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CASE REPORT

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Recurrent sideroblastic anemia during pregnancy

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Abstract

Sideroblastic anemia is a heterogeneous group of disorders typified by the presence of ring sideroblasts in the bone marrow and has congenital and acquired types. Sideroblastic anemia is a rare event in pregnancy. We report a case of a 32-year-old female patient, gravida 4 para 3, 27th weeks pregnant, who presented to the emergency department complaining of palpitation and generalized weakness for 2 weeks. She was found to have severe normochromic normocytic anemia, with hemoglobin of 4.2 g/dl, and low reticulocytes count of 13×10^3/μl. She gave a history of recurrent anemia, which had only occurred during pregnancy. Her bone marrow aspirate showed many ring sideroblasts concluding the diagnosis of sideroblastic anemia (SA). Further investigation revealed a significantly low pyridoxine level (vitamin B6) of (8 nmol/L). The Hb level improved with vitamin B6 replacement, without any transfusion support.

KEYWORDS

acquired sideroblastic anemia, congenital sideroblastic anemia, heme biosynthesis, iron chelation, ring sideroblasts, vitamin B6

1 | INTRODUCTION

Sideroblastic anemia (SA) is a diverse group of disorders that are 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 characterizes all forms of SA and is required for initial diagnosis is the presence of 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, the International Working Group on Morphology of Myelodysplastic Syndrome (IWGM-MDS) recommended that ring sideroblasts should have a minimum of five 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 defects in the heme biosynthesis, and Fe-S biogenesis

pathways, as well as the 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 anemia is conventionally classified as 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 anemia (XLSA), caused by *ALAS2* mutations. The anemia occurs principally in males; however, familial and sporadic cases have been described to 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 includes two principal categories; Clonal SA and acquired types. Clonal SA which is the most common SA encountered in clinical practice is a bone marrow stem cell disorder that is 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 mediate the 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 contrary, 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 anemia secondary to pyridoxin deficiency presented as pregnancy-associated severe, recurrent anemia.

2 | 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 2 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 anemia, which only occurred during pregnancy. The anemia usually occurs in the third trimester, becomes severe and symptomatic, reaches a minimum hemoglobin level of 4 g/dl, and requires a frequent transfusion, but it gradually recovers to a normal level 4 weeks after delivery without any intervention.

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 anemia with hemoglobin of 4.2 g/dl (12.0–15.0 g/dl), Hct 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 by 26.0% (11.6%–14.5%). Platelets were normal $232.0 \times 10^3/\mu l$ ($150–400 \times 10^3/\mu l$) with normal WBC of $6.4 \times 10^3/\mu l$ ($4.0–10.0 \times 10^3/\mu l$) and normal deferential. Peripheral smear showed red cells which were mostly normochromic with some hypochromic cells, otherwise unremarkable with no overt evidence of dysplasia.

A full anemia workup was done which revealed a low reticulocyte count of $13 \times 10^3/\mu l$ ($50–100 \times 10^3/\mu l$). Iron profile, B12, and folate level were within normal range. Haptoglobin and Hb electrophoresis were normal, and LDH was not raised.

Given the unexplained recurrent severe anemia, a bone marrow examination was discussed with the 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 a few with vacuolation and a few with cytoplasmic hypogranulation and there was an adequate number of erythroid precursors with mixed normoblastic and megaloblastoid maturation with few showing nuclear lobation and karyorrhexis. Cytoplasmic vacuolation was noted in a 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

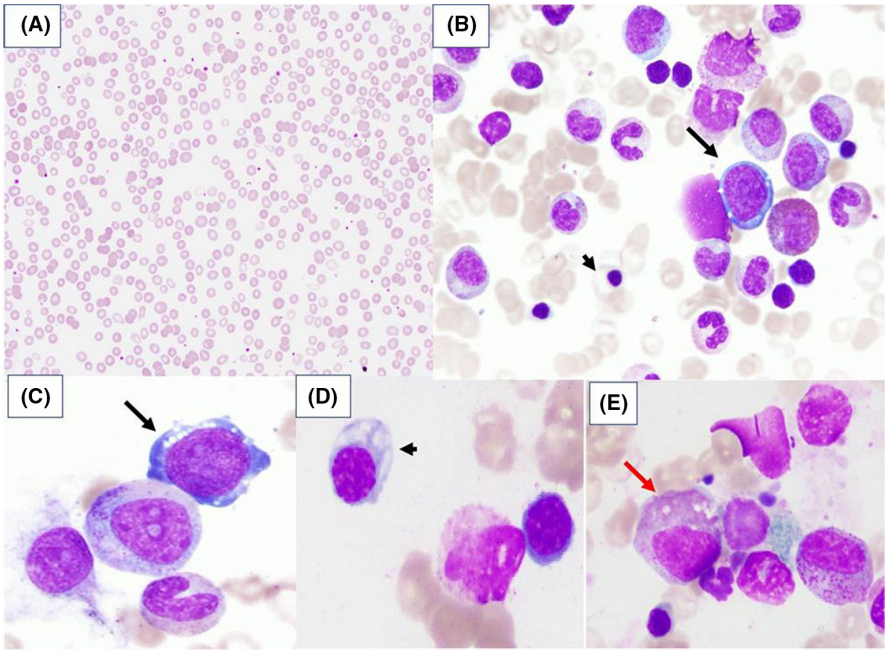

FIGURE 1 (A) Peripheral blood showing normochromic red cells with some hypochromic cells, (B) BM aspirate smears with different stages of granulocytic, vacuolated early precursors (arrowed) and late erythroblast with poorly developed cytoplasm (arrow head), (C) early precursor with cytoplasmic vacuolation, (D) late erythroid precursor with vacuolated poorly developed cytoplasm, (E) myelocyte with cytoplasmic vacuolation. Wright stain 1000×

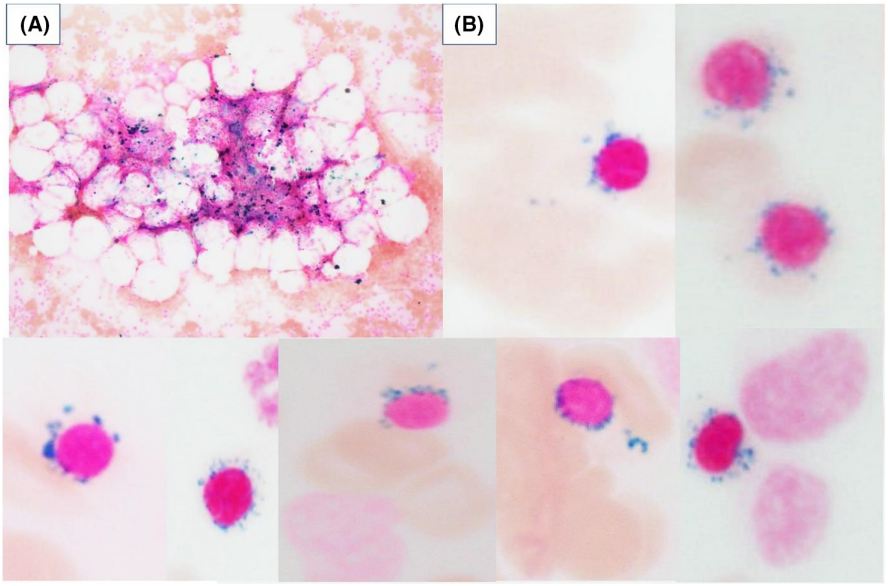

FIGURE 2 Prussian blue stain on marrow aspirate smear. (A) Bone marrow particle with increased iron 400×, (B) ring sideroblasts with iron granules encircling the nucleus 1000×

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 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 a normal hybridization pattern for 5q & 7q deletion.

Following the diagnosis of SA in the bone marrow, further investigations were conducted, including tests for copper, zinc, lead, and pyridoxine (B6) levels, as well as molecular analysis for the *SF3B1* 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, hemoglobin levels improved to a range of 7–8 g/dl without transfusion support and the patient is still under follow-up monitoring.

3 | DISCUSSION

Sideroblastic anemia comprises a wide spectrum of relatively uncommon congenital and acquired disorder of erythropoiesis that is 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. Syndromic SA includes X-linked with ataxia (XLSA/A), Sideroblastic anemia, B-cell immunodeficiency, periodic fevers, developmental delay (SIFD), Myopathy, lactic acidosis, and sideroblastic anemia (MLASA), and variants, Pearson marrow-pancreas syndrome, and Thiamine responsive megaloblastic anemia (TRMA).[8–12] Congenital SA is mostly 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 require extensive investigation to elicit the cause which 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 shows 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 the induction of intestinal metal-binding protein metallothionein.[13]

Although chloramphenicol and isoniazid 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 plays an essential role in ALAS2 enzymatic activity, which catalyzes 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 acquired non-clonal SA is associated with normal or increased MCV, except for 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 and megaloblastic anemia.[15] Anemia affects approximately 30% of reproductive-age females and 40% of pregnant individuals, mostly due to iron deficiency. Pregnant women should be screened for anemia at the 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 is reported to recur. Interestingly, it is 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 g/dl is associated with increased risk for postpostpartum hemorrhage, poor pregnancy outcome, preterm labor, prematurity, spontaneous abortions, low birthweight, 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%) in the first trimester, <10.5 g/dl in the second trimester, <10.5–11 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 anemia in pregnancy, mostly as case reports that have shown the relationship between the toxic effect of orally administered sex hormones or pregnancy alone, and secondary sideroblastic anemia.[22–27]

All the above were thought of within the differential diagnosis as a possible cause for the anemia in the current

reported case and were thoroughly investigated. The absence of family history, dysplasia, *SF3B1* mutation, and the strict association of anemia with pregnancy, make CSA and clonal SA unlikely in our case. Likewise, the normal results for copper, zinc, and lead with the absence of a history of alcoholism or medication linked to SA exclude these acquired causes. The low pyridoxin level was implicated as the cause of recurrent anemia because of increased requirements during pregnancy.

4 | CONCLUSIONS

This case emphasizes the importance of generating a broad differential diagnosis for anemia in pregnancy. Although SA is a rare type of anemia, 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, a 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 causes that can be treated as a pyridoxin deficiency is crucial to avoid both maternal and fetal adverse effects like prematurity, abortions, and even fetal death, especially with Hb drop to a critical level.

AUTHOR CONTRIBUTIONS

Shehab Mohamed: Writing – original draft. **Firyal Ibrahim:** Validation. **Mohamad Najib Alasafar:** Validation. **Awni Alshurafa:** Writing – original draft. **Susanna Akiki:** Conceptualization. **Dina Soliman:** Validation. **Samah Kohla:** Supervision. **Aliaa Amer:** Supervision. **Hana Qasim:** Writing – review and editing. **Honar Cherif:** Supervision.

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CONFLICT OF INTEREST

All authors of this manuscript have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data and materials are available upon reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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