Successful pregnancy in the context of previously undiagnosed chronic lymphocytic leukaemia: A case report and literature review

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Abstract

An asymptomatic 36-year-old woman presented with significantly elevated white blood cells ($165.9 \times 10^9/L$) at antenatal booking, in her first pregnancy. Further investigations revealed the diagnosis of chronic lymphocytic leukaemia with monoallelic deletion of chromosome 13q14. She was supported and monitored through out pregnancy, without treatment, and delivered a healthy baby boy at term with no complications and is currently being followed up by the haem-oncology team.

Keywords

Maternal-fetal medicine, high-risk pregnancy, contraception, maternal mortality

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Introduction

Case report

The case described is of an asymptomatic 36-year-old Caucasian lady, para 0 who was well on booking, with no risk factors. The booking blood results were reported as follows: haemoglobin (Hb) 9.3 g/L (12–15 g/L), mean cellular volume of 111.8 fL (83–101 fL), reticulocyte count of $80.1 \times 10^9/L$ ($50–100 \times 10^9/L$), white blood cell (WBC) $165.9 \times 10^9/L$ ($4–10 \times 10^9/L$), lymphocyte count $162.6 \times 10^9/L$ ($1–3 \times 10^9/L$), neutrophil count $1.7 \times 10^9/L$ ($2–7 \times 10^9/L$), platelets (PLTs) $173 \times 10^9/L$ ($150–410 \times 10^9/L$), normal bilirubin level and a negative direct antiglobulin test. A haemoglobinopathy screen was reported as normal. The patient was referred to the high-risk antenatal clinic and the haematology team. The booking biochemistry and haematology blood tests, along with a blood film were repeated.

On examination, our patient had numerous small lymph nodes in the cervical region and one node, which was approximately 1 cm, in the submandibular region. No organomegaly was evident. A blood film (Figure 1) revealed features of monomorphic lymphocytes, an indication of lymphoproliferative disorder. Leukocyte immunophenotyping was performed which confirmed a clonal population of lymphocytes expressing cell surface markers CD5 and CD23 – typically seen in B-cell chronic lymphocytic leukaemia (B-CLL). Peripheral blood revealed a monoallelic deletion of chromosome 13q14 in 99/100 cells examined. This is a recognised finding in B-CLL and is usually associated with a favourable prognosis. The combination of the blood film, immunophenotyping and cytogenetics confirmed the diagnosis of B-CLL and, as the patient was otherwise well, it was decided that a bone marrow biopsy was not required at this time.

According to the Binet classification,¹ the patient was clinically stage C, which is characterised by anaemia and/or thrombocytopenia. The patient appeared well, and a decision was made to monitor her closely, with no initiation of treatment, with her informed approval.

Further assessment for causes of the associated anaemia and macrocytosis was performed, including vitamin B12, folate, thyroid function and iron studies as follows: iron saturations of 24% (30%–40%), serum ferritin of 40 µg/L (10–160 µg/L), transferrin 3780 mg/L (2000–3380 mg/L) and a total iron binding capacity of 85 µmol/L (45–76 µmol/L). She was HIV antibody 1 and 2 negative. The patient

was started on oral iron tablets in the antenatal clinic due to mild iron deficiency. The theory at this stage was that the anaemia was a mixture of iron deficiency and bone marrow involvement of B-CLL.

She remained under regular review within haematology and obstetric departments with stable blood counts and iron replacement therapy. Clinical examination revealed no significant lymphadenopathy. Blood tests were repeated every three to four weeks (Table 1). She did not require blood transfusion until delivery and developed no significant cytopenias. Obstetric monitoring was planned with serial growth scans at 28, 32 and 36 weeks revealing a normal growth profile. An anaesthetic review was arranged, and the delivery plan was to aim for a spontaneous vaginal delivery, providing she did not require treatment in her pregnancy for B-CLL.

At week 29 of gestation, the patient attended the antenatal clinic having noticed the growth of two small lymph nodes (1 cm × 1 cm) – one right infra-auricular lymph node and one under the left eyebrow. The patient was also noted to have hairline erythema and cutaneous lesions of the right ear and forehead.

Skin biopsies revealed the entire dermis and subcutis contained dense infiltrate of small lymphocytes, which were seen to dissect in between collagen bundles. There was extension into follicular structures. On immunohistochemistry, this lymphocytic infiltrate shows strong widespread positivity for CD5, and a large proportion of cells were positive for CD23 – all of which showed skin infiltration of B-CLL. These skin lesions fluctuated throughout the course of the pregnancy, and no specific management was needed.

At 30 weeks gestation, the patient was diagnosed with an upper respiratory tract infection, treated with a five-day course of amoxicillin and the symptoms fully resolved. At 32 weeks, the patient was admitted to the antenatal ward complaining of shortness of breath

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and pleuritic chest pain with a query of haemoptysis and a concern that her membranes had ruptured. Respiratory examination elicited left basal coarse crepitation's up to the mid-zone. Her blood tests are noted in (Table 1), and she had raised inflammatory markers and normal renal function. She was referred for an urgent chest X-ray which was reported as showing hazy shadowing at the left heart border. A speculum examination confirmed membranes intact. Due to the symptoms, signs and abnormal chest X-ray findings, she underwent a computed tomography pulmonary angiography scan. No pulmonary embolus was evident, but the scan confirmed the original suspicion of pneumonia. The patient was treated with a 10-day course of Penicillin V and Clarithromycin, after which the symptoms resolved.

At the 37-week antenatal review, a birth plan was discussed. The patient was noted to be thrombocytopenic and anaemic (Table 1). The obstetricians wanted to optimise the haemoglobin and prescribed two units of packed red cells. Due to the falling PLT count, a combined decision was made to avoid an epidural with the patients consent.

At 40 weeks and 4 days, she delivered a healthy male infant by vaginal delivery. Post-delivery, she was noted to have a PLT count of $97 \times 10^9/L$, lymphocyte count of $123 \times 10^9/L$ and Hb of 101 g/L. There were no concerns from the paediatric team regarding the infant (weight 3244 g; APGAR Score 8 at 1 min post-delivery; APGAR score 9 at 5 min post-delivery).

Post-delivery, the patient was planned for staging investigations, which included a bone marrow biopsy and a computed tomography (CT) scan of the neck, thorax, abdomen and pelvis. The bone marrow biopsy report revealed a hypercellular bone marrow with 95% infiltration of CD5, CD23 positive lymphocytes and minimal residual haematopoiesis. This confirmed that the anaemia was predominantly due to B-CLL marrow infiltration. As a result, iron deficiency was only a

small contributor to the anaemia, and iron studies were not performed on the bone marrow biopsy. The CT scan revealed enlarged lymph nodes in the neck, chest and abdomen, with no bony infiltration and no hepatosplenomegaly, consistent with the clinical findings. A few months following delivery, the patient started chemotherapy due to the heavy bone marrow infiltration.

Discussion

Chronic lymphocytic leukaemia (CLL) is predominantly a condition diagnosed in the elderly, with the incidence being higher in male patients, and women having a lower risk of progressive disease.² For this reason, it has very rarely been associated with pregnancy. There are few case reports in the literature reporting CLL in pregnancy, with all patients delivering healthy children. What we do know is that the WBCs begin to increase in early pregnancy, mainly due to an absolute increase in neutrophil numbers.^{3,4} Female sex hormones have been shown to have immunomodulatory effects, so it has been speculated that reproductive factors and exogenous hormones may affect risk of lymphoid malignancies.⁵⁻⁸

As our patient was completely asymptomatic at presentation, her results (Table 1) were only revealed when she had her antenatal booking bloods at week 11. However, on further history taking, she did reveal noticing a growth on her forehead and right ear in early pregnancy. Skin biopsies subsequently confirmed cutaneous CLL. The skin lesions did not have any relationship to the pregnancy, and cutaneous lesions occur in up to 25% of patients with B-CLL.⁹ Her WBC remained static, at around $165 \times 10^9/L$, until around week 37 when there was an increase to $249 \times 10^9/L$. This began to drop at the end of pregnancy, returning to levels below the booking blood WBC levels. Her haemoglobin level remained stable, at approximately 90 g/L, on oral iron therapy throughout pregnancy. The PLT levels also remained normal until delivery, when they dropped to 97 g/L. It is now clear that although there was mild iron deficiency, the bone marrow infiltration was the main causative factor in the anaemia. Blood films (Figure 1) consistently revealed lymphocytosis and smear cells.

Due to the indolent nature of the condition,¹⁰ a watch-and-wait approach is advised in the early stages of the disease. With the informed request of the patient, we adopted an active monitoring approach to her B-CLL, with a strong suspicion that anaemia and thrombocytopenia were due to bone marrow infiltration. A similar approach is used in patients who are not pregnant, but there would be a lower threshold to treat, especially with this degree of bone marrow infiltration. Closer monitoring throughout pregnancy is required to look for potential complications. These complications may include increased susceptibility to infection, autoimmune phenomena and cytopenias such as anaemia, thrombocytopenia and leukopenia. The patient was treated with two courses of antibiotics during her pregnancy, for respiratory tract infections, but otherwise remained clinically stable at Binet stage 3.

Indications for treatment include a very high absolute lymphocyte count (ALC), symptoms or risk of leucostasis or antenatal complications. Leucostasis is rarely seen in B-CLL, and patients can be asymptomatic with an ALC as high as $500 \times 10^9/L$.¹¹ A high ALC should not

Figure 1. Blood film of patient during pregnancy week 37, showing lymphocytosis.

Table 1. Timeline of blood tests during pregnancy.

Investigations	11 weeks	15 weeks	17 weeks	25 weeks	29 weeks	32 weeks	37 weeks	40 weeks
Haemoglobin (g/L)	93	91	89	90	90	85	87	101
WBC ($\times 10^9/L$)	165	155	162	162	197	138.8	249	148
Lymphocytes ($\times 10^9/L$)	162	121	124	126	149	127.5	177	123
Platelets ($\times 10^9/L$)	173	191	182	153	153	130	105	97

WBC: white blood cell.

necessarily be a trigger for treatment, unless there is placental insufficiency, intrauterine growth restriction or other antenatal complications that may be CLL-related. If there is a significantly raised ALC, cytoreduction can be achieved with leukapheresis. There is only one case in the literature where this has been performed successfully for CLL during pregnancy.¹²

Reviewing the literature, there does not seem to be a consensus regarding a maintenance level of the ALC with cytoreduction. The patients ALC peaked at $177 \times 10^9/L$ and showed no signs or symptoms of hyperviscosity throughout her pregnancy.

In terms of chemotherapy in pregnancy, the fetus is most vulnerable to drug-related teratogenicity during the first trimester, and hence chemotherapeutic agents, especially genotoxic drugs in combination, should be avoided. The toxicities were discussed and the patient made an informed decision to delay chemotherapy until after delivery. The first-line chemotherapy option outside of pregnancy is based on the fludarabine, cyclophosphamide and rituximab (FCR) regimen and is the current standard of care.^{13,14} Chemotherapy could be considered in the second and third trimester if there is rapidly progressive disease or local compressive disease,^{15,16} and FCR would be the combination of choice.

Single-agent monoclonal antibodies (e.g. rituximab), in the setting of CLL in pregnancy, are potentially attractive as first-line stabilising treatments. Studies of rituximab, in non-human primates, have not demonstrated fetotoxicity but have shown that it crosses the placenta from week 16, achieving fetal serum levels similar to maternal levels.¹⁷ No long-term studies on B-cell or immune function of children, exposed in utero, have been performed with rituximab. The role of single-agent monoclonal antibodies with their low teratogenic risk appears more favourable compared to the clear teratogenic effects of genotoxic drugs.¹⁸

There is no current evidence regarding transplacental transmission of CLL to the foetus, although two cases of placental invasion have been reported in the literature.^{19,20}

In this case, there has been no regression of the B-CLL which has been reported in a previous case report.¹⁹ This case is unusual because the B-CLL, with heavy bone marrow infiltration was diagnosed in a young, healthy individual during antenatal booking tests. Another unusual aspect of the case is the active monitoring throughout pregnancy, with the informed consent of the patient. Even though she had two respiratory tract infections, subsequently treated, alongside a high degree of bone marrow infiltration, she remained clinically very well.

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Contributorship

MG, UH and FT were involved in conception of this case report and literature search following the care of the involved patient and prompting the paper to be created. GS and FT were involved in data collection for the case report, which was written by GS. KH and FT performed the literature review. FT edited the case report and literature review and wrote the introduction, as well as creating the initial draft of the article. KH has contributed in a great deal in revision of the case

report. Final approval of the article was a joint contribution between all listed authors.

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