Annals of Hematology (2019) 98:2299–2302
https://doi.org/10.1007/s00277-019-03757-0

ORIGINAL ARTICLE

# Iron deficiency, an unusual cause of thrombocytopenia: results from a multicenter retrospective case-controlled study

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Received: 18 June 2019 / Accepted: 10 July 2019 / Published online: 23 August 2019


## Abstract

Iron deficiency anemia (IDA) is often associated with mild to moderate thrombocytosis, and iron deficiency–associated thrombocytopenia (IDAT) is much more uncommon and often misdiagnosed as immune thrombocytopenia (ITP). To better describe the features of IDAT, we conducted a retrospective multicenter case-control study. We identified 10 patients (9 women) with a definite diagnosis IDAT, with a median age of 43.5 [range, 16–72] years and a median platelet count of $30.5 \times 10^9$/L [range, 21–80], and 7 patients with a possible diagnosis of IDAT. Bleeding manifestations were absent in all patients but one. All the patients recovered (platelet count $\geq 150 \times 10^9$/L) upon iron therapy ± red blood cell transfusion after a median time of 6 [4–39] days. When compared with 30 randomly newly diagnosed ITP patients matched on age, the baseline platelet count was significantly lower in ITP (median = $7 \times 10^9$/L [4–59], $p < 0.001$) whereas MPV was higher (10.5 fL [9,4–13,8] vs 8.2 fL, for IDAT $p < 0.001$). The median platelet count on day 7 was $337 \times 10^9$/L [113–1000] for IDAT cases vs $72 \times 10^9$/L [13–212] for ITP controls ($p < 0.001$). IDAT is potentially an under-recognized cause of thrombocytopenia that may be easily managed with iron therapy.

**Keywords** Thrombocytopenia · Iron deficiency anemia · Immune thrombocytopenia

## Introduction

Iron deficiency anemia (IDA) is by far the most frequent cause of anemia worldwide, affecting mostly children and women of childbearing age, with an estimated prevalence of 25% [1, 2]. There is experimental evidence in human and mice suggesting that iron acts on the bipotent progenitor biasing lineage commitment and promoting megakaryocytic commitment of megakaryocytic-erythroid progenitors explaining the moderate induced-thrombocytosis that may classically be observed in IDA [3–5]. Conversely, iron deficiency–associated thrombocytopenia (IDAT) is much more uncommon and the underlying mechanisms are not known.

Although already reported in the literature by others, IDAT is an under-recognized cause of thrombocytopenia that can be easily misdiagnosed as immune thrombocytopenia (ITP) with

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bleeding and secondary IDA. Since both the management and outcome of IDAT and ITP are different, distinguishing these 2 entities is important in order to avoid inappropriate treatment.

To better describe the characteristics of patients with IDAT and identify the discrepancies with those of patients with a definite diagnosis of newly diagnosed primary ITP, we conducted a retrospective multicenter case-control study.

## Patients and methods

This study was a retrospective multicenter case-control study including 9 internal medicine or hematology departments in the Paris area between February 2009 and April 2019.

A definite diagnosis of IDAT was defined by: (1) the occurrence of thrombocytopenia (i.e., platelet count < $100 \times 10^9$/L) with (2) concomitant iron deficiency anemia (i.e., hemoglobin level below 130 g/L in men or 120 g/L in women with a ferritin level < 30 μg/L), and (3) a rapid recovery of the platelet count upon the sole iron therapy. Patients with pre-existing thrombocytopenia at the time of IDA diagnosis or with any other obvious cause of thrombocytopenia (drug-induced, liver disease…) were excluded. Inclusion criteria for cases were systematically reviewed and validated by two of the authors (TH, MM). Patients who fulfilled the above-mentioned criteria but were treated with prednisone in combination with iron supplementation were not excluded but were analyzed separately and only considered as "possible" cases of IDAT.

Patients with a definite diagnosis of IDAT were compared, in a 1 to 3 ratio, to a control group of patients with a newly diagnosed primary ITP [6], matched on gender and age ± 5 years. Patients from the control group were recruited throughout the ITP database of the national referral center for adult'cytopenias at Henri Mondor University Hospital.

Data are presented as mean ± SD or median (interquartile range [IQR]) for continuous variables, depending on their distribution. Categorical variables are presented as number (%). Comparison of parameters between groups was analyzed by Wilcoxon-Mann-Whitney (univariate analysis) non-parametric test for continuous variables. A value of $p < 0.05$ was considered significant.

The study was conducted in accordance with the ethical rules of the Helsinki Declaration and approved by our local IRB.

## Results

In total, the data from 20 patients were reviewed among whom 10 patients fulfilled the criteria of definite IDAT whereas 7 patients had a diagnosis of possible IDAT, 2 patients were excluded because of a previous history of intermittent thrombocytopenia, and 1 patient was lost of follow-up before the

**Table 1** Characteristics of the 10 patients with iron deficiency–associated thrombocytopenia

| Patient | Gender | Age (years) | Origin | Hb (g/dL) | MCV (fl) | Plateletcount ($\times 10^9$/l) | MPV (fl) | Ferritin level (μg/l) | Bone marrow aspirate | Cause of iron deficiency | Thrombocytopenia-associated bleeding manifestations | Time to reach a normal pt count (days) | platelet count peak within 7 days after i.v iron ($\times 10^9$/L) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 45 | Caucasian | 2.9 | 61 | 24 | 7.6 | 2 | ND | Malabsorption | No | 4 | 337 |
| 2 | F | 17 | West Africa | 4.4 | 59 | 33 | 7.8 | <3 | Normal, MKs++ | Menorrhagia | No | 4 | 1.000 |
| 3 | F | 38 | West Africa | 2.1 | 75 | 22 | NA | 10 | ND | Menorrhagia + clay intake | No | 4 | 354 |
| 4 | F | 44 | French West Indies | 5.1 | 63 | 28 | 8.7 | 6 | ND | Menorrhagia | Epistaxis | 5 | 341 |
| 5 | M | 72 | Caucasian | 7.1 | 67 | 80 | 8.2 | 5 | Normal, MKs++ | GI bleeding | No | 15 | NA |
| 6 | F | 53 | Caucasian | 5.7 | 65 | 56 | NA | 8 | ND | Menorrhagia | No | 39 | 113 |
| 7 | F | 43 | Caucasian | 5.3 | 54 | 55 | 8.6 | 10 | Normal, MKs ++ | Clay intake | No | 18 | 113 |
| 8 | F | 16 | West Africa | 4.2 | 65 | 21 | NA | 2 | ND | Menorrhagia | No | 7 | 321 |
| 9 | F | 40 | West Africa | 6.4 | 56 | 42 | NA | 6 | ND | Menorrhagia | No | 4 | 182 |
| 10 | F | 23 | West Africa | 3.4 | 55 | 11 | NA | 6 | Normal, MKs ++ | Menorrhagia | No | 3 | 316 |

F = female; M = male; Hb = hemoglobin; MCV = mean corpuscular volume; MPV = mean platelet volume; MKs ++ = increased number of megacaryocytes, GI = gastro intestinal, ND = not done, NA = non available, i.v = intravenous

increase of the platelet count upon iron supplementation could be ascertained.

Baseline characteristics of the 10 cases of IDAT are presented in Table 1. There were 9 women (90%), with a median age of 43.5 [range, 16–72] years and a median platelet count of 30.5 [range, 21–80] × $10^9$/L at time of IDAT diagnosis. The median of the mean platelet volume (MPV) was 8.2 [7.6–8.7] fL. Median hemoglobin level was 4.7 [range, 2.1–7.1] g/dL with a median value of the mean corpuscular volume (MCV) of 64 [54–75] fL.

Iron deficiency was severe with a median ferritin level of 6 [2–10] μg/L. The underlying cause of IDA was menorrhagia ($n = 7$ patients), associated with consumption of clay in one, celiac disease ($n = 1$), occult bleeding from the GI tract ($n = 1$), and consumption of clay ($n = 1$).

All but one patient received intravenous iron therapy, one oral supplementation, and 7 (70%) received a blood transfusion because of severe anemia.

Beyond the underlying cause of IDA, cutaneous and/or mucosal purpura was observed in none of the patients but one who has a single episode of epistaxis. All patients had a rapid platelet increase and recovered (platelet count ≥ 150 × $10^9$/L) without further therapy within a median time of 6 [4–39] days. On day 7 after the initiation of iron therapy or red-blood cell transfusion, the median platelet count was 337 [113–1 000] × $10^9$/L.

The data from 30 randomly selected ITP patients (27 women and 3 men, median age 42.5 [17–74] years) serving as controls were analyzed. The platelet count at time of diagnosis was significantly lower among controls with a median of 7 × $10^9$/L [4–59] versus 30.5 × $10^9$/L for the "cases" ($p < 0.001$) whereas MPV was higher (10.5 fL [9.4–13.8] vs 8.2 fL, $p < 0.001$) among the controls. Clinical bleeding symptoms were present in 25 of the controls (83.3%) at onset compared with only one for the cases (10%, $p < 0.001$). Median hemoglobin level in ITP controls was 12.9 g/dL [7.4–14.4] with a MCV of 88 fL [range, 55-96 fL]. Following steroids therapy ± intravenous immunoglobulin, the platelet count normalized in only 16/30 cases (53.3%) with a median time to normalization of 21 days [7–30] vs only 6 days among the cases ($p = 0.009$). The median platelet count on day 7 was 72 × $10^9$/L [13–212] among the controls vs 337 × $10^9$/L [113–1000] for the cases ($p < 0.001$). For 2 cases for whom repeated counts were available a reactive thrombocytosis was observed.

Comparisons between cases and controls are summarized in Table 2.

Among the 7 patients with a "possible" diagnosis of IDAT, median hemoglobin level was 4.7 [3.5–7.6] g/dL with a median MCV of 61 [50–81] fL and a median platelet count of 26 [9–45] × $10^9$/L without any bleeding except for 1 patient who had a mild epistaxis. Platelets count normalized in 6/7 cases (85.7%), with a median time to normalization of 6.5 days [5–12].

**Table 2** Comparison between cases and controls

| | Definite Cases ($n = 10$) | ITP Controls ($n = 30$) | $p$ value |
|---|---|---|---|
| Age (years) | 43.5 | 42.5 | 0.82 |
| Hemoglobin (g/dL) | 4.7 | 12.9 | < 0.001 |
| MCV (fL) | 64 | 88 | < 0.001 |
| Platelets (× $10^9$/L) | 30.5 | 7 | < 0.001 |
| MPV (fL) | 8.2 | 10.5 | < 0.001 |
| Reticulocytes (× $10^9$/L/) | 39 | 50 | 0.055 |
| Ferritin (μg/l) | 6 | 57 | ND |
| Median time before platelet recovery (days) | 6 | 21 | 0.009 |

*Hb*, hemoglobin; *MCV*, mean corpuscular volume ; *MPV*, mean platelet volume; *ND*, not done

## Discussion

In the present study, we have been able to identify and describe, based on rather stringent pre-established diagnosis criteria, a series of 10 patients (almost exclusively women of childbearing age) suffering from what we defined as IDAT.

We excluded from the main analysis 7 patients with concomitant iron deficiency anemia and thrombocytopenia who had received corticosteroids in combination with iron supplementation in the event of ITP. By analyzing separately these 7 patients, we found that their characteristics were actually very similar to those of the "definite cases" (Table 3). This finding suggests that in clinical practice, a number of patients with IDAT are actually misdiagnosed and treated as they had primary ITP with subsequent bleeding and secondary IDA. In their study, Verma et al. compared the hematologic parameters of 10 patients with IDAT

**Table 3** Comparisons between cases and possible cases

| | Definite cases ($n = 10$) | Possible cases ($n = 7$) | $p$ value |
|---|---|---|---|
| Age (years) | 43.5 | 37 | 0.77 |
| Hemoglobin (g/dl) | 4.7 | 4.7 | 0.89 |
| MCV (fL) | 64 | 61 | 0.85 |
| Platelet count (× $10^9$/L) | 30.5 | 26 | 0.38 |
| MPV (fL) | 8.2 | 10.7 | 0.1 |
| Reticulocytes (× $10^9$/L) | 39 | 48 | 0.68 |
| Ferritin (μg/L) | 6 | 6.7 | 0.7 |
| Median time before platelet standardization (days) | 6 | 6.5 | 0.28 |

*Hb*, hemoglobin; *MCV*, mean corpuscular volume; *MPV*, mean platelet volume

to those of 25 women who had been diagnosed with IDA without thrombocytopenia [1]. Thrombocytopenia appeared to be associated with deeper iron deficiency as the patients had lower hemoglobin and MCV levels, some features that were also observed in our study.

Moreover, as seen in the present study, the decrease of the platelet count was weaker in IDAT when compared with newly diagnosed ITP. That the level of MPV (or the immature platelet fraction when available) was significantly lower in the setting of IDAT suggests that the proportion of "young" reticulated platelets in the peripheral blood is likely to be lower in this situation and one can speculate that profound iron deficiency within the bone marrow niche could also have a negative effect on megakaryopoiesis. As expected though, the analysis of a marrow aspirate was not helpful for discriminating between both conditions [7].

Finally, one of the major differences between IDAT and ITP is the time to platelet recovery on treatment which is significantly shorter in case of IDAT leading even in some patients to a transient rebound thrombocytosis. This phenomenon is not observed in newly diagnosed ITP when an initial CR is obtained with corticosteroids ± Ig.IV unless the patient is treated concomitantly with a thrombopoietin receptor agonist [8]. These data suggests an underlying decrease of platelet release from megakaryocytes in IDAT patients that can be rapidly corrected with iron therapy.

The study limitations are primarily due to its retrospective design and the relatively small number of patients This small sample size is likely to reflect the rarity of this situation which is however likely to be underdiagnosed in clinical practice as suggested by the analysis of the 7 "possible cases."

In conclusion, IDAT is potentially an underestimated and under-recognized cause of thrombocytopenia that should not be misdiagnosed as ITP complicated by iron deficiency anemia. Consultant hematologists should be aware of this unusual presentation in order to avoid the use of corticosteroids and/or IV.Ig but rather promptly consider the use of intravenous iron in the absence of any active bleeding manifestations.

## Compliance with ethical standards

The study was conducted in accordance with the ethical rules of the Helsinki Declaration and approved by our local IRB.

**Conflict of interest** The authors declare that they have no conflict of interest.

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