DOI: https://doi.org/10.2298/SARH210502077M
UDC: 616.155.392

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Chronic lymphocytic leukemia diagnosed during pregnancy – case report and review of literature

Dragomir Marisavljević[1,2], Nada Kraguljac-Kurtović[3], Nataša Stanisavljević[1,2]

[1]Bežanijska Kosa Clinical Medical Center, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]University Clinical Center of Serbia, Belgrade, Serbia

SUMMARY

Introduction B-cell chronic lymphocytic leukemia (CLL) can be easily overlooked in pregnancy, particularly in cases with inadequate antenatal care. We report a case of pregnant woman diagnosed with CLL and evaluate this patient with cases in literature.

Case report An asymptomatic 35-year-old woman presented with slightly elevated absolute lymphocyte count at antenatal monitoring in her second pregnancy. Further hematological investigations disclosed CLL with monoallelic deletion of chromosome 13q14. She was monitored during throughout the pregnancy, being asymptomatic and without treatment, and delivered a healthy child at term with no complications. After almost four years of follow up patient is without any signs of disease progression and her absolute lymphocyte counts remained on predelivery levels.

This is the first published case of CLL diagnosed during pregnancy in Serbia. Rare similar cases published so far have been discussed, especially in terms of disease course, long-term prognosis and available therapeutic modalities.

Conclusion Due to the fact that nowadays many women are delaying childbearing in middle age it can be expected that cancer diagnose could be more often found in pregnant women in the future. In a view of the complex nature of such condition, a multidisciplinary approach for diagnosing and treating of pregnant women is highly recommended.

Keywords: chronic lymphocytic leukemia; pregnancy; treatment; outcome

INTRODUCTION

Approximately 1 in 1000 pregnancies is complicated by any cancer diagnosis, whereby hematological malignancies comprising 11.5–18% of these cases [1, 2, 3]. Among hematological malignancies the most common are Hodgkin's disease, non-Hodgkin's lymphoma and acute myeloid leukemia, accounting for 6%, 4.7%, and 3.2% cases, respectively [1]. The most common reason of induced abortion among pregnancy induced malignancies is hematologic disease (21%) [3]. Although it is the most common adult leukemia, B-cell chronic lymphocytic leukemia (CLL) has been reported in pregnancy in less than 10 cases [4–13]. The median age of CLL is 70 years and approximately 2% of patients are aged < 45 years [14, 15]. Considering the male:female ratio of 2:1, extremely small proportion of patients with CLL are expected to be females of potentially child-bearing age [14, 15]. In such circumstances, CLL can be easily overlooked in pregnancy, particularly in cases with inadequate antenatal care (rural areas, health habits, low social milieu, etc.).

We describe the case of CLL occurring in pregnancy in a Serbian patient, diagnosed three months before delivery. The review of literature data was the basis of discussing some important issues related to diagnosis and management of CLL in women of childbearing age and in pregnancy.

CASE REPORT

We retrospectively analyzed 2020 (1315 males and 705 females, M/F ratio 1.86) consecutive untreated patients with *de novo* CLL referred for diagnosis in the Laboratory for Immunophenotyping and Flow Cytometry, Diagnostic Department, Clinic of Hematology, University Clinical Center of Serbia, in the time period from January 2003 until June 2020. Diagnosis was established according to the standard criteria [16, 17]. Among these 2020 patients with CLL, 320 patients were younger than 55 years (15.8%), including 9.8% (198/2020) male and 6% (122/2020) female, M/F ratio 1.62. Only one of these "younger" CLL patients was a pregnant female and her clinical characteristics, labor outcome and course of the malignant disease are described in the text bellow.

A 35-year-old Caucasian woman in her second pregnancy (first delivery three years prior, delivered via Caesarean section), was first seen by a gynecologist in April 2017 on her first prenatal visit at eight-weeks' gestation. According to Article 16 of the Law on Patients' Rights, written consent was obtained for performing

Received • Примљено: May 2, 2021
Revised • Ревизија: July 1, 2022
Accepted • Прихваћено: July 24, 2022
Online first: July 27, 2022

Correspondence to:
Nataša STANISAVLJEVIĆ
Bežanijska Kosa Clinical Medical Center
11080 Belgrade
Serbia
nacastanisavljevic@gmail.com

invasive diagnostic and therapeutic procedures, as the Approval of the Committee on ethics for the case publishing. Complete blood count (CBC) showed elevated white blood cell count (WBC) of 14.8 × 10^9/l with lymphocyte predomination (65% WBC). Other routine antepartum laboratory results were otherwise within normal range together with hemostasis parameters. She was without symptoms and denied experiencing any weakness, fever, fatigue, or swelling. Since absolute lymphocytosis persisted during next few gynecological checkups, she was referred to a hematologist in August 2017. Physical examination did not reveal any lymphadenopathy or hepatosplenomegaly. Abdominal ultrasonography was normal. Obstetric ultrasonography showed normal fetal anatomy and normal fetal circulation. CBC showed elevated WBC count of 36.4 × 10^9/l accounting for 71% of lymphocytes in differential. Diagnostic immunophenotyping by multicolor flow cytometry of native peripheral blood specimen (September 2017), showed accumulation of atypical monoclonal mature B-cells ($CD19^+CD5^+/SSC^{low}$ cells → 57% WBC → 20.8 × 10^9/l) with specific immunophenotype: $CD19^+$, $CD20^{+low}$, $CD21^{+low}$, $CD22^{+low}$, $CD23^{+intermediate}$, $CD5^{+intermediate}$, $CD79b^{+low}$, $FMC7^{+low}$, $CD43^{+low}$, $CD27^{+low}$, $CD200^{+high}$, $mIgkappa^{+low}$; CLL Score = 4 points). According to these findings, a diagnosis of CLL/variant $FMC7^+$ was made. Expression of prognostic markers, CD38 and CD49d, was not detected.

The patient was clinically doing well, and mutual decision of gynecologist, perinatologist, and hematologist was to carefully monitor pregnancy. In November 2017, the patient was delivered by elective Caesarean section at 39 weeks' gestation. She gave birth to a healthy female infant, weighing 2400 grams with Apgar score of 10. Histopathologic examinations of the chorion and umbilical cord were normal. She had an uneventful postpartum course and regular lactation (lasting for six months). CBC were checked up on six-week periods during pregnancy and lactation and after that, two times a year for almost four-year follow-up period (Figure 1). Whole body computed tomography scan was done in March 2018, and did not reveal significant lymphadenopathy or organomegaly. G-banding and fluorescent in situ hybridization for chromosome 12, 13q14.3 deletion, 17p13 deletion and 11q22 deletion was performed and showed a 13q14.3 deletion in 80% of cells. The patient remained without symptoms and in good clinical condition. On her last follow-up (January, 2021) CBC showed elevated WBC of 33 × 10^9/l with 80% of lymphocytes in differential count.

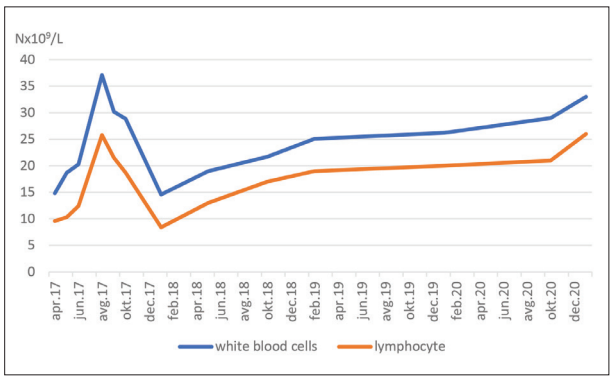

Figure 1. Changes in leukocyte count and absolute lymphocyte count during four-year follow-up of the patient

DISCUSSION

The WBC count begins to increase in early pregnancy, mainly due to an absolute increase in neutrophil numbers, but absolute lymphocyte count (ALC) (normal range 1–4 × 10^9/l) and ratio of B and T cells is essentially unchanged [18]. This increase in the WBC count peaks during the second and third trimester, with return to normal female values within the first week post-delivery. Therefore, any increase in lymphocyte count, especially if it is persistent and/or progressive, requires a detailed differential diagnostic approach.

In a large prospective study of 1744 women of reproductive age (i.e., 15 years and older) with non-Hodgkin's lymphoma, including 198 women with CLL, Adami et al. [19] concluded that the hormonal and immunological changes associated with pregnancy had little or no effect on the development of CLL. Indeed, significant changes in lymphocyte count were not noticed during careful monitoring of our patient during pregnancy, lactation and regular follow-up during four-year period. Histopathologic examination of the chorion and umbilical cord of our patient were normal. There were no evidence regarding transplacental transmission of CLL to the fetus, although two cases of placental invasion have been reported in literature [4, 5].

According to the actual guidelines [16, 17], a watch-and-wait approach is advised in early stages of CLL due to the indolent nature of the disease. Since there are no existing guidelines for CLL in pregnancy, closer monitoring throughout pregnancy is obligatory to look for potential complications, particularly increased susceptibility to infection or occurrence of autoimmune cytopenias. Indications for specific treatment include a very high ALC, followed by symptoms or risk of leukostasis or antenatal complications. Leukostasis is rarely seen in CLL, and patients can be asymptomatic with an ALC as high as 500 × 10^9/l [20]. A high ALC should not 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 ALC raise, cytoreduction could be achieved with leukapheresis. There is only one case in the literature where this has been performed successfully for CLL during pregnancy [7].

In the matter of chemotherapy in pregnancy, the main parameters that influence the choice of treatment are gestational term, type and stage of cancer, the possibility of transplacental transfer and risk of teratogenicity of the drug, but also the patient's opinion on the continuation of the pregnancy if the disease is diagnosed at an early term [21]. The fetus is most vulnerable to drug-related teratogenicity during the first trimester, and consequently chemotherapeutic agents, especially genotoxic drugs in combination, should be avoided. Chemotherapy could

be considered in the second and third trimester if there is a rapidly progressive disease or local compressive disease [22], and fludarabine-cyclophosphamide-rituximab would be the combination of choice. Single-agent monoclonal antibodies (e.g., rituximab), in the setting of CLL in pregnancy, are potentially attractive first-line treatment because of their low teratogenic risk. García et al. [13] reported the only case of rituximab treatment in pregnancy with successful outcome. The safety of novel agents [23] in the treatment of CLL (B-cell receptor pathway inhibitors) in pregnancy is not yet determined and while their efficacy and low side effect profile may be promising, they should therefore be avoided until more data is available. It may be preferable to deliver the infant prior to cytotoxic 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. Also, very important question in this case is the assessment of risk factors for development of venous thromboembolism in pregnancy and the puerperium. Royal College for Obstetricians and Gynecologists classifies pregnant women with cancer as intermediate risk patients and recommends considering of antenatal prophylaxis with low molecular weight heparin [24]. This approach and decision for antenatal prophylaxis requires postnatal prophylaxis for at least six weeks. In our opinion, the decision of ante- and postnatal prophylaxis in group of pregnant women with CLL and other hematological malignancy have to be analyzed individually.

Since the concurrence of cancer and pregnancy is a relatively rare medical problem, single institutional or regional initiatives are not able to provide sufficient information on the safety of cancer treatment during the pregnancy for both mother and fetus [2]. Currently, many women are delaying childbearing in the period 30–49 years, the age group with higher cancer incidence. Due to that it can be expected that cancer will be diagnosed more often in pregnant women in the future [25]. We highly recommend a multidisciplinary approach for diagnosing and treating pregnant women due to the complex nature of such a condition.

Conflicts of interest: None declared.

REFERENCES

1. Dalmartello M, Negri E, Vecchia C, Scarfone G, Buonomo B, Peccatori F, et al. Frequency of Pregnancy-Associated Cancer: A Systematic Review of Population-Based Studies. Cancers. 2020;12(6):1356–68. [DOI: 10.3390/cancers12061356] [PMID: 32466494]
2. Van Calsteren K, Heyns L, De Smet F, Van Eycken L, Gziri M, Van Gemert W, et al. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. J Clinic Oncol. 2010;28(4):683–9. [DOI: 10.1200/JCO.2009.23.2801] [PMID: 19841323]
3. Cottreau C, Dashevsky I, Andrade S, Li DK, Nekhlyudov L, Raebel M, et al. Pregnancy-Associated Cancer: A U.S. Population-Based Study. J Womens Health. 2019;28(2):250–7. [DOI: 10.1089/jwh.2018.6962] [PMID: 30307780]
4. Christomalis L, Baxi LV, Heller D. Chronic lymphocytic leukemia in pregnancy. Am J Obstet Gynecol. 1996;175(5):1381–2. [DOI: 10.1016/S0002-9378(96)70062-5] [PMID: 8942522]
5. Welsh TM, Thompson J, Lim S. Chronic lymphocytic leukemia in pregnancy. Leukemia. 2000;14(6):1155. [DOI: 10.1038/sj.leu.2401799] [PMID:10865984]
6. Gurman G. Pregnancy and successful labor in the course of chronic lymphocytic leukemia. Am J Hematol. 2002;71(3):208–10. [DOI: 10.1002/ajh.10216] [PMID: 12410577]
7. Ali R, Ozkalemkas F, Ozkocamam V, Bülbül-Başkan E, Ozçelik T, Ozan U, et al. Successful labor in the course of chronic lymphocytic leukemia (CLL) and management of CLL during pregnancy with leukapheresis. Ann Hematol. 2004;83(1):61–3. [DOI: 10.1007/s00277-003-0723-0] [PMID: 12961031]
8. Ali R, Ozkalenkas F, Kimya Y, Koksal N, Ozkocaman V, Yorulmaz H, et al. Pregnancy in chronic lymphocytic leukemia: experience with fetal exposure to chlorambucil. Leuk Res. 2009;33(4):565–600. [DOI: 10.1016/j.leukres.2008.05.019] [PMID: 18603296]
9. Hamad N, Kliman D, Best OG. Chronic lymphocytic leukaemia, monoclonal B-lymphocytosis and pregnancy: five cases, a literature review and discussion of management. Br J Haematol. 2015;168(3):350–60. [DOI: 10.1111/bjh.13134] [PMID: 25256787]
10. Winckler P, Vanazzi A, Bozzo M, Scarfone G, Peccatori FA. Chronic lymphocytic leukaemia during pregnancy: management and thoughts. Ecancermedicalscience. 2015;9:592. [DOI: 10.3332/ecancer.2015.592] [PMID: 26635896]
11. Tahmasebi F, Hussain K, Smart G, Gupta M, Hossain U. Successful pregnancy in the context of previously undiagnosed chronic lymphocytic leukaemia: A case report and literature review. Obstet Med. 2017;10(4):189–91. [DOI: 10.1177/1753495X17701319] [PMID: 29225681]
12. Murray N, Orrego S, Lopez MA, Minzer S. Pregnancy in a 31-year-old woman with chronic lymphocytic leukemia: a case report and review of the literature. Hematol Transfus Cell Ther. 2021;43(3):368–70. [DOI: 10.1016/j.htct.2020.01.008] [PMID: 32327395]
13. García R, Hernández-Lorente E, Corella P. Treatment with rituximab of chronic lymphocytic leukemia in pregnancy. Med Clin (Barc). 2021;156(10):525. [DOI: 10.1016/j.medcle.2020.01.037]
14. Chronic Lymphocytic Leukemia — Cancer Stat Facts. [cited 2021 Mar 15]. Available from: http://seer.cancer.gov/statfacts/html/clyl.html
15. Alrawashdh N, Sweasy J, Erstad B, McBride A, Persky D, Abraham I. Survival trends in chronic lymphocytic leukemia across treatment eras: US SEER database analysis (1985–2017). Ann Hematol. 2021;100(10):2501–12. [DOI: 10.1007/s00277-021-04600-1] [PMID: 34279676]
16. Hallek M, Cheson B, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018;131(25):2745–60. [DOI: 10.1182/blood-2017-09-806398] [PMID: 29540348]
17. National Comprehensive Cancer Network website. NCCN clinical practice guidelines in oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma. Version 1.2022 — September 8, 2021. www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed November, 2021.
18. Luppi P, Haluszczak C, Trucco M, Deloia J. Normal pregnancy is associated with peripheral leukocyte activation. Am J Reprod Immunol. 2002;47(2):72–81. [DOI: 10.1034/j.1600-0897.2002.1o041.x] [PMID: 11900591]
19. Adami HO, Tsaih S, Lambe M, Hsieh C, Adami J, Trichopoulos D, et al. Pregnancy and risk of non-Hodgkin's lymphoma: a prospective study. Int J Cancer. 1997;70(2):155–8. [DOI: 10.1002/(sici)1097-0215(19970117)70:2<155::aid-ijc3>3.0.co;2-w] [PMID: 9009153]
20. Ganzel C, Becker J, Rowe JM. Hyperleukocytosis, leukostasis and leukapheresis: practice management. Blood Rev. 2012;26(3):117–22. [DOI: 10.1016/j.blre.2012.01.003] [PMID: 22364832]
21. Benoit L, Mir O, Vialard F, Berveiller P. Cancer during Pregnancy: A Review of Preclinical and Clinical Transplacental Transfer of Anticancer Agents. Cancers (Basel). 2021;13(6):1238–50. [DOI: 10.3390/cancers13061238] [PMID: 33799824]

22. Gribben JG. How I treat CLL up front. Blood. 2010;115(2):187–97. [DOI: 10.1182/blood-2009-08-207126] [PMID: 19850738]
23. Brander D, Islam P, Barrientos JC. Tailored Treatment Strategies for Chronic Lymphocytic Leukemia in a Rapidly Changing Era. Am Soc Clin Oncol Educ Book. 2019;39:487–98. [DOI: 10.1200/EDBK_238735] [PMID: 31099686]
24. Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium, 2015. [online] 37a (RCOG Green-top Guideline), pp. 1–26. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf [Accessed Feb 13, 2021].
25. Stensheim H, Moller B, van Dijk T, Fossa S. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: A registry based cohort study. J Clin Oncol. 2009;27(1):45–51. [DOI: 10.1200/JCO.2008.17.4110] [PMID: 19029418]

Хронична лимфоцитна леукемија дијагностикована током трудноће – приказ болесника и преглед литературе

Драгомир Марисављевић[1,2], Нада Крагуљац-Куртовић[3], Наташа Станисављевић[1,2]

[1]Клиничко-болнички центар „Бежанијска коса", Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Универзитетски клинички центар Србије, Београд, Србија

САЖЕТАК

Увод Б-ћелијска хронична лимфоцитна леукемија може се лако превидети у трудноћи, посебно у случајевима неадекватне антенаталне неге. Приказујемо случај болеснице којој је током трудноће постављена дијагноза хроничне лимфоцитне леукемије и упоређујемо га са досад објављеним случајевима у светској литератури.

Приказ болесника Почетком трећег месеца антенаталног праћења код 35-годишње труднице у другој трудноћи уочен је благо повишен апсолутни број лимфоцита. Хематолошким испитивањем постављена је дијагноза хроничне лимфоцитне леукемије са моноалелном делецијом хромозома 13*q*14. Болесница је током трудноће била без симптома и родила је, без икаквих компликација, здраво дете у термину. После скоро четири године праћења болесница је била без икаквих знакова напредовања болести, а њен апсолутни број лимфоцита остао је на нивоу пре порођаја.

Ово је први приказани случај Б-ћелијске хроничне лимфоцитне леукемије дијагностиковане током трудноће у Србији. Дискутовано је о ретким, досад објављеним сличним случајевима, посебно у погледу тока болести, дугорочне прогнозе и доступних терапијских модалитета.

Закључак У данашње време велики број жена одлаже порођај за средње животно доба, па се чешће може очекивати и дијагноза малигне болести током трудноће. Због комплексности природе оваквог стања препоручује се мултидисциплинарни приступ у постављању дијагнозе и лечењу таквих трудница.

Кључне речи: хронична лимфоцитна леукемија; трудноћа; лечење; исход