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Original Research Article

Thrombocytosis: can it be used as a marker for tuberculosis?

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ABSTRACT

Background: Tuberculosis is a major health problem in India. Early diagnosis and prompt treatment is the key to control this menace. Hence to improve diagnosis in peripheral region, it is imperative that other methods are used to supplement the diagnostic This study aimed at assessing the reactive thrombocytosis in patients with tuberculosis admitted in medicine ward of RGMC and CSMH, Kalwa, Thane, India.
Methods: This study was conducted from 1st January 2016 up to 31st June 2016. Data was collected from the PM register and also from Post mortem records, entered in MS Excel and analyzed.
Results: Newly discovered, 112 patients, diagnosed on basis of sputum AFB positivity, chest x-ray changes, pleural fluid, ascitic fluid and CSF analysis reports suggestive of tuberculosis were selected to be the cases, out of which 50 were males (44.6%) and 62 females (55.4%)and, 127 non-tuberculous patients admitted for other causes who did not have any symptoms or signs of tuberculosis were randomly selected to be the control group of the study. The ages of the patients ranged from 14 to 76 years old. Thrombocytosis was detected in 84 (75%)of the Tb patients, whereas only 3 (2.3%) in Non-Tb Patients. The erythrocyte sedimentation rate (ESR) was increased by more than 20 in 97.4% of the patients.
Conclusions: The changes in these parameters (platelets count and ESR) may reflect a reaction to the inflammatory condition. Therefore, in endemic areas, the presence of such haematological peripheral blood changes may raise the suspicion of pulmonary tuberculosis.

Keywords: ESR, Thrombocytosis, Tuberculosis

INTRODUCTION

Tuberculosis (TB) is a major public health problem inIndia.[1] The differential diagnosis of tuberculosis should be entertained in patients with some abnormal haematological findings.[2] Moreover, haematological parameters are useful indicators of severity in TB infection.[3] Reactive thrombocytosis is defined as an increased number of platelets above 450×10^9/ L due to a reaction to a stimulus e.g. an inflammatory condition[4]. In reactive thrombocytosis, the increase in platelet count is usually temporary, less than 1000×10^9/L, and is not normally associated with any serious clinical problems. Thrombocytosis occurs in many chronic inflammatory diseases, including tuberculosis. The precise stimulus for increased platelet production is not clear, but it is associated with increased numbers of small megakaryocytes in the marrow, which shows reduced nuclear ploidy.[4] The platelets are also small, but it has recently been suggested, that this may simply reflect the thrombocytosis, as there is normally an inverse correlation between the number and volume of platelets.[5] Reactive thrombocytosis is associated with an increase in erythrocyte sedimentation rate (ESR) and acute phase reactants (fibrinogen, VIII.C, VWF: Ag, C-reactive protein, and interleukin-6 (IL-6)). The most potent

stimulator for hepatic synthesis of C-reactive protein is IL-6, which also has thrombopoietic activity.[6] IL-6 is known to promote megakaryocytopoiesis in vitro and raise platelet counts in vivo. Unfortunately, due to short facilities, IL-6 and CRP level was not assessed in this study. ESR is a nonspecific test, it is raised in a wide range of infections, inflammatory, degenerative, and malignant conditions associated with changes in plasma protein, particularly increase in fibrinogen, immunoglobulin, and C-reactive protein. The ESR is also affected by many other factors including anaemia, pregnancy, hemoglobinopathies, haemoconcentration and treatment with anti-inflammatory drugs.[7]

The rate of sedimentation appears to be dependent on the amount of fibrinogen and, to a lesser extent, the number of globulins present in the plasma. In normal blood, the red cells tend to remain separate from one another because they are negatively charged (zeta potential) and tend to repel one another. In many pathologic conditions, the phenomenon of erythrocyte aggregation is caused by alteration of erythrocyte surface charge by plasma protein.[8] Moderately raised sedimentation rates can sometimes be found in healthy people, particularly those living in tropical countries and a "normal" ESR cannot exclude disease. In many tropical countries, ESR measurement has been discontinued, because they added little to diagnosing disease, assessing its progress and monitoring response to treatment.[9]

The ESR may increase in tuberculosis to over 100 mm/1 h, as well as blood viscosity due to the increase in immunoglobulins mainly IgG and IgA.[10] Furthermore, reduction in erythrocyte sedimentation rate was regarded as good indicator for disease control.[11] Although, tuberculosis is endemic in our region, no previous data regarding the haematological changes was reported. So, this work aimed to study the changes in the platelet count and ESR level in patients having tuberculosis.

The objective of this study was to correlate different indices in the TB patients and Non-TB patients especially with reference to the platelet count and ESR. To study the incidence of various types of TB patients admitted in the Ward. To establish if thrombocytosis can be used as a marker in TB patients.

METHODS

This is a record based, case control study conducted in a medicine and TB chest ward, of a Public Hospital located in metropolitan urban area, and catering to the socio economically underprivileged patients from all over Thane District. Ethical clearance of this study was approved from the hospital Institutional Ethical Committee (IEC).

All the patients who came to came to the OPD, in the period from January 2016 up to 31st June 2016, with signs and symptoms suggestive of Tuberculosis were investigated and Tuberculosis was diagnosed as per the procedure employed in RNTCP in India (Chapter 3- Case Finding and diagnosis Strategy, Technical and Operational Guidelines for TB control in India-2016). All newly discovered pulmonary, abdominal, CNS and disseminated tuberculosis patients admitted in medicine wards, constituted the sample of this study. Hundred and twelve newly discovered TB patient's positives with Tubercle bacilli in sputum (Zn stain), ascitic fluid, pleural fluid and CSF reports suggestive of tuberculosis were subjected to the haematological tests.

Inclusion criteria

All tuberculosis patients admitted in wards during period of 1st January 2016 up to 31st June 2016.

Exclusion criteria

Patients on any drugs which affected peripheral blood, and known at the time of study to have a chronic disease which will adversely affect the body systems including the bone marrow and the peripheral blood.

Also, patients admitted in medical wards for other reasons with no clinical signs for TB were stratified according to age and sex to match them with the cases and then 127 were selected randomly to be the control group. Data regarding the age and sex and laboratory reports were collected from the medical records. At CSMH about 2.5 ml blood is collected in dipotassium ethylene diamine tetra acetic acid (EDTA) tube for measuring the platelets count and for ESR blood is collected in citrate solution. Platelet count was done using a coulter method and manual counting method and ESR was measured by Wester green method.

The analysis was performed in the laboratory of Chhatrapati Shivaji Maharaj Hospital by expert technologists. Statistical analysis was done using MS Excel 2007. Summary statistics, Correlation R and Chi squared tests and z test were used for analysis. Differences with $p < 0.05$ was considered significant

RESULTS

Table 1 shows the age- sex composition of the control group and tuberculosis group. Cases comprised of 112 confirmed TB patients, between 16 and 85 years (mean 38.3 years, SD 17.4 years). The control group (non-Tb patients) of 127 patients, age and sex matched individual (chi square=0.42 and z=0.86 respectively), aged between 16 and 85 years (mean age 40.1 years, SD 14.6 years) was chosen.

Among the 112 pulmonary TB patients, 62 (55.4%) were females and 50 (44.6%) were males, whereas in the control group, of the 127 patients, 65 (51.2%) were females and 62 (48.8 %) were males. Among the female Tb patients, mean age was 35.9 years (SD 16.4 years) and

among males, the mean age was 41.2 years (SD 18.4 years). This gender-wise difference in mean age among cases and control is statistically not significant (z= 1.6, p> 0.05).

Table 1: Age-sex composition of the control group and tuberculosis group.

	Controls		Controls total	Tuberculosis		TB total	Grand total
Age groups	Female	Male		Female	Male		
11-20	5	5	10	13	8	21	31
21-30	10	19	29	15	11	26	55
31-40	20	10	30	10	7	17	47
41-50	12	14	26	15	7	22	48
51-60	13	10	23	4	7	11	34
>60	5	4	9	5	10	15	24
Grand total	65	62	127	62	50	112	239

Table 2 shows the Platelet count in TB patients and Non-Tb patients. Thrombocytosis is defined as platelet count more than 450 X103 /ml. There are 124(97.6%) patients in control group with Platelet count less than 450 and only 3 (2.4%) with platelet count more than 450X103 /ml. Whereas in TB patients group, there are 62 (55.35%) patients with platelet count less than 450X103/ml and 50 (44.65%) patients with platelet count of more than 450X103 /ml. This difference is highly significant ($\chi 2$=61.7, p< 0.001).

Table 2: Platelet count in TB patients and non-Tb patients.

Platelets (x 10^9/L)	Controls	%	Tuberculosis	%	Grand total	%
<200	34	26.8	4	3.6	38	15.9
200-350	77	60.6	24	21.4	101	42.3
350-450	13	10.2	34	30.4	47	19.7
450-800	3	2.4	44	39.3	47	19.7
800-1000	-	-	5	4.5	5	2.1
1000-1200	-	-	1	0.9	1	0.4
Grand total	127	100	112	100.0	239	100

Table 3 shows ESR levels of all TB patients in the study. Normal ESR level is 0-20 mm/hr. Most of the Tb patients, 109 (97.3%), had ESR more than 20 mm/hr. As ESR was not recommended in many of the controls, no comparison could be made between ESR levels in cases and controls.

Table 3: ESR levels of all TB patients.

ESR	Frequency	%
<20	3	2.7
20-40	27	24.1
40-60	35	31.3
60-80	26	23.2
80-100	11	9.8
>100	10	8.9
total	112	100.0

There was a linear correlation between the platelet count and ESR. This correlation is significant at 95% confidence level. (r= 0.2054, z=2.17, p < 0.05).

Table 4 shows the types of Tuberculosis in the study population. In our study, we found that pulmonary TB was commonest, (71.4%), followed by abdominal TB, 14.3%, followed by pleural and CNS TB. Of the 16 patients with abdominal TB, 4 patients were diagnosed to have ileocecal Koch's on ultrasonography,5 patients had abdominal lymphadenopathy suggestive of tuberculosis and 7 patients had ascites, which was exudative with high ADA value. Out of 16 abdominal Koch's patients, 7 (43%) patients had thrombocytosis which correlates with the study done by Ramesh J.[12] Four patients were suffering from altered mental status and one patient was admitted with convulsion. CSF and MRI suggested tuberculous meningitis. Of the five CNS patients, four patients had platelet count >3 X 106/ml. Our study had three patients with Koch's lymphadenopathy (extra

abdominal) with involvement posterior cervical lymph nodes. Only one case of Pott's spine, admitted in medicine ward with weakness and fever, had platelet count of more than 400,000/ml.

Table 4: Types of tuberculosis in the study population.

Diagnosis	No.	%
Abdominal tuberculosis	16	14.3
Lymph node tuberculosis	3	2.7
Miliary kochs	3	2.7
Pleural effusion	4	3.6
Pott's spine	1	0.9
Pulmonary tuberculosis	80	71.4
CNS tuberculosis	5	4.5
Total	112	100.0

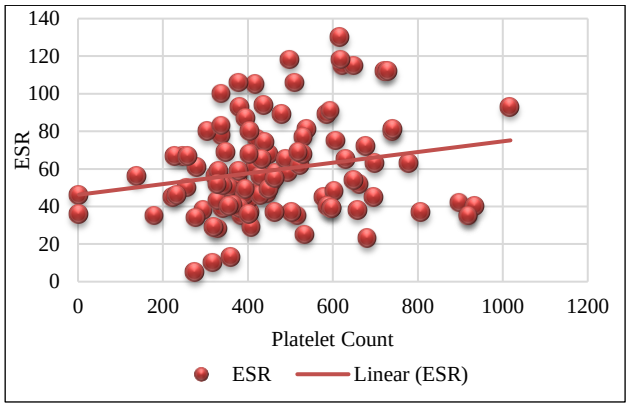

Figure 1: Scatter diagram showing correlation between ESR levels and platelet counts.

DISCUSSION

TB is a major public health problem in the studied area(WHO). To our knowledge, this is the first research that studies the ESR and platelets changes in all forms of tuberculosis. The ESR, a sensitive but not a specific measure of the inflammatory response. In this study ESR was elevated in 97.3% of patients. An ESR value exceeding 100 mm/h has a 90% predictive value for serious underlying disease, such as infection. In our study only 10 (8.9%) patients had elevated ESR values. Significant correlation between thrombocytosis and elevated ESR was observed in our study which matches with other authors. In our study, 75% of the patients with tuberculosis had thrombocytosis. Reactive thrombocytosis is found in a number of clinical situations including infectious diseases. The regulation of thrombopoiesis is under the control of an array of haemopoietic growth factor. Significant elevation of thrombopoietin during the acute phase of infection precedes the development of thrombocytosis, suggesting an important role of thrombopoietin in reactive thrombocytosis. Elevated values of thrombopoietin were found in majority of patients with acute infection and were observed more frequently during the acute phase with fever than after the fever disappeared. The exact mechanism of elevated thrombopoietin levels in reactive thrombocytosis is still unknown; however, it has been observed to be correlated with inflammatory processes. Serum IL- 6 concentration is significantly correlated with thrombocyte count and albumin concentration. IL-6 may play a contributory role on reactive thrombocytosis and the acute phase response in pulmonary tuberculosis. On the other hand, there was one study which showed that there is thrombocytopenia and bone marrow suppression in patients with milliary and disseminated tuberculosis may be due to granuloma formation in bone marrow. Histopathology of lymph nodes suggested granulomatous inflammatory cells and Acid-Fast Bacilli. All lymph nodes had very high platelet count which was similar to the study done by Andrew Renshaw.[1,4,12-22]

CONCLUSION

In the patients treated for various types of tuberculosis at our hospital, we have observed significant incidence of thrombocytosis and raised ESR. The presence of reactive thrombocytosis and/or elevated ESR, in endemic area may raise the suspicion of tuberculosis and patients should be further investigated and followed up for tuberculosis. It is important to mention that thrombocytosis and raised ESR are not specific to tuberculosis, but such simple test can be used as preliminary investigation in locations where other tests like radiology and microbiology are not available. Together these parameters become an indispensable tool for the diagnosis of tuberculosis.

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