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Case Report

Multidisciplinary Rescue: Managing Transfusion Refractory Severe Anemia in Pregnancy with Underlying Rheumatoid Arthritis

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Abstract

This case report details the multidisciplinary management of a 23-year-old primigravida with rheumatoid arthritis (RA) who presented with severe, transfusion-refractory anemia of chronic disease (ACD) at 24 weeks of gestation. Despite receiving seven packed red blood cells (PRBCs) units over six months, her hemoglobin remained critically below 5 g/dL. Investigations revealed high serum ferritin and transferrin saturation, consistent with iron overload. On further history h/o rheumatoid arthritis managed with tofacitinib and a history of previous blood transfusion were elicited. While her RA markers were within normal limits, an elevated ESR (100 mm/hr) indicated ongoing inflammation. Hence the diagnosis of ACD was made. Treatment with high-dose corticosteroids (methylprednisolone followed by oral prednisolone) resulted in a significant improvement in hemoglobin levels (reaching 10 g/dL) without further transfusions. The patient delivered a late preterm male infant at 36+3 weeks of gestation. This case highlights the importance of considering ACD in the differential diagnosis of severe, transfusion-refractory anemia in pregnant women with autoimmune conditions, emphasizing the need for a multidisciplinary approach and the potential efficacy of corticosteroids in achieving hematologic recovery and favorable perinatal outcomes.

Keywords: Transfusion Refractory Anemia in Pregnancy; Anemia of Chronic Disease; High Risk Pregnancy; Multidisciplinary Management; Steroid Therapy

Abbreviations

ACD: Anemia of Chronic Disease; RA: Rheumatoid Arthritis; Anti CCP: Cyclic Citrullinated Peptide; PRBC: Packed Cell Red Blood Cells; TFT: Thyroid Function Test; LFT: Liver Function Test; RFT: Renal Function Test; MCV: Mean Corpuscular Volume; MCHC: Mean Corpuscular Hemoglobin Concentration; MCH: Mean Corpuscular Hemoglobin; TFT: Thyroid Function Test; ANA: Anti Nuclear Antibody; ESR: erythrocyte Sedimentation Rate; CRP: C: Reactive Protein; LDH: Lactate Dehydrogenase; IV: Intravenous; USG: Ultrasonography; FGR: Fetal Growth Restriction

Introduction

Anemia in pregnancy is a prevalent condition, particularly in low- and middle-income countries, and is associated with adverse maternal and fetal outcomes, including preterm delivery, intrauterine growth restriction, and increased perinatal mortality [1]. The World Health Organization (WHO) defines anemia in pregnancy as a hemoglobin level below 11 g/dL, with severe anemia being defined as levels under 7 g/dL [2]. Although iron deficiency is the most common cause, other etiologies—including vitamin B12 deficiency, folate deficiency, hemolytic anemia, bone marrow suppression, anemia of chronic disease and autoimmune disorders—should be considered in cases unresponsive to conventional therapy.

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic synovial inflammation and is often associated with extra-articular manifestations, including anemia [3]. Anemia in RA is typically multifactorial, manifesting as ACD driven by pro-inflammatory cytokines such as IL-1,6, TNF*a* which disrupt iron homeostasis and directly inhibit the differentiation and proliferation of erythroid progenitor cells [4]. While disease activity in RA often improves during pregnancy, a subset of patients may experience continued or subclinical inflammation contributing to complications such as anemia. Although 50% may be considered to have low disease activity, nearly 20% will have worse or moderate-to-high disease activity during pregnancy and may require further therapeutic intervention [5]. It has also been mentioned that women with chronic disorder may develop anemia for the first time during the pregnancy due to the plasma volume expansion and increased iron requirement [6].

This case report describes a 23-year-old primigravida with known RA who presented with severe transfusion-dependent anemia during pregnancy, ultimately diagnosed as ACD with RA as the underlying etiology. The patient's condition responded well to corticosteroid therapy, emphasizing the importance of considering inflammatory causes in persistent anemia during pregnancy and the value of a multidisciplinary management approach.

Case Report

A 23-year-old primigravida known case of rheumatoid arthritis, had been referred to all India institute of medical sciences (AIIMS) at 24 weeks period of gestation on 26-june-2023 with LMP 9-1-23, in view of severe anemia with haemoglobin of 5.1 gm/dl and h/o 7 units PRBC transfusion in the past 6 months (2 units in the first trimester, 5 units in the second trimester). The patient had complaints of generalised weakness, palpitations, and easy fatigability for the past one month. There was no history of joint pain on admission. Initially, she did not give any history of RA; however, on further exploration in view of refractory anemia, the history of RA was elicited. She was diagnosed with RA in June 2022 and had a history of intake of tofacitinib 10 mg once daily. She stopped one month before conception in view of remission and to plan pregnancy. The patient also received two units of blood transfusion one month before her current pregnancy. She had no history of any recent fever, cough, jaundice, photosensitive rash, bleeding per vagina, or oral ulceration.

She had severe pallor with mild pedal edema. Mild splenomegaly. CNS, respiratory system, and musculoskeletal examinations were within normal limits. On cardiac evaluation, ECG and 2D Echo were within normal limits.

Her investigations (values of investigation - table 1) for evaluation for anemia showed severe anemia with hemoglobin (Hb)-5.1g/dl, Total Red blood cells (TRBC) 2.02 million/microlitre. Peripheral blood smear showed microcytic hypochromic anemia, other cell lines intact, with no abnormal cells. Corrected reticulocyte count (CRC) was low, and HPLC was a normal adult Hb pattern. The iron profile was indicating iron overload with increased serum iron, TIBC, % Iron saturation, and serum ferritin. ESR, vitamin B12 level, folic acid level, and serum erythropoietin are elevated. CRP, PT/INR/APTT, LDH, LFT, RFT, TSH, Stool occult blood and DIPSI criteria were within normal limits. Her viral markers, HIV, HbsAg, HCV and RPR, were non-reactive. On workup for autoimmune aetiology, her RA factor, anti CCP, ANA, ANA blot, Indirect Coombs test (ICT), Direct Coombs test (DCT) were negative, Blood culture and Urine culture showed no bacterial growth.

USG Abdomen showed Coarse hepatic echotexture, mild splenomegaly 13.1 cm. Her obstetric ultrasound, including growth scan, anomaly scan, Obstetric Doppler and Fetal Echo were revealed normal parameters. Bone marrow aspiration reported cellular bone marrow, erythropoiesis with normoblastic maturation, myelopoiesis increased with all stages of maturation, and a shift to the left is seen. Bone marrow biopsy was performed subsequently, which revealed a trilineage hematopoiesis with myeloid and megakaryocytic hyperplasia without any abnormal cells. A chest radiograph was performed with abdominal shielding due to a persistent dry cough, which was normal.

A multidisciplinary management approach was initiated, including interdepartmental meetings with clinical hematologist, general medicine consultant and rheumatologist, obstetricians and neonatologist. The initial clinical impression was anemia of chronic disease secondary to rheumatoid arthritis. Initially patient was transfused one unit each of leuco-depleted and washed PRBCs; however, there was no significant improvement in hemoglobin levels and her clinical symptoms. She was considered for Steroids jointly for refractory anemia empirically and started on injection Methyl prednisolone 1 gm IV for 3 days, followed by tablet prednisolone 40 mg daily. Her hemoglobin reached 10 gm/dl after few months of steroid intake without any further blood transfusions. Gradual tapering of prednisolone was done over the subsequent month, and a maintenance dose of 10mg per day was continued. The patient was followed up in antenatal OPD with Complete blood count, fetal monitoring and USG Obstetrics and Doppler 4 weekly. The baby developed stage 1 FGR with a pathological cerebroplacental ratio, which was managed with nutritional supplements.

Investigation	Patients Value	Normal Value
CBC(hb(g/ml)/tlc(x10^3/µl/pltx10^3/µl)	5.1/7.31/234	12-15/4-10/150-410
(MCV(fl)/MCH(pg)/MCHC(g/dl)/RDW)	79/25.2/31.2/22.4	83-101/27-32/31.5-34.5/11-14
Reticulocyte count (%)	0.28	0.5-2.5
Serum iron (mcg/dl)	195	33-193
TIBC (mcg/dl)	212	250-450
% Iron saturation	92	13-45
Serum ferritin (mcg/L)	1109	13-150
Vitamin-B12level (pg/ml	>1960	197-771
folic acid level(ng/ml).	>20	3.1-17.5
CRP (mg/dl)	0.60	<5
ESR (mm/hr)	100	30-70
Serum-erythropoietin (Miu/l)	4-26	1290
LDH (IU/L)	248	230-460
RA factor (U/ml)	5.1	<14 = normal
Anti CCP (U/ml)	15.62	<20 = normal
PT (seconds) INR APTT (seconds)	10.2 1.1 24.5	9.6-12.9 0.8-1.1 20-35
TSH(µiu/l)/Ft3(pmol/l)/Ft4(ng/dl)	1.94/5.2/1.1	0.35-5.5/3.8-6.8/0.93-1.7

Table 1: Value of investigations with normal limit.

The patient went into spontaneous labour at 36+3 weeks of gestation. She delivered vaginally a late preterm male baby of 1.885 kg. Her intra-partum period was uneventful without any postpartum hemorrhage or infections. Postpartum tapering of the steroid was done and then stopped in the next 2 weeks. At six weeks postpartum follow up the patient was maintaining hemoglobin of 10 gm/dl. On further follow-up, the infant demonstrated age-appropriate developmental milestones at three months of age and the mother showed recovery from anemia without any relapses.

Discussion

This case highlights the complex interplay of autoimmune disease, pregnancy, and hematologic abnormalities in a 23-year-old primigravida with a history of rheumatoid arthritis (RA), who presented at 24 weeks of gestation with severe, refractory anemia. The evaluation and subsequent management underscore the importance of a multidisciplinary and individualised approach in pregnant patients with chronic inflammatory conditions.

RA is a systemic autoimmune disorder characterised by chronic inflammation, which can contribute to the development of Anemia of Chronic Disease (ACD) through the overproduction of inflammatory cytokines such as IL-6. These cytokines alter iron metabolism by increasing hepcidin levels, thereby impairing iron availability and suppressing erythropoiesis, even in the presence of adequate iron stores [7]. In this patient, high serum ferritin and transferrin saturation levels along with low TIBC, a low reticulocyte count, and microcytic hypochromic anemia on peripheral smear were all consistent with ACD. The diagnosis was further supported by bone marrow findings showing trilineage hematopoiesis with no dysplasia or infiltration, and a left shift in myelopoiesis, indicating marrow response to systemic inflammation rather than primary bone marrow pathology. Additionally, the elevated ESR (100 mm/hr) was consistent with an inflammatory aetiology commonly seen in autoimmune diseases with subclinical activity [4]. Importantly, no features suggestive of hematologic malignancy or hemolysis were observed, and infectious causes were systematically ruled out through serological and microbiological workup. Hemoglobin level was constantly in the lower range despite repeated blood transfusions with moderate splenomegaly, suggesting extravascular hemolysis as seen in rheumatic arthritis [8]. However LDH, ICT and DCT were negative in the case. There were no clinical signs of active arthritis, and her RA markers were within normal limits at the time of presentation (RA factor 5.1 IU/mL, Anti-CCP 15.6 IU/mL), which added further to the diagnostic dilemma. The elevated ESR (100 mm/hr) and ferritin level (1109 ng/mL) were consistent with ongoing inflammation. Of note, the patient had discontinued tofacitinib, an immunomodulatory agent used in RA prior to con-

ception due to its potential teratogenicity and disease remission. The immunomodulator withdrawal might have led to a flare with low-grade disease activity contributing to the anemia. This phenomenon of subclinical inflammation leading to ACD without joint symptoms has been documented in RA patients during pregnancy. In our patient, despite receiving seven units of packed red blood cells (PRBCs) over a 6-month period, the patient's hemoglobin levels remained critically low. This transfusion-refractory nature suggested that the underlying pathology was not being addressed by blood transfusion alone. Anemia in chronic disease is generally managed with recombinant erythropoietin, injectable iron, blood transfusion and management of the underlying condition will improve the anemia [7]. But in this case, body iron stores were high, and erythropoietin was very high and no response to multiple blood transfusions.

Glucocorticoids are used in rheumatoid arthritis in pregnancy [3]. The erythropoiesis in normal human bone marrow is stimulated by corticosteroid therapy, as also reported by King DJ., *et al*. [9]. The initiation of high-dose corticosteroid therapy with intravenous methylprednisolone followed by oral prednisolone resulted in a marked and sustained improvement in hemoglobin levels without further transfusions. This response highlights the pivotal role of immune suppression in managing ACD in autoimmune conditions.

From an obstetric standpoint, the patient developed stage I fetal growth restriction (FGR) with an abnormal cerebroplacental ratio. Anemia, particularly when severe and chronic, has been associated with intrauterine growth restriction due to reduced maternal oxygen-carrying capacity and placental insufficiency [10]. Nevertheless, the patient had a favorable perinatal outcome with spontaneous delivery of a healthy, albeit late preterm, infant. Continued follow-up confirmed normal developmental milestones in the infant and stable hemoglobin levels in the mother, demonstrating effective disease control postpartum.

This case underscores several important considerations:

- Anemia in pregnancy, particularly when transfusion-refractory, warrants evaluation beyond iron deficiency, including inflammatory and marrow-based causes.
- Autoimmune conditions like RA can present with systemic effects even in the absence of joint symptoms.
- The use of steroids during pregnancy, while requiring cautious monitoring, can be life-saving and effective in treating ACD when other causes are excluded.
- Multidisciplinary coordination between obstetrics, hematology, and rheumatology is essential in managing such complex cases.

In summary, this case reinforces the importance of considering anemia of chronic disease in the differential diagnosis of severe anemia in pregnant women with underlying autoimmune conditions and highlights the potential reversibility of hematologic abnormalities with appropriate immunomodulatory therapy.

Conclusion

This case underscores the importance of considering anemia of chronic disease in pregnant patients with autoimmune conditions presenting with transfusion-refractory anemia. The diagnostic challenge lies in recognizing subclinical inflammation in the absence of overt disease activity. Timely initiation of immunosuppressive therapy, guided by a multidisciplinary team, can lead to hematologic recovery and favorable perinatal outcomes.

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