

ORIGINAL ARTICLE

The importance of CA125 as a predictive tool in ovarian carcinoma

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Abstract

Aims The present study deals with the importance of CA125 as an effective tumor marker in ovarian carcinoma and the clinical presentation observed in patients with high CA 125 levels.

Methods This Serological tests for tumour marker CA125 were performed in 585 patients with either ovarian carcinoma or some other tumours such as kidney, uterine, cervical and testicular tumours referred to the centre for nuclear medicine Lahore for hormonal estimation. Further more, some other clinical presentations were also observed amongst the patients.

Results The serum CA125 levels were elevated in 92% subjects with ovarian carcinoma and 8% in non ovarian tumours. Some elevated CA125 levels were observed in the patients with abdominal pain, abdominal extension, uterine fibroid, ovarian cyst, back ache and pelvic mass.

Conclusion CA125 seems to be a reliable marker as its levels were found to be elevated in 92% ovarian tumours.

***Key words**: Ovarian carcinoma, tumour marker, clinical presentations, specificity, reliability, serological tests*

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Introduction

Ovarian cancer is the fourth major cause of death from cancer in women and accounts for the highest mortality rate of all the gynaecological cancers [1]. In spite of hard line treatments like radical surgery, radiotherapy, or chemotherapy, the mortality rate is still very high. It often remains asymptomatic in early stages hence most patients have widespread disease at the time of diagnosis [2]. Only 25% of cancers are detected as stage I disease. When diagnosed in Stage I, however, the cure rate can approach 90% with currently available cytoreductive surgery and combination chemotherapy [3].

The present study deals with investigation of the importance of this marker in ovarian and non-ovarian tumours. Moreover, some patients with no previous diagnosis of tumour but with observed high CA125 levels, were also included in this study. These patients

were categorized separately and their clinical symptoms were assumed to be due to ovarian carcinoma.

Another focus of the study was to look for the symptoms associated with stage I of ovarian carcinoma with the help of CA125 marker. The group with undiagnosed tumour is large enough to be considered further. As the symptoms of ovarian tumour are still unresolved and disease spreads so fast that the life of patients is at a risk. Therefore we planned to determine the symptoms or clinical presentations in the patients which may result in elevated CA125 levels. Although further work is required on the same lines but these clinical presentations may possibly be the initial symptoms of ovarian tumour.

Patients and methods

Patients

The study comprised of 585 subjects including 577 women (98.6%) and 8 men (1.36%) who were referred to the centre for nuclear medicine Lahore for hormonal assessment over a period of 15 months (Jan 2010-Mar 2011).

The patients presented with a variety of clinical problems including ovarian carcinoma, various tumours, uterine fibroid, abdominal mass, ovarian cyst, menstrual problems etc. (Figure 1).

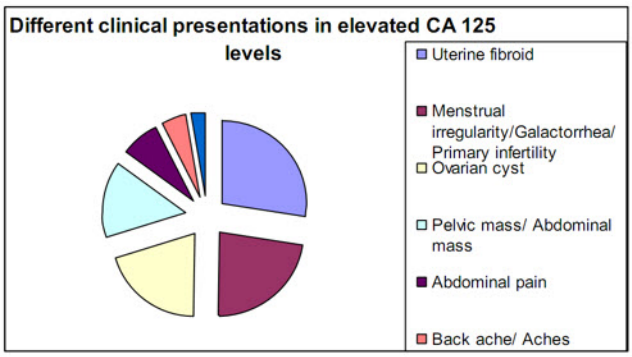

Figure 1 *Different clinical presentations in elevated CA125 levels*

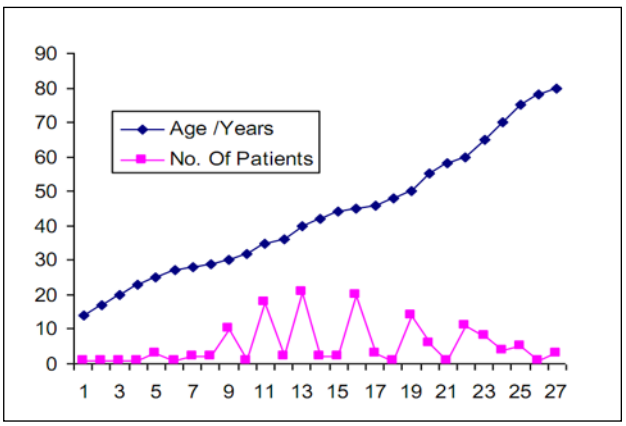

Figure 2 *Age distribution of the patients with ovarian cancer*

The ages of the patients ranged from 9-80 years. (Figure 2). Relevant clinical history was taken from all the patients and recorded. Age, sex and types of disease were observed. The subjects with raised levels were further

Table 1 *Comparison of serum CA 125 levels in subjects (n=150) with ovarian and non-ovarian tumours*

Tumour type	+ve	Percentage	Mean/range in +ve patients (IU/mL)
Ovarian carcinoma	138	92.00	261 (32 to >500)
Ca cervix	1	0.66	36
Tumour uterus	2	1.33	45 (36.8 to 62)
Ca rectum	1	0.66	210
Ca Breast	1	0.66	>500
Liver metastases	8	5.33	355 (31 to >500)

Table 2 *Frequency of selected clinical features in women with high CA125 values (n=40)*

Clinical presentation	Patient numbers	Percentage
Uterine fibroid	11	27.5
Menstrual irregularity, galactorrhoea, primary infertility	9	22.5
Ovarian cyst	8	20
Pelvic/abdominal mass	6	15
Abdominal pain	3	7.5
Backache or aches	2	5
Abdominal distension	1	2.5

Table 3 *Frequency of male patients and associated clinical presentation*

Number of patients	Clinical presentation	Age (years)	CA125 value (IU/ml)	AFP
1	Ca colon	37	6.72	_
1	Testicular tumour	35	14.8	>420
1	Backache	48	8.88	6
1	Abdominal distension	43	189	_
1	Testicular swelling	15	7.72	_
3	Unidentified	52-72	0.94 to 164	3.52

40) comprised of the subjects with complaints other than tumours (table 2). The third category (n = 64) comprised of the subjects of which either sample was brought to the centre or the symptoms/disease was unidentified. A small number (n=8) of male subjects included in the study were also found to have raised CA125 levels (table 3).

Another focus of our study was to look for the symptoms associated with stage I of ovarian carcinoma with the help of CA125 marker.

Methods

The patients' blood samples were transferred to sample tubes with no additives. Serum was separated by centrifugation and aliquots stored at 2-8 °C when the assay was scheduled to be performed within 24 hours CA125 levels were measured using immunoradiometric assay (IRMA) Kit (Immunotech, France). The CA125 antigen assay is a one-step sandwich type assay in which two mouse monoclonal antibodies,

directed against two different epitopes of the molecule, are employed. The assay has no detectable cross reactivity.

The measurement range of the assay is 1-500 IU/mL. Performance of the assay was monitored using one quality control sera (Immunotech, France). The concentration range of CA125 in control sera was 34.5-51.5 IU/mL. The normal range of CA125 in healthy subjects is up to 30 IU/mL.

The assay procedure involves the addition of 100 µL of the sample, calibrators or controls in the antibody coated tubes followed by the addition of 300 µL tracer. The tubes are incubated for 4 hours at 18-25°C while being shaken (400 rpm). The contents of the tubes are then aspirated, washed thrice with wash buffer (2 mL) and then counted for one minute.

The degree of bound radioactivity is directly proportional to the concentration of CA125 in the sample. Standard curve is plotted using cubic spline method. CA125 concentration in the samples is calculated by interpolation from the standard curve.

Results

Out of 585 subjects, 255 (43.6 %) were with raised CA125 values, and remaining 330 subjects had either normal CA125 levels or brought to normal by surgery or medication.

The maximum number of patients in the study (n = 124) ranged in age from 33 to 56 years. Of the 150 diagnosed patients, the majority (n=138) had ovarian carcinoma (92%) with the remaining 8 percent diagnosed with rectal, cervical and uterine cancers and liver metastases (Figures 3 & 4). Two male patients (1.36%) were observed with elevated CA125 levels. The reason in one of them was abdominal distension where as the second one was unidentified. In the group of patients (n=40) without an established diagnosis of tumour but with raised CA125 values, the clinical presentations in decreasing order of frequency were uterine fibroid (27.5%), gynecological symptoms (22.5%) and ovarian cyst (20%) (Table 2).

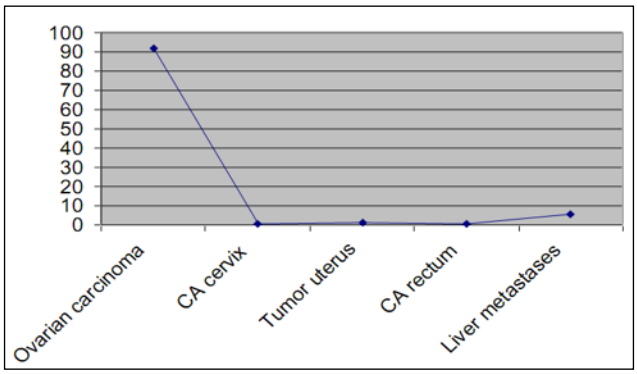

Figure 3 *Tumour types with elevated CA125*

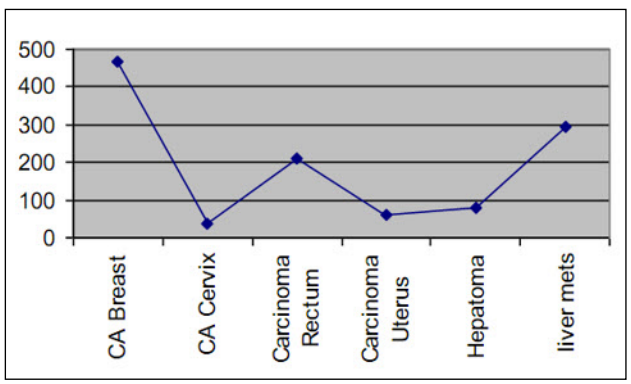

Figure 4 *CA125 values in non-ovarian tumours*

Discussion

Serum CA125 levels were observed to be high in 43.6% of the total subjects. The maximum subjects (47%) with elevated CA125 values were between 33-56 years. Specificity of the marker was found to be 92% in our study. In a similar study carried out in UK the sensitivity and specificity of CA125 was studied. The sera of 58 subjects with histologically proven ovarian carcinomas of all types were examined. Sensitivity of the marker was found to be more than adequate in all types of ovarian carcinomas. Specificity of the marker was however found to be low and CA125 was

cervical and colonic cancers [10]. Berg *et al* determined the role of CA125 in epithelial ovarian cancers and the marker was found to be elevated in 82% of the subjects with the ovarian tumour [11]. The data also suggested that in the patients with no evidence of disease, the false-positive rate of increased CA125 level was low i.e. (1.6%). Out of 449 serum samples, 7 showed increased CA125 values (36-45 IU/mL) without apparent progression. According to them, CA125 appears to be a reliable tumour marker for diagnosing early progression. However, an increase of CA125 levels beyond 35 IU/mL should be followed up after a short period of time. Two consecutive elevated CA125 values strongly suggest progressive disease.

As the symptoms of ovarian tumour are still unresolved and the disease spreads so fast that the life of patients is at a risk, we therefore planned to determine the symptoms or clinical presentations in the patients which may result in elevated CA125 levels. Although further work is required on the same lines, it can be surmised that these clinical presentations may possibly be the initial symptoms of ovarian tumour.

Penelope *et al* [12] investigated the symptoms associated with ovarian cancer and found that 16% of women with borderline tumours, 7% with early cancer and 4% with advanced cancer, experienced no symptoms before diagnosis. Among women with symptoms, abdominal pain (44%) or swelling (39%) were most frequently reported; an abdominal mass (12%) and gynecological symptoms (12%) were less common. Compared to advanced stage cancer, women with early stage cancer were more likely to report an abdominal mass or urinary symptoms but less likely to report gastrointestinal problems or general malaise. Elevated CA125 levels in postmenopausal women with suspected pelvic mass raises the possibility of ovarian cancer [13]. In our study 15% of the patients with raised CA125 levels had pelvic mass too, which makes them at higher risk of developing ovarian carcinoma.

Another aspect of the study was to observe the symptoms amongst the subjects having raised CA125 values but no diagnosed tumours This group of 40 subjects comprises fo 16% (40/255) of our study population. Most common symptoms observed in this group were uterine fibroid, ovarian cyst, abdominal pain and backache or aches. Primary infertility, menstrual irregularity and galactorrhea have also been observed in this group, although these clinical conditions are suggestive of high prolactin levels rather than elevated CA125.

Nonetheless, there is a strong possibility that these subjects may have stage I ovarian carcinoma. This possibility must be ruled out by employing radiological diagnostic tools and follow up measurement of CA125 levels.

Conclusions

CA125 seems to be reliable tumour marker for diagnostic purpose in ovarian carcinoma. It is found to be specific in the disease. Uterine fibroid, menstrual problems, pelvic mass, ovarian cyst and abdominal distension or pain have appeared as the most common features among the subjects with elevated CA125 levels without any diagnosed tumour. These clinical presentations must be investigated further to detect or rule out the disease.

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 21-0288(201201/01)1:1<27:ICPTOC>2.0.TX;2-M