Comparison of the diagnostic utility of ADA and CA125 in tuberculous effusion

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Received 29 August 2016; revised 29 September 2016; accepted 3 October 2016

Abstract  Background: Pleural effusion can be due to various pleural infections like TB as well as neoplasia. CA125 is a tumor marker found on the surface of ovarian and other normal cells as pleural cells. CA125 has been found to increase in serum and hence pleural fluid of patients with pleural effusion due to malignancy as well as due to TB.

This study was conducted to evaluate the utility of CA125 in the diagnosis of pleural effusion resulting from TB, malignancy and pneumonia as well as to evaluate and compare the diagnostic utility of CA125 and ADA in the diagnosis of TB effusion.

Patients and methods: 20 patients with tuberculous effusion (group I), 20 patients with malignant effusion (group II) and 20 patients with parapneumonic effusions (group III) were evaluated for the levels of CA125 and ADA in their pleural fluid. In malignant cases, diagnosis was made through microscopic inspection of pleural biopsy samples and cytology of pleural fluid. For diagnosis of tuberculosis, Ziehl Neelsen sputum smear, pleural fluid smear and culture & sensitivity. Parapneumonic effusions were confirmed by pleural fluid cell count and culture & sensitivity.

Results: The mean ± SD level of CA125 in pleural fluid was 41.732 ± 20.744 U/ml, 309.27 ± 79.564 U/ml and 7.040 ± 5.601 U/ml in tuberculous, malignant and parapneumonic effusions respectively; which showed a statistically significant difference between the three groups (p < 0.01).

Pleural fluid CA125 was significantly higher in group II than group I (P1 = 0.000) and group III (P3 = 0.000). Pleural fluid CA125 was significantly higher in group I than group III (P2 = 0.000). Pleural fluid ADA was significantly higher in group I than group II (P1 = 0.000) and group III (P3 = 0.000). For diagnosing TB, CA125 showed a sensitivity and specificity of 74.1%, 76.9% respectively while ADA demonstrated a sensitivity and specificity of 75% and 75% respectively.

Conclusion: CA-125 levels in pleural fluid may be used for differentiation between TB, pneumonia, and malignancy-induced effusions.

Also CA125 may be added to the diagnostic workup of pleural fluid for accurate diagnosis of TB effusion.

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Introduction

In absence of inflammation, pleural space contains little transudate fluid with small amounts of protein, LDH and few cells, which are mainly lymphocytes, macrophages and endothelial cells. Pleural effusion may occur due to an inflammatory or non-inflammatory etiology. In non-inflammatory etiologies, there might be a decrease in oncotic pressure or an increase in hydrostatic pressure. Otherwise, changes in lymphatic drainage may play an important role. However, changes in the permeability of veins in the pleura result from cross reaction between infectious organisms and defensive inflammatory cells and the secreted cytokines and chemokines. Thus, diagnosis of the underlying cause is not simple in some cases. It is essential to keep this fact in mind for an appropriate treatment approach [1].

Mechanism of accumulation of pleural fluid in tuberculosis is somewhat chronic, just the same as in malignancy. This similarity makes differentiation of the cause of pleural effusion whether due to malignancy or TB difficult to detect. This makes the process of appropriate management also difficult despite the use of several parameters and techniques. Discriminating the etiology of pleural effusion in tuberculosis and malignant cases plays an important role in patients’ treatment [1].

CA125 is glycoprotein with a high molecular weight, mucin-like, exists on the surface of ovarian, and some inflammatory and non-inflammatory cells like pleural cells. Proliferation of these cells causes this antigen to be released in serum. CA-125 was first known as a specific tumor marker that is the basis for a widely used serum assay for the monitoring of the ovary. Gradually it was found that inflammation even without polymorphism (as in the early stage of pregnancy, menstrual cycle, PID, and endometriosis) causes this tumor marker to increase. Increased CA-125 levels in response to tuberculosis were first observed in 1980's. Later, it was revealed that tuberculosis in various sites of the body causes increase in serum Antigen level [2–6].

This study was performed in order to investigate the ability of CA-125 levels to differentiate pleural effusion due to tuberculosis, pneumonias and malignancies. Also to compare the validity of the use of CA125 and ADA for the diagnosis of tuberculous effusion.

Aim of the work

The aim of the present study is to evaluate the diagnostic validity of CA125 and compare the diagnostic utilities of ADA and CA125 in tuberculous effusion.

Study population

This study included 60 patients who were admitted to Alexandria University Hospital during the period between December 2015 and July 2016. Patients were divided into 3 groups as follows: group I included 20 patients with tuberculous effusion, group II included 20 patients with malignant effusion and group III included 20 patients with pneumonic effusion.

Informed consent was obtained from all the participants before the study.

Patients and methods

All patients were subjected basically to thorough history-taking and clinical examination, routine laboratory investigations, plain chest radiography (posteroanterior and lateral views), CT chest and thoracocentesis. The pleural fluid obtained was examined for the following: gross appearance and nature of the fluid, total and differential cell count, total protein and albumin content (g/dl), lactate dehydrogenase enzyme, and bacteriological examination by culture and sensitivity. In malignant cases, diagnosis was made through microscopic inspection of biopsy samples and cytology of pleural fluid. For diagnosis of tuberculosis, Ziehl Neelsen smear and/or culture of pleural fluid or in some cases pleural biopsy. Pneumonic effusions were confirmed by pleural fluid cell count and culture and sensitivity. CA125 was measured in pleural fluid in U/ml using the commercially available ELISA kit (CA125 Test System, Monobind Inc., CA, USA). Pleural fluid ADA measurements were done using Adenosine Deaminase BioAssay™ ELISA Kit, US Biological Life Sciences, Michigan, USA). By utilizing several different serum references of known antigen values, a dose response curve was generated from which the antigen concentration of the samples was ascertained.

ROC (receiver operating characteristic) curves were used to determine the optimal cut-off value of ADA and serum CA125 which could distinguish TB from other pulmonary infections with the highest sensitivity, specificity, and predictive values [7]. The curve obtained, allowed the calculation of the slope and the area under the curve (AUC).

The association between categorical variables was performed using Chi-squared tests. Mann Whitney U test and SPSS ver. 11.5 software were used for statistical analysis to compare CA125 in the three groups and p-values < 0.05 were considered to be statistically significant.

Results

The study comprised 3 groups: group I which included 20 patients with confirmed diagnosis of tuberculous effusions.

In group II, 20 patients had confirmed malignant effusion through positive cytology of pleural fluid or biopsy samples.

In group III, 20 patients had a confirmed diagnosis of para-pneumonic effusion.

Table 1 shows that the age of the studied patients ranged from 26 to 60 years with a mean of 44.87 ± 13.557 in group I, while it ranged from 24 to 68 years with a mean of 47.15 ± 12.963 in group II and it ranged from 23 to 66 years with a mean of 43.00 ± 14.008 in group III, with no statistically significant difference between the three groups as regards age.

Regarding gender, 12 patients (60%) were males whereas 8 patients (40%) were females in group I. 11 patients (55%) were males whereas 9 patients (45%) were females in group II, and 12 patients (60%) were males whereas 8 patients (40%) were females in group III with no statistically significant difference between the three groups as regards gender.

Regarding radiological findings, left pleural effusion was detected in 9 (45%) patients in group I, in 7 (35%) patients in group II and in 10 (50%) patients in group III. Right pleural effusion was detected in 11 (55%) patients in group I, in 13 (65%) patients in group II and in 10 (50%) patients in group
There was no statistically significant difference between the three groups as regards radiological findings. Regarding pleural fluid ADA, it ranged from 76 to 120 IU/L with a mean of 93.30 ± 12.103 in group I, whereas it ranged from 12 to 36 IU/L with a mean of 23.65 ± 6.515 in group II and it ranged from 10 to 34 IU/L with a mean of 22.55 ± 7.430 in group III. Pleural fluid ADA was significantly higher in group I than the other 2 groups (P1 = 0.000, P2 = 0.000, P3 = 0.758, P = 0.000*).

Regarding pleural fluid CA125, it ranged from 23.8 to 98.7 IU/ml with a mean of 41.732 ± 20.744 in group I, whereas it ranged from 212.6 to 454 IU/ml with a mean of 309.27 ± 79.564 in group II and it ranged from 1.1 to 21 IU/ml with a mean of 7.040 ± 5.601 in group III. Pleural fluid CA125 was significantly higher in group II than group I (P1 = 0.000*) and group III (P2 = 0.000*). Pleural fluid CA125 was significantly higher in group I than group III (P3 = 0.000*).

Table 1 shows that the sensitivity and specificity of pleural fluid ADA in the tuberculous group were 75% and 75% respectively with positive predictive and negative predictive values of 64 and 30.2 respectively. The sensitivity and specificity of pleural fluid CA125 in the tuberculous group were 74.1% and 76.9% respectively with positive predictive and negative predictive values of 70 and 33.3 respectively.

### Table 1: Comparison between studied groups as regards Age, gender, radiological findings, pleural fluid ADA and CA125.

<table>
<thead>
<tr>
<th></th>
<th>Group (I) tuberculous effusion</th>
<th>Group (II) malignant effusion</th>
<th>Group (III) parapneumonic effusion</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>26–60 44.87 ± 13.557</td>
<td>24–68 47.15 ± 12.963</td>
<td>23–66 43.00 ± 14.008</td>
<td></td>
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<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (60%)</td>
<td>11 (55%)</td>
<td>12 (60%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8 (40%)</td>
<td>9 (45%)</td>
<td>8 (40%)</td>
<td></td>
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<tr>
<td><strong>Radiological findings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Pleural Effusion</td>
<td>9 (45%)</td>
<td>7 (35%)</td>
<td>10 (50%)</td>
<td>P1 = 0.780, P2 = 0.596, P3 = 0.523, P = 0.631</td>
</tr>
<tr>
<td>Right Pleural Effusion</td>
<td>11 (55%)</td>
<td>13 (65%)</td>
<td>10 (50%)</td>
<td></td>
</tr>
<tr>
<td>Pleural Fluid ADA</td>
<td>93.30 ± 12.103</td>
<td>23.65 ± 6.515</td>
<td>22.55 ± 7.430</td>
<td></td>
</tr>
<tr>
<td>Pleural Fluid CA125</td>
<td>41.732 ± 20.744</td>
<td>309.27 ± 79.564</td>
<td>7.040 ± 5.601</td>
<td></td>
</tr>
</tbody>
</table>

P1 = Comparison between Group (I) and Group (II).
P2 = Comparison between Group (I) and Group (III).
P3 = Comparison between Group (II) and Group (III).
P = Comparison between the three groups.

ROC (receiver operating characteristic) curves for diagnosis of TB by ADA and serum CA125 are shown in Fig. 1 and Fig. 2, respectively. Comparison between sensitivity, specificity and accuracy of both ADA and CA125 for TB diagnosis is shown in Fig 3. As compared to ADA, CA125 is more specific and slightly less sensitive for the diagnosis of TB effusion.

**Discussion**

CA125 antigen is a glycoprotein marker that is primarily produced by amnion, coelomic epithelium of the featus, but can also be produced by epithelium of fallopian tube, endometrium, endocervix, pleura or peritoneum. CA125 was found in high levels in serum in many benign conditions including infections of the peritoneum and pleura, during menstruation, pregnancy, endometriosis, liver diseases (like cirrhosis), benign ovarian tumors, pancreatitis, renal and hepatic insufficiencies, pelvic irradiation, post-menopausal period, pelvic inflammatory disease and tuberculosis [8,11–15].

High serum CA125 levels have also been demonstrated in many malignant processes including several tumors. Classically it has been used to monitor the course of ovarian carcinoma. CA125 levels are also increased in other neoplastic conditions, such as pulmonary, pancreatic, hepatobiliary, gastric, and colorectal neoplasias [9–11].
In a study to evaluate the level of CA125 in serum of patients with history of previous surgery, heart failure, pulmonary disease, cirrhosis and intrabdominal disease, Mirales et al. have reported increased CA125 levels (>35 IU/ml) [16]. Other studies have reported high serum CA125 levels in tuberculosis, mainly in extrapulmonary locations with abdominal involvement [17–25].

Aoki and his colleagues compared the amounts of ADA in pleural fluid, CA125 in serum, and pleural fluid gamma interferon in TB pleurisy and non-tuberculosis cases and stated that there was a considerable overlap between the amounts of pleural fluid ADA and serum CA125 in the two groups. However, the average value of CA125 in tuberculous pleuritis cases was higher compared with other infections[26].

In the present study, the amount of CA125 in pleural fluid of malignant patients was found to be significantly higher than in tuberculous pleural fluid.

This is in agreement with the same results of Shervin et al. who stated that estimating pleural fluid CA125 in patients with an unidentified and unclassical history is very useful. This is because, the chronic nature of this disease whether malignant or tuberculosis makes it very difficult to distinguish these two from each other requiring costly tests which may be avoided by using this method [27,28].

Also, Tomita et al. compared the level of pleural fluid CA125 in 51 patients affected by pleural effusion secondary to malignancy and 38 patients affected by benign effusion in a study to examine the histological distribution of CA125 in patients affected by pleural effusion. They determined, as in agreement with the present study, that the amount of CA125 in malignant effusion is remarkably higher than in the other cases in which effusion is due to other causes. They confirmed that CA125 in pleural effusion is produced by both malignant cells and active mesothelial cells [31].

On the other hand, Hirose and his colleagues reported a case of tuberculous effusion in which the level of serum CA125 was 1150 units per ml [30]. Their study showed that pleural cells were covered with antibodies against CA125 and

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**Table 2** Comparison between sensitivity and specificity of ADA and CA125.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>75%</td>
<td>75%</td>
<td>0.500</td>
<td>64</td>
<td>30.2</td>
<td>50%</td>
</tr>
<tr>
<td>CA125</td>
<td>74.1%</td>
<td>76.9%</td>
<td>0.486</td>
<td>70</td>
<td>33.3</td>
<td>57.5%</td>
</tr>
</tbody>
</table>

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**Fig. 1** Receiver operating characteristic (ROC) curve for diagnosis of TB by ADA.
that CA125 originated from pleural cells. They then concluded that malignant morphologic changes in the cells are not necessary for secretion of CA125. The amount of CA125 in both infection (TB) and malignant cases increases and can be a useful diagnostic guide [30].

Thakur and his colleagues mentioned that abdominal and peritoneum tuberculosis can result in an increase in the amount of serum CA-125, which can be reduced by using the right treatment approach [29].
In the present study, the amount of CA125 was measured in pleural fluid while in most of the previous studies [5,6,26,28,32], the amount of CA125 was considered only in serum.

ADA is an enzyme involved in purine catabolism, found in the majority of cells, but particularly in lymphocytes. It has been reported to have high sensitivity and reasonably good specificity for the diagnosis of pleural TB [33–37]. Since measurement of ADA is simple and inexpensive, it has a great diagnostic potential in the diagnosis of pleural TB in developing countries.

In the present study, pleural fluid ADA was significantly higher in TB group than the malignant and parapneumonic groups which is in agreement with other previous studies [38–42]. 4 of the non-TB pleural fluid samples had increased ADA, 3 of which were from group II and in 1 from group III, but these results were not statistically significant.

The sensitivity and specificity of pleural fluid ADA at a cut-off of 45 IU/L in the tuberculous group of the present study were 75% and 75% respectively i.e. ADA has similar sensitivity and specificity for diagnosing TB effusion.

The sensitivity and specificity of pleural fluid CA125 at a cut-off of 90 IU/L in the tuberculous group of the present study were 74.1% and 76.9% respectively i.e. CA125 is more specific than sensitive in diagnosing TB effusion (Fig. 3).

As compared to ADA, in the present study, CA125 is more specific and slightly less sensitive in the diagnosis of TB effusion.

Ambade et al. reported a sensitivity and specificity of ADA of 80% and 76%, respectively, at a cut-off of 71 IU/L which is quite comparative to the present study.

Similarly, Shalaby et al. reported that pleural CA-125 was more specific than sensitive in the detection of exudates because of tuberculosis, whereas serum CA-125 is more sensitive [43].

Aoki et al. reported that the sensitivity, specificity were 81.8%, 89.3%, respectively, when pADA values of more than 45 U ml⁻¹ were considered, and they were 100%, 75.0%, respectively, when sCA125 values of more than 35 U ml⁻¹ were considered [26].

Fortun et al. concluded that serum CA125 values increased in patients with pulmonary TB and not in patients with non-TB pulmonary infections. The sensitivity and specificity were 68.6% and 77.8%, respectively at cut-off for pulmonary tuberculosis 32.5 IU/ml (Pulmonary TB was the only factor associated with a Ca-125 level > 32.5) [44].

Burgess et al. have reported higher sensitivities and specificities of tuberculous PF ADA in the range of 91–100% and 81–94%, respectively [45], while Goto et al. in his meta-analysis of 40 studies reported a sensitivity range of 47.1–100%, and specificity range of 0–100%, and also suggested that the difference was due to different methods of estimation. They added that choosing a lower value increases sensitivity at the expense of specificity [46].

To conclude, raised CA125 in pleural fluid can be due to diverse aetiologies as tuberculosis and malignancy i.e. benign as well as malignant reasons have to be ruled out in cases of raised fluid CA125 levels.

Also, the use of pleural ADA levels provides a rapid and accurate means of detecting tuberculous effusion and hence early proper treatment. The study advocates a strategy of using ADA as a screening test in all patients presenting with an exudative pleural effusion of uncertain origin.

References

Comparison of the diagnostic utility of ADA and CA125 in tuberculous effusion


