A rare synchronous primary tumour of female genital tract

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Abstract

Introduction: Synchronous primary cancers are very rare in the general population. We present a rare case of synchronous primary endometrial and primary fallopian tube cancers.

Case: The patient, a 61 year old female presented with postmenopausal bleeding, and diagnosed as Carcinoma Endometrium was taken up for Total Abdominal Hysterectomy with Bilateral Salpingo oophorectomy with Bilateral Pelvic Lymph Node Dissection. The histopathology revealed synchronous primary carcinomas of endometrium and left fallopian tube.

Conclusion: The reason for better median overall survival of patients with synchronous primary endometrial and fallopian tube cancers is not intuitively obvious; perhaps because it is low grade and biologically less aggressive, detection of patients at earlier clinical stage is essential for appropriate management.

Keywords: Endometrioid endometrium, fallopian tube, synchronous carcinoma

Introduction

Carcinoma endometrium is the most common invasive tumour of the female genital tract and the most common gynecological malignancy in elderly females, 80% being postmenopausal at time of diagnosis. Based on pathogenesis, the endometrial carcinoma is divided into type I and type II. Type I occurs due to excess estrogen stimulation against a background of endometrial hyperplasia, more common in 40 years or younger with frequently endometrioid prototype. Type II is independent of estrogen stimulation and are seen in older females, whose prototype is serous carcinoma.

Historically and traditionally, primary fallopian tube carcinoma has been considered to be a rare entity, accounting for approximately 1% of primary genital tract malignancies with incidence 0.1 to 1.8%. [1,2].

Synchronous multiple tumours of female genital tract are relatively rare, comprising of 1-6% of genital neoplasms [2]. Embryologically similar tissue when simultaneously exposed to hormonal influences or to same carcinogens may develop synchronous cancers [10] in genetically susceptible individuals such as patients with a more fragile genome and with a prior genetic damage [12, 8]. Mutation of p53, loss of heterozygosity at several foci on chromosome 13q play a role in the pathogenesis of BRCA1 related ovarian and fallopian tube carcinoma [3]. No such association is documented for synchronous endometrial and fallopian tube carcinoma [2].

We present a rare case of synchronous primary endometrioid endometrial carcinoma and primary fallopian tube endometrioid carcinoma. Incidence of synchronous primary endometrioid carcinoma of endometrium and fallopian tube is fewer than 15 cases [4].

Case report

A 61 year old female came with c/o postmenopausal bleeding. Ultrasonogram abdomen revealed increased Endometrial thickness about 15mm. Contrast Enhanced Magnetic Resonance Imaging Pelvis gave the impression as FIGO Stage IB Carcinoma Endometrium. Hysteroscopy showed normal endocervical canal and hyperplastic endometrium.
Endometrial curettings performed for diagnostic purpose showed tumour tissue fragments with villoglandular architecture and branching papillae lined by stratified atypical columnar cells and a diagnosis of Endometrioid carcinoma, villoglandular variant was made. Cervical biopsy showed features of chronic non-specific cervicitis. Total Abdominal Hysterectomy with Bilateral Salpingo-oophorectomy with Bilateral Pelvic Lymph Node Dissection was done. Uterus showed a grey white proliferative growth arising from the uterine fundus and extending into the endometrial cavity. The growth appeared grey white, soft, friable measuring 3 x 2.7 x 0.8 cm occupying > 50% of myometrium. The endometrium showed villoglandular variant of endometrioid carcinoma composed of glands with villous architecture; some of them small, but others large to cystically dilated. Few glands were round to oval with irregular contours. The pathologic staging was pT1bN0 and FIGO Grade 1 Stage IB.

![Fig: A- Photomicrograph showing villoglandular variant of Endometrial Endometrioid Carcinoma (H & E x400); Figure B - Photomicrograph showing glands with villous architecture lined by atypical cells (H & E x400)](image)

Left fallopian tube was edematous and congested and its lumen was dilated. On serial sectioning showed a grey white proliferative friable growth in the middle one third, measuring 0.8 x 0.8 cm. The microscopic examination of the friable mass showed proliferation of closely packed and complex atypical glands with smooth luminal borders; papillae or solid sheets WHO grade G3 Endometrioid Carcinoma.

![Fig: C- Photomicrograph X showing Fallopian tube Endometrioid Carcinoma (H & E x40); Figure D – showing fallopian tube lumen filled with complex glandular structures lined by atypical cells (H & E x100).](image)

Immunohistochemistry: Tumour cells showed a strong diffuse positivity for ER / PR with focal positivity for CK-7, PAX-8, vimentin, p16, MSH-6, PMS2. Also, Beta catenin showed membrane positivity with a proliferation index of Ki 67- 80%. The tumor cells were negative for p53. Thus inspite being p16 positive and p53 negativity, the presence of ER and PR positivity favours an endometrioid endometrial carcinoma. Tumour cells in Fallopian tube Endometrioid carcinoma were positive for CK-7 and PAX-8. Extension from endometrial carcinoma was ruled out as there was no direct extension of the endometrial tumour to the tube. Tubal growth was in the middle one third. Proximal part of fallopian tube was free and also there was no serosal involvement.

**Discussion**

The occurrence of synchronous primary endometrial and fallopian tube cancers is very rare \[4, 6, 7, 8\]. Patients are usually postmenopausal, obese and nulliparous. The main symptoms are abdominal pain, bleeding and palpable pelvic mass \[4, 7, 8\]. As in our case, and also as in other similar studies, the patient was postmenopausal and presented with abnormal uterine bleeding. Many hypotheses are suggested behind the mechanisms of multiple primary cancers such as family history, immunologic and genetic defects, and prolonged exposure to carcinogens, radiation and chemotherapy \[2\]. The morphogenetic origin of uterine corpus, fallopian tubes and ovarian epithelium as a single morphological unit could explain the development of synchronous endometrioid
tumours in different components of Mullerian System. The theory of “Secondary Mullerian System” proposed that the epithelia of cervix, uterus, fallopian tubes, ovaries, and peritoneal surface had shared molecular receptors responding to same carcinogenic stimulus leading to the development of multiple primary malignancies of similar histology synchronously [2, 6, 9]. Culton et al. [14] published 13 cases of synchronous independent primary endometrial and tubal carcinomas [2, 8].

The diagnostic criteria for synchronous tumours include either the detection of dissimilar histologic subtypes or all of the following rules if histologic subtypes are similar: 1. Both tumours confined to primary sites; 2. No direct extension between tumours; 3. No lymphovascular tumour emboli; 4. No or only superficial myometrial invasion; 5. No distant metastasis all of which applies to our tumour.

Historically, fallopian tube carcinoma was considered to be a rare entity. However substantial data have accumulated indicating that at least a subset of serous ovarian cancers actually arise from the epithelium of the fallopian tube. This idea is supported by the frequent identification of serous tubal in situ carcinoma in women at risk for serous carcinoma (Eg. Women with germline BRCA1 mutations) and observations showing that failure to remove the fallopian tubes at the time of oophorectomy is associated with a significant residual risk of fallopian tube cancers.

High grade serous carcinoma is the most common type of fallopian tube cancers. Incidence of Endometroid carcinoma in fallopian tube is 22% to 42.5%. Prognosis for which is good but it depends on stage. 69% confined to one or both tubes at presentation, 62% symptomatic and 38% incidental. Like in other studies, ours too was an incidental finding of primary endometrioid carcinoma of fallopian tube which was not apparent clinically or radiologically. The endometrioid carcinoma is strongly immunoreactive for cytokeratin and epithelial membrane antigen, cytokeratin 7 (CK-7) and negative for cytokeratin 20. There is basal/ perinuclear staining for vimentin. Membranous and nuclear staining for beta-catenin present. Chromogranin, synaptophysin, CD56 may be focally positive. Cytoplasmic CEA expression is uncommon.

Low grade endometrioid carcinoma shows a diffuse and strong estrogen and progesterone receptors (ER and PR) positivity. Normal (wild type) p53 negative or patchy p16 positive and are positive for PAX-8. The over expression of p53 and p16 are seen in 30% of High grade endometrioid carcinoma.

A heritable multiple cancer syndrome of colon and endometrial adenocarcinoma, called Lynch Syndrome, or HNPPC (Hereditary Non Polyposis Colon Cancer) is seen in families that carry constitutive mutations in the DNA mismatch repair pathway. Lifetime endometrial cancer risk is approximately 39%; tumours are microsatellite unstable, can occur at any age, often have Endometrial Intraepithelial Neoplasia (Atypical Hyperplasia) precursors, and present as any histotype. Affected genes may include any element of the mismatch repair pathway. Most commonly MLH1, MLH2, MSH6 or PMS2 genes.

Universal screening of all primary endometrial cancers by immunohistochemical staining for these 4 genes has become a common method to identify previously unknown heritable cases (1%-3% of all endometrial cancers) and thereby offer appropriate counselling.

So the endometrioid carcinoma of endometrium and fallopian tube are two primary synchronous tumours and not metastasis from either site as there is no continuation between the two cancers. Also Immunohistochemistry markers prove that they are primary from both endometrium and fallopian tube.

**Conclusion**

Endometrial cancer usually produces early symptoms, diagnosed in over 70% of patients when it is still confined to the uterus [6]. A clinically silent fallopian tube cancer with no much early symptoms was diagnosed earlier because of the symptomatic endometrial cancer, accounting for the inherent, more favourable outcome of the synchronous primary cancers [7] (compared to the single primary with metastatic disease). Overall survival and treatment would vary considerably as multiple primary synchronous neoplasms of endometrium and fallopian tube have good prognosis in terms of survival.

**References**