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 commen 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 ARTMIŞ CA125'İN ANLAMI

• **Amaç:** CA125 iç hastalıkları pratiğinde sıklıkla istenen ve yüksek çıktığı bazı durumlarda klinisyenin kafasının karışmasına sebep olan bir tümör belirteçidir. Bu çalışmada, iç hastalıkları kliniğine başvuran bir hasta popülasyonunda artmış CA125 seviyesinin prevalansını ve bu artışa sebep olan nedenleri ortaya koymak amaçlanmıştır.

• **Materyal ve Metod:** İstanbul Üniversitesi İç Hastalıkları Bölümü'nde Mart 2003 ve Ekim 2003 tarihleri arasında istenen toplam 420 CA125 tetkiki prospektif olarak incelendi. CA125 seviyesine ek olarak klinik tanı, serosal sıvı 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 (aralık: 15-92). Benign sebepler malignlerden biraz daha fazlaydı.

Bununla birlikte, en sık gözlenen tanı hematolojik maligniteydi (%25,2). Hematolojik maligniteler arasında Hodgkin dışı lenfoma anlamlı olarak daha sıktı (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 sık olduğunu düşündürmektedir. Malign hastalıkla ilişkili olan veya olmayan plöral veya peritoneal efüzyonlar CA125 artışı ile birlikte sık rastlanan hastalıklardır. Çok yüksek CA125 seviyeleri daha sıklıkla malignite ile birliktelik göstermektedir.

• **Anahtar Kelimeler:** CA125, etyoloji, serozal efüzyon, over-dışı 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 specialities other than gynecology or oncology, mostly for screening purposes in various clinical situations other than ovarian cancer.[1, 2] 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.[1-9]

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 →

Table 1: Serum CA125 levels in different clinical situations

Diagnosis	n	%	Median CA125 level (kU/L)	CA125 range (kU/L)	Odds ratio (95% confidence interval)
Solid malignancy	19	18.4	220.4	49-1353	3.23 (1.68-6.20)
Hematological malignancy	26	25.2	105.2	35.3-562	1.85 (1.09-3.15)
Heart failure	22	21.4	134.6	36-863	4.25 (2.13-8.48)
Hepatic cirrhosis	16	15.5	335	77-880	13.2 (4.77-36.6)
Tuberculosis	7	6.8	88	36-267	11.4 (2.34-56.20)
Lung diseases excluding tuberculosis	11	10.7	121.4	37-485	7.30 (3.64-14.67)
Renal failure	8	7.8	97.3	40-485	3.72 (1.31-10.55)
Menses	4	3.9	43.1	39-89	2.39 (0.80-7.05)
Miscellaneous	6	5.8	172.3	52-270	-
Total	119	100	137.3	35.3-1353	-

[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)]

men, with a median age of 63 years (range, 15-92 years).

The pathologies with increased markers were: hematological malignancy, 26 patients (25.2%), heart failure, 22 patients (21.4%), solid malignancy, 19 patients (18.4%), hepatic cirrhosis, 16 patients (15.5%), lung diseases excluding tuberculosis, 10 patients (9.7%), tuberculosis, 8 patients (7.8%), renal failure, 8 patients (7.8%), menses, 4 patients (3.9%), miscellaneous, 6 patients (5.8%). The most frequent diagnosis in women was heart failure; the most frequent diagnosis in men was hematological malignancy. Median value of CA125 was 137.3 kU/L (range, 35.3-1353 kU/L). Hepatic cirrhosis group had the highest median value (335 kU/L). The highest level (1353 kU/L) was in a patient with metastatic ovarian carcinoma. The distribution of the patients according their clinical diagnosis, their median CA125 level and CA125 range are given in Table 1.

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.

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 level> 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).[4] Only 14.7% of the increment →

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.[5, 6] 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.[7, 8]

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[9, 10] or produced by the lymphoma cells themselves.[11, 12] 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.[13]

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.[4, 14-18] 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 effusions with significantly higher increase in patients with effusions.[19] However, in our study, there was not any significant difference in CA125 levels of heart failure patients with and without any serosal effusion. 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.[20-25] 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 Huang et al. (46.6% and 35.4%, respectively). Pleural and peritoneal effusions were almost equal in etiological frequency.

There are several studies pointing CA125 increment associated with serosal effusions.[4, 19, 26, 27] 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 effusion 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.

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