



Immature teratoma diagnosed and treated during pregnancy and later complicated by growing teratoma syndrome: A case review with clinical considerations

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1. Introduction

In the United States, ovarian cancer is the second most common gynecologic cancer found during pregnancy, with an incidence in pregnant women of 1:10,000 to 1:100,000 (Pavlidis, 2002). Immature teratoma is the most common subtype of malignant germ cell tumor. Reports of immature teratoma during pregnancy are rare and Luh et al. estimate it to be about 1% of all immature teratoma cases (Luh et al., 2019).

Immature teratomas are comprised of all three germ cell tissues; endoderm, mesoderm, and ectoderm; and are histologically graded. The five-year survival of immature teratoma is greater than 90% for stage I and II disease but drops to 82% for stage III and 72% for stage IV. High-grade histology significantly worsens prognosis (Jorge et al., 2016). Therefore, treatment should be initiated promptly to maximize effectiveness and survival benefit, and often cannot be delayed in pregnant patients.

Due to the infrequent occurrence, little evidence exists on the diagnosis and management of immature teratomas in pregnancy. Here we present a case of an immature teratoma diagnosed at 26 weeks gestational age (WGA), who received chemotherapy and had a normal pregnancy outcome, and whose postoperative and post-chemotherapy course was complicated by growing teratoma syndrome, a rare finding when associated with ovarian germ cell tumors.

2. Case

A 26-year-old gravida 1 para 0 with no significant medical history, underwent an ultrasound at 15 WGA demonstrating appropriate fetal growth and normal ovaries. At 23 WGA she was evaluated for lower abdominal pain and ultrasound revealed a $10.9 \times 8.2 \times 9.9$ cm complex left adnexal structure. At 26 WGA repeat ultrasound demonstrated growth of the left adnexal mass, now measuring $13.2 \times 10.7 \times 15.6$ cm, and MRI demonstrated a $17.8 \times 12.9 \times 11.2$ cm left ovarian solid-cystic mass. Tumor markers were as follow: AFP of 1567 ng/mL, CA-125 of 233.4 units/mL, and Ca

19-9 of 93.1 units/mL. Gynecologic oncology, maternal fetal medicine and neonatal intensivist consults were obtained. Due to abdominal pain, rapid growth of the masses, and concern for malignancy, surgical intervention was recommended.

The patient completed a betamethasone course at 26 WGA and underwent an exploratory laparotomy, left salpingo-oophorectomy, infracolic omentectomy, and left pelvic side-wall biopsy. Nonstress tests were performed pre- and postoperatively. Indomethacin 50 mg was administered one hour prior to surgery, followed by 25 mg every six hours for 72 h postoperatively. The patient and fetus did well. Final pathology demonstrated FIGO stage IIIA grade 3 immature teratoma with metastasis to the left pelvic sidewall and omentum.

Due to the advanced stage, chemotherapy was recommended. The plan was for two cycles during pregnancy with the second cycle finishing near 34 weeks of gestation; thus allowing time for the fetus's bone marrow suppression to recover prior to planned induction of labor at 37 WGA. Fetal monitoring consisted of serial growth sonograms, weekly biophysical profiles (BPP) and umbilical artery doppler (UAD) measurements after 32 WGA.

The patient began her first chemotherapy cycle of 20 IU/m² bleomycin, 100 mg/m² per day of etoposide, and 20 mg/m²/day cisplatin at 30wks GA. Her second cycle began at 33 weeks GA. A decline in fetal growth velocity was observed, with an EFW of 1437 g (15th percentile) at 32 WGA and 1928 g (< 10th percentile) at 35 WGA, however, BPP and UAD measurements were reassuring. Labor was induced at 37 WGA. She gave vaginal birth to a 1790 g female baby, with Apgar scores of 8 and 9 at one and five minutes respectively. The neonate was admitted to the NICU due to intrauterine chemotherapy exposure and low birth weight. The neonate did well and was discharged from the NICU on day of life seven.

The patient received three cycles of chemotherapy postpartum. Tumor markers normalized prior to cycle four and CT of the chest abdomen and pelvis after the fifth cycle was negative.

Five months post-chemotherapy, a routine surveillance CT demonstrated nodular abnormalities in Morison's Pouch and in the peritoneum. Biopsy confirmed mature glial tissue. Fourteen months post-

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chemotherapy, the nodules enlarged, the largest measuring 5.2×2.3 cm in Morison's pouch. Eighteen months post-chemotherapy, an MRI revealed the Morison's pouch nodule to be further enlarged. Additionally, a right adnexal lesion was enlarged from four months prior and measured $4.6 \times 3.2 \times 3.0$ cm. Given the imaging, there was concern for growing teratoma syndrome as tumor markers remained negative.

Twenty months post-chemotherapy, she underwent a second surgery with excision of an anterior peritoneal mass, small tissue deposits in anterior cul-de-sac, and a 6 cm cystic mass in Morrison's pouch. The patient did well post-operatively. Final pathology was consistent with mature teratoma and peritoneal gliomatosis with calcifications.

The patient is currently twenty-seven months from diagnosis, twenty-three months post-chemotherapy, and three months from her second operation without further benign or malignant disease. The baby is twenty-five months old and is growing and developing normally.

3. Discussion

This case report discusses two rare and not well-studied entities: immature teratoma in pregnancy and growing teratoma syndrome. Treating pregnant patients involves similar methods as nonpregnant patients but introduces additional complexities. There is an increased risk of miscarriage when surgery is in the first trimester and, if possible, operative intervention should be delayed until the second or third trimester (Luh et al., 2019). Additionally, corticosteroids for fetal lung maturity and fetal monitoring, both after 24 WGA, should strongly be considered and discussed (ACOG Committee on Obstetric Practice, 2011). Furthermore, adequate pain control is important as pain can increase the risk of preterm contractions and/or labor (Luh et al., 2019). The use of prophylactic tocolysis is controversial, however, Visser et al found that second trimester prophylactic tocolytic therapy during surgical intervention can reduce preterm labor and premature delivery, and thus, indomethacin was given preoperatively to our patient (Visser et al., 2001). Moreover, abdominal surgery during pregnancy carries the risk of alloimmunization and Rhesus negative patients should receive Rh immunoglobulin within 72 h of surgery and a Kleihauer-Betke test should be performed to determine the need for additional doses (Grimm et al., 2014). Lastly, due to the hypercoagulable state of pregnancy, venous thromboembolism risk should be assessed and proper prophylaxis should be given, and thus, our patient received enoxaparin which was continued for four weeks postoperatively (ACOG Committee on Obstetric Practice, 2011).

The other component of treatment is chemotherapy. In pregnant patients, the second and third trimesters are the ideal time for chemotherapy treatment as teratogen exposure in the first trimester has a higher rate of congenital malformations and fetal death. Chemotherapy in the second and third trimesters can be associated with an increased risk of intrauterine growth restriction, preterm labor, low birth weight, and stillbirth and close monitoring with weekly BPPs and serial growth measurements is recommended (Cardonick and Lacobucci, 2004). Chemotherapy should also be avoided, if possible, after 35–37 WGA due to the risk of fetal and maternal myelosuppression (Grimm et al., 2014).

In regards to chemotherapy dosing, physiologic changes of pregnancy including increased plasma volume, GFR, and hepatic oxidation may cause a decrease in plasma levels of chemotherapy drugs (Cardonick and Lacobucci, 2004). However, our patient was dosed based on weight and height, similarly to a non-pregnant patient, as there is a lack of pharmacokinetic studies on chemotherapy doses in pregnant women. For immature teratomas, a combination of bleomycin, etoposide, and cisplatin (BEP) is an effective chemotherapy regimen and Amant et al described several reports of this regimen being used in pregnancy with a normal neonatal outcome (Gershenson et al., 1990; Amant et al., 2012). However, reports have shown that in-utero

exposure to platinum agents may be associated with sensorineural hearing loss and additional toxicities of chemotherapy such as alopecia and myelosuppression may also affect the fetus (Cardonick and Lacobucci, 2004). While there is not enough evidence on BEP use in pregnancy to make a determination on its safety, to date, our patient's infant has no side effects appreciated aside from low birth weight.

Lastly, this patient also experienced GTS. While this is unlikely related to the fact that her immature teratoma was diagnosed and treated during pregnancy, it does represent a rare phenomenon. GTS is due to growth of mature teratomas in patients with a history of germ cell tumors without residual disease (Li et al., 2016). Literature has more documented cases in testicular tumors as opposed to ovarian germ cell tumors (Li et al., 2016). The incidence of GTS in association with ovarian germ cell tumors is unknown (Li et al., 2016). Historically, the recommendation for suspected GTS is prompt surgical resection of the masses, as was performed in our patient (Li et al., 2016).

In summary, diagnosis and treatment of immature teratomas during pregnancy is rare. This case demonstrates that thorough evaluation of risks and benefits of prompt treatment to both the mother and the fetus should occur with a multi-disciplinary team: maternal fetal medicine, gynecologic oncologists, and neonatal intensivists. Future studies may focus on neonatal long-term sequelae, future pregnancy outcomes, and maternal remission rates / disease progression. Our patient received a combination of surgical treatment and adjuvant chemotherapy and went on to deliver a healthy full-term infant. Despite being diagnosed with growing teratoma syndrome, she has remained in remission. This case suggests that successful outcomes for mother and fetus are feasible, and that both surgical treatment and chemotherapy is possible during pregnancy.

Author contribution

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Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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