CASE REPORT

Antenatal chemotherapy in a case of diffuse large B-cell lymphoma

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SUMMARY

A 28-year-old pregnant woman in the sixth month of gestation presented with complaints of altered bowel habit for a month, on examination found to have generalised lymphadenopathy, pedal oedema and locally infiltrating ano-rectal growth. Rectal growth biopsy was reported as high-grade B-cell lymphoma. After a discussion in a multidisciplinary panel consisting of haemato-oncologists, obstetricians and physicians, she was planned to receive antenatal chemotherapy. She delivered a live baby of 1.86 kg at 36 weeks of gestational age by normal vaginal delivery. After 6 cycles of chemotherapy she had complete regression of the disease.

BACKGROUND

- An approach for pregnant patients presenting with lymphoma.
- To reiterate that chemotherapy can be administered in the second and third trimester without much complications.

CASE PRESENTATION**Introduction**

Management of lymphoma in pregnancy is a challenging task. We describe the case of a pregnant woman who successfully completed rituximab-based multiagent chemotherapy for diffuse large B-cell lymphoma and successfully underwent parturition.

Case report

A 28-year-old pregnant woman presented to our centre in the sixth month of gestation with 10–15

episodes of small volume loose stools per day that were mucoid, non-blood stained for 1 month associated with urgency, incontinence and tenesmus. There was associated low backache. She also had noticed increasing bilateral pedal oedema over the course of a month. Her history was significant for tuberculous lymphadenitis 2 years ago for which she had been adequately treated with weight-based antitubercular therapy for 9 months. Six weeks prior to presentation when she had worsening low backache, she was found to have bilateral renal calculi with mild hydroureteronephrosis for which she underwent bilateral double J stenting.

Clinical examination revealed pallor and bilateral pitting pedal oedema, with multiple enlarged lymph nodes in the bilateral inguinal and right axillary regions. Abdominal examination was significant for a palpable uterus, and there was no organomegaly. Per rectal examination revealed a tender circumferential ulceroproliferative growth 2 cm from the anal verge with significant luminal compromise. Lower one-third of the vagina could not be examined due to the local infiltration by the rectal growth. The rest of the systemic examination was normal.

Thus, this was a middle-aged primigravida presenting in the second trimester with history of multiple episodes of loose stools with symptoms suggestive of rectal involvement on examination found to have pallor, lymphadenopathy and an ulceroproliferative growth in the anorectal region.

DIFFERENTIAL DIAGNOSIS

At this stage, differential diagnosis considered included aetiologies that could present with above presentation and an ulceroproliferative growth in the anorectal region. Differentials included locally advanced anorectal malignancy and lymphoproliferative malignancy. Even though the patient had a significant history of tuberculous lymphadenitis in the past, this was not a typical presentation of tuberculosis.

INVESTIGATIONS

At presentation, she had a haemoglobin of 57 g/LdL, white cell count of $17 \times 10^9/L$ and a platelet count of $374 \times 10^9/L$. Liver function tests revealed mild hypoalbuminaemia and renal functions were normal. MRI of the abdomen revealed an asymmetrical, wall thickening of the entire rectum from the rectosigmoid junction until the anorectal junction (figure 1). There was a similar mass along the greater curvature of stomach, which was infiltrating

Figure 1 MRI pelvis showing asymmetrical wall thickening of the entire rectum from the rectosigmoid junction until the anorectal junction.

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Figure 2 Photomicrograph of the rectal biopsy showing (A) rectal mucosa with a diffuse infiltrate of atypical lymphoid cells (H&E stain), $\times 100$ magnification. (B) Photomicrograph showing diffuse CD20 immunopositivity, $\times 100$ magnification. (C) Photomicrograph showing a high MIB-1 proliferation index in the atypical lymphoid infiltrate, $\times 40$ magnification.

the anteromedial border of spleen and tail of pancreas. A rectal biopsy revealed rectal mucosa with mild crypt disarray, crypt elongation and mild cryptitis and the lamina propria showing fibrosis and moderate to focal dense infiltrates of large cells with hyperchromatic to vesicular nuclei, some with visible nucleoli and moderate amounts of cytoplasm that was consistent with a high-grade lymphoma. Immunohistochemistry confirmed the diagnosis to be diffuse large B-cell lymphoma, Germinal centre B-cell (GCB) type based on tumour being CD20 positive, CD3 negative, BCL2 positive BCL6focal positive, CD10 negative, MUM1 30%–40% cells positive, C-Myc 10% cells positive, MPO negative, CD34 negative and MIB 1%–80% (figure 2). She was risk stratified based on International Prognostic Index score as high intermediate risk.

TREATMENT

She was started on injection dexamethasone 8 mg once a day for 4 days. After a multidisciplinary meeting involving haematologists, obstetricians and general physicians, it was decided to continue with the pregnancy and she was initiated on R-CHOP-21 therapy, which included intravenous rituximab 375 mg/m², cyclophosphamide 800 mg/m², adriamycin 50 mg/m², vincristine 1.4 mg/m² on day 1 and oral prednisolone 60 mg/m² from days 1 to 5 with adequate premedications. The post-chemotherapy period was complicated with neutropaenic fever, which was managed with antibiotics, blood products and G-CSF (Granulocyte-Colony Stimulating Factor).

OUTCOME AND FOLLOW-UP

During the neutropaenic phase following the fourth cycle of chemotherapy, she was admitted with fever and leaking per vaginum. Obstetric examination suggested that she had ruptured her membranes; abdomen examination revealed a term uterus with cephalic presentation with adequate liquor with fetal heart rate of 160/min. She was induced and she delivered a single live female baby of 1.86 kg at 36 weeks of gestational age by normal vaginal delivery with Apgar score of 9 and 10. She completed her 6 cycles of chemotherapy and postchemotherapy assessment of disease status showed complete regression of disease.

DISCUSSION

Occurrence of a malignancy during pregnancy is an uncommon clinical situation and often poses difficulties in management. Pregnancy-associated malignancy is defined as a malignancy

that is diagnosed any time between day 1 of pregnancy until 1 year post partum.¹ Coexistence of malignancy and pregnancy complicates the treatment as both mother and fetus are potentially at risk of complications due to the chemotherapeutic agents. A multidisciplinary approach is often needed in such situation. Lymphoma is the fourth most frequent malignancy diagnosed during pregnancy with a frequency of 1:6000 deliveries, with the frequency more so due to the current tendency for late pregnancy.² Diagnosis of lymphoma during pregnancy poses a diagnostic as well as a management challenge as literature for the same is based on case reports and case series.

Diffuse large B-cell lymphoma is the most common lymphoma seen in pregnancy as per a multicentre retrospective analysis done at 11 academic centres, on a cohort of 90 patients. Pregnancy was terminated in six patients (five patients in the first trimester and one in the early second trimester). Among the remaining 84, 28 patients had chemotherapy deferred until the delivery and 56 received antenatal chemotherapy. This study showed that antenatal chemotherapy in the second and third trimester did not increase the morbidity or mortality of fetus nor the rate of congenital malformations. Even long-term follow-up of these children showed normal physical, neurological development with matching school performance and IQ in comparison with the control.³

Due the low molecular weight of the cytotoxic agents, fetus gets exposed to the same as it crosses the placenta easily. Chemotherapy in the first trimester increases the risk of spontaneous abortions, fetal death and major malformations with a 10%–20% risk for major malformations.⁴ But beyond the first trimester, the risk for the same decreases so much so that in a case series following pregnant women receiving chemotherapy over 30 years, all the four women in third trimester had healthy live births.⁴ Complications anticipated with the second and third trimester treatment are fetal or neonatal death, intrauterine growth retardation (IUGR), preterm delivery and low birth weight.² R-CHOP chemotherapy per se has been considered to be relatively safe in pregnancy especially when administered in the second and third trimester except for the increased risk for preterm delivery.⁵ Due to increased predilection for IUGR, these patients are at an increased risk for neurodevelopmental impairment, increased cardiovascular risk factor and renal dysfunction as long-term complications.^{6–8} Thus, the current recommendation for treatment of non-Hodgkin's lymphoma (NHL) depends on the time of presentation (in terms of the trimester), the nature of the disease and the patient preference. In case of an indolent NHL during first trimester, the treatment can be delayed until the end of the first trimester. In case of aggressive NHL, recommendation is to terminate pregnancy as the patient needs imminent chemotherapy. Despite the possible complications as mentioned for second and third trimester pregnancy

Learning points

- ▶ Multidisciplinary approach is needed for patients with lymphoma during pregnancy.
- ▶ A case-to-case basis decision needs to be taken for decision regarding continuation of pregnancy and initiation of chemotherapy.
- ▶ It is safe to administer chemotherapy in the second and third trimester without any major increase in the fetal mortality or morbidity.

with use of chemotherapy, the overall advantage of treatment is clear, hence the current recommendation is to administer chemotherapy with continuation of pregnancy. Our patient successfully completed all cycles of chemotherapy and delivered a healthy baby at term.

Conclusion

Management of lymphoma in pregnancy poses significant challenges in terms of diagnosis and treatment. However, the treatment decision requires a balance of fetal and maternal risk posed by the disease and its therapy on a case-to-case basis.

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