Recurrent sideroblastic anaemia during pregnancy

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Abstract

We report a 32-year-old pregnant patient, presented with palpitation and generalized weakness. She was found to have a severe anaemia with haemoglobin of 4.2 gm/dL. She gave a history of recurrent anaemia, which only occurred during pregnancy. Bone marrow aspirate showed sideroblastic anaemia. Further investigation revealed significantly low pyridoxine level.

Introduction

Sideroblastic anaemia (SA) are a diverse group of disorders that characterized by anemia of varying severity and unified pathologically by an abnormal accumulation of iron in the mitochondria of the red cells precursors with impaired heme synthesis. The singular feature that characterize all forms of SA and is required for initial diagnosis is the presence iron-laden mitochondria forming a perinuclear ring around the nucleus of the erythroblast, visualized by Prussian blue staining of the bone marrow aspirate smear [1]. To be designated as ring sideroblasts, International Working Group on Morphology of Myelodysplastic Syndrome (IWGM-MDS) recommended that ring sideroblasts should have a minimum of 5 granules in a perinuclear distribution; these granules could either surround the entire nucleus, be localized to portions of the perinuclear area, or cover at least one third of the nucleus [2].

The unique pathology in SA can be primarily linked to defect in the heme biosynthesis, Fe-S biogenesis pathways as well as impaired synthesis of mitochondrial and cytosolic proteins essential for heme synthesis. These defects end in the build-up of iron granules rather than the normal incorporation of iron into the protoporphyrin IX (PPIX) in the mitochondrion [3].

Sideroblastic anaemia conventionally classified into congenital (CSA) or acquired (ASA). CSA is rare and caused by germline mutation affecting a nuclear or mitochondrial gene involved in three mitochondrial pathways: Heme biosynthesis, Iron-sulfur cluster and Mitochondrial protein synthesis and respiration. It is characterized by a heterogeneous pattern of inheritance; X-linked (XLSA), autosomal recessive (ARCSA), or Mitochondrially inherited forms. The most common form is X-linked sideroblastic anaemia (XLSA), caused by ALAS2 mutations. The anaemia occurs principally in males; however, familial and sporadic cases have been described that affect only females, possibly due to excessively skewed X-chromosome inactivation of the normal allele for the ALAS2 gene [3].

Acquired SA is more common and include two principal categories; Clonal SA and acquired types. Clonal SA which are the most common SA encountered in clinical practice are a bone marrow stem cell disorders that are currently classified within the broad group of myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) and named in the updated 2016 World Health Organization (WHO) classification of hematopoietic neoplasms as; MDS with ring sideroblasts and single lineage dysplasia (MDS-RS-SLD), MDS
with ring sideroblasts and multilineage dysplasia (MDS-RS-MLD) and myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) [4]. Mutations in protein constituents of the spliceosome, that mediates maturation of primary mRNA transcripts to mature mRNAs lacking introns, have been identified as being common in MDS-RS. Specifically, the acquired heterozygous missense alleles of the $SF3B1$ (splicing factor 3B, subunit 1) component of the splicing machinery are present in up to 85% of patients with MDS-RS-SLD, MDS-RS-MLD and MDS/MPN-RS-T [5,6].

On the other hand, non-clonal SA could be secondary to drugs, heavy metal poisoning (Lead, Arsenic), copper deficiency, alcohol use, hypothermia, or chronic neoplastic disease [7].

Herein, we report a challenging case of sideroblastic anaemia secondary to pyridoxin deficiency presented as pregnancy associated severe, recurrent anaemia.

Case scenario:

A 32-year-old female patient, gravida 4 para 3, 27th week pregnant, presented to the emergency department complaining of palpitation and generalized weakness for two weeks. She denied any other complaint. There was no history of bleeding from any site.

In response to a further question, she revealed a previous history of recurrent anaemia, which only occurred during pregnancy. The anaemia usually occurs in the third trimester, becomes severe and symptomatic, reaches a minimum hemoglobin level of 4 g/dl, and requires frequent transfusion, but it gradually recovers to a normal level 4 weeks after delivery without any intervention.

The family history is negative for any blood disease or malignancy. The patient was not taking any regular medications other than iron and folic acid supplements, nor was she a smoker or an alcoholic.

Vital signs recorded as BP: 105/55 mm Hg, heart rate: 107 beats/min, temperature: 36.8 C, and respiratory rate: 18/min. On physical examination, she looked tired and pale, with no jaundice or cyanosis, and no organomegaly or palpable lymphadenopathy. Other systems, including fetal examination were unremarkable.

Complete blood count showed severe anaemia with haemoglobin of 4.2 gm/dL (12.0-15.0 gm/dL), Het 13% (36-46%), with normal MCV of 90.3 fl (83-101 fl), and MCH of 29.2 pg (27-32 pg). The CV-RDW was increased, 26.0% (11.6-14.5%). Platelets was normal 232.0 x10ˆ3 / uL (150-400 x10ˆ3 / uL) with normal WBC of 6.4 x10ˆ3 / uL (4.0-10.0 x10ˆ3 / uL) and normal deferential. Peripheral smear showed red cells which were mostly normochromic with some hypochromic cells, otherwise unremarkable with no overt evidence of dysplasia.

Full anaemia workup was done which revealed low reticulocyte count of 13 x10ˆ3/uL (50-100 x10ˆ3/uL). Iron profile, B12 and folate level were within normal range. Haptogloin and Hb electrophoresis were normal and LDH was not raised.

In view of the unexplained recurrent severe anaemia, a bone marrow examination was discussed with patient, who consented to the procedure.

Bone marrow (BM) aspirate was cellular and showed mildly increased megakaryocytes with rare small or hypolobated forms, active granulopoiesis with maturation to segmented cells and including few with vacuolation and few with cytoplasmic hypogranulation and there was adequate number of erythroid precursors with mixed normoblastic and megaloblastoid maturation with few showing nuclear lobation and karyorrhexis. Cytoplasmic vacuolation was noted in substantial number of the early erythroid precursors and poorly developed cytoplasm and vacuolation in late precursors (figure 1). There was no increase in blasts. The BM biopsy was hypercellular with approximately (75-80% cellularity) with active granulocytic cells, adequate erythropoiesis, and increased megakaryocytes. There was no increase in CD34-positive blasts by immunohistochemistry. Most of the biopsy showed no increase in reticulin fibers (MF0) with few focal areas of mildly increased fibers (MF1). Prussian blue stain on bone marrow aspirate smear, revealed increased iron in the
stores and in the erythroblasts with the presence of many ring sideroblasts comprising approximately (31%) (figure 2). The overall findings concluded the diagnosis of sideroblastic anemia

Chromosomal analysis showed normal karyotype and Fluorescence in situ hybridization (FISH) revealed normal hybridization pattern for 5q & 7q deletion.

Following the diagnosis of SA on the bone marrow, further investigations were conducted, including tests for copper, zinc, lead and pyridoxine(B6) levels, as well as molecular analysis for theSF3B1 mutation. All tests came back normal except for a very low level of B6 at 8 nmol/L (20-121 nmol/L).

Considering all the above findings, the case was diagnosed as a case of acquired SA secondary to pyridoxine deficiency in pregnancy and she was started on B6 supplements. With B6 replacement, haemoglobin levels improved to a range of 7-8 gm/dL without transfusion support and patient still under follow up monitoring.

Discussion
Sideroblastic anaemia comprise a wide spectrum of relatively uncommon congenital and acquired disorder of erythropoiesis that are due to various abnormalities in heme synthesis and mitochondrial function. The characteristic feature that typifies all forms of sideroblastic anemia is the presence of ring sideroblasts in the bone marrow aspirate [1].

Congenital SA can be further sub-classified into syndromic and non-syndromic. Non syndromic includes: X-linked (XLSA), Mitochondrial transporter SLC25A38 defects SA, Mitochondrial heat shock pt 70 (HSPA9) defects SA, Mitochondrial heat shock cognate pt 20 (HSCB) defects SA, Glutaredoxin 5 deficiency and Erythropoietic protoporphyria. While syndromic SA include: X-linked with ataxia (XLSA/A), Sideroblastic anemia, B cell immunodeficiency, periodic fevers, and developmental delay (SIFD), Myopathy, lactic acidosis, and sideroblastic anemia (MLASA), and variants, Pearson marrow-pancreas syndrome and Thiamine responsive megaloblastic anemia (TRMA) [8-12]. Most of congenital SA are usually hypochromic microcytic with decreased MCV reflecting a reduction of heme synthesis in the erythroid precursors.

Acquired clonal SA include two MDS category; MDS with ring sideroblasts and single lineage dysplasia (MDS-RS-SLD), and MDS with ring sideroblasts and multilineage dysplasia (MDS-RS-MLD) and third category within the MDS/MPN neoplasm; myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)[4]. The anemia in these cases is usually normocytic or macrocytic, with a variable population of hypochromic cells on the peripheral blood smear.

Acquired SA from reversible causes (non-clonal) is similarly linked to mechanisms of impaired heme biosynthesis and accumulation of siderosomes. It has a very diverse etiology and may requires extensive investigation to elicit the cause that may include copper deficiency, drugs, lead toxicity, alcohol use, hypothermia, pyridoxine deficiency, or chronic neoplastic disease.

Copper is an essential cofactor for the mitochondrial redox enzyme superoxide dismutase and reduced activity of this enzyme can lead to mitochondrial iron accumulation. Deficiency of copper can happen in many conditions such as reduced oral intake, malabsorption in the setting of gastrointestinal surgery and small bowel disorders or excessive gastrointestinal or urinary losses of copper. hypocupremia due to reduced copper absorption from the gastrointestinal tract can result as well from prolonged and excessive exposure to zinc. The anemia typically is normocytic or slightly macrocytic and the bone marrow usually show vacuolization of erythroid and myeloid precursors,

excessive stainable iron in plasma cells and macrophages in addition to the ring sideroblasts. Heavy metal toxicity, specifically from lead poisoning or zinc overdose is associated with SA. Excess exposure to zinc can cause SA by competing with iron incorporation into protoporphyrin and preventing intestinal absorption of copper through induction of an intestinal metal-binding protein metallothionein [13].

Although chloramphenicol and isoniazid and have been the prototypical drugs that cause SA, a list of other agents are implicated such as cycloserine, pyrazinamide, linezolid, fusidic acid, busulfan, melphalan, penicillamine, and Linezolid [7].
Pyridoxal phosphate the active form of vitamin B6 play essential role for ALAS2 enzymatic activity, that catalyze the condensation of glycine and succinyl coenzyme A to form 5-aminolevulinic acid (ALA), the first and rate-controlling enzyme of heme synthesis. Therefore, severe deficiency in vitamin B6 due to malnutrition or malabsorption, alcohol consumption or medication like INH can lead to SA.

Most of acquired non clonal SA associated with normal or increased MCV, except of INH toxicity [14].

During pregnancy anemia is a common problem. It can occur as part of physiological changes in pregnancy (dilutional anemia is part of normal pregnancy physiology, and there is a relative or absolute reduction in Hb concentration). However, the most common true anemia during pregnancy is iron deficiency anemia (IDA) encountered in around 75% of the cases. Other causes of anemia might include folate deficiency megaloblastic anemia [15]. Anemia affects approximately 30 percent of reproductive-age females and 40 percent of pregnant individuals, mostly due to iron deficiency. Pregnant women should be screen for anemia at booking visit and at 28 weeks Recurrent anemia during pregnancy can occur due to any of the aforementioned causes. Pure red aplasia (PRCA) can happen during pregnancy as well and it’s reported to recur. Interestingly it’s reported to have spontaneous recovery after delivery [16].

Severe anemia may have adverse effects on the mother and the fetus. Anemia with hemoglobin levels less than 6 gr/dl is associated with increased risk for post partum hemorrhage, poor pregnancy outcome, preterm labor, Prematurity, spontaneous abortions, low birth weight, and fetal deaths are complications of severe maternal anemia and thus it is critical to distinguish iron deficiency anemia from physiologic anemia, as well as to identify other less common causes of anemia that may require treatment.

The World Health Organization (WHO) defines anemia as a hemoglobin level <11 g/dL (approximately equivalent to a hematocrit <33 percent) in the first trimester, <10.5 g/dL in the second trimester, <10.5 to 11 g/dL in the third trimester, or <10 g/dL postpartum. [17-21].

In our literature search, we came across very limited reports on sideroblastic anaemia in pregnancy, mostly as case reports that have shown the relationship between the toxic effect of orally administered sex hormone or pregnancy alone, and secondary sideroblastic anaemia [22-27].

All of the above were thought of within the differential diagnosis as a possible cause for the anaemia in the current reported case and were thoroughly investigated. Absence of family history, dysplasia and SF3B1 mutation and strict association of the anaemia with pregnancy, make CSA and clonal SA unlikely in our case. Likewise, the normal results for copper, zinc and lead with the absence of history of alcoholism or medication that linked to SA, exclude these acquired causes. The low pyridoxin level was implicated as the cause for the recurrent anaemia because of increased requirement during pregnancy.

Conclusions

This case emphasizes the importance of generating a broad differential diagnosis for anaemia in pregnancy. Although SA is a rare type of anaemia, it should be considered in cases of unexplained pregnancy relapsing anemia. Specifying the type of SA is rather challenging as it requires extensive workup including deep genetic testing. However, careful review of the patient’s constellation of clinical findings and red cells indices and morphology aid in narrowing the differential diagnosis. Identification of possible revisable cause that can be treated as pyridoxin deficiency is crucial to avoid both maternal and fetal adverse effect like prematurity, abortions, and even fetal death specially with Hb drop to a critical level.

References:


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