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Lymphocytopenia as a Mortality Predictor in Non - HIV Pulmonary TB Patients

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ABSTRACT

***Background**: Mortality from tuberculosis is high even in the chemotherapy era. Our study determines the predictor role of lymphocyte count in the mortality of non-HIV tuberculous patients.*

***Materials and Methods**: This case- control study was performed retrospectively in a university hospital, which is a secondary and referral center for tuberculosis in Iran. All documented pulmonary tuberculosis cases that had died while being hospitalized in TB wards during the year 2002 were enrolled. Equal number of documented tuberculosis who had been discharged from hospital with good conditions were also enrolled by simple randomized selection. All pertinent data including the first documented hematologic indices of the cases were gathered and analyzed using X^2, logistic regression, and non-parametric tests.*

***Results**: During the last year, 33 patients died from tuberculosis with an average age of 53 ± 16.5 yr. [11(33%) were female]. The mean lymphocyte percent in CBCs taken from the case group was 15.5 ± 10.2 comparing to 27.1 ± 9.8 for the control group. The frequency of lymphocyte counts below 1000 was 11 (37%) for the cases and 5 (15%) for the controls. The frequency of lymphocyte counts below 15% was 21 (67%) in the case group compared to 3 (9%) for the control group. Both results showed significant differences between the two groups (P = 0001). The odds ratio for total lymphocyte count deficiency was 3.5 and the odds ratio for < 15% was 27.*

Conclusion**: This study revealed that lymphocytopenia may be used as a proper measure for determining mortality risk in non-HIV pulmonary TB patients. However, it seems necessary to confirm this new finding with introspective studies using broader sample sizes.* ***(Tanaffos 2003; 2(7): 25-31)

***Key Words**: Tuberculosis, Mortality, Lymphocytopenia*

INTRODUCTION

Tuberculosis (TB) is among the top ten causes of global mortality and affects low-income countries in particular (1). Mortality from tuberculosis is high even among patients without multidrug resistance who are not known to be infected with HIV (2). TB is responsible for more than two million deaths per year worldwide (3). Decreased survival is

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significantly associated with HIV – seropositivity, old age, and failure to complete the full treatment regimen and a low CD_4 T-lymphocyte counts (4). $CD4^+$ cell counts were reported below 300 cells / mm^3 in HIV-seronegative active pulmonary tuberculosis (5). They had a very poor prognosis during the first weeks of treatment (6). There are several case reports that show relation of T-lymphocytopenia and attribution to disseminated tuberculosis (7,8,9,10).

Knowledge of mortality risk factors in TB patients may improve their survival. With regard to the importance of lowered CD4 cell counts in predicting a poor prognosis for TB patients and due to the lack of flow-cytometric devices in low–income, high- contamination countries, it seems logical to look for an available and simple alternative as a predictor. In this study, we demonstrate that lymphocytopenia detected in peripheral blood count may be a useful predictor of mortality in TB patients.

MATERIALS AND METHODS

This study was conducted at a university-affiliated hospital that provides medical care to tuberculosis patients as a tertiary center.

The study design was retrograde case- control. All deceased cases during March 2002 to February 2003 with a definite diagnosis of tuberculosis (positive cultures for Mycobacterium Tuberculosis) or those cases compatible with a diagnosis of TB (clinically and radiologically) (11) who had not been tested for mycobacteria due to the lack of sputum or a short period of hospitalization were included in the study.

Mortality was defined as death from any cause during the hospitalization period with TB diagnosis.

Following re-evaluation of the case group (deceased), equal number of cases were selected from documented pulmonary TB patients (positive culture for Mycobacterium Tuberculosis) who had been hospitalized and discharged during last year, having been matched for sex and age with the original case group, as controls.

Demographic data and hematologic indices of the first complete blood counts (CBC) of patients at the time of hospitalization were recorded in a specified questionnaire. Cases were classified based on two definitions for lymphocytopenia. Lymphocytopenia was defined as either less than 15% of the total white blood cell count (12) or a total lymphocyte count of less than 1000/ml (13,14,15) or 1500 / ml (16,17) (depending on different classifications).

The data were analyzed, using non-parametric measures for quantitative variables and X^2 for qualitative variables.

To evaluate the behavior of response variables, logistic regression test was used with Wald method. Sampling was sequential for the deceased group (cases) and simple randomized following sex and age matching for the living group (controls).

RESULTS

During the year 2002, 33 patients died with a diagnosis of TB, 11 were female (33%). The mean age of patients was 56 ± 16.5 with a range of 26-82. Thirty-three lived patients were selected as control with above criteria.

Duration of hospitalization for deceased cases was 11 ± 11.9 days (median = 6, range 1-60 days). For the control group, the duration was 31 ± 18.6 days (median =27, range 5-73 days).

In the case group, 3 (9%) were HIV positive. None of the control group cases had HIV sero-positivity. There was not any other documented immunologic defect in both groups.

Hematologic values of each group are shown in tables (1,2).

Table 1. Hematologic Indices in alive TB patients

Indices	Hb	HCT	WBC	PMN	L	M	E	Plat	ESR
Mean	13.16	40.48	8.11	65.30	27.12	3.66	4.50	276.82	53.80
Median	13.50	40.80	7.90	65.00	28.00	3.00	3.00	281.00	48.00
Mode	10.70	40.80	6.70	64.00	32.00	2.00	1.00	369.00	45.00
Std. Deviation	2.41	7.67	2.31	10.79	9.87	1.49	5.83	94.42	34.15
Minimum	7.60	25.30	3.60	30.00	5.00	1.00	1.00	6.40	9.00
Maximum	16.80	54.10	14.10	86.00	54.00	6.00	29.00	469.00	133.00

Table 2. Hematologic indices in dead TB patients

Indices	Hb	HCT	WBC	PMN	L	M	E	Plat	ESR
Mean	12.07	37.51	13.79	77.36	15.56	3.58	2.46	292.23	50.03
Median	12.80	38.10	10.50	81.50	14.00	3.00	2.00	300.00	48.00
Mode	13.10	38.10	3.60	86.00	10.00	3.00	1.00	65.00	55.00
Std. Deviation	2.02	6.36	13.47	15.12	10.23	2.20	2.09	174.58	25.49
Minimum	7.90	23.50	2.70	23	1.00	1.00	1.00	65.00	2.00
Maximum	16.40	50.80	76.00	95.00	42.00	8.00	8.00	681.00	110.00

The frequency of lymphopenia according to both definitions is as follows:

The frequency of lymphocyte counts below 15% was 21(67%) for the deceased group and only 3(9%) for the living group. Total lymphocyte counts below 1000 were detected in 11(37%) of the deceased group and 5(15%) of the living group. For the below 1500 definition, 20 (64%) and 8 (24%) cases were detected in the case and control groups, respectively.

No statistically significant difference was found in the WBC count of two groups. However, there was a significant difference in the percent and the total count of lymphocytes (p=0.0001, p=0.02). Following results were obtained for lymphocytopenia after excluding HIV seropositive cases. For the below 15% definition, OR = 20 with a CI 95% of 4.8-81 was obtained. For the below 1000/ml total lymphocyte count definition, OR = 3.5 with a CI 95% of 1.07 - 11.68 was calculated, and for the total below 1500 definition, OR = 5.6 with a CI 95% of 1.9 -16.7 was obtained.

DISCUSSION

The major protective immune response against intracellular bacteria such as mycobacterium tuberculosis is cell – mediated immunity (18). It has been well established that $CD4^+$ T–cells are the dominant protective T cells (19,20). A cell- mediated

immune (CMI) response of the Th_1 type is essential to mount a protective immunity against M. tuberculosis. (21,22,23)

Based on previous studies, it is evident that in a normal situation $CD4^+$ cells comprise 40-65% (13,24,25) of peripheral blood lymphocyte counts, lymphocytopenic patients show a prominent decrease in this sub-population (13). Alterations in blood lymphocyte have been well-established in pulmonary TB patients (26,27,28). It has been shown that a decrease in the total lymphocyte counts may occur, particularly early in the diagnosis period, and gradually increases with proper treatment. Collazos et al. (17) showed that lymphocytopenia was present in 22% of TB patients before treatment, and it raised to a high percentage following chemotherapy after 27 weeks. Morris et al. (29) also reported lymphocytopenia in 17% of diagnosed patients.

Despite known lymphocytopenia in TB patients, to our knowledge, it has not been reported to date a correlation similar to what we observed between lymphocytopenia and mortality. Although the reasons for the initial decline of lymphocytes are unclear, several arguments support a homeostatic mechanism. First, active tuberculosis has been related to apoptosis of circulating lymphocytes, (30) which can decrease the total number of these cells. Second, a complex network between stimulatory and inhibitory cytokines and other products such as products of Th_1 activation (31) may produce this cytopenia. Third, a paralyzed immunity may occur due to over stimulation with mycobacteria poly - antigens, suppressing cell over production in the bone marrow. Fourth, although mycobacterial infections stimulate antibody responses, humoral immunity seems to play little part in the protection against tuberculosis (31). However, a decrease in B-lymphocyte counts in patients, at different stages of tuberculosis with respect to controls, has been reported (32,33) that indicates a global lymphoid involvement in tuberculosis.

Due to the above reasons, we conclude that lymphocytic response to active tuberculosis involves T and non-T cells that make total circulatory lymphocyte pool. Although Wessels et al. (34) showed that full blood count has no diagnostic predictive value in diagnosis of childhood TB, we showed that full blood count has a good predictive value for mortality due to tuberculosis in adults.

This study demonstrated that lymphocyte counts below 1000 were present in 11 (37%) of the deceased cases and in 5 (15%) of the living cases; the difference was significant ($p= 0.038$). A significant difference was also detected for the below 15% definition of lymphocytopenia which was evident in 21 (67%) and 3 (9%) of the case and controls respectively ($p= 0.0001$). By changing the definition of lymphocytopenia to counts below 1500/ml, such as what Collazos et al. (17) used as a definition, the difference between two groups becomes more significant ($p= 0.02$). Kony et al's study revealed that in the course of TB disease, CD4 counts below 300 correlate with the severity of symptoms. (5)

Recently, authors have also reported a case of disseminated tuberculosis in association with idiopathic CD4 lymphocytopenia (35).

It appears that a decline in $CD4^+$ cell line and dissemination of disease along with high microbial burden of mycobacterium tuberculosis accounts for mortality in patients. Pilheu et al. (6) reported that $CD4^+$ lymphopenia is associated with a poor prognosis in HIV- seronegative pulmonary TB patients.

CONCLUSION

Based on the results of this study it is possible to define lymphocytopenia as an appropriate measure to determine mortality risk during the course of

tuberculosis. Meanwhile, it is necessary to precisely supervise and manage all TB patients with lymphocytopenia and maintain support of these patients until lymphocytopenia subsides.

Prospective studies would help to confirm the evidence presented in this paper and to highlight this association.

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