Platelets, September 2009; 20(6): 401–405

informa
healthcare

ORIGINAL ARTICLE

Platelet counts in adults with iron deficiency anemia

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(Received 10 April 2009; revised 17 June 2009; accepted 23 June 2009)

Abstract
In adults with iron deficiency anemia (IDA), abnormal platelet counts were seen in several studies. However we retrospectively examined the clinical records of a larger number of adults with IDA to assess abnormal platelet counts. From November 2006 to April 2008, 615 consecutive adults (73 men and 542 women; age range, 16–88 years) with IDA were included in this study. The mean initial hemoglobin was 9.0 ± 1.8 g/dL (range 2.7–12.8 g/dL), and the mean initial platelet count was $304 \times 10^3/\mu L \pm 92.3$ (range, $105–700 \times 10^3/\mu L$). The initial platelet counts were normal in 520 (84.6%) adults with IDA. Thrombocytosis ($>400 \times 10^3/\mu L$) and thrombocytopenia ($<150 \times 10^3/\mu L$) were detected in 82 (13.3%) and 13 (2.1%) adults with IDA, respectively. In conclusion, thrombocytosis was seen at lower rates in our study. Furthermore, this study shows that mild thrombocytopenia is not so rare in adults with IDA.

Keywords: *Thrombocytosis, thrombocytopenia, platelet count, iron deficiency anemia*

Introduction

The causes of thrombocytosis are classified as primary (clonal) or secondary (reactive). The clonal thrombocytosis is observed in chronic myeloproliferative diseases such as essential thrombocythemia or in some myelodysplastic syndromes [1]. Reactive thrombocytosis may occur in various conditions such as infections, surgery, malignancies, inflammatory diseases, trauma, asplenic states, and iron deficiency anemia (IDA) [1–6]. Thrombocytopenia may also be observed in various conditions such as infections, malignancies, drugs, connective tissue, idiopathic thrombocytopenic purpura, megaloblastic anemia, and IDA [6, 7].

IDA is the most common type of anemia worldwide. IDA is characterized by a defect in hemoglobin synthesis that results in microcytic red blood cells and decreased amount of hemoglobin. In addition to anemia, abnormal platelet counts also have been reported in both adults and children with IDA [1, 6, 8–14]. IDA may cause reactive thrombocytosis and thrombocytosis is mostly mild to moderate [1, 6, 8–10]. However, thrombocytopenia has also been reported in some patients with IDA, before and after initiation of iron therapy [6, 11–14].

In adults with IDA, although abnormal platelet counts were investigated in several studies, there is still a paucity of literature describing this subject. We therefore conducted an extensive retrospective study in order to assess the changes of platelet counts in adults with IDA.

Materials and methods

Between November 2006 and April 2008, 615 consecutive adults (≥16 years of age) with iron deficiency anemia were included in this retrospective study. All adults with iron deficiency anemia were followed up at a single center called Mehmet Aydın State Hospital, Samsun, Turkey. The inclusion criteria were: hemoglobin level less than 12 g/dL for women and less than 13 g/dL for men, serum ferritin level <15 μg/L. Patients with infections, acute hemorrhage, malignancies, thalassemia, hemolysis, chronic inflammatory disorders, trauma, folate or vitamin B12 deficiency were excluded. Normal platelet count was considered to be between

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ISSN 0953–7104 print/ISSN 1369–1635 online
DOI: 10.1080/09537100903137306

Table I. Hematological data of the 615 patients with IDA. Values are expressed as mean +/- standard deviation and median ± interquartile range within brackets.

	Male	Female	Total	
Parameters	$n=73$	$n=542$	$n=615$	p-value
Hemoglobin (g/dl)	8.8 ± 2.2	9.1 ± 1.7	9.0 ± 1.8	0.38
Hematocrit (%)	29.6 ± 6.2	29.5 ± 4.4	29.6 ± 4.7	0.84
RBC ($\times 10^{12}$/μL)	4.5 ± 0.7	4.3 ± 0.5	4.3 ± 0.5	0.014
MCV (fL)	64.7 ± 7.9	67.6 ± 7.4	67.3 ± 7.6	0.002
MCH (pg)	19.1 ± 3.4	20.6 ± 3.4	20.4 ± 3.4	0.0001
MCHC (g/dl)	29.3 ± 2.1	30.2 ± 2.2	30.2 ± 2.2	0.0001
RDW (%)	14.5 ± 1.9	14.2 ± 2.0	14.3 ± 2.0	0.27
Leukocyte counts ($\times 10^3$/μL)	6.7 ± 1.9	6.4 ± 1.7	6.4 ± 1.7	0.18
Platelet counts ($\times 10^3$/μL)	303 ± 91	304 ± 93	304 ± 92	0.88
MPV (fL)	9.5 ± 1.6	9.4 ± 1.6	9.4 ± 1.7	0.80
Platelet crit (%)	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.98
PDW (%)	12.5 ± 1.5	12.4 ± 1.5	12.4 ± 1.5	0.36
*Ferritin (μg/L)	(3.0 ± 3.5)	(3.0 ± 3.1)	(3.0 ± 3.1)	0.50
*Serum iron (μg/dL)	(13.5 ± 8.0)	(13.5 ± 20.9)	(15.0 ± 20.7)	0.07
Iron-binding capacity (μg /dL)	362 ± 52	352 ± 59	355 ± 59	0.22

Statistical tests: Unpaired t test, *Mann-Whitney U test.

150–400 × 10^3/μL. Thrombocytosis was defined as a platelet count more than 400 × 10^3/μL, while thrombocytopenia was defined as a platelet count lower than 150 × 10^3/μL. The platelet counts were determined using a HeCo counter (SEAC, Radim Company, Italy) with EDTA anticoagulated fresh blood. Ferritin was measured by a Modular Analytics E170 immunoassay analyzer (Roche/Hitachi, Tokyo, Japan). Abnormal platelets counts were confirmed by repeat examinations and/or peripheral smear examination. Upper-gastrointestinal endoscopy, rectosigmoidoscopy and gynecological examinations were performed in some patients for the determination of the bleeding foci.

Statistical analyses

Statistical analysis was performed with SPSS for Windows version 13.0 (SPSS Inc, Chicago, Il, USA). Continuous variables were expressed as means ± standard deviation and median ± interquartile range. Normality for continuous variables in groups was determined by the Shapiro Wilk test. Continuous variables showed normal distribution except ferritin and serum iron. Continuous variables were tested using the unpaired t test (except ferritin and serum iron). Mann Whitney U test was used for ferritin and serum iron variables because of abnormal distribution. Categorical variables were expressed in terms of number and percent. Categorical variables were tested using Pearson chi-square test. Pearson correlation test was used to evaluate the relationships among variables. Values of $P<0.05$ were considered to be statistically significant.

Results

We retrospectively examined the clinical records of 615 consecutive adults with IDA including 73 males (11.9%) and 542 females (88.1%). The mean age of the adults with IDA was 37 ± 14 years (range, 16 to 88 years). At diagnosis, mean hemoglobin level was 9.0 ± 1.8 g/dL (range, 2.7–12.8 g/dL), and mean platelet count was 304 × 10^3/μL ± 92.3 (range, 105–700 × 103/μL), respectively. Initial platelet counts were normal in 520 (84.6%) adults with IDA. Hematological data of the 615 patients with IDA are summarized in Table I.

Thrombocytosis and thrombocytopenia were detected in 82 (13.3%,) and 13 (2.1%) adult patients with IDA, respectively. Of the 82 patients with reactive thrombocytosis, eight were male and 74 female. The observed platelet counts ranged from 401 × 10^3/μL to 700 × 10^3/μL (median 469 × 10^3/μL). Frequency of thrombocytopenia was higher in females with a rate of 13.7% compared to 11.0% observed in males; but the difference was not significant. Of the 13 patients with thrombocytopenia, one was male and 12 were female. The observed platelet counts ranged from 105 × 10^3/μL to 145 × 10^3/μL (median 133 × 10^3/μL). The frequency of thrombocytopenia was higher in females with a rate of 2.2% and 1.4% in males; but the difference was not significant. Comparison of platelet count between male and female is shown in Table II.

There were inverse correlations between platelet counts and hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean platelet volume (MPV), platelet distribution width (PDW), and serum iron. There were linear correlations between platelet counts and

Table II. Comparison of platelet counts between male and female.

Platelet count	Female Number of the patients (%)	Male Number of the patients (%)	*p*-value*
$<150 \times 10^3/\mu L$	12 (2.2)	1 (1.4)	–
$150–400 \times 10^3/\mu L$	456 (84.1)	64 (87.6)	NS
$>400 \times 10^3/\mu L$	74 (13.7)	8 (11.0)	NS
Total patients ($n=615$)	542 (88.1)	73 (11.9)	

*Pearson chi-square test, NS, Non significant.

Table III. The relationship between platelet count and other parameters.

Parameters	Pearson coefficient	*p*-value*
Hemoglobin (g/dl)	−0.192	0.0001
Hematocrit (%)	−0.123	0.002
RBC ($\times 10^{12}/\mu L$)	0.050	0.218
MCV (fl)	−0.239	0.0001
MCH (pg)	−0.274	0.0001
MCHC (g/dl)	−0.222	0.0001
RDW (%)	0.101	0.012
MPW (fl)	−0.124	0.002
Platelet crit (%)	0.885	0.0001
PDW (%)	−0.277	0.0001
Ferritin (μg/L)	−0.051	0.203
Serum iron (μg/dL)	−0.109	0.008
Iron-binding capacity (μg /dL)	0.139	0.001

*Pearson correlation test.

red cell distribution width (RDW), platelet crit, and iron-binding. There was not a significant correlation between platelet counts and red blood cell count (RBC), and ferritin. The relationship between platelet counts and other parameters is shown in Table III.

In patients with severe IDA (hemoglobin <7 g/dL), frequency of thrombocytopenia was significantly higher than non-severe IDA ($P=0.022$).

In the etiology of IDA, 291 (47.3%) had excessive uterine bleeding, 52 (8.5%) had peptic ulceration/gastritis, 17 (2.8%) had hemorrhoid, 15 (2.4%) had gastrectomy, 10 (1.6%) miscellaneous, and 230 (37.4%) had cases of uncertain etiology.

Discussion

IDA has long been documented to be associated with reactive thrombocytosis [4–5]. In several studies, various rates of frequency of reactive thrombocytosis in IDA have been reported [5, 6]. In the present study, we examined clinical records of 615 consecutive adults with IDA, and found 82 (13.3%) who had thrombocytosis at the time of their first evaluation. However, the frequency of thrombocytosis in our analysis was lower than that in previous studies concerning with IDA. In a preliminary report, Kasper et al. [4] defined the platelet counts in 100 hospitalized older patients (53 men, 47 women) with IDA and reported that over 50% had thrombocytosis. Although this preliminary results were higher than the results in our studies, the causes of this difference may be: (1) lower numbers of patients; (2) lower initial hemoglobin levels (median value of 6.5 g/dl); (3) heterogeneous group such as cancer patients involved as well; and (4) platelet counts were done by a different method: indirect venous blood dry slide method. Recently, Kadikoylu et al. [6] examined 86 women with IDA and found that 27.9% had reactive thrombocytosis, roughly twice our results. Although in this study hemoglobin levels (10.3 g/dl) were similar to ours, the number of their patients was smaller than our study group. In another study group children were found with iron deficiency reactive thrombocytosis in up to one-third of them [15]. IDA usually causes mild to moderate thrombocytosis, although occasionally, the platelet count may exceed $1.000 \times 10^3/\mu L$ (extreme thrombocytosis) [1, 4, 16]. In a previous series of patients with IDA, the average platelet count was $499 \times 10^3/\mu L$, about twice the controls [5]. In the present study, iron deficiency-related thrombocytosis was mild to moderate, and extreme thrombocytosis was not observed. Although the mechanisms underlying iron deficiency-induced thrombocytosis are not well understood, it has been suggested that stimulation of platelet production by moderately increased endogenous erythropoietin may play a role in the pathogenesis of thrombocytosis [10]. On the other hand, Bilic and Bilic [17] reported that the amino acid sequence homology of thrombopoietin and erythropoietin might explain thrombocytosis in children with IDA. Reactive thrombocytosis disappears following iron supplementation, thus it is generally ignored. However, some authors suggest that reactive thrombocytosis occasionally may contribute to clinical consequences, such as thrombotic events [16, 18, 19].

Thrombocytopenia has also been reported in some children and adults with IDA at the time of diagnosis [11, 20–24]. Iron deficiency-associated thrombocytopenia generally has been documented as case reports, and there are only a few published series [6, 9, 11, 20–24]. In the present study, thrombocytopenia was found in 13 (2.1%) patients with IDA at diagnosis. Likewise, in a recent study of 86 female patients with IDA, the frequency of thrombocytopenia was 2.3% [6]. In another study, Gross et al. [9] defined the platelet counts in 60 untreated iron-deficient infants and children and reported that 17 (28.3%) had platelet counts of less than $175 \times 10^3/\mu L$ (range $50–175 \times 10^3/\mu L$). The mechanisms for the thrombocytopenia associated with iron deficiency are not well established, although iron plays a

critical role both in the synthesis of platelets and in the regulation of thrombopoiesis [25]. Iron deficiency-related thrombocytopenia can sometimes be severe (platelet count $<20 \times 10^3/\mu L$) at presentation [12, 22], and this may cause complexity at initial diagnosis. Although thrombocytopenia usually improves quickly after administration of iron therapy, it may occasional cause bleeding symptoms such as menorrhagia [22, 26]. We detected only mild thrombocytopenia; severe thrombocytopenia was not observed. Some authors have reported that thrombocytopenia can be seen in patients with more severe IDA, especially when hemoglobin level is <7 g/dL [6, 22, 24, 27]. Our results were partially consistent with their studies. Namely, frequency of thrombocytopenia was significantly higher in severe IDA than in non-severe IDA. Notwithstanding, thrombocytopenia was also observed in non-severe IDA patients. Based on our reports, careful observation of platelet levels before treatment for IDA may lead to detection of more cases. Our findings suggest that mild thrombocytopenia is not so rare in adults with IDA as thought.

Furthermore, thrombocytopenia may occasionally be observed in adults and children with IDA following oral [13] or parenteral [28, 29] iron therapy. In this study, while hemoglobin level returned to normal following oral iron therapy in one of our patients, mild thrombocytopenia ($108 \times 10^3/\mu L$) developed. Although, little is known about the mechanisms and clinical significance, this entity is self-limited even with continued iron therapy [29].

In conclusion, this study demonstrates that the frequency of reactive thrombocytosis in adult with IDA was lower than the previous studies. However the frequency of thrombocytopenia was in agreement with published data for adults. To our knowledge, this is the largest study to investigate the changes of platelet counts in patients with IDA. However it has some limitations. Firstly, there was no control group in this study. Secondly, we did not confirm platelet abnormalities associated with IDA improving after iron therapy in most patients because of their irregular control. Nevertheless, in these patients we assume that quantitative platelet abnormalities were secondary to IDA rather than to other causes. However, further studies are needed to confirm our results.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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