CASE REPORT

A rare case of synchronous right ovarian clear cell carcinoma and an incidental left ovarian endometrioid carcinoma with immunohistochemical study

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ABSTRACT

Bilateral primary synchronous ovarian neoplasms are rarely encountered in clinical practice. Both ovaries harboring neoplasms is predominantly appreciated as, metastasis from a distant primary or secondary from an advanced primary ovarian neoplasm. However in both the above instances, the histomorphological evaluation is of paramount importance. We encountered an incidental left ovarian, International Federation of Gynecology and Obstetrics grade 2, endometrioid carcinoma in a patient presenting with a right ovarian mass immunohistopathologically proven to be clear cell carcinoma. The documentation of such rare occurrence is of utmost importance for better understanding of histogenesis of ovarian cancers, which may impact management strategies.

Key Words: Clear cell carcinoma, endometrioid carcinoma, synchronous, ovarian

INTRODUCTION

Concurrent tumors are a well-known entity, at times posing diagnostic and therapeutic difficulties. They can be synchronous, independently derived, nonmetastatic tumors, or metastatic tumors. Distinguishing between them involves clinicopathologic interpretation based on multiple criteria including histologic type and grade. In general, if tumors at different sites have different histologic features, they are generally regarded as independently derived primary tumors, which generally have a better prognosis than the primary tumor with metastasis.[1]

Very few case reports of synchronous bilateral primary ovarian tumors of different histologic types have been mentioned in the literature. Here, we report a rare case of right ovarian clear cell carcinoma (CCC) with an incidental finding of left ovarian endometrioid carcinoma (EC) in a 65-year postmenopausal female.

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CASE REPORT

A 65-year-old postmenopausal multiparous, female presented to gynecologic outpatient department with history of pain in the right iliac fossa since 15 days. On abdominal examination, firm and tender lump was felt in the right iliac fossa. Vaginal examination revealed a healthy cervix. Uterus was bulky. Other systemic examination findings were noncontributory. Serum Ca-125 was raised to 414 u/ml (normal: 0-35 u/ml). Her routine hematological and biochemical investigations were within normal limits. Computed tomography showed 9.5 cm × 6.9 cm × 6.8 cm sized well-defined, heterogeneous, partly solid and partly cystic lesion in pelvis superior to the urinary bladder. Fat planes between bowel loops and uterus were obscured. Both ovaries were not seen separate from the lesion [Figure 1a]. A radiological diagnosis of ovarian neoplasm was offered. Ascitic fluid sent for cytology was negative

Access this article online

Quick Response Code:

Website: www.jmidlifehealth.org

DOI: 10.4103/0976-7800.133998

for malignant cells. Patient was taken for exploratory laparotomy. Intra-operatively, there was a presence of right adnexal tumor adhered to appendix and omentum. Right adnexal mass was sent for frozen section. Diagnosis of adult granulosa cell tumor (AGCT) was given. Patient underwent trans-abdominal hysterectomy with bilateral salpingo-oopherectomy. Appendix, omentum and peritoneal biopsy were also received.

Gross examination

The right adnexal mass measured 10.5 cm × 7.5 cm × 4.5 cm. External surface was nodular. Cut surface showed predominantly solid with few cystic brownish areas. Solid areas showed yellowish with few whitish areas. Cysts varied in size from 0.5 to 2 cm [Figure 1b]. Right fallopian tube was dilated the cut section of which showed yellowish necrotic material. Uterus cervix with left sided adnexa measured 10 cm × 8 cm × 4.5 cm. External surface showed two subserosal nodules measuring 2.5 cm × 2 cm × 1.2 cm and 1.3 cm × 1.5 cm × 1 cm near the left cornu, cut surface of which showed whitish, whorled and firm areas. Cut surface of the uterus showed distorted endometrial cavity with whitish, firm and whorled intramural nodule measuring 4.8 cm × 4.3 cm × 3 cm. Cervix measured 2 cm in length and was unremarkable. The left fallopian tube was 5 cm in length and showed no gross pathology. The left ovary measured 3.2 cm × 1.5 cm × 1 cm, the cut surface of which showed whitish and yellowish areas [Figure 1b]. Appendix, omentum and peritoneal biopsy specimen were received. They appeared grossly congested and otherwise unremarkable.

Microscopic examination

Right ovary showed typical features of CCC. CCC areas showed tumor cells arranged in solid sheets, tubulopapillary and focal cribriform pattern separated by hyalinized homogenous fibrovascular septae arising in an endometriotic cyst. Hobnailing of cells was noted. Wide areas of necrosis were visualized. Sections from the left ovary showed infiltration by tumor cells at one pole with one focus of endometriosis. Histopathological diagnosis of simultaneous presence of CCC in the right ovary [Figure 2a] with the presence of EC in the left ovary [Figure 2c] was made.

Immunohistochemistry (IHC) was performed with the following panel of antibodies viz. Wilm's tumor gene (WT1) (clone 6F-H2, Dako), epithelial membrane antigen (EMA) (clone E29, Dako), estrogen receptor (ER) (clone 6F11, Novacastra), progesterone receptor (PR) (clone PGR312, Novacastra) and P53 (cloneDO-7, dako) on the tumors. The right ovarian tumor showed positivity for p53, nuclear immunoreactivity for ER and no immunoreactivity for WT1, [Figure 2b] and PR. The left ovarian tumor showed nuclear immunoreactivity for ER and PR, p53 positivity, strong membrane immunoreactivity for EMA [Figure 2d] and no immunoreactivity for WT1. Based on IHC studies, diagnosis of CCC of the right ovary and EC of the left ovary was confirmed.

DISCUSSION

A synchronous malignant tumor is defined as the occurrence of two tumor types within a 6 months period in the same patient. The occurrence of primary synchronous malignancies of the genital tract is rare, the incidence of which varies between 0.7% and 1.5%.[2] Independent primary tumors of the endometrium and ovary are the most commonly encountered synchronous tumors of the female genital tract.[2]

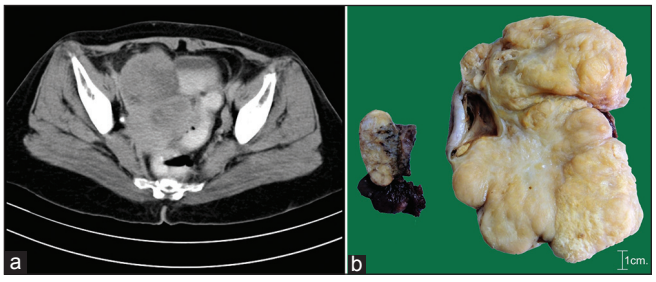

Figure 1: (a) Computed tomography showing 9.5 cm × 6.9 cm × 6.8 cm sized well defined, heterogeneous, partly solid and partly cystic lesion in pelvis superior to urinary bladder. Fat planes with bowel loops and uterus were lost. Both ovaries were not seen separate from the lesion. (b) The cut surface of the left ovary measuring 3.2 cm × 1.5 cm × 1 cm showing whitish and yellowish areas,The cut surface of the right ovarian mass measuring 10.5 cm × 7.5 cm × 4.5 cm showing predominantly solid with few cystic brownish areas. Solid areas showed yellowish with few whitish areas. Cysts varied in size from 0.5 to 2 cm

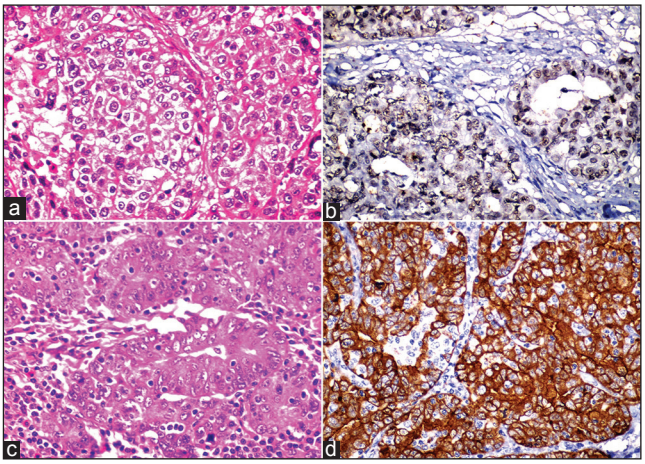

Figure 2: (a) Photomicrograph of CCC showing tumor cells arranged in solid sheets at places separated by hyalinized homogenous fibrovascular septae; (b) The tumor cells of the right ovarian CCC showing absence of WT1 immunoreactivity; (c) Photomicrograph of EC showing glandular structures lined by malignant tumor cells. Surrounding stroma is desmoplastic and shows dense chronic lymphocytic infiltrate; (d) The tumor cells of the left ovary showing strong EMA membrane immunoreactivity

Very few case reports of bilateral synchronous primary ovarian malignant tumors have been mentioned in the literature. First case was reported in a 58 year postmenopausal lady with left ovarian serous papillary carcinoma and right ovarian malignant mixed müllerian tumor.[3] Second case was reported in a 38-year-female who had right ovarian serous papillary carcinoma and left ovarian CCC.[3] Our case showed the presence of right ovarian CCC and incidental left ovarian EC.

Clear cell carcinoma of the ovary, now recognized as a distinct entity, is the third most common ovarian carcinoma. It occurs in <5% of all ovarian tumors. It usually presents in International Federation of Gynecology and Obstetrics (FIGO) stage I and II. These unilateral tumors constitute 20-50% of ovarian carcinomas. Mutations in K-ras and PTEN and microsatellite instability are implicated in CCC.[4]

Endometrioid carcinoma, the second most common ovarian carcinoma, occurs in approximately 10% of all ovarian carcinomas. Like CCC of the ovary, it also presents in FIGO stage I and II. 15-30% of these tumors occur bilaterally. Mutations in CTNNB-1 (A-catenin), PI3CA (encoding phosphatidylinositol 3-kinase), and PTEN have been reported to have high levels of microsatellite instability in EC.[4]

It is known that CCC and EC have analogous derivation. Possible origin from nonovarian, mullerian type tissue has been documented. It is recognized that these tumors develop from endometriosis that is believed to develop as a result of retrograde menstruation. The oxidative stress conditions found within endometriotic lesions are likely to contribute to the transformation process.[5] Findings in our case substantiates this theory. Focus of endometriosis was noted in the left ovary. CCC of the right ovary was seen arising from the endometriotic cyst.

The dichotomy in the histogenesis of endometriosis associated ovarian cancer that is clear cell versus endometrioid type adenocarcinoma is further discussed in the literature. Studies with the hepatocyte nuclear factor 1-β (HNF-1 β) by immunohistochemistry have addressed these issues. EC and CCC arise from the HNF-1 β-negative and HNF-1 β-positive epithelial cells of endometriosis, respectively indicating different cells of origin.[6]

At times, it can be very difficult to differentiate CCC and moderately differentiated EC of the ovary from ovarian serous cyst adenocarcinoma on histopathology alone. However, features such as rounded papillary cores with stromal hyalinization, surrounded by one or two layers of hobnail cells with uniform, but highly atypical nuclei with prominent nucleoli favor CCC. Furthermore, presence of endometriotic cyst gives a clue to the diagnosis. Clinically, disseminated bilateral ovarian CCC at presentation is much less commonly encountered when compared with ovarian serous neoplasms. An endometriosis associated tumor composed of moderately atypical clear cells lining simple, back-to-back tubules helps recognizing ovarian EC.[4]

Immunohistochemistry also aids in the diagnosis of a particular histological variant. Ovarian CCC is typically HNF-1 β positive, ER positive and WT1, p16, and p53 negative. Ovarian EC retain ER, PR positivity and are WT1, p16, p53, and HNF-1 β negative. Ovarian serous neoplasms show diffuse WT1, p53, p16, and ER positivity and are negative for HNF-1 β.[7]

It is known that AGCT with pseudo papillae can mimic CCC as happened while reporting on frozen section in this case. However, nuclear features with IHC can help in arriving at a diagnosis. AGCTs are inhibin, calretinin and CD 56 positive and typically EMA negative.[7]

The CA 125 levels help in approach to the diagnosis, therapeutics and followup of ovarian cancer.[8] Our patient showed high levels of CA 125, which lowered after surgery. Radiological investigations can help in narrowing of the differential diagnosis.

The treatment modality for CCC is cytoreductive surgery with adjuvant platinum based chemotherapy. Ovarian CCC though present at early stages have the propensity for recurrence even after primary chemotherapy. Higher stages of CCC and higher grades of EC are seen to be associated with significantly decreased survival.[9,10]

Findings in this case, thus highlight the role of IHC in histomorphological distinction of rare subtypes of ovarian carcinomas occurring bilaterally.

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How to cite this article: Khandeparkar SG, Deshmukh SD, Lekawale HS, Bhoge A, Maqbool Ahmed AT. A rare case of synchronous right ovarian clear cell carcinoma and an incidental left ovarian endometrioid carcinoma with immunohistochemical study. J Mid-life Health 2014;5:91-4.

Source of Support: Nil, **Conflict of Interest:** None declared.