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Original Article

Frequency of anemia in patients with Pulmonary Tuberculosis.

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Abstract

Background: Tuberculosis affects millions of people across the globe annually. Pakistan is ranked 5th among the leading TB countries in the world. Anemia is a common observation among TB patients with the multifactorial phenomenon. The present study aimed to determine the frequency of anemia in patients with pulmonary TB and its classification as per the severity and morphological characteristics.

Methodology: This retrospective cross-sectional study was conducted at DHQ Hospital Timergara, Lower Dir. A total of 109 TB patients were enrolled and underwent physical and systemic examination. Blood samples were collected to estimate complete blood counts (CBC), liver and renal function tests (LFT; RFT), serum albumin, and C-reactive protein (CRP) levels. Abdominal ultrasound was performed when any organomegaly was suspected. Hemoglobin was estimated using an automated analyzer (SYSMEX-SP100) and repeated manually among doubted cases. Written informed consent was obtained from all patients before inclusion, and the collected data was analyzed using SPSS version 22.0.

Results: There was a female majority (54%) in the studied sample, with a mean age of 38 ± 15.3 years. The majority of them belonged to low socioeconomic status (80%). Moreover, 43% were from Dir Lower, 30% from Dir Upper, and the remaining were from Bajaur district, Chitral, and Malakand Swat districts. Anemia was found in 82.56% of the enrolled TB patients. Most patients were moderately weak (Hb < 10g/dl > 7g/dl), and microcytic anemia was found in more than 80% of the anemic patients. CRP level was raised in 70% of these patients, and there was hypoalbuminemia in 80%. Furthermore, females were more anemic than males.

Conclusion: In our study, anemia, specifically microcytic anemia, was prevalent in TB patients. Hence, TB patients must be monitored for dietary deficiencies and/or inflammatory modulators to avoid such complications.

Keywords

Tuberculosis, Anemia, Iron Deficiency Anemia, Anemia of Inflammation.

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Introduction

Tuberculosis is a potentially severe infection caused by mycobacterium tuberculosis. TB has been known to infect humans for a long time and continues to affect millions of people. With increased efforts to enhance TB care and management, significant progress has been made in reducing the global burden of TB, yet this disease remains a major global health concern. According to a Global Tuberculosis report by the World Health Organization (WHO), around 10 million people developed TB in 2017[1]. TB remained one of the top 10 diseases causing death and the single topmost infection-causing death[1]. The report also states that almost one-third of the population of the world is infected by Mycobacterium tuberculosis, with approximately 8.8 million new cases annually[1].

It is recognized as a disease of resource-poor countries[2-4]. Although the actual statistics of TB in Pakistan are difficult to state due to the underreporting of cases, in 2011, the approximate incidence and prevalence rates of TB in Pakistan were reported to be 231 and 364 per 100,000 population, respectively[3,4]. According to WHO, Pakistan stands fifth among countries with the highest burden of TB worldwide, accounting for 61% of the total burden of WHO Eastern Mediterranean Region[5]. We encounter an estimated 510,000 new cases of TB each year, and approximately 15,000 develop drug-resistant TB[5,6]. The main primary causes for the severity of TB, as declared by WHO, are social inequality, aging, and a large flow of migration.

Along with this, the risk factors associated with TB include smoking, diabetes mellitus, alcoholism, malnutrition, any previous history of TB, and/or low socioeconomic status[6,7]. People with poor immunity are at the highest risk of developing TB. Chronic inflammation in pulmonary TB is mainly reflected by the increased circulating C-reactive protein (CRP) and other inflammatory cytokines[7]. Two interactions have also been identified within the association between TB and malnutrition. These include the effect of TB on the status of nutrition and the effect of malnutrition on the clinical manifestation of TB. Both these interactions result from immunological impairment in TB[7]. Studies suggest that iron homeostasis disturbance may also develop when there is an increase in the uptake and retention of iron in the reticuloendothelial system that gets altered or damaged due to chronic infections like TB[8]. Because iron is a key growth factor for Mycobacterium TB, iron retention in the reticuloendothelial system is regarded as one of the host's defense systems, and numerous treatment studies have been conducted[8].

Anemia, a common diagnosis among TB patients, results from iron deficiency anemia (IDA) or inflammation; the reported prevalence of anemia in TB ranges between 32%-86%[8]. Anemia can be defined as the concentration of hemoglobin that is less than 13 g/dl in males and 12 g/dl in females, as recommended by WHO[8]. The resolution of anemia is defined as the concentration of hemoglobin greater than 13 g/dl in males and 12 g/dl in females, with follow-up of two tests being done more than a month apart[9]. One of the most common micronutrient deficiencies in the world is iron deficiency. Many studies have been conducted to evaluate the association between serum iron levels and IDA[8]. IDA is associated with serum ferritin levels of < 30 ng/ml[9], while in certain malignancies, chronic infections, and autoimmune diseases, serum ferritin levels also increase[10]. However, serum transferrin saturation values drop in these two anemia[11]. Anemia increases lethality among TB patients[12] and is associated with unfavorable outcomes. Furthermore, it is more frequent among patients with HIV-TB than those without HIV.

IDA and anemia due to chronic disease are considered the most common types of anemia, characterized by distorted metabolism of iron[13,14]. Studies also suggest that IDA can also result from chronic blood or urinary losses, poor intake or absorption of iron, and/or elevated blood volume[8]. Patients with IDA have decreased iron plasma levels, ultimately limiting erythropoiesis. Studies suggest that infants and women of childbearing age have a high risk of developing IDA[13]. Studies suggest that with anti-TB therapy, the inflammation

reduces along with the burden of the organism, iron retention, erythropoietin response, nutritional status, and improvement in malabsorption. This may explain why a positive treatment response indicated a predisposition for anemia remission[13].

Like IDA, anemia of chronic disease or inflammation is a clinical syndrome characterized by anemia due to fungal, bacterial, or viral infectious diseases. These autoimmune diseases include tuberculosis, inflammation, autoimmune, and neoplastic diseases[12]. Anemia of chronic disease or inflammation is characterized by the association of decreased levels of serum iron and its binding capacity, along with elevated levels of ferritin[12].

To date, few studies have identified the association of anemia with iron deficiency or chronic disease or inflammation in patients with active TB. The present study aimed to determine the frequency of anemia in patients with pulmonary TB and its classification as per the severity and morphological characteristics.

Methodology

This retrospective cross-sectional study was conducted at the Medicine Department of DHQ Hospital Timergara, Lower Dir, KPK, Pakistan. Of the TB patients presenting at the study site, 127 were enrolled. All TB patients aged 18 to 70 years were deemed eligible, while patients with autoimmune diseases, hematological, and other malignancies were excluded from the study.

Physical and systemic examination was carried out, respiratory system examination was done thoroughly, and the abdomen was palpated for any organomegaly. The precordium examination was conducted for any murmurs, added sounds, etc. Blood samples were collected to estimate complete blood counts (CBC), liver and renal function tests (LFT; RFT), serum albumin, and CRP levels. In case of any organomegaly, abdominal ultrasound was performed.

An automated analyzer (SYSMEX-SP100) was used for hemoglobin estimation, and in some cases, hemoglobin (Hb) was repeated manually.

Statistical analysis was performed on SPSS version 22.0; frequency and percentages were calculated for categorical variables. Mean and standard deviation were used for presenting continuous variables.

The hospital ethical review committee granted the ethical approval for the study [R.No.7313 dated 25/03/2019], and written informed consent was obtained from all patients before inclusion.

Results

Out of 109 TB patients, 59(54%) patients were females, and 50(46%) were males. The mean age was 38 ± 15.3 years, and most patients had low socioeconomic status (80%). Furthermore, 27% were ex-smokers, and 24% were current smokers. Based on the geographical distribution, 43% of the patients belonged to Dir Lower, 30% from Dir Upper, 21% from Bajaur district, and 6% from Chitral Malakand Swat districts. Among the total anemic patients, 29(32.3%) were classified as mild anemic, 48(53.3%) were moderately anemic, and 13(14.4%) were severely anemic. Stratification of anemic patients concerning gender is shown in Table 1.

Table 1: Classification and gender-wise distribution of the patients concerning anemia.

Variables	Total	Males	Females
Mild anemia	29(32.3)	15(37.5)	14(28)
Moderate anemia	48(53.3)	19(47.5)	29(58)
Severe anemia	13(14.4)	06(15)	07(14)

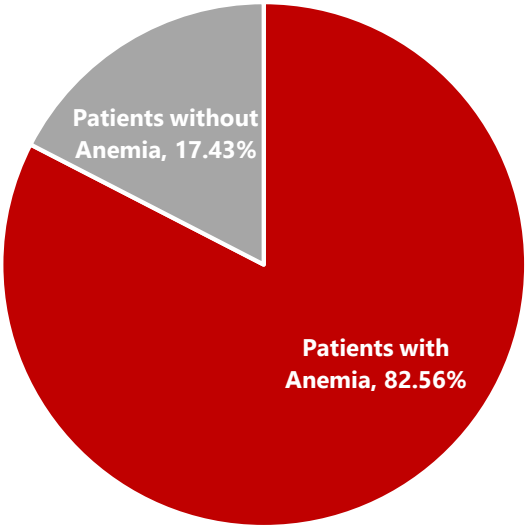

Figure 1: Frequency of anemia among enrolled TB patients.

Of the total, 90(82.56%) patients were found anemic. Furthermore, more female patients had hemoglobin levels below 11.5 g/dl (84.74%) than males (80%) (Figure 1).

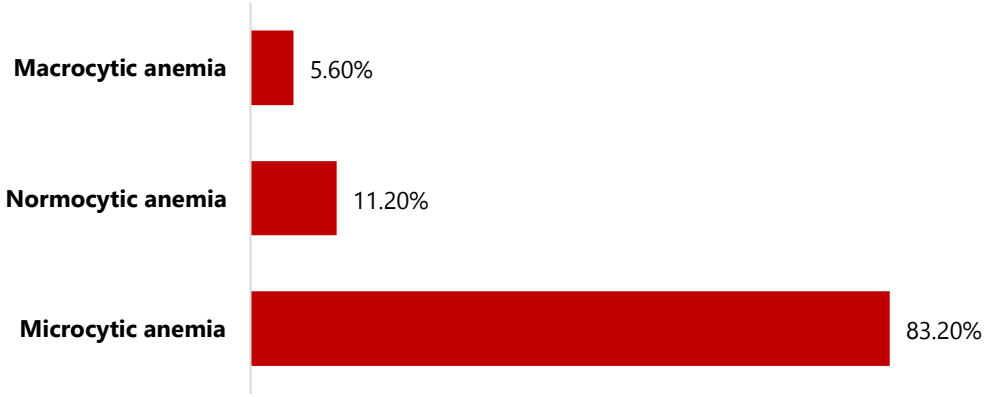

Figure 2: Anemia based on Mean corpuscular volume (MCV).

Of the 90 anemic patients, 83.20% had microcytic anemia, followed by normocytic and macrocytic anemia (Figure 2).

We observed raised CRP in 70% of these patients, and 80% had low serum albumin, reflecting malnutrition. Moreover, the platelet count was normal in 75% of patients; 15% had thrombocytopenia, and 10% were observed with thrombocytosis. The white cell counts were normal in 78% of the enrolled cases. While 13% and 9% developed leukocytosis and leucopenia, respectively. Only two patients were presented with hemolytic anemia.

Discussion

In this study, we found anemia in 82.56% of the total pulmonary TB patients, which is comparatively higher than that reported in studies from South Korea (32%) and Indonesia (63%)[14,15]. While others reported a higher prevalence of anemia than in the present study, i.e., 96% and 88%, respectively[12,16]. TB is considered the most devasting disease in the elderly, with atypical, nonspecific, or confused clinical features, along with already existing diseases[17]. Studies suggest that in such elderly patients of TB, antitubercular chemotherapy is mostly associated with adverse effects[15,16]. While some studies counter-argue that elderly females are at high risk of TB associated with anemia[17]. Studies have shown an association between the increased prevalence rate of anemia with age, increased chronic disease, low marrow cellularity, poor nutrition status, and low vitamin B12[16]. This also highlights that old age or aging can be interpreted as the risk factor for anemia in patients with TB[17]. Results evaluated from different studies also suggest that the iron-retention effect might also be exaggerated in females with TB. This happens because women are more likely to be iron deficient than men, which is also defined by existing literature[17].

Characterizing the variables contributing to TB-associated anemia is crucial to inform clinical decision-making and provide a foundation for therapy recommendations. Iron deficiency is the most common cause of anemia worldwide. However, other factors frequently coexist. In cases where iron deficiency is determined as a major cause of TB-related anemia, supplemental iron may be given to TB patients on a case-by-case basis to boost blood hemoglobin levels and improve clinical outcomes. Iron deficiency without anemia may play a direct role in the progression of tuberculosis disease, as iron deficiency has been linked to poor immunological function and a diminished ability to regulate infection[15,16]. According to experimental and epidemiological evidence, iron is essential for normal immunological function. Hence, iron deficiency has been demonstrated to impair cell-mediated immunity by lowering T-cell counts and proliferative responses, as well as lowering macrophage activity, potentially lowering the host's ability to control infection. Through its influence on the body's cytokine profile, the iron status may also influence the type of immunological response mounted[17,18]. Since anemia without iron deficiency has been linked to TB recurrence, death, and HIV disease progression, it is suggested that variables other than iron deficiency play a role in the link between anemia and poor clinical outcomes[19].

In this study, more than 80% of the participants belonged to low socioeconomic families, supporting the correlation between TB and poverty[18]. Hypoalbuminemia in most patients also further enhances the views of TB's correlation with poor economic conditions and malnutrition. However, most of these patients had normal white cell counts, while those with WBC abnormalities were observed with leucocytosis (13%) and leucopenia (9%). Meanwhile, 15% of patients had thrombocytopenia, and 10% were observed with thrombocytosis. Similarly, Banerjee et al. studied hematological alterations among TB cases; they reported leukocytosis among 28.63% of patients, leucopenia in 2.20%, neutrophilia (66.15%) lymphocytosis (21.53%), thrombocytosis (17.62%), and 5.28% had thrombocytopenia[9]. Other than the CBC, the parameters of LFT and RFT are also altered among TB patients with anemia. In the present study, raised CRP and low serum albumin were observed in most cases, which is also supported by other similar studies reporting hypoalbuminemia[19,20], increased CRP[21], and decreased BMI among TB patients with anemia as compared to non-anemic[21,22]. It is suggested that CRP is considered one of the markers of the treatment effect and the inflammation due to resolution. It has been observed that CRP levels decline during antituberculosis treatment and normalize by the end of treatment[19]. Studies also show elevated concentrations of most proteins in patients with TB. These proteins also include the concentration of transferrin and hemoglobin[20]. Several studies suggest that in anemic TB patients, transferrin concentration gets lower while ferritin concentration increases[21]. It is important to know

the concentration of proteins level since ferritin is the most sensitive to determine in conditions other than inflammation. It is also important for the diagnosis of iron deficiency[22]. It is seen that in patients with TB, the ferritin level determination is mostly used with caution since its levels do not always accurately determine the iron amount in patients with TB because it is observed that such patients can show a deficiency of iron level with as well as elevated levels of ferritin[23].

Furthermore, the decreased MCV and high prevalence of microcytic anemia (83.20%) observed among the enrolled TB cases allow us to speculate that anemia in the existing TB cases might be in response to iron nutritional deficiency or decreased availability to erythropoiesis due to the alterations in the inflammatory metabolism. The higher platelet counts also validate the argument mentioned above in anemic patients due to the bone marrow's lower iron availability, leading to increased production of megakaryocytes with higher ploidy releasing more platelets than in lower-ploidy ones[23]. A study exploring the causes of anemia reported altered inflammation among 15.0% to 75.9% of TB cases, while up to 58.0% had iron deficiency anemia[24]. Literature suggests that microcytosis observation may help observe iron deficiency in TB patients since the RDW might be useful to demonstrate the condition more accurately[25]. Malnutrition is also said to be severe in patients with TB with anemia. A decreased concentration of transferrin and serum is associated with anemia[25].
Regarding the inflammatory state, studies of different regions suggest that ESR may be higher in anemic patients compared to those in which the difference is not significan[t25]. Authors suggest that an increased level of ESR in response to anemia is an important finding that helps collaborate the patient's results[25]. Considering the results of the present study, it can be stated that a high proportion of the sample size was classified as underweight and malnourished, as suggested based on different parameters, along with a high prevalence rate of anemia. With the advancement in health sciences, it is now evident that TB might produce abnormalities in blood from the peripheral, which also include anemia. However, in several studies, anemia is still considered the most common hematological abnormality in TB patients, and close observation is considered sufficient for such patients[24].

The study had certain limitations; as the study was retrospective, we could not assess some more specific parameters for exploring the etiologies of anemia, i.e., the existing data isn't sufficient to distinguish IDA or anemia due to inflammation or other possible causes discussed above. Furthermore, patients were not screened for HIV, as the co-existence of TB/HIV is an important association nowadays. Moreover, we couldn't use all the parameters recommended to differentiate the diagnosis between IDA and anemia due to chronic disease or inflammation.

Conclusion

In conclusion, most TB patients suffer from anemia, predominantly microcytic anemia, which needs to be diagnosed and treated timely. For appropriate management, all diagnosed anemic TB patients must be assessed for total iron-binding capacity, serum ferritin level, transferrin saturation level, serum folate, and serum vitamin B12 level. HIV is an important co-existent infection with TB, and all TB patients must be screened for HIV, although not investigated in the present study, which is one of the major limitations of this study. Further studies are recommended with a large sample size with more parameters for a specific diagnosis, like a peripheral smear of the anemic patients, which could provide significant prognostic information.

Conflicts of Interest

The author(s) have no conflicts of interest.

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