R E S E A R C H   A R T I C L E

High Adenosine Deaminase Level and Erythrocyte Sedimentation Rate of Intestinal Tuberculosis Patients

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Abstract

BACKGROUND: Currently, laboratory diagnosis of intestinal tuberculosis (ITB) is limited based on clinical manifestations, providing opportunities for alternative laboratory tests to diagnose ITB. At the present time, the role of serum adenosine deaminase (ADA) and hematological tests in ITB patients are not widely known. The objective of this study was to determine the role of ADA and hematological tests in patients suspected with ITB.

METHODS: Subjects that were suspected of ITB were classified as ITB group, while subjects with inflammatory bowel disease, hemorrhoid, and intestinal malignancy were classified as non-ITB group. Colonoscopy, histopathological examinations, and hematological test were performed. ADA measurement was also performed with clinical chemistry analyzer based on enzymatic colorimetry principle.

RESULTS: Out of 143 subjects, 16 (11.2%) subjects were diagnosed with ITB and 127 (88.8%) subjects were classified as non-ITB group. ADA level and erythrocyte sedimentation rate (ESR) of ITB group were significantly higher than the ones of non-ITB group ($p<0.05$). Cut-off, sensitivity, and specificity of ADA level were 12.56 IU/L, 75%, and 57%, respectively. Cut-off, sensitivity, and specificity of ESR were 32.5 mm/hour, 81%, and 62%, respectively. Colonoscopy of ITB subjects displayed multiple ulcerations, edema, and hyperemic mucosa. Histopathological examination of ITB subjects exhibited granulomatous inflammation, epitheloid cells, giant cells, and lymphocyte aggregates.

CONCLUSION: ADA level and ESR were significantly higher among ITB patients compared with non-ITB patients. Since the sensitivities of ADA and ESR tests were high, the ADA and ESR tests could be considered as a screening test for ITB.

KEYWORDS: intestinal tuberculosis, adenosine deaminase, hematological tests

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Introduction

According to the Global Tuberculosis Report 2019 from the World Health Organization (WHO), Indonesia was ranked third among the countries with highest burden of tuberculosis (TB).(1,2) The global prevalence of extrapulmonary TB was 14% and the prevalence in Indonesia was ≤9.9%. Intestinal tuberculosis (ITB), as a part of abdominal TB, had a prevalence of approximately 3-16%.(3-5)

Currently, ITB diagnosis was established based on clinical manifestations, Ziehl-Neelsen (ZN) acid fast bacilli (AFB) stain of the stool, fecal culture, colonoscopy, and histopathology.(3,6-10) The limitations of the respective laboratory pose difficulties to diagnose ITB, and hence, providing opportunities for alternative laboratory tests to diagnose ITB.(11)

Adenosine deaminase (ADA) is an enzyme involved in purine metabolism which catalyzes the conversion of adenosine to inosine. ADA is also involved in the proliferation and differentiation of lymphocytes and maturation of monocytes.(11,12) Elevated ADA levels in blood or body fluid during tuberculosis infection is due to the stimulation of T lymphocytes by *Mycobacterium tuberculosis* (MTB) antigen.(12,13) The activity of ADA differs significantly between patients with pulmonary TB and the normal healthy people.(14,15)

In ITB, acute or chronic inflammation is present due to infection process. Hematological tests are often requested by clinicians in patients suspected of having ITB, as several parameters can be utilized as markers of inflammation or infection. Some of them are leukocyte count, leukocyte differential count (basophil, eosinophil, neutrophil, lymphocyte, and monocyte), neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), and erythrocyte sedimentation rate (ESR).(3,6,16,17) At the present time, the role of serum ADA and hematological tests in ITB patients are not widely known. The objective of this study was to determine the role of ADA and hematological tests in patients suspected with ITB.

Methods

Study Design and Subjects

Subjects were recruited at the Gastroenterology Outpatient Clinic, Department of Internal Medicine, Gastrointestinal Endoscopy Center of Dr. Cipto Mangunkusumo Central General Hospital from December 2020 until December 2022, with the inclusion criteria as follows; for the ITB group: ≥18 years old and suspected ITB. Meanwhile the exclusion criteria: being treated with anti-tuberculosis drugs for >3 months, post-treatment with anti-tuberculosis drugs for <6 months.

Patients were suspected of ITB if 3 out of 4 main clinical findings were present, and 1 out of 3 additional history criteria for ITB was met. The main clinical findings of ITB include weight loss, non-specific abdominal pain, fever of unknown origin, and chronic diarrhea or constipation. The additional history includes history of pulmonary TB, active pulmonary TB with or without anti-tuberculosis drugs treatment (<3 months of treatment), and positive contact history with TB patients. Patients with inflammatory bowel disease (Crohn's disease or ulcerative colitis), hemorrhoid, and intestinal malignancy were classified as non-ITB group.

Prior to the recruitment, all subjects were explained and asked for their consents of participation by signing an informed consent form. The research protocol was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia and Dr. Cipto Mangunkusumo Central General Hospital (No. KET-1498/ UM2.F1/ETIK/PPM.00.02/2020).

Colonoscopy Examination

After being given laxatives, sedatives and analgesics, subjects lied in a supine position for a colonoscope insertion. If abnormalities were found, biopsies were taken for histopathological examination. Various features could be identified during colonoscopy of patient with suspected ITB, such as ulceration, nodules, polyps, narrowing of the lumen, and irregular multiple fibrous bands. ITB may affect extensive parts of the intestine, in the form of continuous lesions or single or skip lesions.(16)

Histopathological Examination

Samples for examination were harvested from at least 5 granulomas originating from a single segment. After tissue fixation, grossing, embedding and slicing, tissue sections were stained with hematoxylin (Epredia, Kalamazoo, MI, USA) and eosin (Merck, Darmstadt, Germany), and mounted. Prepared tissue slides will be read by an anatomic pathologist.

ADA Test

Nine mL of venous blood was drawn from the cubital vein. Three mL were collected in an EDTA tube for complete hematological test, while 6 mL in non-anticoagulated tube for ADA test. Blood in non-anticoagulated tubes were

allowed to stand at room temperature for about 30 minutes, until blood clot formed. Immediate centrifugation of 3,000 revolutions per minute (rpm) for 15 minutes was performed to separate the serum from the rest of the remaining sample. Quantitative test of blood ADA was performed by BS-200 automated clinical chemistry analyzer (Mindray, Shenzen, China) with enzymatic colorimetry principle test used. The measurement was determined by the increase of photometric absorbance at a wavelength of 546 nm.

Hematological Test

Hematology test was performed by XN-2000 hematology analyzer (Sysmex, Kobe, Hyogo, Japan) with semiconductor laser flowcytometry for measurement of leukocyte, basophil, eosinophil, neutrophil, lymphocyte, monocyte, NLR, and MLR. K3EDTA blood was diluted by the reagent that lysed erythrocytes and perforated the cytoplasmic membrane of all nucleated cells. This process allowed fluorescent dyes to enter the cells and bind to the nucleic acids of the cells. ESR measurement was performed using Starrsed RS automated ESR analyzer (Sysmex).

Statistical Analysis

Data were processed using SPSS software version 20 (IBM Corporation, Armonk, NY, USA) and Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA). Data distribution was checked using Kolmogorov-Smirnov test. Bivariate analysis was performed to investigate the relationship between two measured variables. Analysis of the difference between the two groups in the abnormal data distribution was done by using the Mann-Whitney U Test. The level of significance used was $p<0.05$.

The calculation of cut-off and area under the curve (AUC) was obtained from the receiver operating characteristic (ROC) curve. Sensitivity and specificity of the examination compared to the gold standard (combined results of histopathology, colonoscopy, and therapeutic response) were then calculated.

Results

A total of 143 subjects, 16 (11.2%) of them were diagnosed with ITB, and 127 (88.8%) subjects were non-ITB (Table 1). In percentage, the ITB group had higher weight loss, loss of appetite, chronic diarrhea, and constipation.

ADA and ESR of ITB and non-ITB groups

From the results of laboratory test, ADA level and ESR of ITB groups were significantly higher than the ones of non-ITB group (Table 2). Meanwhile, all other hematological parameters of ITB and non-ITB groups were almost similar.

The median of ADA level in blood of ITB and non-ITB groups were 16.51 (11.82-35.61) IU/L, and 12.11 (8.89-15.99) IU/L, respectively (Table 2). In the ROC curve analysis, AUC of 0.695 (95% CI: 0.542-0.849) was obtained

Table 1. Characteristics of ITB and non-ITB groups.

Characteristics	ITB (n=16)	Non-ITB (n=127)
Age (years), mean±SD	42.19±18.28	43.53 ±16.65
Gender, n (%)		
Male	10 (62.5%)	40 (31.5%)
Female	6 (37.5%)	87 (68.5%)
Clinical manifestation, n (%)		
Weight loss	13 (81.3%)	69 (54.3%)
Night sweat	1 (6.3%)	5 (3.9%)
Cough	2 (12.5%)	5 (3.9%)
Fever	5 (31.3%)	16 (12.6%)
Loss of appetite	9 (56.3%)	41 (32.3%)
Non-specific abdominal pain	12 (75.0%)	111 (87.4%)
Chronic diarrhea	13 (81.3%)	73 (57.5%)
Constipation	13 (81.3%)	82 (64.6%)
Blood in stool	8 (50.0%)	69 (54.3%)
Mucus in stool	8 (50.0%)	70 (55.1%)
Blood and mucus in stool	8 (50.0%)	68 (53.5%)
TB history, n (%)		
History of contact with TB patient	1 (6.3%)	1 (0.8%)
History of pulmonary and non-pulmonary TB	2 (12.5%)	10 (7.9%)

Table 2. Laboratory results of ITB and non-ITB groups.

Parameter	ITB (n=16)	Non-ITB (n=127)	p- value
ADA level (IU/L)	16.51 (11.82-35.61)	12.11 (8.89-15.99)	0.011*
Leukocyte (10^3/μL)	7.63 (4.85-10.96)	6.98 (5.58-8.45)	0.656
Basophil (%)	0.50 (0.30-0.70)	0.50 (0.40-0.80)	0.358
Eosinophil (%)	1.80 (0.80-4.15)	1.90 (1.00-3.70)	0.941
Neutrophil (%)	63.85 (49.97-74.22)	61.0 (54.10-71.00)	0.522
Lymphocyte (%)	25.70 (16.65-36.82)	29.10 (21.70-34.90)	0.520
Monocyte (%)	7.20 (4.62-8.32)	6.60 (5.40-7.90)	0.670
NLR	2.48 (1.44-4.49)	2.12 (1.56-3.31)	0.495
MLR	0.29 (0.15-0.44)	0.22 (0.19-0.29)	0.401
ESR (mm/hour)	65 (33.50-92.50)	26 (13.00-45.00)	0.002*

Tested with Mann-Whitney U test, *significant if $p<0.05$. Data were presented in median (min-max).

with a cut-off of 12.56 IU/L. Sensitivity of ADA were 75%, and specificity of 57% (Table 3).

The median of ESR of ITB group and non-ITB group were 65 (33.50-92.50) mm/hour and 26 (13.00-45.00) mm/hour, respectively (Table 2). In the ROC curve analysis, AUC of 0.741 (95% CI: 0.623-0.860) was obtained with a cut-off of 32.5 mm/hour. Sensitivity of ESR was 81%, and specificity of 62% (Table 4).

ROC analyses were conducted for the combination of ADA and ESR testing. For the utilization of ADA and ESR in diagnosing ITB, the cut-off was 12.56 IU/L and 32.5 mm/hour, respectively. Subsequently, ROC curve analysis was performed and AUC of 0.768 (95% CI: 0.656-0.880), sensitivity of 81.3%, and specificity of 62.2 % were obtained (Supplementary 1).

Colonoscopic and Biopsy Histopathological Appearances of ITB Subjects
In this study, colonoscopy of subjects with ITB displayed multiple ulcerations, edema, and hyperemic mucosa in various areas, such as descending colon, transverse colon, ascendent colon, caecum, and terminal ileum (Figure 1). Meanwhile, histopathological examination of patients with confirmed ITB exhibited granulomatous inflammation, epithelioid cells, giant cells (Datia Langhans), and lymphocyte aggregates (Figure 2). Some of the other subjects showed incomplete and varied overview.

Discussion

There were 16 ITB subjects among all 143 recruited subjects from the Gastroenterology Outpatient Clinic, Department of Internal Medicine, Gastrointestinal Endoscopy Center of Dr. Cipto Mangunkusumo Central General Hospital. The subject population of 16/143 (11.2%) was in accordance with the previous reported ITB prevalence (3-16%).(1,18)

ADA level was significantly higher in ITB group compared with the one of non-ITB group. The sensitivity

Table 3. ADA results of ITB and non-ITB groups with cut-off=12.56 IU/L.

ADA Result	ITB	Non-ITB	Total
Positive	12	54	66
Negative	4	73	77
Total	16	127	143
Sensitivity	= 75%		
Specificity	= 57%		
Positive Predictive Value (PPV)	= 18%		
Negative Predictive Value (NPV)	= 95%		

Table 4. ESR results of ITB and non-ITB groups with cut-off=32.5 mm/hour.

ESR Result	ITB	Non-ITB	Total
Positive	13	48	61
Negative	3	79	82
Total	16	127	143
Sensitivity	= 81%		
Specificity	= 62%		
Positive Predictive Value (PPV)	= 21%		
Negative Predictive Value (NPV)	= 96%		

and specificity of ADA test were 75% and 57%, respectively, with a cut-off of 12.56 IU/L. These data could be useful for further investigation since in the present time there is not any available data of ITB patients' ADA level. Most studies reported ADA results of patients with pulmonary tuberculosis and abdominal tuberculosis.(15,19) The cut-off value of ADA level in this study was lower than the one in Serbian study on extrapulmonary tuberculosis (24 U/L) (19) and Nepalese study on pulmonary/extrapulmonary tuberculosis (25 U/L) (20).

There was no significant difference in leukocyte count and leukocyte differential count between ITB and non-ITB groups in this study. These results are in accordance with the ones in Ethiopian study, reporting that the counts between the two groups were not significantly different.(21)

Although NLR may indicate an early TB infection, there was not any significant difference between NLR of ITB and non-ITB groups in this study. This result was similar to the findings reported by previous study.(22)
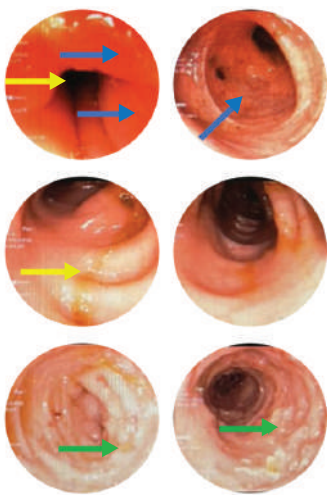

Figure 1. Colonoscopic results of ITB-suspected-subjects with ileocolitis. Blue arrow: hyperemic intestinal mucosa; Yellow arrow: edema; Green arrow: ulceration.

However, contradictory findings were reported in a study in Bandung, Indonesia, whereas pulmonary TB subjects exhibited significantly higher NLR.(23)

There was no significant difference in MLR between ITB and non-ITB groups in this study. Both similar (22) and contradictive findings (24) in the MLR of patients with TB, have been reported which might be influenced by the study site, existence of any comorbidities (HIV, diabetes mellitus), age, and TB treatment.

Compared with non-ITB group (26 (13.00-45.00) mm/hour), the ITB group had significant higher ESR (65 (33.50-92.50) mm/hour). Similarly, a previous study reported that ESR was significantly higher in patients with pulmonary TB compared with those without TB.(25) In this study, high sensitivity of ESR (81%) was calculated, which could be promoted as a screening test for ITB. ESR test has been used for a long time to assess acute phase proteins in chronic diseases, including TB. Pro-inflammatory cytokines produced in ITB will stimulate the liver to produce acute phase proteins, such as fibrinogen which may lead to an increase in ESR. ESR measurement has limitations, such as being affected by anemic conditions and hypoalbuminemia, which cause a false-high ESR.(25-27)

The combination of ADA and ESR test results with cut-offs of 12.56 IU/L and 32.5 mm/hour, respectively, did not provide a significant increase in sensitivity and specificity compared to individual ADA or ESR test result. Therefore, each of ADA or ESR test can be used independently to assist the diagnose of ITB.

Conclusion

ADA level and ESR were significantly higher among ITB patients compared with non-ITB patients. Since the sensitivities of ADA and ESR tests were high, the ADA and ESR tests could be considered as a screening test for ITB.
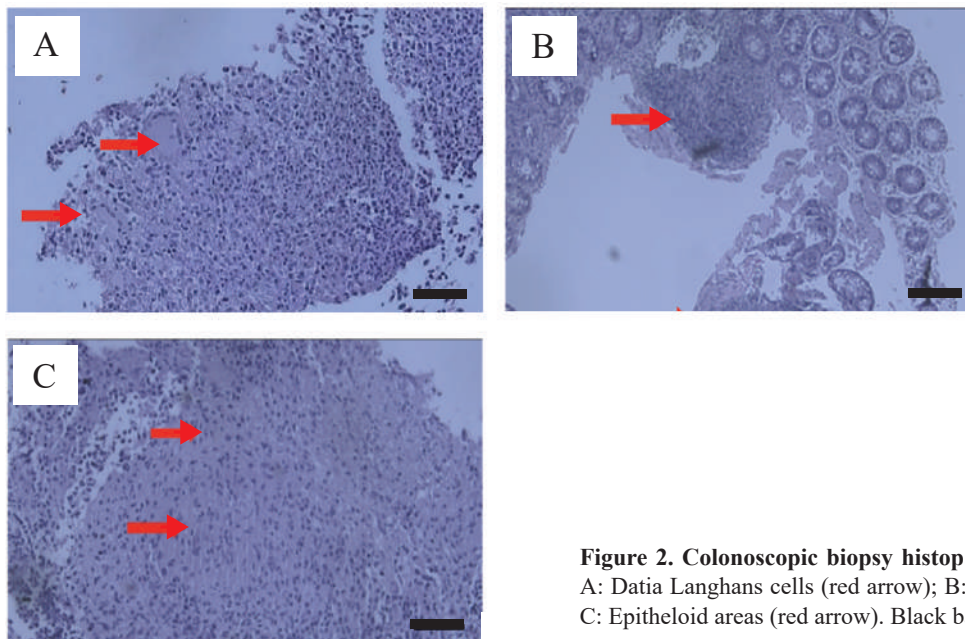
Figure 2. Colonoscopic biopsy histopathological results of ITB group.
A: Datia Langhans cells (red arrow); B: Lymphoid aggregates (red arrow);
C: Epitheloid areas (red arrow). Black bar: 50 μm.

Authors Contribution

NDI, MS, PR, Y, AK, S, ARH, HW, and IP were involved in concepting and planning the research. NDI, MS, PR, AK, ARH, HW, and IP performed the data acquisition/collection. NDI, MS, PR, Y, AK, and S calculated the experimental data and performed the analysis. NDI, MS, PR, Y, AK, ARH, HW, IP, and FS drafted the manuscript. NDI, MS, AK and S designed the figures and tables. NDI, MS, PR, Y, AK, S, ARH, HW, IP, and FS aided in interpreting the results. NDI, MS, PR, Y, AK, and FS took parts in giving critical revision of the manuscript.

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