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Case Study

Menorrhagia, Iron Deficiency Anemia and Thrombocytopenia: A Case Report

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ABSTRACT

Background: Iron deficiency is the most common cause of anemia worldwide. In premenopausal women, iron deficiency anemia is commonly caused by chronic heavy vaginal bleeding (menorrhagia). Iron deficiency anemia is usually associated with either normal or high platelet counts. However, it is rarely reported with low platelet counts. The presentation of menorrhagia, iron deficiency anemia, and thrombocytopenia has been rarely reported in the literature. The present report discusses the management and outcome of the unusual presentation of menorrhagia, iron deficiency, and thrombocytopenia.

Case presentation: A 20-year-old female presented with a history of menorrhagia for two months, severe anemia, and thrombocytopenia. The laboratory investigations confirmed a severe iron deficiency anemia which was secondary to menorrhagia. After excluding other causes of thrombocytopenia, it was attributed to iron deficiency anemia. She was treated with packed red blood cell transfusion and oral iron therapy. Surprisingly, she had a further decline in platelet count then the count improved. Two weeks later, she had a further rebound thrombocytosis. During follow-up, and then the patient recovered completely, and all her hematological parameters returned to normal values.

Conclusion: Iron deficiency anemia-associated thrombocytopenia is an underrepresented cause of thrombocytopenia. This case highlights the importance of considering iron deficiency-associated thrombocytopenia in the differential diagnosis to avoid the use of unnecessary investigations and treatment. Menorrhagia can cause iron deficiency anemia which can be associated with thrombocytopenia. Iron therapy can help to treat menorrhagia, iron deficiency anemia, and thrombocytopenia and it should be considered in the management of such patients.

INTRODUCTION

Anaemia is a major health problem and is considered the most common haematological disorder in the world, with a prevalence of 25% (Gebreweld et al., 2019). Iron deficiency is a common nutritional deficiency and the most common cause of anemia worldwide. It can be diagnosed by obtaining a full history, including nutritional history, full physical examination, and reporting microcytic hypochromic anemia on peripheral blood film. Iron deficiency anemia (IDA) is diagnosed when the hemoglobin level is below 13 g/dl in men or below 12 g/dl in women, and the ferritin level is below 30 µg/L. It usually presents with generalized weakness, fatigue, lethargy, headache, shortness of breath, and tachycardia (Kumar et al., 2022).

IDA is caused by low dietary iron intake, chronic blood loss, or both, and less commonly by malabsorption of iron (World Health Organization, 2011). Insufficient dietary iron intake is the primary cause of IDA in children, especially children from low-income families (Sherry et al., 1997). Chronic blood loss is the most common cause of IDA among adults, especially women.

IDA is a major health problem in premenopausal women of childbearing age, with a prevalence of 11%. IDA is usually treated with iron replacement therapy. However, severe symptomatic patients who are hemodynamically unstable can be treated with a blood transfusion (Mubarak et al., 2004).

In IDA, hemoglobin synthesis is impaired, which results in decreased hemoglobin levels and microcytic red blood cells. Besides anemia, it has been reported that IDA is

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associated with abnormal platelet counts in both adults and children. In most cases, IDA is associated with either normal or high platelet counts. However, few cases have been reported with low platelet counts (thrombocytopenia) (Kuku et al., 2009; Sagar & Veena, 2019). In IDA, few patients may present with thrombocytopenia (TCP) either before or after iron treatment (Cunha et al., 2015) (Elstrott et al., 2022).

The prevalence of TCP in patients with IDA has been reported to be between 2.1% and 2.4% (Kuku et al., 2009; Sagar & Veena, 2019). The exact mechanism of TCP secondary to IDA is not well established. However, it has been reported that IDA-associated TCP may be due to alterations in the iron-dependent enzymes involved in thrombopoiesis (Ganti et al., 2007).

In premenopausal women, chronic heavy vaginal bleeding (menorrhagia) is a common gynecological problem that is mainly due to leiomyomata. Menorrhagia usually leads to severe IDA (Elstrott et al., 2022). IDA may present with TCP, which may worsen the vaginal bleeding. IDA and menorrhagia have been rarely reported with TCP. Menorrhagia, iron deficiency anemia, and thrombocytopenia were first reported in 1978 by Beard and Johnson (Beard & Johnson, 1978) and was then reported in 1987 by Berger and Brass (Berger & Brass, 1987). This triad has been reported in the literature.

In the case of IDA associated with TCP, other causes should be excluded, such as acute blood loss, folate and vitamin B12 deficiency, drugs (chemotherapy, heparin), aplastic anemia, bone marrow failure, malignancy (acute leukemias), autoimmune hemolytic anemia (Evan's syndrome), idiopathic thrombocytopenic purpura and thrombotic thrombocytopenic purpura (Kottke-Marchant & Corcoran, 2002).

This report discusses the unusual case of a Saudi female who presented with the triad of menorrhagia, iron deficiency anemia, and thrombocytopenia. The unexplained thrombocytopenia was not associated with any underlying pathological diseases. Following iron therapy, menorrhagia, platelet counts, and hemoglobin levels were rapidly recovered and normalized within a few weeks. To my knowledge, this is the first reported case of the presentation of menorrhagia, IDA, and thrombocytopenia in Saudi Arabia.

CASE REPORT

Clinical presentation

A 20-year-old Saudi female was referred to the hospital from the primary health center. She presented with a history of progressive generalized weakness, shortness of breath, and dizziness associated with a history of heavy menstrual bleeding for two months. This patient had a history of recurrent gum bleeding and epistaxis but denied skin bruising.

At the age of one year, she was admitted to the hospital and treated with a blood transfusion, then was discharged against medical advice by her parents. At the age of 10 years, she had severe gum bleeding and was admitted to the hospital. She was transfused with fresh frozen plasma (FFP), and she was told she had a bleeding disorder, but no medical reports were provided.

There was no history of purpura, melena, and haematuria. She denied any history of chronic or infectious diseases, fever, joint pain, or skin rashes. Her dietary history showed poor iron intake. She had no history of drinking alcohol or smoking cigarettes, taking medications, or having any other relevant medical or surgical history. She denied any family history of bleeding disorders.

Her gynecology and obstetrics history were notable for heavy menstruation since menarche, which was at the age of 14. Her usual menstrual pattern consisted of menses every 20 days, lasting 7 days with approximately 6-8 heavily soaked pads per day and cramping on the first day.

On physical examination, she was afebrile and tachycardic, and other vital signs were normal. She appeared very pale, but there was no jaundice, edema, petechiae, ecchymosis, or purpuric rashes. She had pale, flat nails. There was no lymphadenopathy. The cardiopulmonary and abdominal examinations were normal. The gynecological examination and ultrasound showed no abnormalities. She did not have to bleed from any other sites.

Laboratory evaluation

On admission, her hematological data revealed a white blood cell count of 5×10^9/L (Normal range: 4-11$\times10^9$/L), a hemoglobin of 5.4 g/dl (Normal range: 12-15 g/dl), a mean corpuscular volume (MCV) of 59 fl (Normal range: 80-100 fl), mean corpuscular hemoglobin (MCH) of 25 pg (Normal range: 27-34 pg), a mean corpuscular hemoglobin concentration (MCHC) of 20.4 g/dl (Normal range: 30-35 g/dl), red cell distribution width (RDW) of 21% (Normal range: 11-15%). Platelet count was 50×10^9/L (Normal range: 150-400$\times10^9$/L), corrected reticulocyte count was 0.5% (Normal range: 0.5-2.5%).

Her coagulation studies revealed a prothrombin time of 12.1 seconds (Normal range: 11-13.5s), an international normalized ratio (INR) of 0.9 (Normal range: 0.8-1.2), partial thromboplastin time (PTT) was 32 seconds (Normal range: 30-40s). Peripheral blood smear showed microcytosis, hypochromia (deficiency of color or pigmentation)., and anisocytosis. No platelet clumping was noticed, and no abnormal cells were reported. The erythrocyte sedimentation rate was 19 mm/h (Normal range: 0-20 mm/hr).

Blood chemistry studies were normal. Iron studies revealed serum iron 20 µg/dl (Normal range: 50-170 µg/dl), total iron binding capacity (TIBC) 480 µg/dl (Normal range: 250-450 µg/dl), and serum ferritin level 5 ng/ml

(Normal range: 12-150 ng/ml). Serum B12 was 435 pmol/L (Normal range: 133-675 pmol/L) and serum folate was 27 nmol/L (Normal range: 6.1-38.5 nmol/L). Stool and urine analysis were normal.

Key findings

The results of complete blood count (CBC), peripheral blood smear, and iron studies were consistent with iron deficiency anemia. In addition, there was thrombocytopenia. Further, the workup for immune and non-immune-mediated thrombocytopenia, thrombotic thrombocytopenic purpura, human immunodeficiency virus (HIV), hepatitis B, hepatitis C, syphilis, autoimmune diseases, infectious diseases, and hemoglobinopathies was unremarkable.

The patient was admitted to the hospital for severe anemia and thrombocytopenia. She was transfused with two units of packed red blood cells and started on oral iron sulfate tablets 325 mg three times a day and oral vitamin C 500 mg daily. The platelet count was evaluated daily; the results are summarised below (Table 1). The platelet count decreased gradually and reached the level of 11×10^9/L on day 5. The patient was treated with a platelet transfusion. Consequently, the count improved and reached 96×10^9/L on day 9.

The patient was discharged on oral iron supplementation and followed up in an outpatient hematology clinic. Ten days after discharge, her hemoglobin was 11.1 g/dl, MCV was 73.3 fl, MCH was 30.5, and platelet count was 980×109/L. She was advised to adhere to oral iron therapy. Sixteen months later, her hemoglobin was 8.5 g/dl, MCV was 70 fl, MCH was 30.5, and platelet count was 150×10^9/L.

Table 1. *Hematological parameters on admission and after initiation of iron therapy.*

Test	On admission	After 10 days	After 16 months
Hb (g/dL)	5.4	11.1	8.5
MCV (fL)	59	73.3	70
Platelets ($\times10^9$/L)	50	980	150

Hb: Hemoglobin; **MCV:** Mean corpuscular volume.

DISCUSSION

IDA is commonly associated with thrombocytosis. In clinical practice, IDA rarely presents with low platelet counts. IDA associated with thrombocytopenia was first reported in infants and children by Gross and colleagues (Gross et al., 1964) and in adults by Sonneborn D (Sonneborn, 1974). It has been documented that the prevalence of TCP in patients with IDA was 2.1-2.4%.

Several investigators have reported that platelet production is affected by the duration and degree of IDA (Kadikoylu et al., 2006). Mild IDA is usually associated with thrombocytosis due to increased levels of endogenous erythropoietin (EPO), which may stimulate thrombopoiesis. On the other hand, severe IDA is associated with thrombocytopenia due to high Epo response (Beguin, 1999). This may indicate that iron may be necessary for platelet production. It has been suggested that in severe iron deficiency anemia, few of the iron-dependent stages of thrombopoiesis are affected (Karpatkin et al., 1974). In addition, it is reported that the activity of iron-dependent enzymes is altered in IDA (Ganti et al., 2007).

The mechanism of TCP in patients with IDA is not well understood. Garg et al. documented that iron-deficient animals severely reduced platelet count (Garg et al., 1972). It was demonstrated that iron has an important role in platelet protein synthesis (Freedman & Karpatkin, 1973). Iron is also found to have an important role in controlling the synthesis of platelets.

IDA is associated with a variation in platelet counts, which can be explained by the two-compartment model (Karpatkin et al., 1974). Freedman and Karpatkin postulated a two-compartment model to study the role of iron in controlling platelet counts (Karpatkin et al., 1974). This model includes inhibitors and essential compartments. Iron is required for the synthesis and production of platelets. In addition, iron has an inhibitory role, inhibiting the rise in platelet counts above the steady state. The inhibitory compartment is first affected during iron deficiency, stimulating platelet synthesis and leading to thrombocytosis (Gupta & Joseph, 2001). On the other hand, severe iron deficiency is associated with thrombocytopenia due to impairment of the essential compartment (Gupta & Joseph, 2001).

At the time of presentation, the patient of the present report had heavy menstrual bleeding (menorrhagia), a low hemoglobin level of 5.4 g/dl (severe anemia), and a low platelet count of 50×10^9/L (thrombocytopenia). The iron stores in the essential compartment are exhausted, and therefore, the patient is presented with thrombocytopenia.

The patient had severe menorrhagia, which was most likely due to the severe IDA associated with TCP. After excluding all the other causes, thrombocytopenia was attributed to iron deficiency anemia. Iron deficiency may also affect mucous membranes, which become unhealthy and have an increasing tendency to mucosal bleeding (Mubarak et al., 2004).

The patient was presented with symptomatic severe IDA, which required admission, blood transfusion, and iron replacement therapy. After initiating iron therapy, the

patient in the present case initially decreased platelet count, which the stem cell steal phenomenon can explain. In severe IDA, the iron supply is inadequate, and erythrocyte precursors show a high demand for iron. Consequently, the level of erythropoietin may increase and cause thrombocytosis. Following iron replacement, the pluripotent hematopoietic stem cells commit towards erythrocyte lineage, and other cell lineage precursors may be transiently decreased, such as megakaryopoiesis. In case of increased iron supply, the pluripotent hemopoietic stem cells are induced to produce more erythropoiesis than other hemopoietic cell lines. In a study by Ganti and associates, a case of a 39-year-old woman presented with severe IDA (Hb 3.1 g/dl), thrombocytopenia (platelet count 127×10^9/L), and menorrhagia who was treated with packed RBC transfusion and intravenous iron infusion. After the initiation of treatment, she had a further drop in hemoglobin to 2.7 g/dl, platelet count to 39×109/L, and WBC to 1.6×10^9/L. Ten days later, her CBC improved and normalized four months after iron therapy (Ganti et al., 2007).

Two weeks after initiating iron therapy, the patient of the present case had rebound thrombocytosis (980×10^9/l) before normalization of platelet count, which is explained by the role of iron in the inhibitor compartment. Perlman et al. discussed six children with IDA and thrombocytopenia. They were treated with iron replacement therapy and had thrombocytosis after the initiation of iron supplementation (Perlman et al., 2002). In a case report by Morris and co-workers who presented four pediatric patients with severe IDA (Hb < 7 g/dl) and thrombocytopenia (platelet counts < 50×10^9/L). After iron therapy, patients had platelet overshoot phenomenon. Within 3 weeks of iron therapy, hemoglobin levels and platelet counts returned to normal values (Morris et al., 2010). Bilic and Bilic attributed this reactive thrombocytosis to the sequence homology between erythropoietin (EPO) and thrombopoietin (TPO) (Bilic & Bilic, 2003). It has been shown that amino acid sequence homology between Epo and Tpo may explain the presentation of rebound thrombocytosis. Therefore, IDA-associated thrombocytosis is due to the stimulation of megakaryopoiesis by EPO production. Beguin Y hypothesized that standard doses of recombinant human Epo might cause a moderate increase in platelet counts, whereas the intense dose of Epo is associated with thrombocytopenia (Beguin, 1999).

The presentation of heavy vaginal bleeding (menorrhagia), IDA, and thrombocytopenia have been rarely reported in the literature. In 1978, Beard and Johnson (Beard & Johnson, 1978) reported menorrhagia, IDA, and TCP, which was reported in 1987 by Berger and Brass (Berger & Brass, 1987). In animal models, Polette and Blache showed that iron has a vital role in platelet aggregation through lipid peroxidation and releasing oxygen-free radicals, which induce the production of arachidonic acid thromboxane A2 (Polette & Blache, 1992). Akay and colleagues studied women with IDA and found that they are more susceptible to increased menstrual blood loss due to arachidonic acid-induced platelet dysfunction (Akay et al., 2008). All these studies have demonstrated that iron has a key role in platelet synthesis and aggregation.

In 2012, Kang and Li described a 31-year-old woman with severe IDA (Hb 2.9 g/dl), TCP (platelet count 12×10^9/L) and menorrhagia. She was treated with a packed RBC transfusion and intravenous iron infusion. She also received oral iron therapy. One month later, her hemoglobin level and platelet count improved (Kang & Li, 2012). Furthermore, Ibrahim et al. reported a 40-year-old female with severe IDA (Hb 3.5 g/dl), TCP (platelet count 30×10^9/L), and heavy vaginal bleeding. She was treated with intravenous and oral iron therapy. After two months of iron supplementation, hemoglobin improved to 10.9 g/dl and platelet count to 447×10^9/L (Ibrahim et al., 2012). Moreover, Verma and co-workers presented 10 adult female patients with severe IDA (Hb 1.9-6.7 g/dl) and TCP (platelet counts 7-103×10^9/L). Nine patients had menorrhagia due to uterine fibroids, and one patient had menorrhagia due to chronic diverticulosis. After initiating iron therapy, all patients recovered rapidly, and all hematological parameters returned to normal values (Verma et al., 2015). In a recent study, Torrejan et al. documented a 30-year-old female who presented with heavy menstrual bleeding (menorrhagia) secondary to uterine fibroid tumor, severe IDA (Hb 4.9 g/dl), and TCP (platelet count 77×10^9/L). She was treated with two units of packed RBC transfusion and intravenous iron. Two months after discharge, all her hematological parameters recovered completely (Torrejon et al., 2018).

All these reported cases emphasize that IDA-associated thrombocytopenia and vaginal bleeding is a treatable condition and support the hypothesis that iron has a potential role in the synthesis of platelets and megakaryocytes and in improving and treating such conditions.

CONCLUSION

Mild to moderate IDA is usually associated with reactive thrombocytosis. Thrombocytopenia is seen in patients with severe IDA, especially when the hemoglobin level is below 7 g/dl. IDA-associated thrombocytopenia is a common condition with a rare complication.

IDA-associated TCP is an underrepresented cause of thrombocytopenia, which can be treated with iron therapy. Therefore, after excluding the most common pathological diseases associated with thrombocytopenia, iron deficiency-associated thrombocytopenia should be considered in the differential diagnosis to avoid unnecessary investigations and treatment.

IDA may present with thrombocytosis or thrombocytopenia, and initiating iron replacement therapy may induce further thrombocytopenia or thrombocytosis. These conditions may disappear after iron supplementation. All the reported cases of IDA-associated thrombocytopenia showed complete recovery with iron replacement therapy. This case report also highlights the use of iron therapy in treating patients with IDA-associated TCP.

Menorrhagia can cause IDA, which can be associated with TCP. Iron therapy helps to treat menorrhagia, iron deficiency anemia, and thrombocytopenia. Therefore, iron therapy should be considered in the management of such patients.

AUTHOR CONTRIBUTIONS

SH conceived and designed the study, collected and organized data, analyzed and interpreted data, and wrote the initial and final drafts of the article.

DECLARATIONS

Ethical Approval

The study was approved by the institutional review board (IRB—number 14237) of Al-Noor Specialist Hospital and performed following the principles of the Declaration of Helsinki. Before starting the study, the patient gave formal written informed consent to publish the case details.

Participants Consent

All participants gave informed consent at the onset of the study. They were assured of confidentiality and their right to withdraw from the study.

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Conflict of Interest

All authors have declared that no financial support was received from any organization for the submitted work. All authors have declared that no other relationships or activities could appear to have influenced the submitted work.

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