Mediastinal dysgerminoma complicating pregnancy

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Summary: Malignancy complicating pregnancy represents one of the most challenging clinical situations. Lack of evidence and the presence of the dependent fetus contribute to the management dilemma. A 26-year-old primigravida presented at 23 weeks of gestation with a bulging substernal mass. Fine-needle aspiration was reported as mediastinal dysgerminoma. She was treated with weekly bleomycin and three weekly cisplatin and etoposide (BEP). Maternal neutropenia after 11 weeks of bleomycin required colony stimulator factor. Fetal growth restriction necessitated delivery at 31 weeks. Significant clinical and radiological tumour regression was noted after chemotherapy. Postnatally mother received external beam radiotherapy but the disease worsened two weeks after the completion of radiotherapy. Mediastinal dysgerminoma differs from the ovarian counterpart and therefore therapeutic success reports on ovarian germ cell tumours complicating pregnancy cannot be extrapolated. The safety of the BEP regimen for the fetus is yet to be established.

Keywords: maternal–fetal medicine, high-risk pregnancy, oncology, cancer, mediastinal dysgerminoma

INTRODUCTION

Malignancy complicating pregnancy poses significant clinical dilemmas as any intervention may raise conflicts between maternal versus fetal interests. Paucity of good evidence and expert opinions further complicates the decision-making. We describe the clinical presentation, work-up, management and maternal–fetal outcome in a pregnancy complicated by mediastinal dysgerminoma.

CASE REPORT

A 26-year-old booked primigravida was referred to us at 23 weeks of gestation with several weeks of retrosternal pain associated with an enlarging substernal mass. At presentation, she was sick with pain and mildly dehydrated, weighed 56 kg and was 151 cm tall (body mass index 21.9 and body surface area 1.5 m²). There was a large, tender mass bulging from just under the xiphoid process extending onto the epigastrium. Her gravid uterus size corresponded to the period of amenorrhea and fetal heart sounds were present. She did not have lymphadenopathy, hepato-splenomegaly, icterus, bone tenderness or ascites. A chest radiograph showed a large anterior mediastinal mass and left-sided pleural effusion. Magnetic resonance imaging of the chest revealed an infiltrating mass from the anterior mediastinum eroding the sternum and the anterior abdominal wall (Figure 1). Obstetric ultrasound reported a single live fetus, adequate liquor and no anomalies. Fetal biometry corresponded to the gestational age assigned as per her last menstrual period. Fine-needle aspiration cytology from the mass was reported as dysgerminoma. Immunocytochemistry study was not done. The pleural fluid

was negative for malignant cells; biochemical examination of the pleural fluid was not done. Baseline tumour marker levels were: lactate dehydrogenase (LDH) 1375 IU/L, alkaline phosphatase 146 IU/L and alphafetoprotein (AFP) 146.7 ng/mL.

After oncology consultation, she was started on BEP (bleomycin, etoposide, cisplatin) regimen. Bleomycin (15 U) was given every week, 150 mg of etoposide for four days per cycle and 30 mg of cisplatin for four days per cycle were given. The etoposide–cisplatin cycle was repeated once in 21 days. Although there was a significant symptomatic improvement and clinically evident tumour shrinkage, she continued to have a constant dull ache retrosternally and progressive cachexia. At 28 weeks, fetal growth scan showed subjectively decreased liquor but consistent growth in biometry. Two weeks later, oligohydramnios developed and growth restriction was evident. She received dexamethasone for fetal lung maturity and the fetus was closely monitored with alternate-day biophysical profile and Doppler studies twice a week. Meanwhile, after her 11th weekly dose of bleomycin, she developed neutropenia and received a colony-stimulating factor. At 31 weeks, there was anhydramnios, biophysical score of 4/10 and absent end-diastolic flow in the umbilical artery. Labour was induced following transcervical Foley and intracervical prostaglandin E₂ gel ripening. A growth-restricted 1400 g male fetus was delivered by caesarean section as intrapartum fetal distress developed. The neonate expired after 24 hours due to prematurity and hypoxia. Both ovaries appeared normal. Histological examination of the placenta revealed multiple haemorrhagic areas and chorioamnionitis.

The tumour marker levels on post-delivery day 10 were: human chorionic gonadotropin (HCG) 55 mIU/mL, AFP 74 ng/mL and LDH 610 IU/L. A computerized tomographic scan of the chest confirmed tumour regression (Figure 2). In view of her general condition and neutropenic response to previous cycle, the fourth cycle of chemotherapy was withheld.

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Figure 1 Magnetic resonance imaging of the chest showing tumour in the anterior mediastinum invading the subternal skin

She received external beam radiation (EBRT) from postoperative day 10: a total of 36 Gy in 20 fractions over four weeks (19.8 Gy in 11 fractions first by anteroposterior–posteroanterior portals to the mediastinum and left chest, followed by 16.2 Gy in nine fractions by anterior chest and mediastinal tangents) was delivered. She returned two weeks after completion of EBRT with cachexia, severe central and lateral chest pain. Chest X-ray showed a mass in the anterior mediastinum. There was no evidence of radiation pneumonitis, pulmonary thromboembolism or cardiac failure. A diagnosis of disease relapse was made based on the clinico-radiological presentation. Over the next few days she developed rapidly accumulating ascites and worsening chest pain. She was offered a re-challenge with the same chemotherapy which she declined and was discharged against medical advice.

Figure 2 Computerized tomographic scan of the chest showing tumour regression

DISCUSSION

Extragenital germ cell tumours (GCTs) are rare.¹ Among the extragenital sites, the mediastinum is reported to be the commonest, especially in women.² Among all mediastinal tumours, about 10% are germ cell tumours. They have been reported across all age groups, but as with the gonadal variety, they most commonly present in the reproductive age group.^{3–6} Most benign germ cell tumours in adults are incidental findings on chest X-rays performed for other indications. The malignant GCTs are almost always symptomatic and can present due to their mass effect or due to infiltration into an adjacent structure in the mediastinum. The most common presentations reported in the literature are cough, chest pain, dyspnoea, chills, fever and superior vena cava syndrome.^{3–5} All large case series have shown a male preponderance in primary mediastinal GCTs.

GCTs of the mediastinum can be benign or malignant. Mature cystic teratomas come under the former group, while malignant GCTs can be seminoma or non-seminomatous tumours such as choriocarcinoma, embryonal carcinoma, yolk sac tumour and mixed GCT.^{3,4} The diagnosis is usually by a combination of serum tumour markers, imaging and biopsy. A serum level of AFP of >1000 IU or beta-HCG levels of more than 5000 IU (outside pregnancy) is considered diagnostic of non-seminomatous GCT, obviating the need for a histological confirmation.⁶ Although a separate, well-defined staging system exists for gonadal GCTs, the mediastinal GCTs do not have their own staging system yet.

Although the mediastinal GCTs resemble their ovarian counterpart histologically, they differ in their biological behaviour and prognosis. They are more aggressive and consequently have a poorer outlook. Whereas, the primary therapeutic modality in most instances of ovarian GCT would be surgical, in mediastinal malignant GCTs, the primary therapeutic approach is non-surgical. Only in the case of benign cystic teratomas is a completely surgical approach practised. The treatment of malignant GCTs has evolved over time and has become multimodal.⁶ Surgical resection is attempted only for lesions that do not have defining levels of serum tumour markers and are small. Seminomas are treated primarily with cisplatin-based chemotherapy or infrequently with radiotherapy. Malignant non-seminomatous GCTs are usually treated with chemotherapy initially, the regimen of choice being the combination of bleomycin, etoposide and cisplatin. In both instances, surgery is reserved for resecting the residual tumour mass after the primary therapy is over.

Mediastinal GCTs have poorer prognosis compared with their gonadal counterparts. Overall, seminomatous GCTs fare better than non-seminomatous GCTs in the mediastinum. Large case series reported from single centres usually quote an overall survival of more than 90% for seminomas and around 40–50% for non-seminomatous GCTs.⁶ Prognostic factors have been reported based on retrospective analysis of case studies and case series. Serum levels of tumour markers after the primary therapy, tumour histology, tumour margin positivity for viable cancer cells and surgical resectability have all been associated with the overall survival.^{6,7}

The natural history and the prognostic factors associated with mediastinal GCTs are unclear due to their rarity. The effect of pregnancy on the behaviour of the tumour is not known. Similarly, the effect of the tumour or its treatment on pregnancy is also not clear. Several case reports^{4–14} have mentioned the successful employment of the BEP regimen during pregnancy for GCTs. With the exception of the case reported by Thanaboonyawat *et al.*,¹⁶ others have reported a generally

Table 1 Case reports of BEP regimen in pregnancy

Year	Author	Tumour	GA at start of treatment	No. of cycles	Maternal outcome	Fetal outcome
1994	Horbelt ⁸	Mixed GCT	21	3	Remission	Term; alive
2005	Han ¹¹	(1) EST	22	5	Remission	Alive
		(2) Immature teratoma	30	2	Remission	Alive
2007	Hubalek ¹²	Dysgerminoma	24	3 + 3 PT*	Remission	Term; alive
2007	Robova ¹³	EST	22	4 P + 3 BEP	Remission	35 Weeks; alive
2008	Karimi Zarchi ¹⁴	Immature teratoma	29	2	Remission	Alive
2008	Poujade ¹⁵	Immature teratoma	22	3	Remission	Term; alive
2008	Thanaboonyawat ¹⁶	EST	20	7	Death	TOP
2009	Ghaemmaghami ¹⁷	Immature teratoma	21	3	Remission	Mild glandular hypospadias; term; alive
2010	Benjapibal ¹⁸	EST	15	4	Remission	Alive

GCT, germ cell tumour; EST, endodermal sinus tumour; BEP, bleomycin, etoposide, cisplatin; PT, cisplatin, paclitaxel; TOP, termination of pregnancy

*Three cycles as neoadjuvant and three cycles as adjuvant

good outcome for the fetus (Table 1). Publication bias as a cause for the non-availability of case reports with negative outcome cannot be ruled out. Reports of successful pregnancy outcome for ovarian GCTs treated with conservative surgery plus various chemotherapeutic regimens cannot be extrapolated to mediastinal disease as the biological behaviour is different and the first line of treatment is non-surgical.

In the absence of published good evidence on the outcome or the management of mediastinal GCTs in pregnancy, clinical decision-making has to be based on data from non-pregnant population and anecdotal evidence. To our knowledge, this is the first case report of mediastinal dysgerminoma complicating pregnancy. The fetal growth restriction could be due to a combination of factors such as the maternal cancer-cachexia and the cytotoxic chemotherapy. The haemorrhagic areas and histological chorioamnionitis on the placenta are presumably the effects of the cytotoxic chemotherapy. We delayed the delivery of the fetus as long as possible taking into account the prematurity of the fetus and the salvage rate of our neonatal intensive care unit. It is not uncommon in our hospitals to encounter poor patients who refuse hospital care for terminal illnesses due to various social, financial and cultural reasons. Although this patient did not die in hospital, her general condition was deteriorating so rapidly at the time of discharge that it was not thought that she would recover. In contrast to case reports on ovarian GCTs in pregnancy, this case illustrates the potential fetopathic effect of the BEP regimen and the aggressive behaviour of mediastinal GCT. It is possible that pregnancy had accelerated the disease progression in our patient as her survival was much less than that expected based on the series published by Rivera *et al.*⁶

DECLARATIONS

Competing interests: None declared.

Funding: None.

Ethical approval: Written consent to publish was not obtained because the patient is deceased.

Guarantor: KM.

Contributorship: SS conceived the paper. KM and SS drafted the primary manuscript. KM, PV, and SE researched the literature and contributed to the revisions. All authors reviewed, edited the manuscript and approved the final version.

Acknowledgements: None.

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