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Original Research Article

A clinical study of febrile thrombocytopenia at a Tertiary Care Hospital in North Karnataka

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Abstract

Background: Fever is one of the most common presentations in clinical practice. The clinical spectrum of fever with thrombocytopenia requires the study of clinical and investigations profile.
Objective: The study of clinical profile and laboratory diagnoses of fever with thrombocytopenia. The study aims in diagnoses and studying the course of diseases.
Methods: The prospective study of 200 patients more than 13 years presenting with fever and thrombocytopenia. The study was conducted at KIMS Hospital Hubli Karnataka, in the department of General Medicine. The subjects were evaluated for diagnosing the aetiologies and received treatment.
Results: In this study, males outnumbered females, the platelet count was in the range of 50000- 150000/µl in 47% patients, 20000-50000/µl in 33.5% patients and was lesser than 20000 in 19.5% patients. The diagnoses was made in 37.5%, with most common being Malaria followed by Sepsis, Dengue, Enteric fever. The 62.5% patients were classified as undetermined viral febrile illness as definite diagnosis was not reached with available investigations. There were manifestations of thrombocytopenia in the form of bleeding in 14.5% patients; improvement was noted clinically in 90.5% patients. The mortality was 5.5% and the cause was sepsis. Platelet transfusion was given in 18.5% patients and blood transfusion in 12.5%. The study noted anaemia in 32.5% and pancytopenia in 16%. The associated complications noted were hepatitis in 6.5% and AKI in 3.5%.
Conclusion: Malaria, sepsis, dengue and enteric fever constitute majority of etiologies in cases of fever with thrombocytopenia.
Keywords: Fever, thrombocytopenia, malaria, dengue, sepsis, enteric fever.

1. Introduction

Fever is one of the most common presentations; it is a manifestation of various infections as well as non infective disease process. Temperature has diurnal variation. Fever is defined as A.M. temperature more than 98.9 degree F and P.M. temperature more than 99.9 degree F.[1] Fever is manifested as an end point event where a series of events take place starting from infection or injury, blood cells involvement, generation of pyrogens and cytokines ILs, IFNs, TNF, PGE_2 and hypothalamic response to these

changes. Fever may affect any system in the body. The diagnosis of fever is a challenge when approached clinically. However the diagnosis may be narrowed down when there is associated thrombocytopenia. Thrombocytopenia defined as platelets less than 1,50,000/µl in blood.[2] Fever with thrombocytopenia may be due to viral fever like dengue, malaria, enteric fever, leptospirosis, sepsis, rickettsial diseases etc. The manifestations of these diseases may be mild to severe. These diseases may be

associated with morbidity and mortality. The following study was undertaken to evaluate the clinical profile and laboratory diagnosis of fever with thrombocytopenia.

3. Methods

3.1 Setting

This study was undertaken at in the department of General Medicine at Karnataka Institute of Medical Sciences, a Government run tertiary care hospital in Hubli, Karnataka from November 2009 to November 2010.

3.2 Design

Prospective, Observational, non-comparative, non-randomised, analytical study.

3.3 Participants

Patients aged more than 13 years who were admitted with fever and had thrombocytopenia were included in the study.

Patients with fever without thrombocytopenia and patients with thrombocytopenia without fever were excluded from the study. Patients who were positive for retroviral status and those who were de novo detected positive for HIV were excluded from the study. Hepatitis B and C were also excluded.

3.4 Sample size

200 patients admitted in medicine department were included based on above inclusion and exclusion criteria.

3.5 Ethical approval

The approval was taken from the Institutional Ethical Committee, KIMS, Hubli. Informed written consent was taken from all patients.

3.6 Protocol

Patients were evaluated with history and examination thoroughly at admission and all basic investigations with necessary specific investigations for evaluating febrile thrombocytopenia were done. The patients were followed up daily clinically and platelets monitoring was done on individual basis. The subjects received appropriate symptomatic and where necessary specific treatment. Few patients were given blood or blood products as treatment based on clinical and lab criteria.

4. Results

In this study, males comprised 134 and females 66 patients. The duration of stay in hospital ranged from 3 days to 21 days. 94 cases (47%) had platelets count between 50000 and 150000/µl, 67 cases (33.5%) had platelets between 20000 and 50000/µl, 39 cases (19.5%) had platelets below 20000/µl. Clinical manifestations of thrombocytopenia were noted in 29 cases. 9 patients had malaena, 1 had haematuria, 3 patients had haemoptysis, 3 patients had epistaxis, 3 cases had haematemesis, 5 had skin rashes and 5 patients had gum bleeding. Four patients had manifestations of multiple bleeding tendencies.

The other important association which was noted was 65 cases (32.5%) cases had anemia. Further study with peripheral smear showed following points: Pancytopenia in 32 cases, normocytic normochromic anemia in 16 cases, dimorphic anaemia in 9 cases, microcytic hypochromic anemia in 5 cases, macrocytic anemia in 3 cases.

Malaria was diagnosed in 26 cases, *P. vivax* malaria in 14 cases, *P. falciparum* in 7 cases, 5 cases had mixed infections with *P. vivax* and *P. falciparum*; 3 cases of malaria went into sepsis. Dengue haemorrhagic fever was diagnosed in 13 cases, with 2 cases of dengue showing features of polyserositis. Sepsis was diagnosed in 16 patients, 3 cases secondary to malaria, 1 due to dengue and 11 cases were secondary to undetermined viral febrile illness category.

A single case of sepsis had features suggestive of pneumonia. Enteric fever was diagnosed in 13 cases, 3 had agglutination titres of 1:320 and remaining 13 cases had 1:160. 1 case had features suggestive of hepatitis in association with enteric fever. Four cases showed features suggestive of pyelonephritis. One case had positive IgM chikungunya and 1 case clinically could be categorized as *varicella zoster*. 13 cases among the 200 had hepatitis. 3 cases due to malaria, 1 case due to enteric fever and 7 cases secondary to undetermined viral febrile illness. 7 cases had acute kidney injury, 5 due to undetermined viral febrile illness and 2 *P.vivax* malaria. 7 cases showed polyserositis, 2 secondary to malaria and 5 secondary to undetermined viral febrile illness. Cases which did not show improvement with antibiotics, blood transfusion and platelet transfusion were subjected to bone marrow studies. 1 case had picture of hyperplastic bone marrow and 3 cases had hypoplastic bone marrow. 11 patients expired due to sepsis. All patients were treated with symptomatic measures and where a diagnosis of Enteric and Malaria fever was done, they received appropriate antibiotics and antimalarial drugs respectively.

During the hospital stay majority showed improvement -181 patients (90.5%). Among these 37 patients (18.5%) received platelet transfusion and 25 patients (12.5%) received blood transfusion. All patients showing improvement were discharged and were asked to follow up on OPD basis. 8 patients left against medical advice.

Table 1: Total number of cases

Total number of cases	200 cases
Age range	13 to 79 years
Male to female ratio	134 to 66
Range of hospitalisation	3 to 21 days
Definitive diagnosis	75 cases (37.5%)
Malaria	26 cases (13%)
Undetermined viral febrile illness	125 cases (62.5%)
Sepsis	16 cases (8%)
Bleeding manifestations	29 cases (14.5%)
Pancytopenia	32 cases (16%)
Anaemia	65 cases (32.5%)
Severe thrombocytopenia	39 cases (19.5%)
Mortality (Sepsis)	11 cases (5.5%)
Recovery at discharge	181 cases (90.5%)
Platelet transfusion	37 cases (18.5%)
Blood transfusion	25 cases (12.5%)

5. Discussion

The following etiologies were recognised in febrile thrombocytopenia. A definite diagnosis was possible in 75 cases. Among the diagnosed cases, the most common cause was Malaria in 13%, sepsis accounted 8 % cases, Dengue and Enteric fever constituted 6.5% each. Based on clinical and investigational indications 1.5% cases had aplastic anaemia on bone marrow study. The remaining 125 cases were diagnosed as undetermined viral febrile illness as no specific etiologies were found out.

In our study vivax malaria, falciparum and mixed infections were noted in 53.2%, 26.6% and 19 % cases respectively. A related study done at Dr D.Y. Patil Medical College, Kolhapur[3] noted the most common cause for febrile thrombocytopenia is Malaria in 54% followed by other infections in 21%, dengue in 15%, and enteric fever in 6% and sepsis in 4%. Shaikh *et al*, JPMC, Karachi [4] associated malaria and thrombocytopenia in majority of cases and Malik *et al*, Karachi [5] noted 11.7% patients had malaria and among these 70% had thrombocytopenia. At Sir T. Hospital and GMC, Bhavnagar, Gujarat [6] study revealed vivax as cause in 22% and falciparum in 21% and mixed infection in 3% cases.

A similar study by Lohitashwa *et al*[7] in 2004 found malaria to be commonest cause for febrile thrombocytopenia. Another study involving 228 patients at Hayat Abad Medical Complex [8] between 2008 and 2010 noted malaria to be commonest cause in 53% patients. A study at Sri Ram Murti Smarak institute of Medical Sciences at Bhojipura, Barielly, UP [9] concluded Malaria (32.6%) as common cause followed by sepsis, dengue, acute leukemia, viral fever as other causes for fever with thrombocytopenia. Nair *et al* [10] study and Srinivas[11] study found malaria to be cause for febrile thrombocytopenia in 9 % and 41 % respectively.

Among 8% sepsis patients the primary source was due undetermined infection in 68.75% followed by Malaria, Dengue and Pneumonia. Lee *et al* [12] studied 53 patients with sepsis and noted that 57% patients had thrombocytopenia. A study at D.Y. Patil medical college hospital reported sepsis as a cause in 4% cases. Nair *et al* study noted 26% patients had sepsis and another study. By Srinivas at tertiary care hospital Davangere noted 19% patients had sepsis. A study at SRMS-IMS noted sepsis in 31.2%.

Dengue was seen as cause in 6.5% patients. In SRMS- IMS related study dengue was noted in 15% cases, Nair and Srinivas study showed dengue as a cause in 14% cases in both studies. A study at D.Y. Patil hospital associated 15% cases was due to dengue. A study at GMC and Sir T. Hospital the etiology was dengue in 52% patients.

In our study enteric fever constituted 6.5% cases. A study at GMC, Gujarat showed 3% cases were due to enteric fever. IN SRMS-IMS 7% cases were due to enteric fever. The etiology of enteric was noted in 6%, 24% and 15% in D.Y. Patil hospital study, Srinivas study and Nair study respectively.

In our study 14.5% cases had manifestations of thrombocytopenia in the form of bleeding tendencies. The other related studies showed thrombocytopenia manifestations in 41.3%, 49%, 23%, 10% in Nair, Srinivas, D.Y. Patil hospital study and SRMS-IMS studies respectively.

In our study, bone marrow studies though did not prove exact etiologies, however 3 cases had hypoplastic bone marrow and the others had hyperplastic bone marrow.

There were 13 cases (6.5%) with hepatitis secondary to undetermined infection followed by Dengue and Enteric fever. A study at SRMS-IMS showed hepatitis in 24.73% cases.

The other complication noted was AKI which was seen in 7 cases (3.5%) in our study. The most common aetiology being again undetermined fever and next was vivax malaria. SRMS-IMS study showed abnormal RFT in 32.63% cases.

Polyserositis was noted again in 7 cases in our study, commonly being among undetermined viral fever and next among Dengue fever. Our study recorded recovery in 181 cases (90.5%), recovery was noted in Lohitashwa *et al* study in 82% cases, at SRMS-IMS recovery was noted in 76.8% cases. A study at D.Y. Patil medical college hospital reported recovery in 95% cases. There were 11 cases of mortality (5.5%). Again in 9 cases the primary etiology was not associated and it could be associated with sepsis secondary to undetermined viral illness. Single cases of Dengue and Pneumonia also contributed to mortality. A

study at D.Y. Patil hospital recorded mortality in 5% cases (sepsis, malaria and viral illness). A study at SRMS-IMS 18 cases expired (9.47%) due to sepsis followed by malaria. Lohitashwa *et al* reported 18% mortality and sepsis in 78% as a cause for mortality.

In our study 62.5% cases were classified as undetermined febrile illness. The other studies classifying etiology as viral fever were 21% in a study at D.Y. Patil hospital, 18% in Nair study and 2% in Srinivas study. At SRMS-IMS study, 6.31% of mortality was due to viral fever.

A virus causing severe fever with thrombocytopenia syndrome (SFTS)[13] was discovered in east asian region which was a Phlebovirus, causing 30% mortality, presenting with systemic manifestations along with febrile thrombocytopenia. It was studied in animal models with respect to its pathology and isolation.

In our study it can be noted the etiological factor in majority of patients with febrile thrombocytopenia were not diagnosed and were secondary to undetermined viral illness. The majority improved and was discharged, except 11 mortalities. The same situation is faced in day to day clinical practice. This is reflected in explaining the prognosis to the patient relatives as they do not understand the spectrum of illness and they remain unaware of this "undetermined viral" fever terminology. Thus, clinicians also remain clueless and uncertain with respect to undiagnosed fever and further course of management.

These undetermined cases may be due to seasonal variations, partially treated and referred cases, the diagnostic materials which are sensitive in different phases of illness and even the viral, protozoal or bacterial load or their antigenic variations which makes lab diagnoses difficult and possibility of some unknown virus circulating.

In our study there were significant cases of pancytopenia. Megaloblastic anaemia is commonly associated with pancytopenia[14], the undetermined viral fever category may include these cases of pancytopenia. Lastly there is hindrance from patient side as serial investigations are needed to pick up certain changes in blood or urine.

Our study and literature correlation points us to certain hints which may help to narrow down our spectrum of undetermined etiologies. Among the infections which cause anemia and febrile thrombocytopenia – Malaria is common possible diagnosis.[15]

Those who present with febrile thrombocytopenia and improve gradually over weeks with only symptomatic therapy – Dengue is possibility.[16,17] Undetermined fever with polyserositis – Dengue is possibility.[18] Those with febrile thrombocytopenia and Gastrointestinal problems – Enteric may be possibility.[19] These points guide us that in diagnosing febrile thrombocytopenia we need to have a set of clinical criteria along with lab criteria.

6. Conclusion

The diagnosis of febrile thrombocytopenia is a challenging entity. Based on above study and related Indian studies infections are the commonest causes of febrile thrombocytopenia. Among the infections Malaria, Dengue, Enteric and sepsis account for majority of cases. As many cases remain subclinical or undiagnosed there is a need in managing such cases. This may need frequent investigations, avoiding unnecessary drugs, health education to patients and their relatives, better diagnostic tools in different periods of illnesses and follow up. Lastly seasonal trends, microbial changing patterns and varied clinical manifestations need to be kept in mind before labelling any illness or refuting any illness.

Table 2: Comparisons of various studies

Studies	Malaria (in %)	Sepsis (in %)	Dengue (in %)	Enteric fever (in %)	Others (in %)
D.Y. Patil hospital	54	4	15	6	21
SRMS-IMS	32.6	31.2	15	7	6.31
Nair *et al*	9	26	14	15	18
Lohitashwa, Srinivas	41	19	14	24	2
GMC, Gujrat	46	-	52	3	-
Our study	13	8	6.5	6.5	62.5

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