

Very High CA125 due to Non-neoplastic Lesion of Ovary

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High CA-125 levels have been strongly associated with ovarian malignancy. But due to nonspecific nature of this tumor marker it has been found to be raised to high levels above 1000u/ml even in some non neoplastic conditions which have to be kept in mind. A young woman was found to have very high Ca125 levels of 3500u/ml after rupture of endometrioma. Endometrioma, pelvic inflammatory disease, abdominal tuberculosis are some of the nonneoplastic conditions associated with very high levels of Ca125.

Key words: CA-125, endometrioma, ovarian malignancy, pelvic inflammatory disease

INTRODUCTION

CA-125 is a high molecular weight glycoprotein that is expressed by tissues derived from celomic epithelial and mullerian tissues. Therefore it can be produced by a wide variety of conditions both gynecological and nongynecological, benign and malignant lesions, nonneoplastic conditions and in physiologic states also. CA-125 level < 35 u/ml is considered as normal.¹ CA-125 was first described by Bast and colleagues in 1981 and found the over expression of this antigen in ovarian malignancy cases.² Since then CA-125 has been associated with ovarian malignancy and raised levels were synonymously linked to ovarian malignancy.³ But with time the nature of this tumor marker has been exposed and it has been found to be associated with a variety of conditions, some of which are of non-neoplastic nature. This fact is well exemplified by a case described below.

A 21 year old primipara with last childbirth 10 years back, was admitted from emergency with severe pain abdomen and abnormal vaginal bleeding. She gave history of having

cystic ovary of 6x6cm for last one year for which she had taken Danazol for 5 months with no change in size of mass. There was no associated history of vomiting, fever, decreased appetite and weight loss. Bladder and bowel functions were essentially normal. Examination revealed a 6x8cm, fixed, firm to cystic, tender mass in the pelvis not separable from uterus. Urine pregnancy test was negative. Ultrasonogram showed bilateral mass with septations in right mass. No solid component or calcification was noted. Serum CA-125 level was 1250 u/ml which was repeated in another lab and it was 3500 u/ml. CT scan confirmed bilateral complex masses. Uterus was normal, upper abdominal scan was normal with no ascites or lymphadenopathy. With provisional diagnosis of endometrioma or ovarian malignancy, she underwent laparotomy. Intra-operative findings showed the omentum discoloured with blackish hue, dark brownish staining also over the uterus, uterovesical fold and anterior abdominal wall and bilateral chocolate cysts (right 6x8cm and left 4x6cm) were present with small rent sealed by old clot in the left cyst. Dense adhesion was present between the mass, pouch of Douglas and uterus.

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She underwent right salpingo-oophorectomy and left cystectomy with conservation of normal ovarian tissue. Cut section of the cyst revealed chocolate colored thick fluid. Histopathological examination confirmed bilateral endometriosis.

So we must be aware of the fact that raised CA-125 is not specific for malignancy and even non-neoplastic lesions of ovary can give rise to highly raised CA-125 to even above 1000u/ml. The very high level of CA-125 can be attributed to the intense peritoneal irritation caused by leakage of endometriotic content from the cyst.

Raised levels of CA-125 are found in 1% of normal women.

Table 1. Conditions associated with high levels of CA-125^{4,5}

Physiological	Menstruation, pregnancy
Non neoplastic :	
i) Gynecological	Endometriosis, adenomyosis, fibroid, pelvic inflammatory disease, ovarian hyperstimulation syndrome
ii) Non- gynecological	Infective peritonitis, ascites, cirrhosis, pancreatitis, uremia and renal failure, abdominal tuberculosis, nephrotic syndrome, fulminant hepatic failure
Neoplastic	
i) Gynecological	
• Benign	Benign ovarian tumors, fibroma (Meig's syndrome)
• Malignant	Ovarian cancer, endometrial cancer, fallopian tube cancer, primary peritoneal cancer
ii) Non -gynecological	Pancreatic cancer, stomach cancer, colon cancer, rectal cancer, bladder cancer, lymphoma with peritoneal involvement, advanced hepatocellular cancer

The association of raised CA-125 with ovarian malignancy is well known and levels above 35u/ml are considered as abnormal. Very high levels above 1000u/ml are essentially associated with malignant disease which is usually disseminated type or those associated with ascites and gross papillary lesions in the abdomen and pelvis. Even among ovarian tumors it is the serous type in which high

levels of CA-125 are more commonly seen. The specificity of CA-125 for ovarian cancer increases with concentrations >1000u/ml.⁶ But there are various non-malignant gynecological lesions that can also be associated with high CA-125 levels.^{4,5,7} A study done in Women's Hospital in China found that not only malignant epithelial ovarian tumor but also non-malignant gynecological diseases were also associated with CA-125 >1000 u/ml especially in the reproductive age patients with complaints of acute abdomen or abnormal vaginal bleeding. Among the non-malignant gynecological diseases endometriosis was found in 44% of the cases.⁷ Another study in Tehran also found very high CA-125, > 1000u/ml in cases of uterine myoma and endometrioma. Due to the high CA-125 levels, these cases were provisionally thought to be leiomyosarcoma and ovarian cancer respectively before surgery.⁸ The highest level of CA-125 recorded for non-neoplastic ovarian lesion is 7900u/ml in a case of unruptured endometrioma with stage IV endometriosis. So the high CA-125 level in this case was due to the extensive endometriosis and adhesions.⁹ Such high levels i.e. 7988u/ml have also been seen in non-gynecological conditions like disseminated abdominal tuberculosis.¹⁰

Serum CA-125 concentration is seldom > 100u/ml in endometriosis.¹¹ But there are many case reports of very high CA-125 levels in endometriosis. Both ruptured and unruptured endometriomas can be associated with high CA-125 levels.^{9,11,12}

Shiau and colleagues narrate a case of unilateral endometrioma with high CA-125 level associated with abnormally high serum CA-125 level (> 6000 u/ml) and after excision of the ovarian tumor, the CA-125 levels returned to normal.¹¹ Highest levels of 7900u/ml were seen in endometriosis with disseminated stage IV endometriosis.⁹ Also endometriosis involving uterine serosa and those associated with other conditions like fibroids and adenomyosis can also be associated with very high levels. The consequent inflammation of peritoneal surfaces in such cases is probably responsible for the very high levels of CA-125. Therefore in endometriosis it seems that rupture of endometrioma or disseminated endometriosis with extensive peritoneal implants is associated with very high levels of CA-125.^{9,12} CA-125 serum levels are thus found to be related to endometriosis and R-AFS score but not with symptoms of pelvic pain in patients with endometriosis. There could be consequences of such high levels of CA-125 in endometriosis as there are reports of clear cell carcinoma on follow up of women who had only endometriosis initially with CA-125 >1000u/ml.¹³ Therefore it is very important to rule out Endometriosis Associated Ovarian Cancer (EAOC) in these cases and removal of both ovaries, especially if family completed, could be options. Prolonged follow up will also be needed in these cases.

CONCLUSIONS

High levels of CA-125 over 1,000 u/ml, may be found in endometriosis and especially so in cases of ruptured endometrioma and advanced stage. The suspicion of malignancy in reproductive age group women with adnexal mass, therefore should not be based only on CA-125 levels and such non-neoplastic conditions should always be kept in mind .

REFERENCES

1. Bast RC Jr, Klug TL, St John E, Jenison E, Niloff JM, Lazarus H, Berkowitz RS, Leavitt T, Griffiths CT, Parker L, Zurawski VR Jr, Knapp RC: A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. *N Engl J Med.*1983;309:883-7.
2. Bast RC Jr, Feeney M, Lazarus H et al. Reactivity of a monoclonal antibody with human ovarian carcinoma. *J Clin Invest*1981;68:1331-37.
3. Hogdall E. Cancer antigen 125 and prognosis. *Curr Opin Obstet Gynecol.* 2008;20:4-8.
4. Alper S, Mustafa A , Mehmet EK , Celalettin C. Benign causes of increased serum CA-125 concentration. *The Lancet Oncology.* 2007;12:1054–55
5. Haga Y, Sakamoto K, Egami H. Evaluation of serum CA-125 values in healthy individuals and pregnant women. *Am J Med Sci.*1986;292:25–9.
6. Moss EL, Hollingworth J, Reynolds TM. The role of CA-125 in clinical practice. *Clin Pathol.* 2005;58:308-12
7. He RH, Yao WM, Wu LY, Mao YY. Highly elevated serum CA-125 levels in patients with non-malignant gynecological diseases. *Arch Gynecol Obstet.* 2011;283Suppl 1:107-10.
8. Ghaemmaghami F, Karimi ZM, Hamed B. High levels of CA-125 (over 1,000 IU/ml) in patients with gynecologic disease and non malignant conditions: three cases and literature review. *Int J Gynecol Cancer.* 2006 ;16Suppl 1:315-8.
9. Kahraman K, Ozguven I, Gungor M, Atabekoglu CS. Extremely elevated serum CA-125 level as a result of unruptured unilateral endometrioma: the highest value reported. *Clin Exp Obstet Gynecol.* 2008;35(3):231-2.
10. M. Afzal Ud Din. Tuberculosis resembling a malignant tumor. *S Afr J Sci.* 2009;47: 31
11. Shiau CS, Chang MY, Chiang CH, Hsieh CC, Hsieh TT. Ovarian endometrioma associated with very high serum CA-125 levels. *J Med Assoc Thai.* 2004;87(9):1108-11.
12. Uharcek P, Mlyncek M, Ravinger J. Elevation of serum CA 125 and D-dimer levels associated with rupture of ovarian endometrioma. *Int J Biol Markers.* 2007;22(3):203-5
13. Check JH, Check ML, Kiefer D, Aikins J Jr. Ovarian cancer in a woman previously diagnosed with endometriosis and an extremely high serum CA-125 level. *Clin Exp Obstet Gynecol.* 2001;28(2):83-5.