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A clinical and serological study of acute febrile illness with thrombocytopenia

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Abstract

Background and objectives: Infection is a commonest cause of thrombocytopenia. Thrombocytopenia associated with fever helps to narrow differential diagnosis and management of fever. It also helps to know the various complications of thrombocytopenia and its management.

Methods: 100 patients aged >14 years with fever and thrombocytopenia between January 2015 - June 2016 were included for this study.

Results: Infection was the commonest cause of thrombocytopenia and dengue fever was the commonest infections. Bleeding manifestations were seen in 43% of patients. Among them 63% patients had petichae/ purpura as the commonest bleeding manifestation followed by spontaneous bleeding in 37%. Good recovery was noted in 95% while mortality was 5%. Septicemia accounted for 40% of deaths and dengue 40% followed by malaria 20%.

Interpretation and Conclusion: Infections, particularly dengue fever was the commonest cause of fever with thrombocytopenia. In majority of patients, thrombocytopenia was transient and asymptomatic but in significant number of cases there were bleeding manifestations. Spontaneous bleeding was noted in platelet count of <20,000 in majority of patients, petichae/purpura was seen in platelet count in range of 20,000-40,000. On treating the specific cause drastic improvement in platelet count was noted during discharge and further follow - up.

Keywords: Infection, malaria, petichae/purpura, spontaneous bleeding, mortality

Introduction

Fever has been recognized as a cardinal manifestation of disease since ancient times, as recorded by ancient scholars like Hippocrates [1]. Seen first as a disease but later recognized as an accompaniment to a variety of disease entities, fever is an easily noted and reliable marker of illness [2].

Fever is such a common manifestation of illness that it is not surprising to find accurate descriptions of the febrile patients in early-recorded history [3].

Although Gallieo in the 16th century and Santori S in the 17th century constructed devices to measure body temperature, an effective thermometer was not developed until beginning of the 18th century by Dutch instrument maker Gariel Daniel Fahrenheit [4]. Since then physicians have used fever as a reliable guide to the presence of disease and the response of disease to therapy. The widespread availability of highly specific and sensitive immunologic testing has reduced the number of undetected cases of adult Still's disease, systemic lupus erythematosus, and polyarteritis nodosa [5].

Modern research had its beginning in 1948 when Dr. Paul Beeson determined that fever is caused by a product of host inflammatory cells. Initially thought to be a product of polymorphonuclear leukocyte, this endogenous pyrogen is generated by mononuclear phagocytes. It is identical or very similar in composition to substances previously identified as lymphocyte activating factor (LAF), mononuclear cell factor and leukocyte endogenous mediator collectively known as interleukin - 1 (IL-1). IL-1 has now been shown to have a major role in thermoregulation and fever.

Though thrombocytopenia is encountered in various diseases, it is fortunate that potentially fatal bleeding due to thrombocytopenia is rare [6].

The causes of thrombocytopenia are impaired platelet production, accelerated platelet destruction or dilution and/or splenic sequestration [7]. Even though there is no absolute relation between platelet counts and bleeding, certain broad generalizations can be made,

with counts less than 10,000/cumm, bleeding is likely and may be severe [8]. Thrombocytopenia correlates inversely with mortality and morbidity in various febrile illness, serial monitoring of platelet counts has prognostic value. This highlights the importance of thrombocytopenia in various febrile disorders [9].

Platelets play a central role in normal haemostasis and therefore also in thrombosis. Thrombocytopenia is characterized by bleeding most often from small vessels. This can manifest as petechiae over the skin, hemorrhages from mucosa of gastrointestinal and genitourinary tract. Intracranial haemorrhage is a dangerous consequence in thrombocytopenic patients.

Thrombocytopenia is defined as platelet count <1,50,000/cumm. This is due to decreased production, increased destruction (immunogenic and non-immunogenic) and increased sequestration in spleen. Of these, infections being the commonest cause of thrombocytopenia.¹⁰

Infections like dengue, leptospirosis, malaria, typhoid, military TB, HIV, septicemia are some of the common causes of fever with thrombocytopenia.

Therefore a well-organized systematic approach that is carried out with an awareness of causes of fever with thrombocytopenia narrows the differential diagnosis of the clinical entity and brings out diagnosis. Timely recognition and treatment of the underlying condition, platelet transfusions are required to prevent fatal outcomes. Hence a need for study to know the clinical profile and complications of fever with thrombocytopenia.

Objectives

- To study the clinical and serological profile of patients with acute febrile illness with thrombocytopenia in Shadan Institute of Medical Sciences.

Materials and Methods

Method of study

This study was done on patients, who were admitted to Shadan Institute of Medical Sciences, Hyderabad during the period of Jan 2015 to July 2016.

We prospectively collected a series of 100 patients with acute febrile illness and thrombocytopenia.

Inclusion criteria

- The patients of both sexes aged > 14years.
- Patients admitted with fever and found to have thrombocytopenia are included in the study.

Exclusion criteria

- Patients <14years are excluded
- Patients with fever and no thrombocytopenia are not included.
- Patients with thrombocytopenia and no fever are not included.

Once the patients admitted with fever and those who had thrombocytopenia, a careful history was recorded, general physical examination was done. Detailed examination of various systems was done. Routine investigation was done, the specific and special investigations were done as and when indicated.

Septicemia

Patient is said to have septicemia if patient has two or more of the following conditions:

1. Temperature >38c or <36c
2. Heart rate >90 beats/min
3. Respiratory rate >20/min or PaCO₂ <32mmhg
4. WBC count >12,000 or <4,000 or >10% immature (band) forms.

Peripheral smear

Two thick and two thin smear should be collected. Any parasite at any stage of development (Trophozoites / Sporozoites) should be seen on the smears for confirmation. At least 3 samples should be taken 8-12 hours apart for positivity.

In whom a final definite diagnosis was reached, were treated for the disease and in those who were affordable platelet count was repeated at the time of discharge and no effort was made to gather follow-up information, if the patient was not followed up in our institution.

Details of history, general physical examination and laboratory and technical investigation reports were noted down from time to time.

Once the specific diagnosis was reached, patients were treated for it specifically and symptomatically (Mechanical ventilations, haemodialysis etc.). For bleeding complications platelet transfusions was done if platelet count was <20,000/cumm.

The causes of fever with thrombocytopenia are so numerous, a simple workable classification is presented in –

1. **Viral causes:** CMV; Dengue; Parvo-B19; HSV, HIV, Hantana etc.
2. **Bacterial causes:** Gram +ve and -ve septicemia, military tuberculosis, leptospirosis, typhoid etc.
3. **Protozoal causes:** Malaria.
4. **Others:** Leukemia, lymphoma, etc.

Results

A total number of 100 patients admitted over a period of one and a half years in our hospital were studied.

No particular age group was considered, but the study subjects were in the age group of 15-75 years.

The sex of the patient was not taken into consideration for the study. Out of 100 cases of fever with thrombocytopenia, 61 were males and 39 were females.

The duration of hospitalization varied between 3 days to 21 days. The average duration of hospitalization was 7 days.

Out of 100 patients of fever with thrombocytopenia, 96 of them had definitive diagnosis with dengue (44%) as the commonest cause, followed by malaria (38%); vivax malaria (55%) was commonest followed by falciparum malaria (34%) and mixed malaria (11%). septicemia (7%), enteric fever (4%), brucella (2%) and leptospirosis (1%). 4(4%) cases were undiagnosed.

In our study 46% of the patients had platelet count in the range of 50,000 – 1,00,000, followed by 32% and 17% of the patients had platelet count in the range of 20,000 – 50,000; 0-20,000 respectively.

Common range of platelet count at the time of admission was 61-80 thousands in 36 cases, followed by platelet count in range of 81-100 thousands in 10 cases; 21-40 thousands in 16 cases; 41-60 thousands in 16 cases and 0-20 thousands in 17 cases.

Clinical manifestation of thrombocytopenia was there in 43 patients and there was no clinical manifestation of thrombocytopenia in 57 patients. Out of 43 patients, 27 patients (63%) had petichae / purpura and spontaneous bleeding was seen in 16 patients (37%).

Out of 100 patients, 95 of them had good recovery and 5 of them expired. In 95 cases, who had good recovery, 28 cases were followed up and platelet count were within normal limits at that point.

In 5 mortality cases, 2 (40%) were due to septicemia and multiorgan dysfunction syndrome and 2 (40%) were due to dengue fever and 1(20%) was due to malaria.

In 5 mortality cases, majority of platelet count was in the range of 10000-20000 cell/cumm in 3 cases.

Table 1: Preliminary Data of the Study

Total no. of patients	100
Male and female	61:39
Age range in years	15-75
Range of duration of hospitalization (days)	3-21
Average duration of hospitalization (days)	7
Definitive diagnosis	96
Dengue fever as the common cause	37
In malaria, vivax as common cause	19
61,000-80,000 was common range of platelet count at	36
Clinical manifestation of thrombocytopenia	43
Bleeding manifestations of thrombocytopenia (petichae/purpura :spontaneous bleeding)	27:16
Good recovery	95
Mortality	5
Sepsis as the common cause of mortality	3
10- 20,000 was the range of platelet count in mortality cases	2
Undiagnosed cases	4

Table 2: Incidence of Males and Females

Sex	Frequency	Percentage
Males	61	61%
Females	39	39%
Total	100	100%

Table 3: Distribution of Age

Age	Frequency	Percentage
15 To 30 Years	49	49%
31 To 45 Years	26	26%
46 To 60 Years	21	21%
Above 60 Years	4	4%
Total	100	100%

Table 4: Distribution of platelets

Platelet Count	Frequency	Percentage
0 To 20000	17	17%
20000 To 50000	32	32%
50000 To 100000	46	46%
1 To 1.5 Lakh	5	5%
Total	100	100%

Table 5: Clinical manifestations of thrombocytopenia

Bleeding	Frequency	Percentage
Absent	57	57%
Present	43	43%
Total	100	100%

Table 6: Bleeding Manifestations

Bleeding Manifestations	Frequency	Percentage
Petechiae	13	13%
Petechiae/Purpura	6	6%
Purpura	8	8%
Spontaneous Bleeding	16	16%
Total	43	43%

Table 7: Clinical Manifestations of Thrombocytopenia in Relation to Platelet Count

Bleeding Manifestations	0-20000	20000-50000	50000-1 Lakh	1-1.5lakh
Petechiae	1	5	7	0
Petechiae/Purpura	4	2	0	0
Purpura	0	5	3	0
Spontaneous Bleeding	12	4	0	0

Incidence of various causes of fever with thrombocytopenia:

Out of 100 cases, a definitive a diagnosis was made in 96 cases. Among them dengue fever was the major cause accounting for 44 cases and 44% of the total cases. Second major cause was malaria 38(38%) cases. In malaria, vivax malaria accounted for 21 cases and 55.3% of the malaria cases, followed by falciparum malaria accounted for 13 (34.2%) cases and mixed malaria accounted for 4 (10.5%). followed by septicemia 7(7%), enteric fever 4(4%), brucellosis 2(2%) and leptospirosis 1 (1%) case. 4(4%) cases remain undiagnosed.

Table 8: Incidence of various causes

Diagnosis	Frequency	Percentage
Dengue	44	44%
Malaria	38	38%
Septicemia	7	7%
Typhoid	4	4%
Brucella	2	2%
Leptospirosis	3	3%
Undiagnosed	4	4%
Total	100	100%

Out of 38 cases of malaria, 21 patients had vivax malaria. 13 patients falciparum and 4 were mixed malaria. Out of 100 cases 95 patients had good recovery and remaining 5 cases expired.

Out of 5 mortality cases, 2 cases were due to septicemia accounting for 40% of death. 2 cases were due to dengue (40%) and 1 case due to malaria (20%) accounting together for 60% of death.

Table 9: Causes of mortality

Disease	No. Of Cases	Percentage
Dengue	2	40%
Malaria	1	20%
Septicemia	2	40%

Out of 95 patients who good recovery, 28 patients came for the follow up after 1 week. Repeat platelet count done during follow up were within normal limits.

Discussion

For a study of fever with thrombocytopenia, patients must satisfy the above mentioned criteria. Prospective case collection is necessary and careful follow up is warranted.

These three conditions allow the delineation of a standard study population.

The depth and means of exploration are also important but rather difficult to evaluate.

Indian study

This study was conducted by Nair PS, Jain A, Khanduri U, Kumar V. (2003) at St. Stephen's hospital, New Delhi, for period of one and half years. A total of 109 cases (76 male, 33 female patients) were studied with the same criteria as in our study^[11].

Septicemia with 29 cases was the leading cause of fever associated with thrombocytopenia. Second common cause was enteric fever followed by dengue, megaloblastic anaemia, malaria, haematological malignancy with 16, 15, 13, 10, 4 cases respectively^[11].

Out of 109 patients 62 patients (56.8%) had platelet count between 50,000-1,00,000 followed by 28 patients (25.7%) had count between 20,000 to 50,000. Out of 109 patients 45 patients had thrombocytopenic signs accounting for 41.3%. Out of 45 patients spontaneous bleeding was seen in 31 patients accounting for 69% of the bleeding manifestations^[11].

During the course of follow up platelets showed increasing trends in 69 patients (63.3%) and continuously decreasing trends in 8 patients (7.3%)^[11].

Totally infections represented the most important cause of fever with thrombocytopenia with a relative frequency ranging from 68% - 100%.

In our study infections (96%) was the established diagnosis as compared to other study in which along with infection (68%), hematological conditions (15%), was also documented.

This may be due to seasonal and regional variations. But infection was the commonest cause of fever with thrombocytopenia.

Among infections, dengue fever (44%) was the commonest cause as compared to other study in which septicemia (27%) was the commonest cause. This is more likely due to seasonal and regional variations.

Atypical manifestations of dengue:

2 patients (2%) presented with atypical manifestations of dengue.

Patients presented with fever and features of hepatitis like right hypochondriac pain, hepatomegaly and raised aminotransferases. When evaluated for persistent fever, patient was found to have dengue.

In our study septicemia was (7%) was the 3rd most common cause of fever with thrombocytopenia. Whereas dengue (9.2%) was the 3rd common cause in other study. Among 7 cases of septicemia, 1 patient died due to septic shock and 1 patient due to Acute Respiratory Distress Syndrome (ARDS).

Among patients who presented with fever and were diagnosed septicemia, 3 patients (3%) fulfilled the criteria of septicemia on initial investigations while 4 patients (4%) became septicemic during the course of hospital.

In our study, haematological condition did not present as fever with thrombocytopenia but in other study it accounted for 15%. In our study malaria (38%) is the 2nd most common cause, where as it was the 5th common cause in other study.

Atypical manifestation of malaria:

18 patients had atypical hematological manifestations like anemia. 1 patient (1%) presented with fever and

subconjunctival haemorrhage and on investigation for persistent fever was diagnosed malaria.

Peripheral smear for malaria was positive in 31 out of 38 patients with malaria as per criteria.

In our study enteric fever (4%) is the 4th common cause, where as in other study it was the second most common cause accounting for 14.7% of cases.

Atypical manifestations of typhoid:

1 patient (1%) presented with complaints of arthralgia and was found to have typhoid fever on further evaluation.

In our study 4% are undiagnosed but in other study 18.3% cases remained undiagnosed.

Analysis in relation to other blood cells like RBCs & WBCs:

Plasmodium falciparum: 3% had anaemia, 2% had leukopenia, 3% had leukocytosis, and 1% had anaemia with leukocytosis.

Plasmodium vivax: 4% had anemia 1% had leukopenia, 2% had leukocytosis, 3% had anaemia with leukocytosis and 1% had anaemia with leukopenia.

Plasmodium vivax / Plasmodium falciparum: 1% had anaemia, 3% had leukocytosis, 1% anaemia with leukocytosis.

Dengue: 15% had anaemia, 6% had leukocytosis, 6% had anaemia with leukocytosis.

Typhoid: 2% had anaemia, 1% had leukocytosis.

Septicemia: 1% had leukopenia, 1% had leukocytosis, 1% had anaemia with leukocytosis.

Brucellosis: 1% had anaemia.

Leptospirosis: 1% had leukocytosis.

Undiagnosed: 2% had anaemia and 1% had anaemia with leukocytopenia.

In our study thrombocytopenic signs was present in 43% as compared to 41.3% in other study. In our study Petechiae / purpura (63%) was the commonest bleeding manifestations followed by spontaneous bleeding (37%). In other study spontaneous bleeding was the commonest bleeding manifestation (68%) followed by petechiae / purpura accounting for (22.22%), others (9.88%)^[11].

In our study distribution of platelet count in the range of 50-100 thousands is seen in 60% as compared to 56.8% in other study. Platelet count in the range of 20- 50000 was seen in 23% and 25.7% in our study and other study respectively³⁶.

During the course of follow up platelet count showed increasing trends accounting for 63.3% and continuously falling counts in 7.3% in their study^[11].

In our study all the patients were monitored for platelet count on daily basis and except the mortality cases (7%) all other patients showed increasing trend during the hospital stay.

Later 34% patients were followed up after 7days and their platelet counts were within normal range. There was no decreasing trends of platelet count observed. In conclusion our study of fever with thrombocytopenia reveals that infections as the commonest cause, among infections dengue fever was the common cause because of seasonal and regional variations. Definitive increase in platelet count was noted after the underlying cause was treated. Septicemia accounted for 44% of mortality in our study followed by dengue and malaria 22% each.

Infectious diseases group formed the major portion of patients presenting with fever and thrombocytopenia lacking

any specific signs. Dengue, Malaria, enteric fever, leptospirosis and other infectious diseases formed the major chunk of this group. Response to empirical therapy for locally prevalent disease may help the physician for better management of the patients. In future various pathological and microbiological imaging modalities should be needed for research and diagnosis of many viral hemorrhagic fevers.

Thrombocytopenia is common finding in malaria and about 80% of malaria patients have the same.^{12,13}. In a study conducted by UM Jadav, "thrombocytopenia in malaria - correlation with type and severity of malaria". Normal platelet count was noted in 21.6% cases n=1565. But in our study, n=38, no patients had normal platelet Count¹³.

It was observed that thrombocytopenia was rarely accompanied by clinical bleeding or biochemical evidence of DIC both in our and their study. Platelets count can fall to below 25,000/ μ l but this is uncommon 43. Platelet count rise rapidly with recovery so no need of platelet transfusion in malaria cases¹³. The prevalence of thrombocytopenia was 78.4% of cases in UM Jadav et al study of thrombocytopenia in malaria and it highlighted that persistent platelet count is unlikely in the lab findings of malaria. Thrombocytopenia was seen in 40- 90% of patients infected with plasmodium falciparum in India⁴³. The mechanism of thrombocytopenia in malaria could be due to peripheral destruction and consumption by DIC.^{14,15}. Profound thrombocytopenia with platelet count as low as 5000/ μ l has been reported in Indian literature in a 43 year old female patients with vivax malaria¹².

Conclusion

1. Fever with thrombocytopenia is one of the most challenging problems in the field of medicine.
2. Fever with thrombocytopenia consists of occult presentations of common diseases rather than rare disease.
3. Infection is the commonest cause of fever with thrombocytopenia.
4. Among infection, dengue was the commonest cause.
5. Malaria; typhoid; dengue, still present clinically in atypical and occult forms, making diagnosis difficult and delayed. So high index of clinical suspicion is needed. Hence they should be investigated with some routine and specific test like rapid spot test for malaria antigen; IgM ELISA and NS1 antigen for dengue, IgM ELISA leptospiral antibodies, etc. for correct diagnosis.
6. In majority of patients thrombocytopenia was transient and asymptomatic.
7. In significant number of cases thrombocytopenia lead to various bleeding manifestations and influenced the clinical profile of these febrile illness.
8. Generally, spontaneous bleeding was noted when platelet count was <20,000/cumm but in some due to qualitative defects it was seen in platelet count in the range of 40,000 /cumm also.
9. Some patients with platelet count of 10,000/cumm did not have spontaneous bleeding.
10. Spontaneous bleeding patients should be evaluated for disseminated intravascular coagulation also.
11. Platelet count increased rapidly with treatment of malaria and dengue infection, so no need of platelet transfusion in these cases unless there is bleeding manifestation. 4% of the patients remain undiagnosed,

which needs work up for some rare infectious causes. Or it could be due to inadequate clinical or laboratory methods.

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Conflict of Interest

None

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