



Case report

Germ cell cancer in pregnancy – Successfully treated with chemotherapy and surgery

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ABSTRACT

A 31-year-old primigravida, with spontaneous singleton pregnancy, presented in 21 weeks of gestation with abdominal pain. Abdominal ultrasound (USS) and Magnetic Resonance Imaging (MRI) showed a 12 × 14cm large complex lesion arising from the right ovary suspicious for an ovarian malignancy. The radiological staging demonstrated no further metastatic disease; however, it also revealed a 6 cm lesion in the contralateral ovary, consistent with a dermoid cyst. After tumour board discussion the patient underwent a mid-line laparotomy with right oophorectomy, cytology, and peritoneal and omental staging, under oral tocolysis with indomethacin. The left presumed ovarian dermoid was left in situ to avoid additional surgical and obstetrical morbidity. Histology confirmed a grade 3 immature teratoma with primitive neuroepithelium focally present on the capsular surface and atypical cells in the cytology amounting to a stage 1 C2 disease at least. Due to high-risk disease, she was offered adjuvant treatment. The patient received one cycle of intravenous paclitaxel, etoposide, and cisplatin chemotherapy, in an adjuvant setting. She underwent an elective caesarean section at 36 weeks, with the safe delivery of a healthy baby girl. After 6 weeks of her delivery, she received three further cycles of etoposide, and cisplatin to complete her course of adjuvant chemotherapy. Three months after the last chemotherapy cycle, she underwent a laparoscopic removal of the left ovarian dermoid that had increased in size to 8 cm. Final histology revealed no immature elements. To this point, 2 years after initial diagnosis, both mother and child are healthy with no long-term complications. The patient has resumed her normal menstrual cycle and being in remission, she wishes soon to try for a second child. To our knowledge, this is the only reported case of ovarian immature teratoma in pregnancy treated successfully with surgery and adjuvant iv paclitaxel, etoposide, and cisplatin chemotherapy regime.

1. Introduction

Incidence of cancers diagnosed during pregnancy is 1/1000 (Korenaga and Tewari, 2020) with those of ovarian origin being the fifth most common (Fruscio et al., 2017). Epithelial cancers represent the most common type of malignant ovarian neoplasia with germ cell tumours including immature teratomas representing a very small and rare tumour entity and more commonly seen in younger patients (Brewer et al., 2011). First line treatment of germ cell ovarian tumour is in general surgical intervention with or without adjuvant chemotherapy based on the staging and disease characteristics, followed by intensive surveillance, (Fruscio et al., 2017). The regime of bleomycin, etoposide

and cisplatin (BEP) is routinely used for this patient group (Korenaga and Tewari, 2020; Fruscio et al., 2017). The behaviour of such tumours' during pregnancy is poorly understood while no gold standard chemotherapy treatment is well defined.

Oncologic management during pregnancy continues to represent a challenge for both mother and foetus and even though there is increasingly more evidence about the relative safety of anticancer treatment especially in the later stages of the pregnancy; experience on obstetrical outcomes is still scarce and treating physicians are always faced with a therapeutic dilemma (Giacalone et al., 1999). We present here a case of immature teratoma in pregnancy, whereby bleomycin was replaced with paclitaxel to reduce risks to both mother and foetus. To

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our knowledge, this is first reported case of paclitaxel, etoposide, and cisplatin-based chemotherapy for immature teratoma malignancy in pregnancy.

2. Case report

A 31-year-old otherwise healthy primigravida presented with increasing abdominal pain at 21 weeks' gestation. She was a non-smoker and social drinker. She has been previously well, with no significant comorbidities and had conceived spontaneously. All obstetrical scans and examinations were normal up to this date.

An initial abdominal ultrasound showed a mass arising from the right ovary and the patient was referred to a specialised abdominopelvic Magnetic Resonance Imaging (MRI) which confirmed a multiloculated and multiseptated large complex right ovarian mass measuring $12 \times 14 \times 9$ cm with a 10 cm solid internal component with restricted diffusion (Figs. 1 and 2). The lesion was suspicious for a malignant germ cell tumour. Furthermore, there was a 6 cm mass in the contralateral ovary consistent with a benign dermoid cyst. The staging MRI did not reveal any evidence of metastatic spread. Tumour marker profile included an alpha-fetoprotein (AFP) of 110 ng/ml (0–40 ng/ml), Cancer Antigen 125 (CA 125) of 17 kU/L (0–35 kU/L), beta human chorionic gonadotrophin (b-HCG) of 47,935 U/L and Serum Lactate Dehydrogenase (LDH) of 330 U/L (105–333 U/L).

In view of the sinister features of the mass, the patient was referred to a tertiary gynaecological cancer centre, for further investigations and input. As per the multidisciplinary team advice, it was decided to offer the patient surgical removal of the mass at 22 gestational weeks as the optimal way of management. The patient underwent a mid-line laparotomy with right salpingoophorectomy, cytology and omental/ peritoneal biopsies (Fig. 3 and 4). The mass was removed intact without intraoperative rupture and the final specimen measured $200 \times 130 \times 80$ mm and weighed 1293 g. The patient received indomethacin 100 mg twice a day starting 2 days before the operation and continued one day postoperatively for tocolysis. The left ovarian dermoid was located behind the uterus deep in the pelvis so the intraoperative decision was made not to resect to avoid over manipulation and endanger the pregnancy. Daily fetal scans were performed to ensure viability while the

patient was inpatient. A second trimester scan showed no structural fetal abnormalities. The patient and fetus were stable throughout the entire perioperative period and no uterine contractions were registered. The patient could be discharged 2 days after the operation.

The final histology confirmed a grade 3 immature teratoma with capsular breach of the tumour and atypical cells in the cytology, omental biopsy was clear. The tumour was partly necrotic with haphazard admixture of predominantly mature teratomatous elements admixed with foci of immature neuroepithelium forming rosettes, tubules and focally arranged in sheets. These were present in > 3 LPFs (lower power fields $\times 40$ magnification). Immature mesenchyme, cartilage, pigmented neuroepithelium and cellular nodules of glia with vascular proliferation were noted. The mature elements comprising cysts lined by stratified squamous, intestinal, respiratory and cervical-type glandular epithelium, cartilage, bone, choroid plexus, ganglion cells, mesenchyme and mature adipose tissue. Primitive neuroepithelium was focally present on the capsular surface (1 C2 at least). No vascular invasion was seen. No other germ cell components or somatic malignancy were identified.

In view of the high-risk histopathological features disease, and the size and grade of the tumour, the patient was offered adjuvant treatment with the following chemotherapy regime - etoposide (165 mg/m² Day 1,2 and 3), cisplatin 50 mg/m² (day 1,2,3) and paclitaxel 175 mg/m². Palonosetron, dexamethasone, metoclopramide and cyclizine were given as supportive medications. Filgrastim 300 ug was also given for five days. Apart from grade 1 nausea and grade 2 peripheral neuropathy, no other side effects were noted. The obstetrical scans subsequently were all normal and the patient underwent an elective Caesarean section at 36 weeks with no complications. She delivered a baby girl weighing 2.415 kg on delivery. Two months post-partum, she received three cycles of cisplatin (79 mg/m²) and etoposide (300 mg/m²) chemotherapy. Paclitaxel was omitted due to peripheral neuropathy and sufficient action of cisplatin and etoposide. She tolerated treatment well apart from grade 1 nausea and constipation. Repeat MRI showed increase of the known dermoid cyst in her contralateral ovary from 6 to 9 cm. The patient later underwent 3 months after end of the last chemotherapy cycle a laparoscopy to remove the left ovarian dermoid cyst with preservation of the residual healthy ovarian tissue. The histology confirmed here the presence of a dermoid without any immature components. To date at 22 months post diagnosis, the patient is well and in remission, and the child has shown no signs of developmental delay, congenital abnormalities, or hearing problems. The patient has resumed her normal menstrual cycle (October 2021) after the last chemotherapy. Last MRI showed features of locally residual or recurrent disease and no distant metastases. Most recent tumour markers were low (AFP = 2 ng/ml, b-HCG = 2 U/L).

3. Discussion

Chemotherapy in pregnancy must be a balance between maternal benefit and risk to the foetus – Delay in treatment is likely to have an adverse effect on prognosis. Chemotherapy in the first trimester is not recommended due to high risk of foetal teratogenicity and major malformations occurring in up to 20% pregnancies (Ko and Van Le, 2011; He et al., 2022). Additionally, chemotherapy should be avoided in the last few weeks of gestation due to risk of infection and bleeding during delivery secondary to maternal myelosuppression. Furthermore, physiological changes in hepatic, renal and gastrointestinal function occur during pregnancy meaning metabolism and absorption of chemotherapy agents can be difficult to predict (He et al., 2022). Due to rarity and ethical considerations, there are no randomised controlled trials nor prospective studies for chemotherapy in pregnancy. Intrauterine growth restriction and low birth weight are suggested to be the most common foetal complications following chemotherapy (Ko and Van Le, 2011).

Management of gestational ovarian malignancy beyond surgery is debated and due to its rarity, there is no clear standard for chemotherapy in this population. The International Network of Cancer,

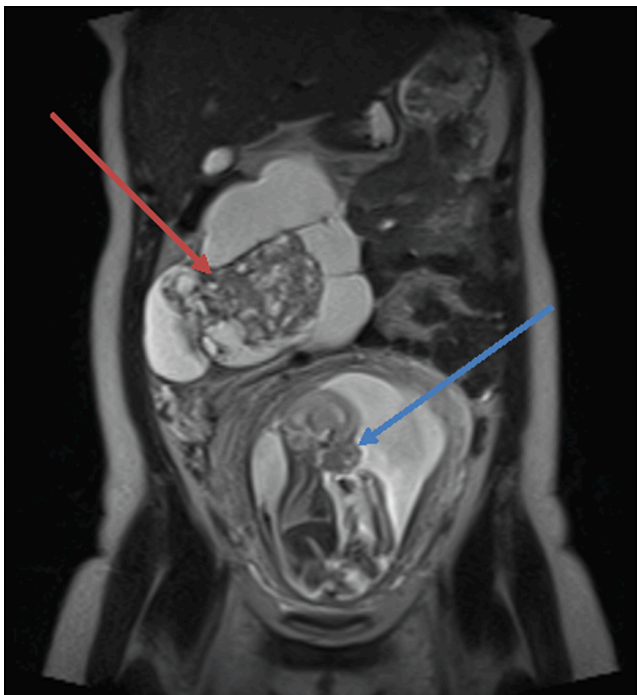


Fig. 1. Initial Abdominal-Pelvic Magnetic Resonance Imaging (coronal view).

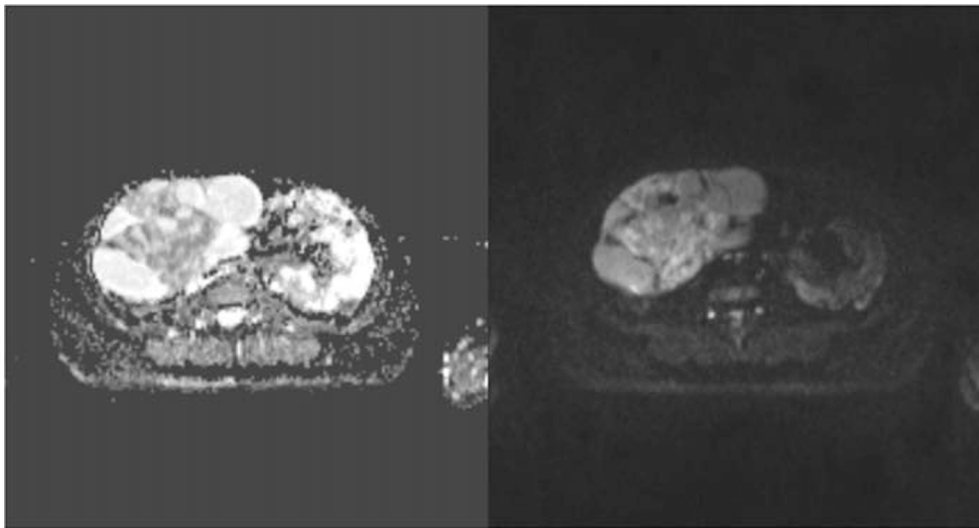


Fig. 2. . Initial Diffusion weighted Abdominal-Pelvic Magnetic Resonance Imaging (axial view).

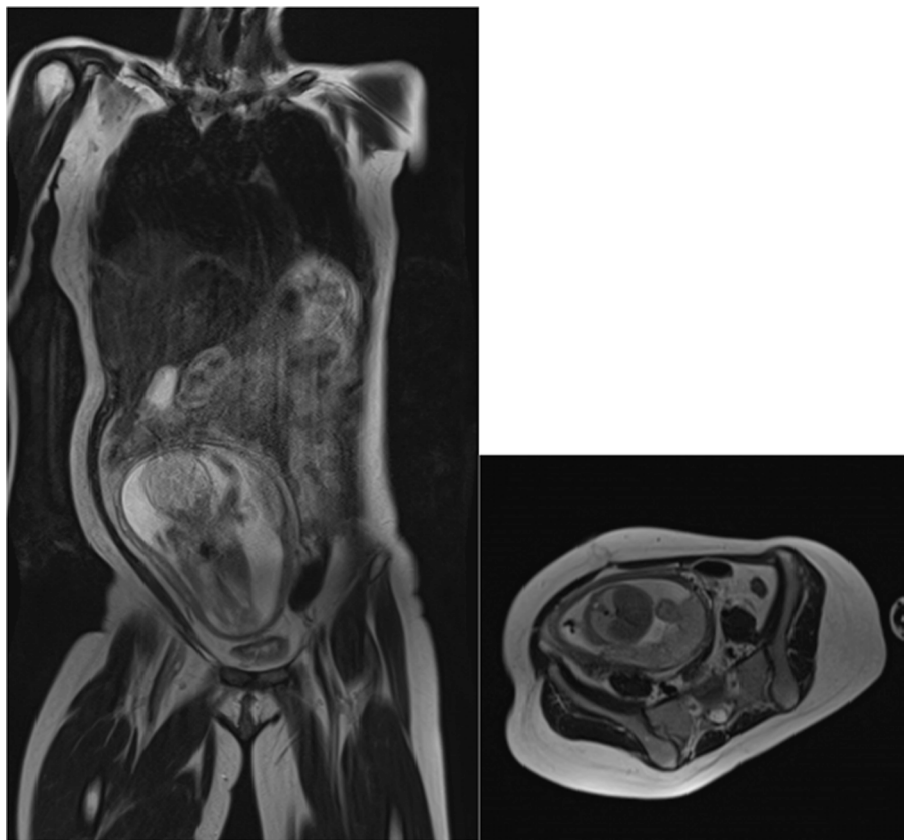


Fig. 3 and 4. Magnetic Resonance Imaging following surgical intervention (coronal and axial view).

Infertility and Pregnancy (INCIP) have developed guidance for treatment in gynaecological malignancy in pregnancy suggesting etoposide and cisplatin with or without bleomycin to be the most prescribed regime for nonepithelial ovarian malignancy (Amant et al., 2019). Furthermore, a recent review of the literature (Jiang et al., 2021) showed that the most commonly used regimen for immature teratoma in pregnancy is BEP.

Although, outcomes for foetus and mother were satisfactory in these case studies, bleomycin is associated with both maternal and foetal risks. The use of bleomycin in pregnancy has been linked to congenital

malformations such as plagiocephaly and finger syndactyly (Ngu and Ngan, 2016). In addition, pulmonary toxicity is a common but significant side effect of bleomycin which can lead to pulmonary fibrosis and increased mortality (Brandt and Gerriets, 2022). During pregnancy, respiratory changes occur including a decrease residual volume residual capacity and chest wall compliance (LoMauro and Aliverti, 2015). Dyspnoea is commonly reported in pregnancy therefore this physiological change may be difficult to clinically distinguish from pathological causes such as fibrosis. Additionally, Computed Tomography of the chest is part of the diagnostic work up for pulmonary

fibrosis which is not recommended in pregnancy unless necessary due to radiation exposure to the foetus (Yoon and Slesinger, 2022). A patient under the authors (AS) care, who had bleomycin in pregnancy, developed dyspnoea and required CT chest to rule out fibrosis.

For our case, bleomycin was replaced by paclitaxel due to risks to the foetus but also the mother's lungs. Paclitaxel is used for various types of ovarian malignancy during pregnancy in combination with either cisplatin or carboplatin. A systematic review (Jiang et al., 2021) reported good maternal outcomes in case reports for clear cell carcinoma, serous adenocarcinoma, mucinous adenocarcinomas, endometrioid adenocarcinoma and ovarian dysgerminoma. Moreover, Paclitaxel is used in combination with ifosfamide and cisplatin as second-line regime for ovarian germ cell tumours (Simone et al., 2016).

Follow up of children exposed to paclitaxel in utero is also reassuring (Cardonick et al., 2022). Specifically, paclitaxel in combination with cisplatin has been used to treat ovarian mucinous adenocarcinoma during pregnancy with no negative outcomes to the child, however the patient died after 35 months due to disease (Serkies et al., 2011). Our case is the first recorded case to use the regime of paclitaxel, etoposide, and cisplatin for germ cell malignancy in pregnancy and the outcome for both the patient and the child have been positive setting a positive example for potential management of those cases in the future.

4. Consent

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

Author contributions

SA Oncology Consultant involved in care of the patient, conception, manuscript editing. RI conception, manuscript writing. GA Radiology Consultant involved in care of the patient, manuscript editing, provider of images. BK Histopathology Consultant involved in care of the patient, manuscript editing. FC Professor of Gynaecological Cancer Surgery involved in care of the patient, manuscript editing.

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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