Serum Level of Tumor Marker Carbohydrate Antigen-CA125 in Heart Failure

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Objective: To assess serum levels of tumor marker carbohydrate antigen 125 (CA125) in patients with heart failure (HF) and to investigate possible correlation with echocardiographic parameters and level of brain natriuretic peptide (BNP).

Patients and methods: We included 76 patients with different cardiac symptoms hospitalized at Clinic for heart disease and rheumatism. Control group (n=26) was consisted of patients without signs and symptoms of HF, normal left ventricle ejection fraction (LVEF) and normal BNP level. Patients with diagnosis of HF (n=50) were subdivided into 2 group depending on signs and symptoms of fluid overload: compensated (compHF, n=10) and decompensated group (decompHF, n=40). Serum CA125 and BNP were measured on admission and all patient underwent ECG recording and trans thoracic echocardiographic examination.

Results: The median CA125 level in HF group was significantly higher compared to control group (71.05 [30.70-141.47] U/ml vs 10.75 [8.05-14.32] U/ml, p<0.0005). Higher CA125 levels were found in decompHF group compared to compHF group (94.90 [49.75-196.75] U/ml vs 11.90 [10.25-15.80] U/ml, p<0.0005). In decompHF group 13 of patients had pleural and/or pericardial effusion- their CA125 levels were significantly higher compared to patients without serosal effusion (n=27) (205.10 [106.50-383.90] U/ml vs. 71.50 [47.30-109.55] U/ml, p<0.002). We found significant difference in CA125 levels between patients with atrial fibrillation and sinus rhythm (98.40 [48.20-242.70] U/ml vs. 71.50 [47.30-109.55] U/ml, p=0.015). There was no significant difference in CA125 levels in group with enlarged left atrium compared to normal sized atrium (p=0.282), as well as in group with moderate/severe mitral regurgitation compared to group with no/mild mitral regurgitation (p=0.99). Finally, levels of serum CA125 positively correlated with serum level of BNP (r=0.293, p =0.039), but not with LVEF (p=0.369) and left atrium diameter (p=0.636). Conclusion: Serum CA125 is elevated in decompensated HF patients: more pronounced elevation was found in patients with pleural and/or pericardial effusion compared to patients with no serosal effusion. CA125 level correlated with BNP, but not with left atrium diameter nor with LVEF. Tumor marker CA125 could be used as a maker of systemic congestion and volume overload in decompensated HF. We hypothesized that high CA125 level indicates that measured high BNP is actually wet BNP.

Key words: heart failure; tumor marker CA125; volume overload

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1. INTRODUCTION

Over the last years a growing interest for the biochemical abnormalities detectable in heart failure (HF) has become evident. Tumor markers are used for the screening, diagnosis and stratification of cancer disease, but recently the role of some tumor markers has also been explored in the context of patients with HF. Among them carbohydrate antigen 125 (CA125) has been investigated most extensively (1).

CA125 is a tumor marker classically associated with ovarian cancer, but it may be elevated in cancers originating in the endometrium, fallopian tubes, lungs, breast (2) and gastrointestinal tract, as well as in acute leukemia, non-Hodgkin's lymphoma. It could be also elevated in relatively benign conditions, such as early pregnancy, the ascites, cirrhosis and hepatitis, presence of any inflammatory condition in the abdominal area. Several studies have been reported increased serum CA125 levels in HF patients (3, 4, 5).

2. GOAL OF THE STUDY

Goal of this study is to assess the serum levels of tumor marker CA125 in HF and to determine any potential correlation with clinical status- compensated vs decompensated (with vs without fluid congestion), echocardiographic indices and level of BNP (brain natriuretic peptide).

3. PATIENTS AND METHODS

3.1. Patients

We prospectively evaluated 76 patients admitted at the Clinic for Heart...
diagnostic examination on TOSHIBA POWER VISION 7000 and Philips I30e ultrasound device and it were estimated: left atrium end-systolic diameter (LA), left ventricle ejection fraction (LVEF), diastolic function, valvular stenosis/regurgitation and the existence of pericardial fluid.

3.3. Statistical analysis

If normally distributed continuous variables are presented as mean +/-SD, or if non-normally distributed as median-interquartile range. Normally distributed continuous variables were compared with Student’s t-test. Non-normally distributed continuous variables were compared with Mann-Whitney U test. Categorical variables are presented as percentages and compared using the chi-squared test. Correlation between two variables was studied with Pearson’s correlation test. A p value <0.05 was considered statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 10.0 for Windows.

4. RESULTS

There was no significant difference in age between control and HF group (71.00 [63.0-80.75]vs. 73.50 [61.00-79.25] years, p=0.895), but in control group were more female patients (71.05 [36.82-108.10] vs. 73.1% vs. 44%, p<0.03). The etiology of HF was ischemic heart disease in 36% patients, dilated cardiomyopathy in 52%, valve heart disease in 10% and congenital in 2% of patients. Mean LVEF of control group was higher compared to HF group (56.46 +/-5.78% vs. 53.1% +/-5.78%, p<0.0005) (table 2, figure 1). We found higher BNP levels in decomHF group (wet BNP) compared to HF group (dry BNP) (p<0.0005) (table 2).

In HF we didn’t find significant difference in CA125 between female and male patients (71.05 [36.82-108.10] vs. 71.95 [14.22-233.30] U/ml, p = 0.807). Also there was no significant differences in CA125 levels in group with enlarged left atrium compared to normal

Table 1. CA125 levels in control and HF group (n=number of the individuals, p-level of significance)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>CA125 (U/ml)</th>
<th>Mann-Whitney Test p</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>11.90 (10.25-15.80)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>HF group</td>
<td>9.40 (49.75-196.75)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. CA125 and BNP values in compensated versus decompensated HF patients (n-number of the individuals, p-level of significance) (*: outlier values of CA125, n=number of individuals)

<table>
<thead>
<tr>
<th>CA125 (U/ml)</th>
<th>decomHF with no effusion n=13</th>
<th>decomHF with effusion n=27</th>
<th>HF with atrial fibrillation n=28</th>
<th>HF with sinus rhythm n=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>25th percentile</td>
<td>47.30</td>
<td>106.50</td>
<td>48.20</td>
<td>12.95</td>
</tr>
<tr>
<td>50th percentile</td>
<td>71.50</td>
<td>205.10</td>
<td>98.40</td>
<td>47.30</td>
</tr>
<tr>
<td>75th percentile</td>
<td>109.55</td>
<td>383.90</td>
<td>242.70</td>
<td>99.05</td>
</tr>
</tbody>
</table>

Table 3. CA125 levels according to presence of serosal effusion and heart rhythm (n-number of the individuals, p-level of significance)
5. DISCUSSION

Principle result of our study is that serum levels of CA125 are elevated in patients with decompensated HF.

The pathophysiological underlying mechanism for the production and secretion of CA125 in HF remains unclear (6). It has been found that CA125 will be released from surfaces of pleuropericardial or peritoneal mesothelial cells in response to mechanical stress such as fluid overload and inflammatory stimuli. This lead to hypothesis about at least double etiology of it synthesis, therefore CA125 might be a surrogate for both processes (7).

We don't know whether CA125 in HF simply reflects the increased activation of the cytokine pathway or other pathophysiological pathways, or whether CA125 is an active substance truly responsible for myocardial and/or peripheral dysfunction (8, 9). It is interesting fact that CA125 release is also unclear in malignancy. CA125 levels are more frequently abnormal in cancer with serosal involvement and Camera et al. (10) have reported that neoplastic cells do not produce CA125. Serum CA125 may be increased due to stimulation of pleuropericardial or peritoneal mesothelial cells by interleukin-1β and tumor necrosis factor-α derived from malignant cells.

According to our results CA125 levels were elevated in decompensated HF patients compared to compensated. Our results are consistent with results of Kouris et al. (11) who also found higher CA125 levels in HF patients with pulmonary congestion and ankle edema.

In our study patients with pleural and/or pericardial effusion had higher CA125 levels. Ma et al. (2) investigated CA125 level in patients aged 85 years and older and found higher values in patients with pleural effusion.

We found higher CA125 level in patients with atrial fibrillation - similar result reported Yilmaz et al. (12).

In our study patients with enlarged left atrium didn't have elevated CA125 values. Also there was not significant correlation of LA diameter and CA125 level. Contrary to these, Duman et al. (13) found elevated CA125 levels in patients with increased left atrium volume index. Potential reason for these contradictory results could be a fact that we didn't correctly estimate LA size measuring only antero-posterior diameter in parasternal short axis. It would be more accurate to measure LA volume index.

There was no significant correlation of CA125 and LVEF (p=0.369) - we think that could be due to fact they had been reflecting different pathological processes in HF. Our results are different from ones of Yilmaz et al. (12) who found significant although weak negative correlation of CA125 and LVEF (r=-0.269, p=0.001). Potential explanation for discrepancy in results could be a fact that in our population 5 patients had valvular and 1 patient congenital heart disease (atrial septal defect) with preserved LVEF.

We found positive correlation of CA125 and BNP levels. Ordu et al. (14) also found significant correlation with NT-proBNP (r=0.496, p=0.001).

Knowing CA125 as a marker of volume overload, we hypothesize that simultaneously elevated CA125 and BNP means that measured BNP is actually wet BNP. Wet BNP is BNP in volume overload when patient is decompensated and decreases rapidly as cardiac filling pressures are reduced after aggressive therapy (15). But in real clinical practice we don't know where is border between wet and dry BNP or how deep to go in reduction of wet BNP to get to the level of dry BNP. Solution of this dilemma could be repeated simultaneous measurement of CA125 and BNP after diuretic therapy. High CA125 and high BNP after aggressive diuresis could be a clue that patient is still in volume overload and needs more diuretic therapy. Contrary if CA 125 drops after adequate diuresis, patient has no dyspnea-
he is probably in euvolemic state and his elevated BNP level could be his own dry or optivolemic BNP. Searching the literature we didn’t find studies exploring potential role of CA125 as a point of distinction of wet and dry BNP- this could be interesting topic for future studies.

Limitation of this study is small sample size, one center and only one measurement on the admission. Further studies with larger population are needed to establish the pathophysiological and clinical significance of elevated CA125 in HF. It would be also interesting to continue observing patient from this study in future and investigate CA125 as a potential predictor of recurrent decompensation and mortality- this already has becoming interesting topics of today studies (16). Another idea is to measure CA125 not only at the admission but also on the discharge and to determine pattern of its release (rising or falling), change with drug treatment and impact on survival.

6. CONCLUSION

CA-125 is elevated in decompen-sated HF especially among patients with pleural and/or pericardial effusion. CA125 significantly correlated with BNP level and higher levels were found among patients with atrial fibrilla-tion. Elevation of CA 125 might be used as a marker of systemic congestion and volume overload. We specu-late that simultaneous determination CA125 with BNP could be used for determination of wet BNP. This is interesting idea for future studies. Future studies with longer follow-up are also needed to discover prognostic role of CA125 in HF.

REFERENCES


