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Case Report

Pregnancy in a 31-year-old woman with chronic lymphocytic leukemia: a case report and review of the literature

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Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the western world, with a median age at diagnosis of 72 years and only approximately 2% of the patients being females younger than 40 years.[1] As such, the number of patients with CLL who become pregnant is extremely rare, with only a few clinical cases being reported.[2,3]

We report the case of a 31-year-old woman, who had been diagnosed two years earlier with CLL and who became pregnant. We discuss the possible management options.

Clinical case

A 28-year female was referred to the hematology outpatient unit for a lymphocytosis and the full blood count showed a normal total leukocyte count, but with an absolute lymphocyte count of 5500 lymphocytes/mm^3. There was no anemia and the platelet count was normal. The blood smear showed some smudge cells (Gumprecht shadows). The patient was asymptomatic and clinical examination revealed no evidence of lymphadenopathy or splenomegaly. The patient was followed up with full blood counts every 4 months.

Two years later, the full blood count was normal, except for an absolute lymphocytosis of 8200 lymphocytes/mm^3. She had remained asymptomatic and clinical examination revealed no lymphadenopathy or splenomegaly. The diagnosis of B-CLL stage Rai 0 was established and, as the patient was young and in possible need of future treatment, a full evaluation of the patient was performed, according to the Chilean Health Ministry guidelines.[4]

The flow cytometry of peripheral blood showed that 27% of the nucleated cells were B-lymphocytes expressing CD45, CD19, CD 20 and CD 23 and positive for CD5, CD43 and CD200. These B-lymphocytes were negative for CD10, CD38, CD56 and showed light chain restriction, being lambda positive.

The direct anti-globulin test was negative; electrophoresis of serum proteins was normal with no evidence of a monoclonal spike or hypo-gammaglobulinemia. A bone marrow

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aspiration and biopsy, although recommended in the Chilean guidelines, was not performed, as it was not clinically indicated. The cytogenetic analysis using chromosome banding showed no evidence of abnormalities, including the 17p and 11q deletions or 13q deletions. The polymerase chain reaction (PCR) analysis showed a positive V_H mutational status. Molecular cytogenetics using fluorescence *in situ* hybridization (FISH) for del (13q), del (11q), del (17p) and add (12) and zeta-chain-associated protein kinase 70 (ZAP-70) status are not available. The serum beta-2-microglobulin was 1 mg/mL (normal range < 2 mg/mL). A computed tomography (CT) scan of the neck, thorax, abdomen and pelvis was normal, with no evidence of splenomegaly or lymphadenopathies. The Chilean guidelines suggest a CT scan or chest radiograph with abdominal ultrasound.

A diagnosis of B-cell CLL stage Rai 0 was established, the CLL-IPI (international prognostic index) score was 0.[5] The patient was kept under a watchful waiting, with full blood counts every six months.

At the age of 31 years, the patient was found to be pregnant; the pregnancy was uneventful. The full blood count remained normal during pregnancy, except for an absolute lymphocyte count of 8870 lymphocytes/mm^3, which increased to 10,520/mm^3 in the pre-delivery. The direct and indirect antiglobulin tests remained negative and the serum beta-2-microglobulin was 0.9 mg/mL. Clinically, the patient remained classified as stage Rai 0. The delivery was uneventful with a healthy infant and the placenta was free from CLL infiltration. The flow cytometry of cord blood did not detect CD5 positive lymphocytes.

After pregnancy, the absolute lymphocyte count decreased to 9630 lymphocytes/mm^3 and then slowly increased over the next three years to 11,490 lymphocytes/mm^3. At the present time, the patient remains asymptomatic.

Discussion

Managing CLL during pregnancy requires close cooperation between obstetricians and hematologists; due to the paucity of cases there are no specific guidelines and patient care should be individualized. The risk of disease progression and the possible need for treatment must be carefully assessed, as well as the potential side effects for the fetus.

The indolent nature of CLL permits a watchful waiting approach in patients with asymptomatic early-stage disease (Rai 0, Binet A). Early treatment of these patients with anti-leukemia drugs, including signaling inhibitors or BCL-2 antagonists, is not recommended,[6] as no survival benefit for early treatment has been shown.[7] The recent International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines of 2018 recommend immunophenotyping of peripheral blood lymphocytes to confirm the diagnosis, but additional tests are only recommended when considering treatment.[6] The 2019 National Comprehensive Cancer Network (NCCN) guidelines are similar, with prognostic parameters assessed only if treatment is considered, but include unilateral bone marrow aspiration and biopsy.[7] However, a recent publication recommended that all patients should undergo risk stratification, according to the CLL-IPI, at the time of diagnosis and those with low- or intermediate-risk CLL should be monitored for disease progression every 6–12 months.[8]

In the case report, CLL was confirmed using immunophenotyping of peripheral blood lymphocytes. The Chilean Health Ministry recommendations for CLL differ in that they stress the need to perform karyotyping using cytogenetic studies. The FISH, although preferred, is not widely available in Chile and that the detection of ZAP 70 and the V_H mutational status is optional.[4] The serum beta-2-microglobulin is a routine test in Chile, although not mentioned in the Ministry guidelines.[4] The CLL-IPI score in this reported case was 0 (low risk); in addition, the B-lymphocytes were CD38 negative, the expression of which is associated with un-mutated V_H status and a poorer prognosis.[6] The CLL B-cells co-expressed CD200, this has been reported to be associated with older age, higher absolute lymphocyte counts, hepatosplenomegaly, higher Rai score and worse prognosis.[9] The CT scanning is not routinely recommended at the time of diagnosis; an association between CT-detected thoracic or abdominal lymphadenopathy in Rai 0 CLL and shorter progression and treatment-free survival times was not confirmed in a recent meta-analysis.[10]

During pregnancy there is a physiological effect on the white cell count, mainly due to an absolute increase in neutrophils, whereas the absolute lymphocyte count and ratio of B and T-cells remains unchanged.[2] The decrease in the absolute post-delivery lymphocyte count seen in this case may be a result of lymphocyte re-distribution.[2]

Indications for treatment are essentially the same as in non-pregnant patients, namely progressive bone marrow failure, massive lymphadenopathy or splenomegaly, autoimmune complications, B-type symptoms and progressive lymphocytosis with an increase of ≥50% in a period of two months or a lymphocyte doubling time of <five months.[6,7] Leukostasis is rarely seen in CLL, however there is the potential risk of placental insufficiency due to a high white cell count. This leads to low birth weight, prematurity and increased fetal mortality, if left untreated.[2] Although there is limited evidence for the use of leukopheresis in reducing the white cell count and the effect on fetal growth, it could be considered as a temporary therapy until post-delivery.

A recent retrospective analysis of first-line treatments for CLL between 2007 and 2013 indicated that chlorambucil and the combination of fludarabine, cyclophosphamide and rituximab (FCR) were the most common treatment regimens.[11] Chlorambucil, fludarabine and cyclophosphamide are all category D drugs and congenital defects have been reported, especially when these drugs are used during the first trimester.[2] Chemotherapy could be considered in the second or third trimester if there is rapidly progressive disease or compressive disease.[2] Although exposure to chemotherapy is less likely to be teratogenic, the risk of intra-uterine growth retardation is increased. In animal models, rituximab has not been shown to be toxic to the fetus, however in humans it crosses the placenta from week 16 onwards and has been reported to cause neonatal lymphopenia and/or B-cell depletion when used in the second or third trimester.[2]

The monoclonal antibodies ofatumumab and obinutuzumab are both category C drugs, although no teratogenicity was observed in animal studies.[2]

Newer agents used in the treatment of CLL, such as the Bruton tyrosine kinase inhibitor ibrutinib, the inhibitor of the anti-apoptotic protein B-cell lymphoma 2 venetoclax, are of unknown risk to the fetus and their use is not recommended. Lenalidomide has shown activity in CLL and ongoing trials in its use for maintenance are underway, however, as it is structurally related to thalidomide, it is considered a category X drug and, as such, is contraindicated in pregnancy.

Cytopenias may complicate pregnancy, red cell and platelet transfusions being required as a result of bone marrow infiltration. It has been suggested that the hemoglobin level should be maintained around 10 g/dL and a platelet count of 50–100 $\times$ 10^6/mm^3, with closer monitoring as delivery is approaching, especially if cesarean section has had obstetric indication.[3] Auto-immune disease and hypogammaglobulinemia can be treated with steroids and infusions of immunoglobulins, as in non-pregnant patients.

The CLL is associated with immune suppression and increased risk of infection, especially if hypogammaglobulinemia is present. Cytomegalovirus, herpes virus, toxoplasma and rubella (part of the TORCH group of infections), which can cause severe fetal complications and be reactivated in CLL patients, are of particular concern during pregnancy.

Conclusions

Pregnancy occurring during CLL is very rare and, as such, no specific guidelines are available. The CLL is usually an indolent disease that permits an observational approach during pregnancy, but each case must be treated on an individual basis. If treatment is unavoidable, as delaying therapy until the second or third trimest, but does not eliminate, the risk of fetal malformations. Reactivation of infections, such as CMV and Herpes virus due to the combined immunosuppressive effects of CLL and pregnancy, needs to be considered.

Ethical considerations

The local ethics committee approved this case report and the patient provided written informed consent.

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Author contribution

All authors contributed equally in the writing of this case report.

Conflicts of interest

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