ORIGINAL ARTICLE

Serum Cancer Antigen 125 in Patients with Pleural Effusions

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Summary

We studied the prevalence of raised serum CA125 in patients with pleural effusions and explored factors affecting its level. Sixty four patients with benign effusions and 36 patients with malignant effusions admitted to the University Malaya Medical Centre from May 2001 to January 2002 were included in the study. There were no significant differences in age, gender and ethnicity of the patients with benign and malignant effusions. There was also no difference in the frequency of the side of pleural effusion between the two groups but compared to benign effusions, a higher proportion of malignant effusions was moderate to large in size (66% versus 39%, p = 0.011). Serum CA125 levels were above 35U/dL in 83.3% and 78.1% of patients with malignant and benign effusions, respectively (p = 0.532). All patients with underlying malignancy and 95.3% of patients with benign effusions had pleural fluid CA125 levels above 35U/dL (p=0.187). The median levels of CA125 were higher in the pleural fluid than in the serum in all aetiological groups. Higher serum CA125 levels were more likely to be found in patients with moderate to large effusions (p=0.015), malignant effusions (p=0.001) and in female patients (0.016). Serum CA125 level showed significant correlation with pleural fluid CA125 level (r = 0.532, p<0.001) but not with pleural fluid total white blood cell count (r = -0.092, p = 0.362), red blood cell count (r = -0.082, p = 0.417) and lactate dehydrogenase level (r = 0.062, p = 0.541). We conclude that serum CA125 is commonly elevated in patients with benign and malignant pleural effusions.

Key Words: CA125, Pleural effusion, Benign, Malignant

Introduction

Cancer Antigen 125 (CA125) is a high molecular weight glycoprotein produced by epithelial ovarian tumours and mesothelial cells. It has been used in the diagnosis of ovarian cancer for many years. It is also useful in monitoring response to treatment in patients with ovarian cancer. There have been many case reports on elevated serum CA125 levels in benign conditions such as Meigs' Syndrome[1], liver cirrhosis[2], chronic heart failure[3] and in haemodialysis patients[4]. The causes of elevated serum CA125 levels in these conditions were not clear. Several studies have attributed falsely raised serum CA125 to serosal involvement [2,5,6].

We conducted this study to determine the prevalence of raised serum CA125 levels in patients with pleural effusions due to various aetiologies. We were also interested to explore factors affecting raised serum CA 125 levels in patients with pleural effusions.

This article was accepted: 23 September 2006

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Materials and Methods

A prospective study was conducted at the University Malaya Medical Centre (UMMC), a community teaching hospital in Kuala Lumpur, Malaysia from May 2001 to January 2002. All patients with clinical and chest radiograph evidence of pleural effusion admitted to the medical wards of the hospital or referred to the respiratory team from non-medical wards during this period were included in the study. Patients with minimal effusion noted on computed tomography (CT) of the thorax but not on chest radiograph and/or coagulopathy (prothrombin time greater than 2.0 by International Normalised Ratio, INR) and/or platelet count less than 20 x 10^9/L were excluded from the study. Informed consent was obtained from each patient before recruitment into the study. The study design was approved by the UMMC ethics committee. Demographic data of the patients, characteristics of the pleural effusion, clinical presentation, investigation results and the final diagnosis were recorded. Small pleural effusions were defined as effusions occupying less than 1/3 of the hemi-thorax while effusions occupying more than 1/3 of the hemi-thorax were categorised as moderate to large effusions. The size of pleural effusions in patients with bilateral pleural effusions was determined by adding the sizes of the effusions on both sides.

All patients routinely underwent diagnostic thoracocentesis using a 16G needle to obtain 60 mL of pleural fluid for cell count; measurement of protein, lactate dehydrogenase (LDH) and CA125 levels; cytological examination; Gram-stain; culture; Ziehl-Neelsen staining and mycobacterial culture. Serum was taken at the same time for the measurement of protein, LDH and CA125 levels. Serum and pleural fluid CA 125 were assayed using commercial immunometric assays (CA125, IMMULITE OM MA kit units produced by EURO/DPC Ltd, United Kingdom), which were supplied by Antah Pharma Sdn Bhd.

The pleural fluid specimens were collected in EDTA tubes for cell count and in plain tubes for the other tests. Pleural biopsy was performed using the Abram's needle if the effusion was found to be exudative or when the diagnosis was uncertain. Other investigations that might contribute to the diagnosis were carried out. These included but were not limited to sputum direct smear for acid-fast bacilli (AFB), 2-D echocardiography for heart failure, CT of the thorax and bronchoscopic examination for suspected lung carcinoma and pulmonary tuberculosis.

The pleural effusions were classified according to the aetiologies. A malignant pleural effusion was defined as an effusion due to an underlying malignancy confirmed histologically. Tuberculous pleural effusions were diagnosed when one or more of the following criteria were satisfied: pleural fluid was culture-positive for *Mycobacterium tuberculosis* or smear-positive for AFB; presence of epithelioid granulomas with or without caseating necrosis and/or the presence of AFB on histological examination of pleural biopsy specimens; positive direct smear for AFB and/or positive culture for *Mycobacterium tuberculosis* from respiratory tract specimens which included sputum, bronchoalveolar lavage (BAL) or bronchial biopsy specimens; or clinical and radiological response to antituberculosis treatment in the absence of bacteriological and histological confirmation of tuberculosis.

Parapneumonic pleural effusions included effusions associated with an acute febrile illness, cough which might be productive of purulent sputum, chest radiograph revealing pulmonary infiltrates and response to antibiotic treatment. Empyema thoracis was diagnosed when there was pus in the pleural cavity or when a microorganism was identified in the pleural fluid by Gram stain or bacteriological culture. Transudative effusions were defined according to Light's criteria[7] when the cause of the transudative effusion could be determined and the effusion resolved on follow up following appropriate treatment of the underlying cause. Causes of other exudative effusions which were not due to malignancy or infection and in which a definite underlying cause could be found included systemic lupus erythematosus (SLE), serositis and pulmonary embolism.

Statistical Analysis

All data were analysed using SPSS version 10 software (SPSS Inc., Chicago, IL, USA). Differences in age between groups were examined using Student's t-test. Mann Whitney U or Kruskal Wallis tests were used to examine the differences between tumour marker levels of the various groups and χ-squared test was used for the comparison of proportions. Correlations were made using the Spearman correlation coefficients test. A p value of less than 0.05 for a two-tailed test was considered statistically significant.

Results

A total of 100 patients were studied. The patients were grouped according to the cause of the pleural effusions

(Figure 1). Sixty-four patients had benign effusions and 36 patients had malignant effusions. The effusions was attributed to primary lung carcinoma in 22 patients [adenocarcinoma (15 patients), squamous cell carcinoma (three patients), poorly differentiated non-small cell lung cancer (three patients) and small cell carcinoma (one patient)] and other malignancies in 14 patients [lymphoma (three patients), breast cancer (three patients), endometrial carcinoma (two patients), carcinoma of cervix (two patients), colonic carcinoma (one patient), carcinoma of the tongue (one patient), fallopian tube carcinoma (one patient) and teratoma (one patient)].

There were 53 male and 47 female patients. A higher proportion of malignant effusions occurred in females (52.7%) compared to effusions due to benign causes (43.7%). The majority of the patients are Chinese (56%) followed by Malays (23%) and Indian (17%). There were no significant differences in age, gender and ethnicity of the patients with benign and malignant effusions. There was also no difference in the frequency of the side of pleural effusion between the two groups but compared to benign effusions, a higher proportion of malignant effusions was moderate to large in size (66% versus 39%, p = 0.011) (Table I).

Serum CA125 levels were above the normal cut-off level of 35U/dL in 83.3% of patients with malignant effusions as compared to 78.1% of patients with benign effusions (p=0.532). In contrast, all patients with malignancy and 95.3% of patients with benign effusions had pleural fluid CA125 levels above 35U/dL (p=0.187). The proportions of patients with raised serum and pleural fluid CA125 levels according to the diagnosis are shown in Table II.

The median levels of pleural fluid CA125 were higher than the median serum levels in all aetiological groups (Table III). Overall, the median pleural fluid to serum ratio for CA125 was 5.18 (Range 0.1 – 441.0). Only five patients (5%) had a reversed CA125 ratio (two patients had transudative effusions and one patient each had parapneumonic effusion, carcinoma of cervix and teratoma).

The patients with moderate to large effusions had higher median serum CA125 levels than patients with small effusions (p=0.015) (Table IV). The serum CA125 level was higher in patients with malignant effusions than in those with benign effusions (p=0.001). Overall, female patients had higher serum CA125 levels than male patients (0.016). However, in benign effusions, the median serum CA125 levels in male and female were 97 U/dL and 85 U/dL respectively, which were not significantly different (p=0.989). The side of the effusion did not have an effect on the serum CA125 level (p=0.767). Serum CA125 levels showed significant correlation with pleural fluid CA125 levels (r=0.532, p<0.001) but no correlation with pleural fluid white blood cell count (r = -0.092, p = 0.362), red blood cell count (r = -0.082, p = 0.417) and LDH levels (r = 0.062, p = 0.541).

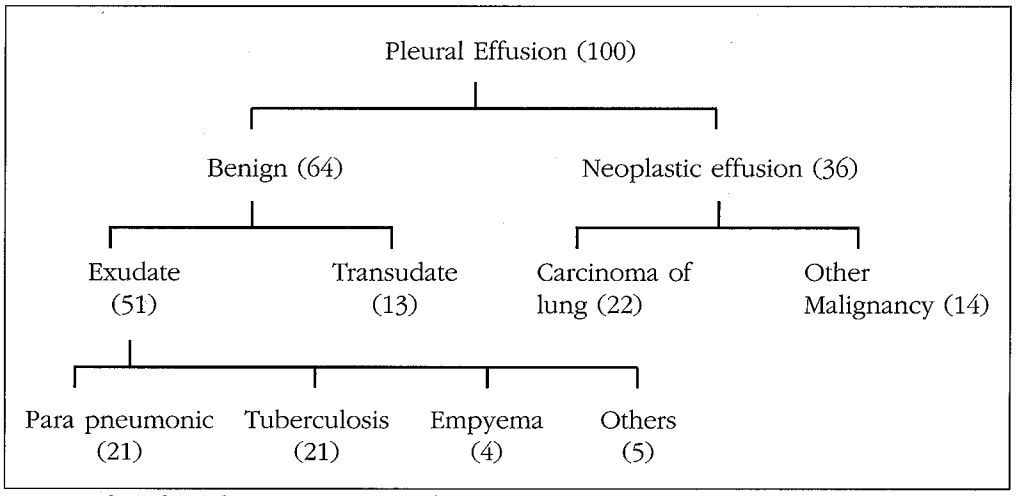

Fig 1: Flow chart showing the causes of pleural effusions (the number of patients are shown within parentheses)

Table I: Comparison of characteristics of 100 patients with malignant and benign pleural effusions

Characteristic	Malignant effusion (n = 36)	Benign effusion (n = 64)	p
Male : female	17:19	36:28	0.385
Age (± SD) (years)	59 (± 14)	53 (± 19)	0.090
Ethnicity, Malay : Chinese : Indian and Others	8:25:3	15:31:18	0.090
Side, Left :right :bilateral effusion	8:22:6	18:32:14	0.560
Size, Small : moderate to large *	12:23	38:24	0.011

* Total number of patients was 97 as 3 patients had no documentation of the size of the effusion and their chest radiographs could not be traced

Table II: Proportions of patients with serum and pleural fluid CA125 above 35 U/dL according to different aetiologies

Cause of pleural effusion	Serum n/ N (%)	Pleural fluid n/ N (%)
Malignant		
Carcinoma of lung	16/22 (72.7)	22/22 (100)
Other malignancies	14/14 (100)	14/14 (100)
Benign Exudate		
Tuberculosis	17/21 (77.2)	21/21 (100)
Parapneumonic effusion	16/21 (76.2)	20/21 (95.4)
Empyema	2/4 (50)	3/4 (75)
Other exudative effusion	5/5 (100)	5/5 (100)
Transudate		
Transudative effusion	10/13 (76.9)	12/13 (92.3)

n = No. of patients with CA125 above 35U/mL
N = No. of patients in whom the test was performed

Table III: Median and range of CA125 levels in serum and pleural fluid according to aetiological groups

Type of effusion	Serum CA125 level (U/dL)		Pleural fluid CA125 level (U/dL)	
	Median	Range	Median	Range
Malignant effusion	167	11 - 2915	782	79 - 11532
Tuberculous effusion	90	3 - 279	492	83 - 2140
Parapneumonic effusion	103	5 - 483	614	2 - 3042
Empyema	45	15 - 108	325	30 - 1000
Other exudate	81	15 - 193	688	225 - 1451
Transudate	146	2 - 291	489	3 - 882

Table IV: Serum CA125 in different categories

	Median serum CA125 (interquartile range) (U/dL)	p
Size of effusion		
Small	91 (122)	0.015
Moderate to large	128 (368)	
Type of effusion		
Benign	89 (115)	0.001
Malignant	172 (398)	
Gender		
Male	91 (126)	0.016
Female	124 (364)	
Side of effusion		
Bilateral	112 (118)	0.767
Left	103 (128)	
Right	124 (242)	

Discussion

CA125 was the first clinically useful marker for epithelial ovarian cancer. Approximately 83% of patients with these tumours have serum CA125 levels higher than 35U/dL as compared to only 1% of healthy individuals. Currently, serum CA125 is widely used to screen for malignancy even though many studies have found falsely raised CA125 in various benign conditions, particularly when there is serosal involvement such as pleural effusion, pericardial effusion and ascites[1-4]. This is because CA125 antigen is expressed in coelomic epithelial cells such as the epithelium of fallopian tube, endometrium, endocervix, ovary, pleura, peritoneum and pericardium[7]. Insults to mesothelial cells such as thoracic and abdominal surgical procedures are known to result in high serum CA125 levels[6,8].

A study by Lingren et al (65 patients) found 64% of patients with pleural effusions due to carcinoma and 38% of patients with benign diseases had serum CA125 higher than 35U/dL[9]. In another study by Topalak et al (21 patients), raised serum CA125 was seen in 82% of patients with benign pleural effusions and 95% of patients with malignant effusions[10]. Our study which included a larger number of patients showed similar results to this latter study with 78.1% of our patients with benign effusions and 83.3% of our patients with malignant effusions having elevated serum CA125 levels.

The raised serum CA125 levels in patients with pleural effusions are probably due to the benign proliferation of mesothelial cells in the pleura which secrete CA125. In our study, 76.9% of patients with transudative effusions had raised serum CA125 with the highest level being 291 U/dL, suggesting that the insult to the pleural mesothelial cells is probably not related to inflammation. Poor correlation with pleural fluid red blood cell count, white blood cell count and LDH levels further supports our hypothesis. Most of our patients had higher pleural fluid CA125 levels than serum CA125 levels which suggests of re-absorption of CA125 from the pleural fluid into the serum. In our study, the size of the pleural effusion is an important factor affecting serum CA125 level. Similar findings were reported by Topalak *et al* who showed a very good correlation between the amount of ascites and the serum CA125 level ($r=0.81$, <0.01)[10].

In conclusion, serum CA125 is commonly elevated in patients with pleural effusions irrespective of whether the underlying aetiology is a benign or a malignant condition.

References

1. Sabos CV, Leonardo HCP, Jose CCBR *et al.* Meigs' syndrome with elevated CA125: Case report. Sao Paulo Med J 2003; 121: 210-12.
2. Bergmann JF, Bidart JM, George M, *et al.* Elevation of CA 125 in patients with benign and malignant ascites. Cancer. 1987; 59: 213-7.
3. D'Aloia A, Faggiano P, Aurigemma G, *et al.* Serum levels of carbohydrate antigen 125 in patients with chronic heart failure: relation to clinical severity, hemodynamic and Doppler echocardiographic abnormalities, and short-term prognosis. J Am Coll Cardiol. 2003; 41: 1805-11.
4. Sevinc A, Buyukberber S, Sari R, *et al.* Elevated serum CA-125 levels in hemodialysis patients with peritoneal, pleural, or pericardial fluids. Gynecol Oncol. 2000; 77: 254-7.
5. Mezger J, Wilmanns W, Lamerz R. Elevated serum CA 125 levels in patients with benign ascitic or pleural effusions. Tumour Biol. 1988; 9: 47-52.
6. Miralles C, Orea M, Espana P, *et al.* Cancer antigen 125 associated with multiple benign and malignant pathologies. Ann Surg Oncol. 2003; 10: 150-4.
7. Light RW. Malignant pleural effusions. In: Light RW (ed). Pleural diseases, 3rd ed. Baltimore: Williams & Wilkins, 1995; 94-116.
8. Bischof P. What do we know about the origin of CA 125? Eur J Obstet Gynecol Reprod Biol. 1993; 49: 93-8.
9. Lindgren J, Kuusela P, Hellstrom PE, *et al.* The ovarian cancer associated antigen CA 125 in patients with pleural effusions. Eur J Cancer Clin Oncol. 1988; 24: 737-9.
10. Topalak O, Saygili U, Soyturk M, *et al.* Serum, pleural effusion, and ascites CA-125 levels in ovarian cancer and nonovarian benign and malignant diseases: a comparative study. Gynecol Oncol. 2002; 85: 108-13.