

Haematological changes associated with typhoid fever

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Objective: To determine haematological changes associated with typhoid fever.

Methodology: This study was conducted at King Edward Medical University, Lahore from March 2010 to March 2011. A total of 150 patients with confirmed diagnosis of Typhoid fever on the basis of Widal test or Typhidot test were enrolled in the study. CBC, peripheral smear, reticulocyte count, PT, APTT, FDPs and D-Dimers were performed on all the patients. Bone marrow biopsy was performed on 48 patients as a part of work up for pancytopenia and to get a bone marrow culture. Data was analyzed by SPSS. T test was applied to determine significant differences between

quantitative variables and qualitative clinical data was compared using Chi square test.

Results: Cytopenias were found in 98% of the patients. Bone marrow showed prominent hemophagocytic activity in 100% of the patients. PT and APTT was also deranged in 48% of the patients.

Conclusion: Typhoid fever affects hematological parameters significantly and these parameters may help not only in making the diagnosis but also help to guide management. (Rawal Med J 2013;38:32-35).

Keywords: Typhoid fever, *Salmonella typhi*, leukopenia.

INTRODUCTION

Typhoid fever, also known as enteric fever, is a potentially fatal multisystemic illness caused by *Salmonella typhi*. The protean manifestations of typhoid fever make this disease a true diagnostic challenge.¹ The classic presentation includes fever, malaise, diffuse abdominal pain, and constipation. Untreated, it is a grueling illness that may progress to delirium, obtundation, intestinal hemorrhage, bowel perforation and death within one month of onset and survivors may be left with long-term or permanent neuropsychiatric complications.²

S typhi has been a major human pathogen for thousands of years, thriving in conditions of poor sanitation, overcrowding and social chaos.³ Mucosal penetration occurs in the distal ileum resulting in transient asymptomatic bacteremia, the organism survive and multiply within the mononuclear phagocytes and characterized by a rapidly developing infiltration which is associated with necrosis of the upper mucosa in large areas of the

terminal ileum and colon.⁴ Since blood complete picture is first to be ordered in any condition, this may provide a clue to the diagnosis. Apart from diagnosis, the hematological manifestations can help in monitoring the response to therapy and disease course.⁵ Pancytopenia, bicytopenia and unicytopenia are well known hematological manifestations of typhoid fever. Bone marrow findings including marrow aplasia and hemophagocytosis are also seen.⁶ The aim of this study was to assess hematological parameters in patients with typhoid fever. This study may provide a direction for further research to determine the prognostic role of hematological parameters.

METHODOLOGY

The study was conducted at King Edward Medical University, Lahore from March 2010 to March 2011. A total of 150 patients who were confirmed to have typhoid fever on the basis of Widal test or Typhidot test were enrolled in the study. CBC,

peripheral smear, reticulocyte count, PT, APTT, FDP and D-Dimer were performed on all patients. Bone marrow biopsy was performed on 48 patients as requested by physicians as a part of work up for pancytopenia and to get a bone marrow culture. Data was analyzed by SPSS software.

Pancytopenia was taken as hemoglobin <13 g/dl for males and 12 g/dl for females, total leukocyte count <3 x 10⁹/L and platelet count <100 x 10⁹/L. A value of > 2 seconds from the control was taken as prolonged PT and APTT. D-Dimer value of >200U was taken as significant.

RESULTS

Out of 150 patients, 58 (38.6%) were found to have pancytopenia. Hb<10 g/dL, TLC <1.5 x 10⁹/l, Platelet count <150 was taken as pancytopenia. Anemia only was found in 92 patients (61.33%). Hemoglobin value as low as 2G/dL was found in 5 patients. Leucopenia was found in 78 (52%) patients. TLC as low as 1.0 x 10⁹/l was found in 3 patients. Leucopenia was found either with anemia or as part of pancytopenia (Table 1).

Table 1: CBC in typhoid fever.

Parameter	%
Pancytopenia	38.6%
Anemia	61.33%
Leucopenia	52%
Neutropenia	32%
Neutrophilia	23%
Lymphopenia	8%
Lymphocytosis	12%
Monocytosis	30.67%
Thrombocytopenia	37.3%

Neutropenia was found in 48 (32%) patients, lymphopenia in 12 (8%), lymphocytosis in 18 (12%), monocytosis in 46 (30.67%) patients. Thrombocytopenia alone was found in 3 (2%) patients. 56 patients presented with thrombocytopenia as a part of pancytopenia (37.3%). Lowest platelet count found was 5 x 10⁹/l (Table 2).

Table 2: Hematological parameters.

Parameter	Number ± SD
WBC /ul	2,442.2±1643
PCV %	28.14±4.7
Hb g/dl	7.6±3.1
Retics %	4.54±1.7
Neutrophils	21.84±8.0
Lymphocytes	53.1±16.6
Monocytes	3.12±2.5
Eosinophils	1.32±2.4
Platelets x 10 ⁹	75.6±15.1

Peripheral smear revealed fragmented RBCs in 34 (22.6%) patients. Leukoerythroblastic picture was found in 26 (17.3%) patients. Burr cells were found in 4 (2.67%) and acanthocytes in 2 (1.3%) patients.

Table 3: Peripheral Smear findings.

Finding	Number	%
Fragmented RBCs	34	22.6%
Leukoerythroblastic Picture	26	17.3%
Burr cells	4	2.67%
Acanthocytes	2	1.3%
High Reticulocyte count	43	28.6%

Reticulocyte count was raised in 43 (28.6%) patients, whereas in other patients either normal or low reticulocyte count was found (Table 3).

Table 4: Bone marrow findings.

Cellularity	Number	%
Reduced	16	10.6%
Normocellular	81	54%
Hypercellular	53	35.5%
Dysplasia	43	28.6%
Hemo phagocytic activity	48	100%

Because of pancytopenia and to find the cause of fever 48 patients underwent Bone marrow biopsy. 16 (10.6%) patients showed slightly reduced cellularity for age and 43 (28.6%) showed dysplastic changes. All 48 cases showed increase hemophagocytic activity (Table 4). Most of the changes developed during second week of illness and resolved in 2-3 weeks.

Table 5: Comparison of hematological parameters of patients suffering from Typhoid fever with DIC and septic patients.

Parameter	% of Patients with Typhoid fever	% of Patients with DIC (n= 26)	P value(comparison of typhoid patients with DIC)	% of Patients with Sepsis (n=78)	P value(comparison of typhoid patients with Septic patients)
Pancytopenia	38.6%	12.1%	0.18	16.4%	0.09
Thrombocytopenia	37.3%	98.1%	<0.001	87.8%	<0.001
Peripheral smear Fragmented RBCs	22.6%	89.4%	<0.001	23.7%	0.2
PT (mean±SD)	21.6 ± 4.78	56.2±14.7	0.001	34.1±6.9	0.02
APTT(mean±SD)	46.1 ± 8.93	98.4±23.1	0.001	108.7±43.1	0.001
D-Dimers	234±12.3	1023.4±134.1	<0.001	675.3±24.6	0.04

Both PT and APTT were prolonged in 67 (44.7%) patients. D-dimers were raised >200 ng/ml but were always less than 400 ng/ml in 18 (12%). Two patients presented with DIC like picture.

DISCUSSION

The findings revealed that peripheral smear in typhoid patients can mimic thrombotic thrombocytopenic purpura and disseminated intravascular coagulation that is not only supported by peripheral picture but also by the hemostatic profile. Most of the typhoid patients are referred to the hematologists for bone marrow biopsy, as a part of work up for pancytopenia or pyrexia of unknown origin. Bone marrow findings may give transiently aplastic bone marrow look, hemophagocytic syndrome or reactive bone marrow.

Since pancytopenia is an alarming finding and sometimes considered synonymous with aplastic bone marrow, typhoid patients might give an aplastic like picture but it is transient. Pancytopenia was found in 38% of the patients in our study, as has been reported by others as severe pancytopenia and bone marrow hemophagocytosis.⁶ In our study, in patients who underwent bone marrow biopsy it revealed marrow hypoplasia in 11% and hemophagocytosis in 100% of the cases, secondary to infection related cytokine release. Bone marrow biopsies have shown granulomas,⁷ however, in our

study no marrow granuloma was noted.

Normocytic normochromic anemia is most commonly found in typhoid fever.⁸ In our study, 92% patients presented with anemia 90% of which had normocytic normochromic picture. Leucopenia was found in 52% of our patients and relative lymphocytosis was seen in 12% of the patients. Neutropenia in typhoid fever has been attributed to increased margination and defective granulopoiesis.⁸ Relative lymphocytosis is followed by neutrophilia during recovery phase, however, neutrophilic leucocytosis is considered to be a feature of complicated typhoid fever.⁹ Thrombocytopenia was found in 37% of the patients. Only 2% had isolated thrombocytopenia, which has been reported by Serefhanoglu et al.¹⁰

An interesting finding in our study was that 20% of the patients presented with microangiopathic hemolytic anemia like picture showing schistocytes, nucleated RBCs, polychromasia and low platelets. This has occurred in very toxic patients but the percentage of patients reported was just 4%, whereas in our study 20% patients showed these features.¹¹ Another report mentioned such a case where the patient required plasma exchange therapy and was treated as Thrombotic thrombocytopenic purpura.¹²

46% of the patients in our study presented with prolonged PT and APTT and increased D-Dimers. A DIC like picture favored by peripheral smear and

deranged hemostatic profile can result in misdiagnosis of condition since typhoid patients present with these findings transiently and do not need aggressive therapy, however, studies by Butler et al¹³ and Kansenshogaku et al¹⁴ mentioned that one needs to be vigilant in toxic patients since a true DIC due to septicemia is not very uncommon in typhoid patients and that does demand aggressive approach.

Thus, in a patients presenting with high grade fever and cytopenias with prolonged PT and APTT, and provided D-Dimers is not >400U, typhoid fever can be suspected and they should be worked up on such lines. Further research is needed to run salmonella cultures presenting with above features to further reinforce this conclusion. As shown in Table 5, significant differences exist in terms of PT, APTT, D-Dimers and platelet count between typhoid fever and DIC and septic patients. Hence, though the above parameters derange in typhoid fever, still these are not as marked as in DIC and sepsis.

CONCLUSION

Based on above findings, we conclude that typhoid fever can lead to cytopenia of variable degree, coagulopathies and hypo or hypercellular bone marrow. One needs to be vigilant as conditions like DIC or bone marrow aplasia could be there as a transient finding or present concomitantly with enteric fever. Haematological parameters can be employed in the effective diagnosis of typhoid fever and can provide a reliable and earlier diagnosis thus leading to an early and timely management of the condition.

Conflict of Interest: None declared

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