Unusual presentation of more common disease/injury

Extremely elevated CA-125 in benign ovarian disease due to stretch of the peritoneum

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Summary

Serum concentrations of CA-125 are rarely elevated beyond 1000 U/ml in benign conditions of the ovary in postmenopausal women. In this report, the authors present an unusual case of a 78-year-old woman with an extremely elevated CA-125 concentration of 2897 U/ml without the presence of a malignancy, ascites or pleural effusion. Imaging revealed a large intra-abdominal cystic mass with irregular solid deviations on CT scan, most likely arising from an ovary. Exploratory laparotomy was performed with suspicion of ovarian cancer but histopathological analysis revealed benign serous cystic adenofibroma. This case report highlights the diagnostic challenge of extremely increased levels of CA-125 in postmenopausal women. A possible explanation for this CA-125 elevation could be the mechanical stretch of the peritoneum.

BACKGROUND

The normal blood concentration of CA-125 ranges from 0 to 35 U/ml. This value is based on the original work of Dr Bast in 1983, according to which only 1% of 888 apparently healthy persons and only 6% of 143 patients with non-malignant disease had serum CA-125 levels above 35 U/ml.¹ In benign ovarian disease, the serum concentration of CA-125 is rarely elevated beyond 1000 U/ml, and this is even more uncommon in cases of ovarian fibromas.²⁻³ Moreover, the increased concentrations, present in 6% of the benign conditions, are mostly mild to moderate, the commonest causes being endometriosis and pelvic inflammatory disease (PID). Recent studies also support these findings stating a specificity of 99.1% for ovarian cancer for concentration greater than 1500 U/ml.³ In general, the sensitivity and specificity of CA-125 for detecting malignancy are relatively low (both 78%) in premenopausal and postmenopausal women together.⁴ An increased CA-125 level therefore remains a diagnostic challenge in the evaluation of cystic masses. Here, we present a rare case of serous cystic adenofibroma leading to an extremely elevated serum CA-125 concentration of 2897 U/ml in benign disease without pleural effusion.

CASE PRESENTATION

A 78-year-old Caucasian woman was referred from the emergency department of a rural hospital with increased abdominal girth and weight loss. Medical history reveals a hysterectomy in the 1970s because of menorrhagia and hypertension. Family history is negative for gynaecological and breast malignancies. On clinical investigation, an extremely enlarged abdomen was found with damped percussion over the whole abdomen; no abnormalities were

seen on speculum examination and no lymphadenopathy was noted.

INVESTIGATIONS

In the rural hospital, laboratory results showed no abnormalities other than slightly elevated liver function tests. The serum concentrations of the tumour markers were CA-125 2897 U/ml and CA-19.9 12 U/ml (0.0–40.0 U/ml). A chest x-ray showed no pleural effusion or other abnormalities. Ultrasound showed a large cystic mass that filled the whole abdominal cavity. A puncture was performed to relieve the symptoms and 5.5 litres of cystic fluid were removed. There was too little cell material for a pathological diagnosis of the fluid. Afterwards, a CT scan was performed in the rural hospital. In the revision in our

Figure 1 CT-abdomen: cystic mass originating from left ovary.

academic hospital, the CT-abdomen showed a large thin-walled, intra-abdominal cyst with some irregular solid deviations, most likely originating from the left ovary, which can make the diagnosis of a serous cyst with malignant degeneration plausible (figure 1). The right ovary could not be identified separately. There was no ascites. There were no enlarged lymph nodes nor signs of peritoneal carcinomatosis. The risk of malignancy index (RMI) had been calculated, which incorporates absolute CA-125 serum levels (2897 U/ml), ultrasound findings (bilateral, multilocular cystic mass with solid areas, without ascites and without intra-abdominal metastases) and menopausal status (postmenopausal). The RMI formula used is ultrasound score (U)×menopausal status (M)×CA-125. This results in a RMI Score of $3 \times 3 \times 2897 = 26\,073$. A score over 200 indicates a high risk of malignancy.⁵

DIFFERENTIAL DIAGNOSIS

Adnexal masses present a diagnostic dilemma; the differential diagnosis is extensive, with most masses representing benign disease. However in this case, in the absence of a preoperative histopathological diagnosis, the postmenopausal status, the presence of complex internal structure of the cystic mass on CT scan and extremely elevated CA-125 heightened substantially the risk of a malignancy.

The gynaecological differential diagnosis based on the above-mentioned findings are

- ▶ Ovarian cancer
- ▶ Borderline ovarian tumour
- ▶ Serous cystadenoma
- ▶ Mucinous cystadenoma
- ▶ Ovarian fibroma
- ▶ Dermoid cyst.

Guidelines for The Recommended Management of Ovarian Masses with Imaging recommend removal of the mass in case of complex ovarian mass in a postmenopausal woman.⁶ According to our guidelines, the patient was referred to the gynaecological oncology unit in the University Hospital. Since the RMI exceeded 200, the laparotomy should be performed by a registered gynaecological oncologist.

TREATMENT

The patient underwent a midline laparotomy and a bilateral oophorectomy and omentectomy were performed. A flabby cystic left ovary with a diameter of 20–25 cm was found which was partly attached to the sigmoid colon. The smaller right ovary filled up the pouch of Douglas and was adhered with the peritoneum. There was no ascites. There were no macroscopical pathological lymph nodes and the omentum was macroscopically normal. The surgery was without complications and the patient recovered well.

Histopathological analysis of the surgical specimen revealed bilateral serous cystic adenofibroma. The left ovary was 23 cm in diameter, with a smooth surface, a thick wall and serous fluid. The right ovary was 13 cm in diameter, multilocular with serous fluid and with many cysts and solid parts.

FOLLOW-UP

Eight days after surgery, the patient could be discharged in good condition. Six weeks after surgery, she was seen in the outpatient clinic and was completely recovered. The CA-125 was almost normalised (68 U/ml). No further follow-up was indicated.

DISCUSSION

CA-125, though, perhaps, best known as a marker for epithelial ovarian cancer, is often found to be elevated in other conditions: benign and malignant, gynaecological and non-gynaecological.⁷ The elevation associated with benign conditions is usually mild. Generally, high concentrations of CA-125 are suggestive of malignancy, thus posing a diagnostic challenge to the physician. Since this patient was postmenopausal and did not have ascites or any signs of pleural effusion, conditions like endometriosis, adenomyosis, functional cysts, pelvic inflammatory disease or Meig's syndrome were excluded from the differential diagnosis. We performed an extensive literature search to find postmenopausal women with benign gynaecological disease and an extremely elevated CA-125. However, no reports were found with a CA-125 above 1000 IU/ml in postmenopausal patients with benign gynaecological disease and without pleural effusion. Therefore, this case report describes the highest level of CA-125 ever reported in a postmenopausal woman without underlying malignancy, borderline tumour or Meig's syndrome.

This case reiterates the lack of specificity of CA-125 as a tumour marker for ovarian cancer and it demonstrates that no level of CA-125 is completely diagnostic of a malignancy, thus requiring the clinician to interpret the laboratory results always in the appropriate clinical context.

In a large meta-analysis, the sensitivity and specificity for CA-125 were both 78%, regardless of menopausal status.⁴ When taking the menopausal status into account, sensitivity and specificity were substantially better in postmenopausal women. In postmenopausal women, the pooled sensitivity and specificity were, respectively, 80% and 88%, compared to 63% and 70% in premenopausal women. This might be explained by the fact that the incidence of ovarian malignancies is higher in postmenopausal women and that CA-125 is not as commonly elevated in non-epithelial ovarian cancers, such as stromal and germ cell tumours. These tumours are proportionately more common in premenopausal women; therefore, the sensitivity of CA-125 is lower in premenopausal women.⁴ The specificity is lower in premenopausal women, as elevations may occur in the presence of more common premenopausal conditions as adenomyosis, uterine fibroids, pelvic inflammatory disease or endometriosis.⁸ In premenopausal women, several cases of ruptured or unruptured endometrioma and adenomyosis have been reported with CA-125 concentrations as high as 9300 U/ml,⁹ 6114 U/ml,¹⁰ 7900 U/ml,¹¹ 1796 U/ml¹² and 1138.¹ One case of pelvic inflammatory disease reported a CA-125 level of 2067 U/ml.¹³ Recently, a review by Moore *et al*¹⁴ demonstrated the range of CA-125 in different groups of benign gynaecological conditions. CA-125 levels up to 2260 U/ml (serous epithelial borderline tumours), 2409 U/ml

(endometriosis), 2545 U/ml (group of abscess, hydrosalpinx and PID) and 1339 U/ml (cystadenomas and adenofibromas) were found in a review of 1042 cases. A benign condition with extremely elevated CA-125 which can occur also in postmenopausal woman is the Meig's syndrome. This syndrome is a triad of benign ovarian mass in association with massive ascites and pleural effusion.¹⁵ A review of literature of 37 cases of Meig's syndrome reported only nine values of CA-125 above 1000 U/ml.¹⁶

In this case, the question arises how this patient could have such high levels of CA-125 in the absence of a malignancy. In adult tissue, CA-125 is primarily expressed in mesothelial cells lining the peritoneum, fallopian tube, endometrium and pleura.¹⁷ The CA-125 level can be increased by various mechanisms, for instance, by increased production owing to greater cell turnover in cancer cells or increased production due to irritation or inflammation of tissue producing CA-125. Furthermore, stretch of the peritoneum and decreased clearance by the liver can cause a rise of CA-125.¹⁸ In this case, there were no signs of inflammation. Also, a normal liver function test ruled out the possibility of decreased clearance. These findings help us to narrow down the possibilities for the raised CA-125 to mechanical stretch of the peritoneum. The grossly enlarged cystic adenofibroma could have stretched the peritoneum of the whole abdominal cavity and, therefore, could have stimulated the mesothelial lining to produce CA-125. This hypothesis is supported by circumstantial as well as experimental evidence. Circumstantial evidence includes a fall in serum CA-125 following paracentesis for massive ascites.¹⁸ Moreover, evidence includes falsely elevated CA-125 due to peritoneal manipulation during abdominal surgeries and its correspondence with the duration of the surgery.¹⁹ Also, a case report of significant increases in serum CA-125 following torsion from an adenofibroma of the ovary supports this, which also would have led to peritoneal stretching.²⁰ The evidence based on laboratory experiments in support of this theory is the stimulation of peritoneal macrophages leading to release of IL-6, IL-1b and tumor necrotic factor (TNF) following experimentally induced peritoneal stretch,²¹ and a positive relation between TNF α -related intraperitoneal release of CA-125 in vitro.²² However, these findings need further research and confirmation.

Finally, regarding the diagnostic work-up, it should be noted that fine-needle aspiration (FNA) of any complex ovarian cysts is not recommended to diagnose ovarian cancer, because of its low sensitivity (25%), FNA does have a high specificity though (90%).²³ Its utility is limited in perimenopausal or postmenopausal women with complex and solid-cystic adnexal masses, because these should be investigated by operative intervention.²⁴ Moreover, the risk of rupture of cystic ovarian tumours with tumour dissemination on top of risk of complications, such as haemorrhage and infection, has limited the technique's utilization.²⁴

In conclusion, this case demonstrates the diagnostic challenge of an extremely raised CA-125 and describes the highest reported CA-125 level in a postmenopausal woman with benign ovarian disease without pleural effusion.

Learning points

- The level of CA-125 does not always correlate well with the presence of malignancy.
- In the diagnostic workup for adnexal masses in premenopausal and postmenopausal women together, sensitivity and specificity are both 78%.
- The level of CA-125 correlates better with the presence of malignancy in postmenopausal than in premenopausal women, which is represented in a higher sensitivity and specificity.
- An extremely elevated CA-125 (>1500 U/ml) in a postmenopausal woman can still be due to a benign gynaecological condition.
- Extremely elevated CA-125 in benign ovarian disease could be due to mechanical stretch of the peritoneum.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Bast RC Jr**, Klug TL, St John E, *et al*. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. *N Engl J Med*. 1983;**309**:883–7.
2. **Ghaemmaghami F**, Zarchi MK, Hamed B. High levels of CA125 (over 1,000 U/ml) in patients with gynecologic disease and no malignant conditions: three cases and literature review. *Arch Gynecol Obstet* 2007;**276**:559–61.
3. **Moss EL**, Hollingworth J, Reynolds TM, *et al*. The role of CA125 in clinical practice. *J Clin Pathol* 2005;**58**:308–12.
4. **Myers ER**, Bastian A, Havrilesky LJ. Management of adnexal mass. *Evid Rep Technol Assess* 2006;**130**:1–145.
5. **Jacobs I**, Oram D, Fairbanks J, *et al*. A risk of malignancy index incorporating CA125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *Br J Obstet Gynaecol* 1990;**97**:922–9.
6. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin. Management of adnexal masses. *Obstet Gynecol*. 2007;**110**:201–14.
7. **Jacobs I**, Bast RC Jr. The CA 125 tumour-associated antigen: a review of the literature. *Hum Reprod* 1989;**4**:1–12.
8. **Bast RC Jr**, Badgwell D, LuZ, Marquez R, *et al*. New tumor markers: CA125 and beyond. *Int J Gynecol Cancer* 2005;**15**:274–81.
9. **Johansson J**, Santala M, Kaupila A. Explosive rise of serum CA 125 following the rupture of ovarian endometrioma. *Hum Reprod* 1998;**12**:3503–4.
10. **Kashyap RJ**. Extremely elevated serum CA125 due to endometriosis. *Aust N Z J Obstet Gynaecol* 1999;**39**:269–70.
11. **Kahraman K**, Ozguven I, Gungor M, *et al*. Extremely elevated serum CA-125 level as a result of unruptured unilateral endometrioma: the highest value reported. *Fertil Steril*. 2007;**4**:968–7.
12. **Sato H**, Borsari R, Yajima EK, *et al*. Adenomyoma associated with high level of CA 125 and CA 19-9: case report. *Eur J Gynaecol Oncol* 2011;**32**:455–6.
13. **Zheng H**, Gao Y. Serum HE4 as a Useful Biomarker in Discriminating Ovarian Cancer From Benign Pelvic Disease. *Int J Gynecol Cancer* 2012;**22**:1000–5.
14. **Moore RG**, Miller MC, Steinhoff MM, *et al*. Serum HE4 levels are less frequently elevated than CA 125 in women with benign gynaecologic disorders. *Am J Obstet Gynecol* 2012;**206**:3511–18.
15. **Meigs JV**, Cass JW. Fibroma of the ovary with ascites and hydrothorax, with a report of seven cases. *Am J Obstet Gynecol* 1937;**33**:249–66.
16. **Liou J**, Su TC, Hsu JC. Meigs' syndrome with elevated serum cancer antigen 125 levels in a case of ovarian sclerosing stromal tumor. *Taiwanese J Obstet Gynecol* 2011;**50**:196–200.
17. **Kabawat SE**, Bast RC Jr, Welch WR, *et al*. Tissue distribution of a coelomic-epithelium-related antigen recognized by the monoclonal antibody OC125. *Int J Gynecol Pathol* 1983;**2**:275–85.
18. **Zuckerman E**, Lanir A, Sabo F, *et al*. Ca 125 as a marker for detection and quantitation of ascites in liver disease. *Hepatology* 1995;**22**:163–6.
19. **Pasqual E**, Bacchetti S, Morabito G, *et al*. The length of peritoneal surgical manipulation correlates with serum CA 125 levels. *In Vitro* 2011;**25**:105–9.

20. **Fujiwara K**, Moriya T, Mikami Y, *et al*. Significant increases in serum CA125 and CA19-9 following torsion from an adenofibroma of the ovary: a case report. *Jpn J Clin Oncol* 1994;**24**:116–19.
21. **Wehner Buchholz BM**, Schuchtrup S, Rocke A, *et al*. Mechanical strain and TLR4 synergistically induce cell-specific inflammatory gene expression in intestinal smooth muscle cells and peritoneal macrophages. *Am J Physiol Gastrointest Liver Physiol* 2010;**299**:1187–97.
22. **Georgios K**, Kostoula A, Economou M, *et al*. Tumor necrosis factor- α -related intraperitoneal release of Ca-125 in cirrhotic patients with sterile ascites. *Clin Chem* 2005;**11**:2207–8.
23. **Higgins RV**, Matkins JF, Marroum MC. Comparison of fine-needle aspiration cytologic findings of ovarian cysts with ovarian histologic findings. *Am J Obstet Gynecol* 1999;180:550–3.
24. **Layfield LJ**, Berek JS. Fine-needle aspiration cytology in the management of gynecologic oncology patients. *Cancer Treat Res*. 1994;**70**:1–13.

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