CASE REPORT

Iron deficiency anemia and reactive thrombocytosis in a woman with heavy menstrual bleeding: A case report

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ABSTRACT

Thrombocytosis is frequently encountered in clinical practice and requires a rigorous diagnostic approach to accurately determine its underlying cause. It could be primary, such as essential thrombocythemia (ET), or secondary to chronic inflammation, hemorrhage, or iron deficiency anemia (IDA). Herein, a 32-year-old woman had iron deficiency-induced thrombocytosis; she was treated with intravenous iron supplements for one month, but thrombocytosis persisted. Therefore, the subsequent differential diagnosis was a JAK2-negative ET, and she was managed with cytoreduction and an antiplatelet agent. Despite this, her erythrocyte counts and thrombocytes increased, accompanied by microcytic hypochromic anemia. Laboratory tests and detailed clinical reassessment ultimately identified IDA secondary to heavy menstrual bleeding. Subsequently, she missed her cycle for three months, with continuing iron supplements, which together led to the correction of anemia and subsequently resolution of the reactive thrombocytosis. This case report reminds clinicians to provide sufficient time following treatment before reassessing cases with thrombocytosis secondary to IDA, and the definitive diagnosis of clonal neoplasms, such as ET, requires fulfilment of the well-established diagnostic criteria. (www.actabiomedica.it)

Key words: case report, heavy menstrual bleeding, iron deficiency anemia, secondary thrombocytosis

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Introduction

Thrombocytosis (platelets ≥ 450 x 10^9/L) may be primary (clonal) or secondary (reactive) (Table 1) (1). Iron deficiency anemia (IDA) is the most frequent anemia worldwide; it is a nutritional microcytic hypochromic anemia (2). Iron deficiency (ID) results from either reduced iron intake and absorption or increased iron demand (2, 3). Most patients are asymptomatic at diagnosis; others may exhibit symptoms (2, 3). For an accurate diagnosis of IDA, physical examination, complete blood count (CBC), blood film, and iron studies should be performed (4). In addition to hemoglobin electrophoresis and other specialized investigations that help exclude closely related hemoglobinopathies (4). Treatment aims to address the trigger of ID, correct anemia, and replenish iron stores (4). About one-third of IDA patients exhibit secondary mild to moderate thrombocytosis that correlates with the severity of anemia and resolves within 2-6 weeks of treatment; persistent thrombocytosis is reassessed after that (5, 6). Essential thrombocythemia (ET) is a rare Philadelphia chromosome-negative myeloproliferative neoplasm (MPN) (7); it results from the acquisition of mutually exclusive mutations in genes of Janus kinase 2 (*JAK2*), calreticulin (*CALR*), and myeloproliferative leukemia virus oncogene (*MPL*); about 15% of patients are wildtype of the three genes, termed "triple negative" (7, 8). Approximately half of patients are diagnosed incidentally due to thrombocytosis, presenting no symptoms at the time of diagnosis (9). Accurate diagnosis of ET requires meeting the World Health Organization (WHO) diagnostic criteria (10). This case report reminds clinicians to provide sufficient time following iron replacement therapy before reassessing the cases with thrombocytosis reactive to IDA.

Table 1. Etiologies of primary (clonal) and secondary (reactive) thrombocytosis.

Primary thrombocytosis	Secondary thrombocytosis
• Essential thrombocythemia (ET)	• Systemic infection
• Polycythemia vera (PV)	• Chronic inflammation
• Primary myelofibrosis (PMF)	• Iron deficiency anemia (IDA)
• Chronic myeloid leukemia (CML)	• Hemorrhage
• MDS with isolated del (5q)	• Solid tumors
• MDS/MPN-RS-T	• Post-operation (splenectomy)

Abbreviations: MDS with isolated del (5q), myelodysplastic syndrome with isolated deletion of the long arm of chromosome 5; MDS/MPN-RS-T, myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis.

Case presentation

A 32-year-old married female was previously diagnosed with hypertension controlled with irbesartan 150 mg and amlodipine 5 mg, hypothyroidism on thyroxine 150 mcg by a cardiologist and endocrinologist, respectively. She was referred to the hematologist's consultation after an incidental thrombocytosis; on physical examination, she exhibited no specific signs or symptoms except dysuria. A urine culture grew *Staphylococcus* and *Enterococcus* species. Her complete blood count (CBC) showed marked leukocytosis and thrombocytosis, with a normal count of microcytic hypochromic erythrocytes and a low hemoglobin level (Table 2). At this point, the investigation of thrombocytosis was initiated with iron studies that revealed markedly reduced serum ferritin and iron, with elevated total iron binding capacity (TIBC) (Table 2), highlighting a case of reactive thrombocytosis to iron deficiency anemia (IDA). Celiac disease testing (anti-tissue transglutaminase (anti-TTG) antibodies), family history of gastrointestinal malignancies, and tumor markers, including CA 15-3 (breast cancer), CEA (colorectal and other adenocarcinomas), CA 125 (ovarian cancer), and CA 19-9 (pancreatic adenocarcinoma), were negative, and she did not declare any incidence of recent bleeding. So, she underwent a double endoscopy; it revealed no evidence of gastrointestinal bleeding. She received 400 mg of intravenous ferric carboxymaltose, with continuous monitoring of thrombocyte count. One month later, iron stores were replenished to a level that corrected the anemia; however, thrombocytosis persisted. Markers of systemic inflammation, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), were within reference intervals, excluding

reactive thrombocytosis due to inflammation. Abdominal ultrasonography revealed a normal spleen and liver. Philadelphia chromosome workup was negative, ruling out chronic myeloid leukemia (CML). She declined a bone marrow (BM) examination to evaluate essential thrombocythemia (ET). *JAK2 V617F* testing was also negative. Therefore, she was labeled as *JAK2*-negative ET and initiated twice daily doses of oral hydroxyurea 500 mg, once daily dose of oral aspirin 100 mg, and Zyloric 300 mg, a prophylaxis against hyperuricemia, for sex months. During the monthly follow-up, leukocyte count decreased significantly, whereas thrombocytes and erythrocytes increased. These erythrocytes were markedly microcytic and hypochromic, with a Mentzer index (mean corpuscular volume (MCV)/ erythrocytes) of 12. Investigations of alpha- and beta-thalassemia were negative. At this point, she declared suffering from heavy menstrual bleeding with the passage of clots for several months, holding that from the hematologist. Then, a gynecological consultation was requested, and abnormal vaginal bleeding due to structural gynecological lesions (endometrial abnormality) was identified as the underlying cause. A few months later, she missed her menstrual cycle for three months while still receiving iron supplements; her iron stores and hemoglobin levels were markedly improved, and thrombocyte count normalized (Table 2). This led to definitively reclassifying her as a case of IDA with reactive thrombocytosis.

Discussion and conclusion

Thrombocytosis is a common finding in routine clinical practice, requiring a rigorous approach to differentiate its underlying cause (1). This case detailed a 32-year-old iron-deficient woman with thrombocytosis. During the time of iron replacement therapy, thrombocytosis persisted, and she was subsequently misclassified as essential thrombocythemia (ET). However, the inconsistent laboratory findings, following cytoreduction, led to a definitive diagnosis of

Table 2. Complete blood count, inflammatory parameters, and iron studies of the patient at different time points.

Parameter	Baseline assessment	Preliminary diagnosis	Initial treatment phase	Definitive treatment phase
Erythrocytes (x 10^{12}/L)	4.7	4.69	5.2 **	5.35
Hb level (g/dL)	10.2	12 **	10.1 *	15.9 **
Hematocrit (%)	33.7	37.8 **	35.5	46.1 **
MCV (fL)	72.7	80.7 **	68.4 *	86.1 **
MCHC (g/dL)	29.9	31.6 **	29.6 *	34.5 **
RDW (%)	14.1	14.3	19.9 **	16.3 *
Thrombocytes (x 10^9/L)	945	539 *	672 **	418 *
Leukocytes (x 10^9/L)	21.44	11.68 *	9.57 *	10.25
Neutrophils (x 10^9/L)	12.86	7.26 *	5.89 *	5.69
Lymphocytes (x 10^9/L)	6.09	2.96 *	2.58 *	3.01
Monocytes (x 10^9/L)	1.50	0.77 *	0.46 *	0.73 **
ESR (mm/h)	11.0	11.0	--	--
CRP (mg/L)	< 1.0	3.84	--	--
Ferritin (ng/mL)	3.55	17.9 **	2.8 *	102.5 **
Iron (mcg/dL)	20.09	--	16.5	--
TIBC (mcg/dL)	429	--	450	--

Abbreviations: Hb, hemoglobin; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TIBC, total iron binding capacity; *, decreased considerably from the earlier measurement; **, increased considerably from the earlier measurement.

iron deficiency anemia (IDA) with reactive thrombocytosis. Reactive mild to moderate thrombocytosis has been observed in about one-third of IDA patients; it typically resolves within 2-6 weeks of iron replacement therapy (5, 6). In this case, thrombocytosis persisted following one month of intravenous iron treatment. This led to the classification as ET based on the exclusion of other closely related myeloid neoplasms, and the ruling out of reactive thrombocytosis due to bleeding, as claimed by the patient, or systemic inflammation through normal values of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). However, the unexpected increase in thrombocyte and erythrocyte count, despite cytoreduction, shed light on sustained erythroid lineage abnormalities. A Mentzer index less than 13 is suggestive of beta-thalassemia trait (11). However, the alpha- and beta-thalassemia workups were negative in our patient, while the iron profile was indicative of an unresolved IDA. After a thorough clinical investigation, the patient disclosed that she had heavy menstrual bleeding with clots for several months; a gynecological evaluation disclosed the presence of abnormal vaginal bleeding due to structural gynecological lesions (endometrial abnormality). Upon resuming intravenous iron, her platelet counts steadily decreased from 672 x 10^9/L to 418 x 10^9/L over a few months. In addition to supplements, her ferritin was greatly improved from 2.8 ng/mL to 102.5 ng/mL due to the absence of menstruation, the trigger of iron deficiency. Together with the absence of meticulous bone marrow (BM) examination and negative testing for *JAK2 V617F*, these observations confirmed the correct reclassification to reactive thrombocytosis due to IDA, excluding the presence of ET. Initially, she also had marked leukocytosis, consistent with chronic myeloid leukemia. However, it was excluded due to a negative result of the Philadelphia chromosome workup; leukocytosis with neutrophilia was mainly attributed to the urinary tract infection. This case is of clinical interest because it showed the diagnostic challenge in our patient arose because the history of heavy menstrual bleeding was undisclosed during the initial assessment, which led to improper management and a delay in allocating and treating IDA. If the patient had remained misclassified as a case of ET, she would have continued unnecessary antiplatelet and cytoreductive agents, increasing risk for bleeding and potential peripheral cytopenias (8), while reactive thrombocytosis only requires the management of the underlying trigger without requiring any specific treatment that may affect platelets or the process of hematopoiesis (1). In a relevant context, Voigt et al. reported a young female with occult celiac disease who presented with profound IDA and extreme thrombocytosis, which complicated the diagnosis (12). The exact mechanisms of thrombocytosis secondary to IDA remain unclear. However, Xavier-Ferrucio et al. found that the reduced iron in the BM milieu perturbs megakaryocyte-erythroid progenitors (MEPs) metabolism, reduces phosphorylated extracellular signal–regulated kinase (ERK), and induces bias towards megakaryocyte proliferation and platelet production (13). This case report serves as a reminder to clinicians to provide the appropriate time to resolve reactive thrombocytosis by addressing the underlying trigger. Furthermore, the definitive diagnosis of rare clonal neoplasms, including ET, requires a rigorous approach and fulfilment of the well-established WHO criteria. In the absence of driver mutation, evidence-based exclusion of each cause of secondary thrombocytosis is required, especially if the BM examination is refused or contraindicated. We also recommend educating patients about the significance of BM examinations in such cases. Furthermore, the patients must disclose their relevant health status to their physicians. A limitation of this report is that, as a single case, it cannot determine the rate of diagnostic delays caused by incomplete clinical histories.

Ethical Approval: In accordance with the Declaration of Helsinki, this report was received consent from the Scientific Research Ethics Committee at the Hashemite University (Number: 28/3/2024/2025) and Jordan University Hospital (Number: 10/2025/14992).

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