CHANGES IN SERUM PROTEINS, ERYTHROCYTE SEDIMENTATION RATE AND MANTOUX TUBERCULIN SKIN TEST REACTIVITY IN ACTIVE TUBERCULOSIS

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ABSTRACT: The records of 141 consecutive patients with proven tuberculosis (TB) were reviewed to examine for changes in their serum proteins, erythrocyte sedimentation rate (ESR) and tuberculin skin test reactivity. Hypoalbuminaemia was present in 73% of patients and hyperglobulinaemia was seen in 92% of patients. ESR showed a negative correlation with the serum albumin level but a positive correlation with the serum globulin level. In the case of pulmonary TB, ESR was higher in patients with radiologically more extensive disease. Tuberculin reactivity was reduced in patients who were older, those with more severe hypoalbuminaemia and those with disseminated TB. *(JUMMEC 1998 1&2: 47-53)*

KEYWORDS: Albumin, erythrocyte sedimentation rate, globulin, tuberculin reactivity, tuberculosis

Introduction

Protein-energy undernutrition and hypoalbuminaemia are common observations in patients with active tuberculosis (TB). (1-8) The tuberculin skin test response in TB is related to the nutritional status of the patient which is reflected by the serum albumin level (9-11). Negative response to tuberculin may be seen in 8% to 30% of patients with active TB (1,12,13). Hyperglobulinaemia is a feature in patients with newly diagnosed TB and is mainly due to an increase in the gamma-globulin fraction (1,5). The erythrocyte sedimentation rate (ESR) is usually raised in active TB (1,13,14) but a normal value does not exclude active disease (15).

The objectives of this study are 1) to determine the frequency of abnormalities in the levels of serum albumin and globulin in a group of Malaysian patients with newly diagnosed TB, and 2) to examine the relationships between the different forms of TB and their severity on the one hand, and the serum albumin level, globulin level, ESR and tuberculin skin test reactivity, on the other.

Patients and methods

This is a retrospective analysis of patients with TB diagnosed at the University Hospital, Kuala Lumpur. The records of consecutive patients with newly diagnosed TB which was proven by bacteriology and/or histology in the hospital from September 1994 to December 1996 were reviewed. Confirmation of the diagnosis of TB was based on one or more of the following criteria in the relevant tissue or specimen: 1) positive smear for acid-fast bacilli (AFB) by the Ziehl-Neelson method, 2) positive culture for *Mycobacterium tuberculosis in* Lowenstein-Jensen medium, and 3) typical histology showing epithelioid granulomas with or without caseous necrosis and with or without positive staining for AFB. Disseminated TB was considered to be present when the chest radiograph showed miliary mottling in both lung fields and at least one of the above three criteria was met or when TB could be proven in at least two different organs.

Blood specimens were taken from patients with newly diagnosed TB for the measurement of ESR and liver function test which included serum total protein and albumin. The level of serum total globulin for each patient was obtained by subtracting the level of serum albumin from the total protein measured at the same time. ESR was considered elevated if it exceeded 35 mm/hr for elderly patients aged 65 years and above and for those below 65 years, if it exceeded 10mm/hr for male patients and 20 mm/hr for female patients. Testing for HIV antibody was not routinely done unless a patient belonged to a high risk category or other acquired immunodeficiency syndrome (AIDS) defining illnesses were present.

Plain postero-anterior chest radiographs taken at the time of presentation were reviewed and graded 1 to 6 to assess the extent of pulmonary disease (Table I) (16). The Mantoux test was performed by injecting 10 tuberculin units of Tween-80 stabilised purified protein derivative (PPD) (CSL Limited, Victoria, Australia) intradermally into the ventral surface of the upper part of the forearm and reactions were read at 72 hours. Reactions with indurations of 10 mm or more in diameter measured across the transverse axis of the forearm were regarded as positive and those with no induration or with indurations of less than 10 mm in diameter were considered negative (10,12,13,17,18).

Results were expressed as mean (± one standard deviation). Correlation coefficients (r) between variables were determined by simple linear regression analysis. Statistical comparisons of continuous variables were assessed by unpaired Student's *t*-test and analysis of variance using the Newman-Keuls multiple comparison technique. Categorical data were analysed using chi-square test (χ^2) or the Fisher's exact test. *P* values of less than 0.05 were accepted as statistically significant.

Results

Patient characteristics

During the period of review, tuberculosis was diagnosed and confirmed in 141 patients (87 male, 54 female) in the hospital. Table 2 summarises the distribution of the methods of confirming the diagnosis of TB. There were 77 (54.6%) cases of pulmonary TB of which 19 cases were associated with pleural effusions (Table 3). Thirty-one patients had pleural TB without chest radiographic evidence of lung parenchymal infiltrate, 15 had tuberculous lymphadenitis, 14 had disseminated TB and four had bone and/or joint TB. The age distribution of the patients is shown in Figure 1. The mean age of the patients was 41.2 (± 17.0) years (range, 17 - 84 years). Seventy-five (53.2%) patients were aged 40 years or below while 17 (12.1 %) were 65 years or older. The mean age of male patients, 41.9 (± 16.9) years was not significantly different from the mean age of female patients which was 40.0 (± 17.3) years ($p = 0.516$). The mean age of patients with lymph node TB, 27.3 (± 9.5) years was significantly younger than those of patients with the other forms of TB; while patients with pulmonary TB alone was significantly older than the other patients ($p = 0.003$) (Table 3). Of the 50 patients who had pleural involvement by TB, those without chest radiograph evidence of lung infiltrate (n = 31) was younger [mean age 38.4 (± 17.1) years] than those with

Table 1. Grading of anatomical extent of lung involvement in pulmonary tuberculosis (16)

1. Trivial: that is, minimal lesions which the assessor regarded, purely on radiographic grounds, as inactive
2. Slight: that is, minimal or rather larger lesions which he regarded as radiographically active
3. Limited: that is, lesions of greater extent than in (2) but involving a total area of lung less than that occupied by the right upper lobe as visualized on a posteroanterior radiograph
4. Moderate: that is, lesions of greater extent than in (3) but whose total extent, even if bilateral, did not exceed an area equivalent to the whole of one lung
5. Extensive: that is, lesions which involved an area of more than the whole of one lung
6. Gross: that is, very extensive bilateral disease

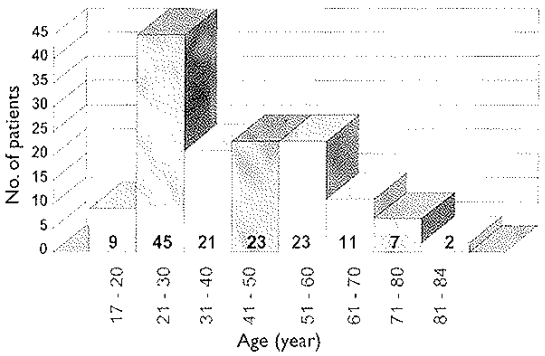

Figure 1. Age distribution of patients with tuberculosis

Table 2. Methods of confirming the diagnosis of tuberculosis

Bacteriological or histological confirmation*	No. of patients#
Sputum smear- and culture-positive	47
Bronchial washing smear- and culture-positive	8
Bronchial washing smear-negative but culture-positive	7
Bronchial biopsy positive histology	8
Lung biopsy positive histology	4
Pleural biopsy positive histology	49
Pleural effusion culture-positive	1
Lymph node biopsy positive histology	16
Vertebral biopsy positive histology	2
Psoas abscess culture-positive	2
Hip joint synovial biopsy positive histology	1
Liver biopsy positive histology	1
Pericardial biopsy positive histology	1
Peritoneal biopsy positive histology	1

*Smear-positive for acid-fast bacilli; or culture-positive for Mycobacterium tuberculosis; or biopsy showing epithelioid granulomas with or without caseating necrosis and with or without the presence of acid-fast bacilli

#Seven patients had positive results from 2 diagnostic procedures

of lung infiltrates (n = 19) [mean age 39.3 (± 15.1) years]. However, this difference did not reach statistical significance.

The distribution of the radiographic extent of lung involvement in the 77 patients who had pulmonary TB with or without pleural involvement is shown in Table 4. There was no relationship between the radiographic extent of lung involvement and the age of the patient.

The most common underlying disease was diabetes mellitus which was present in 35 patients. AIDS was present in three patients with pulmonary TB, one patient with pulmonary TB accompanied by pleural involvement and three patients with lymph node TB. One patient with CD4+ T-lymphocytopenia of unknown cause had pulmonary TB. Three patients had end-stage renal failure. Four patients were on prednisolone for underlying collagen vascular disease and one was receiving cytotoxic chemotherapy for seminoma.

Tuberculin skin test (Mantoux test)

Eighty-four (59.6%) patients showed positive reactions to the Mantoux test. All seven patients with AIDS and the patient with idiopathic CD4+ T-lymphocytopenia did not react to the Mantoux test. Excluding these eight patients (mean age, 31.5 years, range 24 - 46 years) who had obvious reasons for nonreactivity to the tuberculin skin test, patients who were Mantoux test negative (n=49), whose mean age was 46.2 (± 17.0) years, were significantly older than patients who were Mantoux test positive, mean age 39.1 (± 17.0) years (p = 0.021). Significantly more patients with disseminated TB were Mantoux test negative than Mantoux positive (p = 0.02) (Table 5). There was no relationship between Mantoux test reactivity and the radiographic extent of lung involvement in pulmonary TB with or without pleural involvement (Table 6). Although seven (58.3%) out of 12 patients with grade 5 and 6 chest radiograph changes were Mantoux test negative, this proportion was not significantly higher than that of 18 (31.3%) of 65 patients with lower grades of X-ray changes who were also Mantoux test negative (χ^2 =3.053, p = 0.081).

Table 3. Type of tuberculosis and age, serum albumin and globulin levels, and ESR

Type of tuberculosis	No. of patients (n = 141)	Mean age year	Mean serum albumin# g/L	Mean serum globulin* g/L	Mean ESR mm/hr
Pulmonary TB alone	58	46.8 (17.2)	27.8 (7.2)	46.1 (7.9)	69.0 (40.0)
Pulmonary TB with pleural involvement	19	39.3 (15.1)	28.3 (6.2)	48.5 (9.9)	58.2 (44.1)
Pleural TB alone	31	38.4 (17.1)	29.6 (5.5)	45.4 (6.5)	76.9 (30.6)
Lymph node TB	15	27.3 (9.5)	34.6 (7.5)	48.7 (9.3)	73.2 (46.3)
Bone and/or joint TB	4	39.8 (11.4)	31.8 (9.2)	47.0	72.6 (47.6)
Disseminated TB	14	42.0 (18.0)	28.1 (6.3)	49.1 (12.5)	66.1 (45.2)

136 patients: pulmonary TB alone (58 patients), pulmonary TB with pleural involvement (18), pleural TB alone (29), lymph node TB (13), bone and/or joint TB (4), disseminated TB (14)

* 97 patients: pulmonary TB alone (30 patients), pulmonary TB with pleural involvement (17), pleural TB alone (28), lymph node TB (11), bone and/or joint TB (1), disseminated TB (10)

Numbers in parentheses are the standard deviations

Table 4. Radiographic extent of pulmonary tuberculosis and age, serum albumin and globulin levels, and ESR

Grade of chest radiograph extent	No. of patients (n = 77)	Mean age years	Mean serum albumin# g/L	Mean serum globulin* g/L	Mean ESR mm/hr
2	4	54.5 (5.5)	34.3 (2.1)	40.3 (4.2)	23.8 (29.0)
3	33	46.0 (19.4)	29.1 (6.9)	46.6 (9.1)	67.6 (38.1)
4	28	43.8 (15.1)	27.5 (6.9)	46.7 (9.3)	59.6 (35.6)
5	9	46.8 (14.9)	24.0 (6.4)	50.8 (7.1)	101.6 (18.3)
6	3	25.0 (6.9)	22.7 (5.8)	51.7 (5.0)	78.0 (46.9)

76 patients: grade 2 (4 patients), grade 3 (32), grade 4 (28), grade 5 (9), grade 6 (3)

* 47 patients: grade 2 (3 patients), grade 3 (22), grade 4 (15), grade 5 (4), grade 6 (3)

Numbers in parentheses are the standard deviations

Serum albumin and total globulin levels

The liver function test including the serum albumin was not performed in 5 patients while an additional 39 patients did not have the serum total protein measured so the serum globulin levels for these patients could not be calculated. The mean serum albumin level of the patients at the time of diagnosis was 29.0 (± 6.9) g/l (range, 12 - 45 g/l) (n = 136). Hypoalbuminaemia (serum albumin level less than 34 g/l, the lower limit of normal in our laboratory) was present in 72.8% (99/136) of patients at diagnosis before commencement of anti-tuberculosis treatment. The serum albumin level showed a modest negative correlation with the patient's age ($r = -0.199, p = 0.02$). Patients with lymph node TB had the highest mean serum albumin level at 34.6 (±7.5) g/l and this was significantly higher than those of patients with the other forms of TB ($p = 0.038$) (Table 3). Patients who had pulmonary TB alone had a significantly lower mean serum albumin level at 27.8 (± 7.2) g/l compared to patients with the other forms of TB.

In patients with pulmonary TB with or without pleural involvement, those with chest radiographs showing more extensive lung involvement tended to have lower serum albumin levels although the differences in albumin levels of patients with the various grades of radiographic extent were not significant (Table 4). The mean serum albumin level of Mantoux test positive patients (n = 79) which was 31.0 (± 6.1) g/l, was significantly higher than the mean serum albumin level of 26.4 (± 7.1) g/l of patients who were Mantoux test negative (n = 57) ($p < 0.001$).

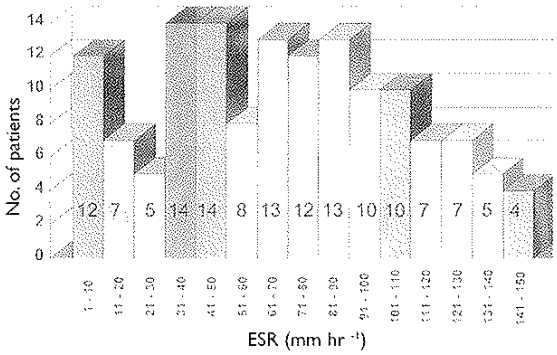

Figure 2. Distribution of ESR in patients with tuberculosis

The mean serum total globulin level of the patients before the commencement of anti-tuberculosis chemotherapy was 46.9 (± 8.5) g/l (range, 26 - 70 g/l) (n = 97). There was no significant correlation between the serum albumin and globulin levels ($r = -0.094$, $p = 0.362$). Hyperglobulinaemia (serum globulin above 35 g/l) was seen in 93.8% (91/97) of patients. The serum globulin level also showed a modest negative correlation with age ($r = -0.205$, $p = 0.044$). The serum globulin level was not affected by the form of TB (Table 3) or the extent of lung involvement in patients with pulmonary TB with or without pleural disease (Table 4). The mean serum globulin level of Mantoux test positive patients (n = 62), 47.1 (± 7.9) g/l was not

Table 5. Types of tuberculosis and Mantoux test reaction

Type of tuberculosis	Mantoux positive patients (%) (n = 84)	Mantoux negative patients (%) (n = 57)	P value
Pulmonary TB alone	37 (44%)	21 (37%)	0.497
Pulmonary TB with pleural involvement	12 (14%)	7 (12%)	0.928
Pleural TB alone	19 (23%)	12 (21%)	0.989
Lymph node TB	11 (13%)	4 (7%)	0.282
Bone and/or joint TB	1 (1%)	3 (5%)	0.303
Disseminated TB	4 (5%)	10 (18%)	0.02

Table 6. Extent of lung involvement on chest radiograph and Mantoux test reaction in patients with pulmonary tuberculosis with or without pleural involvement

Grading of extent of lung involvement on chest radiograph	Mantoux positive patients (%) (n = 52)	Mantoux negative patients (%) (n = 25)	P value
1	0	0	
2	2 (4%)	2 (8%)	0.592
3	24 (46%)	9 (36%)	0.551
4	21 (40%)	7 (28%)	0.421
5	3 (6%)	6 (24%)	0.051
6	2 (4%)	1 (4%)	0.698

significantly different from that of Mantoux test negative patients (n = 35) which was 46.6 (± 9.7) g/l (p = 0.759).

Erythrocyte sedimentation rate

The ESR distribution is shown in Figure 2. The mean ESR of the patients was 69.6 (± 38.9) mm/hr (range, 2 - 150 mm/hr). The mean ESR of male patients, 67.8 (± 39.3) mm/hr was lower than the mean ESR of female patients which was 72.4 (± 38.4) mm/hr. The difference, however, was not statistically significant (p= 0.502). The ESR was not elevated in 18 (12.8%) patients. These patients included two out of 17 who were aged 65 years and above. In patients younger than 65 years, 9 of 75 male patients and 7 of 49 female patients had normal ESR. There was no relationship between ESR and the patient's age. The ESR showed a weak negative correlation with the serum albumin level (r = -0.32, p <0.00 1) but a weak posit ive correlation with the serum globulin level (r = 0.213, p = 0.036). No differences in the ESR were observed with respect to the various forms of TB (Table 3). In the case of pulmonary TB with or without pleural involvement, the ESR of patients with grade 5 and grade 6 chest X-ray changes was higher than the ESR of those with radiologically less extensive lung involvement (Table 4) (p = 0.005). The mean ESR of Mantoux test positive patients, 67.0 (± 37.0) mm/hr, was not significantly different from that of Mantoux test negative patients, 73.4 (± 41.6) mm/hr (p = 0.339).

Discussion

This study confirms the observation of other investigators that hypoalbuminaemia (2-8) and hyperglobulinaemia (1,5) are common in patients with active TB. Hypoalbuminaemia was present in 73% of the patients and 92% of them had hyperglobulinaemia. The serum albumin level showed a negative correlation with the patient's age and in the case of pulmonary TB, a negative correlation with the radiographic extent of lung involvement. Chan *et al* (19) found that low serum albumin level is more common in patients with TB who are older than 65 years. Patients with lymph node TB in the present study had significantly higher serum albumin levels than patients with the other forms of TB. This is probably related to the fact that the patients with lymph node TB were significantly younger than the rest. In a study on pulmonary tuberculosis, (20) a negative correlation was similarly demonstrated between the serum albumin level and the radiographic extent of lung disease. Other workers (21) have also shown that patients with whole lung TB to have lower serum albumin than those with nonwhole lung TB. Deficit in the nutritional status as assessed by anthropometric measurements, hand-grip dynamometry and serum albumin in patients with pulmonary TB has been shown to increase with the radiographic extent of the disease. (3)

In patients with TB, there is a decrease in serum total protein and albumin with a corresponding increase in globulin, mainly due to an increase in gamma-globulin fraction.(5,7) Total plasma globulin consists of alpha- beta- and gamma-globulins or immunoglobulins. Serum levels of beta- and gamma-globulins, particularly IgG and IgM and acute phase proteins including alpha 1-antitrypsin and haptoglobulin are increased in active pulmonary TB.(8,22) In the present study, the serum globulin level showed a negative correlation with age. However, there was no relationship between the serum globulin level and the type of TB, the extent of lung involvement in patients with pulmonary TB, or Mantoux test reactivity. Onwubalili *et al* (1) found no correlation between cellular immunity and the levels of serum immunoglobulins in patients with active TB.

The Mantoux test response in tuberculosis has been shown to be related to the serum albumin level and the nutritional status of the patient. (9-11) Although no relationship between the serum globulin level and Mantoux test reactivity was found in the present study, hypoalbuminaemia was worse in patients who were Mantoux test negative. As the patient's nutritional status is reflected by his serum albumin level, (1,2,23,24) a higher serum albumin level would mean a better cellular immunity, delayed hypersensitivity reaction and cutaneous reactivity to tuberculin. (21) Malnutrition is a well documented cause of cutaneous anergy. (10) Non-reactors to tuberculin skin test among patients with untreated TB have been found to be more malnourished in one study.(11) The same study also showed an increase in dermal reactivity to tuberculin as abnormal nutrition-related indices improved during anti-tuberculous chemotherapy which supports the notion that tuberculin skin anergy in patients with TB may be a temporary phenomenon.(12)

In the present study, negative tuberculin skin test was seen in about 40% of patients, a proportion which is comparable to that of 30% in a study by Onwubalili and colleague (1) but much higher than that of 8% reported by Maher *et al* (12) and 16% of patients with pulmonary TB in a BCG vaccinated area reported by Hussain *et al.* (13) The acquisition of tuberculin sensitivity as a result of previous vaccination with Bacille Calmette-Guerin (BCG) makes the interpretation of tuberculin skin test more difficult. (17) As this is a retrospective study, the number of patients who had been vaccinated with BCG was not known. There is no reliable way to distinguish tuberculin reactions due to BCG vaccination from those due to natural mycobacterial infection. Tuberculin sensitivity induced by BCG vaccination often diminishes considerably over a period of years. The longer the period between vaccination and skin testing, the less likely it is that a large reaction is due to the BCG. Unless tuberculin sensitivity is maintained by repeated tuberculin testing, repeated vaccination, or repeated

mycobacterial infections, most persons vaccinated ten or more years ago are unlikely to manifest large reactions to tuberculin (17). The pathophysiology and immunology of the disease may be modulated due to vaccine intervention. However, little is known regarding the pathophysiology of tuberculosis following BCG vaccination.

As reported in previous studies, (12,25,26) TB patients who were Mantoux test negative were older than Mantoux test positive patients in the present study. Patients with disseminated TB were more likely to be non-reactive to tuberculin.

In the study by Hussain *et al*, (13) tuberculin test responsiveness as measured by the size of skin induration was found to have a negative correlation with the extent of lung involvement in pulmonary TB. Other researchers have also found tuberculin skin test anergy to be more common in TB patients with chest radiographs showing more advanced or bilateral disease or miliary changes (12, 21). On the other hand, one study has demonstrated that cellular immunity as assessed by in vitro cellular responses and cutaneous reactivity to tuberculin has no correlation with the radiological extent of pulmonary TB (1). In this study, although the proportion of pulmonary TB patients who were Mantoux test negative was higher in those with radiologically more extensive lung infiltrates compared to those with radiologically less extensive disease, the difference was not significant probably because of the small number of patients in the former category.

The ESR is usually elevated in active tuberculosis (1,13,14) but a normal value does not exclude active disease (1) as demonstrated by the present study in which about 13% of the patients had a normal ESR. Elevated ESR at diagnosis has been found by Maher *et al* (12) to be more common among tuberculin skin test anergic patients. However, the present study did not find any correlation between the ESR and Mantoux test reactivity which is similar to the finding by Onwubalili *et al.* (1) In the present study, even though the ESR tended to be higher in Mantoux test negative patients, it was not significantly different from the ESR in Mantoux positive patients. The ESR showed a negative correlation with the serum albumin level but a positive correlation with the serum globulin level. In the case of pulmonary TB, the ESR was significantly higher in patients with radiologically more extensive disease. A positive association between the radiological extent of pulmonary TB and ESR elevation was found in a study by Yanagisawa *et al* ., (27) while the study by Hussain *et al* (13) finds no such correlation. In the study by Yanagisawa *et al.*, (27) the ESR in TB patients tends to be higher in aged subjects but in this study there was no relationship between the ESR and the patient's age.

In conclusion, patients with newly diagnosed active TB frequently had hypoalbuminaemia and hyperglobulinaemia. A small proportion of patients with active TB had a normal ESR. The ESR in patients with pulmonary TB was higher in those with radiologically more extensive disease. Cutaneous response to tuberculin is more likely to be negative in patients who were older, those with more severe hypoalbuminaemia and those with disseminated TB.

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