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The Prevalence and Evolution of Anemia Associated with Tuberculosis

Tuberculosis (TB) may produce abnormalities in the peripheral blood, including anemia. However, the evolution of TB-associated anemia with short-term combination anti-TB chemotherapy has not been well elucidated. The aim of this study was to characterize TB-associated anemia by clarifying its prevalence, characteristics, and evolution, through involving large numbers of patients with TB. The medical records of adult patients with TB diagnosed between June 2000 and May 2001 were reviewed. Among 880 patients with TB, 281 (31.9%) had anemia on diagnosis of TB, however, the hemoglobin concentration was less than 10 g/dL in only 45 patients (5.0%). Anemia was more frequently associated with the female and old age. Good treatment response, young age (≤65 yr-old) and initial high hemoglobin were the predictive factor for resolution of anemia. In 202 patients with anemia (71.9%), anemia was normocytic and normochromic. During or after anti-TB treatment, anemia was resolved in 175 (64.6%) out of 271 patients without iron intake. The mean duration of resolution from the initiation of anti-TB treatment was 118.8±113.2 days. In conclusion, anemia is a common hematological abnormality in patients with TB and close observation is sufficient for patients with TB-associated anemia, because TB-associated anemia is usually mild and resolves with anti-TB treatment.

Key Words : *Tuberculosis; Anemia; Treatment; Treatment Outcome*

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INTRODUCTION

Tuberculosis (TB) is the world's second most common cause of death from infectious disease, after HIV/AIDS. There were an estimated 8.3 million new cases of TB in 2000 and 1.8 million deaths from TB were reported in the same year. Moreover, TB was the cause of 11% of all adult AIDS deaths (1).

TB can cause diverse laboratory abnormalities such as anemia (2, 3), increased erythrocyte sedimentation rate (4-6), low serum albumin level (5, 7), hyponatremia (5), abnormal liver function (5), leukocytosis (5), and hypocalcemia (7). A number of studies have documented anemia in patients with TB (3, 5, 8-11), however, these studies involved only small numbers of patients and the results were not uniform. Moreover, there has been no study on the evolution of TB-associated anemia after establishment of short-term combination anti-TB chemotherapy in the 1980s. In this context, we attempted to characterize TB-associated anemia by clarifying its prevalence, characteristics, and evolution with anti-TB treatment involving large numbers of patients.

MATERIALS AND METHODS

Study settings and subjects

We included patients aged 15 yr or older who were diagnosed with TB and administered first-line anti-TB medications between June 2000 and May 2001 at Seoul National University Hospital, a university-affiliated tertiary referral hospital. The following cases were diagnosed with TB; patients with positive smear or culture, compatible pathology result, positive TB PCR or lymphocyte dominant exudate pleural effusion with high ADA, low CEA and negative cytology. We excluded patients with any other medical conditions that can cause anemia, such as bleeding, nutritional deficiency, malignancy, AIDS, autoimmune disease, aplastic anemia, chronic renal disease, chronic liver disease, and taking of medication that can cause anemia within four weeks. We also excluded patients who could not be followed up for more than four weeks. In the analysis of anemia resolution, those patients were excluded who took iron for more than one month during anti-TB medication.

Definition of anemia, its resolution, and good clinical response to the treatment

The definition of anemia used in this study was hemoglobin concentration less than 13 g/dL in men and 12 g/dL in women (WHO recommendation) (12). The resolution of anemia was defined as a hemoglobin concentration greater than 13 g/dL in men and 12 g/dL in women following two tests more than a month apart. Good treatment response was defined as negative conversion of sputa and no evidence of relapse

after completion of treatment. Improvement of radiographic or bronchoscopic findings was also defined as a good treatment response if the result of a sputum study conducted subsequent to treatment was not available.

Data collection and statistical analysis

We retrospectively reviewed the medical records of the enrolled patients, which included demographic data, the type of TB, the treatment regimen and duration, and the serial hemoglobin concentration. Univariate comparisons between patients with anemia and patients without anemia were performed using Fisher's exact test for categorical variables and the Student's t test for continuous variables. All tests of significance were two sided, and a p value of less than 0.05 was considered significant. Multivariate logistic regression analysis was conducted using SPSS (version 11.0) to identify the predictor variables for the development of anemia.

RESULTS

Clinical characteristics of enrolled patients

Among the 974 eligible patients, 94 were excluded from the analysis because they had other medical conditions that can cause anemia. The excluded patients were 42 with AIDS, 20 with malignant disease who were taking anti-cancer chemotherapy, 12 with systemic lupus erythematosus, 14 with liver cirrhosis, and six with other diseases. The clinical data of the remaining 880 patients were analyzed.

Among the 880 patients, 472 patients (53.6%) were male and 408 (46.4%) were female. The median age was 44 yr old (range 15-93). Pulmonary TB was the most common form of TB (596 patients, 67.7%). Treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol was applied to 615 patients (69.9%), and the median treatment period was 211 days (range 28-1,463 days) (Table 1).

Table 1. Clinical characteristics of the 880 patients with tuberculosis

Total number	880
Male:Female	472 (53.6%):408 (46.4%)
Age (yr)	44 (15~93)
Types of TB	
Pulmonary TB	596 (67.7%)
TB pleurisy	72 (8.2%)
TB lymphadenitis	67 (7.6%)
Musculoskeletal TB	47 (5.3%)
Others	98 (11.1%)
Initial treatment regimen	
HREZ*	615 (69.9%)
HRE*	145 (16.5%)
HREL*	16 (1.8%)
Others†	104 (11.8%)
Treatment period (range)	211 (28-1463) days

*H abbreviates isoniazid, R rifampicin, E ethambutol, Z pyrazinamide and L lovofloxacin; †Others included various regimens of first line drug combination such as isonizaid plus rifampicin, isoniazid, rifampicin plus pyrazinamide or ethambutol, levofloxacin plus streptomycin and so on.

Prevalence and characteristics of anemia

Anemia was identified in 281 patients (31.9%) at the time of diagnosis of TB. 133 (28.2%) of men and 148 (36.3%) of women with TB had anemia. In 45 patients, the hemoglobin concentration was less than 10 g/dL. No male patient had a hemoglobin concentration less than 8.0 g/dL and no female patient had a hemoglobin concentration less than 7.0 g/dL (Table 2). Normocytic and normochromic anemia was most common, and was identified in 202 (71.9%) patients; and microcytic hypochromic anemia was next common (26 patients, 9.1%) (Table 3). The presence of anemia was associated with age older than 65 yr and female sex (Table 4).

Evolution of anemia with anti-TB treatment

10 patients with iron replacement during anti-TB medication were excluded for the analysis of evolution of anemia. In 175 (64.6%) out of the other 271 patients with TB-associated anemia, the anemia resolved during or after completion of anti-TB treatment. Mean duration from initiation of

Table 2. Distribution of hemoglobin concentrations in patients with tuberculosis

Hemoglobin concentration (g/dL)	Male	Female	Total patients	Cumulative number of patients
-6.9	0	0	0	0
7.0-7.9	0	3 (0.7%)	3 (0.3%)	3 (0.3%)
8.0-8.9	7 (1.5%)	3 (0.7%)	10 (1.1%)	13 (1.4%)
9.0-9.9	12 (2.5%)	20 (4.9%)	32 (3.6%)	45 (5.0%)
10.0-10.9	22 (4.7%)	41 (10.0%)	63 (7.2%)	108 (12.2%)
11.0-11.9	36 (7.6%)	81 (19.9%)	117 (13.3%)	225 (25.5%)
12.0-12.9	56 (11.9%)	137 (33.6%)	193 (21.9%)	418 (47.5%)
13-	339 (71.8%)	123 (30.1%)	462 (52.5%)	880 (100%)
Total	472	408	880	880

Table 3. Morphologic characteristics of anemia in 281 patients with TB-associated anemia

	MCHC (g/dL)†			Total
	Hypochromic	Normochromic	Macrocytic	
MCV(fL)*				
Microcytic	26 (9.1%)	14 (5.0%)	0	40
Normocytic	23 (7.7%)	202 (71.9%)	3 (1.1%)	228
Macrocytic	0	13 (4.6%)	0	13
Total	49	229	3	281

*Reference range of MCV, 81-96 fL; †Reference range of MCHC, 32-36 g/dL.

Table 4. Risk factors for the presence of anemia

	Anemia	Normal hemoglobin	*p* value (Univariate analysis)	*p* value (Multivariate analysis)	OR (95% CI)
Sex					
Male	133	339	0.10	0.006	1
Female	148	260			1.51 (1.13-2.01)
Type of TB					
Pulmonary TB	208	460	0.37	n-a	n-a*
Extrapulmonary TB	73	139			
Age (yr)					
<65	195	507	<0.001	<0.001	1
≥65	86	92			2.49 (1.77-3.50)

*n-a, not applicable.

Table 5. Predictive factor of resolution of anemia with anti-TB medication

Factor	Resolution	Persistent anemia	*p* value (Univariate analysis)	*p* value (Multivariate analysis)	OR (95% CI)
Sex					
Male	79	51	0.21	n-a*	n-a
Female	96	45			
Type of TB					
Pulmonary TB	126	70	0.87	n-a	n-a
Extrapulmonary TB	49	26			
Age (yr)					
<65	129	57	0.02	0.07	1.66 (0.96-2.89)
≥65	46	39			1
Initial higher hemoglobin concentration			<0.001	<0.001	1.59† (1.25-2.03)*
Treatment response					
Good	162	81	0.03	0.06	2.17 (0.96-5.12)
Not good	13	15			1

*n-a, not applicable; †As initial hemoglobin increased by 1 mg/dL.

treatment to resolution of anemia was 118.8±113.2 days. Resolution of anemia took longer if the initial hemoglobin concentration was lower. It took 232.3±179.1 days to resolution for patients whose hemoglobin concentrations were less than 10 g/dL, 152.5±95.5 days for 10.0-10.9 g/dL, 117.8±99.0 days for 11.0-11.9 g/dL, and 71.6±73.8 days for more than 12.0 g/dL (p=0.02).

Among the other 96 patients with persistent anemia, the hemoglobin concentration increased more than 1 g/dL in 25 patients and was stationary within 1 g/dL from the initial level in the other 71 patients. There were no patients in whom the hemoglobin concentration decreased by more than 1 g/dL. In 63 of the 71 patients with stable hemoglobin levels, the initial hemoglobin concentration was greater than 11.0 g/dL. Seven of the remaining eight patients with persistent anemia, whose hemoglobin concentration was less than 11.0 g/dL, had

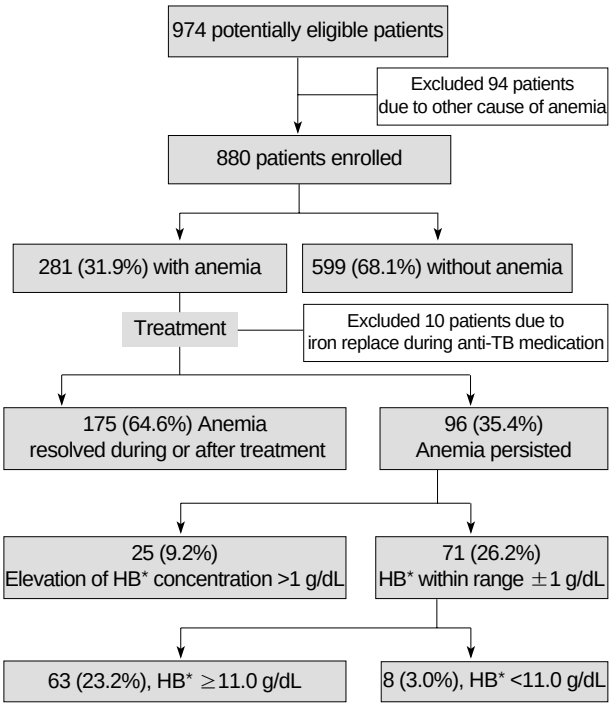

Fig. 1. Prevalence and evolution of anemia in 892 patients with TB. *hemoglobin.

a poor performance status; poor oral intake, severe parkinsonism, old age (85 yr old), or were bedridden. The remaining patient had endometrial polyps with menorrhagia (Fig. 1).

Good treatment response, young age, and initial higher hemoglobin concentration were related with resolution of anemia. In multivariate analysis including these three variables, initial higher hemoglobin was the only predictive factor for resolution of anemia although younger age and good treatment response showed marginal association (Table 5).

DISCUSSION

Anemia has been reported in 16% to 94% in patients with pulmonary TB, (3, 5, 6, 8-11) although a different definition was applied. These reports recommend TB as one of the differential diagnoses of anemia. Anemia occurred in 31.9% of our patients, but it had a benign course in most cases. TB-associated anemia completely resolved with anti-TB treatment in 64.5% of patients. In addition, the anemia improved considerably in the other patients, with rare exceptions.

All chronic infections including TB can cause anemia (13). Various pathogeneses have been suggested in TB-associated anemia, but most studies have shown suppression of erythropoiesis by inflammatory mediators (2, 3, 5, 14, 15) as a cause of anemia. Nutritional deficiency (16) and malabsorption syndrome (17) can deepen the severity of anemia. However, the observation that patients with TB-associated anemia display an absence of bone marrow iron (8, 11) and the same red blood

cell distribution width as that observed with iron-deficiency anemia (2), suggests that iron-deficiency is a possible cause of anemia in patients with TB.

Although a normocytic, normochromic anemia was most common in this study, other types of anemia, including hypochromic microcytic anemia, were not rare. Considering the diverse morphology of anemia and various suggestions for the cause of TB-associated anemia, the anemia in patients with TB may result from several mechanisms instead of one sole pathogenesis. In addition, that the anemia did not resolve completely, even after successful treatment in 81 patients with TB-associated anemia, suggests that anemia of other causes could have combined with TB-associated anemia.

Female sex and old age were risk factors for TB-associated anemia in our data. The prevalence of anemia usually increases with age (18), especially after age 60 yr (19-22). The increasing prevalence of anemia with age has been explained by increased chronic disease, poor nutritional status, decreased marrow cellularity (23), and low serum vitamin B_{12} levels (24). In this context, old age could be interpreted as a risk factor for TB-associated anemia. 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 TB (15, 25, 26). Because iron is important growth factor of *Mycobacterium tuberculosis*, the iron retention to reticuloendothelial system is considered one of host defense mechanisms and many therapeutic trials are performed (27). The effect of iron-retention might be exaggerated in women with TB because women are more likely than men to be iron deficient (28). This can explain female sex is the risk factor of anemia.

Iron retention, erythropoietin response (29), nutritional state, and malabsorption can improve, as inflammation and burden of organism decreases by anti-TB medication. This can explain good treatment response showed tendency toward resolution of anemia with marginal statistical significance in our study (OR=2.17, 95% CI 0.96-5.12, p=0.06). The report association between the resolution of anemia and negative sputum conversion in pulmonary TB could be appreciated in this context (30).

In conclusion, anemia is a common hematological abnormality in patients with TB. Because TB-associated anemia is usually mild and resolves with anti-TB treatment, close observation is sufficient without other cause of the anemia.

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