

Serum CA 125 is a Biomarker of Tuberculous Peritonitis and its Inflammatory Severity in Female Patients

Khan A*, Haider I, Ayub M and Tahir AA

Department of Medicine, Khyber Teaching Hospital (KTH), Peshawar, Pakistan

*Corresponding author: Khan A, Department of Medicine, Khyber Teaching Hospital, Peshawar-25000, Pakistan, Tel: 923335039009; E-mail: dr.abidk@yahoo.com

Received date: November 28, 2016; Accepted date: December 12, 2016; Published date: December 23, 2016

Copyright: © 2016 Khan A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Background: The tumor marker CA 125 is commonly used in the screening and diagnosis of ovarian malignancy. However, recent studies have proven a limited role for CA 125 as a diagnostic marker for ovarian cancer. Moreover, it is often elevated in non-cancerous and inflammatory conditions as well.

Aims: To evaluate the utility of CA 125 in the workup of intestinal tuberculosis/ tuberculous peritonitis in female patients.

Methods: In this observational study, patients with ascites were divided into two groups; tuberculous (group A), and non-tuberculous (group B). Each group had serum CA 125 measured and compared using independent sample t-test. CA 125 was correlated with ESR by using Pearson's correlation test.

Results: CA 125 was higher in patients with tuberculous peritonitis. (N=20, M=117.75, SD=35.95), than in patients without tuberculous peritonitis, (N=20, M=49.65, SD=25.28). The difference between the two groups was statistically significant, $t(38)=6.93$, $p<0.001$, Cohen's $D=2.20$. Furthermore, CA 125 correlated positively with ESR, $r=0.73$, $p<0.001$.

Conclusion: Tuberculous peritonitis must be considered in the differential diagnoses of patients with elevated CA 125 levels. Moreover, CA 125 correlates with the severity of peritonitis.

Keywords: Tuberculosis; Peritonitis; Ascites; CA 125; Gynecologic malignancy; Tumor markers

Abbreviations: KTH: Khyber Teaching Hospital; ESR: Erythrocyte Sedimentation Rate; PID: Pelvic Inflammatory Disease; PCR: Polymerase Chain Reaction; MTB: Mycobacterium Tuberculosis

Background

Carbohydrate antigen 125 (CA 125) has been in the clinical practice for years, and is often measured as an indicator of ovarian malignancy. However, the popularity of CA 125 in the diagnosis of ovarian cancer has rapidly declined [1-3]. This is because, CA 125 is often elevated in a variety of other non-ovarian conditions namely; pregnancy, endometriosis, pelvic inflammatory disease (PID) and so forth. Moreover, a number of researchers observed that CA 125 was not elevated in most primary ovarian mucinous neoplasms. Because of the non-specificity of CA 125 in truly predicting ovarian cancer, many gynecologists and oncologists recommend the use of CA19-9 as a preoperative marker in the workup of an ovarian mass, but the evidence is still scarce [3-8].

Mycobacterium tuberculosis is endemic in Pakistan. As tuberculous peritonitis manifests in the form of ascites, abdominal pain, abdominal mass and elevation of serum CA-125, it can be easily confused with ovarian malignancies [9].

Considering the latest research trend regarding the examination of CA 125 in non-cancerous conditions, we conducted this study to evaluate the role of serum CA 125 in the diagnosis of tuberculous peritonitis in female patients presenting with ascites.

Material and Methods

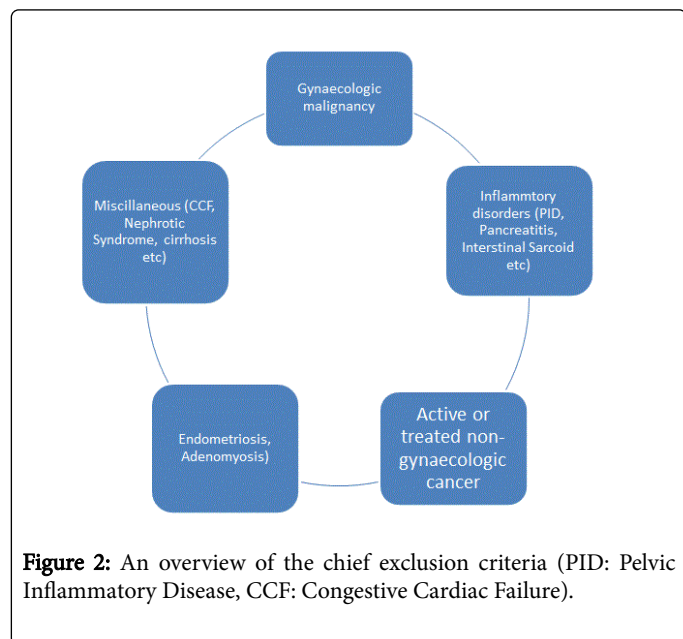
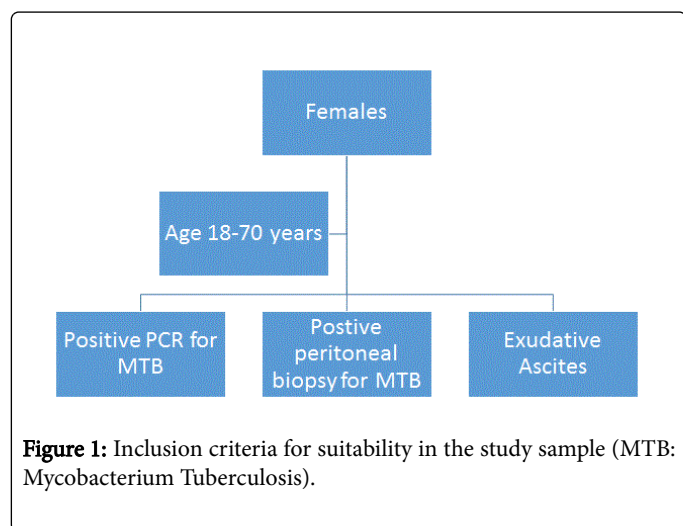
This cross sectional study was conducted on 40 patients, aging 18-70 years, in the departments of medicine, surgery, and obstetrics and gynecology, of Khyber Teaching Hospital Peshawar, Pakistan, between January and October 2016. The study was approved by the ethics review committee of our hospital and informed written consent was obtained from every participant.

The study design was prospective and observational. The inclusion criteria included; 1) female patients, 2) age limit 18-70 years, 3) positive ascitic fluid polymerase chain reaction (PCR) for mycobacterium tuberculosis (MTB) or peritoneal biopsy proven tuberculous peritonitis 4) patients with clinically or radio-logically apparent ascites.

All the patients, who did not fulfill the above criteria, were excluded from the study. Similarly, those with suspected or confirmed gynecologic malignancy, pelvic inflammatory disease (PID), endometriosis, adenomyosis, endometrial thickening on trans-vaginal ultrasound, and vulval mass lesions were excluded. Furthermore, patients with suspicion of any neoplastic or non-neoplastic pancreatic lesions, gut malignancy, inflammatory bowel disease, liver cirrhosis,

congestive cardiac failure, sarcoidosis and so forth were also excluded from the study.

All the patients, who fulfilled the inclusion criteria, were worked up with detailed clinical evaluation and relevant investigations, in order to assess their suitability for inclusion in the final study. A total of 150 patients were assessed initially; however, only 40 satisfied the strict inclusion/exclusion criteria, and were thus, the final subjects of the study (Figures 1 and 2).



On the basis of histopathology reports of the peritoneal biopsy or PCR for MTB, the finally suitable 40 patients were divided into two equal groups; group A included 20 patients with proven tuberculous peritonitis, and group B had another 20 patients with tuberculous peritonitis excluded.

All the data was collected on a structured questionnaire; specifically, designed for this purpose. The questionnaire had a combination of closed and open ended questions, and included information regarding demography, clinical findings, histopathology report, ESR and CA 125 levels.

All the data was stored and analyzed by SPSS version 16. Percentages and frequencies were determined for qualitative variables like ethnic background, marital status and so forth. Means and standard deviations were measured for quantitative variable like age, parity, CA 125, ESR and so forth. Finally, independent sample t-test was run to compare the means of CA 125 in the two groups. Pearson's test was used to assess any relationship between CA 125 and ESR.

Results

The descriptive statistics of patients with tuberculous peritonitis and those otherwise, are given below (Tables 1 and 2). Of all the participants, only 83% were married. Furthermore, 85% of the participants were from Pakistan and the rest of Afghan origin (Tables 1 and 2).

Variables	Mean	Standard Deviation
CA 125 (IU/L)	118	35.95
Age (years)	45.25	6.35
Parity	2.75	1.92
ESR	58.7	12.1
Ascitic fluid protein content (gm/dl)	3.32	0.62
Ascitic fluid neutrophil count (per ml)	168.7	23.27

Table 1: Descriptive statistics of the study variables in patients with tuberculous peritonitis.

Variables	Mean	Standard Deviation
CA 125 (IU/L)	49.65	25.288
Age (years)	46.4	6.344
Parity	3.4	1.729
ESR	21.2	5.854
Ascitic fluid protein content (gm/dl)	1.7	0.657
Ascitic fluid neutrophil count (per ml)	218.7	13.554

Table 2: Descriptive statistics of the study variables in patients without tuberculous peritonitis.

As can be seen, the mean value of CA 125 was higher in patients with tuberculous peritonitis; group A, (N=20, M=117.75, SD=35.95), than in patients without tuberculous peritonitis; group B, (N=20, M=49.65, SD=25.28).

In order to compare the means of the two study groups, an independent sample t-test was run. The assumption of normality was tested and was found tenable (skewness=0.12, kurtosis=1.17). Similarly, the assumption of homogeneity of variance was not violated, levene statistic (F)=1.12, P=0.29. The results of independent sample t-test revealed that CA 125 levels were different amongst the two groups at a statistically significant level, t (38)=6.93, p<0.001, Cohen's D=2.20. Thus it can be concluded that, there is enough evidence to suggest that, CA 125 levels are higher in patients with tuberculous peritonitis, and can therefore, be used in the diagnostic workup of suspected tuberculous peritonitis.

The erythrocyte sedimentation rate (ESR), was higher in patients with tuberculous peritonitis (N=20, M=58.70, SD=12.10), than those without a diagnosis of tuberculous peritonitis, (N=20, M=21.20, SD=5.85). Similarly, ESR was higher in patients with massive and clinically obvious ascites (N=23, M=55, SD=10.36), than those with clinically occult, but radio-logically detectable ascites (N=17, M=36, SD=5.23).

Finally CA 125 was correlated with ESR by using Pearson's correlation test. The results showed a statistically significant, positive correlation between CA 125 and ESR, $r=0.73$, $p<0.001$. Thus it can be concluded that, CA 125 will be higher in patients with high ESR and vice versa. Considering this data, CA 125 can be used as an independent marker of the severity of inflammation in patients with tuberculous peritonitis.

Discussion

In our study, we observed that, tuberculous peritonitis can potentially elevate serum CA 125 level. This is particularly true of those with increasing or clinically obvious ascites. Moreover, we found a significant positive relationship between ESR and CA 125. Having said that, CA 125 can alone predict the severity of inflammatory damage within the peritoneum.

Blood CA-125 level is often high in patients with epithelial ovarian cancer; it is therefore useful in the diagnosis and surveillance of treatment responses. However, CA 125 has several limitations. Firstly, the sensitivity and specificity of CA 125 in ovarian cancer has recently been questioned. Secondly, it has been shown to be elevated in other benign conditions like peritonitis [4,5]. Considering these data, many researchers have put their energy to surface new tumor markers for the better screening and monitoring of ovarian cancer. As is known that, CA 125 can be elevated in peritonitis, we conducted this study to evaluate the role of CA 125 in the workup of ascites, resulting from tuberculous peritonitis.

Generally, in clinical practice, in a female patient with ascites and elevated blood CA-125, the first impression is usually that of an advanced ovarian cancer. However, some recent studies demonstrated raised CA 125 levels in patients with tuberculous peritonitis [8,9]. It has been suggested that the proportion of high CA 125 levels in those with tuberculous peritonitis may depend on the prevalence of tuberculosis in a given community. This is particularly true of countries with higher rates of acquired immunodeficiency syndrome. Therefore, it is crucial to differentiate ovarian cancer from tuberculous peritonitis [9-11]. This is important because, tuberculous peritonitis is more treatable than advanced ovarian cancer [10-12]. Previous studies have demonstrated that, the probability of ovarian malignancy increases when CA 125 exceeds 1000 IU/L. However, tuberculous peritonitis must always be considered as a potential differential diagnosis in patients with CA 125 level below 1000 IU/L. Although, we did not check the cutoff value for CA 125 at which, it can truly differentiate between ovarian cancer and tuberculous peritonitis; generally speaking, our study is consistent with these studies, as CA 125 levels were higher at a statistically significant level in patients with tuberculous peritonitis [13-16].

It has been established that the most common symptoms of tuberculous peritonitis are abdominal pain, ascites and/or abdominal mass. It is noteworthy that, such symptoms can be the initial presentation of ovarian cancer. Depending upon the clinical features and radiological evaluations, up to two-third of tuberculous peritonitis

patients can be mistaken for ovarian malignancy and peritonitis carcinomatosis [17,18]. Although, we excluded patients with ovarian mass lesions from our study, all the patients included in the study had clinically detectable ascites and CA 125 was much raised in patients with tuberculous peritonitis than those without it.

ESR is marker of inflammation and has a prognostic significance. In our study, CA 125 correlated with ESR. It must be noted that ESR was higher in those with massive ascites and in those with exudative picture. Considering the fact that, CA 125 had a strong positive correlation with ESR; CA 125 can be used as an independent predictor of the severity of tuberculous peritonitis.

Despite its usefulness, our study had few limitations. Firstly, the sample size was smaller. Secondly, cultures for MTB were not taken. We therefore recommend further studies in this regard, and would advocate bigger sample sizes, in order to arrive at a more logical conclusion.

Conclusion

In summary, the probability of tuberculous peritonitis must always be considered in the differential diagnoses of patients with ascites and elevated serum CA 125 level. Furthermore, CA 125 alone can be used as an effective marker of the severity of peritoneal inflammation.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Review Committee of Khyber Teaching Hospital/Khyber Medical College, Peshawar, Pakistan. An informed written consent was obtained from every participant of this study.

Availability of Data and Material

The supporting data can be presented to researchers and the Editor-in-chief of this journal on request.

Competing Interests

The authors declare no conflict of interest regarding the publication of this manuscript.

Authors' contributions

AK, MA, IH and AAT conceived the idea and formulated the study design. All the authors collected the data and helped in analyzing it. All the authors contributed to the drafting of this manuscript. All the authors approved the final version before submission.

Acknowledgements

We are thankful to the laboratory service of our hospital for their help. We are grateful to all the participants included in the study.

References

1. Cho H, Kyung MS (2014) Serum CA19-9 as a Predictor of Malignancy in Primary Ovarian Mucinous Tumors: A Matched Case-Control Study. *Med Sci Monit* 20: 1334-1339.
2. Rosen DG, Wang L, Atkinson JN (2005) Potential markers that complement expression of CA125 in epithelial ovarian cancer. *Gynecol Oncol* 99: 267-277.

3. Hart WR (2005) Mucinous tumors of the ovary: a review. *Int J Gynecol Pathol* 24: 4-25.
4. Nossov V, Amneus M, Su F, Lang J, Janco JM, et al. (2008) The early detection of ovarian cancer: from traditional methods to proteomics. Can we really do better than serum CA-125? *Am J Obstet Gynecol* 199: 215-223.
5. Ozasa H, Noda Y, Mori T (1987) Progesterone increases serum CA-125 in endometriosis. *Fertil Steril* 47: 699-701.
6. Halila H, Stenman UH, Seppala M (1986) Ovarian cancer antigen CA 125 levels in pelvic inflammatory disease and pregnancy. *Cancer* 57: 1327-1329.
7. Niloff JM, Klug TL, Schaetzl E, Zurawski VR, Knapp RC, et al. (1984) Elevation of serum CA125 in carcinomas of the fallopian tube, endometrium, and endocervix. *Am J Obstet Gynecol* 148: 1057-1058.
8. Molina R, Filella X, Bruix J, Mengual P, Bosch J, et al. (1991) Cancer antigen 125 in serum and ascitic fluid of patients with liver diseases. *Clin Chem* 37: 1379-1383.
9. Bae SY, Lee JH, Park JY (2013) Clinical significance of serum ca-125 in korean females with ascites. *Yonsei Medical Journal* 54: 1241-1247.
10. Runyon BA, Montano AA, Akriviadis EA, Antillon MR, Irving MA, et al. (1992) The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. *Ann Intern Med* 117: 215-220.
11. Hwangbo Y, Jung JH, Shim J, Kim BH, Jung SH, et al. (2007) Etiologic and laboratory analyses of ascites in patients who underwent diagnostic paracentesis *Korean J Hepatol* 13: 185-195.
12. Bilgin T, Karabay A, Dolar E, Develiogu OH (2001) Peritoneal tuberculosis with pelvic abdominal mass, ascites and elevated CA 125 mimicking advanced ovarian carcinoma: a series of 10 cases. *Int J Gynecol Cancer* 11: 290-294.
13. Vardareli E, Kebapci M, Saricam T, Pasaoglu O, Acikalin M (2004) Tuberculous peritonitis of the wet ascitic type: clinical features and diagnostic value of image-guided peritoneal biopsy. *Dig Liver Dis* 36: 199-204.
14. Nistal F, Fernández B, Simón R, Pérez E, Nistal C, et al. (1996) Pelvic-peritoneal tuberculosis simulating ovarian carcinoma: report of three cases with elevation of the CA 125. *Am J Gastroenterol* 91: 1660-1661.
15. Panoskaltis TA, Moore DA, Haidopoulos DA, McIndoe AG (2000) Tuberculous peritonitis: part of the differential diagnosis in ovarian cancer. *Am J Obstet Gynecol* 182: 740-742.
16. Candocia SA, Locker GY (1993) Elevated serum CA 125 secondary to tuberculous peritonitis. *Cancer* 72: 2016-2018.
17. Jakubowski A, Elwood RK, Enarson DA (1988) Clinical features of abdominal tuberculosis. *J Infect Dis* 158: 687-692.
18. Tanrikulu AC, Aldemir M, Gurkan F, Suner A, Dagli CE, et al. (2005) Clinical review of tuberculous peritonitis in 39 patients in Diyarbakir, Turkey. *J Gastroenterol Hepatol* 20: 906-909.