Chronic lymphocytic leukaemia in pregnancy: a case report and literature review

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Summary: Chronic lymphocytic leukaemia is a rare condition reported in pregnancy. We review a case of a woman presenting for pregnancy care with active disease and review the literature on this condition. This case raises several important issues with regard to managing complex medical diseases such as leukaemia in pregnant women, including the role of multidisciplinary care.

Keywords: leukaemia, pregnancy

CASE

The patient was a 31-year-old gravida 1 para 0 presenting at nine weeks gestation. She had been diagnosed with chronic lymphocytic leukaemia (CLL) eight years earlier. At initial presentation, she was noted to have cervical lymphadenopathy. Her leukocyte count was $59 \times 10^9/L$. Flow cytometry showed the proliferative cells to be CD5 positive, CD23 positive and FMC negative, consistent with the diagnosis of CLL. Cytogenetic evaluation revealed a chromosomal deletion, del 13q. She was treated with multiple courses of fludarabine and cyclophosphamide. She underwent investigations for haematopoietic cell transplantation, but no human leukocyte antigen (HLA) matches could be identified in her family.

Booking blood pressure was 110/60 mmHg. Bilateral posterior triangle lymphadenopathy was noted. A 2 cm jugular node was palpable. Multiple axillary nodes measuring 1–2 cm were noted, in addition to multiple bilateral inguinal nodes measuring 1–2 cm. No hepatosplenomegaly was detected.

She presented with antepartum haemorrhage at 27 weeks gestation. Fetal and placental ultrasound assessments were reassuring. However, she was admitted to the antenatal ward for observation and received antenatal corticosteroids for fetal lung maturity. Serial fetal ultrasounds performed at 29, 32, 34 and 37 weeks revealed a well-grown fetus with growth percentiles ranging from 50th to 85th for gestational age.

She received an antenatal anaesthetic consultation at which time no contraindication to neuraxial anaesthesia was noted. In the event of peripartum haemorrhage, arrangements were made to have irradiated blood products available.

At 38 weeks her blood pressure increased to 120/90 mmHg. There were no symptoms of gestational hypertension. Laboratory assessments revealed normal liver enzymes, normal platelet count. However, uric acid was elevated at $377 \mu\text{mol/L}$ and a 24-hour urine collection returned with a proteinuria level of 3040 g/day and a normalized creatinine clearance of 1.0 mL/second. With regard to CLL, her leukocyte count was $41 \times 10^9/L$, haemoglobin was 102 g/L and platelet count was $117 \times 10^9/L$. The patient had no clinical signs of infection but continued to have cervical lymphadenopathy. Induction of labour was planned given the diagnosis of gestational hypertension with proteinuria (preeclampsia).

However, six days later she presented in spontaneous labour. The fetal heart rate became non-reassuring, and there was minimal progress in labour. Thus the patient underwent a caesarean delivery without complication. Apgar scores were 8 and 9 at one and five minutes, respectively, and the birth weight of the infant was 3690 g. Umbilical cord blood was collected for cytogenetic studies as well as stem cell banking. Inspection of the pelvic organs and retroperitoneal surfaces was unremarkable. The placenta was sent for pathological analysis.

Following delivery, a sample of umbilical cord blood was sent for flow molecular diagnosis. Polymerase chain reaction revealed no evidence of B-cell monoclonality. The placental pathology revealed that the maternal intervillous spaces demonstrated proliferation of mature lymphocytes. There were no signs of funisitis or chorioamnionitis. The placental disc did reveal multiple infarcts, less than 3 cm in size. The placental weight was 628 g, greater than the 90th percentile for gestational age.

In the year following the delivery, the mother experienced multiple relapses requiring repeated courses of oral chemotherapy.

DISCUSSION

CLL is a monoclonal proliferation of immunologically incompetent B lymphocytes.¹ The most common presenting signs are

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lymphadenopathy, splenomegaly, hepatomegaly, lymphocytosis, anaemia and thrombocytopaenia. Constitutional symptoms are similar to those associated with other leukaemias and may include weight loss, fevers, night sweats and extreme fatigue. The diagnosis is established by the presence of an absolute lymphocyte count of $>5 \times 10^9/L$ with characteristic morphology and demonstration of clonality by flow cytometry. Bone marrow aspiration typically shows a hypercellular marrow with $>30\%$ of nucleated cells being lymphocytes.¹ Various chromosomal changes are associated with CLL, including trisomy 12, del(13q14), del(11q) and del(17p).¹

CLL is felt to be incurable with current therapy, with the possible exception of allogeneic stem cell transplantation. Treatment is reserved for progression in signs such as anaemia, thrombocytopaenia, lymphadenopathy, hepatosplenomegaly and recurrent infection.² Chemotherapeutic agents include chlorambucil, cyclophosphamide, corticosteroids, nucleoside analogues (fludarabine, cladribine, pentostatin) and, more recently, the monoclonal anti-CD20 antibody rituximab. The use of chemotherapy during pregnancy requires specific counselling by both the oncologist and obstetrician given potential for fetal side-effects. However, a more reassuring treatment choice may be corticosteroids if indicated, as they are commonly used in pregnancy to treat many autoimmune disorders.

Pregnancy, leukostasis and increased viscosity may predispose to thrombosis. Antiplatelet therapy (i.e. aspirin) prophylaxis can be used safely in pregnancy.³ Alternatively, in severe cases leukapheresis can be performed safely during pregnancy.^{4,5} Leukapheresis may be used as a temporary and rapid therapy for reducing leukocyte counts and prophylaxis against potential vascular occlusion during pregnancy if chemotherapy is being deferred.⁵

Testing of umbilical cord blood did not show evidence of leukaemic cells in the fetal circulation. Although still investigational, in the future stem cells derived from the umbilical cord may be used in adult haematopoietic cell transplantation.⁶

As CLL typically follows an indolent course, chemotherapy can often be delayed until after delivery. Chemotherapy may be associated with fetal anomalies, miscarriage, fetal growth restriction, preterm birth and stillbirth. Therefore, each agent must be carefully reviewed for safety and side-effects if used during pregnancy.⁷ It may be preferable to deliver the infant prior to treatment, particularly during the third trimester. If delivery is planned during the courses of chemotherapy, delivery should be timed 3–4 weeks after treatment to avoid myelosuppression and infectious risk in both the mother and newborn. It is important to remember that given the state of relative hypogammaglobulinaemia, that pregnant women with CLL should be closely monitored for signs of infection throughout gestation and the postpartum period.

To date, only five other case reports describe pregnancies complicated by CLL.^{5,8–11} None of the patients received chemotherapy during pregnancy. In one case, leukapheresis was used to manage leukocytosis during pregnancy.⁵ One patient

developed Richter's syndrome (transformation to diffuse large cell lymphoma) seven months postpartum and subsequently died.⁵

In a large, prospective study of women of reproductive age with non-Hodgkin's lymphoma, including 198 women with CLL, Adami *et al.*¹² concluded that the hormonal and immunological changes associated with pregnancy had little or no effect on the future development of CLL.

CONCLUSIONS

This case demonstrates many of the challenges faced by the pregnant woman with CLL. Given the need to coordinate care across specialities including obstetrics, neonatology, oncology and anaesthesiology, a team approach is critical to safe pregnancy care. The major areas for discussion and counselling include maternal prognosis, prenatal screening, fetal monitoring, mode of delivery, risks of chemotherapy during pregnancy, neonatal outcome and monitoring for complications such as infection, haemorrhage and thrombosis. On the basis of the six known cases of CLL in pregnancy, it is apparent that successful pregnancy outcome is possible.

COMPETING INTEREST

The authors express no competing interests.

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