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Clinical and etiological profile of patients with thrombocytopenia at tertiary care centre in north eastern part of India

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Abstract
Introduction: Thrombocytopenia is one of the common causes of morbidity and mortality. This is not a disease or infection, rather a symptom of other underlying medical condition or diseases. If left untreated these underlying problems of the disease which lead to thrombocytopenia can lead to serious medical illness even death.
Objective: To study the causes and clinical presentation of thrombocytopenia in north eastern part of India
Material and Methods: Hospitalized patients of age more than or equal to 18 years with thrombocytopenia of any degree were included in study. Baseline platelet counts were done on the day of presentation and confirmed by manual method. Repeat platelet counts were done in subjects with marked thrombocytopenia until normal or near normal values were reached. Patients were followed up for 6 weeks for normalization of platelet counts and those who achieved it were classified as acute and those who were still thrombocytopenic classified as persistent or chronic.
Results: A total of 800 patients admitted in medicine ward with low platelet counts were analyzed. Common causes of thrombocytopenia in our setting were sepsis in 14.4%, CLD in 12.9%, malaria in 12.2%, aplastic anemia in 11.9% and viral illness in 9.9%. Out of total 800 cases, 401 had acute and 399 had chronic thrombocytopenia. Bleeding occurred in only 28.6% patients. 61.7% patients also had fever.
Conclusion: Thrombocytopenia is a common problem encountered in clinical practice. Knowledge of common causes of thrombocytopenia and their clinical manifestations will help in deciphering the cause of thrombocytopenia and formulating diagnostic and therapeutic strategy.

Keywords: Immune thrombocytopenia, sepsis, malaria, transfusion

Introduction
Platelets (thrombocytes) derived from bone marrow megakaryocytes are colorless blood cells that help to stop bleeding by primary hemostasis [1, 2]. A fully mature megakaryocyte is estimated to produce about 2000-5000 platelets [3]. Normal human platelet count ranges from 150,000 to 450,000 platelets per microliter of blood [4]. No concrete definition of mild, moderate, or severe thrombocytopenia exists. However, cases can be divided in mild moderate and severe on the basis of platelet counts depending on study done by Buckley *et al*. Patients with a platelet count more than 50 x 10^3 per µL often are asymptomatic. Patients with a count from 30 to 50 x 10^3 per µL rarely present with purpura, although they may have excessive bleeding with trauma. However, counts from 10 to 30 x 10^3 per µL may cause bleeding with minimal trauma and count less than 10 x 10^3 per µL increase the risk of spontaneous bleeding, petechiae and bruising. Spontaneous bleeding (i.e; mucosal, intracranial, gastrointestinal and genitourinary bleeding) is more likely in patients with platelet count less than 5 x 10^3 per µL and considered a hematologic emergency [5, 6, 7]. Thrombocytopenia is one of the common causes of morbidity and mortality. This is not a disease or infection, rather a symptom of other underlying medical condition or diseases [8]. If left untreated these underlying problems of the disease which lead to thrombocytopenia can lead to serious medical illness even death. Hence identifying the cause is vital for its management. There are several reasons for thrombocytopenia. Only few studies have done to identify the common causes and clinical profile of thrombocytopenia especially in this part of country. Hence a study to identify the common causes for thrombocytopenia in a tertiary care centre is required.

Objectives
To study the causes and clinical presentation of thrombocytopenia in eastern Uttar Pradesh,

adjoining part of Bihar, Madhya Pradesh and Chhattisgarh.

Material and Methods

Present study was carried out at Department of General Medicine, at a tertiary care centre between November 2014 to April 2016. Hospitalized patients of age more than or equal to 18 years with thrombocytopenia of any degree were included in study. Exclusion criteria: Patients who were not willing to participate in the study, Age less than 18 years, Patients with thrombocytopenia who died in hospital without diagnosis. A pre designed proforma was prepared to evaluate the patients. Informed consent was taken from all participating patients or their relatives. All the Patients were examined thoroughly and detailed history was taken. All the patients were subjected to routine haematological investigation like complete blood count, general blood picture, liver function test, renal function test. Other investigations such as Bone marrow aspiration /trephine biopsy, Serological study for HIV infection, Dengue NS1antigen and Dengue IgM, Parachek, Prothrombin time with INR, Activated partial thromboplastin time, rK -39 test, Lymh node biopsy, Ultrasound abdomen, Endoscopy and Chromosomal or molecular studies were done in selected patients.

Baseline platelet counts were done on the day of presentation and confirmed by manual method. Repeat platelet counts were done in subjects with marked thrombocytopenia until normal or near normal values were reached. Patients were followed up for 6 weeks for normalization of platelet counts and those who achieved it were classified as acute and those who were still thrombocytopenic classified as persistent or chronic.

Statistical analysis

Results of study were analysed by using SPSS version 16.0 for window software (IBM Corp., Armonk, NY). Data are expressed as the mean SD and percentage.

Results

A total of 800 patients admitted in medicine ward with low platelet counts were analyzed using SPSS software. Of the total, 37.4% were female and 62.6 % were male. 33.5% patients were of age group 18-25, 40.8% were of age group 26-50 and 25.8% were of age more than 50 years. Common causes of thrombocytopenia in our setting were sepsis in 14.4%, CLD in 12.9%, malaria in 12.2%, aplastic anemia in 11.9% and viral illness in 9.9% [Table 1]. Patients, whose platelet counts returned to normal within 6 weeks followup, were classified as acute and whose not, classified as chronic.

Out of total 800 cases, 401 had acute and 399 had chronic thrombocytopenia. Causes of acute thrombocytopenia include megaloblastic anemia, sepsis, malaria, typhoid fever, dengue and other viral illness. Out of which most common cause was sepsis (28.6%) followed by malaria (24.4%). Likewise causes of persistent (chronic) thrombocytopenia were aplastic anemia, myelodysplastic syndrome (MDS), hypersplenism, hematological malignancies and chronic liver disease. Most common cause was chronic liver disease (25.3%) followed by aplastic anemia (23.3%) [Table.2].

2 chronic liver disease patients had transient thrombocytopenia. In majority of kalaazar patients, platelet counts returned to normal within 6 weeks of treatment, however there were 10 patients who were persistently remained thrombocytopenic. Mild thrombocytopenia was present in 330 (41.2%) out of which 240 were from acute group and 90 from chronic group. Moderate thrombocytopenia was present in 279 (34.9%) out of which 132 were from acute group and 147 from chronic group. Likewise severe thrombocytopenia was present in 191 (23.9%) and included 162 from chronic group and only 29 from acute group. Most common cause of mild thrombocytopenia was sepsis which was present in 76 patients. The causes of mild, moderate and severe thrombocytopenia is enumerated in Table 3. At admission only 2 dengue patients out of 19 presented with severe thrombocytopenia. Out of 38 patients of ITP 33 developed severe thrombocytopenia. There is significant seasonal variation of diseases causing acute thrombocytopenia especially infectious one. We found that out of 401 patients, 100 admitted in winter, 139 in summer and 162 in rainy season. In rainy season malaria was most common diagnosis. In other season sepsis was most common. Although malaria, sepsis and acute viral illness was common diagnosis in all seasons. Dengue patients were distributed in rainy season and summer only [Table.4]. In our study bleeding occurred in only 28.6% patients. 71.4 % did not developed any bleeding. Most common presenting symptom was body rash or ecchymosis in 13% followed by gum bleed / epistaxis in 8.6% patients. Major bleedings such as gastrointestinal and excessive vaginal bleed occurred in 7% and 2.4% patients respectively [Table 5]. In present study 61.7% patients also had fever and the common diagnosis were sepsis (23.3%), malaria (19.8%),acute viral illness(15.9%).Aplastic anemia constituted 8.2% cases of febrile thrombocytopenia. 16 patients of megaloblastic anemia also developed fever.

Splenomegaly is an important sign while evaluating thrombocytopenia especially chronic one.In our study we found splenomegaly in 163 patients out of which 95 were from chronic thrombocytopenia group.In chronic group the most common cause was CLD(42.1%)followed by CLL (19%) and hypersplenism (14.7%). Table 6, is showing different causes of isolated thrombocytopenia, bicytopenia and pancytopenia. Isolated thrombocytopenia was present in 27.5% cases. Only 6.4% of cases required platelet transfusion. out of which 68.6% were aplastic anemia and 15.7% acute leukemia.

Table 1: Etiological distribution of acute and chronic thrombocytopenia

Acute thrombocytopenia	Number (percent)
Megaloblastic anemia	53 (13.2%)
Sepsis	115 (28.6%)
Malaria	98 (24.4%)
Dengue	19 (4.7%)
Acute viral illness	79 (19.7%)
Kala azar	26 (6.4%)
CLD	2 (0.5%)
Typhoid fever	9 (2.2%)

Chronic thrombocytopenia	Number (Percent)
Aplastic anemia	93 (23.3%)
MDS	48 (12.0%)
Hypersplenism	14 (3.5%)
CML	10 (2.5%)
Acute leukemia	44 (11.0%)
ITP	38 (9.5%)
Kala azar	10 (2.5%)
CLD	101 (25.3%)
Drug induced	13 (3.2%)
CLL	28 (7.0%)

Table 2: Etiological distribution of thrombocytopenia

Diagnosis	Frequency	Percent
Sepsis	115	14.4
Chronic liver diseases	103	12.9
Malaria	98	12.2
Aplastic anemia	93	11.6
Dengue fever	19	2.4
Other viral illness	79	9.9
Typhoid	9	1.1
Kala azar	36	4.5
Myelodysplastic syndrome	48	6
Megaloblastic anemia	53	6.6
Immune thrombocytopenic purpura	38	4.8
Chronic myeloid leukemia	10	1.2
Chronic lymphoblastic leukemia	28	3.5
Acute leukemia	44	5.5
Drug induced	13	1.6
Hypersplenism	14	1.8
Total	800	100.0

Table 3: Eiological distribution on basis of severity:

Mild thrombocytopenia	Number
Megaloblastic anemia	47
Hypersplenism	3
Sepsis	76
Malaria	46
Dengue	2
Acute viral illness	41
Kala azar	29
CLD	68
Typhoid fever	7
CLL	11
Total	330
Moderate thrombocytopenia	**Number**
Aplastic anemia	3
MDS	30
Megaloblastic anemia	6
Hypersplenism	9
CML	10
Acute leukemia	37
ITP	5
Sepsis	31
Malaria	50
Dengue	15
Acute viral illness	28
Kala azar	5
CLD	32
Drug induced	2
Typhoid fever	2
CLL	14
Total	279
Severe thrombocytopenia	**Number**
Aplastic anemia	90
MDS	18
Hypersplenism	2

Acute leukemia	7
ITP	33
Sepsis	8
Malaria	2
Dengue	2
Acute viral illness	10
Kala azar	2
CLD	3
Drug induced	11
CLL	3
Total	191

Table 4: Seasonal distribution of acute thrombocytopenia:

Diagnosis	Month						Total	
	Winter Nov-Feb		Summer March-June		Rainy July-Oct			
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Megaloblastic anemia	10	10	25	17.9	18	11.1	53	11.7
Sepsis	41	41	44	31.6	30	18.5	115	27.2
Malaria	22	22	27	19.4	49	30.2	98	23.9
Dengue	0	0	5	3.5	14	8.6	19	4.2
Acute viral illness	14	14	20	14.4	45	27.7	79	18.5
Kala azar	10	10	12	8.6	4	2.4	26	8.0
CLD	0	0.0	1	0.7	1	0.6	2	1.5
Typhoid fever	3	3	5	3.5	1	0.6	9	2.0
Total	100	100	139	100	162	100	401	100

Table 5: Etiological distribution of thrombocytopenia, bicytopenia and pancytopenia

Diagnosis	Only Thrmbocytopenia	Bicytopenia Anemia + thrmbocytopenia	Bicytopenia Leucopenia + Thrombocytopenia	Pancytopenia	Total
Aplastic anemia	0	0	0	93	93
MDS	0	8	0	40	48
Megaloblastic anemia	0	32	0	21	53
Hypersplenism	0	0	0	14	14
CML	0	10	0	0	10
Acute leukemia	7	37	0	0	44
ITP	26	12	0	0	38
Sepsis	62	53	0	0	115
Malaria	24	74	0	0	98
Dengue	14	2	3	0	19
Acute viral illness	53	3	17	6	79
Kala azar	0	0	0	36	36
CLD	23	72	0	8	103
Drug induced	0	2	0	11	13
Typhoid fever	3	6	0	0	9
CLL	8	20	0	0	28
Total	220	331	20	229	800

Discussion

The present study was carried out on 800 patients with low platelet counts admitted in medicine ward, S.S. Hospital, BHU. Out of which 62.6% were male and 32.4% were female. Most of the cases were of middle age group (40.8%). Only 25.8% patients were older than 50 years. In the present study sepsis (14.4%), malaria (12.9%), chronic liver disease (12.2%), aplastic anemia (11.6%), acute viral illness other than dengue (9.9%) comprise the main causes of thrombocytopenia overall. We followed up cases at 6 weeks so that able to classify in acute and chronic group. Sepsis, malaria, megaloblastic anemia, acute viral illness was more prevalent in acute thrombocytopenia group whereas chronic liver diseases, aplastic anemia, myelodysplastic syndrome and acute leukemia in chronic thrombocytopenia group.

Two CLD patients presented with thrombocytopenia which recovered within 6 weeks. Although no definite cause could be found which might be due to some transient infection or deficiency of vitamin B 12 or folic acid. Platelet count returned to normal in most of kala azar (Visceral leishmaniasis) patients after treatment with amphotericin B however few patients including HIV positive cases did not achieved normal platelet count at the end of 6 weeks. Possible explanation might be that since amphotericin B is cumulative drug so its full effect can take some time or patient could have some other cause of thrombocytopenia. In a study by Shah H. R., the most common cause of thrombocytopenia was malaria (31%) followed by Megaloblastic anemia (26%) and dengue fever (18%) [9], while a another study conducted by Bhalara *et al*., dengue (28.6%), malaria (22.8%), CLD (15.2%), hypersplenism (12.3%) were common causes of thrombocytopenia [4].

In our study dengue fever constitutes only 2.4% of cases because most of patients were treated on outpatient basis. Only those patients were admitted who had active bleeding or platelet count less than 10,000.

Since this part of country (gangetic belt of Bihar and Uttar Pradesh) is endemic zone for kala azar therefore this was also

the cause of thrombocytopenia in our study and constitutes 4.5% of cases.

Causes of thrombocytopenia show seasonal variation especially infectious one which are the causes of acute thrombocytopenia. So we also tried to see the distribution of diseases with acute thrombocytopenia in different seasons. Sepsis occurred in all seasons with almost equal frequency. Mosquito borne diseases occurred mainly in rainy seasons. In our study 14 dengue patients in rainy season and 5 in summer admitted in the ward. Since purvanchal is endemic region of malaria so it occurred in all seasons [Table 4]. In our study sepsis, CLD, malaria, megaloblastic anemia and kala azar were common causes of mild thrombocytopenia. Malaria, acute leukemia, sepsis, MDS were causes of moderate thrombocytopenia. Severe thrombocytopenia was found in comparatively less no. of patients and most of them were persistently thrombocytopenic. [Table 3] In a study by Nair *et al* out of 109 patients 19 had severe thrombocytopenia [10]. In a similar study by Bhalara *et al* 54 patients had severe thrombocytopenia out of 327 [4].

Majority of patients with diagnosis of malaria, sepsis or acute viral illness developed mild to moderate thrombocytopenia. At admission 17 dengue patients out of 19 had platelet count more than 20,000 per microliter. CLD patients also had mild to moderate thrombocytopenia only. Study by Bhalara *et al* which included 94 patients of malaria showed mild thrombocytopenia in 24 patients, moderate in 56 and severe in only 14 cases [4]. However in our study out of total 98 malaria patients, 46 developed mild, 50 moderate and only 2 severe thrombocytopenia. [Table 3].

Skin manifestations in the form of petechiae, ecchymosis were most common bleeding manifestation in the present study and was seen in13% patients. Gum oozing and epistaxis was present in 8.6% of cases. Patients complaining of acute onset blurred vision were examined with direct ophthalmoscope to look for fundal bleed which was present in 5.6%. These were non-life-threatening manifestations and were improved spontaneously. Active gastrointestinal bleed and vaginal bleed was present in 7% and 2.4% cases and required urgent platelet transfusion except for CLD patients who bleed due to varices and managed with terlipressin and therapeutic endoscopy. In the study by Nair *et al.*, the most common bleeding manifestation was purpura, followedby gum bleed and epistaxis [10]. While in other study, gum bleed was the most common bleeding manifestation followed by purpura [4].

A number of studies has been done in the past to show the causes of febrile thrombocytopenia [11-14]. Causes of fever may be infection, febrile neutropenia or malignancy. In our study fever was present in 494 patients. Infectious causes were most common like sepsis in 23.3%, malaria in 19.8%, and acute viral illness in 15.9% and dengue in 3.8%. Many studies including ours found megaloblastic anemia as a cause of fever and acute thrombocytopenia which responds to vitamin B-12 and folic acid. So it also should be kept in mind as a cause of fever with thrombocytopenia. Diagnosis of acute viral illness could not be proven however patients with transient bone marrow suppression along with mildly deranged liver enzymes were thought to be due to its which recovered with conservative management. In a study conducted by Dash *et al.*, over 100 patients malaria was found in 45%, sepsis in 21% and dengue in 20%. Other causes includes enteric fever, leptospirosis, leukemia and megaloblastic anemia [15]. A similar study was conducted over 190 patients who presented with fever and thrombocytopenia. they found malaria (32.6%) and sepsis (31.2%) as most common diagnosis. other causes were dengue (15.8%), viral illness (6.3%), leukemia (8.4%) [16]. Splenomegaly is an important finding in a patient with thrombocytopenia as platelets can be sequestered in spleen. It is common in CLD, CML, Kalaazar, Hypersplenism. While in other disease like ITP, diagnosis is questionable if it is present. In our study splenomegaly was present in 163, out of which 95 were in chronic thrombocytopenia group. We studied causes of chronic thrombocytopenia with splenomegaly. Most common cause was CLD followed by CLL and hypersplenism. All the patients with CML, Hypersplenism and kalaazar had splenomegaly.

In present study platelet transfusion was done in 51. Platelets were transfused in active bleeding and prophylactically below platelet count 10,000 per microliter and common features requiring transfusion were with malena, hematochezia or excessive vaginal bleed. Out of 93 patients of aplastic anemia, 35 required platelet transfusion at presentation. Remaining patients did not required transfusion during initial few days of hospitalization however they might need it later in the course of illness. Other causes requiring platelet transfusion were MDS, Acute leukemia, ITP, CLL and drug induced thrombocytopenia. Infectious causes did not required platelet transfusion. We followed up cautiously patients with platelet count less than 20,000 by doing manual platelet count every 12 hourly. None of dengue patient admitted in our ward with dengue shock syndrome and all the patients recovered with conservative treatment without platelet transfusion.

Thrombocytopenia may be present along with leucopenia or anemia or both and pathophysiology may be different in different diseases. In our study isolated thrombocytopenia, thrombocytopenia with anemia, thrombocytopenia with leucopenia and pancytopenia was present in 29.1%, 37.1%, 31.2% and 2.5% patients respectively. Macrocytic anemia was present in megaloblastic anemia in all other cases it was of mainly normocytic normochromic type. Diagnosis of megaloblastic anemia was made by presence of macro-ovalocytes, hyper segmented neutrophil, high LDH and most important by response to therapy which is indicated by raised reticulocytes count between day 3 to day 5 of injectable folate and vitamin B12. Blood level of folic acid or vitamin B12 was not sent in these patients due to affordability issue. Kala azar patients treated with liposomal amphotericin B and at end of 6 weeks platelet count and TLC came to normal level. A few relapsed and HIV positive patients did not recovered over this period and required extended therapy. Methotrexate, Imatinib and other chemotherapeutic agents caused thrombocytopenia in our study. In a similar study, only thrombocytopenia was present in 31%, bicytopenia in 59.4% and pancytopenia in 9.4%. Percentage of pancytopenia was very less in this study probably because only 0.48% were of aplastic anemia and none of patients was of MDS or kala azar which was major cause of pancytopenia in our study [4].

Limitation

This study was conducted in hospitalized patients and patients who presented with thrombocytopenia and died without any definite diagnosis were not included.

Conclusion

Thrombocytopenia is a common problem encountered in clinical practice. Knowledge of common causes of thrombocytopenia and their clinical manifestations will help

in deciphering the cause of thrombocytopenia and formulating diagnostic and therapeutic strategy. Rapid diagnostic tests for malaria and dengue are helpful in ruling out these diseases. Most of patients with thrombocytopenia did not have problem due to thrombocytopenia. It is essential to work up all cases of thrombocytopenia so that curable disease can be segregated and treated. Present study will certainly help in identifying clinical and etiological profile of patients with thrombocytopenia in this part of country (Purvanchal) thus making prompt diagnosis and treating the cause.

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