Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Pancytopenia Revealing Severe Iron Deficiency Anemia: An Unusual Presentation: A Case Report

Rihab Ben Sghaier

dr.rihab.bs@gmail.com

Hôpital Farhat Hached

Ghassen Saidi

Hôpital Farhat Hached

Nesrine Ben Sayed

Hôpital Farhat Hached

Nadia Sassi

Hôpital Farhat Hached

Haifa Regaieg

Hôpital Farhat Hached

Yosra Ben Youssef

Hôpital Farhat Hached

Case Report

Keywords: iron deficiency anemia, pancytopenia, thrombocytopenia, leukopenia, bone marrow, hematopoiesis

Posted Date: November 25th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10919339/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Iron deficiency anemia (IDA) is the most common cause of anemia worldwide, affecting an estimated 1.2 billion individuals, and is classically associated with reactive thrombocytosis (1, 2). Leukopenia and thrombocytopenia are uncommon findings, and pancytopenia is an exceptionally rare presentation that typically raises concern for bone marrow failure, hematologic malignancy, infection, or autoimmune disease (3).

Aim

To report a rare case of severe iron deficiency anemia presenting as pancytopenia and to highlight the importance of systematically excluding other etiologies before attributing trilineage suppression to iron deficiency alone.

Case Summary:

A 43-year-old woman presented with progressive pallor and fatigue. Laboratory evaluation revealed profound pancytopenia with hemoglobin 3.2 g/dL, WBC 2,300/mm³, and platelets 69,000/mm³, alongside severely depleted ferritin (2.17 ng/mL). Bone marrow biopsy was normocellular with no evidence of malignancy or dysplasia. Following red cell transfusion and iron repletion, complete hematologic recovery was achieved at four months, confirming iron deficiency as the sole etiology.

Conclusion

Severe iron deficiency may, in rare instances, present as pancytopenia. This diagnosis requires careful exclusion of other causes. Prompt recognition and iron repletion can lead to full recovery of all three hematopoietic lineages.

Introduction

Iron deficiency anemia (IDA) is a global health burden, representing the most prevalent nutritional deficiency and the leading cause of anemia worldwide, affecting an estimated 1.2 billion individuals (1, 2). Its hematologic profile is well characterized: microcytic hypochromic anemia with elevated red cell distribution width (RDW), low serum ferritin, reduced transferrin saturation, and, classically, reactive thrombocytosis (3, 4). This thrombocytosis has historically been attributed to structural homology between thrombopoietin and erythropoietin, but more recent experimental data suggest that iron deficiency directly biases megakaryocytic–erythroid progenitors (MEPs) toward the megakaryocytic lineage, providing a more refined mechanistic explanation(5).

The concurrent occurrence of leukopenia and thrombocytopenia in the setting of iron deficiency is far less established. Leukopenia has been documented in a significant subset of IDA patients, correlating inversely with hemoglobin level (6). Thrombocytopenia, rather than thrombocytosis, occurs in approximately 2.1–2.3% of IDA patients (3, 7). Pancytopenia—defined as simultaneous reduction in all three hematopoietic lineages—is considered an exceptional and poorly understood complication of iron deficiency (8, 9). Its presence inevitably triggers an extensive diagnostic workup to exclude more ominous conditions, including aplastic anemia, myelodysplastic syndrome (MDS), hematologic malignancies, infections such as parvovirus B19 or Epstein-Barr virus, and autoimmune disorders.

We report a case of a 43-year-old woman in whom profound pancytopenia was the initial presentation of severe IDA, with complete trilineage recovery following iron supplementation. This case illustrates a rare and diagnostically challenging scenario and underscores the need for systematic etiologic evaluation.

Case Report

A 43-year-old woman was referred to the Clinical Hematology Department of Farhat Hached University Hospital (Sousse, Tunisia) for investigation of progressive pallor and severe asthenia evolving over several months. She had no prior hematologic history, no family history of hematologic disease, and no known chronic illness. She denied any use of medications known to cause marrow suppression, and there was no history of recent infection, toxic exposure, or autoimmune disease.

Physical examination revealed marked pallor with a WHO performance status of 2. There were no hemorrhagic manifestations (petechiae, purpura, or ecchymoses), no signs of infection, no peripheral lymphadenopathy, and no hepatosplenomegaly. The patient was hemodynamically stable.

Initial laboratory evaluation (06/09/2025) demonstrated pancytopenia with severe microcytic hypochromic anemia: hemoglobin 3.2 g/dL, MCV 56 fL, MCH 16.4 pg, MCHC 16 g/dL, and RDW of 21%. White blood cell count was 2,300/mm³ with an absolute neutrophil count (ANC) of 1,500/mm³. Platelet count was 69,000/mm³. Peripheral blood smear revealed no blasts, no dysplastic features, and no abnormal lymphocytes. Reticulocyte count was low. Biochemical workup showed no evidence of hemolysis (normal bilirubin, haptoglobin, and LDH). Renal and hepatic function tests were unremarkable.

Etiological investigations revealed normal serum vitamin B12 (275 pg/mL) and folic acid levels (5.21 ng/mL). Serum ferritin was profoundly reduced at 2.17 ng/mL, and transferrin saturation was markedly decreased, consistent with severe iron deficiency. Serum ferritin is the most reliable single marker of iron depletion severity, with values below 30 µg/L defining absolute iron deficiency (10, 11). Viral serologies (HIV, hepatitis B and C, EBV, CMV, parvovirus B19) were all negative. Autoimmune screening, including antinuclear antibodies (ANA) and anti-dsDNA, was negative. Thyroid function was normal.

Given the unexpected association of profound iron deficiency with pancytopenia, a bone marrow biopsy was performed to exclude marrow failure or infiltration. It revealed a normocellular marrow with

preserved trilineage maturation, no dysplastic changes, no increase in blasts, and no evidence of malignant infiltration or fibrosis. Cytogenetic analysis was normal (46,XX).

The patient was transfused with two units of packed red blood cells, achieving partial hemoglobin correction to 5.0 g/dL. Intravenous iron therapy was subsequently initiated and continued for four weeks, followed by oral iron supplementation. A progressive and sustained recovery of all hematopoietic lineages was observed throughout follow-up (Table 1).

At the four-month follow-up (27/01/2026), hemoglobin had normalized to 13.2 g/dL, WBC to 6,400/mm³ (ANC 4,600/mm³), and platelets to 119,000/mm³. Ferritin had increased to 104 ng/mL. The complete and exclusive recovery of all three lineages following iron repletion confirmed iron deficiency as the underlying and sole etiology of pancytopenia. Given the multifactorial etiology of iron deficiency, including chronic menstrual blood loss and inadequate dietary iron intake, the patient was referred for gynecological assessment and provided with nutritional advice to address these contributing factors and prevent recurrence.

Table 1
Evolution of hematologic parameters and ferritin level during follow-up.

Parameter	06/09/25	09/09/25	16/09/25	30/09/25	28/10/25	27/01/26
WBC (/mm³)	2,300	2,800	4,300	4,000	4,900	6,400
ANC (/mm³)	1,500	1,800	3,000	2,700	3,600	4,600
Hemoglobin (g/dL)	3.2	5.0	8.4	7.6	10.6	13.2
MCV (fL)	56	56.8	65	74	76	86
Platelets (/mm³)	69,000	70,000	122,000	120,000	146,000	119,000
Ferritin (ng/mL)	2.14	—	—	—	—	104
Treatment	*2 units pRBC*		*IV Iron (4 weeks)*		*Oral Iron*	

pRBC: packed red blood cells; IV: intravenous; ANC: absolute neutrophil count.

Discussion

This case illustrates an exceptionally uncommon presentation of iron deficiency anemia: the simultaneous suppression of all three hematopoietic lineages mimicking a primary bone marrow disorder.

IDA is among the most frequently encountered hematologic conditions globally (1, 2), and its classical hematologic signature includes microcytic hypochromic anemia, elevated RDW, and reactive thrombocytosis. Large epidemiological series have consistently confirmed this thrombocytosis: a retrospective analysis of 615 adults with IDA found thrombocytosis in 13.3% and thrombocytopenia in

only 2.1% of patients, with normal platelet counts in the remaining 84.6% (3). The largest published series to date, encompassing nearly 5,000 subjects, confirmed a significantly higher prevalence of thrombocytosis in IDA compared to controls and demonstrated an inverse relationship between platelet count and both ferritin and hemoglobin levels (7). In our patient, the opposite picture was observed—a platelet count of 69,000/mm³, far below the normal range, illustrating the rare occurrence of thrombocytopenia in iron deficiency anemia. Leukopenia in the context of IDA is less appreciated but not negligible. A retrospective study of 516 adults with IDA documented leukopenia in 17.6% of cases, with its severity correlating directly with the degree of anemia and predominantly affecting the lymphocyte compartment (6). The simultaneous occurrence of thrombocytopenia, leukopenia, and severe anemia—constituting frank pancytopenia—in our patient therefore represents a rare presentation of iron deficiency anemia.

The physiopathology of IDA-associated pancytopenia is multifactorial and not yet fully elucidated, but several converging mechanisms have been proposed. At the molecular level, iron is an obligatory cofactor for ribonucleotide reductase (RNR), the rate-limiting enzyme responsible for reducing ribonucleoside diphosphates to their deoxyribonucleoside counterparts, the building blocks required for DNA synthesis and repair (12, 13). In conditions of iron scarcity, RNR activity is selectively preserved through redistribution of its small subunit from the nucleus to the cytoplasm, but this compensatory mechanism has finite capacity: when iron depletion is profound and sustained, RNR activity eventually becomes limiting across all proliferating cell populations (12, 13). Hematopoietic progenitors — among the most rapidly dividing cells in the body — are therefore disproportionately vulnerable to iron-restricted DNA synthesis, and suppression of erythroid, myeloid, and megakaryocytic lineages may occur simultaneously when depletion is sufficiently severe.

Experimental studies have shown that iron deficiency may influence the differentiation of megakaryocyte–erythroid progenitors (MEPs), favoring megakaryocytic commitment at the expense of erythroid maturation (5). This phenomenon has been proposed as a contributor to the reactive thrombocytosis frequently observed in iron deficiency anemia. However, the mechanisms responsible for thrombocytopenia and pancytopenia in severe iron deficiency remain poorly understood. It has been hypothesized that profound iron depletion may impair megakaryocyte maturation and overall hematopoietic proliferation, ultimately leading to suppression of platelet production (14). The occurrence of thrombocytopenia in patients with severe iron deficiency, such as the present case, suggests that the hematopoietic response to iron deprivation may vary according to the severity and duration of deficiency, although the precise biological mechanisms remain to be elucidated.

Iron is essential for normal hematopoiesis through its critical role in mitochondrial function, cellular respiration, and DNA synthesis. Within mitochondria, iron is required for the biosynthesis of heme and iron–sulfur (Fe-S) clusters, which serve as indispensable cofactors for multiple enzymes involved in oxidative phosphorylation and energy production (2). Consequently, severe iron deficiency may impair mitochondrial metabolism and reduce the proliferative capacity of hematopoietic progenitor cells (2, 13). In addition, iron is a necessary cofactor for ribonucleotide reductase, the rate-limiting enzyme in DNA

synthesis, providing a potential mechanism for impaired cell division across erythroid, myeloid, and megakaryocytic lineages. Iron homeostasis is further regulated by iron-regulatory proteins (IRPs), which modulate the expression of key genes involved in intracellular iron handling, including transferrin receptor 1 and ferritin(15). Although the precise pathophysiology of pancytopenia in severe iron deficiency remains incompletely understood, disruption of these iron-dependent metabolic pathways may contribute to transient suppression of trilineage hematopoiesis in susceptible individuals (2).

Published case reports of IDA-associated pancytopenia are sparse. A case series of six Indian adults with severe IDA presenting with pancytopenia demonstrated complete hematologic recovery with iron supplementation alone, without any other intervention (8). A case report in an adolescent girl described an unusual course in which pancytopenia initially worsened after iron replacement — attributed to a transient redistribution of available iron to the erythroid lineage — before full trilineage recovery occurred (9). A French multicentre series of eight patients specifically characterized iron deficiency–induced thrombocytopenia and highlighted its potential to be misdiagnosed as immune thrombocytopenia (ITP), leading to inappropriate immunosuppressive therapy (16); in that series, platelet recovery occurred within a median of six days after iron supplementation alone. Pediatric cases of reversible pancytopenia due to severe IDA have also been documented, including a 12-year-old girl with a ferritin of 1 µg/L and a hemoglobin of 3.3 g/dL whose complete blood count normalized after six months of oral iron supplementation (17). Cytopenia has also been observed paradoxically following initiation of iron therapy itself in pediatric cases, likely reflecting the rapid mobilization of iron toward erythropoiesis at the transient expense of other lineages (18). Collectively, these reports confirm that IDA-associated pancytopenia is a real, reversible, and potentially misdiagnosed entity across all age groups.

The differential diagnosis of pancytopenia is broad and potentially life-threatening. It encompasses bone marrow failure syndromes (aplastic anemia, myelodysplastic syndrome), hematologic malignancies (acute leukemia, lymphoma with marrow infiltration), infectious etiologies (parvovirus B19, EBV, CMV, HIV), autoimmune disorders (systemic lupus erythematosus), drug- or toxin-induced marrow suppression, hypersplenism, and combined nutritional deficiencies. Iron deficiency as a cause of pancytopenia should only be considered after rigorous exclusion of these conditions. The diagnostic workup must include a complete blood count with peripheral smear, reticulocyte count, vitamin B12 and folate levels, hemolysis markers (LDH, bilirubin, haptoglobin, direct Coombs test), viral serologies, autoimmune screening, and bone marrow examination (19). Iron studies — including serum ferritin, serum iron, TIBC, and transferrin saturation — should be incorporated into this workup when microcytic anemia coexists with pancytopenia, as the combination is a key diagnostic clue pointing toward IDA as a contributing or causal factor (10). In our patient, this systematic approach allowed us to confidently attribute pancytopenia to iron deficiency after excluding all other etiologies.

Bone marrow biopsy remains a cornerstone of the evaluation of unexplained pancytopenia and is indispensable for excluding marrow failure, infiltration, and dysplasia (19). In IDA-associated pancytopenia, the marrow may be normocellular, mildly hypocellular, or occasionally erythroid-hyperplastic, without dysplasia or pathological infiltration (8, 9). The normocellular marrow with

preserved trilineage maturation observed in our patient is consistent with a functional rather than structural hematopoietic defect — a pattern that sharply distinguishes this entity from aplastic anemia and myelodysplastic syndrome and supports iron deficiency as the primary driver of cytopenias.

The management of IDA-related pancytopenia rests on prompt and adequate iron repletion. Intravenous iron formulations offer the advantage of rapid replenishment of iron stores and are preferred when oral absorption is unreliable or when rapid correction is clinically required (2, 20). In a post-hoc analysis of 440 IDA patients with thrombocytosis, platelet counts began normalizing within two weeks of iron supplementation and fully resolved within six weeks in all affected patients (20); in our patient, an analogous and prompt response of all three lineages was observed, with platelets normalizing by day 10 of treatment. The complete and durable recovery of hemoglobin, WBC, and platelets exclusively following iron repletion — with no other intervention or alternate diagnosis identified — is the strongest available evidence for iron deficiency as the causal factor, and is consistent with the excellent prognosis reported in similar cases when treatment is initiated without delay (8, 9, 16). Failure to recognize this entity carries the risk of unnecessary and potentially harmful interventions, including empirical immunosuppressive therapy for presumed aplastic anemia or bone marrow transplantation evaluation. The underlying etiology of iron deficiency was multifactorial, combining chronic menstrual blood loss and insufficient dietary iron intake; both factors should be addressed to prevent recurrence.

Conclusion

We report a rare and diagnostically challenging case of severe iron deficiency anemia presenting as pancytopenia in an adult woman. The complete and durable recovery of all three hematopoietic lineages following iron repletion, in the absence of any other identified etiology, establishes iron deficiency as the causal factor. This case reinforces the importance of including iron deficiency in the differential diagnosis of pancytopenia — particularly when accompanied by severe microcytic anemia — and of conducting a rigorous etiologic workup, including iron studies, before attributing trilineage suppression to a primary bone marrow disorder. Early recognition of this rare presentation can avoid unnecessary diagnostic procedures and treatments, and can lead to a simple, definitive cure.

Declarations

Ethics and consent to participate: Not applicable.

Consent to publish: Written informed consent was obtained from the patient for publication of this case report and any accompanying images/clinical information. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

Availability of data and materials: All data generated or analyzed during this study are included in this article.

Competing interests: The authors declare that they have no competing interests.

Funding: The authors received no specific funding for this work.

Authors' contributions: Rihab Ben Sghaier, Ghassen Said and Nadia Sassi contributed to the conception of the manuscript, literature review, data collection, and writing of the manuscript. The other authors contributed to supervision, critical review, and correction of the manuscript. All authors read and approved the final version of the manuscript.

Acknowledgements: Not applicable.

Authors' information: Not applicable.

References

1. Worldwide prevalence of anaemia 1993–2005 [Internet]. [cité 4 juin 2026]. Disponible sur: https://www.who.int/publications/i/item/9789241596657
2. Li X, Finberg KE. Iron Deficiency Anemia. In: Pantopoulos K, éditeur. Iron Metabolism in Human Health and Disease [Internet]. Cham: Springer Nature Switzerland; 2025 [cité 4 juin 2026]. p. 163–78. Disponible sur: https://doi.org/10.1007/978-3-031-92033-2_12 doi:10.1007/978-3-031-92033-2_12
3. Kuku I, Kaya E, Yologlu S, Gokdeniz R, Baydin A. Platelet counts in adults with iron deficiency anemia. Platelets. 1 janv 2009;20(6):401–5. doi:10.1080/09537100903137306
4. Full article: Platelet levels before and after iron replacement therapy in patients with iron deficiency anemia [Internet]. [cité 4 juin 2026]. Disponible sur: https://www.tandfonline.com/doi/full/10.1080/16078454.2025.2458358
5. Low iron promotes megakaryocytic commitment of megakaryocytic-erythroid progenitors in humans and mice | Blood | American Society of Hematology [Internet]. [cité 4 juin 2026]. Disponible sur: https://ashpublications.org/blood/article/134/18/1547/374971/Low-iron-promotes-megakaryocytic-commitment-of
6. Leukopenia in Patients with Iron Deficiency Anemia | Blood | American Society of Hematology [Internet]. [cité 4 juin 2026]. Disponible sur: https://ashpublications.org/blood/article/118/21/5279/81834/Leukopenia-in-Patients-with-Iron-Deficiency-Anemia
7. Mhadgut H, Galadima H, Tahhan HR. Thrombocytosis in Iron Deficiency Anemia. Blood. 29 nov 2018;132(Supplement 1):4985. doi:10.1182/blood-2018-99-119352
8. Meena M, Khichar S, Pawar A, Midha N, Kumar S, Purohit A, et al. Iron Deficiency Anemia Presenting With Pancytopenia: A Study From India. Cureus. 15(9):e45034. doi:10.7759/cureus.45034 PubMed PMID: 37829950; PubMed Central PMCID: PMC10566395.
9. Jhamb R, Kumar A. Iron deficiency anemia presenting as pancytopenia in an adolescent girl [Internet]. Vol. 23. 1 mars 2011;23(1). doi:10.1515/ijamh.2011.012

10. Biochemical Markers and Hematologic Indices in the Diagnosis of Functional Iron Deficiency | Clinical Chemistry | Oxford Academic [Internet]. [cité 4 juin 2026]. Disponible sur: https://academic.oup.com/clinchem/article-abstract/48/7/1066/5642324
11. Volume18,Issue2. International Journal of [Internet]. [cité 4 juin 2026]. Disponible sur: https://ijcpr.com/volume18issue2/
12. Sanvisens N, Bañó MC, Huang M, Puig S. Regulation of ribonucleotide reductase in response to iron deficiency. Mol Cell. 9 déc 2011;44(5):759–69. doi:10.1016/j.molcel.2011.09.021 PubMed PMID: 22152479; PubMed Central PMCID: PMC3240860.
13. Thelander L, Reichard P. Reduction of Ribonucleotides. Annu Rev Biochem. 1 juill 1979;48(Volume 48, 1979):133–58. doi:10.1146/annurev.bi.48.070179.001025
14. Evstatiev R, Bukaty A, Jimenez K, Kulnigg-Dabsch S, Surman L, Schmid W, et al. Iron deficiency alters megakaryopoiesis and platelet phenotype independent of thrombopoietin. Am J Hematol. 12 avr 2014;89(5):524–9. doi:10.1002/ajh.23682 PubMed PMID: 24464533; PubMed Central PMCID: PMC4114532.
15. Muckenthaler MU, Galy B, Hentze MW. Systemic iron homeostasis and the iron-responsive element/iron-regulatory protein (IRE/IRP) regulatory network. Annu Rev Nutr. 2008;28:197–213. doi:10.1146/annurev.nutr.28.061807.155521 PubMed PMID: 18489257.
16. Huscenot T, Luc D, Wagner Ballon O, Valentine L, Gobert D, Le cann M, et al. Iron Deficiency Anemia, a Rare and Potentially Underestimated Cause of Thrombocytopenia and a Differential Diagnosis of Immune Thrombocytopenia (ITP): Results from a Retrospective Case-Controlled Study. Blood. 29 nov 2018;132(Supplement 1):4984. doi:10.1182/blood-2018-99-118532
17. Al Amri T, Al Mamari I, AlSawafı AS, Al Moosawi M, Al-Battashi A. Reversible Pancytopenia Due to Severe Iron Deficiency Anemia in a 12-Year-Old Girl. Cureus. 16(6):e62175. doi:10.7759/cureus.62175 PubMed PMID: 38993399; PubMed Central PMCID: PMC11238895.
18. Özdemir N, Celkan T, Kebudi R, Bor M, Yıldız İ. Cytopenia associated with iron deficiency anemia and iron therapy: A report of two cases. Turk J Haematol Off J Turk Soc Haematol. 5 sept 2011;28(3):243–4. doi:10.5152/tjh.2011.65 PubMed PMID: 27264378.
19. Chew S, Kamangar M. Approach to pancytopenia: From blood tests to the bedside. Clin Med. 17 août 2024;24(5):100235. doi: 10.1016/j .clinme.2024.100235 PubMed PMID: 39159748; PubMed Central PMCID: PMC11399640.
20. Li X, Li N, Zhao G, Wang X. Effect of iron supplementation on platelet count in adult patients with iron deficiency anemia. Platelets. 17 nov 2022;33(8):1214–9. doi:10.1080/09537104.2022.2091772 PubMed PMID: 36050842.