Original Research Article

Assessment of Hematological and Coagulation profile of patients diagnosed as Tuberculous lymphadenopathy on cytology: A cross sectional study in Industrial belt in Northern India

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A B S T R A C T

Aims & Objectives: Study of the hematological and coagulation parameters in cytologically diagnosed cases of tuberculous lymphadenopathy.

Materials and Methods: A cross sectional study of 60 newly diagnosed cases of tuberculosis on cytology was done. Venous blood samples were collected in EDTA and Citrate vacutainers. XN 1000 fully automated hematology analyzer and Vesmatic were used for hematology parameters and ESR respectively. Stago analyzer was used for coagulation studies. Hematological and coagulation parameters were studied and were analyzed using t test with significance level of 5%.

Results: 60 cases presenting with tuberculous lymphadenopathy on cytology were analyzed which showed a M: F of 1.2 :1. Anemia was noted equally in both sexes. ESR and WBC count was raised in 92% and 45% of cases respectively. Prothrombin Time was raised in 87% of cases while Activated Partial Thromboplastin Time was raised in 45% of cases. Platelet count was normal in 88% of cases. Lymphocytosis was noted in 85% of cases while 52% cases revealed neutrophilia. Smoking and literacy rate had positive correlation. Paired t test shows positive correlation between age and WBC count (p<0.001) and age and Hemoglobin value (p<0.001).

Discussion & Conclusion: Tuberculosis is a hypercoagulable state with alteration in the hematological profile. These simple blood tests with no additional cost can serve as guide to physicians in establishing the early diagnosis along with clinical findings and ancillary investigations. Such Pilot studies can be extended to larger populations and corporate setups to start early treatment and reduce the morbidity and mortality.

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1. Introduction

Tuberculosis is a granulomatous infection caused by Mycobacterium tuberculosis which primarily affects the lungs but other organs may also be affected.1

Tuberculosis has a global incidence of 10.4 million, a mortality of 1.3 million. It is the 9th leading cause of death from infectious agent and ranks above HIV/AIDS.2 India contributes to the highest incidence of tuberculosis in the world and is estimated as 2.79 million.3

Reversible peripheral blood abnormalities are commonly associated with pulmonary tuberculosis and these hematological changes act as marker for the diagnosis, prognosis and response to therapy. Tuberculosis cause profound bone marrow and peripheral blood abnormalities by modulating normal hematopoiesis and the disease become more severe when it is co-infected with HIV because of weakened immunity.4

Hematological alterations and changes in coagulation profile as hypoprothrombinemia, thrombocytopenia was observed in Pulmonary Tuberculosis which results in
hemoptysis. The most common hematologic findings are mild anemia, leukocytosis, and thrombocytosis with a slightly elevated erythrocyte sedimentation rate.\(^5\) Hemoptysis has some relation to hypoprothrombinemia in Tuberculosis because of the fact that destruction of prothrombin normally occurs in the lungs. Vitamin K acts by restoring the Prothrombin level and correcting the hypoprothrombinemia in tuberculosis.\(^6\) The aberrant expression of tissue factor (TF), the primary activator of coagulation cascade, is known to be responsible for thrombotic disorders in many diseases including bacterial infections.\(^7\)

A study showed the prevalence of anemia among tuberculosis patients to be 31.9%.\(^8\) It affects predominantly the females and has a benign course.\(^9\)

Hematological and biochemical abnormalities are common in pulmonary tuberculosis and they are valuable aids to diagnosis.\(^7\)

2. Aims and Objective

1. The purpose of the study is to assess the hematological parameters and ESR in tuberculosis patients presenting with lymphadenopathy.
2. To study the coagulation profile consisting of PT, APTT in patients of tuberculous lymphadenopathy

3. Materials and Methods

This cross-sectional study was carried out as per the ICMR STS (Short Term Studentship) guidelines and the approval was taken from the Institutional Ethics Committee of ESIC Medical College and Hospital, Faridabad.

Informed consents of 60 patients presenting with lymphadenopathy in cytology lab who presented during the 3 month of study duration was taken. Complete Blood Count (CBC), Erythrocyte sedimentation Rate (ESR) and coagulation profile which included Prothrombin time (PT) and Activated Prothrombin Time (APTT) and Bleeding time (BT) and clotting time (CT). About 3 to 4ml of Venous blood samples were collected using vacutainer containing EDTA for the hematological parameters and citrate for coagulation profile. Complete Blood Count (CBC) included hemoglobin, Packed cell volume, White blood cell count, Red Blood Count, platelet counts, all of which were analyzed using fully automated hematology analyzer XN 1000. ESR was calculated using Vesmatic Cube 80 analyzer. Stago analyzer was used for coagulation profile like PT, APTT.

3.1. Inclusion criterion

All the patients newly diagnosed as tuberculous lymphadenopathy on cytology but not started with anti-tubercular treatment were included in the study.

3.2. Exclusion criterion

Cases of relapse, incomplete treatment, noncompliance or recurrence cases were excluded. Patients having fever due to viral, bacterial, pyrexia of unknown origin, urinary tract infections etc or having any other active inflammation were excluded. Detailed clinical history and examination were done to rule out any other illness which may derange the hematological profile were also excluded.

3.3. Data collection

The profile of the study participants who met the criteria and consent to participate were recorded in a semi-structured pre designed questionnaire. The socio demographic profile of the patient, relevant clinical history and lab findings were noted in the study tool when patient visited the cytology lab followed by blood sampling using universal precautions.

3.4. Statistical analysis

The categorical data was presented in form of proportions and continuous data in form of mean. After checking for normality of distribution of data relevant statistical tests were applied to test difference between variables. Chi square test was applied to test the difference between categorical variables and student t test to test difference between continuous variables. Pearson’s correlation statistics was used to calculate the correlation between two continuous variables. The significance level was set at 5%.

4. Observations and Results

60 cases presenting with tuberculous lymphadenopathy on cytology were analyzed which showed a M: F of 1.2:1. The age range of patients was 12 to 74 yrs. The mean age of the patients is 32.86 ± 10.86 years. Anemia was noted equally in both sexes but was not statistically significant. ESR was raised in 92% and was higher in females and was found to be statistically significant while WBC Count was higher in 45% of cases but was not statistically significant. PT was raised in 87% and but not statistically significant. APTT was raised in 45% and 59% of males had raised APTT and this was statistically significant. BT and CT were within normal range in almost all cases and platelet count was within normal range in 88% of cases. Lymphocytosis was noted in 85% of cases while 52% cases revealed neutrophilia. Smoking and literacy rate had positive correlation with male sex and was statistically significant (p<0.001) (Table 1). Paired t test showed positive correlation between age and WBC count (p<0.001) and age and Hb value (p<0.001).

5. Discussion

Tuberculosis is one of the oldest diseases known to mankind primarily affecting lungs although other organs may be affected.\(^9\)
The present study shows there is slight predominance of males over the females, 1.2:1. (Figure 1)

Similar results were obtained in studies by Olivia et al in Brazil along with several other studies. However, studies by kutiyal et al, Ayaz et al, Baloch et al, Ullah et al, Shafee M et al showed the disease was more prevalent in females.

The slight preponderance of males in this study could be due to difference in immunity, exposure to TB bacilli associated with different social behavior and habits including smoking and alcohol which are more prevalent in males in this population. The study reinforces the fact that 47% of the males were smokers who are the predominant factory workers while only 4% are females.

The age range was 12 to 74 years. (Figure 2) The mean age was 32.86 ± 10.86 years. Babylon study showed mean age was 44 ± 2 years while in Quetta it was 46.58 ± 13.28.

As per WHO criteron Mild anemia (males< 12g/dl and females <11gm/dl) was noted equally in both sexes and was seen in 85% of cases (Figure 3). Equal incidence of anemia in both the sexes were also seen in a study by Shafee M.

### Table 1: Distribution of various parameters in relation to sex

<table>
<thead>
<tr>
<th>S.No</th>
<th>Parameter</th>
<th>Males</th>
<th>Females</th>
<th>Percent</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sex</td>
<td>33</td>
<td>27</td>
<td>1.2:1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Literate</td>
<td>27</td>
<td>20</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Smoking</td>
<td>16</td>
<td>1</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Anemia</td>
<td>26</td>
<td>25</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Raised ESR</td>
<td>30</td>
<td>25</td>
<td>92</td>
<td>Mean ESR 23.43</td>
</tr>
<tr>
<td>6</td>
<td>Mild</td>
<td>33</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Moderate</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Severe</td>
<td>Nil</td>
<td>Nil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Raised PT</td>
<td>28</td>
<td>24</td>
<td>87</td>
<td>Mean PT 14.09</td>
</tr>
<tr>
<td>10</td>
<td>Raised APTT</td>
<td>16</td>
<td>11</td>
<td>45</td>
<td>Mean APTT 30.34</td>
</tr>
<tr>
<td>11</td>
<td>Raised CT</td>
<td>1</td>
<td>None</td>
<td>98.3</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Normal BT</td>
<td>33</td>
<td>27</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>TLC (highest 29600) (lowest 1500)</td>
<td></td>
<td></td>
<td></td>
<td>Mean 7886</td>
</tr>
<tr>
<td>14</td>
<td>Neutrophils Raised</td>
<td>16</td>
<td>15</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Neutrophils Normal</td>
<td>9</td>
<td>07</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Neutrophils Low</td>
<td>5</td>
<td>8</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Lympho</td>
<td>26</td>
<td>25</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Lympho Normal</td>
<td>04</td>
<td>01</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Lympho Low</td>
<td>03</td>
<td>01</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Platelet normal</td>
<td>28</td>
<td>25</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Low (lowest 60,000/cu mm)</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>High (highest 6.8lac/cu mm)</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 1:** Sex distribution

**Fig. 2:** Age distribution
Kutiyal noted anemia was more in males. However, Prevalence of anemia was more in females in several studies. \(^8\) Lombard and Masnvelt and Charles et al noted that anemia was present in Tb Patients. \(^{18,19}\)

Anemia is a common hematological complication in Tb pts and a strong risk factor for mortality. \(^{20}\) Studies suggest Tb can be an important differential for anemia. \(^{21,22}\)

Suppression of erythropoiesis by inflammatory mediators or cytokines liberated by macrophages against the tubercle bacilli causes anemia. Chronic inflammation leads to hyperplasia of the mononuclear phagocytic system resulting in extravascular hemolysis and trapping of the iron leading to decreased stainable iron in the erythrocytes (hypochromia). \(^{23}\)

Present study showed WBC count is raised in 45% cases while Lymphocytosis and neutrophilia in 85% and 52% cases respectively. (Figure 4)

Neutrophilia and lymphocytosis were also noted in Tb pts in Ibadan, Nigeria. \(^{24}\) The increase is due to encounter in body with bacteria resulting in cellular immunity. \(^{17}\)

WBCs increases during infection, due to the increased polymorphonuclear leukocytes and macrophages as a part of the body’s immune defense mechanism to combat the invading bacterial population. \(^{25}\)

Positive correlation between age and WBC count (p<0.001) was noted in this study, possibly because multiple infections and inflammation are more prevalent in the elderly population.

WBC count was higher in patients with associated sepsis and acute inflammatory states. \(^{26}\)

However, study by Hungund in India showed decreased number of formed elements. \(^{27}\)

Platelet count was normal in 88% of cases in the present study. (Figure 4) This is in concordance with study by Hungund B R et al which also showed Platelet count was normal in 89% cases. \(^{26}\)

Studies by Oliva et al revealed that Platelet count is increased at the early stage of the disease when there is strong proinflammatory activity which promotes thrombocytosis while with disease progression the anti-inflammatory activity increases and the platelet count normalizes. \(^{10}\) The normal platelet count in majority of the cases included may not in early phase of the disease although this was by chance.

Plasma fibrinogen which is functionally a important ligand for glycoprotein IIB/IIIA, also causes platelet aggregation. Study by Meade et al., shows plasma fibrinogen concentration is an important determinant of platelet aggregation. \(^{28}\)

High platelet count is associated with abnormal fibrinolytic activity leading to hypercoagulability. \(^{10}\)

Increase in ESR was noted in 92% of cases and was more in females in the present study and was statistically significant. (p< 0.03) (Figure 4). Studies by Sidram and Prasappa also noted raised ESR in 100% and 92% cases respectively. \(^{29,30}\)

ESR is a known diagnostic criterion in Tb pt and rises whenever there is focus of inflammation in the body. Our findings are also in concordance with study by Rohini, Oliva, kutiyal. \(^{10,25,26}\)

Early in the disease there is activation of the pro inflammatory cytokines (IFN gamma and TNF alpha) which stimulate acute phase proteins and thrombocytosis and in turn reduces the fibrinolytic activities. \(^{31}\)

Various inflammatory cells, cytokines and mediators are involved in the formation of granulomatous lesions encountered in tuberculosis. \(^{32}\) These epithelioid cell granulomas are clue to the diagnosis of tuberculosis on cytology.

5.1. BT and CT were within normal limits. (Figure 4)

In this study, PT was raised in 87% of cases of which 54% were males but this was not statistically significant. (Fig 4) Abdallah et al also noted increase in PT in 80% cases. \(^{7}\)

Kartaloglu noted increased PT in 56% of cases \(^{33}\) while kutiyal noted in 50% \(^{26}\)
Kaushal et al also observed prolonged PT in 38% of cases. Immune complexes and many other factors elaborated in various infectious diseases are shown to induce pro-coagulant tissue factor (TF) expression in monocytes/macrophages and in the endothelium, which under normal healthy state doesn’t express it.

Cytokines and mediators emerging from a tuberculosis lesion prolong the PT. APTT was raised in 45% of cases in the present study and was statistically significant. (Figure 4) while 44% of the cases with prolonged APTT was also noted in a study by Abdulah in concordance with present study. Kaushal et also showed prolonged APTT in 42% of cases. Deranged APTT in 18% cases was seen in study by Kutiyal et al.

Kaminskaia et al studied the hemostatic system in 23 patients in fibro cavitary pulmonary tuberculosis and observed an increase in APTT and PT and reduction in values of various prothrombin indices, antithrombin III activity and heparin levels. Fibrinogen level was either normal or reduced. Liesbeth et also noted both prothrombin time (PT) and activated partial thromboplastin time (APTT) were both prolonged in primary and recurrent TB patients (P < 0.001 and <0.05) respectively.

The prolonged PT and APTT signifies an underlying latent disseminated intravascular coagulation (DIC) in tuberculosis patients making these patients more predisposed to thrombo hemorrhagic complications. Lowering of the antithrombin III activity and increased thrombin formation may be responsible for this phenomenon. Tuberculosis and disseminated malignancies are associated with prolonged PT, mainly due to hypoprothrombinemia, but may result from fibrinogen deficiency or presence of circulating inhibitors of coagulation. The cytokines also induce the hepatic acute-phase response and can lead to deranged levels of coagulation proteins. Our concordance of prolonged PT and APTT with other studies reassures and establishes the fact Tb causes deranged coagulation profile.

Smoking was noted in 28% cases in our study. (Figure 3) It causes structural and immunological changes in the organism’s defense mechanism like rupture of the pulmonary epithelium, altered adhesion mechanism of the organism, changes in the muco ciliary clearing mechanisms and defective macrophage phagocyte action and lowered CD4 activity leading to increased vulnerability to pulmonary TB.

Systemic inflammation results in activation of coagulation, due to tissue factor-mediated thrombin generation, down regulation of physiological anticoagulant mechanisms, and inhibition of fibrinolysis. Pro-inflammatory cytokines play a central role in the differential effects on the coagulation and fibrinolysis pathways.

The literate number in the present study is 78 percent (Figure 3) and is statistically significant. Similar findings were noted by Shafee M.

Literacy rate reduces the number of Tb cases as it creates awareness about disease process, risk factors, prevention and improved sanitary conditions which can combat the disease. Tb is more among the lower socioeconomic group in whom the literacy rate along with living conditions are poor.

6. Conclusion

Tuberculosis is a national health burden. To eradicate tuberculosis by 2025 as per the Tb Report 2018, the Government of India is implementing RNTPC (Revised National Tuberculosis Program) nationwide which incorporates WHO recommended Directly Observed Treatment Short Course (DOTS) in most of the Government hospitals.

This study was done to explore the significance of routine hematological and coagulation parameters to raise suspicion and help the physicians diagnose tuberculosis in patients presenting with cervical lymphadenopathy in the cytology laboratory at a very early stage.

In all these cases tuberculosis was confirmed on cytology by noting necrotizing granulomatous lesion with or without AFB positivity. A positive correlation could be established between the hematological and coagulation parameters and cytologically proven positive cases of tuberculosis.

These simple non-invasive routinely performed tests like CBC, ESR, PT and APTT which do not require additional expertise and expenditure, can be very useful aid in helping establish the diagnosis along with ancillary investigations for tuberculosis.

However, the study is limited by the small sample size which might not be sufficient to establish a significant statistical association between the various hematological and coagulation parameters and tuberculosis.

Hence, this pilot study can be used as basis for larger longitudinal studies in various government and corporate hospitals to create widespread awareness among the treating physicians and also to help incorporate the DOTS by RNTPC and help reduce the morbidity and mortality from the disease.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

8. Source of Funding

None.
References


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