The Use of Adenosine Deaminase as a Diagnostic Tool for Tuberculous Pericardial Effusion in Thailand

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Abstract

Background: Tuberculous pericardial effusion is associated with high mortality and serious complications. In fact, it is difficult to establish a definite diagnosis of tuberculous pericardial effusion because of the low sensitivity of diagnostic tools.

Objectives: To evaluate the accuracy of adenosine deaminase (ADA) for the diagnosis of tuberculous pericardial effusion in Thailand.

Methods: The study population consisted of 71 consecutive patients with pericardial effusion in Siriraj hospital who underwent a pericardiocentesis from January 2004 to January 2008. The medical records of all patients were reviewed with respect to clinical examination, biochemistry, microbiology, cytology, differential white blood cell count, ADA activity, Polymerase chain reaction (PCR) for tuberculosis and culture for tuberculosis. The cut-off level for ADA as a diagnostic index was optimized using receiver operating characteristic (ROC) curves.

Results: Seventy-one patients were classified into 2 groups. Twenty-two patients had tuberculous pericardial effusion and 49 patients had non-tuberculous pericardial effusion. Mean ADA activity was significantly higher in the tuberculous pericardial effusion group (62.6 U/L) than the other group (29.5 U/L) (p = 0.01). With a cut-off level for ADA activity of 55 U/L, the diagnostic accuracy were as follows; sensitivity of 63.6%, specificity of 91.8%, positive predictive value of 77.8% and negative predictive value of 84.9%.

Conclusion: Pericardial fluid ADA is helpful in the diagnosis of tuberculous pericardial effusion in Thailand.

Keywords: ADA, Pericardial effusion, Tuberculous pericarditis, Tuberculosis

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Introduction

Tuberculous (TB) pericardial effusion is a rare form of extrapulmonary tuberculosis (1-2) which is frequently associated with high mortality and serious short and long-term complications, especially when the diagnosis and the correct treatment are delayed (3). The leading complications are constrictive pericarditis and cardiac tamponade, which are associated with high mortality unless it is detected and properly managed (1). Transthoracic echocardiogram is a useful test to detect and quantify the pericardial effusion as well as a tool to guide the pericardiocentesis (4).

But it is difficult to establish a definitive diagnosis of TB pericardial effusion because the direct smear of pericardial fluid has a low sensitivity for detecting tubercle bacilli (sensitivity 0-42%) (1, 5-7), while the culture is both slow and insensitive (sensitivity 53%) (8). Pericardial biopsy is invasive and is often not diagnostic (sensitivity from biopsy 10-64%) (9-11). Adenosine deaminase activity (ADA) is an interesting test for the diagnosis of TB pericardial effusion because this test has a high sensitivity and specificity (9,12-15).

ADA is a polymorphic enzyme that is found in lymphoid tissue, mainly in the T-lymphocyte (16). The presence of ADA in pericardial effusion reflects the activity of the cellular immune response to activation of T-lymphocytes and macrophages especially those T-lymphocytes which are activated in an antigenic response to TB bacilli (17).
Several previous studies have suggested ADA activity as a marker for the diagnosis of TB pericardial effusion (9,12-15). Results of these studies have shown that the sensitivity and specificity of ADA activity were within the range of 84-100% and 68-97% respectively.

But the clinical use of ADA activity in the diagnosis of TB pericardial effusion has been controversial. Therefore, it was the aim of this study to evaluate ADA activity in patients with pericardial effusion from different etiologies.

Methods
Patients

Patients who presented with pericardial effusion in Siriraj hospital and continued pericardiocentesis or pericardial window with biopsy from January 2004 to January 2008 were studied. Routinely this pericardial effusion was sent for differential white-cell count, biochemistry (protein, lactic dehydrogenase or LDH, ADA), microbiology (gram stain, acid fast bacilli or AFB stain, culture for bacteria and tuberculosis) and cytology. If a surgical pericardial biopsy was performed, the pericardial tissue was sent for histopathology and microbiology (gram stain, AFB stain, culture for bacteria and tuberculosis) and cytology. HIV analysis and blood chemistry (total protein, LDH) tests for each patient.

The hospital records of all patients were retrospectively reviewed and the diagnosis was made. Diagnosis for TB pericardial effusion were made by one or more of the following criteria (6); identification of the tubercle bacillus in the pericardial effusion or biopsy specimen by AFB stain, a positive culture result for tuberculosis in the pericardial effusion or biopsy, caseating granuloma found on histological examination of the pericardial tissue, tuberculosis demonstrated elsewhere in the body and absence of other causes together with responsive to antituberculous therapy.

This study was approved by the Ethics committee of Siriraj Hospital.

Data collection

At the time of pericardiocentesis the pericardial fluid was collected on ice or frozen within 30 min for ADA activity analysis. ADA activity was determined in all pericardial fluid specimens within 7 days (including pericardial fluid in surgical cases). Results of ADA activity are divided into two groups (tuberculous and a non-tuberculous group) (Figure 1).

Statistical analysis

The two-sample t-test was employed for the analysis of data. The ADA activity in TB pericardial effusion was compared to the levels of activity in the other various diagnostic groups. The median and range of ADA activity in the various diagnostic groups were calculated. In addition, ADA activity was evaluated at various cut-off levels by calculation of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). These values were compared on the basis of a receiver operating characteristic curve (ROC).

Results

From January 2004 to January 2008, 71 patients presented to Siriraj hospital with large pericardial effusion requiring pericardiocentesis. TB pericardial effusion accounted for 22 effusions (31.4%), malignant effusions

<table>
<thead>
<tr>
<th>ADA (U/L)</th>
<th>n</th>
<th>Median</th>
<th>Minimum</th>
<th>maximum</th>
<th>Mean</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB pericardial effusion group</td>
<td>22</td>
<td>72.12</td>
<td>10.58</td>
<td>166.00</td>
<td>62.68</td>
<td>37.49</td>
</tr>
<tr>
<td>Non-TB pericardial effusion group</td>
<td>49</td>
<td>20.00</td>
<td>6.04</td>
<td>129.85</td>
<td>29.56</td>
<td>24.99</td>
</tr>
</tbody>
</table>
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**Figure 1.** Classification of study groups

![Classification of study groups](image)

**Table 2.** The result as a diagnostic tool at cutoff ADA level of 55 U/L

<table>
<thead>
<tr>
<th></th>
<th>TB pericardial effusion group</th>
<th>Non-TB pericardial effusion group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA ≥ 55 U/L</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>ADA &lt; 55 U/L</td>
<td>8</td>
<td>45</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>49</td>
</tr>
</tbody>
</table>

for 31 (43.6%), effusions associated with systemic lupus erythematosus (SLE) for 8 (11.2%), septic pericarditis for 3 (4.2%) and ‘other’ effusions for 7 (9.8%).

Twenty-two patients were classified in the TB pericardial effusion group by diagnostic criteria. This included 4 patients with pericardial effusion with a positive AFB stain, 1 patient with pericardial effusion with a positive polymerase chain reaction (PCR) for TB, 3 patients with pericardial biopsy with caseating granuloma, 8 patients with extracardiac TB and 6 patients classified by absence of other causes responsive to antituberculous therapy.

No significant difference was found in the mean age between the two groups (p = 0.497). Patients with TB pericardial effusion had a mean age of 52 years and the others had a mean age of 48 years. Mean ADA activity was significantly higher (62.6 U/L) in the TB pericardial effusion group than the other group (29.5 U/L) (p = 0.01)(Table 1).

The receiver operating characteristic curve (ROC) proved that a pericardial ADA ≥ 55 U/L was a cut off level with excellent sensitivity and specificity to diagnose TB pericardial effusion (Figure 2).

Results using the cutoff level of 55 U/L as being diagnostic of TB pericardial effusion are shown in Table 2. Eight patients (36%) with TB pericardial effusion had false negative results and 4 patients (8%) with non TB pericardial effusion had false positive results. The diagnosis of the patients with false negative results included 1 patient from positive AFB stain in pericardial effusion, 1 patient from pericardial biopsy with caseating granuloma, 3 patients from evidence of extracardiac TB and 3 patients classified by absence of other causes responsive to antituberculous therapy. Most of the patients with false positive results were classified as malignancy related.

With a cut-off level for ADA activity at 55 U/L, the diagnostic accuracy were as follows; sensitivity of 63.6%,
specificity of 91.8%, positive predictive value of 77.8% and negative predictive value of 84.9% (Table 3). The diagnostic accuracy of this test at this cutoff level was 83.1% (95% CI, 72.7%-90.1%).

Discussion

ADA is a polymorphic enzyme that is found in lymphoid tissue, mainly in the T-lymphocyte. The presence of ADA in pleural or other fluids reflects the cellular immune response to activation of the T-lymphocyte.

TB pericardial effusion is characterized by a relative lymphocytosis. High lymphocyte counts also can be found in effusions secondary to malignancy or other causes. A few small studies regarding the use of ADA in TB pericardial effusion have been conducted (9, 12-15).

In this study, ADA levels in the TB pericardial effusion group were significantly higher than in the non-TB pericardial effusion group. The best cutoff ADA level for diagnosing pericardial effusion was 55 U/L, which corresponds to sensitivity, specificity, PPV, NPV and diagnostic accuracy of 63.6%, 91.8%, 77.8%, 84.9% and 83.1% respectively.

This study has some limitations. The sensitivity in this study is lower than previous studies (9, 12-15). One explanation could be the defects in specimen collection. Because of the restrospective design, it was impossible to control for proper temperature in the specimen collection for this study. In fact, ADA is an enzyme that is stable for at least 24 hrs at 25°C, 7 days at 4°C and 3 months at -20°C (5, 18), thus the specimen should be collected at below 4°C.

In conclusion, the use of pericardial ADA level is useful for diagnosing TB pericardial effusion in Thailand.

References


Figure 2. Receiver operating characteristic curve (ROC) shows sensitivity and specificity of pericardial ADA for diagnosing tuberculous pericardial effusion.


การใช้ตัว adenosine deaminase (ADA) เพื่อช่วยในการวินิจฉัยการคิดเชื่อวัณโรคที่เยื่อหุ้มหัวใจในประเทศไทย (Tuberculous pericarditis)

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บางกอก

วัตถุประสงค์: การคิดเชื่อวัณโรคที่เยื่อหุ้มหัวใจเป็นโรคที่มีความรุนแรงและมีการระบาดขึ้นที่ยิ่งมากขึ้นในปัจจุบัน ซึ่งเป็นที่่ย่องน่าจับใจในการวินิจฉัยโรคที่มาจากโรคที่ไม่สามารถตรวจได้โดยการวินิจฉัยที่ถูกความไปสู่การตรวจ adenosine deaminase (ADA) จึงเป็นสิ่งน่าสนใจที่นำมาใช้งานเพื่อให้การคิดเชื่อวัณโรคที่เยื่อหุ้มหัวใจการคิดเชื่อวัณโรคที่เยื่อหุ้มหัวใจการคิดเชื่อวัณโรคที่เยื่อหุ้มหัวใจ

วิธีการศึกษา: การศึกษานี้เป็นการศึกษาแบบอิสระ ที่ประกอบด้วยผู้ป้ ทำให้การคิดเชื่อวัณโรคที่เยื่อหุ้มหัวใจ ที่โรงพยาบาลวิวัฒนาการตั้งแต่การเป็น 2547 ถึง 2551 จำนวนทั้งหมด 71 คน และทำให้การคิดเชื่อวัณโรคที่เยื่อหุ้มหัวใจ

ผลการศึกษา: ผู้ป้ จำนวน 72 คน แบ่งเป็น 2 กลุ่ม ทำให้การคิดเชื่อวัณโรคที่เยื่อหุ้มหัวใจมี จำนวนทั้งหมด 22 คน และกลุ่มที่มีในเยื่อหุ้มหัวใจจากอาการต่อมีจำนวนทั้งหมด 49 คน โดยจากการศึกษาพบว่า ค่าต่อมีที่ที่ต่อมีในเยื่อหุ้มหัวใจ (ADA 62.6 U/L) มีค่าที่สูงกว่าค่าต่อมีในเยื่อหุ้มหัวใจจาก สาเหตุ (ADA 29.5 U/L) ซึ่งมีค่ามากกว่าค่าต่อมีในการคิดเชื่อวัณโรคที่เยื่อหุ้มหัวใจ ทำให้การคิดเชื่อวัณโรคที่เยื่อหุ้มหัวใจมีความไว้ระอุน 63.6, ความจุเพาะร้อยละ 91.8, ทำให้เป็นไปได้ในการเป็นโรค (PPV) รองรับ 77.8 และ ทำให้เป็นไปได้ในการเป็นโรค (NP) รองรับ 84.9

สรุป: การตรวจ ADA ในเยื่อหุ้มหัวใจ (pericardial effusion) มีประโยชน์ในการวินิจฉัยการคิดเชื่อวัณโรคที่เยื่อหุ้มหัวใจในประเทศไทย (tuberculous pericarditis)