Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

Clear Cell Carcinoma of ovary, uterine corpus and cervix-Synchronous or metastatic ?

Tushar Kar, Asaranti Kar*, Jagannath Mishra, Lity Mohanty, Shilpa Anupurba

O & G Department, S.C.B.Medical College, Cuttack, India.

ARTICLE HISTORY

Received: 14.05.2015

Accepted: 16.07.2015

Available online: 30.08.2015

Keywords:

Clear cell carcinoma, cervix, ovary, uterine corpus

***Corresponding author:**

Email : asarantikar@yahoo.co.in
Tel.: +91-9437170442

ABSTRACT

Clear cell carcinoma is a rare type of ovarian epithelial malignancy accounting for less than 5% of all ovarian epithelial cancers. It is characterized by appearance of special type of cells with abundant clear cytoplasm and centrally placed nuclei arranged in solid or tubulo-cystic/glandular pattern with presence of hobnail cells frequently. Due to bad prognosis, it is considered as a high grade tumor. Ovarian clear cell carcinoma spreading to uterus and cervix is a very rare presentation. In such instances it becomes difficult to distinguish a metastatic lesion to uterus and cervix from ovarian primary from synchronous or simultaneous appearance of multiple cancers. We present such a case of ovarian clear cell carcinoma with concurrent involvement of uterus and cervix in a 60-year-old multiparus female. Simultaneously, we have tried to solve the conflict of metastatic and synchronous lesions in ovary and uterus.

INTRODUCTION

Ovarian clear cell carcinoma (O-CCC) is a distinct rare histopathologic subtype of epithelial ovarian cancer (EOC) with an incidence of <5% of all ovarian epithelial malignancies [1]. In 1973, the World Health Organization (WHO) strictly defined O-CCCs as lesions characterized by clear cells growing in solid/tubular or glandular patterns as well as hobnail cells lining tubules and cysts [2]. Though it can spread directly to adjacent structures like tube, broad ligament, intestine, omentum and uterus but spread to cervix is considered rare as in our case. But the lady presented with complaints of post menopausal bleeding due to spread to endometrium. Extensive search on literature didn't find any case report on ovarian clear cell carcinoma with spread to endometrium and cervix without affecting other surrounding structures like omentum, bladder and bowel . We present this case due to occurrence of multiple cancers in female genital tract with approach to acurate diagnosis in this situation as synchronous primary tumors or as one primary tumor associated with its metastasis,

CASE REPORT

A 60 year multiparous, diabetic and obese postmenopausal lady was admitted for evaluation of post-menopausal bleeding. She had history of unilateral oophorectomy for dermoid cyst 20 years back. Per abdominal examination showed an irregular mass on right side of 18-20 weeks size. Per speculum and per vaginal examination didn't show any abnormality. Other than routine hematologic parameters and ultrasonography (USG), she was advised endometrial biopsy which revealed atypical hyperplasia of endometrium. USG showed a right side solid adnexal mass, possibly ovarian tumor of size 12×8x6 cm with normal doppler study other than bulky uterus. Her CA-125 was mildly elevated (56U/ml) and CEA, CA 19.9 were normal. After controlling blood sugar she was planned for exploratory laparotomy. On opening the abdomen there was mild adhesion between different pelvic viscera which was released. The sole ovary was found to be enlarged with nodular appearances and hemorrhagic areas in between.(Fig.1) So maximal debulking surgery with total abdominal hysterectomy and salpingo-oophorectomy was done along with partial omentectomy and lymphadenectomy and specimen was sent for histopathological study. There was no ascites. Peritoneal fluid washing was collected and sent for cytology. Abdomen was closed after maintaining hemostasis. Postoperative period was uneventful and she was referred to regional cancer institute for chemotherapy and further follow up. The gross specimen received in Pathology Department was uterus and cervix and one side ovarian tumor , fallopian tube, omentumm and pelvic lymphnodes. Uterus and cervix measured 8x5x4cm and endometrium appeared thickened and irregular(Fig.1). Cervix appeared healthy. Ovarian tumor was 12x8x6 cm with nodular surface. Cut surface was solid with necrotic areas. Fallopian tube was 4x1x1cm and wall was uniformly thickened without any nodularity or mass. Multiple sections were taken from different areas. Hematoxylene & Eosin stained sections from ovarian tumor revealed tumor cells arranged in tubulo-cystic pattern with solid foci comprising of large round to polygonal cells having moderate to abundant

amount of pale eosinophilic to clear cytoplasm and centrally placed large hyperchromatic nuclei.(Fig.2a) Many cells showed hobnailing of nuclei. Section from uterine wall (endo-myometrium) revealed similar appearing tumor cells in endometrium. On thorough searching, there was no myometrial invasion.(Fig.2b) Section from cervix also revealed presence of foci of tumor cells in the stroma. (Fig.2c&d) Sections from fallopian tube did not reveal any intraepithelial leison or malignancy. Lymphovascular space invasion was not found in any of the sections. Malignant cells were not detected in the peritoneal fluid cytology. Immunohistochemical study of sections from ovary, endometrium and cervical mass showed positivity for CA-125 and CK-7. Due to large size of ovarian tumor, raised CA 125, small lesion in endometrial cavity, absence of myometrial and lymphovacsular invasion, lack of precursor lesions in endometrium and cervix , a final diagnosis of clear cell carcinoma in ovary with metastasis to endometrium and cervix was rendered. Omentum and lymph node analysis came out negative and the case was assigned FIGO stage IIB (FIGO-2009). Post operatively patient received 6 cycles of carboplatin and paclitaxel based chemotherapy and is doing well..

DISCUSSION

Ovarian CCC is an aggressive subtype of ovarian cancer because of poor chemosensitivity, which results in worse prognosis than the more common serous cell type cancers adjusted for stage [3,4] The poor response rate of CCC (15% in contrast to 80% of high grade serous carcinomas-HGSCs),

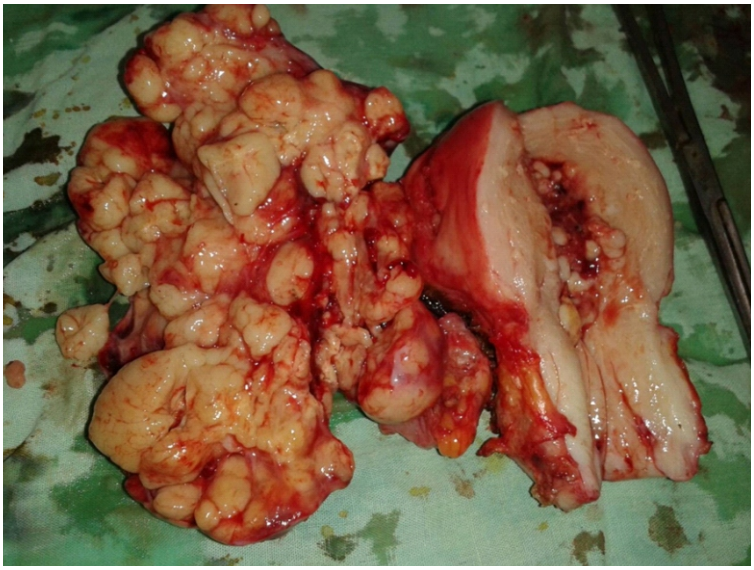

Fig 1. Enlarged multinodular ovarian tumor with uterus showing thickened endometrium.

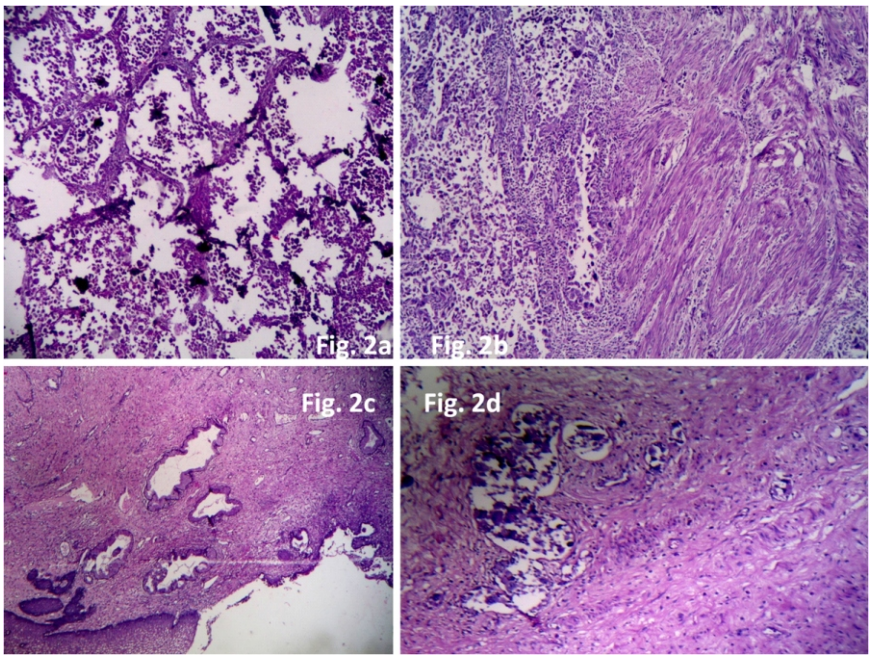

Fig 2. **a**- Photomicrograph of ovarian tumor revealing tubulo-cystic pattern of clear cell carcinoma, **b**- Clear cell carcinoma in endometrium without myometrial invasion, **c**- Cervical tissue with stratified squamous epithelial lining. **d**- Multiple small and solid foci of clear cell carcinoma amidst cerviccal stroma. H&E stainx100.

results in a lower 5-year survival for clear cell carcinoma in patients with advanced stage tumors (20% versus 30%) . From a histopathological perspective, O-CCCs have conventionally been considered a uniform entity and are usually classified as high-grade carcinomas.[5] The peak age of presentation is 52 years and the presenting symptoms are enlarging abdominal mass. 50% of patients are at FIGO Stage I at the time of diagnosis. Pattern of metastases in O-CCC is not well described. There is one review of 44 cases of O-CCC from the Brigham Hospital (spanning 1944 to 1981) in the literature where there is no specific mention about spread to uterus and cervix and another large study of 1411 clear cell ovarian cancers comparing it with other variety of EOCs also has no specific mention about its pattern of spread.[1] The common sites of metastasis are lymphnodes, distant visceral organs and rarely bone and brain. Cervical metastasis in O-CCC is infrequent in literature. In the present case there is metastasis to endometrium and cervix from O-CCC. This patient was 60 year old and presented with postmenopausal bleeding . She had metastasis to endometrium and cervix but without involvement of omentum and lymphnodes and was in stage IIB.

During simultaneous occurrence of malignancies in female genital tract, it becomes very important to distinguish synchronous primary from metastasis from a single primary as independent primary tumors of low histologic grade and with involvement limited to the endometrium and ovary, are associated with favorable outcome. The most practical criteria for distinguishing independent primary tumors from a primary tumor with metastasis till date are the conventional macroscopic and microscopic parameters. The different clinico-pathological criteria considered are unilateral/bilateral ovarian tumor, patteran of involvement (multinodular or surface implants), size of tumor, histologic type and grade, presence or absence of coexistent lesions, lymphovascular invasion, myomatrial invasion and fallopian tube involvement. In the present case, large ovarian tumor (> 10 cm), single unilateral ovarian mass, uniform histological features within ovarian parenchyma which are consistent with ovarian primary epithelial (clear cell) carcinoma, small endometrial lesion, absence of atypical hyperplasia and myometrial invasion, spread of similar lesion to cervix favors a diagnosis of ovarian primary malignancy with metastasis to endometrium and cervix. Moreover clear cell carcinoma in comparison to other epithelial cancers of ovary is less often synchronous primary involving ovary and endometrium simultaneously. [6] So the authors conclude that classical histomorphological features still is the most reliable clue to distinguish synchronous primary tumors from metastatic tumors of female genital tract. Immunohistochemical analysis can help to solve this controversy as primary ovarian cancers are CK7 and CA125 posiitve but CA19.9 and CK20 negative. However molecular analysis can be done to corroborate the diagnosis.

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