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Case Report

Clear Cell Carcinoma Ovary Masquerading High Grade Serous Adenocarcinoma- A Case Report with Brief Review of Literature

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ABSTRACT

The different types of surface epithelial tumors of ovary can show considerable overlap in the morphological features and hence pose diagnostic challenge for the pathologist. It is important to accurately type these tumors, because of differences in their therapeutic management. We present a case of a 58 year old female, diagnosed with high grade serous adenocarcinoma ovary by a peripheral hospital, which on review was classified as clear cell carcinoma. We describe the role of immunohistochemistry in establishing the correct diagnosis. This article also highlights the lack of uniformity and consensus to diagnose clear cell carcinoma ovary. We also emphasize on its precise diagnosis, as it has poorer prognosis and does not respond well to conventional therapy.

Key words- Clear cell carcinoma, serous adenocarcinoma, ovarian malignancy, immunohistochemistry

INTRODUCTION

Ovarian carcinoma is 4th highest cause of cancer death among Indian women, with an estimated 26,834 cases diagnosed in 2012 and with 19,549 deaths in 2012. [(1)] Serous and mucinous tumors are the most common surface epithelial ovarian neoplasm. Clear cell carcinoma (CCC) is an uncommon subtype with distinct clinico-pathological, immunohistochemical and molecular characteristics. [(2)] The distinction between CCC and high grade serous carcinoma (HGSC) ovary often pose a histologic diagnostic challenge. As CCC ovary responds poorly to conventional chemotherapy compared to HGSC, its accurate diagnosis is of paramount importance for prognostication. Immunohistochemistry (IHC) is an extremely valuable diagnostic tool which has revolutionized and changed the practice of surgical pathology in past 25 years. [(3)] Since a good tentative diagnosis is required for its success, IHC is considered only an important extension of surgical pathology practice. We have used antibodies WT1, ER and P53 to establish the diagnosis as CCC ovary.

CASE REPORT

We received paraffin blocks for review, of a 58 year old female who was diagnosed with an ovarian malignancy and underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy. A diagnosis of high grade serous cyst adenocarcinoma was given at the peripheral hospital and she was referred to our tertiary center for treatment. On review, sections showed an invasive tumor with solid nests, sheets, tubulocystic pattern and micro-papillary arrangement. Tumor cells were polyhedral with abundant eosinophilic to clear cytoplasm, round to oval pleomorphic nuclei with vesicular chromatin, prominent nucleoli and occasional mitotic figures (Fig 1). Few cells showed signet ring morphology and focal intraluminal eosinophilic Periodic acid Schiff (PAS) positive hyaline material (Fig 2,3). IHC revealed WT1 and ER negativity. P53 was faint to moderate positive in the tumor cells (Fig 4). On the basis of histology and IHC a diagnosis of clear cell carcinoma ovary was given. Patient underwent staging laparotomy in our hospital and the peritoneum, lymph nodes and omentum were free of tumor deposits. She was referred to oncology for adjuvant chemotherapy. She was referred to oncology. As optimal cyto-reduction was not achieved in the initial surgery, she received three cycles of chemotherapy (Paclitaxel and Carboplatin intravenously) followed by interval cyto-reduction by a surgical oncologist which revealed no tumour deposits in the peritoneum, lymph nodes, omentum or peritoneal fluid washings. She completed three more cycles of the same chemotherapy and was apparently disease free at her first follow-up.

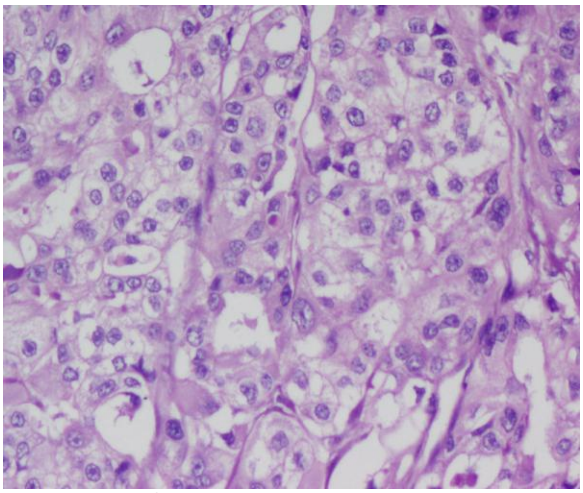

Fig 1- Nests of cells with abundant eosinophilic to clear cytoplasm, round to oval nuclei with vesicular chromatin and prominent nucleoli H&E, X200

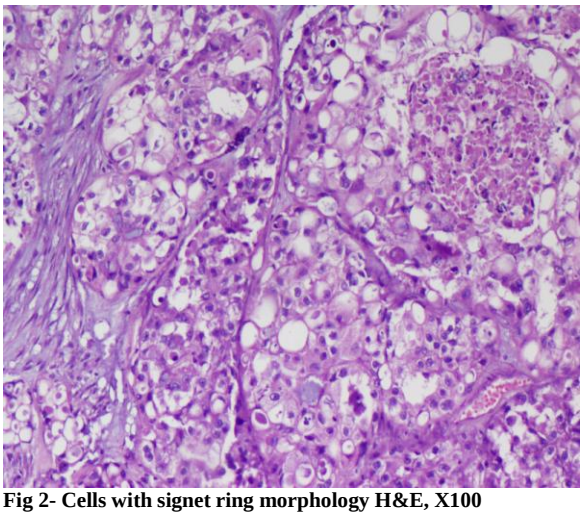

Fig 2- Cells with signet ring morphology H&E, X100

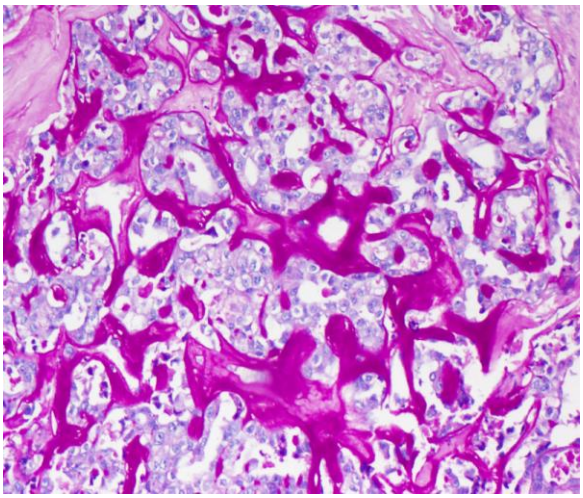

Fig 3- Intraluminal eosinophilic hyaline material PAS, X100

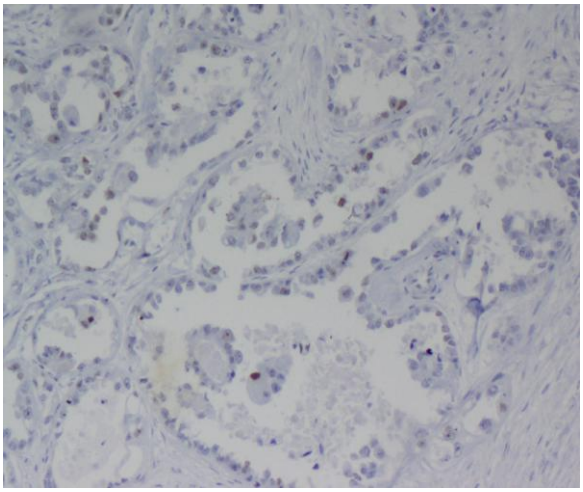

Fig 4- Faint to moderate positivity in tumor cells p53, X100

DISCUSSION

CCC is a rare histologic subtype of ovarian neoplasm accounting for 2-15% of the cases with higher incidence in East Asia particularly Japan. [4,5] This wide range of incidence highlights the diagnostic uncertainties and difficulties faced in diagnosing CCC ovary. Most important problem faced is to categorize the clear cell areas within an ovarian neoplasm. They may represent a CCC or a component of CCC in mixed tumors or clear cells within another surface epithelial ovarian tumor. [6] There is a tendency to over diagnose CCC or its component due to the presence of clear cells within a serous or endometrioid adenocarcinomas. In this regard, the presence of areas typical of serous or endometrioid adenocarcinoma favor their diagnosis. Also, one should remember that mere presence of clear cells does not constitute a diagnosis of CCC. There is a considerable histologic overlap between CCC and HGSC with regard to tumor architecture and nuclear grade. The precise morphologic criteria to distinguish the two are yet to be defined. However, features favoring HGSC are wide morphologic variation with solid sheets and slit like spaces, papillary growth with cells showing marked stratification, tufting and abundant mitoses. [4] Hence, adequate sampling of the tumor tissue for histologic study is recommended. Molecular studies reveal that HGSC are characterized by mutations in TP53 and BRCA1 or BRCA2 pathway whereas CCC possess a different pattern of molecular events which include activating mutations in PIK3CA and loss of PTEN and ARID1A. The distinct molecular characteristics may suggest the need for subtype-specific therapeutic approaches for ovarian neoplasm. No molecular study was performed in our case. [7]

IHC serves as an immensely valuable tool in the surgical pathologists' armamentarium in present era. It is used for determination of cell types, sub-typing for various classifications and most importantly in identifying the possible primary for metastatic tumor of unknown origin. Its role in prognostication of tumors and targeted therapy is also well established. [8] In CCC ovary, tumor cells are immuno-negative or weak positive for WT1, ER and p53 markers while most HGSCs are strong positive for them. IHC profile in our case favored diagnosis of CCC ovary. Recently, hepatocyte nuclear factor 1-beta (HNF - beta) has been found to be a reliable and promising nuclear marker for CCC. [4] However, this could not be done in present case as it was not available in our lab. IHC is immensely useful and employed for the cases where diagnostic uncertainty exists pertaining to clear cell areas in the tumor.

The precise diagnosis of CCC ovary is important as it has a chemo-resistant phenotype, and carries worse prognosis especially if diagnosed at later stages as compared stage-by-stage with serous adenocarcinoma. Even the residual tumor responds poorly to the conventional chemotherapy. The response rates to conventional platinum based chemotherapy is been reported between 11-27% as compared with 73-81% with serous

adenocarcinoma. [4,7] The variability in treatment response rates also reflect variable diagnostic criteria followed by different pathologists' due to their limited experience with this tumor. A phase II study (JGOG3014) tried Cisplatin with Irinotecan against Paclitaxel and Carboplatin with no added benefit. Accrual for a phase III trial trying the 2 regimes is (JGOG 3017/GCIG) is complete and the results are awaited. Also, complete removal of the tumor at primary surgery with no macroscopic residual tumor is of utmost importance in cases of CCC ovary. [8]

CONCLUSION

In this case report, we highlight the variable incidence and therapeutic response rates for CCC ovary as documented in literature, pointing towards the diagnostic uncertainties and lack of uniformity and consensus to diagnose this enigmatic tumor. We need to establish uniform morphologic criteria for its precise diagnosis and distinction from other surface epithelial ovarian tumors with clear cells. In developing countries we can perform only a limited number of IHC markers; hence its judicious use is recommended.

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