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Case studies on the association of Iron Deficiency Anemia with Thrombocytopenia and Reactive Thrombocytosis

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ABSTRACT

Iron Deficiency Anemia (IDA) is the most prevalent blood disorder. Iron deficiency stands as a major cause for most of the anemia cases in the country. So, suggestions and efforts are being made to signify the importance of iron in regular diet and in the form of supplementation. Iron deficiency can be addressed effectively but when untreated it can lead to other severe disorders. Thrombocytosis and Thrombocytopenia are two interlinked related to iron deficiency in most cases. Literature suggests that Reactive thrombocytosis (RT) is common in patients with iron deficiency. This study focusses on the retrospective investigations and correlation of the relationship between the ferritin content, anemia, platelet counts and normalization of the same with iron supplementation. Out of the 165 patients, 72 were fit for the study after subjecting to the exclusion criteria of inflammatory diseases, infections, neoplasms etc. These 72 were segregated on the basis of the diagnosis of Thrombocytosis or Thrombocytopenia to establish proper correlation. 61 of 72 patients were diagnosed with thrombocytosis which constituted about 84.72% of the selected patients. 11 of 72 patients were diagnosed with thrombocytopenia. In this study it is clearly evident that both reactive thrombocytosis and thrombocytopenia are resultant of IDA. The platelet levels were elevated in many patients and in few their levels were lowered . The determining factor of platelets count is ferritin saturation. The changes in the iron saturation resulted in both elevation and depression in the platelet count. The platelet morphology lead to the changes in the platelet parameters. it can be advocated that both the conditions are rare and can occur concurrently in patients with IDA.

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INTRODUCTION

Iron Deficiency Anemia (IDA) is the most prevalent blood disorder (Beutler *et al.*, 2003). It is also common in pregnant women and few adult women who follow abnormal dieting patterns which facilitates low iron (Looker *et al.*, 1997). Novel initiatives had been started by the governments to meet the nutritional requirements of the poor population (Sherry *et al.*, 1997). Still iron deficiency stands as a major cause for most of the anemia cases in the country. So, suggestions and efforts are being made to signify the importance of iron in regular diet and in

the form of supplementation (Desforges and Oski, 1993). Iron deficiency can be addressed effectively but when untreated it can lead to other severe disorders. The patient gets lethargic, irritable, tachycardic followed by tachypnea, reduced appetite and experience events of CHF.

Thrombocytosis and Thrombocytopenia are two conditions and is related to iron deficiency in most cases. Literature suggests that Reactive thrombocytosis (RT) is common in patients with iron deficiency (Hiçsönmez *et al.*, 1978; Akan *et al.*, 2000; Beguin, 1999). There are rare cases where thrombocytopenia is associated with the low ferritin levels in the body (Guralnik *et al.*, 2004; Van K. Morris *et al.*, 2010). Overall, both the diagnoses are commonly associated with variations in the iron levels and are often normalized with iron supplementation (Perlman *et al.*, 2002).

Although above studies suggest the correlation between iron deficiency and altered platelet count, the dilemma still exist if the low iron content or anemia stands as etiology for thrombocytopenia or thrombocytosis. This study focusses on the retrospective investigations and correlation of the relationship between the ferritin content, anemia, platelet counts and normalization of the same with iron supplementation. All the groups would be compared to the normal groups to establish the correlation.

METHODOLOGY

Case presentation

Case reports of 165 out-patients were collected which ranged across 6 months from the time of study. Patients with initial presentation of platelets count <70x10^9/L and diagnosed with thrombocytopenia, platelets count >400x10^9/L and diagnosed with thrombocytosis (Cantor *et al.*, 2018), Heamoglobin levels <10.5 g/dL for male patients and <8.5 g/dL for female patients diagnosed with anemia and serum iron levels <30 μg/dL were selected for the study. Neoplasms or cancers, Immune disorders like Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Inflammatory Disorders and infections, severe haemorrhages or wounds were considered as exclusion criteria. These case reports were subjected to scrutiny based on the inclusion and exclusion criteria and reports of 72 patients were selected for the study.

Statistical Analysis

The data was expressed as mean and their respective standard deviations. The obtained data was subjected to the statistical analysis and the correlation was tested using Pearson's Correlation test. The linear relationship was studied between the iron parameters and platelet parameters with respect to the haemoglobin content. It was also analysed using One-way ANNOVA with P>0.05 were found to be significantly different.

RESULTS

The case reports of almost 165 patients were studied who were diagnosed with anemia and the iron deficiency was estimated through the lab results of the iron saturation, serum ferritin and serum iron content. Their blood profile at their initial presentation was given in Table 1. Out of the 165 patients, 72 were fit for the study after subjecting to the exclusion criteria of inflammatory diseases, infections, neoplasms etc. These 72 were segregated on the basis of the diagnosis of Thrombocytosis or Thrombocytopenia to establish proper correlation. 61 of 72 patients were diagnosed with thrombocytosis with an elevated platelet count of above 400x10^9/L of blood. It constituted to about 84.72% of the total patients selected for the study. 11 of 72 patients were diagnosed with thrombocytopenia which constituted about 15.27% of the selected patients.

All the patients had a very low haemoglobin level, and were diagnosed with anemia. The correlation between anemia and iron deficiency was made through the serum iron content. Physician diagnosed the type of anemia as iron deficiency type except in 2 patients wherein the etiology was unknown and the anemia type was unspecified. They satisfied all the other parameters, and so were included in the study. With the iron supplementation the iron deficiency was normalised and the patients recovered completely from anemia after 60 days. There was a significant increase in the iron and ferritin level in the blood during 15, 30, 45 and 60 days of treatment. haemoglobin levels were restored to normal in the specified period.

The presentation of the patients with thrombocytosis had a very high count of platelets of about 424.57±8.45 which was higher than normal platelet count. The count eventually normalized during the course of treatment. when the patient completely recovered from anemia and his iron content replenished, the platelet count also was became normal to about 274.27±9.11. The Mean Platelet volume (MPV), Platelet crit (PCT) remained normal through the hospital visits and treatment. The platelet distribution width (PDW) was random and accounted to about 32.17±4.87% in the initial visit to the hospital.

The one-way ANNOVA test results showed that

Table 1: Haematological parameters in the initial presentation (n=72)

Patient parameter	Initial Value (n=72)	Limits of normal range
Blood cell paramters		
Haemoglobin (g/dL)	9.6±1.3 (Male) 7.1±0.9 (Female)	14-16 (Male) 12-14 (Female)
RBC Count (x10^6 cells/μL)	2.45±0.61 (Male) 1.80±0.48 (Female)	4.7-6.9 (Male) 3.9-5.1 (Female)
Hematocrit (%)	34.4±2.1 (Male) 30.7±2.8 (Female)	39-49 (Male) 34-44 (Female)
Blood Iron parameters		
Serum Ferritin (μg/DL)	9.24±3.08	15-150
Serum Iron (μg/DL)	25.14±8.36	60-170
Transferritin saturation (%)	12.4±3.6	25-35
Platelet parameters		
Platelet count (PC) (x10/L)	424.57±8.45 Thrombocytosis 60.49±5.41 Thrombocytopenia	150-390
Mean Platelet Volume (MPV) (fL)	9.93±1.42	9.4–12.3
Plateletcrit (PCT) (%)	0.24±0.04	0.22-0.24
Platelet Distribution Width (PDW) (%)	20.04±1.74	

Table 2: Change in the blood profile during the treatment in thrombocytosis patients (n=61)

Blood parameter	15 days	30 days	45 days	60 days
Haemoglobin (g/dL)	11.5±0.4 ^{a}(Male) 8.6±0.5 (Female)	13.0±0.2 ^{a}(Male) 9.9±0.6 (Female)	13.8±0.3 ^{a}(Male) 12.6±0.7 (Female)	14.1±0.3 a (Male) 12.7±0.8 (Female)
RBC Count (x10^6 cells/μL)	2.91±0.24 (Male) 2.26±0.62 (Female)	3.72±0.61 (Male) 2.99±0.74 (Female)	4.81±0.74 (Male) 3.87±0.82 (Female)	5.24±0.65 (Male) 4.40±0.71 (Female)
Hematocrit (%)	35.4±0.6 (Male) 31.7±0.5 (Female)	39.7±0.6 (Male) 34.2±0.4 (Female)	42.4±0.6 (Male) 36.1±0.8 (Female)	44.2 (Male) 38.0±0.9 (Female)
Serum Ferritin (μg/DL)	13.47±6.24 ^{b}	21.05±5.17 ^{b}	35.22±5.82 ^{b}	50.51±4.08 ^{b}
Serum Iron (μg/DL)	33.63±3.88 ^{b}	50.74±6.75 ^{b}	61.35±5.27 ^{b}	71.81±7.09 ^{b}
Transferritin saturation (%)	18.0±2.4^a	22.3±2.1 ^{a}	34.4±3.0 ^{a}	42.9±4.8 a
Platelet count (PC) (x10^9/L)	410.61±15.83*	378.77±13.27*	339.13±7.90	274.27±9.11
Mean Platelet Volume (MPV) (fL)	9.96±1.08	9.74±1.34	9.81±0.97	9.90±1.22
Platelet crit (PCT) (%)	0.25±0.03	0.24±0.06	0.24±0.04	0.23±0.02
Platelet Distribution Width (PDW) (%)	32.17±4.87*	26.08±3.08*	21.65±3.87*	20.72±2.79*

*P>0.05 indicating there is significant relative difference. ^{a} significant correlation as per pearson's analysis r>0.140; ^{b} non significant correlation as per pearson's analysis -0.10<r>0.010.

Table 3: Change in the blood profile during the treatment in thrombocytopenic patients (n=11)

Blood parameter	15 days	30 days	45 days	60 days
Haemoglobin (g/dL)	11.3±0.7[a] (Male) 8.5±0.3 (Female)	12.1±0.8 [a](Male) 10.4±0.5 (Female)	14.5±0.4[a](Male) 12.2±0.2 (Female)	14.2±0.6 a(Male) 12.5±0.4 (Female)
RBC Count (x10^6 cells/μL)	2.87±0.15 (Male) 2.05±0.47 (Female)	3.61±0.42 (Male) 2.97±0.17 (Female)	4.34±0.87 (Male) 3.65±0.47 (Female)	5.12±0.24 (Male) 4.35±0.43 (Female)
Hematocrit (%)	36.2±0.7 (Male) 31.5±0.4 (Female)	38.6±0.5 (Male) 33.4±0.2 (Female)	40.8±0.8 (Male) 35.3±0.9 (Female)	43.2±0.4 (Male) 37.5±0.5 (Female)
Serum Ferritin (μg/DL)	12.78±5.61[b]	20.67±4.82 [b]	34.66±6.07 [b]	49.54±2.75 [b]
Serum Iron (μg/DL)	34.91±4.87 [b]	51.24±7.82 [b]	62.57±6.69 [b]	70.51±8.07 [b]
Transferritin saturation (%)	17.9±3.1[a]	21.8±3.0 [a]	32.5±4.2 [a]	39.6±2.5 [a]
Platelet count (PC) (x10^9/L)	70.61±6.98 *	106.34±11.17*	143.88±10.69*	180.91±9.07
Mean Platelet Volume (MPV) (fL)	9.76±1.13	9.89±1.07	9.46±0.91	9.96±1.20
Plateletcrit (PCT) (%)	0.21±0.06	0.24±0.05	0.23±0.05	0.23±0.04
Platelet Distribution Width (PDW) (%)	11.72±2.15	18.21±1.34	12.55±0.65	8.65±2.06

*P>0.05 indicating there is significant relative difference. [a] significant correlation as per pearson's analysis r>0.140; [b] non significant correlation as per pearson's analysis -0.10<r>0.010.

there is a significant difference in the PDW and the haemoglobin content in the patient. The P<0.05 in the Table 2 indicates that there is a significant elevation in platelet count with the treatment using iron supplements. The pearson's analysis results showed that the r value lied between -0.376 and -0.311 when correlated to the ferritin saturation of blood. Correlation between the iron and ferritin in serum and the platelet counts ranged between -0.08 to -0.01. The platelet distribution width ranged till 32.17±4.87 and slowly the range normalized indicating the equality of the sizes of platelets. Similar to the above values of thrombocytopenia, the patients with thrombocytosis also exhibited values that indicates the iron concentration in serum doesn't correlate with the platelet count that much as the iron saturation and the platelet size had a positive correlation to the iron supplementation therapy.

In the initial presentation to the hospital, patients who suffered from thrombocytopenia had a platelet count of <60.49±5.41. This count was gradually elevated and normalized with the iron supplementation only. The elevation in the serum iron and ferritin levels had an influence on the normalization of the platelet count. The Mean Platelet volume (MPV), Platelet crit (PCT) remained constant through the hospital visits and treatment. The platelet distribution width (PDW) was also normal in the cytopenic patients (Table 3).

Statistical tests results showed that the platelet count till the duration of 30 days was significantly different from the values after 60 days. These were compared with the normal values. Pearson's analysis was performed to correlate the platelet count and iron parameters along with haemoglobin. Results showed r value between 0.141 and 0.350 when compared with iron saturation and haemoglobin. When serum iron content and serum ferritin content correlated with platelet count, the pearson's coefficient r value lied between -0.06-0.07. Platelet Distribution ranged between 11.72 and 8.65 through 60 days. This indicates the platelet sizes did not vary to a larger extent in the blood samples and were not dependant on the iron supplementation.

DISCUSSION

All patients who were diagnosed for the Iron deficiency , the correlation was made by estimating the Serum iron and Serum Ferritin levels. Iron sup-

plementation was prescribed for the patients and they responded well and recovered completely in 60 days.

There was also an analysis to determine platelet count (thrombocytosis/ thrombocytopenia). The patients with thrombocytosis had an elevated platelet counts and there was a wide distribution of the platelet width which ranged over the normal limits. This indicates that the platelets were high in number in varying stages of their maturation. The levels were normalized with iron supplementation and there was no correlation with serum iron content or the serum ferritin levels. Serum iron saturation had a direct correlation with the elevated platelet count and the varying sizes of platelets. There were researches to prove IDA is sometimes associated with reactive thrombocytosis (Van K. Morris *et al.*, 2010; Guralnik *et al.*, 2004). The platelet distribution width was variable in the patients which suggests that the iron saturation affected the megakaryopoeisis. This effect resulted in the improper and different stages of maturation of the platelets. It can be inferred that iron saturation only influenced the stabilization of the platelets and the iron supplementation resulted in normalization of the thrombocytosis.

Patients who were diagnosed with thrombocytopenia had a mean platelet count of 60.49 while presentation. The platelet crit and platelet volume remained in normal limits indicating that the platelets were large and occupied more volume. The platelet distribution width was also unchanged to most extent indicating that the available platelets are of same size. There were researches that confirm that there are rare instances where thrombocytopenia is associated with IDA (Berger and Brass, 1987; Beard and Johnson, 1978). Even though there is less correlation of thrombocytopenia and IDA, the platelet count was significantly elevated with the iron supplementation. The patient recovered from thrombocytopenia (Kasper *et al.*, 1965).

The platelet volume and platelet crit were not correlated to the iron supplementation and iron saturation. Serum iron and Serum ferritin had less correlation compared to the ferritin saturation to the Platelet count. There was a correlated change in the platelet distribution. This indicates that the thrombocytopenia was caused due to the low iron saturation in the blood which interfered with the platelet formation and the lowering of platelet content. The iron supplementation caused thrombopoiesis and the platelet count was normalized in our case and other studies too (Ganti *et al.*, 2007). The underlying mechanism was explained by correlating high epo to the platelet count and there by IDA causing thrombocytopenia (Loo and Beguin, 1999).

CONCLUSIONS

In this study it is clearly evident that both reactive thrombocytosis and thrombocytopenia are resultant of IDA. The platelet levels were elevated in some patients and in few their levels were lowered. The determining factor of platelets count is ferritin saturation. The changes in the iron saturation resulted in either elevation or depression in the platelet count. The platelet morphology leads to the changes in the platelet parameters. It can be advocated that both the conditions can occur concurrently in patients with IDA. A diphasic pattern of the response of the platelets was noted in the IDA diagnosed patients. Usually low to moderate IDA is often associated with reactive thrombocytosis. Severe IDA where hemoglobin ranged below 7 g/dL can be attributed with thrombocytopenia. But both the conditions were normalized with iron supplementation. Furthermore, it requires a detailed research to establish a proper correlation between the IDA and platelets. Mechanism of the platelet lowering or elevation is also to be established clearly.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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