Role of cancer antigen-125 from pleural & ascitic fluid samples in non malignant conditions

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Received May 28, 2006

Background & objectives: CA-125, an ovarian tumor marker is known to increase in non malignant conditions such as tubercular and non tubercular pleuritis and ascites. We undertook this study to evaluate non-specific rise in CA-125 levels in conditions associated with pleural effusion and ascites and also to understand the mechanism of its secretion.

Methods: CA-125 levels in 38 pleural and 46 ascitic fluid samples from non malignant cases and 10 blood samples from pulmonary tuberculosis cases were estimated by ELISA. The ascitic fluid samples were collected from cases of bacterial peritonitis, tuberculosis, hepatitis, cirrhosis of other aetiology and pleural fluid samples were from cases of tubercular, pyogenic, cardiomegaly and other conditions.

Results: Both ascitic and pleural fluid samples (transudative and exudative) showed elevated CA-125 levels. The CA-125 levels were significantly higher in ascitic fluid samples than in pleural fluid samples.

Interpretation & conclusion: Our findings showed that elevated levels of CA-125 in pleural and ascitic fluid could be because of varied aetiologies which need to be ruled out before considering malignancy. Peritoneum has a greater capacity to secrete CA-125 than the pleural epithelium and the secretion occurs following inflammation or mechanical distress. Pulmonary tuberculosis as a closed lesion without involvement of pleural epithelium does not evoke high CA-125 release.

Key words Cirrhosis - exudate - hepatitis - peritonitis - pleuritis - pyogenic - transudate - tubercular

CA-125, a glycoprotein of 220 kDA molecular weight expressed on the surface of coelomic epithelium is elevated in about 80 per cent of women with carcinoma of ovary. It has been used to differentiate malignant from benign pelvic masses and is widely used for monitoring patients with ovarian cancers and to define progression of ovarian cancer. Serum levels of CA-125 greater than 65 U/ml offered more than 90 per cent accuracy in differentiating malignant
from non-malignant cases among postmenopausal women\textsuperscript{17}. We estimated serum CA-125 levels in 273 cases of suspected malignancy in our hospital. Only 24 (8.8\%) cases were confirmed histologically to be malignant and all of them had CA-125 level greater than 65 U/ml. Other 93 (34\%) cases had elevated CA-125 level but malignancy was excluded based on laparoscopy and additional investigations (unpublished observation).

The rise in CA-125 level in non ovarian malignancy such as lymphoma, melanomas, cancer of liver, kidney and colon has been reported\textsuperscript{3,12}. Increased levels of CA-125 have also been shown in conditions such as chronic renal failure, autoimmune disease, pancreatitis, cirrhosis and inflammation of peritoneum, pleura and pericardium including tuberculosis\textsuperscript{7,11,12,18}. Presentation of pleural effusion and ascites is frequently seen in various conditions and elevated CA-125 may lead to incorrect diagnosis. The present study was therefore carried out to evaluate non specific rise of CA-125 in various conditions associated with pleural effusion and ascites and also to understand the mechanism of the non specific rise of this antigen.

Material & Methods

All cases of ascitis and pleuritis admitted in Choithram Hospital and Research Centre, Indore, during May to December 2004 were included in the study. The CA-125 assessment was made on 38 pleural fluid samples (22 males and 16 females) 46 ascitic fluid samples (25 males and 21 females) and 10 blood samples from bacteriologically confirmed cases of pulmonary tuberculosis (PTB). The PTB cases without pleural effusion were included to compare their CA-125 level with those of tuberculous pleuritis cases. The cases with pleural effusion had no noticeable ascitis but 25 per cent of the cases with ascites had concomitant pleural effusion. However, pleural fluid from the cases of ascites was not included for CA-125 tests.

CA-125 assay: CA-125 was assayed by single step sandwich ELISA using monoclonal antibody to OC125 on random access AIA-600 (Tosoh, Japan) analyzer. The reagents from TOSOH Corporation, Japan were used and ‘Lymphocheck Immunoassay Plus Trilevel’ (Biorad, USA) controls were included for each batch for quality assurance. Preliminary work on simultaneous assay of CA-125 on the blood and ascitic fluid/pleural fluid indicated higher levels of CA-125 in fluid samples and hence, in the present study the CA-125 activity was measured in fluid samples. However, for bacteriologically confirmed pulmonary tuberculosis cases, CA-125 was measured in blood since there was no pleural effusion.

Exudate and transudate: Fluid samples with protein content >3 g\% were considered as exudative. The serum albumin level checked for all the cases from whom transudative fluid samples were received and the cases had serum albumin levels in the range of 3.0 to 5.5 g\%. Diagnosis of tubercular pleuritis was based on lymphocytic predominance with raised adenosine deaminase (ADA) values (>35 U/l), radiological findings, clinical presentations and response to anti-TB drugs.

The diagnosis of tuberculous ascites/peritonitis was based on cytology, ADA, ultra-sound studies showing pelvic mass, retroperitoneal/mesenteric adenopathy, mesenteric stranding, laparoscopy with histological evidence and response to anti-TB drugs. ADA estimation was carried out by the method described by Giusti\textsuperscript{19}.

The diagnosis of pyogenic pleuritis/peritonitis was based on the culture examination. The other clinical presentations have been cirrhosis, hepatitis, chronic renal failure and pancreatitis. The five cases had congestive cardiac failure leading to cardiomegaly and pleural effusion. The malignancy was confirmed histopathology over the biopsies/operated tumour in the three cases (Table I).
The study was approved by the ethical committee of Choithram Hospital and Research Centre, Indore.

Statistical analysis: CA-125 levels in different groups were statistically assessed by Kruskal Wallis-test followed by Mann-Whitney test. Stats-Direct software, UK (Version 2.5.7) was used for the statistical analysis.

<table>
<thead>
<tr>
<th>Table I. Raised CA125 level in pleural/ascitic fluid in various clinical presentations</th>
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<td><strong>Pleural (N=38)</strong></td>
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| **Ascitic fluid (N=46)** | Exudate (N=25) | Transudate (N=21) |
| Conditions | Raised CA-125 level | Conditions | Raised CA-125 level |
| Malignancy (ovarian) | 2 | 2 |
| Pyogenic (peritonitis) | 10 | 10 |
| Tuberculosis | 10 | 7 |
| Alcoholic liver | 1 | 2 |
| Hepatitis | 1 | 1 |
| Chronic renal failure | 1 | 1 |
| Blood (N=10) | Raised CA-125 level |
| Condition | PTB (10) | 1 |

| Raised CA-125 level >65U/ml |

Results & Discussion

Fifteen out of 22 cases with exudative tubercular pleuritis and four of the five cases of empyema showed elevated CA-125 levels. Among transudative pleural fluid samples all except one from amoebic lung infection had raised CA-125 (Table I).

Exudative ascitic fluid samples apparently showed higher CA-125 levels than the transudative ascitic fluids. However, the differences were not statistically significant. Similarly, differences in CA-125 levels in pyogenic ascites and the exudative ascites were not statistically significant. Differences among transudative ascites specimen from cirrhosis and hepatitis were also not statistically significant (Table II).

CA-125 levels were distinctly higher among exudative ascites as compared to exudative pleural fluid samples (P<0.05). Further, the tubercular ascites cases had higher CA-125 levels compared to tubercular pleuritis (P<0.005).

CA-125 is not a specific marker for ovarian cancer since it can be elevated in patients with other malignant conditions like adenocarcinomas, lymphomas, malignant mesotheliomas, immature teratomas and carcinomas of pancreas, colon, breast and lung. CA-125 elevations are also reported in benign conditions including endometriosis, adenomyosis, uterine fibroids, ovarian cysts, salpingitis, pleuritis, peritonitis, alcoholic hepatitis, and pregnancy. In fact, our earlier findings (unpublished observations) showed that 93 of the 273 suspected malignancy cases with raised CA-125 were found to have no malignancy after elaborate laparoscopic procedures and extended investigations and thus pointed out a distinct limitation of CA-125 as a cancer marker. The present data showed raised CA-125 levels in most of the cases of ascites and pleural effusion irrespective of the pathology. The observations remained similar for both transudates.
and exudates suggested that rise in CA-125 occurs in both inflammatory and non-inflammatory conditions, besides ovarian tumours or malignancies.

Rise in CA-125 in tuberculous pleuritis and ascites needs a special emphasis since the disease is rampant in the developing world and even in developed world extrapulmonary manifestations in the form of tubercular ascites/peritonitis cannot be overlooked. Raised CA-125 in ascites and pleuritis have been reported by several workers. In the present study, 22 of the 31 exudative pleural fluid samples and 10 of 25 ascites samples had tuberculosis and CA-125 was raised in the majority of them.

Culture proved pyogenic bacterial infections resulting in pleuritis and peritonitis had shown raised CA-125 values similar to observations reported earlier. The reason for this rise appears to be severe inflammatory signal for the coelomic epithelium.

All the ascites samples in the present study had elevated CA-125 values suggesting that CA-125 was elevated in ascites irrespective of the aetiology. Rubin & Rockey made similar observations and further suggested that if CA-125 levels are raised, the presence of ascites not detected by physical examination should be kept in mind. Mollina et al suggested that the presence of ascites plays a key role in the mechanism responsible for increased CA-125. They further observed that concentration of CA-125 was more in ascitic fluid than in serum, especially in cases of bacterial peritonitis. Based on these observations, it was suggested that increase in CA-125 may be due to non-specific stimulation of pleural and peritoneal mesothelium. Our observations also support the hypothesis that CA-125 is released from peritoneum and ascitic fluid acts as a reservoir form where it goes to circulation. We found higher CA-125 values in exudative ascitic fluid than in exudative pleural fluid. Our observations support a view that peritoneum has a greater capacity to secret CA-125 than the pleural epithelium. The stimulation to secret CA-125 by the epithelium could be following an inflammatory process as in the case of infective process or may be mechanical distress as in ascites or in cardiomegaly. It was interesting to note that CA-125 was not raised in 9 of the 10 cases of pulmonary tuberculosis where there was no pleural effusion. This observation points out that pulmonary tuberculosis, as a closed lesion without involvement of pleural epithelium is not likely to evoke CA-125 secretion.

To conclude, raised CA-125 in pleural and ascitic fluid can be due to diverse aetiologies and other causes need to be ruled out before considering malignancy. The study confirms the limitation of using CA-125 as a cancer marker. The origin of CA-125 may be pleural or peritoneal epithelium in cases of pleural effusion and ascites following inflammation or mechanical distress suggesting that peritoneum has greater capacity than pleural epithelium to release CA-125.

### Acknowledgment

Authors acknowledge with thanks the financial and infrastructural support from the Management, Choithram Hospital & Research Centre, Indore, India.
References


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