Ovarian Endometrioma Associated with Very High Serum CA-125 Levels

Chii-Shinn Shiau, MD; Ming-Yang Chang, MD; Chi-Hsin Chiang, MD; Ching-Chang Hsieh, MD; T'sang-T'ang Hsieh, MD

CA-125 is a 220-kD cell surface glycoprotein present in over 80% of non-mucinous epithelial ovarian carcinomas and it occurs in the serum of healthy males and females at low concentrations (< 35 U/mL). Serum CA-125 concentration may also be moderately elevated in several benign conditions, such as pelvic inflammatory disease, uterine fibroids, pregnancy, spontaneous abortion with chromosomal abnormality, and especially in endometriosis. However, serum CA-125 concentration is seldom > 100 IU/ml in endometriosis. In this paper, we present a patient with unilateral ovarian endometrioma 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. Our case further emphasizes the association of high levels of CA-125 with benign gynecologic conditions and we discussed the possible explanations for this abnormal elevation of CA-125 levels. *(Chang Gung Med J 2003;26:695-9)*

Key words: **endometrioma, CA-125.**

In 1981, the antigen CA-125 was identified by Bast et al.[1] through the use of monoclonal antibodies raised against cells derived from the ovarian cancer cell line OVAL 433 and was proposed as a specific marker of ovarian carcinoma. CA-125 is a high molecular weight antigenic determinant expressed on the surface of the coelomic epithelium, including the epithelium of the endocervix, endometrium, fallopian tube, pelvic peritoneum, and placental tissues. Serum CA-125 concentration may also be moderately elevated in patients with advanced endometrial and cervical adenocarcinomas and several benign conditions such as pelvic inflammatory disease, uterine fibroids, and especially endometriosis.[2,3] Several authors[4-6] specifically investigated the presence of high values of tumor markers in patients with benign diseases, usually associated with only slightly increased levels of the marker. Serum CA-125 measurements >65 U/mL were associated with nonmalignant conditions in 13% of patients and endometriosis was the most common benign condition associated with serum CA-125 > 65 U/mL in patients with benign gynecologic conditions.[7]

We present a patient with moderate sized unilateral ovarian endometrioma who was undergoing laparotomy and who had CA-125 levels > 6000 U/mL. Our case further emphasizes that very high levels of CA-125 are not always associated with malignant disease and no critical cutoff value for CA-125 is diagnostic of malignancy.

CASE REPORT

A 30-year-old woman (gravida 0, para 0) was admitted to our hospital on June 25, 1999 because of a palpable abdominal mass noted by herself occasionally for 2 weeks. Her menarche was at 12 years old and her last menstrual period was June 15, 1999.

From the Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Taipei.
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Address for reprints: Dr. T'sang-T'ang Hsieh, Department of Obstetric and Gynecology, Chang Gung Memorial Hospital. 199, Duenhua N. Road, Sungshan Chiu, Taipei, Taiwan 105, R.O.C. Tel.: 886-2-27135211 ext. 3345; Fax: 886-2-25147643

The patient's medical history was unremarkable except for one episode of sudden onset of left lower abdominal pain without fever and nausea 3 days before she came to our hospital. The pelvic pain resolved spontaneously 15 minutes later after complete bed rest. Her menstrual cycle was regular and a mild degree of dysmenorrhea was noted since her puberty. The transvaginal sonography revealed a normal uterus an normal right adnexa. The left adnexal area had a mean diameter of 75 mm and consisted of round fine homogenous hypoechoic 'tissue' of low-level echoes within the ovary. Color Doppler sonographic examination showed the typical pericystic blood flow signal and blood flow impedance of capsular artery showed pulsatility index, PI = 1.04; resistance index, RI = 0.76. The ultrasonographic picture suggested the diagnosis of ovarian endometrioma. Computed tomography (CT) scan of the lower abdomen revealed a normal sized uterus and a 7×6 cm unilocular cystic tumor on the left adnexal area without ascites, which favored a benign ovarian cystic tumor.

The physical examination revealed the patient to be in minimal distress with stable vital signs. Bimanual pelvic examination revealed a normal sized uterus and a mobile, elastic goose-egg-sized adnexal mass with a smooth surface that fit in the cul-de-sac completely. On admission, her general condition was assessed by measuring pulse rate (95/min), temperature (36.5 ˚C), and blood pressure (120/85 mmHg). Hematocrit, electrolyte, plasma proteins, complete blood count, and creatinine clearance were also recorded during hospitalization. Laboratory data showed normal biochemical parameters and complete blood count. Laboratory evaluation taken on the ninth day of the menstrual phase was significant because the serum CA-125 level was 6310 U/ml (reference range below 35 U/ml), alpha-fetoprotein (AFP) level was 5 ng/ml (reference range below 20 ng/ml), and carcinoembryonic antigen (CEA) level was 0.3 ng/ml (reference range below 5 ng/ml).

The high CA-125 concentration raised the suggestion of an ovarian malignancy and the patient was scheduled for explorative laparotomy in July 1999. At laparotomy, the uterus was normal and there was a large ovarian cystic mass that measured 7×8 cm on the left side without rupture. No other adhesions were seen in the cul-de-sac or around the left ovarian cystic tumor and the left ovarian tumor was easily taken out from the pelvic cavity to the outside of the incision wound. The left ovary was free from the uterus and the cul-de-sac with thick chocolate-colored fluid-filled cyst. The cystic tumor was opened and the cyst lining of the left ovary was excised and the remaining normally appeared ovarian tissue was approximated. The fallopian tubes bilaterally looked normal with health-appearing fimbria. Some endometriotic implants were disseminated on the sigmoid, parietal peritoneum, vesicouterine fold and pouch of Douglas, and scattered endometriotic foci were also seen on the surface of the left ovarian tumor. The diagnosis was stage IV endometriosis according to the revised American Fertility Society (rAFS) classification. The histology report confirmed the diagnosis of endometrioma. The postoperative course was unremarkable and serum CA-125 levels decreased to 21 U/ml 3 weeks after operation.

DISCUSSION

In 1981, CA-125 was identified as an ovarian cancer antigen and was investigated as a specific marker of ovarian malignancy.[1] The reference value of 35 U/mL was based on the pioneering work by Bast at al.,[1] who reported that only 1 % of apparently healthy women and 6.3% of women with benign disease had values above that level. Levels of CA-125 > 65 U/mL correlate highly with ovarian malignancy and distinguish malignant from benign disease with a specificity of 88 to 92% and a sensitivity of 75% to 83%.[4,5] Plasma CA-125 > 194 U/mL is considered a positive criterion for differentiating malignant pelvic masses from benign pelvic masses.[6] It is generally believed that the greater the CA-125 value, the greater the probability that an abdominopelvic mass is malignant. We described a woman with an ovarian endometrioma associated with an extremely high serum CA-125 concentration usually typical of malignant ovarian tumor.

In addition, plasma CA-125 concentration is known to be elevated in a variety of benign conditions, especially in premenopausal patients. Increased plasma levels of CA-125 can also be found in several benign conditions such as superficial and deep endometriosis, adenomyosis, pelvic inflammatory disease, and uterine fibroids or physiological conditions such as menstruation and early

pregnancy.[2] The most common benign gynecologic conditions associated with elevated serum CA-125 concentrations in patients appear to be caused by ovarian endometriomas and deeply infiltrating endometriosis, especially in the more severe forms (revised American Fertility Society classification, classes III and IV). In one study, 79% of patients with endometriomas had CA-125 levels > 35 U/ml.[6]

During the normal menstrual cycle, the eutopic endometrium is the major source of CA-125 production and secretion into the lumina of the glands and the blood vessels. During menstruation, high levels of CA-125 are found in the plasma concentrations probably due to resorption by the damaged endometrial vascular bed.[8,9] As we know, endometriotic cyst fluids contain very high concentrations of CA-125 but the thick walls of the endometriotic cyst prevents the large CA-125 glycoprotein molecules from reaching the peripheral circulation, although the block is not total.[10] In general, plasma CA-125 concentrations reflect the endometrial production, the volume of the ovarian endometriotic cysts, and the volume of the deeply infiltrating endometriotic nodules.

Patients with endometriosis rarely have a CA-125 concentration > 100 IU/ml.[11] The mechanisms by which endometriosis may elevate serum CA-125 concentrations are only partly understood, and may be caused by many reasons. As for the mechanisms of the presence of very high levels of serum CA-125, it must be taken into consideration that sudden spontaneous untwisting of partial ovarian torsion can either damage the ovarian peritoneum or augment the release of cellular antigens from damaged cells of the cyst. Although, the definite proof of torsion-detorsion of the ovarian tumor was impossible to obtain by visual examination, the possibility of the extreme elevation of CA-125 plasma levels in patients with benign adnexal masses correlated with episodes of partial ovarian torsion with subsequent detorsion can not be ruled out. There is evidence that peritoneal mesothelial cells are even more potent than ovarian cancer cells in producing CA-125.[12] Some of the CA-125 molecules leaking from the endometriotic cyst may be transferred through the peritoneum and the associated inflammatory reaction of the mesothelial cells of the peritoneum was probably the most important contributor to the presence of very high level of serum CA-125. In addition, superficial endomertiotic implants of the ovarian endometriomas mainly secret towards the peritoneal cavity from where CA-125 is slowly resorbed through the peritoneum. An explosive rise of serum CA-125 of up to 9300 IU/ ml following the rupture of ovarian endometrioma has been reported[13] and the sudden release of endometriotic cyst fluids containing very high concentrations of CA-125 combined with pelvic peritoneal irritation may contribute to the unusual rise of serum CA-125. This is the highest value reported so far with histologically confirmed endomertiosis. However, our present case demonstrated that abnormally high levels of plasma CA-125 may be encountered in large ovarian endometrioma without rupture and without the overflow of the thick, "chocolate" cyst fluid throughout the abdominal cavity. In 1991, Check et al. reported two women with severe endometriosis associated with extreme elevation of serum CA-125, and the highest value of these two cases was 1385 IU/ml.[14]

Although CA-125 has been proposed as a specific marker for ovarian cancer, it may present in many other benign and malignant conditions of both gynecological and non-gynecological origin. As we know, high serum CA-125 levels have been associated with gynecologic malignancies, however, no level of CA-125 occurred exclusively with gynecologic cancers.

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卵巢子宮內膜異位瘤合併異常上升血清CA-125指數

蕭啓信 張明揚 江其鑫 謝景璋 謝燦堂

CA-125是一種細胞表面的醣蛋白，它在非黏液性上皮性卵巢癌的個案中，百分之八十可見上升的情形；而在一般正常人血清中CA-125濃度通常是小於35。血清中CA-125濃度的上升在幾種良性的婦科病灶中也可見到，例如骨盆腔發炎、子宮肌瘤、子宮肌腺瘤、妊娠、自然流產，尤其以子宮內膜異位症最爲常見。然而，子宮內膜異位症患者血液中CA-125濃度很少上升超過100 IU/mL。在本篇文章中報告案例爲單側卵巢子宮內膜異位瘤合併異常升高之血清CA-125濃度（>6000 IU/mL），在病患接受卵巢內膜異位瘤切除後，血清CA-125濃度值回復爲正常。本案例的報導說明了即使在婦科方面的良性疾病也有可能合併極度異常上升的CA-125濃度，併討論此類極度異常上升CA-125濃度的可能解釋。(長庚醫誌 2003;26:695-9)

關鍵字：卵巢子宮內膜異位瘤，血清CA-125濃度。

長庚紀念醫院 台北院區 婦產科系
受文日期：民國91年5月21日；接受刊載：民國92年3月14日。
索取抽印本處：謝燦堂醫師，長庚紀念醫院 婦產科系。台北市敦化北路199號。Tel.: (02)27135211轉3345; Fax: (02)27197368