Scientific Research Publishing

Case of Refractory Thrombocytopenia in Pregnancy Associated with May-Heglin Anomaly after Repeated Platelet Transfusions

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Abstract

May-Heglin Anomaly is an autosomal dominant disorder characterized by macrothrombocytopenia with a platelet function that is usually preserved. Platelets play an essential role in hemostasis. During pregnancy, a woman is susceptible to complications, including postpartum hemorrhage. Monitoring patients' hemostatic functions and observing the patient's clinical picture to maintain patient safety is paramount, while avoiding unnecessary therapeutic measures. This case report presents a rare instance of May-Heglin Anomaly (MHA) in a 35-year-old pregnant patient, with refractory thrombocytopenia despite receiving multiple platelet transfusions. Initially referred to as gravida 5 para 4 with severe thrombocytopenia at 28 weeks gestation, throughout her pregnancy, she was closely monitored and received over 40 units of platelets, which failed to increase her platelet count significantly. She delivered a healthy baby via vaginal delivery at 38 weeks, with her platelet count still critically low. This report highlights the challenges of managing MHA in pregnancy, the inefficacy of standard thrombocytopenia treatments such as platelet transfusion in MHA patients, and the importance of tailored management strategies to ensure maternal and fetal safety.

Keywords

Platelets, Pregnancy, Macrothrombocytopenia, MHA

1. Introduction

Platelets play a crucial role in normal hemostasis, aiding blood loss limitation following vascular injury. During pregnancy, their importance is heightened,

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particularly in preventing excessive bleeding during and immediately after childbirth. Maintaining normal platelet function and levels is a vital aspect of prenatal care. Healthcare providers routinely monitor platelet counts and may recommend appropriate treatments if levels fall below the acceptable range [1].

Throughout pregnancy, thrombocytopenia is a relatively common hematologic condition. A platelet count below 150,000/μL has been reported in 6% to 15% of pregnant women, and 1% have a platelet count below 100,000/μL [2]. There are a variety of causes of thrombocytopenia, such as immune thrombocytopenic purpura (ITP), pre-eclampsia (PE), and Hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome, and most commonly gestational thrombocytopenia (GT) accounting for 75% of the affected cases. Rarely, other conditions might affect the platelet count during pregnancy [2].

Macrothrombocytopenia describes the phenomena of a low platelet count (<150,000/lL) with an increased platelet size (>12 fl). It may be inherited or acquired, and inherited macrothrombocytopenia is less prevalent. The clinical spectrum of Inherited macrothrombocytopenia (IMTPs) has various mutations and clinical presentations and is frequently misdiagnosed as immune thrombocytopenia.

Autosomal dominant MYH9-related disease (MYH9RD) is the most commonly occurring IMTP. Mutations in the myosin heavy chain nine gene lead to the premature release of platelets from the bone marrow, causing the characteristic macrothrombocytopenia and leukocyte inclusion bodies [3].

Most patients with MYH9-related disease do not exhibit clinically significant bleeding and are often diagnosed incidentally. These individuals typically do not require specific treatment. However, in rare instances of severe bleeding, platelet transfusions may be necessary. Prophylactic platelet transfusions may be warranted before surgical procedures, and consultation with a hematologist is recommended. The use of corticosteroids, immunosuppressive agents, or splenectomy is not indicated in these cases [4].

This case report aims to describe a rare presentation of MYH9-related disease (MYH9RD) during pregnancy and to highlight the importance of early diagnosis and appropriate management. The objective is to detail the clinical presentation, diagnosis, and management of a pregnant patient with MYH9RD, a rare and frequently misdiagnosed condition.

2. Case Report

A 35-year-old Pakistani was referred from the local health center, to the Obstetrics and Gynaecology emergency in Salmaniya Medical Complex (SMC) as a gravida 5 para 4 at 28 + 1 weeks of gestation. She was referred to as a case of thrombocytopenia with a platelet level of 6000 platelets per microliter (6000/μL). Her previous platelet levels ranged from 20,000 plt/μL to 60,000 plt/μL. She was admitted for further workup.

The patient was clinically free, giving no history of any bleeding, menorrhagia, bruising, ecchymosis or petechiae. She was diagnosed with May Hegglin Ano-

maly (MHA) in Bahrain Defence Force (BDF) hospital during her previous pregnancy.

Upon examination, the patient was clinically well and vitally stable, with generalized skin discolourations noted throughout her body, which was non-palpable, non-tender, and non-blanching. The obstetric ultrasound showed a single live fetus with normal anthropometric values corresponding to gestational age (Table 1).

Table 1. Lab investigations.

Blood group	B+
White blood cell count	6.36 plt/μL
Platelets	checked manually and were found to be 45 giant platelets
Hemoglobin	10.6 grams per deciliter (g/dL)
Coagulation Profile	Normal
Liver function test (LFT)	Normal
Vitamin B12	134.6 picograms per milliliter (pg/mL)
Hepatitis B surface antigen	Negative
Peripheral smear	Thrombocytopenia with many giant platelets and normocytic anemia with no RBC fragmentation

As advised by hematology, the patient was discharged on vitamin B12 supplements because of her vitamin B12 deficiency, and the patient should have her CBC checked manually before delivery to keep the platelet level above 50 and if they are less than 50 to transfuse six units of platelets to the patient.

The patient had multiple admissions with the complaint of sluggish fetal movement, first at 31 weeks, then at 36 weeks of gestation, and at both times, she was discharged after confirming both maternal and fetal well-being, and she did not have any bleeding manifestation during the antenatal period. She was advised on admission for induction of labor between 37 to 38 weeks, and she presented at 38 + 3 weeks of gestation for admission.

Upon admission, her platelets were manually checked and found below 50,000 plt/μL. She received 42 units of platelets and three doses of prednisolone; however, there was no improvement in her platelet count. She delivered a healthy female baby via normal vaginal delivery, with a birth weight of 2.7 kg. Her postpartum period was uneventful. She was discharged on a vitamin B12 regimen to manage her deficiency and prednisone despite her low platelet count of 27,000 plt/μL. She was advised to follow up in the hematology clinic as she was clinically stable.

The patient presented for a routine postnatal follow-up, was asymptomatic, and had a platelet count of 30,000/μL.

3. Discussion

MHA is an autosomal dominant disease characterized by a variable degree of thrombocytopenia, giant platelets and blue inclusion bodies in leukocytes, which results from the deposition of myosin heavy chain (MHC) within white blood cells. The presence of the inclusion bodies on leukocytes in comparison to platelets differentiates MHA from immune thrombocytopenia. In 1909, May reported the first asymptomatic woman with giant platelets and sky-blue crescent-shaped inclusion bodies within the cytoplasm of leukocytes. Hegglin, in 1945, found white blood cell inclusion bodies and large platelets in a family with mild bleeding symptoms. The incidence of this anomaly is unknown, but less than a hundred cases are reported in the literature. The clinical manifestations of MHA vary from mild to severe bleeding. Clinically, MHA may present as epistaxis, easy bruising, gum bleeding, heavy menstrual bleeding and postoperative bleeding [5].

The MYH9 gene is located on chromosome 22q11.2, consisting of 40 exons and encodes human non-muscle myosin heavy chain IIA (NMMHC-IIA), a polypeptide with 1960 amino acids, which is part of an enzyme complex that binds actin, has ATPase activity and is required for motor activity in many different tissues including platelets, leukocytes, kidneys and the cochlea. There are three distinct isoforms: MYH9 (NMMHC-IIA), MYH10 (NMMHC-IIB) and MYH14 (NMMHC-IIC). Platelets express only the NMMHC-IIA protein. To date, more than 30 MYH9 mutations have been described. The degeneration of the actin cytoskeleton may be responsible for all the phenotypic alterations induced by the depletion of NMMHC-IIA and the elimination of its motor function [6].

MHA is diagnosed by the presence of macrothrombocytes and granulocyte inclusion bodies in blood smears stained with May-Grunwald-Giemsa (MGG) [6].

Routine inspections of blood smears and automated blood analyzers sometimes dismiss giant platelets as microcytic red blood cells or their fragments, causing an underestimation of the mean platelet volume (MPV) and the misdiagnosis of patients with macrothrombocytopenia. The hematology counter ADVIA120 has a two-dimensional method of light scattering measurements to simultaneously assess platelet size and density, yielding a more accurate estimate of platelet volume. The ADVIA120 identified four patients with hereditary macrothrombocytopenia from 112 patients previously diagnosed with ITP [7].

MYH9 gene mutations can be identified by detecting the granular localization of NMMHC-IIA in neutrophils using an immunofluorescence assay [6].

Molecular analysis provides an accurate diagnosis for optimal treatment and appropriate genetic counseling [8].

Platelet function and lifespan are typically normal in MHA, and the platelet count can vary from 10×10^9 cells/l to normal values. Electron microscopy examination of platelets reveals an irregular lentiform morphology due to aberrant microtubule structure. Megakaryocytes in the bone marrow are normal.

Aberrant megakaryocyte fragmentation is believed to be the root cause of thrombocytopenia [5].

In a review of 26 articles involving 40 women, 75 pregnancies, and five twin pregnancies, 11 women had incidental thrombocytopenia during routine antenatal screening. Of these, five women were misdiagnosed as ITP and three underwent splenectomy for resistant ITP.PPH was reported in four pregnancies; three were primary PPH, one managed by blood transfusions, the other had platelet and cryoprecipitate transfusion and the third was managed conservatively, as was the case of secondary PPH. MHA can be challenging with possible maternal and fetal adverse outcomes; hence, joint management by obstetricians and hematologists is required to minimize these risks [5].

The perinatal management of pregnant women with *MYH9* disorders involves getting an accurate diagnosis, genetic counseling, management of delivery with rapid blood access, and management of complications based on genetic testing. Genetic counseling should include discussing the mode of inheritance and the investigations needed for the patient and the baby, emphasizing the importance of genetic analysis, and an explanation of the potential delivery risks for pregnant women with *MYH9* disorders and their babies.

Hussein *et al.* reported that 79% of pregnant patients with *MYH9* disorders delivered their babies without hemostatic prophylaxis, with 5% being complicated by massive PPH. Concerning the mode of delivery, 55% of the cases had vaginal delivery, 4% had forceps delivery, 24% had elective Caesarian section, and emergency Caesarian section was required in 15%. The mean blood loss during the deliveries was 600 mL. Four pregnancies showed that three had PPH with *MYH9* disorders; in one patient, transfusion was needed in her first and second deliveries, and the others were treated conservatively. Concerning infant outcomes, 44% showed similar phenotypes to their mothers. None of the babies suffered from bleeding during the delivery. Pregnant patients should receive perinatal care where blood transfusions are rapidly performed, if necessary, with close cooperation among pediatricians, hematologists, nephrologists, and anesthesiologists. If the patient has no history of severe bleeding, vaginal delivery is permitted. For patients with a platelet count above $5.0 \times 10^4/\mu L$, special delivery management is not necessary for patients with an *MYH9* disorder, except for rapid blood access [9].

Vaginal delivery is permitted in MHA. Prophylactic platelet transfusion is not required without a bleeding diathesis and if bleeding times are normal. Nonetheless, platelets should be available for transfusion in the event of unusual bleeding [10].

With regards to the anesthesia used with MHA during delivery, some studies illustrated the uncomplicated use of neuraxial anesthesia, others described uncomplicated spinal anesthetic with cesarean delivery, others involved uncomplicated general anesthesia with cesarean delivery, and some avoided neuraxial anesthesia during normal delivery due to severe thrombocytopenia. Some authors favored cesarean deliveries to avoid possible neonatal hemorrhagic com-

plications during normal delivery in the case of thrombocytopenia. In contrast, others prompted vaginal delivery in the absence of bleeding or platelet dysfunction. The most recent guidelines for obstetrical anesthesia from the American Society of Anesthesiologists indicated that routine platelet count could not predict anesthesia-related complications in the uncomplicated parturient. Platelet function is usually preserved in patients with MHA, even with severe thrombocytopenia, signifying that adequate clinical coagulation relies on adequate platelet function instead of platelet count [11].

In the case of MHA, a woman with severe thrombocytopenia with a platelet level of 16,000/mm^3, regional anesthesia was avoided, and instead, intravenous patient-controlled analgesia consisting of fentanyl was used. The patient delivered by normal vaginal delivery, with an estimated blood loss of 300 mL [12].

In another case, severe macrothrombocytopenia and MHA were documented in monochorionic twins delivered at 32 weeks of gestation to a mother with MHA. Their serial hemostatic assessments through a viscoelastic system and thromboelastography demonstrated functionally normal primary hemostasis and coagulation cascade. Thus, prophylactic and unnecessary PLT transfusions were avoided. This report supports the implementation of viscoelastic assays for the hemostatic monitoring [13].

A 22-year-old woman previously diagnosed with ITP was initially managed with oral prednisone for four weeks, followed by intravenous methylprednisolone for three days, and then by intravenous immunoglobulin and anti-D for persistent thrombocytopenia not responding to treatment. She was considered a candidate for splenectomy. Pre-operative hematological workup showed thrombocytopenia with hypochromic microcytic red blood cells, and her peripheral blood smear illustrated macrothrombocytes. Her platelet count was re-evaluated and found to be higher through peripheral blood smear and hemocytometer; hence, splenectomy was not indicated anymore [14].

The guidelines for diagnosing and treating ITP indicate that it is a diagnosis made by excluding other causes of thrombocytopenia, such as inherited thrombocytopenias. Patients with inherited or constitutional thrombocytopenia are usually asymptomatic and diagnosed incidentally during routine blood counts, and negative family history does not exclude the possibility of inherited thrombocytopenias since some disorders are transmitted recessively while most cases are sporadic. In a study, eight of 19 consecutive patients with MYH9-related disease (MYH9-RD) had unaffected parents. In another study, 11 cases of 170 previously diagnosed as ITP were affected by inherited thrombocytopenias, yet all had splenectomies, steroids and IVIG for retractable ITP. In another study, seven of 46 consecutive subjects with inherited thrombocytopenias had splenectomies since they were misdiagnosed with ITP. These studies have signified the importance of identifying reliable tests to differentiate between ITP and inherited thrombocytopenias, such as the presence of autoantibodies, yet they have low specificity [15].

4. Conclusion

The diagnosis of MHA is initially based on simple diagnostic measures such as the peripheral smear and is confirmed through molecular diagnosis. However, physicians should maintain clinical suspicion to avoid unnecessary and potentially invasive therapeutic measures, such as splenectomies. A clinical correlation between the patient's clinical presentation and the hemostatic status demonstrated by laboratory results should be established. The presence of platelet autoantibodies, although not specific to Immune Thrombocytopenic Purpura (ITP), has been found in the literature to be associated with some cases of MHA. Our patient was not screened for such autoantibodies, which may have explained her lack of response to the significant number of platelet transfusions she received.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Boothman, L. (2016) Platelets in Pregnancy: Their Role and Function in Disease. *British Journal of Midwifery*, **24**, 550-555. https://doi.org/10.12968/bjom.2016.24.8.550

[2] Valera, M., Parant, O., Vayssiere, C., Arnal, J. and Payrastre, B. (2010) Physiologic and Pathologic Changes of Platelets in Pregnancy. *Platelets*, **21**, 587-595. https://doi.org/10.3109/09537104.2010.509828

[3] Ghosh, K., Bhattacharya, M., Chowdhury, R., Mishra, K. and Ghosh, M. (2018) Inherited Macrothrombocytopenia: Correlating Morphology, Epidemiology, Molecular Pathology and Clinical Features. *Indian Journal of Hematology and Blood Transfusion*, **34**, 387-397. https://doi.org/10.1007/s12288-018-0950-0

[4] Sehbai, A.S., Abraham, J. and Brown, V.K. (2005) Perioperative Management of a Patient with May-Hegglin Anomaly Requiring Craniotomy. *American Journal of Hematology*, **79**, 303-308. https://doi.org/10.1002/ajh.20446

[5] Hussein, B.A., Gomez, K. and Kadir, R.A. (2013) May-Hegglin Anomaly and Pregnancy. *Blood Coagulation & Fibrinolysis*, **24**, 554-561. https://doi.org/10.1097/mbc.0b013e32835fad03

[6] Provaznikova, D., Geierova, V., Kumstyrova, T., Kotlin, R., Mikulenkova, D., Zurkova, K., *et al.* (2009) Clinical Manifestation and Molecular Genetic Characterization of *MYH9* Disorders. *Platelets*, **20**, 289-296. https://doi.org/10.1080/09537100902993022

[7] Gohda, F., Uchiumi, H., Handa, H., Matsushima, T., Tsukamoto, N., Morita, K., *et al.* (2007) Identification of Inherited Macrothrombocytopenias Based on Mean Platelet Volume among Patients Diagnosed with Idiopathic Thrombocytopenia. *Thrombosis Research*, **119**, 741-746. https://doi.org/10.1016/j.thromres.2006.06.011

[8] Kim, B. (2022) Diagnostic Workup of Inherited Platelet Disorders. *Blood Research*, **57**, S11-S19. https://doi.org/10.5045/br.2022.2021223

[9] Yamashita, Y., Matsuura, R., Kunishima, S., Oikawa, Y., Ariizumi, H., Hamada, S., *et al.* (2016) Perinatal Management for a Pregnant Woman with an *MYH9* Disorder. *Case Reports in Obstetrics and Gynecology*, **2016**, Article ID: 6730174.

https://doi.org/10.1155/2016/6730174

[10] Chabane, H., Gallais, Y., Pathier, D., Tchernia, G. and Gaussem, P. (2001) Delivery Management in a Woman with Thrombocytopenia of the May-Hegglin Anomaly Type. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, **99**, 124-125. https://doi.org/10.1016/s0301-2115(01)00349-9

[11] Fishman, E.B., Connors, J.M. and Camann, W.R. (2009) Anesthetic Management of Seven Deliveries in Three Sisters with the May-Hegglin Anomaly. *Anesthesia & Analgesia*, **108**, 1603-1605. https://doi.org/10.1213/ane.0b013e31819d1e71

[12] Urato, A.C. and Repke, J.T. (1998) May-Hegglin Anomaly: A Case of Vaginal Delivery When Both Mother and Fetus Are Affected. *American Journal of Obstetrics and Gynecology*, **179**, 260-261. https://doi.org/10.1016/s0002-9378(98)70283-2

[13] Amodeo, I., Raffaeli, G., Vianello, F., Cavallaro, G., Cortesi, V., Manzoni, F., *et al.* (2021) Individualized Bleeding Risk Assessment through Thromboelastography: A Case Report of May-Hegglin Anomaly in Preterm Twin Neonates. *Children*, **8**, Article 878. https://doi.org/10.3390/children8100878

[14] Ghorbani, M., Niazkar, H.R., Ejtehadi, M.M., Mahmoudi, R. and Abbasnezhad, A. (2018) Can Macrothrombocytopenia Mislead the Treatment of Idiopathic Thrombocytopenia Purpura? *Iranian Journal of Blood & Cancer*, **10**, 133-135.

[15] Noris, P., Klersy, C., Zecca, M., Arcaini, L., Pecci, A., Melazzini, F., *et al.* (2009) Platelet Size Distinguishes between Inherited Macrothrombocytopenias and Immune Thrombocytopenia. *Journal of Thrombosis and Haemostasis*, **7**, 2131-2136. https://doi.org/10.1111/j.1538-7836.2009.03614.x