

Diagnosis and treatment of Waldenstrom's macroglobulinemia in a twin pregnancy

Brian Harrison, Mae-Lan Winchester

ABSTRACT

Introduction: Waldenstrom's macroglobulinemia (WM) is a rare neoplastic disease with bone marrow involvement and overproduction of immunoglobulin M (IgM). The clinical manifestations range from asymptomatic disease diagnosed incidentally to severe pancytopenia and hyperviscosity syndrome. This disease is incredibly rare in women of reproductive age, let alone pregnancy. **Case Report:** The patient presented here was diagnosed with WM during her first trimester. Due to disease severity, she required both plasmapheresis and rituximab. She delivered healthy twin infants vaginally at 34 weeks gestation, after induction of labor for preeclampsia with severe features. **Conclusion:** This case highlights the need for a high index of suspicion, and early multidisciplinary involvement to obtain good outcomes for the mother-fetal dyad.

Keywords: Lymphoma, Pregnancy, Waldenstrom's macroglobulinemia

How to cite this article

Harrison B, Winchester ML. Diagnosis and treatment of Waldenstrom's macroglobulinemia in a twin pregnancy. J Case Rep Images Obstet Gynecol 2020;6:100058Z08BH2020.

Brian Harrison¹, Mae-Lan Winchester²

Affiliations: ¹Kansas University School of Medicine, Kansas City, Kansas 66160, USA; ²Department of Obstetrics & Gynecology, Kansas University Medical Center, Kansas City, Kansas 66160, USA.

Corresponding Author: Brian Harrison, Kansas University School of Medicine, Kansas City, Kansas 66160, USA; Email: b130h147@kumc.edu

Received: 04 March 2020

Accepted: 30 April 2020

Published: 15 May 2020

Article ID: 100058Z08BH2020

doi: 10.5348/100058Z08BH2020CR

INTRODUCTION

Waldenstrom's macroglobulinemia (WM) is a lymphoplasmacytic lymphoma characterized by increased immunoglobulin M protein [1]. Epigenetic changes have been implicated in the pathophysiology of this condition [2]. Current therapy for this disease varies widely based on severity of symptoms and the individual patient, and asymptomatic patients are frequently not treated. These regimens include rituximab, cyclophosphamide, dexamethasone, bortezomib, and bendamustine, an alkylating agent that has been shown to be relatively safe and efficacious in multiple myeloma, among numerous additional agents [3, 4]. Current therapies are not curative, and patients eventually relapse [5]. The yearly incidence rate in million person years is 1.7 among women and 3.4 among men [6]. However, the incidence is much lower in women of reproductive age, with a yearly incidence of 0.1 new cases per million women <45 years old, and an incidence of 16.4 per million women >75. The exceedingly low incidence of WM makes a co-occurrence with pregnancy extremely rare, with only two previously published cases [7, 8].

CASE REPORT

We present a case of WM diagnosed and treated during pregnancy. The patient is a 30-year-old Caucasian female who initiated prenatal care for her second pregnancy. Her past medical, surgical, and family history were not significant. Specifically, the patient did not have a family history of WM. She established prenatal care at 12 weeks gestation and was noted to have a marked splenomegaly on physical exam and pancytopenia on routine prenatal complete blood count. Her hemoglobin was 9.1 mg/dL, white blood cells (WBCs) count was 2.8 K/uL,

and platelets were 134 K/uL. Further workup showed an abnormal kappa/lambda ratio (3.02) and an IgM level of 3200 mg/dL. Serum electrophoresis exhibited IgM kappa paraprotein, and a bone marrow biopsy demonstrated a lymphoplasmacytic proliferation (CD5 negative, CD10 negative, small B lymphocytes, and clonal plasma cells). Molecular studies did not detect MYD88 L265P mutation. Chromosomal analysis exhibited the following: 92-127,XXXX<4n>,del(1)(q32q42),add(19)(p13)x2[cp2]/46,xx[18]. Peripheral smear demonstrated pancytopenia with normochromic normocytic anemia, rouleaux formation, and red cell agglutination.

With her new diagnosis, she was placed on prophylactic low molecular weight heparin, which was continued through the postpartum period. She received weekly laboratory surveillance comprising of complete blood count, IgM levels, and viscosity levels. At 22 weeks of gestation, plasmapheresis was performed for new onset hyperviscosity symptoms of fatigue and left arm numbness with an IgM level over 5000 mg/dL and a blood viscosity of 1.7 cP. After plasmapheresis, the patient's IgM levels decreased to 1860 mg/dL. The patient then began therapeutic plasmapheresis every three weeks for four hours. She was also given 100 mg prednisone daily for five days following each plasmapheresis treatment in addition to rituximab 375 mg/m² every 56 days (received two cycles during her pregnancy). She had marked clinical and laboratory improvement with treatment. As is routine in our institution, fetal monitoring was performed during plasmapheresis. Fetal status always remained reassuring. In addition, growth of both fetuses remained within normal limits throughout gestation. At 34 weeks gestation, she was noted to have elevated blood pressures up to 170/95. She denied any associated symptoms including headache, shortness of breath, blurry vision, or abdominal pain. Laboratory workup for preeclampsia was significant for an alanine aminotransferase (ALT) of 85 u/L. Given this diagnosis of preeclampsia with severe features, induction of labor was performed. She delivered twin A spontaneously and twin B via forceps-assisted delivery due to non-reassuring fetal heart tones.

After delivery, the patient had a mild postpartum hemorrhage (estimated blood loss 600 mL), for which she received uterotonic agents and tranexamic acid. She was discharged home on postpartum day 3 in stable condition. However, the following day, the patient complained of left upper quadrant pain. She was noted to be tachycardic (120 bpm) and was readmitted for further evaluation. She had significant neutropenia (WBC 0.9 K/uL). Blood cultures ultimately grew *Clostridium perfringens*, suspected GYN source. She received intravenous (IV) piperacillin/tazobactam and clindamycin and demonstrated clinical improvement. Her leukopenia improved (3.2 K/uL).

Approximately four weeks after delivery, the patient started therapy with rituximab and bendamustine. She chose to forego breastfeeding in order to begin more aggressive therapy. Rituximab crosses the placenta and is present in human breast milk, though the relative infant

dose is expected to be 0.08%. It is unknown what effects bendamustine has on pregnancy and lactation, and as such, is not recommended.

Both of the patient's infants are doing well with no major complications. Twin A weighed approximately 2070 grams at birth and was in the neonatal intensive care unit (NICU) for 12 days. This child had some difficulty feeding and had a nasogastric tube placed for two days. Twin B weighed approximately 1500 grams and was in the NICU for 14 days. Neither child experienced any complications or infections, and both children were discharged home in stable condition.

Of note, consideration for an alternative diagnosis of splenic marginal zone lymphoma was made, but due to the patient's hyper IgM and associated hyperviscosity, her diagnosis is more consistent with WM.

DISCUSSION

Waldenstrom's macroglobulinemia is extremely rare in women of reproductive age. Co-occurrence with pregnancy has been reported twice in the literature, though to our knowledge this is the first case diagnosed during pregnancy, and the first case in pregnancy with a phenotype severe enough to require plasmapheresis and rituximab.

In 2015, Rady et al. reported a case of smoldering macroglobulinemia during pregnancy [7]. The patient's only symptom was persistent fatigue, and during the workup for fatigue she was found to have an elevated IgM with bone marrow involvement. The patient had an unplanned pregnancy several years after her diagnosis. She did not receive any treatment for her disease and delivered a healthy child at term.

In 1993, Cheung et al. reported on a case of WM in pregnancy in a patient who had hypergammaglobulinemic purpura [8]. She was diagnosed with this condition at 10 years of age and was treated with 15 milligrams of prednisone every other day both before and during her pregnancy. Her pregnancy was complicated by fetal growth restriction and ultimately delivered via cesarean section at 33 weeks gestation due to non-reassuring fetal status. Her WM remained stable through pregnancy and the postpartum period. At time of their publication, the patient was completing a 6-cycle treatment of bendamustine and was doing well, clinically.

The patient we present here had a markedly different clinical course than either of the cases discussed in the literature. In both prior cases the patients had already been diagnosed with WM before their pregnancies. Additionally, neither previous case demonstrated disease progression whereas this patient needed to begin therapeutic plasmapheresis due to the onset of hyperviscosity symptoms.

Waldenstrom's macroglobulinemia exists in both sporadic and familial forms. Up to 80% of patients have some form of chromosomal abnormality [9]. The

chromosomal changes in the sporadic and familial forms are similar, and an association with a deletion on the long arm of chromosome 6 has been found in up to 50% of patients [10]. The tumor suppressor *BLIMP 1* is found in this location and it is hypothesized that partial or complete deletion of these gene yields a genetic predisposition to WM. Given the patient had no family history of this disease, she is presumed to have the sporadic form of the disease. The patient has not yet had genetic testing performed on any of her children. Relapse is almost inevitable for patients with WM, and research is lacking on guidance for subsequent pregnancies. The manufacturers of her current therapy, bendamustine, advise avoiding conception for at least six months after treatment.

This case highlights the need for increased investigation of rare hematological diseases in pregnancy. The differential for asymptomatic splenomegaly and pancytopenia in pregnancy is broad. In this case, early aggressive workup led to the diagnosis of WM. This allowed a plan of treatment to be developed early in pregnancy and raised suspicion and awareness for the development of related symptoms and disease comorbidities.

CONCLUSION

The patient presented in this case provides a look at the unique intersection of a rare lymphoplasmacytic lymphoma with a twin pregnancy. The patient underwent significant workup during her pregnancy to reach the diagnosis, and her treatment course was significantly altered by pregnancy. Ultimately, conservative and symptomatic management was provided over the course of the pregnancy in the form of rituximab and plasmapheresis until the delivery of healthy twins. After delivery, the patient chose to forego breastfeeding in order to start more definitive therapy with bendamustine.

REFERENCES

1. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. *Blood* 1994;84(5):1361–92.
2. Sacco A, Issa GC, Zhang Y, et al. Epigenetic modifications as key regulators of Waldenstrom's Macroglobulinemia biology. *J Hematol Oncol* 2010;3:38.
3. Leblond V, Kastritis E, Advani R, et al. Treatment recommendations from the Eighth International Workshop on Waldenström's Macroglobulinemia. *Blood* 2016;128(10):1321–8.
4. Naymagon L, Abdul-Hay M. Novel agents in the treatment of multiple myeloma: A review about the future. *J Hematol Oncol* 2016;9(1):52.
5. Castillo JJ, Olszewski AJ, Kanan S, Meid K, Hunter ZR, Treon SP. Overall survival and competing

risks of death in patients with Waldenström macroglobulinaemia: An analysis of the Surveillance, Epidemiology and End Results database. *Br J Haematol* 2015;169(1):81–9.

6. Groves FD, Travis LB, Devesa SS, Ries LA, Fraumeni JF Jr. Waldenström's macroglobulinemia: Incidence patterns in the United States, 1988–1994. *Cancer* 1998;82(6):1078–81.
7. Rady K, Wallace E, Seymour JF. An uncomplicated pregnancy in a woman with smoldering Waldenström macroglobulinemia. *Leuk Lymphoma* 2015;56(7):2222–4.
8. Cheung VY, Bocking AD, Hollomby D, Gagnon R, Walton J. Waldenström hypergammaglobulinemic purpura and pregnancy. *Obstet Gynecol* 1993;82(4 Pt 2 Suppl):685–7.
9. Poulain S, Braggio E, Roumier C, et al. High-throughput genomic analysis in Waldenström's macroglobulinemia. *Clin Lymphoma Myeloma Leuk* 2011;11(1):106–8.
10. McMaster ML, Giambarresi T, Vasquez L, Goldstein AM, Tucker MA. Cytogenetics of familial Waldenström's macroglobulinemia: In pursuit of an understanding of genetic predisposition. *Clin Lymphoma* 2005;5(4):230–4.

Acknowledgments

We thank our anonymous patient and her desire to contribute to this field for the betterment of others.

Author Contributions

Brian Harrison – Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Mae-Lan Winchester – Conception of the work, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

Copyright

© 2020 Brian Harrison et al. This article is distributed under the terms of Creative Commons Attribution

License which permits unrestricted use, distribution and reproduction in any medium provided the original author(s) and original publisher are properly credited. Please see the copyright policy on the journal website for more information.

Access full text article on
other devices



Access PDF of article on
other devices

