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Case Report

May-Hegglin Anomaly, a Familial Thrombocytopenia in Pregnancy is No More Benign: A Case Report

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Abstract

Introduction: May-Hegglin anomaly is an autosomal dominant disorder characterized by varying degrees of thrombocytopenia that may be associated with easy bruising, recurrent epistaxis, gingival bleeding, menorrhagia and sometimes excessive bleeding may happen with surgical procedures. In the peripheral morphology one can see giant platelets containing few granules, and large basophilic, cytoplasmic inclusion bodies (resembling Dohle bodies) in the granulocytes. It is a rare cause of familial thrombocytopenia. The effect of May-Hegglin anomaly on pregnancy and its outcome is not clearly known, our knowledge is mainly based on case reports.

Case Presentation: A 27 years old primigravida lady who had been diagnosed to have idiopathic thrombocytopenic purpura was admitted to our maternity ward with the diagnosis of preterm premature/prelabor rupture of membrane at gestational age of 33 weeks. She had been on high dose predensolone (60mg PO per day) for 4months. A detail history reviled her personal and family history of epistaxis and menorrhagia and may-hegglin anomaly was confirmed after repeating the peripheral morphology and workup of family members. The patient had severe abruption with intrauterine fetal death and she survived postpartum hemorrhage. She was discharged with strict counseling of danger signs. At a postpartum follow up visits, the thrombocytopenia improved gradually and steroid was tapered and discontinued. In her second pregnancy; she had severe thrombocytopenia; preterm premature /prelabor rupture of membrane followed by moderate placental abruption and caesarian section was done for fetal distress. Neonatal and maternal outcomes were good at second pregnancy.

Conclusion and Recommendation: May-Hegglin anomaly should be considered in the differentials of severe thrombocytopenia especially if it is not responding for steroid therapy. The diagnosis needs high level of suspicion. Detail past medical and menstrual history and family history will give a clue. Failure to diagnose will result inappropriate treatment. Complications such as recurrent premature/prelabor rupture of membrane; recurrent moderate to severe placental abruption; intrauterine fetal death and postpartum hemorrhage may happen in pregnancy. Steroid therapy and splenectomy are unnecessary and harmful interventions.

Keywords: *Familial Macrothrombocytopenia; May Hagglin Anomaly; Pregnancy*

Abbreviations

MHA: May Hagglin Anomaly; CBC: Complete Blood Count; ITP: Idiopathic Thrombocytopenic Purpura; MPV: Mean Platelet Volume

Introduction

May-Hegglin anomaly is an autosomal dominant disorder characterized by varying degrees of thrombocytopenia [1]. Patients have a mutation of MYH9 gene present in chromosome 22q12-13 [2]. The mutation results in disordered production of non-muscle myosin heavy chain type IIA. This leads to macro-thrombocytopenia secondary to defective megakaryocytic maturation and fragmentation [1]. In 1909, German physician 'May' described a young female patient who had leukocytic inclusions, who was asymptomatic. In 1945, Swiss doctor Hegglin described a father and his two sons who had a triad of thrombocytopenia, giant platelets, and leukocytic inclusions as a rare cause of familial thrombocytopenia [3].

Four overlapping syndromes, known as May-Hegglin anomaly, Epstein syndrome, Fechtner syndrome and Sebastian syndrome describe different clinical manifestations of MYH9 gene mutations. Macrothrombocytopenia is present in all affected individuals, whereas only some develop additional clinical manifestations such as renal failure, hearing loss, and presenile cataracts [4,5]. The prevalence of MYH9-related disorders is probably underestimated because of underreporting and frequent misdiagnosis [4]. The effect of May-Hegglin anomaly on pregnancy and its outcome is not clearly known, our knowledge is mainly based on case reports and systemic review of few case reports. The rarity of MHA has led to conflicting literature regarding the risk for bleeding and management in pregnant women. This case report may add some fact in the clinical presentation and approach to patients with MHA in pregnancy.

Case Presentation

This is a 27 years old primigravida lady referred to our maternity ward with the diagnosis preterm premature rupture of membrane after she complains passage of liquor of 11 hours duration. The gestational age of the pregnancy was 33 weeks from early ultrasound. She had regular antenatal care at nearby primary hospital, a total of 3 visits. She was vaccinated with tetanus toxoid two times and she was on therapeutic iron for the three months. She was told to be nonreactive for serologic test of syphilis, retroviral infection and hepatitis B and C virus.

In addition, she had one visit to tertiary hospital after she experience exacerbated profuse nasal bleeding and gum bleeding of one month duration, at that time, peripheral morphology and bone marrow aspiration done and she was diagnosed to have severe thrombocytopenia secondary to idiopathic thrombocytopenic purpura. She was transfused with platelets and had been on prednisolone 60 mg/day for four months after hematologist consultation. She also had multiple course of treatment with different antibiotics for atypical pneumonia. Before her pregnancy, she had a long history of heavy menstrual bleeding and intermittent nasal bleeding but she did not seek care. She also had family members with intermittent spontaneous bilateral nasal bleeding and gum bleeding. She had no history of joint swelling, easy bruising or skin color changes. No drug or herbal medication intake. The pregnancy was planned, wanted and supported. At the time of admission, she presented with the chief complaint of a sudden gush of clear fluid per vagina while she was on bed-rest. She had no fever, chills or rigor. She also had no headache, blurring of vision, vaginal bleeding or other danger symptoms. She was feeling fetal movements regularly.

On physical examination, she had typical moon face (cushingoid face). As to her vital signs; Temperature was 36.4 degree Celsius, respiratory rate was 20 breaths per minute, pulse rate was 76 beats per minute and blood pressure was 110/70 mmHg at brachial artery. She had pink conjunctiva and white sclera. No lymphadenopathy, no neck mass and no breast mass or nipple retraction. Chest and Pericardial exam was non-revealing. Upon abdominal examination; she had no organomegaly, no signs of fluid collection. Leopold examinations revealed; 34 weeks sized gravid uterus, longitudinal lie and fetal back was on the left, cephalic presentation with flexed attitude. Fetal heart rate was 144 beats per minute. No uterine contraction, no abdominal tenderness. She had watery, non-foul smelling vaginal discharge wetting her perineum. No vaginal bleeding. Sterile speculum exam showed leakage through closed cervix and pooling in posterior fornix but no fetal cord or membrane. She had petechial skin rash on abdomen and extremities but no bruising or purpura. There was no pedal edema. She was conscious and oriented to person, place and time. Deep tendon reflex was 2/4 and no motor weakness or sensory loss.

Bedside ultrasound showed singleton viable intrauterine pregnancy with 33 weeks of gestational age. Cephalic presentation and estimated fetal weight was 2300grams. Biophysical profile was reassuring. Complete blood count (CBC) showed white blood cells of 16,800/microliter, hemoglobin was 11gm/dl, and platelet count 14,000/microliter, Urine analysis was non-revealing, her blood group was O+. Mean platelet volume (MPV) was 17fl and there was abnormal platelet distribution (See figure 1A and 1B). Liver function test showed serum glutamic pyruvic transaminase (SGPT) of 21 IU/L, serum glutamic oxaloacetic transaminase (SGOT) of 25 IU/L, alkaline phosphatase (ALP) of 359, total bilirubin of 1.2 mg/dl and Lactate dehydrogenase (LDH) was 334 IU/L. Renal function test was found to be blood urea and nitrogen of 17 mg/dl, and serum creatinine was 0.64 mg/dl. Her Prothrombin Time was 13.2 seconds and Partial Thromboplastin Time 39 seconds. Peripheral morphology was repeated that showed large (about 4 micrometer) and giant (about 7 micrometer) thrombocytes and leukocyte inclusion body (See figure 2A and 2B).

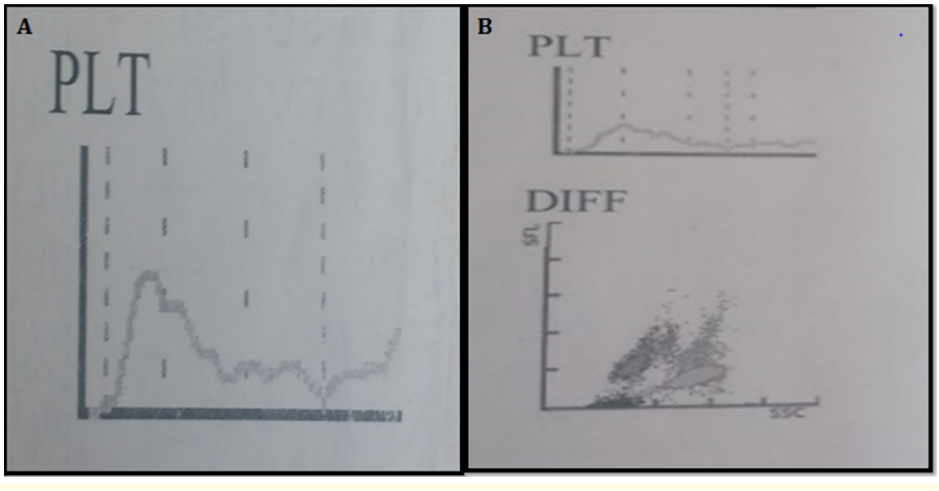

Figure 1: *The histogram of platelet and white blood cells in a patient with May Hagglin Anomaly, (A) abnormal distribution of platelet typical of broad distribution, (B) see the peak of platelet distribution precedes the peak of white blood cells.*

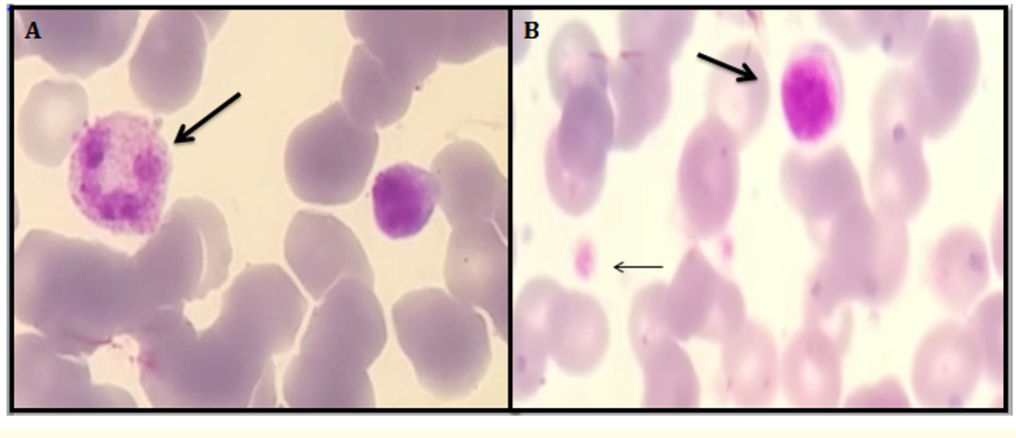

Figure 2: *Peripheral morphology of a patient with MHA, (A) note the mature granulocyte with multiple inclusion body (thick arrow), (B) note the large platelet with ill-defined granules (thin arrow) and giant platelet to the size of RBCs (thick arrow).*

She was admitted to maternity ward with the impression of preterm premature rupture of membrane plus May hagglin anomaly as a familial macro-thrombocytopenia rather than ITP was considered. She was put on Ampicillin 2 gram IV QID and erythromycin 500 gram PO TID as prophylaxis. Dexamethasone 6mg IM BID was started for fetal lung maturity. Prednisolone 60 mg/day PO was continued to avoid adrenal crisis. Further plan was to induce labor after completing the dexamethasone. However, after 14 hours of admission, she developed massive vaginal bleeding and abdominal pain. After maternal resuscitation measures had taken fetal heart beat was found to negative. She delivered vaginaly a stillborn within one hour of the diagnosis of severe abruption. Following the delivery, she developed postpartum hemorrhage that was managed medically and transfusion of three units of whole blood. At the second postpartum day, platelet was 24,000/microliter and her hemoglobin was 9.8 gm/dl. Based on her history, physical examination and investigation, the diagnosis of MHA was made, patient and her family was counseled. At the third postpartum day, she was discharged with strict counseling about the need for further workup.

She had close follow-up. CBC and renal function were done. White blood cells were ranging from 12,000 - 32000/microliter. Platelet count was in the mild range of thrombocytopenia (between 100,000 - 150,000/microliter). On follow up; she had gradual increment in platelet count and prednisolone was tapered and discontinued within two months of follow up. She was counseled about methods of family planning and Norplant was inserted. CBC of her sister who was having bleeding diathesis was found to be thrombocytopenic (97,000/microliter).

After two years of follow-up, she conceived her second pregnancy. She was having intermittent nasal and gingival bleeding which responds to conservative management such as frequent tooth brush and nasal packing. Her platelet count was in the mild range of thrombocytopenia in the first half of the pregnancy. But in the second half of pregnancy, her platelet count had decreased to the level of 37,000/microliter. She was not given steroid or platelet in this gestation. At 36weeks of gestation, she presented with premature rupture of membrane of 4 hours duration which later associated with lower abdominal pain and admitted with the diagnosis of latent stage of labor. Then after, she developed vaginal bleeding due to placental abruption. Caesarian section was done for the indication of severe fetal bradycardia secondary to moderate placental abruption. It was done under general anesthesia. The surgery was uneventful. There was no postpartum maternal or neonatal complication. The new born had normal platelet count (178,000/microliter) and there was no bleeding from the umbilical stamp. The woman was discharged at fourth postpartum day with stable condition.

Discussion

MHA is a rare autosomal dominant disorder. The exact incidence of the syndrome is unknown [3]. As to the literature review, there are few cases from Europe, United States and Asia. The incidences of thrombocytopenia vary in patient with May hagglin anomaly, it ranges from 50-100% of patients, some patients may be asymptomatic and severe bleeding is unusual. Patients may experience easy bruising, recurrent epistaxis, gingival bleeding, menorrhagia and sometimes excessive bleeding associated with surgical procedures. Fatal bleeding has not been reported in this syndrome [1,3,5,6]. In the case presented, she had recurrent epistaxis, gingival bleeding, menorrhagia and recurrent excessive vaginal bleeding associated with labor and delivery which make unusual.

A careful evaluation of platelet and granulocyte morphology is important for the laboratory diagnosis of MHA. All modern cell counters determine the MPV and most machines also generate a histogram showing size distribution of platelets. An MHA-related macrothrombocytopenia should be suspected in individuals that have large platelets, a high MPV, a broad platelet histogram, and a peak preceding the leukocyte histogram [4,6]. In the reported case, the machine was not including large platelets in the count and MPV was ranging from 14.7 - 18fl. When MPV was high, the machine didn't include in the report. In addition there was abnormal distribution of platelet on histogram which is broad (See figure 1A) and the peak of platelet precede the peak of leukocyte histogram (See figure 1B).

In the approach of individuals with an MHA disorder, it is important to be aware of the risk of obtaining an artifactually low platelet count by standard automatic particle counters as the large platelets are often counted as red blood cells or leukocytes. Thus, platelet and

white blood cell enumeration should be performed manually, especially when the individual also has "leukocytosis" [4,7]. In our case report, she was having persistent leukocytosis that was misdiagnosed as bacterial infection and she was mismanaged with antibiotics repeatedly. However, patients with MHA are not at increased risk of infections [3].

The association of macrothrombocytopenia and one or more of the recognized clinical presentations, are the minimal diagnostic criteria highly suggestive of MYH9-related disorder. Platelet counts are typically in the range of 20 - 130,000/microliter and most patients show an elevated mean platelet volume and a conspicuous population of very large platelets [1,5,6,8]. These findings are similar to the case presented. The absence of nephritis, cataract and blindness in the presented case may suggest May hagglin anomaly rather than Fechtner syndrome, Epstein syndrome or Sebastian syndrome. However, definitive diagnosis requires the demonstration of a causative mutation within MYH9 gene.

The diagnosis of MHA was missed and ITP was considered frequently [4,8]. The same thing happened to our case even after peripheral morphology was done. This is due to failure to take detail personal and family history and lack of high degree of suspension. ITP is a diagnosis of exclusion that should be considered after exhausting the differentials [9]. The patient had long lasting heavy menstrual bleeding and intermittent epistaxis. She also had family history of similar complaints (her brother and sister) which make ITP unlikely in this case. In addition, the patient was started on high dose steroid in the first pregnancy. But she was not responding for it. The use of high dose steroid or MHA itself (as disordered of non-muscle myosin heavy chain production) may explain the development of preterm premature rupture of membrane that caused severe abruption, fetal death and postpartum hemorrhage. Although uteroplacental vascular thrombosis couldn't explain the sudden stillbirth in this case, there is a case report of stillbirth in patient with MHA secondary to possible uteroplacental vascular thrombosis [7].

Generally, patients with MHA may not have significant bleeding problem. Therefore, treatment should be based on clinical evaluation, laboratory evaluation, personal and family hemostatic history [3,8]. Furthermore, corticosteroids, as seen in this case, intravenous immunoglobulin (IVIG), and splenectomy are reported to be ineffective management for MHA [6].

The effect of MHA in pregnancy is not clearly known. Our knowledge is based on case reports. Patient may be diagnosed in antenatal routine workup or may manifest clinical features due to the physiologic change of pregnancy which may exacerbate the thrombocytopenia, epistaxis and gum bleeding. Management may be like non-pregnant in the antenatal period. They can have premature rupture of membrane and fetal complications [7]. Intrapartum follow up should be in the best setup which can manage the possible excessive bleeding. Vaginal delivery was reported safe and if there is a need for expedite delivery; caesarian section is preferred to instrumental delivery for the latter may associate with high risk of maternal and fetal complications. In the case presented, she gave birth of a stillbirth vaginaly in the first and a male neonate by emergency caesarian section for fetal indication under general anesthesia on her second pregnancy.

A systematic review of literature for MHA during pregnancy was done in 2013. The review revealed 26 articles (25 case reports and one case series) including 75 pregnancies (five twin pregnancies) in 40 women. In 11 women, first presentation was incidental thrombocytopenia during routine antenatal blood test. Of these, five women were misdiagnosed as idiopathic thrombocytopenic purpura (ITP), including three who underwent splenectomy for resistant ITP. Postpartum haemorrhage and bleeding after miscarriage were presenting symptoms in two women [10]. Unlike the above review our case use presented with exacerbated nasal and gum bleeding during pregnancy and was misdiagnosed as ITP and it was resistant to steroid therapy. She also developed recurrent prelabor rupture of membrane and hemorrhage.

Furthermore, the systemic review showed neonatal outcome of 78 live neonates and two intrauterine fetal deaths. Thirty-four neonates had thrombocytopenia and subsequently were diagnosed with MHA; three of them required platelet transfusion prophylactically as they developed very low platelet counts. No obvious bleeding complications were reported among the neonates [10]. In the reported

case, she had sudden fetal death in her first pregnancy that can be explained by severe abruption. Fetal outcome in her second pregnancy was alive and there was no thrombocytopenia or bleeding tendency.

Desmopressin acetate (DDAVP) is a synthetic vasopressin analogue that has been used perioperatively in patients with MHA [3]. These may be helpful in the case with severe thrombocytopenia. There is a case report of using aspirin in pregnancy to prevent uteroplacental vascular thrombosis which may cause fetal complication [7]. None of these was used in our case. Clinical follow-up consisting of renal function studies, ophthalmologic examination, and sensor-neural hearing studies is recommended for a patient with MHA [2]. This are especially true for cases in which genetic study was not done in order to prevent complications.

Differential diagnosis of macrothrombocytopenia

The differential diagnoses of thrombocytopenia are a lot and they can be classified in to pregnancy associated causes and causes independent of pregnancy [11]. The much narrowed approach will be differential diagnosis of macrothrombocytopenia which can make the diagnosis approach easy. The top differentials are

- May Hagglin Anomaly
- Alport syndrome,
- Bernard-Soulier syndrome,
- Montreal platelet syndrome,
- Immune thrombocytopenia,
- Gray platelet syndrome.
- Pseudothrombocytopenia

Conclusion and Recommendations

May-Hegglin anomaly should be considered in the differential diagnoses of severe thrombocytopenia especially if it is large platelet and if doesn't responding for steroid therapy. The diagnosis needs high level of suspicion and peripheral morphology. Detail past medical and menstrual history and family history will give a clue. Failure to diagnose will result inappropriate treatment. Complications such as recurrent premature rupture of membrane; recurrent severe abruption; intrauterine fetal death and postpartum hemorrhage may happen. Steroid therapy and splenectomy are unnecessary interventions.

Acknowledgment

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Competing Interests

The author declares that there is no competing interest.

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