THE MEANING OF INCREASED CA125 IN INTERNAL MEDICINE PRACTICE

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ABSTRACT

• **Objective:** CA125 is a tumor marker that is commonly ordered in internal medicine and sometimes confuses the clinicians. In this study we evaluated the prevalence and causes of CA125 increase in a patient population attending an internal medicine clinic.

• **Material and Method:** A total of 420 CA125 assays were prospectively analysed between March 2003 and October 2003 in Istanbul University, Internal Medicine Department. Clinical diagnosis, presence of any serosal effusion, age and sex were evaluated.

• **Results:** 103 (24.5%) patients had a value of CA125>35 kU/L. 60 were women and 43 were men. Their median age was 63 years (range, 15-92 years). Benign causes were slightly more frequent than malignant ones. The most frequent diagnosis was hematological malignancy (25.2%). In this group, there was significant superiority of non-Hodgkin's lymphoma (13 patients; 50%). Effusions were found in 48 patients (46.6%). All the 3 patients with CA125>1000 kU/L had a metastatic solid malignancy.

• **Conclusion:** Our study suggests that pathologies causing increase in CA125 is quite frequent in internal medicine practice. Pleural and peritoneal effusions due to malignant or nonmalignant diseases are the common disorders associated with CA125 increment. Very high levels of CA125 are more commonly associated with a malignancy.

• **Key Words:** CA125, etiology, serosal effusion, non-ovarian causes. Nobel Med 2008; 4(3): 32-36
ÖZET
İÇ HASTALIKLARI PRATİĞİNDE ARTMİŞ CA125'İN ANLAMI

• **Amaç:** CA125 iç hastalıklar pratiğinde sıkılaştı istenen ve yüksek çıktı bazı durumlarda klinikinin kafasının karşmasına sebep olan bir tümör belirtecidir. Bu çalışmada, iç hastalıkları kliniginne başvuran bir hasta popülasyonunda artmış CA125 seviyesinin prevalansını ve bu artışı sebep olan nedenleri ortaya koymak amaçlanmıştır.

• **Materyal ve Metod:** Istanbul Üniversitesi İç Hastalıkları Bölümü’nde Mart 2003 ve Ekim 2003 tarihleri arasında istenen toplam 420 CA125 testi konulan nüfus, hasta popülasyonu olarak incelendi. CA125 seviyesine ek olarak klinik tani, serosal sıvi varlığı, yaş ve cinsiyet değerlendirildi.

• **Bulgular:** Çalışmamızda 103 (%24.5) hastada CA125>35 kU/L saptandı. Hastaların 60 tanesi kadın, 43 tanesi erkekti. Ortanca Yaş 63 idi (aralik 15-92). Benign sebepler malignlerden biraz daha fazluydu.

Bununla birlikte, en sık görülen tanı hematolojik maligniteli (%25.2). Hematolojik maligniteler arasında Hodgkin'ın dizi lenfoma anlamış olarak daha sık (13 hasta, %50). Efüzyon 48 hastada (%46.6) saptandı. CA125 seviyesi >1000 kU/L olan her 3 hastanın da metastatik malignitesi mevcuttu.

• **Sonuç:** Çalışmamız, iç hastalıkları pratiğinde CA125 artışına sebep olan patolojilerin oldukça sik olduğunu düşünündürmektedir. Malign hastalıkla ilişkili olan veya olmayan plöral veya peritoneal efüzyonlar CA125 artış ile birlikte sık rastlanan hastalıklardır. Çok yüksek CA125 seviyeleri daha sıkılaştı malignite ile birlikteğil göstermektedir.

• **Anahtar Kelimeler:** CA125, etyoloji, serozal efüzyon, over-dişi sebepler. Nobel Med 2008; 4(3):32-36

INTRODUCTION

CA125 is a sensitive, but nonspecific, tumor marker for ovarian cancer. Although its use is only approved for evaluation of a suspected ovarian mass or follow-up of an ovarian carcinoma, the clinical practice is not accordingly. Requests for CA125 testing are increasing. A large proportion of this increase is a result of its use by specialties other than gynecology or oncology, mostly for screening purposes in various clinical situations other than ovarian cancer. Consequently, when the level is high, multiple investigations are performed for a possible occult malignancy. Therefore, studies focusing on the factors causing CA125 increment other than ovarian carcinoma are needed. We performed this study to evaluate the prevalence of CA125 increase and to establish the common conditions associated with it in internal medicine practice.

MATERIAL and METHOD

441 CA125 assays were performed prospectively in consecutive patients between March 2003 and October 2003 in Istanbul University, Internal Medicine Department. Informed consents were obtained from each patient. Blood was drawn from the forearm by Injectors in the morning following a starvation. Serum CA125 was measured with electrochemiluminescence immunoassay (ECLIA, used on the Roche Elecsys 1010/2010 and Modular Analytics E170 (Elecsys module) immunoassay analyzers; Roche Diagnostics). A value >35 kU/L was considered increased. Age, sex, clinical diagnosis, presence of pleural, pericardial, or peritoneal effusions were noted. Patients were divided into nine groups according to clinical diagnosis: solid malignancy, hematological malignancy, heart failure, hepatic cirrhosis, tuberculosis, lung diseases excluding tuberculosis, renal failure, menses, and miscellaneous.

Statistical Analysis

Statistical evaluation was carried out by SPSS pocket program. The mean values, median values, and standard deviation (X±SD) were noted. P values less than 0.05 were accepted as statistically significant. The difference between the group means and degrees of importance were determined by Mann-Whitney U test.

RESULTS

441 CA125 assays were performed. During the evaluation, the patients (n=21) whose accurate diagnoses have not been made were ruled out. Therefore total patient number was 420 in the outcome evaluation. 103 (24.5%) patients had a value of CA125 >35 kU/L. 60 were women and 43 were...
Effusions were found in 48 patients (46.6%) with marker increment. 27 of them (56.2%) had pleural effusion. Its most frequent etiology was heart failure (10 patients), 28 patients (58.3%) had ascites. Its most frequent etiology was cirrhosis (14 patients). Pericardial effusion was found in 2 patients (4%). The pathologies with the highest rates of effusion were hepatic cirrhosis (14 cases), heart failure (12 cases), and solid malignancies (12 cases). In 2 patients with heart failure, heart failure was not associated with any pleural effusion but ascites (in one patient due to hepatic cirrhosis; in the other due to peritoneal involvement of myelofibrosis). Among heart failure patients, 10 had no serosal effusion in contrast to 12 heart failure patients with serosal effusion. There was not any significant difference in CA125 levels of heart failure patients with and without any serosal effusion (p>0.05).

There were only 3 patients having CA125 levels>1000 kU/L. All of the 3 patients had solid malignancy with serosal involvement (1 patient with ovarian carcinoma and malignant ascites-pleural effusion, 1 patient with pancreas carcinoma and malignant ascites-pleural effusion, and 1 patient with hepatocellular carcinoma and malignant ascites).

**DISCUSSION**

In our study, 103 (24.5%) patients had CA125 increment out of 420 patients. To our knowledge, the only other report that studies prevalence of CA125 increment in internal medicine practice is the study by Le Thi Huong, et al.³

They retrospectively evaluated 328 patients in internal medicine department in 1988 and yielded a similar percentage as increment in 110 (33.5%) assays. Both of these studies indicate quite frequent CA125 increment in internal medicine practice. However, both are from a university hospital. The quite high frequency of increased CA125 might be partly related to this fact.

The etiological factor causing CA125 increment may differ related to the clinic it is ordered from. Therefore, similar to our report, studies focusing on the factors causing CA125 increment are needed from different departments. Clearly, the ovarian carcinoma is expected as most common etiological factor in a gynecology service. However, from clinics other than gynecology, different etiological causes might be expected. In a study from a medical oncology service, the most frequent cause was previous surgery (27.8%) (abdominal surgery, heart-lung surgeries, and CNS surgeries). Only 14.7% of the increment would have been due to ovarian carcinoma.

### Table 1: Serum CA125 levels in different clinical situations

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>%</th>
<th>Median CA125 level (kU/L)</th>
<th>CA125 range (kU/L)</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid malignancy</td>
<td>19</td>
<td>18.4</td>
<td>220.4</td>
<td>46-1353</td>
<td>3.25 (1.28-8.20)</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>28</td>
<td>25.2</td>
<td>105.2</td>
<td>55-3-569</td>
<td>1.95 (1.09-3.15)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>22</td>
<td>21.4</td>
<td>124.6</td>
<td>36-853</td>
<td>4.25 (2.13-8.48)</td>
</tr>
<tr>
<td>Hepatic cirrhosis</td>
<td>18</td>
<td>15.5</td>
<td>335</td>
<td>77-880</td>
<td>13.2 (4.77-36.8)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>7</td>
<td>6.6</td>
<td>88</td>
<td>36-267</td>
<td>11.4 (2.34-56.20)</td>
</tr>
<tr>
<td>Lung diseases excluding tuberculosis</td>
<td>11</td>
<td>10.7</td>
<td>121.4</td>
<td>37-465</td>
<td>7.30 (3.94-14.57)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>8</td>
<td>7.3</td>
<td>57.3</td>
<td>40-496</td>
<td>3.72 (1.31-10.55)</td>
</tr>
<tr>
<td>Menses</td>
<td>4</td>
<td>3.9</td>
<td>43.1</td>
<td>38-49</td>
<td>2.66 (0.86-7.35)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>6</td>
<td>5.6</td>
<td>172.3</td>
<td>52-270</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>119</td>
<td>100</td>
<td>137.3</td>
<td>335-1353</td>
<td></td>
</tr>
</tbody>
</table>

(n=119; 14 patients had 2 clinical diagnoses and 1 patient had 3 clinical diagnoses that can cause CA125 increment leading to a total patient number of n=103.)

In hematological malignancy group, there was significant superiority of non-Hodgkin’s lymphoma (13/26 patients; 50%). 18.4% (19 patients) of the CA125 increment was due to solid tumors including lung cancer (4 patients), colon cancer (3 patients), pancreas cancer (2 patients), breast cancer (2 patients), hepatocellular carcinoma (2 patients), ovarian carcinoma (2 patients), renal carcinoma (1 patient), metastatic adenocarcinoma with unknown primary (2 patients) and mesothelioma (1 patient). There was not significant superiority of any solid malignancy.

men, with a median age of 63 years (range, 15-92 years).
was due to cancer, ovarian carcinoma constituting only 1/9 cases. In their study, Le Thi Huong, et al. reported the most frequent causes as various nonspeciﬁed nonmalignant and noninfective diseases (40.9%), solid tumours (39%) and infectious diseases (30.9%). 2.7% cases had malignant blood disease (3). In our study, the causes of increment were: hematological malignancy (25.2%), heart failure (21.4%), solid malignancy (18.4%), hepatic cirrhosis (15.5%), lung diseases excluding tuberculosis (9.7%), tuberculosis (7.8%), renal failure (7.8%), menses (3.9%), miscellaneous (5.8%). Only two of them were due to ovarian carcinoma. On the contrary, among malignant tumors, most common diagnosis was non-Hodgkin’s lymphoma (NHL) (28.8%). However, Le Thi Huong et al. reported only 3 cases of hematological malignancy as the etiological factor. It is not easy to explain this signiﬁcant difference.

A possible explanation is that there is a signiﬁcant increase in the prevalence of especially non-Hodgkin’s lymphomas in the recent years. Another possible explanation might be, although not mentioned, the center which they reported the ﬁndings from, may not deal with the hematological malignancies. CA125 is suggested as a prognostic marker in NHL in the recent years. It is found as related to clinical stage, disease activity and prognosis.

There are different suggestions for the origin of CA125 in NHL. It was suggested as secreted by the coelomic epithelium cells when inﬁltrated with lymphoma or produced by the lymphoma cells themselves. How the lymphoma cells stimulate the production of CA125 is not clear. The cytokines such as IL-1 beta and TNF-alfa derived from the lymphoma cells might induce the mesothelial cells for CA125 secretion.

Among solid tumors, nongynecological tumors as stomach, lung, breast, pancreas, colon, melanoma, liver tumors, biliary tract, renal tumors and mesothelioma are all associated with serum CA125 increment. Similarly, in our study, patients with lung cancer (3.8%), colon cancer (2.9%), pancreas cancer (1.9%), breast cancer (1.9%), hepatocellular carcinoma (1.9%), ovarian carcinoma (1.9%), renal carcinoma (0.9%), metastatic adenocarcinoma with unknown primary (1.9%) and mesothelioma (0.9%) had CA125 increment.

Only 3 patients had very high (>1000 kU/L) CA125 levels and all 3 patients had metastatic solid tumors with serosal involvement. Le Thi Huong, et al. also reported that the frequency of cancer increased with the CA125 level. So, we suggest that although CA125 increment should not be used for screening of a malignancy, any serious increase i.e. >1000 kU/L should be aggressively evaluated for a possible malignancy.

Heart failure was the second most common cause of CA125 increase (21.4%) in our study. Increase in CA125 is suggested in heart failure patients with and without serosal efﬂusions with signiﬁcantly higher increase in patients with efﬂusions. However, in our study, there was not any signiﬁcant difference in CA125 levels of heart failure patients with and without any serosal efﬂusion. This ﬁnding suggests that there might be some other mechanisms causing increment in CA125 in heart failure other than involvement of the serosal structures.

Cirrhotic patients comprised the 15.5% of the CA125 increment with the highest median value. The other less common diseases causing CA125 increment were lung diseases, tuberculosis, renal failure, and menses. Besides heart failure, liver cirrhosis, benign pleuropulmonary diseases, tuberculosis, gynecological processes, renal failure are all associated with increased levels of CA125. The probable etiology of this marker increment is a diffuse insult to the mesothelial cells. When mesothelial cells of the pleura, peritoneum, pericardium, tunica vaginalis testis, or fallopian tube are abnormally stimulated, they can increase their normal production of CA125, and its serum level increases. This might explain its increment in various different clinical situations. Effusions were the most common association with CA125 increment in our study similar to the study of Le Thi Huong et al. (<4.6% and 35.4%, respectively). Pleural and peritoneal efﬂusions were almost equal in etiological frequency.

There are several studies pointing CA125 increment associated with serosal efﬂusions, again, the probable etiology of this marker increment is the diffuse insult to the mesothelial cells of the pleura, peritoneum or pericardium.

In conclusion, our study suggests that in internal medicine practice, the pathologies causing CA125 increment is frequent. The most frequent association was any serosal efﬂusion and the most frequent etiological causes were hematological malignancies and heart failure. Benign causes were at least as frequent as the malignant ones. In a patient with an increased CA125 level, before any detailed investigation directed for a possible ovarian carcinoma, these more common pathologies should be considered. Very signiﬁcant evaluation of CA125 may evoke the clinician for a solid malignancy.
REFERENCES