

Mass lesions of ovary - Tumor markers can be misleading

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ABSTRACT

Background: Ovarian mass lesions could be neoplastic or non neoplastic. The less aggressive lesions should be distinguished from carcinomas which require extensive surgical procedures. CA-125 is a tumor marker used for evaluating ovarian carcinomas. In this series we found seven cases of sex cord stromal tumors (SCT) and endometriotic cysts with raised CA-125 levels, the highest value being 1540 IU/ml. **Aims and Objectives:** 1) To retrospectively evaluate cases which presented as mass lesions of ovary over a two year period along with CA-125 levels if available. 2) To find out the number of non carcinomatous lesions with elevation of the tumor marker CA-125. **Materials and Methods:** Total number of ovarian tumors and endometriotic cysts reported in the Department of Pathology, Amala Institute of Medical Sciences, Thrissur, Kerala, India in the two year period of 2012 and 2013 were retrospectively identified. CA-125 levels if available were noted. **Results:** Primary ovarian tumors comprised 180 cases, the rest being metastatic adenocarcinomas. There were 15 cases of SCT and 21 endometriotic cysts. CA 125 levels were increased in 2 cases each of granulosa cell tumors and fibrothecomas and 3 cases of endometriotic cysts. Highest value was 1540 IU/ml. **Conclusion:** Elevation of the tumor marker CA 125 often tricks the clinician into making a provisional diagnosis of carcinoma of ovary. It is important to understand the limitations in the interpretation of tumor markers so that more aggressive treatment modalities are avoided.

Key words: Sex cord stromal tumors, Endometriosis, Tumor markers, CA-125

INTRODUCTION

Ovarian mass lesions could be neoplastic or non neoplastic. Neoplastic lesions can be benign, malignant or potentially malignant. Neoplasms may be surface epithelial tumors, sex cord stromal tumors, germ cell tumors, other miscellaneous primary tumors and metastatic tumors. Sex cord stromal tumors (SCT) of the ovary are comparatively rare and occur in a wide age range. They are potentially malignant tumors and may be functional, resulting in menstrual irregularities, infertility and sometimes androgenic effects. They present as solid or cystic adnexal masses. Endometriosis of the uterine adnexa can also present as mass lesions. These lesions may need to be distinguished from the more aggressive carcinomas which require extensive surgical procedures.

Tumor markers are biomarkers found in the blood, urine or body tissues. CA-125 is a tumor marker used for evaluating

ovarian carcinomas. Normal value is less than 35 IU/ml. It has been found to be elevated significantly in ovarian surface epithelial malignancies. An elevated CA-125 level often makes the clinician to over diagnose a case as carcinoma even though there are many gynecologic and non gynecologic conditions associated with increased levels. Our objective in this study is to emphasize this point and to identify non carcinoma cases with significant elevations of CA-125 levels.

In this series there were 180 cases of primary ovarian tumors and 21 cases of endometriotic cysts. We found seven cases with raised CA-125 levels which included 4 cases of SCT and 3 cases of endometriotic cysts.

MATERIALS AND METHODS

Total number of ovarian tumors reported in the Department of Pathology, Amala Institute of Medical

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Sciences, Thrissur, Kerala, India in the two year period of 2012 and 2013 were retrospectively identified.

CA-125 values in these cases if available were analyzed. Endometriotic cysts biopsied during this period were also taken into account along with CA-125 values if available.

RESULTS

Primary ovarian tumors comprised 180 cases, the rest being metastatic adenocarcinomas. 144 cases were surface epithelial tumors, 15 were SCT and 17 were germ cell tumors. CA-125 levels were available in 67 cases.

The commonest tumors were serous tumors -95 cases- belonging to different subcategories (Table 1). One case each of benign and borderline mucinous tumors showed minimal elevations of CA-125 values, 49 and 51.6 IU/ml.

Among the SCT there were granulosa cell tumors, thecomas, fibrothecomas and sclerosing stromal tumor of ovary, (Table 2).

Germ cell tumors comprised 17 cases. None showed elevated CA-125 values (Table 3). Metastatic carcinoma and NHL completed the list. Among the 21 cases of endometriotic cysts diagnosed during this period 4 cases had CA-125 levels done preoperatively and 3 cases showed increased levels (Table 4).

CA 125 levels were increased in 2 cases of granulosa cell tumor- 48 IU/ml and 86.15 IU/ml. The two cases of

fibrothecomas had values of 713 IU/ml and 1540 IU/ml. Both cases had undergone torsion with free fluid in the abdominal cavity. The values were high in the 3 cases of endometriosis with the highest being 1450 IU/ml. The latter case was associated with pancreatic cyst and elevated CA-19-9.

Among the seven cases of granulosa cell tumors all were perimenopausal. One patient showed simple hyperplasia of endometrium indicating estrogenic effect. Two cases of thecomas showed endometrial changes. One case showed disordered proliferation of endometrium and the other, endometrial adenocarcinoma in a background of hyperplasia. The one case of sclerosing stromal tumor had concurrent hypothyroidism.

DISCUSSION

The SCT of ovary arise from the ovarian stroma which is derived from sex cords of embryonic gonad.¹ Sex cord stromal tumors of the ovary occur over a wide age range, with individual tumors occurring in different age groups. Because patients are often young and most tumors are unilateral, accurate diagnosis is necessary for proper treatment and maintenance of fertility, where desirable.

Accuracy of terminology is important. It is not enough that pathologists knowledgeable in the field know the meaning of the terms used. The name of the tumor or condition should reflect its biological behavior as accurately as possible because clinicians may be influenced in their choice of therapy by the terminology used and lay people may not readily grasp the implications of the diagnosis.²

SCTs are relatively infrequent and accounts for about 7% of all primary ovarian tumors.³ In our series they form 8.1% of the total. They comprised granulosa cell tumors, thecomas,

Table 1: Surface epithelial tumors

Types of tumor	No of cases	Cases with CA-125 values	Levels increased in
Benign serous tumors	45	11	1
Borderline serous tumors	7	3	2
Serous carcinoma	42	22	19
Benign mucinous tumors	25	7	1
Borderline mucinous tumors	8	2	1
Mucinous carcinoma	7	2	Nil
Endometrioid carcinoma	3	1	Nil
Clear cell adenofibroma and carcinoma	4	2	1
Transitional cell carcinoma	2	2	1

Table 2: Sex cord stromal tumors

Types of tumor	No of cases	Cases with CA-125 values	Levels increased in
Granulosa cell tumors	7	4	2*
Fibrothecomas	4	3	2**
Thecomas	3	1	0
Sclerosing stromal tumors	1	1	0

*48 IU/ml and 86.15 IU/ml, **713 IU/ml and 1540 IU/ml

Table 3: Germ cell tumors

Types of tumor	No of cases	Cases with CA-125 values	Levels increased in
Benign cystic teratoma	13	1	0
Immature teratoma	3	1	0
Mixed germ cell tumors	1	0	0

Table 4: Others

Types of tumor/lesion	No of cases	Cases with CA-125 values	Levels increased in
NHL	2	0	0
Metastatic carcinoma	5	2	1
Endometriotic cysts	21	4	3*

*160 IU/ml, 917 IU/ml, 1450 IU/ml

fibrothecomas and a case of sclerosing stromal tumor. The endometrial changes observed which could be attributed to the functional tumors were simple hyperplasia, endometrial carcinoma in a background of hyperplasia and one case of endometrial polyp. Only 4 cases (26.6%) showed evidence of hormonal activity. In a 20 year retrospective study by Haroon et al there were 480 cases of SCT of which 29 showed endometrial changes.³

Early detection is important in the treatment and prognosis of ovarian cancers. Use of serum markers for early detection has largely focused on CA-125 a high molecular weight mucin that was initially detected with a homologous double determinant radio immunoassay.⁴

Ca-125 is expressed in celomic epithelium during embryonic development.⁵ It is not expressed by normal adult or fetal ovary. It has been detected in fetal Mullerian duct derivatives as well as fetal serosal surface epithelia including pleura, peritoneum and pericardium. In adult tissues traces have been detected in fallopian tube, endometrium and endocervix. There have been many studies relating to the sensitivity and specificity of CA-125. Niloff et al in 1984 found no single gynecological disease to be associated with CA-125 levels exceeding 65 IU/ml and that a minority of pregnant women in 1st trimester had increased levels.⁶ Canney et al in 1984 found the sensitivity of CA-125 more than adequate extending to all histologic subtypes of epithelial neoplasms including mucinous subtype.⁵

Specificity of CA-125 is inadequate for screening particularly in premenopausal population in which endometriosis, adenomyosis and retrograde menstruation can produce elevations of antigen levels.⁴ However it is extremely useful in the follow up of surface epithelial malignancies.

Many reports are there in literature of increased levels of CA-125 in other types of ovarian tumors especially sex cord stromal tumors. There are also studies which reveal that CA-125 values were found elevated in cases of Non Hodgkin Lymphoma correlating with advanced disease and poor outcome.⁷ In our series CA-125 levels were not available in the 2 cases of NHL. Choi K et al in 2006 reported a case of granulosa cell tumor associated with Meigs'syndrome and elevated CA-125 levels of 82.49 IU/ml.⁸ There are reports of thecoma and fibrothecoma associated with Meigs syndrome and elevated CA-125 values upto 600 IU/ml.^{9,10} Macci et al in 2014 reported an ovarian fibroma in association with Meigs' syndrome, hemolytic anemia and raised CA-125 values along with increased inflammatory markers –CRP and fibrinogen- where the clinical diagnosis was advanced ovarian cancer. In addition to the effusions, torsion with

subsequent necrosis can result in elevated CA-125 levels.¹¹ A case of twisted sclerosing stromal tumor also has been recently reported with Ca-125 levels of 339.20 IU/ml.¹²

In the present series we had 4 SCTs with above normal Ca-125 values. The two granulosa cell tumors did not show any effusions and one case had only marginal elevation to 48 IU/ml. The two fibrothecomas had undergone torsion and had free fluid in the abdomen. Both showed considerable elevation of CA-125; 713 and 1540 IU/ml respectively. Both were clinically diagnosed as malignancies. The 3 cases of endometriosis also were suspected to harbor tumor due to elevated levels of tumor markers.

CONCLUSION

Sex cord stromal tumors may be benign as in thecomas or potentially malignant as in the case of granulosa cell tumors. They are not aggressive like surface epithelial carcinomas. Endometriosis is a non neoplastic condition. We found seven cases belonging to these two categories with raised values of the tumor marker CA-125. This often tricks the clinician into making a provisional diagnosis of malignancy. It is important to understand the limitations in the interpretation of tumor marker levels so that more aggressive treatment modalities are avoided in such situations.

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Authors Contribution:

MCS: Concept, Design, Definition and intellectual content, Literature search, Clinical search, Experimental search, Data acquisition, Data analysis, Manuscript preparation, Manuscript editing, Manuscript review, Guarantor; **UMA:** Definition and intellectual content, Literature search, Clinical search, Experimental search, Data acquisition, Data analysis.

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