



Spectrum of febrile thrombocytopenia in tertiary care hospital of India

KEYWORDS

Titanium elastic nailing system , Flynn,s criteria

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ABSTRACT Thrombocytopenia is a common finding in the setting of various infections like malaria, dengue, leptospirosis, undifferentiated viral fevers, rickettsial infections. Before the evaluation of the mechanism of thrombocytopenia is considered, it is imperative to validate the platelet count to exclude the possibility of spurious or pseudothrombocytopenia and be certain that actual thrombocytopenia exists. our study aims at identifying the common etiological agents, clinical presentation, biochemical abnormalities and various outcomes in these patients. Total of 300 patients were kept as subjects in this study. Our study revealed infection as the commonest cause of fever with thrombocytopenia and among infection dengue accounted for the majority of cases [a total of 184 cases of dengue (61.33%) including 179 pure cases (59.67%), 1 case of dengue with falciparum malaria (0.33%), 4 cases of dengue with vivax malaria (1.33%)].

INTRODUCTION

Thrombocytopenia is a common finding in the setting of various infections like malaria, dengue, leptospirosis, undifferentiated viral fevers, rickettsial infections etc. The normal blood platelet count is 1,50,000 – 4,50,000/cumm. The major regulator of platelet production is the hormone thrombopoietin (TPO), which is synthesized in the liver and its synthesis is increased with inflammation and specifically by interleukin 6. Platelets circulate with an average life span of 7–10 days. Thrombocytopenia can occur due to decreased bone marrow production, sequestration, usually in an enlarged spleen, increased platelet destruction. Disorders of production may be inherited or acquired if a low platelet count is obtained in the EDTA anticoagulated blood, a blood smear should be evaluated and a platelet count determined in blood collected into sodium citrate or heparin tubes, or a smear of freshly obtained unanticoagulated blood, such as from a finger prick can be examined. Thrombocytopenia has been found to be a common occurrence in fever cases of different etiologies in various tertiary care centers in India and our study aims at identifying the common etiological agents, clinical presentation, biochemical abnormalities and various outcomes in these patients.

Normal platelet count varies from 1,50,000 – 4,50,000/cumm, with mean values of 237,000 and 266,000/cumm in males and females, respectively. Thrombocytopenia is defined as a platelet count below 1,50,000/cumm.

James Homer Wright, in year 1906, demonstrated that circulating platelets and a giant bone marrow cell now known to be the megakaryocyte shared common tinctorial properties when subjected to a modified Romanofsky stain. Wright went on to show that megakaryocytes sent out pseudopodia into the bone marrow sinusoids from which platelets appeared to be shed. In humans, megakaryocytes normally account for approximately 0.05 to 0.1 percent of all nucleated bone marrow cells. Their number increases as the demand for platelets rises. In contrast to the erythrocyte, which has a diameter of 7 to 8 microns and a volume of 85 to 100 fL, megakaryocytes have an average diameter of 20 to 25 microns and a volume of 4700 ± 100 fL. Some of the largest megakaryocytes have diameters of 50 to 60 microns and volumes of 65,000 to 100,000 fL. It has been estimated that about 1000 to 5000 platelets are produced by each megakaryocyte. In normal individuals, platelet production is

approximately 35,000 to 50,000/microL of whole blood per day, this value can be increased up to eight-fold during times of increased demand. Megakaryocytes are derived from the pluripotential stem cell. Appearance of the platelet glycoprotein receptor on the surface of megakaryocyte is one of the earliest signs of differentiation along the megakaryocyte lineage followed on later by von Willebrand factor, GPIb, and collagen receptors.

The major mechanisms for a reduced platelet count are either decreased production and increased destruction. Two additional mechanisms include dilutional or distributional thrombocytopenia. However, before the evaluation of the mechanism of thrombocytopenia is considered, it is imperative to validate the platelet count to exclude the possibility of spurious or pseudothrombocytopenia and be certain that actual thrombocytopenia exists.

AIM AND OBJECTIVES

Aim:

To study various clinical and laboratory profile of febrile patients with thrombocytopenia of short term duration (3 weeks)

Objectives:

1. To study clinical presentation of patients of short duration fever with thrombocytopenia
2. To determine various etiologies
3. To study the outcome

MATERIALS & METHODS

The study was carried out at a tertiary care center between January 2013 till September 2014. All patients admitted with fever and thrombocytopenia of short duration (< 3 weeks) in different wards of a tertiary care centre were taken as subjects.

INCLUSION CRITERIA:

- All consecutive cases of fever of less than 3 weeks duration presenting with thrombocytopenia in different medical wards of a tertiary care centre

EXCLUSION CRITERIA:

- Patients on cancer chemotherapy.

- Patients with previous history of thrombocytopenia
- Patient with established liver and kidney disease

Total of 300 patients were kept as subjects in this study. It was an observational study and no follow up was involved. There were no therapeutic implications associated with the study, however clearance from the ethical committee was obtained. Detailed history was taken including duration of fever, grade of fever, associated chills and rigors and other associated symptoms. Past history of any blood transfusion, any past malignancy, any established liver and kidney diseases were taken. All subjects were subjected to detailed clinical examination including presence or absence of bleeding manifestations in the form of petechiae and purpura. Patients were then evaluated for the following:

- Complete hemogram including platelet counts, confirmation of platelet adequacy/inadequacy through peripheral smear examination
- For exclusion criteria: Bone marrow aspiration and biopsy (if indicated), Drug history, USG Abdomen, LFTs, RFTs
- To know the etiology: PBS- MP, Atypical lymphocytes, atypical cells, Sepsis, RDT for malaria, Dengue serology, Blood C/S, Urine C/S, HbsAg/AntiHCV/HIV, work up for common viral etiologies that are done in AFMC and Command hospital Pune [CH(SC)]
- Special situations: Weil felix, Serological tests for leptospira, Bone marrow aspiration and biopsy, Serology for Brucellosis etc.

All patients satisfying the inclusion criteria were observed during hospital stay for various outcomes ranging from complete recovery to disability (Temporary/Permanent) to death.

RESULTS

During our study which was conducted over a period of one and a half year, a total of 300 cases admitted in a tertiary care center were studied. All cases presenting with fever with thrombocytopenia and satisfying the inclusion criteria as mentioned above were taken into consideration. Out of 300 patients 186 were males (62 %) and 114 were females (38 %). Age and gender characteristics of the patients is described in table 1.

Table 1: Age and sex profile of patients

Age (Years)	Number of patients n=300	Percentage (%)
<20	41	13.67
21 -30	53	17.67
31 – 40	54	18.00
41 – 50	58	19.33
51 – 60	61	20.33
> 60	33	11.00
Gender		
Male	186	62.00
Female	114	38.00

Bleeding manifestations were seen in 21 patients (7.00 %). Petechiae, subconjunctival haemorrhages and epistaxis were the commonest manifestations. Petechiae were seen in 6 patients (2.00 %), subconjunctival haemorrhages in 6 patients (2.00 %), epistaxis in 6 patients (2.00 %) followed by purpura in 1 patient (0.33 %), UGI bleed (haemetemesis and malena both) in 1 patient (0.33 %), intracerebral haemorrhage in 1 patient (0.33 %).

A definitive diagnosis was made in all 300 patients. Dengue alone was the major etiology in 179 patients (59.67 %) followed by vivax malaria (23 %), sepsis (14.67 %), non specific viral illnesses (7.00 %),

falciparum malaria (2.33 %), combined vivax malaria and dengue (1.33 %), enteric fever (1.00 %), combined falciparum malaria and dengue (0.33 %), combined falciparum malaria and sepsis (0.33 %), scrub typhus (0.33 %). Table 2 summarizes various causes of fever with thrombocytopenia. Table 2

Table 2: Various causes of fever with thrombocytopenia

Diagnosis	Number of patients	Percentage (% age)
Dengue	179	59.67
Vivax malaria	69	23.00
Non specific viral illnesses	21	7.00
Sepsis	14	4.67
Falciparum malaria	7	2.33
Vivax malaria + dengue	4	1.33
Enteric fever	3	1.00
Falciparum malaria + dengue	1	0.33
Falciparum malaria + sepsis	1	0.33
Scrub typhus	1	0.33

At admission platelet counts below 50,000/cumm were present in 25 patient (8.33 %), between 50,000 – 1,00,000 /cumm in 164 patients (54.67 %), between 1,00,000 – 1,50,000 /cumm in 111 patients (37 %). Maximum and minimum platelet counts at admission were 9700 /cumm and 1.37 lłkh/cumm respectively.

At discharge platelet counts between 1,50,000 – 2,00,000/cumm were seen in 281 patients (93.66%), between 2,00,000 – 2,50,000/cumm in 8 patients (2.66%), between 2,50,000 – 3,00,000/cumm in 3 patients (1%). 8 patients died during the study. Maximum and minimum platelet counts at discharge were 1.50 lakh/cumm and 2.98 lakh/cumm respectively.

Among laboratory parameters anemia was present in 82 patients (27.33%), leucopenia in 77 patients (25.67%), leucocytosis in 16 patients (5.33%). Deranged SGOT was seen in 67 patients (22.33%). SGPT in 67 patients (22.33%) and ALP in 1 patient (0.33%) respectively. Deranged Urea was seen in 16 patients (5.33%) and deranged creatinine was also seen in 16 patients (5.33%). Deranged SGOT/SGPT were seen in 43 dengue cases alone (14.33%), 20 vivax malaria cases (6.66%), 2 falciparum malaria cases (0.66 %), 1 combined falciparum malaria and dengue case (0.33%) and 1 combined falciparum malaria and sepsis case (0.33%). Deranged urea and creatinine were seen in 16 patients each (5.33%).

Radiologically hepatomegaly was seen in 157 patients (52.33%) and splenomegaly in 66 patients (22%). Ascites was seen in 4 patients (1.33%). Chest X-ray revealed pleural effusion in 5 cases (1.67%) and consolidation in 4 cases (1.33%). To conclude results 300 patients were studied out of which 292 survived (97.3%) and 8 patients succumbed to their illnesses (2.7%).

DISCUSSION

Fever with thrombocytopenia is a common phenomenon in many illnesses including infectious as well as non-infectious causes. Very few studies related to febrile thrombocytopenia have been conducted in the past. This study was carried out in an attempt to find out the most common etiologies and various outcomes. It was an observational study and hence no follow up was done after discharge. One such study was conducted by Nair PS, Jain A, Khanduri U, Kumar V at St. Stephen's Hospital New Delhi for a period of one and half years. The study began in year 2003. A total of 109 patients (76 males and 33 females) were included in the study. Inclusion criteria in this

study were: Age > 12 years, Fever ≥ 100.0 F at least once a day and duration ≤ 15 days, platelet count < 1,00,000/cumm. Haematological malignancies were not excluded in this study. Septicemia was found to be the leading cause of death in that study (29 cases). Second common cause was enteric fever followed by dengue, Megaloblastic anemia, malaria, haematological malignancies with 16, 15, 13, 10, 4 cases respectively. Out of 109 patients 62 patients (56.8%) had platelet count between 50000–100000/cumm followed by 28 patients (25.7%) with platelet count between 20000–50000/cumm. Out of 109 patients clinical manifestations of thrombocytopenia were present in 45 patients (41.3%). Out of these 45 patients spontaneous bleeding was seen in 31 patients (69%). Infections represented the most common cause of fever with thrombocytopenia with a relative frequency ranging from 68 - 100%. In our study, total of 300 subjects were studied. Only those patients who were having fever and thrombocytopenia at the time of admission were taken into consideration. Inclusion and exclusion criteria were different compared to older studies mentioned above in a sense that haematological malignancies were excluded which were there in the studies conducted by Nair PS et al and Lohitashwa SB et al.

In the study conducted by Lohitashwa SB et al only 100 patients were taken. Age criteria was not taken into our study whereas in the study conducted by Nair PS et al only those patients with age more than 12 years were taken as study subjects. Moreover in the same study cut off for thrombocytopenia was set at 1,00,000/cumm whereas in our study cut off was taken as 1,50,000/cumm. A fever ≥ 100.0 F was taken in that study whereas in my study fever was graded into low, moderate and high grades. Cut off values for low, moderate and high grades were taken as 99.8–100.8 F, 101–103 F and ≥ 104 F respectively. Cut off duration was ≤ 15 days in the previous two studies done by Nair PS et al and Lohitashwa SB et al whereas in the current study a cut off of 3 weeks was taken.

In our study 100% diagnosis was there whereas in the study conducted by Nair PS et al 18.3% cases remained undiagnosed. 100% diagnosis was also established in the study conducted by Lohitashwa SB et al. In our study Infection was the 100% etiology in all cases. Among infections, dengue (179 patients) was found to be the commonest etiology of febrile thrombocytopenia (59.67%) followed by vivax malaria (23%), non specific viral illnesses (7%), sepsis (4.67%), falciparum malaria (2.33%), combined vivax malaria and dengue (1.33%), enteric fever (1%), combined falciparum malaria and sepsis (0.33%), scrub typhus (0.33%). These variations in relation to above mentioned studies may be due to seasonal and regional variations. Moreover our tertiary care hospital caters to a special group of clientele (defence personnel and their dependents) beside civilian patients. This special group comprises people belonging to different parts of India with differences in the incidence and prevalence of infectious diseases in their corresponding states. Moreover a lot many people among this special group admitted in our tertiary care center were just back from their annual/casual leaves and they might be harbouring infectious agents of their corresponding states in the incubation periods.

In our study 8 people succumbed to their illnesses (2.67%). Sepsis alone (4 patients) was the major cause of mortality (1.33%) followed by dengue (1%), combined falciparum malaria and gram negative sepsis (0.33%). Among sepsis alone (4 cases), urosepsis was responsible for death of 3 patients (75%) and sepsis secondary to pneumonia was responsible for the death of 1 patient (25%). In the study conducted by Lohitashwa SB et al, a total 18 patients died out of 100 patients (18%). 14 patients died due to septicemia (78%) and 4 patients died due to dengue (22%). These differences can happen as our study was an observational study with infectious diseases as the diagnosis in all patients and infectious diseases generally differ in their incidence, prevalence, mortality and morbidity due to seasonal and geographic variations. Moreover host characteristics also play an important role in determining the final outcome.

In study by Nair PS et al haematological conditions accounted for 15% cases of fever with thrombocytopenia. However in our study haematological conditions were kept as exclusion criteria.

In our study thrombocytopenic manifestations were present in 21 patients (7%). This was quite low compared to previous two studies (49% in Lohitashwa SB et al and 41.3% in Nair PS et al). These differences can happen as it was an observational study including patients with different characteristics and from different geographical locations.

In our study petechiae were seen in 6 patients (2%), subconjunctival haemorrhage in 6 patients (2%), epistaxis in 6 patients (2%), purpura in 1 patient (0.33%), Upper gastrointestinal bleed (haemetemesis and melena both) in 1 patient (0.33%), intracerebral haemorrhage in 1 patient (0.33%). In study conducted by Lohitashwa SB et al, petechiae/purpura (63%) was the commonest manifestation followed by spontaneous bleeding (37%).

Anaemia was seen in 82 patients (27.33%) as defined by WHO cut off value of <13 gm/dL in males and <11 gm/dL in female. Out of 82 patients, 60 were males (73.17%) and 22 were females (26.83%). Leucopenia was present in 77 patients (25.67%), Leucocytosis in 16 patients (5.33%). Normal total leucocyte count (TLC) was taken in the range of 4000–12000/cumm as per our tertiary care hospital laboratory cut off values. No such parameters were studied in above two studies.

Among other laboratory parameters deranged liver enzymes ie SGOT, SGPT and ALP were seen in 67 patients (22.33%), 67 patients (22.33%) and 1 patient (0.33%) respectively. Cut off values for SGOT, SGPT and ALP were 5–40 U/L, 5–40 U/L & 36–113 U/L respectively as per the cut off given by our standard laboratory. Among pure dengue patients, SGOT was deranged in 43 patients (14.33%) & SGPT in 43 patients (14.33%). Among vivax malaria patients SGOT and SGPT were deranged in 20 patients each (6.66%), falciparum malaria accounted for deranged SGOT and SGPT in 2 patients each (0.66%), combined falciparum malaria and dengue were responsible for deranged SGOT and SGPT in 1 patient each (0.33%), combined falciparum malaria and sepsis were responsible for deranged SGOT and SGPT in 1 patient each (0.33%), ALP was deranged in a single patient (0.33%) and that patient succumbed to his illness due to combined falciparum malaria and gram negative sepsis.

Rapid diagnostic tests (RDTs) for malaria were positive in 82 patients (27.33%). Among 82 patients 72 were positive for vivax malaria (87.80%) and 10 were positive for falciparum malaria (12.2%). Among dengue serology positivity, 184 patients were positive for NS-1 antigen (61.33%) and 87 patients were positive for IgM antibody (29%). Widal test showed significant titres in 3 patients (1.00%) diagnosed to have enteric fever based on clinical profile and culture positivity for Salmonella typhi. Blood culture was positive in 4 patients (1.33%). Among positive blood culture patients, Klebsiella pneumonia was grown in 1 patient (25%) and Salmonella typhi in 3 patients (75%). All 3 patients with positive blood culture for S.typhi recovered whereas the patient with K.pneumoniae died due to combined falciparum malaria and gram negative sepsis.

Urine culture was positive in 10 patients (3.33%). Among these 10 patients, 8 grew E.coli (80%) and 2 were positive for klebsiella (20%). All these patients were clinically managed as urosepsis. Among 8 patients with E. coli positivity in urine, 5 recovered (62.5%) and 3 died (37.5%). Among 2 patients with klebsiella positivity, there was complete clinical recovery with no mortality and morbidity.

In our study radiologically hepatomegaly was seen in 157 patients (52.3%), splenomegaly was seen in 66 patients (22%). Combined hepatosplenomegaly was present in 55 patients (18.33%). Hepatomegaly cut off value was taken as 15 cm and splenomegaly cut off values were taken as 13 cm for males and 12 cm in females.

Our study revealed infection as the commonest cause of fever with thrombocytopenia and among infection dengue accounted for the majority of cases [a total of 184 cases of dengue (61.33%) including 179 pure cases (59.67%), 1 case of dengue with falciparum malaria (0.33%), 4 cases of dengue with vivax malaria (1.33%)]. This could be due to seasonal and geographic variations. Dengue epidemic that happened during current year (year 2014) also contributed to the majority of cases. Sepsis accounted for the majority of deaths in my study (50.0%) followed by dengue (37.5%) and combined falciparum malaria and sepsis (12.5%). In study conducted by Lohitashwa SB et al, sepsis accounted for 78% of mortality and dengue accounted for 22%.

CONCLUSION

Fever with thrombocytopenia is a common laboratory abnormality seen as a common manifestation of a lot many common diseases rather than rare and orphan diseases. Infectious diseases are the most common cause of febrile thrombocytopenia. Dengue was found to be the commonest underlying etiology, so every case of suspected dengue must be verified with dengue serological assays utilizing NS-1 antigen and IgM antibody. Bleeding manifestations that were seen in this study were petechiae, purpura, subconjunctival haemorrhage, epistaxis, haemetemesis/malena and intracerebral haemorrhage. Petechiae were seen with an average platelet count below 40,000/cumm in my study. Most of the common etiologies that were seen in this study ie Dengue and Malaria don't require very expensive set of investigations to arrive at a definite diagnosis.

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