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SYNCHRONOUS PRIMARY TUMORS OF THE KIDNEY AND THE OVARIES: CASE REPORT

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ABSTRACT

CASE REPORT

Synchronous primary tumors are a rare finding and that to dual malignancy involving the kidney and ovary is extremely rare. Diagnosing double malignancy is always a clinical challenge. Only a few cases are reported in the literature with synchronous primary malignancies of the kidney and the ovaries. We present a case of a 60-year-old lady, presenting with pain abdomen. Her reports showed a right kidney mass and ovarian mass which suggested it to be a metastatic case but after surgery immunohistochemistry (IHC) from the ovarian mass was immunoreactive to CK7, WT1, ER and non-immunoreactive to CK20, RCC, CD10. Cells from the right kidney tumor were immunoreactive to PAX8 on the basis of IHC patient was diagnosed with bilateral ovarian adenocarcinoma and a simultaneous clear cell carcinoma of the right kidney. Right renal cell carcinoma was pT1bN0 whereas bilateral ovarian carcinoma was stage pT1cN0. As per current treatment guidelines, patient has been started on adjuvant chemotherapy.

INTRODUCTION

Diagnosis of multiple primary malignancies (MPMs) in a patient has been on the rise during the past decade [1] but the coexistence of double primary is rare. The first case of-of synchronous primary ovarian cancer and renal cell carcinoma (RCC) was reported in Nov 1988 from Japan by Myoga et al [2]. Since only a few cases have been reported there is no clear insight to pathogenesis of the disease. Besides this, there is always a clinical dilemma in diagnosing double primary and metastatic disease. Therefore we report a case of synchronous clear cell carcinoma of the kidney with adenocarcinoma of bilateral ovaries, the diagnostic challenge we faced, peeping into the pathogenesis with a hint to the etiology.

CASE REPORT

A 60 years female with normal menstrual history presented to our hospital with complaints of pain in right flank for about a month with a CECT done from outside which showed ill-defined soft tissue mass (6.5×5.8cm) at upper and mid pole of right kidney and a thick-walled cystic lesion 3.5×4.2 cm in right adnexa with right-sided mild pleural effusion. The first look of the reports suggested it to be the metastatic case. The patient was further advised for CA-125 which was raised 499IU/ml and PET-CT showed heterogeneous enhancing mass lesion with

central necrosis and peripheral increased FDG uptake involving the upper half of the right kidney.

Mildly enlarged lymph nodes with increased FDG uptake in periportal, portocaval, aortocaval (1.5×1.2cm, SUV max30.1), left paraaortic and retrocaval regions. A bilateral complex solid cystic mass lesion with increased FDG uptake in bilateral adnexal regions. With left adnexal cyst 4.5x4.2cm SUV max12.4.Mild ascites in the pelvic and perihepatic region. Mild right pleural effusion with the passive collapse of basal segments of the right lower lobe. Few small lymph nodes with increased FDG uptake were seen in left internal mammary, right paratracheal, subcarinal and right internal mammary regions.

On the above reports, it was pretty conclusive that we were probably dealing with metastatic carcinoma ovary. For histopathological diagnosis patient was further evaluated with FNAC from pleural effusion which came out to be negative then she was advised USG guided FNAC from ovary which was inconclusive then FNAC from kidney was advised which was suggestive of renal cell carcinoma. Now the picture was in favor of metastatic renal cell carcinoma. Ascitic fluid cytology was negative so after discussion in tumor board, it was decided to go ahead with the surgery.

The patient underwent Right nephrectomy and transabdominal hysterectomy with bilateral salpingo-oophorectomy and omentectomy with peritoneal fluid washings. Histopathology of the Right nephrectomy specimen confirmed conventional clear cell carcinoma whereas bilateral ovaries suggestive of high-grade papillary adenocarcinoma. Further immunohistochemistry (IHC) was done to confirm dual malignancy. IHC from the ovarian mass was immunoreactive to CK7, WT1, and ER and nonimmunoreactive to CK20, RCC, and CD10. Cells from the right kidney mass were immunoreactive to PAX8. The patient has been planned for adjuvant chemotherapy and has received one cycle of paclitaxel and carboplatin.

DISCUSSION

Billroth in 1889 was the first to describe multiple primary malignant neoplasms (MPMN). [3] Warren and Gates in 1932 came up with a report of 1,259 cases [4] and enumerated criteria for Diagnosis Double Primary Malignancies as 1. Histological confirmation of malignancy in both the index and secondary tumors. 2. There should be at least 2 cm of normal mucosa between the tumors. If the tumors are in the same location, then they should be separated in time by at least five years. 3. Metastatic probability of each other must be excluded.

Further Double primary malignancies could be divided into two categories, depending on the interval between tumor diagnosis. Synchronous malignancies are defined as second tumors which have been occurring either simultaneously, or within 6 months after the first malignancy while metachronous malignancies are secondary tumors that have developed after 6 months, or even more than that from the first malignancy[5]. In literature, multiple malignancies in the same patient are reported to be about 1.84–3.9% of all cancers. But in same individual coexistence of double primary is extremely rare. [6] Reports of incidence of synchronous primary malignancy are about 0.7% [7] with no clear insight to pathogenesis. However, common etiologies, such as exposure to the same hormone or carcinogen, are often suspected [8] There have been few reports which point towards an association between RCC and steroid hormone target organs (breasts, uterus, ovaries). Di Silverio et al reported 17 cases of RCCs among which, only three RCCs were associated with ovarian carcinoma.[9] Concolino et al found that cytosol from normal human kidney specimens showed binding activity for steroid hormones, which was related to a receptor specific only for estradiol and progesterone.[10]

Several reports have described the presence of androgen receptors, ER, and PR, in RCC tissue. [10, 11] Banerjee et al also found that estradiol-induced the development of micronuclei and aneuploidy in renal tissue. [12] How estrogen induces tumorigenesis in

the kidney remains to be clarified. However, we did detect the presence of ER in the ovary but not in RCC in our case.

Etiology of epithelial ovarian cancer is unknown but estrogen has been suspected to be the causative agent in some patients [13]. Currently, in the English literature, Balat et al. in 1996 reported synchronous clear cell renal cell carcinoma of the right kidney and epithelial cell carcinoma of the right ovary [6]. The similar case report also reported by Wong C et al in 2003[13].

In our case histopathology of the kidney was clear cell carcinoma and ovary was adenocarcinoma but to confirm dual malignancy IHC was undertaken because IHC is very helpful in differentiating between tumor types and diagnosing rare malignancies [14]. PAX8 is expressed at high levels in specific types of tumor, including thyroid and renal carcinomas and pancreatic neuroendocrine tumors. [15] Six markers including cytokeratin-7 (CK7), CK20, carcinoembryonic antigen (CEA), cancer antigen 125 (CA125), estrogen receptor (ER) and Wilms' tumor 1 (WT1) to help classify various surface epithelial tumors as well as to differentiate them from tumors metastatic to the ovary. [16]. in our case IHC from the ovarian mass was not immunoreactive to CK20, RCC, C D10, proving it to be not a metastasis from kidney and was immunoreactive to CK7, WT1, ER suggesting ovarian primary. Cells from right kidney mass were immunoreactive to PAX8, specific for kidney proving it to be double primary.

Prat, divided epithelial ovarian carcinoma (EOC) in five groups: high-grade serous (HGSC), endometrioid (ECs), clear cell (CCCs), mucinous (MCs), and low-grade serous (LGSC) [17]. Incidence of HGSCs is around 70% and the most common variant, usually occurring in the advanced stage and spread beyond the ovary at diagnosis. They are positive for p53, BRCA, WT1, and p16 mutation, have high ki67 levels and commonly express estrogen receptors (ERs). In our case, genetic testing was not done but IHC showed WT1 and ER positivity suggesting it to be High-grade tumor and maybe BRCA or p53 or p16 mutation. ERs are also expressed in LGSCs and ECs, but they are negative in almost all CCCs and MCs. LGSCs account for <5%of all cases of EOC, are frequently associated with a serious borderline tumor and follow a relatively indolent course. They show KRAS and BRAF mutations but not BRCA and p53 alterations.

MCs account for 3-4% of ovarian tumors, large size, unilateral, usually confined to the ovary and shows gastrointestinal differentiation. KRAS mutations are usually seen with immunoreactivity for cytokeratin 7 and 20.

10% of all ovarian carcinomas ECs are occurring mostly in perimenopausal age and at an early stage. 28%of cases are bilateral, associated in 15–20% of cases with endometrium carcinomas, and likely to arise from endometriotic cysts.

CCCs account for 10% of ovarian carcinomas, presenting at an early stage and associated with endometriosis. These tumors carry ARID1A mutations and are usually positive for HNF1-β [17].

The most common genetic alteration associated with the development of clear cell renal cell carcinoma (ccRCC) is loss of the short arm of chromosome 3 (loss of 3p), seen in approximately 95% of cases of ccRCC. The common genes involved in the pathogenesis of ccRCC include *VHL*, *PBRM-1*, *SETD2*, *BAP-1*, *KDM5C*, and *MTOR*. Other genetic alterations include gain of 5q (69%), partial loss of 14q (42%), 7q gain (20%), 8p deletion (32%), and 9p loss (29%)[18]

The two most common genes involved in the pathogenesis of RCC are the Von Hippel–Lindau (VHL) gene and the protein polybromo-1 (PBRM-1) gene. The most common acquired risk factors for RCC are smoking, hypertension, obesity, chronic analgesic use, and diabetes [19]. In our case, the lady was known hypothyroid but was not having any of the listed acquired risk factors.

VHL is a tumor suppressor gene transmitted in an autosomal dominant fashion (VHL disease) or in a sporadic manner that plays a pivotal role in the development of ccRCC. VHL can be altered and VHL gene

alterations through genetic and epigenetic mechanisms can be found in up to 90% of ccRCC cases [20] Musso et al.[21] reported a case of a 29-year-old young female VHLD point mutation of the VHL gene associated with ovarian carcinoma

PBRM-1, a tumor suppressor gene, encodes a protein called BAF180, which is a subunit of the nucleosome remodeling complex resulting in unchecked cell growth and subsequent tumorigenesis.[22] Mutations in *BRCA1* are associated with 60-90% lifetime risk of developing breast cancer and 50% for ovarian cancer [23]. BRCA1-associated protein-1 (BAP-1) is a tumor suppressor gene located on 3p. This gene is mutated in approximately 15% of ccRCC cases [24]. Our case does not suggest a common etiological factor or any classical genetic presentation but it needs to be further investigated.

Although extremely rare, the possibility of coexistent RCC and ovarian cancer should be considered in clinical practice.

CONCLUSION

Only a few reports of double primary tumors involving the kidney and the bilateral ovaries are reported. Once the possible etiological factors are ruled out genetic susceptibility should always be thoroughly investigated. Careful attention should be paid to the differential diagnosis between double primary and metastatic tumors, based on the pathologic and clinical characteristics

Such cases always remain a diagnostic challenge and with no clear cut guidelines for treatment the management should be decided on histology, stage and performance status of the patient.

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