breast cancer susceptibility gene 1 (BRCA 1) associated esophageal cancer (age of onset 64 and death at 65). Her paternal grandmother had ovarian cancer (onset at age 50) and type II diabetes. Social history was negative for alcohol, illicit drugs, and cigarette use.

Upon arrival to the emergency department, vital signs were significant for tachycardia to 116 beats per minute and were otherwise unremarkable. Body mass index (BMI) was elevated at 34.66 kg/m^2. Physical exam was remarkable only for abdominal tenderness without rebound or guarding. Labs were significant for alanine aminotransferase (ALT) 262, aspartate aminotransferase (AST) 153, alkaline phosphatase 134, albumin 2.2, lipase 27, and leukocytosis of 13.62. Urine β-hCG and hepatitis antibodies were negative. Right upper quadrant ultrasound revealed cholelithiasis with top normal caliber common bile duct and a positive sonographic

Murphy's sign. A magnetic resonance cholangiopancreatography (MRCP) to evaluate for choledocholithiasis revealed an 11mm high T2 signal lesion within the anterior right hepatic lobe with peripheral nodular enhancement as well as multiple gallstones within nondistended gallbladder. There was a small right pleural effusion detected as well as bilateral large multilocular pelvic cystic masses measuring 13.8x9.2cm on the right and 12.4x6.8cm on the left (Figure 1). A laparoscopic cholecystectomy was performed for cholelithiasis and the patient was discharged home.

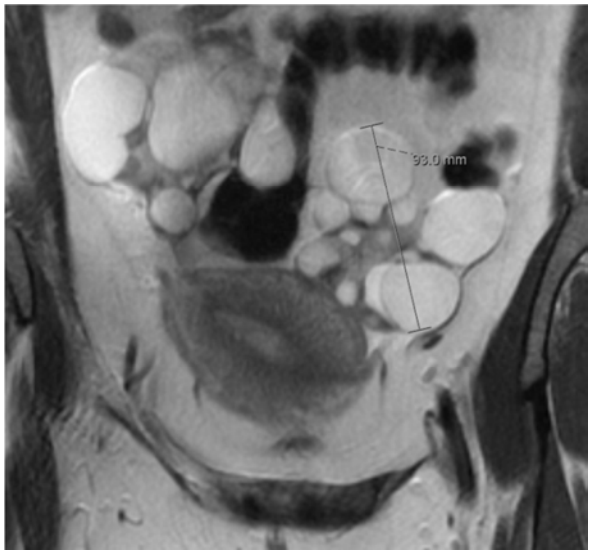

Figure 1. *MRI abdomen revealing bilateral large multilocular pelvic cystic masses measuring 13.8x9.2cm on the right and 12.4x6.8cm on the left.*

While the patient's nausea initially improved following the cholecystectomy, it subsequently worsened and was accompanied by vomiting and a non-productive cough. The patient sought repeat evaluation one month later at which time she reported intermittent clear galactorrhea, midline lower abdominal tenderness with increasing abdominal girth, and an unintentional weight loss of 25 pounds over the previous month. Labs revealed prolactin 212.9 ng/mL and a serum beta-HCG of 1,583,805 mIU/mL. In the setting of an elevated hCG with bilateral multicystic masses on prior magnetic resonance imaging (MRI), transabdominal and transvaginal ultrasounds were performed two months after initial presentation of the abdominal pain that preceded cholecystectomy. Ultrasound revealed massively enlarged bilateral ovaries with multiple simple and complex cysts. The ovaries were noted to have a small amount of normal ovarian stroma with normal blood flow. The uterus was noted to be enlarged uterus with a thickened and heterogeneous endometrium measuring 27mm; there was no evidence of increased flow by color doppler or focal endometrial mass to suggest gestational trophoblastic disease. There was no intrauterine pregnancy identified.

Following this ultrasound, the patient sought obstetrics evaluation. Physical exam at that time revealed tachycardia to 130 beats per minute, palpable enlarged ovaries bilaterally to the level of the umbilicus, and a hand tremor. CA 125 was elevated at 170. TSH < 0.01, free T4 2.56. An MRI of the head was ordered in the setting of elevated prolactin which revealed an unremarkable pituitary gland and extensive mucosal thickening of the paranasal sinuses. With concern for malignant trophoblastic disease from her antecedent pregnancy 18 months prior, a computed tomography (CT) abdomen and pelvis was obtained which revealed diffuse micro-nodular changes in the visualized portions of the right lung with posterior consolidation in the right lower lobe. CT chest (Figure 2) revealed numerous small pulmonary nodules throughout the right lung predominantly in the mid to lower lung fields. Biopsy of the pulmonary nodules (Figure 3) revealed abundant histocytes and rare atypical epithelioid cells with crush artifact and necrosis consistent with a metastatic gestational trophoblastic tumor.

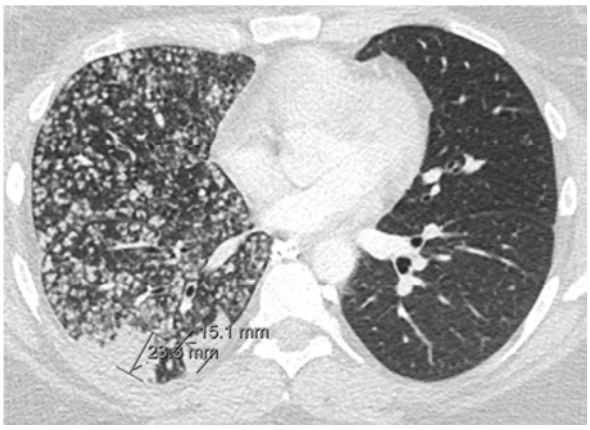

Figure 2. *CT chest with numerous unilateral small pulmonary nodules throughout the right lung.*

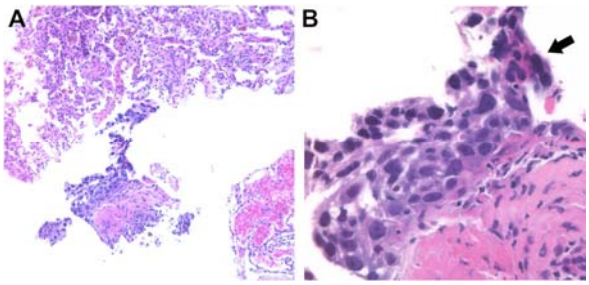

Figure 3. *A lung core biopsy shows an infiltration of lung parenchyma by metastatic carcinoma composed of clusters of pleomorphic cells in the background of hemorrhage and necrosis (A). Hemosiderin representing old hemorrhage is also seen. (B) A high-power view demonstrates syncytiotrophoblasts (arrow) admixed with mononucleated trophoblasts (arrowhead) with atypical nuclei of variable sizes and shapes, and abundant amphophilic cytoplasm. Magnifications for (A) and (B) are 100X and 400X, respectively.*

Immunohistochemical stains were attempted but staining artifact and insufficient tissue precluded immunostaining evaluation. The patient received methotrexate, etoposide, dactinomycin, and filgrastim which she tolerated well. Surveillance of β-hCG yielded a downtrending value and therapy with propranolol was initiated in the setting of hyperthyroidism with improvement in her tremor and heart rate.

2. Gestational Trophoblastic Disease

Gestational trophoblastic disease stems from either fertilization of an empty egg or polyspermy [1] and may aggressively metastasize by hematogenous spread [2]. Gestational trophoblastic disease includes five types of pathology: Choriocarcinoma; hydatidiform mole; invasive mole; placental site trophoblastic tumor; and epithelioid trophoblastic tumor. Molecular genetic analysis differentiates gestational trophoblastic disease from non-gestational trophoblastic disease; the detection of only maternal genomes in products of conception suggests a non-gestational tumor, while the detection of both maternal and paternal genomes suggests gestational origin [3].

Beta-human chorionic gonadotropin (β-hCG) is a placental glycoprotein produced by syncytiotrophoblasts. It is comprised of two distinct subunits: an alpha subunit similar to glycoprotein hormones produced by the pituitary and a beta subunit that is solely produced by the placenta [4]. Peptide variants of β-hCG are present in urine and serum of women with both pregnancy and gestational trophoblastic disease [5, 6]. Surveillance monitoring of β-hCG hormone following uterine evacuation of hydatidiform moles can lead to a diagnosis of gestational trophoblastic disease [7]. The presence of a corpus luteum and elevated β-HCG levels in a woman of reproductive age favor the diagnosis of gestational trophoblastic disease over non-gestational trophoblastic disease [3]. Definitive diagnosis of gestational trophoblastic disease integrates findings from transvaginal ultrasound, β-HCG, histopathology, and molecular genetic analysis.

Diagnosis, prognosis, and treatment of gestational trophoblastic tumors are guided by the International Federation of Gynecology and Obstetrics (FIGO). Classification of gestational trophoblastic disease is determined by application of any one of the following four FIGO criteria: 1) Four values or more of β-hCG plateau over at least three weeks 2) A rise in β-hCG of 10% or greater for three or more values over at least two weeks 3) The presence of a histologic choriocarcinoma 4) Persistence of β-hCG six months after molar evacuation [8]. FIGO scores that are greater than seven denote high-risk gestational trophoblastic disease while scores equal to or less than six represent low risk gestational trophoblastic disease [9]. Differentiation between low and high-risk gestational trophoblastic disease is pertinent and carries implications for therapy; high-risk disease is more commonly resistant to single-agent chemotherapy and has a higher likelihood of recurrence [9]. High-risk gestational trophoblastic disease often requires combination chemotherapy involving variations of methotrexate, etoposide, dactinomycin, cisplatin, and cyclophosphamide [10]. Low-risk gestational trophoblastic disease is often treated successfully with single-agent methotrexate or dactinomycin, with cure rates estimated at 98% [3, 10].

3. Choriocarcinoma

Choriocarcinoma is a malignant tumor characterized by abnormal trophoblastic hyperplasia and anaplasia, hemorrhage, necrosis, and absent of chorionic villi [11]. While choriocarcinomas can develop after a normal pregnancy [10], they are most commonly preceded by a complete or partial mole [12]. Choriocarcinomas are comprised of two cell lines: cytotrophoblasts, primitive mononuclear trophoblastic stem cells, and syncytiotrophoblasts, multinucleated cells differentiating from the fusion of underlying cytotrophoblasts and secrete β-hCG [2, 13]. While β-hCG is an endocrine peptide produced by syncytiotrophoblasts that stimulates luteinizing hormone (LH) and hCG receptors on corpus luteal cells, the variant of β-hCG produced by choriocarcinoma cells is hyperglycosylated and autocrine in nature, stimulating its own development and perpetuating tumor growth [6]. Levels of β-hCG produced by a choriocarcinoma are 3–100 times higher than those of normal pregnancy [14]. At the time of diagnosis of a choriocarcinoma—of either gestational or non-gestational origin—β-hCG averages at 16,000 mIU/mL, with 597,000 mIU/mL being among the highest values reported to our knowledge [6, 15, 16]. Levels of β-hCG on presentation of choriocarcinoma are of both diagnostic and prognostic value [17]. Traditionally, choriocarcinomas are intrauterine, although they have been reported in the ovaries, fallopian tubes, and in other parts of the abdomino-pelvic cavity [18]. There are four accepted origins of choriocarcinoma: maternal germ cell; ovarian pregnancy; metastases from a regressed or occult uterine primary; or in infants from metastases of the placenta [19, 20]. The timeline for development of a choriocarcinoma stems from five weeks following antecedent gestation all the way up through 15 years following gestation, even after menopause [21-23].

While a deficiency of dietary vitamin A precursor carotene has been associated with the development of gestational trophoblastic disease, the ultimate etiology is hereditary [12]. Additional risk factors for the development of choriocarcinoma include women of Asian, American Indian, and African American descent [4, 7]. Other features that may augment the risk of choriocarcinoma include viral infection, poor nutrition, defective germ cells, prior pregnancies, and maternal age [24]. The increased risk associated with maternal age is biphasic, with peaks in the teenage years as well as after age 40 [24]. Molar pregnancy [22], long term oral contraceptive use [25], and group A blood type [26] are also postulated to contribute.

Ovulatory stimulation and assisted conception in the form of in vitro fertilization (IVF) have been associated with formation of a hydatidiform mole, however there are very few cases linking IVF with choriocarcinoma [27]. Assisted conception may increase the risk of extrauterine pregnancies and therefore may increase the risk of gestational choriocarcinoma in atypical locations [19, 28]. This data however is controversial, and more recent studies have not demonstrated a correlation between infertility, infertility treatments, and the development of gestational trophoblastic disease [24]. Although IVF has been correlated with an increased risk of ovarian cancer [29], this relationship is

controversial. While some hypothesize that infertility is a result of a previously undiagnosed malignancy, others propose that the hormonal stimulation of the IVF increases the risk of malignancy [29].

At the time of choriocarcinoma diagnosis, 30% of women have metastases and 80% of these metastases are pulmonary [30]. Risk factors that predispose patients with gestational trophoblastic neoplasia to early respiratory failure from pulmonary metastases include cyanosis, pulmonary hypertension, anemia, and >50% lung opacification [10]. Sequelae of metastatic spread are responsible for the most common presenting symptoms of choriocarcinomas. However, patients with choriocarcinomas can also present with vaginal bleeding, anemia, hyperemesis gravidarum, hyperthyroidism, uterine and ovarian enlargement, and pregnancy-induced hypertension [12, 30, 31]. The diagnosis of choriocarcinoma is challenging due to the non-specificity of its symptomatology which may also suggest hemorrhagic ovarian cysts, tubo-ovarian abscesses, ovarian cyst torsion, and ectopic pregnancy [14, 18]. Late and atypical presentation often contribute to delayed diagnosis [17].

4. Ovarian Choriocarcinomas

Ovarian choriocarcinomas are extremely rare malignancies that are categorized as either gestational or non-gestational in origin. Both gestational and non-gestational choriocarcinomas produce beta-HCG and metastasize to the lung, liver, and brain [10]. Furthermore, both types of ovarian choriocarcinoma are characterized by abnormal trophoblastic hyperplasia and anaplasia, absence of chorionic vili, and the presence of hemorrhage and necrosis [16]. While both gestational and non-gestational ovarian choriocarcinoma share indistinguishable histopathology, neoplastic structure, and clinical presentation, differentiating between them is essential as they have distinct therapies and prognoses [32-33]. Traditionally, molar pregnancies undergo malignant transformation to become ovarian choriocarcinomas, however ovarian choriocarcinomas can also follow normal term pregnancy, spontaneous abortion, and ectopic pregnancy [14, 22, 34].

Primary extra-uterine gestational choriocarcinomas are atypical [11]. Very rarely, gestational choriocarcinomas arise following an ovarian pregnancy [35]. Ovarian choriocarcinomas can also present as metastasis from a choriocarcinoma originating in the uterus or fallopian tube [36]. The incidence of gestational ovarian choriocarcinomas is estimated at one per 369 million pregnancies [37]. Although 48 cases of primary ovarian choriocarcinoma have been reported in the literature from 1982-2017, further analysis yielded that only two gestational primary ovarian choriocarcinomas were confirmed, 24 were non-gestational choriocarcinomas, and the remaining 22 cases were of uncertain etiology [19]. As of 2019, only 4 cases of confirmed gestational ovarian choriocarcinomas have been confirmed and reported to our knowledge [19, 38-39]. The rarity of ovarian choriocarcinomas reflects the lack of standardized treatment guidelines.

5. Case Discussion

We present a case of gestational ovarian choriocarcinoma that developed in a 33-year-old woman and presented 18 months after delivery of a healthy infant. The delayed presentation after a normal antecedent pregnancy is unique, as choriocarcinomas are typically seen after an abnormal pregnancy complete or partial mole [12]. This patient presented at age 33, in between the biphasic peaks of choriocarcinoma incidence in the teenage years and after age 40. Furthermore, although she had metastatic disease in the lung at the time of diagnosis, as is common in choriocarcinomas, she did not present with vaginal bleeding as is a common presenting symptom [12]. Sequelae of hyperthyroidism and hyperprolactinemia in the setting of gestational trophoblastic disease with marked elevation of β-hCG are also intriguing. The two alpha subunits of the β-hCG molecule likely stimulated the anterior pituitary to release prolactin with resultant galactorrhea. The serum prolactin level of 212.9 ng/mL is similar to the level usually associated with near-term pregnancy of 210ng/mL [40]. In the absence of pregnancy, serum prolactin > 150ng/mL is typical of a prolactinoma [41]. Estrogen elevation and stimulation of pituitary lactotrope cells by the alpha subunit of β-hCG are postulated to explain hyperprolactinemia [42].

The β-hCG hormone also likely acted on the anterior pituitary to release thyroid stimulating hormone which manifested clinically as tremor and tachycardia on exam. Both of these symptoms improved with initiation of methimazole and propranolol. In addition to abnormalities of thyroid and prolactin hormones, incongruencies between urinary and serum β-hCG further differentiate this case as an anomaly. Diagnostically, it is atypical to have a negative urine β-hCG and such a profoundly high serum level. In normal urine volumes, the serum β-hCG is estimated as the same as the urinary level [43]. A positive serum β-hCG with a negative urine β-hCG may be explained by 'the hook effect' by which a positive β-hCG overwhelms the urinary assay to produce a negative result [44].

The degree of elevation of β-hCG is inversely correlated with BMI [45]. However, this patient exhibited an astronomically high β-hCG along with an elevated BMI consistent with obesity. Histopathologically, ultrasound with doppler flow did not indicate any hypervascularity among either ovary or the uterus, known classic findings of ovarian choriocarcinomas [14]. From an epidemiologic perspective, although this patient is Caucasian, gestational trophoblastic disease is more common in women of American Indian, Asian, and African-American descent [4, 7]. It remains unclear if prior medication administrations for assisted conception or her history of PCOS contributed to the development of gestational trophoblastic disease. Furthermore, despite the well-established increased risk of breast and ovarian malignancies with the breast cancer antigen (BRCA) genes 1 and 2, while this patient has a family history of BRCA 1-associated stomach cancer, it is not yet known if there is a correlation between gestational

trophoblastic disease and BRCA mutations. Further research is needed to elucidate this relationship, although the rarity of the condition presents a challenge.

6. Conclusion

We present an intriguing presentation of a rare disease. The presentation of persistent nausea, vomiting (morning sickness) likely was a result of extremely elevated β-hCG as can be common in gestational trophoblastic disease. Although symptoms of hyperthyroidism, including tachycardia and tremor, have been reported in gestational trophoblastic disease, other elements of this case are quite unique. Pulmonary metastases are common in gestational trophoblastic disease, however unilateral pulmonary metastases as this patient had are atypical. Gestational trophoblastic disease following a normal pregnancy 18 months prior in a 33-year-old Caucasian woman without vaginal bleeding and with discordance between urine-β-hCG and serum β-hCG is perplexing. The impact that a family history of BRCA 1 mutation, although unclear if present in our patient, and the role of assisted conception on the development of gestational trophoblastic disease remains opaque. Lastly, ultrasound evidence of ovaries with proteinaceous material similar to as expected with ovarian hyperstimulation treatments in the setting of PCOS while not receiving fertility treatments is peculiar and unexpected. Gestational trophoblastic disease is a heterogenous and rare group of pathologies. While prompt diagnosis and early treatment contribute to improved outcomes, further genomic and environmental investigations are needed to improve our comprehension of the disease.

Highlights

1. Choriocarcinomas are typically intra-uterine and follow a molar or ectopic pregnancy
2. Choriocarcinomas typically present with either vaginal bleeding or symptoms of pulmonary metastases
3. Ovarian choriocarcinomas are an extremely rare type of gestational trophoblastic tumor

Conflict of Interest

There are no conflicts of interest to report.

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