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CASE REPORT

The treatment of diffuse large B-cell non-Hodgkin's lymphoma in pregnancy: a case report and a literature review

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Summary

Aim: Hodgkin's lymphoma (HL) is the most common type of lymphoma diagnosed during pregnancy while the occurrence of non-Hodgkin's lymphoma (NHL) is rare because the peak incidence of disease occurs after reproductive age.

Case report: We present a case of 36-year-old woman, in the 13th week of pregnancy, admitted to our department for suspected thyroid lymphoma. She presented with neck swelling, respiratory distress, and dysphagia. After biopsy, histopathological analysis led to the diagnosis of primary diffuse large B-cell mediastinal NHL. The recommendation of multidisciplinary medical team was to start the treatment immediately with R-CHOP for a total of 6-8 cycles. Five years have passed since the beginning of the treatment, the disease is still in remission and the child is at normal level of growth for their age.

Conclusion: Lymphomas in pregnancy represent a challenge for the medical team as well as for the patient. With early diagnosis and appropriate therapy, despite all the risks, it is possible to bring mother into remission without endangering the offspring.

Key words: non-Hodgkin's lymphoma, pregnancy, chemotherapy

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INTRODUCTION

Lymphomas are heterogeneous malignant diseases of the lymphatic system. Hodgkin's lymphoma is the fourth most common malignancy diagnosed during pregnancy and some reports estimate its frequency in approximately 1 in 6000 pregnancies (1). Non-Hodgkin lymphomas occur later, affecting between 0.2 and 0.7 of 100.000 pregnant women (2). However, in the latest studies, the incidence of 1 to 5 cases per 100.000 pregnancies was reported. This can be explained by the trend of delaying first childbirth in developed countries (3). It appears that NHL associated with pregnancy often has an aggressive histology, with diffuse large B-cell lymphomas being most common. It is believed that hormonal and immune changes during pregnancy can act as a trigger and affect the course and prognosis of the disease (4).

CASE PRESENTATION

This report joins a small number of diffuse large B-cell lymphoma cases complicating pregnancy which resulted in survival of the mother and a normal full-term fetus. Thirty-six-year-old woman was admitted to our department for suspected thyroid lymphoma. The patient noticed a fast-growing lump in the neck region, a few weeks before hospital admission, together with respiratory distress and dysphagia. She was 13 weeks pregnant, had proven thrombophilia (FV Leiden heterozygote V), and a previous miscarriage in the 9th week of pregnancy. Her hormonal status was within the reference range, and she had unremarkable medical and family history. Laboratory evaluation demonstrated normal blood counts and inflammatory markers.

MRI revealed conglomerates of enlarged lymph nodes, on both sides of the neck, which compressed the surrounding thyroid tissue that appeared to be infiltrated by the primary tumor located in the anterior mediastinum. There were no enlarged axillary or abdominal lymph nodes or hepatosplenomegaly.

The patient underwent surgery, a tumor infiltrating subhyoid muscles was identified and biopsy led to the diagnosis of primary diffuse large B-cell mediastinal non-Hodgkin's lymphoma.

A team of specialists from general obstetrics, hematology, oncology, and neonatology was assembled to discuss the patient's care plan. Given that the patient was in the second trimester of pregnancy and in the second stage of disease (IIA), the recommendation of multidisciplinary medical team was to start the treatment promptly, with R-CHOP therapy, for a total of 6-8 cycles. Namely, the standard for treating diffuse large B-cell lymphoma is a combination regimen containing cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone with or without rituximab.

After receiving the first cycle of therapy NMR showed dramatic response with tumor regression by 50%. Thereafter, another five cycles of R-CHOP therapy were administered at three-week intervals. The patient's pregnancy was regularly monitored by a gynecologist during the administration of R-CHOP therapy, and it successfully ended with the birth of a healthy baby (Apgar score 9/10) in the 37th week of pregnancy by caesarean section. The delivery in the 37th week balanced the risk of adverse outcomes associated with preterm birth, with the risk of disease progression.

On the 40th day after delivery, a PET scan was performed, where scar tissue was detected in the area of previous tumor mass. Thereafter, the patient was regularly monitored every six months. Five years have passed since the beginning of the treatment and the disease is still in remission. The child has been repeatedly seen by a pediatrician and his growth and developmental status are completely normal.

DISCUSSION

Simultaneous pregnancy complicates the treatment of a malignant disease affecting not only the mother but also the fetus. The goal of treatment is not only to bring the mother into remission, but also to ensure a safe course of pregnancy and healthy offspring. When it comes to non-Hodgkin lymphoma, current clinical practice is based largely on case reports and small case series. The treatment decision is influenced by the type and malignant potential of lymphoma, the stage of the disease, the associated maternal diseases, the stage of pregnancy, side effects, and contraindications of therapy.

It is advised that in patients at low risk, i.e., patients with indolent NHL (follicular lymphomas and small lymphocytic lymphomas) therapy should be postponed until the end of the first trimester to minimize the risk to the fetus. However, the majority of NHL diagnosed during gestation includes aggressive forms (large B-cell lymphomas, mantle cell lymphoma, mature T cell and NK cell lymphomas, Burkitt's lymphoma), and most patients with this form of lymphomas should be treated without delay with intensive combination chemotherapy (1,2).

Most cytotoxic agents cross the placenta due to their low molecular weight. The teratogenicity of these chemotherapeutic agents largely depends on the timing of exposure and almost all of them have been documented to be teratogenic in animal models (5). Chemotherapy during the first trimester of pregnancy may increase the risk of spontaneous abortions, fetal death, and major malformations, as chemotherapy could interfere with organogenesis (3,6).

Although the available literature has not shown CHOP chemotherapy administered during the second and the third trimester to adversely affect the fetal outcome, perinatal risks are present. A higher frequency of

miscarriages, premature births, intrauterine fetal growth retardation and low birth weight was documented, compared to pregnancies of healthy women (6,7).

Lately, much attention has been drawn to the use of immunotherapy in pregnancy as a form of lymphoma treatment. The CHOP regimen usually in combination with rituximab, a monoclonal anti-CD20 antibody, has been commonly used for treating patients with diffuse large B-cell lymphoma. Not many cases of rituximab administration during pregnancy have been reported so far, usually for treatment of different autoimmune diseases. According to these reports the use of rituximab, even in the first trimester of pregnancy, was not associated with an increased risk of adverse fetal outcome (8,9). However, in the latest report from the International network of cancer, infertility and pregnancy, the administration of rituximab during the second and the third trimester of pregnancy (from 13 to 35 weeks) in 36 cases resulted in five neonatal complications (three cases of neonatal systemic infection and one case of neonatal neutropenia), and three maternal infections. In this series rituximab was not used as a single drug, but in combination with chemotherapy, so it is difficult to determine whether complications are due to the use of rituximab or other chemotherapeutical agents (10). In a 2001 study, Aviles and Neri evaluated morbidity in children exposed to chemotherapy in utero. The series included 84 children whose mothers were exposed to chemotherapy during pregnancy to treat a variety of hematologic malignancies. In this group, there were 32 mothers suffering from NHL and nine of them were treated with R-CHOP regimen. Six of their children developed late toxic complications in the form of severe infections. Although it was difficult to prove that rituximab therapy was the unique cause, the authors ceased to use it in the therapy of diffuse NHL in pregnancy (11).

Another major concern regarding the lymphoma treatment during pregnancy is postnatal development of children exposed to chemotherapy in utero and their long-term fertility. In the previously mentioned study, all children of the 32 mothers treated for NHL have had normal physiological, physical, and mental development during the nineteen-year-long observation. This study also partly addressed the issue of fertility; all children showed normal sexual development and 12 of them had become parents (11). A more recent study compered neurocognitive development of children exposed to chemotherapy in utero (n=35) with unexposed children (n=22) and confirmed that there were no significant differences (12).

CONCLUSION

To sum up, the diagnosis of lymphoma in pregnancy poses challenges for the patient and her family as well as for the medical team. Informed consent of the patient is required, and all treatment decisions should be made by a multidisciplinary medical team. Based mainly on small series and case reports it could be said that although the course of diffuse large B-cell lymphoma during pregnancy is often progressive and rapid, treatment with R-CHOP therapy can be considered after the first trimester, with reassuring maternal and fetal outcomes.

Authorship

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication.

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LEČENJE DIFUZNOG B-KRUPNOĆELIJSKOG NON-HOČKIN LIMFOMA U TRUDNOĆI: STUDIJA SLUČAJA I PREGLED LITERATURE

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Sažetak

Uvod: Hočkinov limfom je najčešće dijagnostikovan tip limfoma u trudnoći, dok je pojava non-Hočkin limfoma u trudnoći retka, budući da se oni najčešće javljaju nakon reproduktivnog perioda.

Prikaz slučaja: Prezentujemo slučaj tridesetšestogodišnje pacijentkinje koja je primljena u Kliniku za endokrinu hirurgiju u trinaestoj nedelji trudnoće zbog sumnje na postojanje limfoma štitaste žlezde. Pacijentkinja se javila sa simptomima respiratornog distresa, otežanog gutanja i otoka vrata. Nakon otvorene biopsije postavljena je histološka dijagnoza primarnog difuznog B-krupnoćelijskog non-Hočkin limfoma. Zaključak multidisciplinarnog stručnog tima je bio da se što pre započne sa R-CHOP terapijom, u šest do osam ciklusa. Od početka lečenja je prošlo pet godina, bolest je i dalje u remisiji, a dete se normalno razvija.

Zaključak: Limfomi u trudnoći predstavljaju izazov, kako za medicinski tim tako i za pacijenta. Uz ranu dijagnozu i odgovarajuću terapiju, uprkos svim rizicima, moguće je postići remisiju bolesti, bez ugrožavanja ploda.

Ključne reči: non-Hočkin limfom, trudnoća, hemioterapija

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