Iron-Induced Thrombocytopenia: A Mini-Review of the Literature and Suggested Mechanisms

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Abstract

Anemia constitutes a major global health burden, and iron deficiency is the most common cause of it. Iron deficiency and replacement affect not only hemoglobin (Hb) levels but also other hematological parameters such as platelet count. In this mini-review, we explore thrombocytopenia as a side effect of iron replacement therapy. We searched for relevant articles published in English, and all case reports/series of iron-induced thrombocytopenia were collected and analyzed. A total of 11 case reports and one case series were found relating to very low Hb at a baseline level of 5.25 +/- 2.2 g/dl and variable platelet count at baseline that dropped in 9 +/- 3 days to an average of 121 +/- 112 x 10^9/L, which in most of the cases was self-corrected. The parenteral route was more commonly reported to be associated with thrombocytopenia, and discontinuation of therapy was needed in two patients.

The mechanisms, prevalence, and clinical significance of thrombocytopenia associated with iron replacement are unknown; several effects of iron on the primary hematopoietic cells and stromal cell lines have been proposed, such as influence on common progenitors, effects on cytokines, and thrombopoietic effect of erythropoietin, which is directly affected by iron levels. Iron replacement can lead to significant thrombocytopenia. Further research is needed to describe the exact incidence, mechanism, and clinical significance of thrombocytopenia associated with iron supplementation.

Introduction And Background

Anemia is defined by the World Health Organization as "a condition in which the number of red blood cells (and consequently their oxygen-carrying capacity) is insufficient to meet the body's physiologic needs" [1]. The worldwide prevalence of anemia at ~24.8% [2] and its association with increased morbidity and mortality and decreased work productivity have made it an important public health burden [1,2]. Iron deficiency is the most common cause of anemia worldwide. Approximately 5% and 2% of American women and men, respectively, suffer from iron deficiency anemia (IDA) [3]. It occurs due to the unmet demand for iron to form normal red blood cells.

IDA is generally caused by inadequate intake of iron, chronic blood loss, or a combination of both [3-5]. A less common cause is malabsorption of iron secondary to gastric and/or duodenal resection or inflammatory conditions like infectious or atrophic gastritis, or tropical sprue. A rare cause includes a genetic mutation in TMPRSS6 leading to iron-refractory IDA [6]. Iron deficiency is often associated with thrombocytosis rather than thrombocytopenia; however, both have been described in the literature for more than 50 years [7]. On the other hand, iron replacement has a similar range of effects on thrombopoiesis [8].

In this article, we review the relevant literature published in English to shed light on the link between iron replacement and thrombocytopenia in patients with IDA.

Review

Methods

We searched the databases PubMed and Scopus for all relevant articles published in the literature in English using the following Medical Subject Headings (MeSH) terms: [deficiency, Iron] [replacement] [supplement] [anemia] [thrombocytopenia] [platelet]. Data were then collected, recorded, and analyzed.

Results

A total of 11 individual case reports and one case series (containing 9 patients) were found, which are summarized in Tables 1-4 [9-19]. The age of the patients in the study ranged between 15 and 42 years, and a female predominance was observed (a female-to-male ratio of approximately 3:1) (Table 1). At baseline,
the hemoglobin (Hb) concentration was 5.25 +/- 2.2 g/dl, serum iron concentration was 20 +/- 12.8 ug/dl, and serum ferritin level was 9 +/- 11.8 ng/dl, denoting a severe form of IDA. After iron replacement, Hb concentration increased to 8.03 +/- 1.47 and serum iron concentration increased to 78 +/- 22.5 ug/dl (Table 2). Before iron therapy, the platelet count was 469 +/- 404 x 10^9/L. The nadir platelet count occurred after 9 +/- 3 days to a mean count of 121 +/- 112 x 10^9/L (Table 3). The intravenous route was associated with a higher incidence of iron-associated thrombocytopenia than oral and intramuscular routes. Two patients needed platelet transfusions. Thrombocytopenia led to discontinuation of iron replacement in two patients. Both were receiving iron sucrose (Table 4). In the last follow-up of those patients, Hb concentration was found to be increased to 11.5 +/- 2.3 g/dl, and platelet count had increased to 322 +/- 233 x 10^9/L.

| No | Authors                          | Year of publication | Patient gender | Patient age (years) | Patient ethnicity |
|----|----------------------------------|---------------------|----------------|---------------------|-------------------|
| 1  | Giordano et al. [9]              | 2019               | Male           | 16                  | African           |
| 2  | Bayhan et al. [10]               | 2016               | Female         | 15                  | NA                |
| 3  | Kahraman et al. [11]             | 2016               | Male           | 17                  | NA                |
| 4  | Cunha et al. [12]                | 2015               | Female         | 16                  | NA                |
| 5  | Lindgren et al. [13]             | 2009               | Male           | NA                  | NA                |
| 6  | Ganti et al. [14]                | 2007               | Female         | 39                  | African American  |
| 7  | Taskapan et al. [15]             | 2003               | Female         | 37                  | NA                |
| 8  | Go et al. [16]                   | 2000               | Female         | 30                  | NA                |
| 9  | Soff and Levin (case 1) [17]     | 1988               | Female         | 17                  | NA                |
| 10 | Soff and Levin (case 2) [17]     | 1988               | Female         | 17                  | NA                |
| 11 | Knizley et al. [18]              | 1972               | Male           | 42                  | Black             |
| 12 | Lioger et al. (series) [19]      | 2016               | 1 male, 8 females | NA                  | NA                |

**TABLE 1: Cases publication year, and age, gender, and ethnicity of patients**

NA: not available
| No | Authors                        | Hb at baseline | MCV | Hb during replacement | Hb after replacement | Iron at baseline | Iron after replacement | Fe sat at baseline | Fe sat after replacement | Ferritin at baseline | Ferritin after replacement |
|----|--------------------------------|----------------|-----|-----------------------|----------------------|-----------------|------------------------|-------------------|--------------------------|----------------------|-----------------------------|
| 1  | Giordano et al. [9]            | 5.2 g/dL       | 54.5 fl | 8.4 g/dL               | 13.3 g/dL            | NA              | NA                     | NA                | NA                       | 3.1 ng/mL             | NA                         |
| 2  | Bayhan et al. [10]             | 4.7 g/dL       | 64.2 fl | 8.2 g/dL               | 9.6 g/dL             | NA              | NA                     | 9.5%              | Na                       | 2.4 ng/mL             | NA                         |
| 3  | Kahraman et al. [11]           | 7.6 g/dL       | 66 fl  | NA                    | NA                   | 27 µg/dl        | NA                     | NA                | NA                       | 3 ng/mL               | NA                         |
| 4  | Cunha et al. [12]              | 5.8 g/dL       | 63 fl  | 8.1 g/dl              | 8.8 g/dl             | NA              | 78 mcg/dl              | NA                | NA                       | NA                   | NA                         |
| 5  | Lindgren et al. [13]           | NA             | NA     | NA                    | NA                   | NA              | NA                     | NA                | NA                       | NA                   | NA                         |
| 6  | Ganti et al. [14]              | 3.1 g/dL       | 58.6 fl | 5.2 g/dl               | 14.0 g/dL            | 17 µg/dl        | NA                     | 4%                | NA                       | <2 ng/dL              | 121 ng/mL                  |
| 7  | Taskapan et al. [15]           | 10.1 g/dL      | 88.2 fl | 8.9 g/dl               | 9.9 g/dl             | 19 µg/dl        | NA                     | 7%                | NA                       | 35.5 µg/L             | NA                         |
| 8  | Go et al. [16]                 | 3.1 g/dL       | 77 fl  | NA                    | NA                   | 5 µ/dL          | NA                     | 1%                | NA                       | 8 mg/L               | NA                         |
| 9  | Soff and Levin (case 1) [17]   | 3.2 g/dL       | NA     | 22 µg/dl               | NA                   | NA              | NA                     | <10 ng/ml         | NA                       | NA                   | NA                         |
| 10 | Soff and Levin (case 1) [17]   | 3.2 g/dL       | Low    | 7 µ/dL                | NA                   | NA              | NA                     | NA                | NA                       | NA                   | NA                         |
| 11 | Knizley et al. [18]           | 6.1 g/dL       | 9.4 g/dL | 13.6 g/dL              | 43 mg/dl             | NA              | 8%                     | NA                | NA                       | NA                   | NA                         |
| 12 | Lioger et al. (series) [19]    | 5.7 ± 2.3 g/dL | 63 fl  | NA                    | NA                   | NA              | NA                     | NA                | NA                       | NA                   | NA                         |

**TABLE 2: Hemoglobin and iron profile at baseline and during and after iron therapy**

Hb: hemoglobin; MCV: mean corpuscular volume; Fe sat: iron saturation; NA: not available
Table 3: Platelet count before, during, and after replacement

| No | Authors                          | Route of iron replacement | Type of iron replacement | Dose            | Discontinuation |
|----|----------------------------------|---------------------------|--------------------------|-----------------|-----------------|
| 1  | Giordano et al. [9]              | Oral                      | Ferrous sulfate          | NA              | No              |
| 2  | Bayhan et al. [10]               | Oral                      | Ferrous glycine sulfate  | 4 mg/kg         | No              |
| 3  | Kahraman et al. [11]             | IV                        | Iron sucrose             | 100 mg/day      | No              |
| 4  | Cunha et al. [12]                | IV                        | Iron sucrose             | 100 mg          | Yes             |
| 5  | Lindgren et al. [13]             | NA                        | NA                       | NA              | NA              |
| 6  | Ganti et al. [14]                | IV                        | Iron sucrose             | 100 mg 2xwk    | No              |
| 7  | Taskapan et al. [15]             | IV                        | Iron sucrose             | 200 mg daily    | No              |
| 8  | Go et al. [16]                   | IM                        | Iron dextran             | 100 mg/day      | Yes (changed to oral) |
| 9  | Soff and Levin (case 1) [17]     | Oral                      | Ferrous sulfate          | 300 mg TID      | NA              |
| 10 | Soff and Levin (case 2) [17]     | Oral                      | Ferrous gluconate        | NA              | NA              |
| 11 | Knizley et al. [18]              | Oral                      | Iron sucrose             | 235 mg TID      | No              |
| 12 | Lioger et al. (series) [19]      | IV: 8, IM: 1              | Iron sucrose/ferric carboxymaltose | NA | NA |

Table 4: Iron replacement route, preparation, and dose, and whether discontinuation/transfusion was required

| No | Authors                          | Route of iron replacement | Type of iron replacement | Dose            | Discontinuation |
|----|----------------------------------|---------------------------|--------------------------|-----------------|-----------------|
| 1  | Giordano et al. [9]              | Oral                      | Ferrous sulfate          | NA              | No              |
| 2  | Bayhan et al. [10]               | Oral                      | Ferrous glycine sulfate  | 4 mg/kg         | No              |
| 3  | Kahraman et al. [11]             | IV                        | Iron sucrose             | 100 mg/day      | No              |
| 4  | Cunha et al. [12]                | IV                        | Iron sucrose             | 100 mg          | Yes             |
| 5  | Lindgren et al. [13]             | NA                        | NA                       | NA              | NA              |
| 6  | Ganti et al. [14]                | IV                        | Iron sucrose             | 100 mg 2xwk    | No              |
| 7  | Taskapan et al. [15]             | IV                        | Iron sucrose             | 200 mg daily    | No              |
| 8  | Go et al. [16]                   | IM                        | Iron dextran             | 100 mg/day      | Yes (changed to oral) |
| 9  | Soff and Levin (case 1) [17]     | Oral                      | Ferrous sulfate          | 300 mg TID      | NA              |
| 10 | Soff and Levin (case 2) [17]     | Oral                      | Ferrous gluconate        | NA              | NA              |
| 11 | Knizley et al. [18]              | Oral                      | Iron sucrose             | 235 mg TID      | No              |
| 12 | Lioger et al. (series) [19]      | IV: 8, IM: 1              | Iron sucrose/ferric carboxymaltose | NA | NA |

Discussion

Thrombocytopenia may occur in patients with severe IDA who receive iron therapy; however, it is very uncommon [3]. Its pathogenesis remains undetermined but is thought to be related to the alteration in the
activity of iron-dependent enzymes involved in thrombopoiesis [14,20].

Iron has a synthetic and regulatory role in platelet production, and animal models have suggested a common progenitor cell for erythroid and megakaryocytic cell lineages [21]. The reviewed cases who developed thrombocytopenia after iron replacement, especially parenteral iron, had a significant reduction in platelet count that was self-corrected in most of the cases. The mechanisms, prevalence, and clinical significance of this thrombocytopenia are unknown [15-18,22]. Iron has a synthetic and regulatory role in platelet production. Iron can induce cell death by generating free radicals as it interconverts between ferrous (Fe2+) and ferric (Fe3+) forms. A randomized, placebo-controlled, double-blind, parallel-group study was performed on 38 peritoneal dialysis patients before and after a single intravenous infusion of 500 mg iron sucrose. Iron infusion increased in total (Δ 601 μg/100 mL, CI 507, 696) and non-transferrin-bound iron (Δ 237.2 μmol/L, CI 173.6, 300.8) increased approximately by 10-fold, as well as redox-active iron by nearly five-fold (Δ 0.76 μmol/L, CI 0.54, 0.98) [23].

Animal models have suggested a common progenitor cell for erythroid and megakaryocytic cell lineages [21]. An in vitro study examined the effects of iron load (that may simulate the process of iron infusion in patients with IDA) on the function of primary hematopoietic cells and stromal cell lines and found that iron overload impairs normal hematopoietic cells and modifies the function of stromal cells, indicating that iron overload impairs the whole hematopoietic system. The authors suggested that the deleterious effects of iron were mediated through its impact on hematopoietic stem/progenitor cells as well as in differentiated hematopoietic via reactive oxygen species (ROS) accumulation [24]. In addition, an in-vitro study showed that ferrous ammonium sulfate (FeAS) induced growth arrest and apoptosis in immature hematopoietic cells and led to insulin-like growth factor binding protein 2 (IGFBP2) and insulin-like growth factor 1 (IGF-1) down-regulation. Both have been found to stimulate the survival, proliferation, and cycling of hematopoietic stem cells (HSCs) [25].

Although thrombopoietin is the primary growth factor and regulator of megakaryopoiesis, several other cytokines such as interleukin (IL)-1, IL-3, IL-6, IL-11, and tumor necrosis factor are also involved in this process [26-28]. Erythropoietin shares some structural features with thrombopoietin and may exhibit a synergistic effect on platelet production. The levels of endogenous erythropoietin significantly decrease during the correction of iron deficiency. This reduction in endogenous erythropoietin might decrease the productivity of megakaryocytes and lead to transient thrombocytopenia [29,30].

In this study, we observed that young females are more likely to be affected by IDA. Further research is needed to explore whether this is because IDA per se is more common in this population or if there are other explanations related to female sex hormone or genetic profile. Another observation was that platelet nadir occurred within 15 days of iron replacement initiation; however, the number of cases was too small to recommend following platelet count in asymptomatic patients within this timeframe.

Conclusions

Significant thrombocytopenia occasionally occurs in patients receiving iron therapy for IDA. This condition is transient and self-limited in most of these cases. Various mechanisms can contribute to this thrombocytopenia. Dedicated observational and experimental studies are needed to describe the correlation between iron profile, hemoglobin level, genetic factors, cytokines, growth factors and thrombopoiesis; these studies should look for predictors that could determine which individuals will get thrombocytopenia on receiving iron supplements.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors declare that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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