Anemia among patients with pulmonary tuberculosis in Port Sudan, Eastern Sudan

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ABSTRACT

Background: Pulmonary tuberculosis (PTB) and anemia are both prevalent in Red Sea State. There is limited and inconsistent literature on the association between anemia and pulmonary tuberculosis in the studied area. Aim: This study aimed at assessing the anemia among patients with pulmonary tuberculosis living in Port Sudan city, Red Sea state, Sudan. Method: A prospective study was conducted from June 2006 to December 2008 at Port Sudan Tuberculosis Diagnostic Center. Hundred newly discovered Ziehl Neelsen stain positive randomly selected along with fifty apparently healthy adult also randomly selected were enrolled. Hemoglobin concentration (Hb), serum iron, total iron binding capacity (TIBC) and transferrin saturation were measured. Results: Anemia was observed in 44(44%) of pulmonary tuberculosis patients of which 15 (34%) of cases were anemia of chronic disease, 12 (27%) of cases were iron deficiency, 7 (16%) of cases were iron deficiency anemia, 2 (5%) of cases were macrocytic anemia and 8 (18%) of cases were normocytic normochromic anemia. Conclusion: Anemia of chronic disease is the most condition associated with pulmonary TB, iron deficiency with or without anemia may contribute to advancing the disease.

INTRODUCTION

Pulmonary tuberculosis (PTB) is still a common disease in developing countries [1, 2]. The diagnosis of tuberculosis mainly relies on acid fast bacilli smear and culture result [3]. However, nucleic acid amplification test and polymerase chain reaction (PCR) test were also found reliable [4, 5]. A variety of haematological changes have been described in patients with PTB such as anaemia, sideroblastic anaemia, and folate deficiency [6]. Anaemia is considered to be present if the hemoglobin concentration (Hb) of the red cells is below the lower limit of the 95% reference interval for the individual; age, sex, and geographic location [7]. Anaemia can develop as a secondary effect of a disease process that does not physically invade the bone marrow or markedly accelerated the destruction of erythrocyte. One of the most common infections causing anaemia is tuberculosis; the extent of anaemia associated with tuberculosis depends on the extension of the disease. When tuberculosis is localized mainly in one organ e.g. the lung, the haemoglobin level is usually normal until the disease has made considerable progress leading to a mild to moderate normochromic normocytic, or a slightly hypochromic anaemia. The anaemia takes several weeks to develop after the onset of infection, and then progresses slowly over several months until the haemoglobin level eventually stabilizes [8]. Anaemia is a common complication of pulmonary tuberculosis. The precise mechanism of anaemia in pulmonary tuberculosis is not clearly known but anaemia due to inflammation as well as of iron deficiency has been implicated, both are common in developing countries [9, 10]. The possible cause of observed anaemia in PTB patients might be due to cytokines production and eventually many biochemical changes detected [11]. Nutritional deficiency and malabsorption syndrome can deepen the severity of anaemia. However, the observation that patients with tuberculosis-associated anaemia display an absence of bone marrow iron, suggests iron deficiency is a possible cause of anaemia in patients with tuberculosis [12]. The prevalence of anaemia among TB patients ranges between 30 – 94% [12 – 16]. The increasing prevalence of anaemia with age has been explained by increased chronic disease, poor nutritional status, decrease marrow cellularity, and low serum B12 level. Therefore, old age could be considered as a risk factor for tuberculosis associated anaemia. On the other hand, a disturbance of iron homeostasis develops with increased uptake and retention of iron within the reticuloendothelial system in chronic infections such as tuberculosis because iron is an important growth factor of mycobacterium tuberculosis. The iron retention in reticuloendothelial system is considered as one of the host defense mechanisms and many therapeutic trials are performed. The effect of iron –retention might be exaggerated in women with tuberculosis because women are more likely than men to be iron deficient. This can explained female sex is a risk factor of anaemia [12]. Anemia with similar haematological features occurred in a number of chronic disorders other than tuberculosis [8]. The antituberculous (Isoniazid, cycloserine, and pyrazinamide) reportedly may

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cause a form of sideroblastic anemia by inhibit and interfere with the conversion of vitamin B12 to its active coenzyme form. This in turn, reduces δ-aminolevulinic acid synthase activity and could produce secondary acquired sideroblastic anemia with characteristics similar to those in the hereditary form. The laboratory diagnosis is made according to the cause [17]. Many of the TB patients show haematological evidence of folate deficiency, and the cause of this deficiency in tuberculous patients is not obvious. The deficiency is equally common among treated and untreated patients, and it is not related to the length or type of antituberculosis. Malabsorption of folate is not excluded. It is possible that increased utilization of folate occurs in tuberculosis owing to chronic inflammation, and this increased demand cannot be met by an ordinary diet. Alternatively, folate deficiency might predispose to tuberculosis, and this could be a factor responsible for the known high incidence of tuberculosis in malnourished subjects. Although several studies have shown significantly lower levels of serum folate in patients with active tuberculosis when compared with controls the incidence of significant megaloblastic anaemia is low [18]. Tuberculosis can cause different types of alterations of normal marrow including fibrosis. The characteristic findings are leuco-erythroblastic peripheral blood smear, extramedullary haemopoiesis, and bone marrow fibrosis. Tuberculosis is a rare cause of myelofibrosis in developed countries; however, it is still frequent in some regions due to the high prevalence in the general population [19]. Rare cases of myelofibrosis have been described and thought to be due to disseminated tuberculosis [8]. The diagnosis is established with certainty only if the marrow biopsy specimen includes a tuberculous focus [20]. The present study was designed to assess the anaemia and find out the variations in hemoglobin, serum iron, total iron binding capacity and transferrin saturation.

MATERIALS AND METHODS

This study was conducted prospectively for a period from June 2006 to December 2008 in Port Sudan tuberculosis diagnostic center in Red Sea State. This study consisted of hundred newly discovered pulmonary TB patients positive with *Tubercle bacilli* in sputum (Zn stain) were randomly selected. The inclusion criteria were patients first time diagnosis, no current or previous anti-tuberculous drug treatment, and not to be suffering from any other chronic disease.

The exclusion criteria included past history of pulmonary TB, currently on antituberculosis drug or any other drugs which affected bone marrow or 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. Fifty, apparently healthy normal individuals with no clinical signs for pulmonary TB were selected randomly to be the control group. Blood samples were collected from all of the studied population.

About 3 ml blood was placed in potassium ethylene diamine tetra acetic acid (EDTA) and 3 ml in plain container. The samples under standard laboratory temperature were processed to obtain serum by using a centrifuge. The analysis was performed in Port Sudan Tuberculosis Diagnostic Center by expert technologists.

**Patient’s indicators**

Patients characteristics of interest included: 1) Demographic: sex, age, residence, tribe, and occupation; 2) Hematological: Hemoglobin concentration (Hb) was measured by cyanmethaemoglobin method using (WP21B Tough biochemistry analyzer, mindary (Genius Electronic Co, Ltd, China); 3) Chemical tests: Serum iron and total iron binding capacity (TIBC) were examined within 2 hours of collection using biochemistry analyzer. Percentage saturation obtained by calculation. Chemical tests were determined by (linear chemicals 1135005, 11402AB, Barcelona (Spain).

**Statistical analysis**

Measurements of laboratory data hemoglobin, serum iron, TIBC, and transferrin saturation with pulmonary TB were statistically tested by compare mean and chi-square test which ever was appropriate. A *P* value less than 0.05 were considered statistically significant. The Statistical Package for Social Sciences (SPSS 16.0 version, IBN. Chicago, USA) was used for data analysis.

**Ethical consideration**

This study was approved from the regional Ethical Review Committee (ERC) and written informed consent was obtained from all the patients.

**RESULTS**

This is a case control-analytical study conducted in Port Sudan Tuberculosis Diagnostic center, Red Sea State. The total number of the confirmed diagnosed pulmonary TB patients was 100. The age of the patients in this study was between 14 and 70 years (mean age 33 years). The control individuals aged between 19 and 63 years (mean age 27 years). Of the 100 pulmonary TB patients, 77% were males and 23% were females.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>patients (n=100)</th>
<th>Control (n=50)</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>33 ± 12</td>
<td>27 ± 9</td>
<td>0.004</td>
</tr>
<tr>
<td>(Range)</td>
<td>14 – 70 y</td>
<td>19 – 63 y</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.892</td>
</tr>
<tr>
<td>Male</td>
<td>77 (77%)</td>
<td>38 (76%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>23 (23%)</td>
<td>12 (24%)</td>
<td></td>
</tr>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
<td>0.073</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>Eastern area</td>
<td>32 (32%)</td>
<td>24 (48%)</td>
<td></td>
</tr>
<tr>
<td>Southern area</td>
<td>52 (52%)</td>
<td>18 (36%)</td>
<td></td>
</tr>
<tr>
<td>Downtown</td>
<td>16 (16%)</td>
<td>8 (16%)</td>
<td></td>
</tr>
<tr>
<td>Tribe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hadandwa</td>
<td>24 (24%)</td>
<td>6 (12%)</td>
<td></td>
</tr>
<tr>
<td>Bani amar</td>
<td>33 (33%)</td>
<td>7 (14%)</td>
<td></td>
</tr>
<tr>
<td>Northern Sudan</td>
<td>38 (8%)</td>
<td>29 (58%)</td>
<td></td>
</tr>
<tr>
<td>Western Sudan</td>
<td>35 (35%)</td>
<td>8 (16%)</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>Students</td>
<td>11 (11%)</td>
<td>25 (50%)</td>
<td></td>
</tr>
<tr>
<td>Workers</td>
<td>42 (42%)</td>
<td>12 (24%)</td>
<td></td>
</tr>
<tr>
<td>House wife</td>
<td>13 (13%)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Other jobs</td>
<td>20 (20%)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Employees</td>
<td>14 (14%)</td>
<td>13 (26%)</td>
<td></td>
</tr>
</tbody>
</table>
In the control group, 38 (76%) were males and 12 (24%) were females. Table 1 shows the comparison of different characteristics between patients and controls. It shows that the southern part of the study area (Darussalam) represented the highest incidence (52%) region affected by tuberculosis infection and the workers were the most common segment of occupation affected (42%). Also, table 1 illustrates that the overwhelming majority of pulmonary TB is among the western tribe (35%), followed by Bani amer (33%), Hadandwa tribe (24%), and northern tribe (8%). The differences between the patient group and the control group were found to be significant in haemoglobin concentration, iron, total iron binding capacity, transferrin saturation (Table 2). Hemoglobin concentration, serum iron, TIBC, and transferrin saturation were lower in the patient group than in the control group (P< 0.000). Anemia was present in 44(44%) pulmonary TB cases. Accordingly, most of cases in the current study are anemia of chronic disease (ACD) 15 (34%); followed by iron (Fe) deficiency 12 (27%), severe iron deficiency anemia (IDA) 7 (16%), macrocytic anemia 2 (5%), and normocytic normochromic anemia 8 (18%) (Table 3). The low Hb concentration found in 15(34%) of anemia of chronic disease was correlated positively with low serum iron in 18(37%) and the decreased TIBC in 27 (66%) (P< 0.000). The low Hb concentration found in 12(27%) and 7(16%) of the iron deficiency and severe iron deficiency anemia respectively were correlated with low serum iron in 15(31%), 7(14%) and the increased TIBC in 16 (70%), 7(30%) and decreased transferrin saturation in 14(64%), 6(27%) respectively (P< 0.000) (Table 3).

DISCUSSION

To our knowledge, this is the first study to assess the anemia in Pulmonary TB patients in Red Sea State, Sudan. In this study we found the majority of patients had anemia of chronic disease anemia (microcytic hypochromic anemia). These findings are different from those of a study by Muzaffar TM et al, 2008; Morris CW et al, 1989; Dosumu EA, 2001; Singh KJ et al, 2001; Baynes RD et al, 1986; Lombard EH, 1993 and Lee SW et al, 2006 who found normocytic normochromic anaemia in the majority of their patients, the difference may be due to nutritional factors and small sample size [12, 17, 24 – 28]. Anemia with and without iron deficiency were positively associated with increased risk of mortality. Anemia without iron deficiency was associated with an increased risk of TB recurrence. Similar to other studies, we found a high burden of anemia in TB patients supporting the clinical importance of this routinely measured indicator [29, 30]. Previous study data also suggest, in their population the iron deficiency is an important contributor to anemia [12].

We found a strong positive association of anemia of chronic disease (15/44: 34%) and iron deficiency with TB recurrence and mortality, suggesting that iron deficiency (12/44: 27%) also contribute to poor clinical outcomes. The possible explanation for the findings is that the presence of macrocytic anemia (2/44: 5%) and normocytic normochromic anemia (8/44: 18%) in our study due to factors associated with poor health status or advanced disease. The other causes of anemia including inflammation, parasitic infection, hemoglobinopathy, and other nutritional deficiencies are also important in adult with PTB.

Studies to identify these other contributing factors are necessary to reduce the burden of TB-associated anemia [31]. Kaminskaia GO and Abdullaev R studying the iron metabolism in patients with different degrees of severity of pulmonary tuberculosis stated that in patients with acutely progressive pulmonary tuberculosis, serum iron and serum total iron binding capacity were drastically decreased, while serum unsaturated iron binding capacity was reduced [32, 33]. These findings are considerably in agreement with our present study. This study has a limitation, we did not have information on several factors that may be associated with both iron imbalance and TB infection, including smoking, alcohol history, and diabetes; therefore we cannot exclude the possibility that such factors may contribute to the associations observed.

CONCLUSION

Anemia of chronic disease is the most condition associated with pulmonary TB, iron deficiency with or without anemia may contribute to advancing the disease.
Reference


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