Value of D-dimer and alkaline phosphatase in the diagnosis of pleural effusion

Mahmoud M. El-Habashy a,*, Ibrahim I. Elmahalawy a, Ahmed Sonbol b

a Chest Department, Faculty of Medicine, Menoufiya University, Egypt
b Clinical Pathology Department, Faculty of Medicine, Menoufiya University, Egypt

Received 24 June 2014; accepted 9 July 2014
Available online 2 August 2014

KEYWORDS
Pleural fluid (PF); Alkaline phosphatase (ALP); D-dimer

Abstract  Introduction: Pleural effusion is a common clinical presentation in several diseases. Various parameters from pleural fluid have been studied to identify the cause of effusion. D-dimer is a degradation product of cross-linked fibrin and alkaline phosphatase (ALP) is one of the biochemical markers found in pleural effusion. ALP is a plasma membrane derived enzyme of uncertain physiologic function that hydrolyzes synthetic phosphate esters at pH 9. It is present in the serum in several forms, i.e., ALP-1 alpha 2, ALP-2 beta 1 and ALP-3 beta 2.

Aim: The present study was carried out to evaluate the value of alkaline phosphatase and D-dimer concentration in the pleural effusions and serum as a diagnostic tool.

Methods: This study was carried out on one hundred patients with pleural effusions of different aetiologies. 75 patients had exudative pleural effusions (35 patients had tuberculous effusion, 20 patients had malignant effusion, 10 had parapneumonic effusion, 5 had empyema and 5 patients had systemic lupus erythematosus) and 25 patients had transudative effusions (20 patients had hepatic and 5 patients had cardiac effusions). Serum and pleural effusion D-dimer (measured by ELISA), ALP, LDH and protein levels were measured.

Results: There was a highly significant difference in the pleural fluid D-dimer and ALP levels between exudative and transudative effusions ($P < 0.001$). Also, there was a highly significant difference in both the pleural fluid D-dimer and ALP levels between tuberculous and non tuberculous pleural effusions ($P < 0.001$). There were no significant differences in the pleural levels of either the D-dimer or the ALP between malignant and non malignant pleural effusions ($P > 0.05$). Lastly there was no significant difference ($P > 0.05$) in the serum levels of either the ALP or the D-dimer between different types of effusions.

Conclusion: Measurement of pleural fluid D-dimer and ALP levels aids in the differentiation between exudative and transudative pleural effusions. Also, both pleural fluid D Dimer and ALP are significantly higher in tuberculous pleural effusions.

© 2014 Production and hosting by Elsevier B.V. on behalf of The Egyptian Society of Chest Diseases and Tuberculosis. Open access under CC BY-NC-ND license.
Introduction

A correct diagnosis of the underlying disease is essential for rationale management of pleural effusion. Transudative pleural effusion is caused by a limited number of diseases, whereas the exudative effusion requires more extensive diagnostic investigations. Therefore, the first step is to classify them as transudate or exudate effusion, even if this differentiation does not contribute to the etiological diagnosis. Diagnosing the etiology of pleural effusion clinically with certainty is a challenging task for physicians. Various pleural fluid parameters have been used to identify the cause. Light et al. [1] have classified pleural effusions into transudate and exudate using pleural fluid protein and LDH concentrations.

Coagulation system plays an important role in pleural diseases. Understanding the pathophysiological mechanisms of the coagulation and pleural disorders may open possibilities for novel diagnostic and therapeutic approaches. Several studies have reported that exudative pleural effusion is associated with enhanced local fibrinolytic activity. Thus, D-dimer level; a marker of solid phase fibrin dissolution; was found to be high in patients with exudative pleural effusion [2,3].

Tuberculosis (TB) remains a public health problem worldwide. According to the latest 2012 global tuberculosis report, in 2011; there were 8.7 million new cases of TB and 1.4 million people died from TB, including almost 1 million death among HIV-negative individuals and 430,000 among people who were HIV-positive [2]. Tuberculous pleural effusion (TPE) occurs in up to 30% of patients with TB and constitutes the major portion of the extrapulmonary TB morbidity [3]. To establish or exclude TPE diagnosis is of great importance when dealing with patients with pleural effusion [4,5].

Methods

This study included 100 patients with pleural effusion admitted to the Chest department; Menoufia University Hospital. All patients were subjected to the following after taking an informed consent: detailed history taking, general and local chest examination, plain chest X-ray postero–anterior and lateral views and chest CT (Computed Tomography) when needed; routine laboratory investigations, electrocardiography (ECG) and echocardiography, tuberculin skin test, sputum examination for AFB (acid fast bacilli) by ZN (Ziehl Nielsen) staining when needed, serum protein and LDH (lactate dehydrogenase), pleural fluid protein and LDH, pleural fluid gram stain and bacterial culture, pleural fluid ZN staining for AFB, assessment of pleural fluid ADA (adenosine deaminase) level, cytological examination of the pleural fluid, blind pleural biopsy by Abram’s needle and/or thoracoscopy when needed to reach the diagnosis. Lastly assessment of the levels of D dimer and ALP in both serum and pleural fluid was done for all patients.

Results

Fig. 1 shows that hundred pleural effusion patients were studied; 75% were exudative effusions (35% tuberculous, 20% malignant, 10% parapneumonic, 5% empyema and 5% collagen) and 25% were transudative effusions (20% hepatic and 5% cardiac).

Discussion

Our results revealed a highly significant difference between exudative and transudative pleural effusions regarding both pleural fluid ALP and D-dimer levels [(100.47 ± 43.17 in exudates versus 54.4 ± 10.8 in transudates for pleural ALP and 0.72 ± 0.2 in exudates versus 0.12 ± 0.02 in transudates for pleural fluid D Dimer (p < 0.001 for both)] (Table 1).

Table 1 shows that, there were highly significant differences between exudative and transudative effusions according to the pleural levels of ALP and D-dimer (p < 0.001), but there were no significant differences according to the serum levels of ALP and D-dimer (p > 0.05).

Table 2 shows that, there were highly significant differences between tuberculous and non tuberculous effusions according to the pleural levels of ALP and D Dimer (p < 0.001), but there were no significant differences regarding the serum levels of ALP and D Dimer (p > 0.05).

Table 3 shows that, there were no significant differences according to the serum and pleural levels of ALP and D-dimer (p > 0.05).

Table 1 Distribution of exudative and transudative pleural effusions in the study.
differences regarding pleural D Dimer levels between transudates and exudates ($p = 0.277$).

Also, Table 2 reveals a highly significant difference between tuberculous and non tuberculous pleural effusions according to the pleural levels of ALP and D Dimer ($p < 0.001$), both were significantly higher in tuberculous than non tuberculosis effusions [130.14 ± 41.12 in TB effusions versus 66.77 ± 22.24 in non TB effusions for pleural ALP and 0.99 ± 0.08 in TB effusions versus 0.42 ± 0.29 in non TB effusions for pleural D Dimer ($p < 0.001$ for both)]. Table 3 shows no significant differences between malignant and non malignant pleural effusions regardless pleural or serum ALP or D Dimer ($p > 0.05$).

Jadhav et al. [12] reported that the values of pleural ALP and pleural to serum ALP ratio were significantly higher in TPE than other causes of pleural effusion. Also they found that the sensitivity and specificity of the pleural ALP for the diagnosis of TPE were 90% and 86.66%, respectively, for a cut off level of 71 IU/L ($p < 0.0001$) and those of the pleural to serum ALP ratio were 90% and 86.66%, respectively, for a cut off value of 51.1 ($p < 0.0001$). Metintas et al. [13] found that pleural ALP and pleural to serum ALP ratio were significantly raised in TPE compared to non TPE ($p < 0.001$). On the other hand, Carrion F and Perpina [14] found that pleural ALP was significantly elevated in malignant pleural effusion compared to TPE and other causes of pleural effusion.

Table 1 Comparison between exudative and transudative effusion levels of ALP and D-dimer in serum and effusion.

<table>
<thead>
<tr>
<th></th>
<th>Exudate Mean ± SD</th>
<th>Transudate Mean ± SD</th>
<th>t test</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ALP</td>
<td>248.93 ± 101.96</td>
<td>240.07 ± 76.24</td>
<td>0.4</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Pleural ALP</td>
<td>100.47 ± 43.17</td>
<td>54.4 ± 10.8</td>
<td>5.3</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Serum D Dimer</td>
<td>0.69 ± 0.29</td>
<td>0.58 ± 0.19</td>
<td>1.6</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Pleural D Dimer</td>
<td>0.72 ± 0.2</td>
<td>0.12 ± 0.02</td>
<td>17.3</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

$p > 0.05$ non significant & $p < 0.05$ significant & $p < 0.001^{**}$ highly significant.

Table 2 Comparison between tuberculous and non tuberculous effusion levels of ALP and D-dimer in serum and effusion.

<table>
<thead>
<tr>
<th></th>
<th>Non TB Mean ± SD</th>
<th>TB Mean ± SD</th>
<th>t test</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ALP</td>
<td>212.62 ± 92.22</td>
<td>258.86 ± 95.44</td>
<td>-2.363</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Pleural ALP</td>
<td>66.77 ± 22.24</td>
<td>130.14 ± 41.12</td>
<td>-10.022</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Serum D Dimer</td>
<td>0.51 ± 0.54</td>
<td>0.64 ± 0.14</td>
<td>-1.469</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Pleural D Dimer</td>
<td>0.42 ± 0.29</td>
<td>0.99 ± 0.08</td>
<td>8.613</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

$p > 0.05$ non significant & $p < 0.05$ significant & $p < 0.001^{**}$ highly significant.

Table 3 Comparison between malignant and non malignant effusion levels of ALP and D-dimer in serum and effusion.

<table>
<thead>
<tr>
<th></th>
<th>Malignant Mean ± SD</th>
<th>Non malignant Mean ± SD</th>
<th>t test</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ALP</td>
<td>278.55 ± 74.68</td>
<td>238.74 ± 99.3</td>
<td>1.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Pleural ALP</td>
<td>92.38 ± 45.52</td>
<td>75.25 ± 25.29</td>
<td>-1.617</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Serum D Dimer</td>
<td>0.83 ± 0.68</td>
<td>0.65 ± 0.23</td>
<td>2.01</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Pleural D Dimer</td>
<td>0.61 ± 0.09</td>
<td>0.49 ± 0.42</td>
<td>-1.583</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

They also found that the plasma D dimer levels were also significantly different between samples from TPE compared to other etiologies ($p < 0.05$). They concluded that D-dimer may be a possible marker for TPE with a sensitivity of 84.38% and specificity of 85.45% with a cut-off value of 622.5 mg/L FEU.

Lu et al. [16] reported that D-dimer levels were significantly higher in pleural fluid from patients with tuberculous pleuritis and empyema than those in pleural fluid from patients with malignant pleural effusions. Philip-Joët et al. [17] also noticed that D-dimer levels in patients with tuberculosis tend to be higher than in patients with heart failure, empyema, and/or malignant pleural effusion, although there was no significance.

On the other hand, Matveychuk et al. [18] found high D dimer levels among malignant pleural effusions, and concluded that D-dimer might be useful as a simple, noninvasive, surrogate marker for malignant pleural effusion. Also, Costa Vaz et al. [11] found no significant differences between parapneumonic, tuberculous and malignant pleural effusions regarding the pleural levels of D Dimer.

Conclusion

Measurement of pleural fluid D-dimer and ALP levels aids in the differentiation between exudative and transudative pleural effusions. Also, both pleural fluid D Dimer and ALP are significantly higher in tuberculous pleural effusions.

Conflict of interest

We have no conflict of interest to declare.
References