J Pediatr Res 2020;7(2):97-101
DOI: 10.4274/jpr.galenos.2019.38159

Original Article

Ratio of Monocytes to Lymphocytes in Peripheral Blood in Children Diagnosed with Active Tuberculosis

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ABSTRACT

Aim: The ratio of monocytes to lymphocytes (ML) could reflect an immunity to Mycobacterium tuberculosis (TB). The objective of this study was to evaluate the relationship between the ratio of ML and the clinical status of patients with active TB.

Materials and Methods: This was a retrospective review of data collected from the clinical database of the Behcet Uz Children's Research Hospital. One hundred thirty-eight patients were diagnosed with pulmonary and extra-pulmonary TB from January 2006 to January 2015. White blood cell count, absolute monocyte and absolute lymphocyte counts, the ML ratio, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were compared between extra-pulmonary and pulmonary TB cases. Pre-treatment and after treatment values of the parameters were also compared in both of the groups.

Results: A total of 138 patients were diagnosed as having pulmonary or extra-pulmonary TB during the study period. No significant difference between pulmonary and extra-pulmonary TB was present regarding white blood cell count, absolute ML, ESR and CRP ($p>0.05$). In patients with pulmonary TB and extra-pulmonary TB, a significant decrease in white blood cell count, absolute monocyte count, ESR and CRP values after treatment compared to pretreatment was observed ($p<0.05$). The ML ratio was not significantly different in the extra-pulmonary TB group ($p>0.05$) while a significant difference was present between the pre- and post-treatment groups in pulmonary TB ($p=0.000$).

Conclusion: The hematological markers including the ML ratio were found to be more useful for monitoring the response of TB therapy, rather than as a differential diagnosis of pulmonary TB from extra-pulmonary TB.

Keywords: Extra-pulmonary tuberculosis, pulmonary tuberculosis, ratio of monocyte to lymphocyte counts, children

Introduction

Tuberculosis (TB) remains a major global health problem affecting millions of people annually. It is the second leading cause of death from infectious disease following human immunodeficiency virus (HIV) worldwide (1). TB is still a major health problem for children as well as adults. Although children constitute 5% of the TB population in low-burden countries, it is reported to be as high as 20–40% in other countries (2-5). Globally, there were an estimated 8.6 million new cases of TB in 2013 and 1.3 million deaths (6).

Knowledge about the hematological manifestations of Mycobacterium TB infection is important to provide insight into its pathogenesis. Myeloid-specific cells have been known to serve as host cells for Mycobacterium TB growth and lymphoid cells are thought to be the major effector cells in TB immunity. Given the central role of monocytes and lymphocytes in the induction of immune responses, their levels (hereafter termed "ML ratio") in peripheral blood might be expected to reflect the state

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Received: *18.10.2018* **Accepted:** *10.06.2019*

of an individual's immunity to the infection. In a recent clinical analysis of peripheral blood mononuclear cells from a cohort of South African infants, the relative ratio of monocytes to lymphocytes at the start of monitoring was shown to predict the risk of developing TB disease during follow-up (7).

The ratio of monocytes to lymphocytes (ML) in peripheral blood correlated with the extent of TB in both rabbits and humans (8). The number of studies were small and the strength of the conclusions that could be reached in humans seemed to be modest. There was no strong evidence that the ML ratio was affected by Mycobacterium TB infection in humans.

In this study, we reviewed our experience of children with active TB admitted into a tertiary hospital over a 9-year period in Turkey.

We aimed to evaluate the relationship between the ratio of monocytes to lymphocytes, the clinical status of patients with active TB and how the ML ratio could be affected by TB or ongoing anti-TB treatment. This study hypothesized that ML could be a marker for TB in countries with limited resources.

Materials and Methods

Study population and ethics statement

Data from all subjects were collected retrospectively from the clinical database of the Pediatric Infectious Disease Department in Behcet Uz Children's Research Hospital, between January 2006 and January 2015. This study was approved by the Ethics Committee of Behcet Uz Children's Research Hospital, and was in compliance with national legislation and the Declaration of Helsinki guidelines. Written patient consent was obtained according to institutional guidelines.

Clinical data base

We obtained information about patients from archive records retrospectively. The demographic characteristics of the patients [age, gender, complaints, physical examination, contact history with Mycobacterium tuberculosis, treatment), laboratory tests (white blood cell (WBC) count, absolute monocyte counts (AMC) and absolute lymphocyte counts (ALC), monocyte / lymphocyte (ML) ratio, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), gastric fluid / sputum / bronchoalveolar lavage / biopsy cultures, polymerase chain reaction (PCR) and imaging methods such as tomography and chest radiography] were noted from patient files and electronic database. Patients who had comorbid disease and immunodeficiency were excluded from the study.

Statistical Analyses

A retrospective cohort study was planned as statistical data using SPSS 20 (Statistical Package for Social Sciences; v20; SPSS Inc, Chicago, USA). Parametric methods were used to analyze the data with normal distribution, nonparametric methods were used to analyze the data and categorical data which did not conform to the normal distribution. Evaluation of normalization was determined according to Kolmogorov-Smirnov analysis. Numerical data was calculated as mean ± standard deviation or median, nominal number (n) and percentage (%). Student t-test and Mann-Whitney U test (in nonparametric conditions) were used in comparisons of two independent groups. Nominal data rate portions were compared with chi-square test. For the comparison of data before and after treatment, the dependent student group t-test was used. In nonparametric conditions Wilcoxon signed-rank test was used. In this study, $p<0.05$ was considered statistically significant.

Results

Characteristics of the study population

A total of 138 patients were diagnosed as pulmonary or extra-pulmonary TB during the period of January 2006 to January 2015.

Demographic and clinical characteristics of the study sample

There were 138 individuals enrolled in the study: 103 (74.6%) patients were diagnosed as pulmonary TB, 17 patients as extra-pulmonary TB. Eighteen patients who had both extra-pulmonary and pulmonary TB were excluded. The distribution of cases with extra-pulmonary TB was as follows;

In the study, 49 patients were male (40.8%) and 71 patients were female (59.2%). The median age was 10 years old ranging from 1.5 months to 18 years.

Laboratory features

Comparison of laboratory markers in extrapulmonary and pulmonary TB

No significant difference between pulmonary and extra-pulmonary TB was present regarding WBC, ALC, AMC, M/L ratio, CRP and ESR in the pre-treatment group ($p>0.05$; Table I).

Comparison of laboratory markers in the pretreatment and after treatment groups.

All patients with pulmonary TB had a significant decrease in WBC count (p=0.000), ALC (p=0.03), AMC (p=0.000), ESR (p=0.000) and CRP (p=0.000) values after treatment compared with pre-treatment (Table II). In the extra-pulmonary TB group, a significant decrease was achieved regarding ESR, WBC count, AMC and CRP after treatment, however no significant difference was present in ALC in extra-pulmonary TB cases (p>0.05) (Table II).

All patients with TB were evaluated before and after treatment and the ML ratio was significantly lower after treatment (p=0.000). The ML ratio was not significantly different in the extra-pulmonary TB group (p>0.05) while a significant difference was present between the pre- and post-treatment groups in pulmonary TB (p=0.000) (Table II).

Table I. Comparison of laboratory markers in the extrapulmonary and pulmonary tuberculosis groups

	Pulmonary tuberculosis (median) (min-max)	**Extrapulmonary tuberculosis (median) (min-max)**	**p**
White blood cell count (/mm³)	8,500 (3,400-24,350)	8,720 (4,010-28,650)	>0.05
Absolute lymphocyte count (/mm³)	2800 (900-12,060)	3,200 (1,367-10,124)	>0.05
Absolute monocyte count (/mm³)	700 (151-3,560)	600 (300-3,140)	>0.05
ESR (mm/hour)	27 (1-122)	31 (2-92)	>0.05
CRP (mg/dL)	1.1 (0.11-13)	0.34 (0.1-19)	>0.05
M/L ratio	0.22 (0-1.7)	0.21 (0.08-0.49)	>0.05

M/L: Monocytes to lymphocytes, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, Min: Minimum, Max: Maximum

Table II. Comparison of laboratory markers in pretreatment and treatment groups in the extrapulmonary and pulmonary tuberculosis groups

	Pulmonary Tuberculosis	**p value**	**Extra-pulmonary Tuberculosis**	**p value**
	Median		Median	
WBC (/mm³)				
Pretreatment	8,500	0.000	8,720	0.044
After treatment	7,460		6,300	
Absolute Lymphocyte count (/mm³)				
Pretreatment	2,800	0.003	3,200	0.642
After treatment	2,610		2,400	
Absolute Monocyte count (/mm³)				
Pretreatment	700	0.000	600	0.010
After treatment	530		500	
ESR (mm/hour)				
Pretreatment	27	0.000	31	0.010
After treatment	12		9	
CRP (mg/dL)				
Pretreatment	1.1	0.000	0.34	0.016
After treatment	0.34		0.34	
Monocyte/lymphocyte Ratio				
Pretreatment	0.22	0.000	0.21	0.099
After treatment	0.19		0.20	

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, WBC: White blood cell

Discussion

The ML ratio in peripheral circulation may reflect an individual's capacity to mount an effective immune response. The ML ratio has been shown to correlate with inhibition of mycobacterial growth in vitro (9,10) and risk is higher among individuals with either a low or high ML ratio (11). This ratio could herald a previously unknown pathophysiologic change of TB. In the literature, ML ratios were reported to be disrupted with TB; ML ratios in the extreme percentiles are associated with active TB (12).

New diagnostic strategies for sputum smear-negative tuberculosis are urgently needed. CRP is a non-specific inflammatory protein that is usually elevated in patients with TB, but its role in the diagnosis of TB is uncertain (13). In this study, CRP and ESR were found to be higher in patients with active TB and the decrease observed in these parameters after treatment suggested that they could be used for monitoring the treatment of TB.

The ML ratio in peripheral circulation may reflect an individual's capacity to mount an effective immune response. The ML ratio has been shown to correlate with inhibition of mycobacterial growth *in vitro* (10,14) and risk is higher among individuals with either a low or high ML ratio (11). These results add to evidence supporting that extremes of immunity are associated with TB. This ratio could herald a previously unknown pathophysiologic change of TB. As demonstrated by one study, patients with active TB had a higher or lower ML ratio compared to healthy donors. Healthy donors were mostly in the group with an ML ratio between the 9^{th} and 25^{th} percentile, while patients were mainly in the group with an ML ratio greater than the 25^{th} percentile or in a group with an ML ratio less than the 9^{th} percentile. In order to further evaluate whether the ML ratio could be affected by anti-TB therapy, the difference between before treatment and after treatment was analyzed. The results indicated that the high ML ratio decreased, and the low ML ratio increased to be close to the ML ratio of healthy donors. It was suggested that the ML ratio of patients may change with anti-TB therapy and the alteration of the ML ratio may also reflect the effectiveness and phase of therapy (10). In our study, a high ML ratio in peripheral blood before treatment showed activity of M. tuberculosis infection and this high ML ratio decreased but not close to the ML ratio of healthy donors in accordance with previous findings (10,11). According to our findings, the ML ratio might be used as a useful marker in children to compare pretreatment and treatment. Wang et al. (12) detected that the median ML ratio before treatment was found to be 0.21, in our study, this ratio was 0.36. This difference was explained by the fact that the lymphocyte count in the pediatric age group is higher than the adult age group. In the previous article focusing on adults, those patients older than 60 years were reported to be more likely to be in the group of ML ratio <9% or ML ratio >25% compared to younger adults, suggesting age might be an important factor for the ML ratio (12).

Study Limitations

Our study has some limitations. This study was a retrospective study and needs to be confirmed by prospective studies with wider participation. All patients were immunocompetent, thus the response of the ML ratio in a specific group such as immunosuppressed patients could not be determined with this study. Another limitation of this study was the fact that there was no control group of healthy patients to compare their values before and after treatment. Therefore, the ML ratio was evaluated as before and after treatment.

Conclusion

In conclusion, hematological markers including M/L rate were found to be useful for monitoring the response of tuberculosis therapy, rather than as a differential diagnosis of pulmonary tuberculosis from extra-pulmonary tuberculosis.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Behcet Uz Children's Research Hospital, and was in compliance with national legislation and the Declaration of Helsinki guidelines.

Informed Consent: Written patient consent was obtained according to institutional guidelines.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: N.B., H.A., İ.D., Design: N.B., Data Collection or Processing: A.D., M.D., A.K., H.A., Analysis or Interpretation: İ.D., Literature Search: M.D., Writing: A.D., M.D., N.B., A.K., H.A., İ.D.

Conflict of Interest: The authors have no conflicts of interest relevant to this article to disclose.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

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