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Synchronous Malignancies: Pathological Analysis of Three Patients, Each with Dual Malignancies

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Abstract

Multiple primary malignancies are defined as two or more malignancies arising independently to each other in the same or different anatomical sites, while excluding the possibility of metastasis from the primary malignancy. Here, we present three cases, each with dual malignancies involving different anatomical locations.

Keywords

- multiple malignancies
- metachronous
- primary
- synchronous

Introduction

Multiple primary malignancies (MPMs) are seen in 2.4 to 17% of all tumors.[1,2] MPMs can be further divided into synchronous and metachronous, based on the time interval between the first and second tumor. In the synchronous group the diagnosis of the second malignancy is made within 6 months of primary, while the metachronous group is defined as occurrence of second diagnosis after 6 months of primary malignancy. It is imperative for the surgeons to distinguish between MPMs and metastatic tumors, as this has impact on both prognosis and subsequent therapeutic strategies.

Case Series

Case 1

A 40-year-old female diabetic patient presented with a lump in the right breast for 8 months. This was associated with pain that was continuous in nature. There was no history of trauma, ulceration, nipple discharge, or retraction. She was amenorrheic for the past 1 year and was on oral hypoglycemic drugs and injectable soluble insulin. Laboratory investigations revealed mild anemia (Hb 10 g/dL) along with elevated glycosylated hemoglobin (Hb; 12.5%). Kidney function tests were normal. Ultrasound (USG) of breast revealed a lobular mass measuring $4.5 \times 4 \times 2.5$ cm in the right upper quadrant along with few echogenic areas of calcification. For the possibility of metastatic spread, a positron emission tomography scan was done which confirmed the tumor in the right breast along with an incidentally detected metabolically active lesion in the mid pole of right kidney. Magnetic resonance imaging of abdomen showed a well-defined, round, heterogeneous, encapsulated, hypodense mass measuring $4.2 \times 3.9 \times 4.3$ cm in the mid pole of right kidney. A possibility of oncocytoma or renal cell carcinoma was given on imaging. Although, she had no urinary

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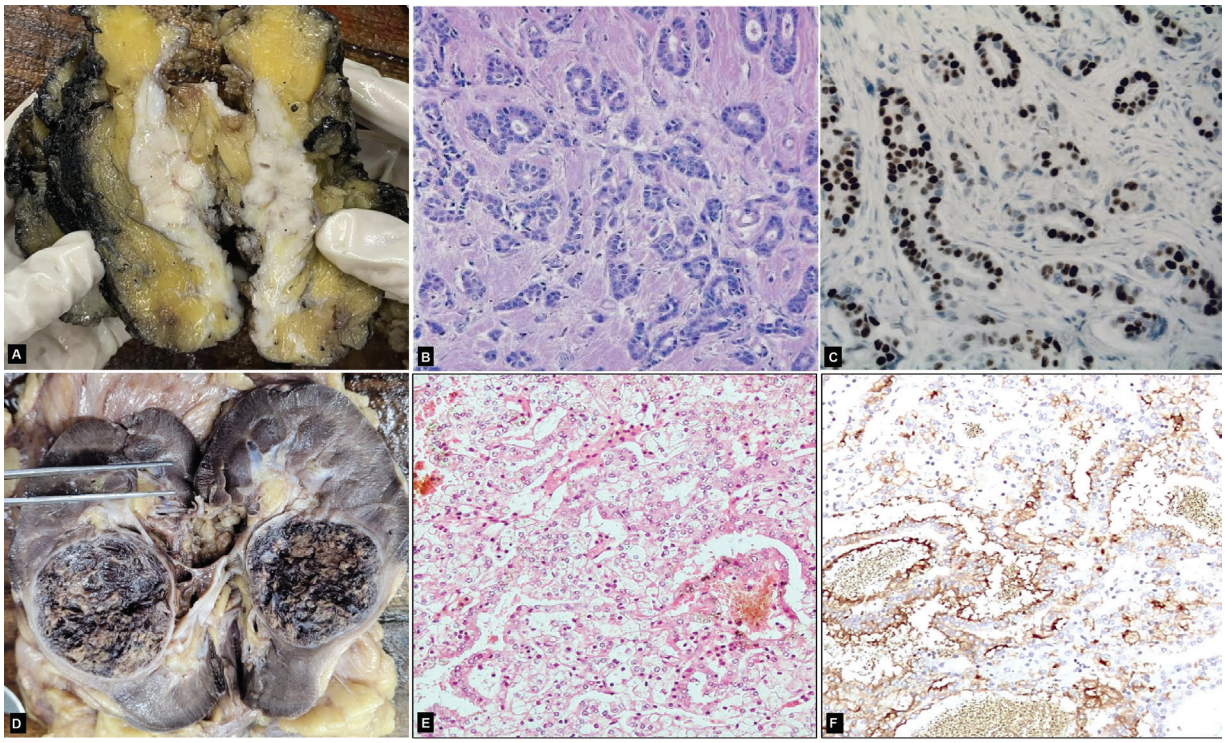

Fig. 1 Case 1: (**A**) Gross image of the breast showing a tumor with ill-circumscribed borders with firm gray white cut surface. (**B**) Invasive breast cancer—Tumor cells arranged as tubules and cords in desmoplastic stroma (hematoxylin and eosin [HE] 100 ×). (**C**) Immunohistochemistry (IHC): estrogen receptor (ER) positive (100 ×). (**D**) Cut surface of kidney showing a well-circumscribed tumor with a variegated cut surface. (**E**) Clear cell renal cell carcinoma—Tumor cells arranged in sheet and focal alveolar pattern, cells with abundant clear to eosinophilic cytoplasm (HE 40 ×). (**F**) IHC: CD10 positive (40 ×).

complaints or any palpable mass per abdomen. Modified radical mastectomy along with axillary lymph node dissection and right nephrectomy was done and sent for histopathological examination. Serial sectioning of the breast showed an ill-circumscribed, gray white firm tumor measuring 5 × 3 × 2 cm, which on microscopic examination showed tumor cells arranged in tubules and cords (►**Fig. 1A**). The Nottingham score obtained was 6 (tubule formation 50–60%; moderate nuclear pleomorphism; mitosis 8–10/10 high-power field [hpf]) (►**Fig. 1B**). On immunohistochemistry (IHC), the tumor cells were estrogen receptor (ER) positive and negative for progesterone receptor (PR), Her2neu (►**Fig. 1C**). Cut surface of kidney showed a variegated tumor measuring 4.2 × 3.9 × 4 cm which on histologic examination showed tumor cells arranged in sheet and focal alveolar pattern separated by thin fibrovascular septa (►**Fig. 1D**). Individual cells showed abundant clear to eosinophilic cytoplasm with round to ovoid pleomorphic nuclei (►**Fig. 1E**). IHC stain showed diffuse CD10 positivity in the tumor cells (►**Fig. 1F**). Thus, a final diagnosis of synchronous invasive breast carcinoma and renal cell carcinoma was given.

Case 2

A 36-year-old diabetic female patient presented with complaints of irregular menstrual cycle sine 1 year and heavy uterine bleeding for the past 3 months. The menstrual bleeding usually lasted for 10 to 12 days, soaking 8 pads/day. Patient also complained of right breast mass for 2 to 3 months. She had a past history of left breast carcinoma in 2016 for which she underwent modified radical mastectomy along with six cycles of chemotherapy. On admission, she had moderate anemia (Hb < 7.8 g/dL). USG right breast revealed an irregular hypoechoic lesion of 2.7 × 1.5 cm with irregular margins and peripheral vascularity in the upper outer quadrant. Endometrial biopsy showed a high-grade malignant spindle cell tumor, possibility of leiomyosarcoma and high-grade endometrial stromal sarcoma was given. Intraoperatively, the uterus was enlarged to 14 to 16 weeks gravid uterus size and was soft and vascular. A fundal mass of 5 × 5 cm with submucosal extension was observed. Total abdominal hysterectomy and bilateral salpingo-oophorectomy along with modified radical mastectomy of right breast was done. Serial sectioning of the uterine mass showed a polypoidal tumor measuring 11 × 7 × 6.5 cm projecting into the endometrial cavity and infiltrating into myometrium (►**Fig. 2A**). Microscopic examination of the uterine mass showed a highly cellular malignant spindle cell tumor, arranged in sheet and fascicular growth pattern, composed of cells with eosinophilic fibrillary cytoplasm, cigar-shaped nuclei with blunt ends showing moderate to marked pleiomorphism along with many atypical mitotic figures (►**Fig. 2B**). On IHC, the tumor cells showed positivity for smooth muscle actin and desmin and were negative for ER, PR, epithelial membrane antigen, CD10, and p53 (►**Fig. 2C** and inset). The breast tumor was well circumscribed, measured 4 × 3 × 2.5 cm with a gray white cut surface and was arranged as solid nests and tubules (►**Fig. 2D**). Nottingham score obtained was 7 (tubule formation 60%; moderate

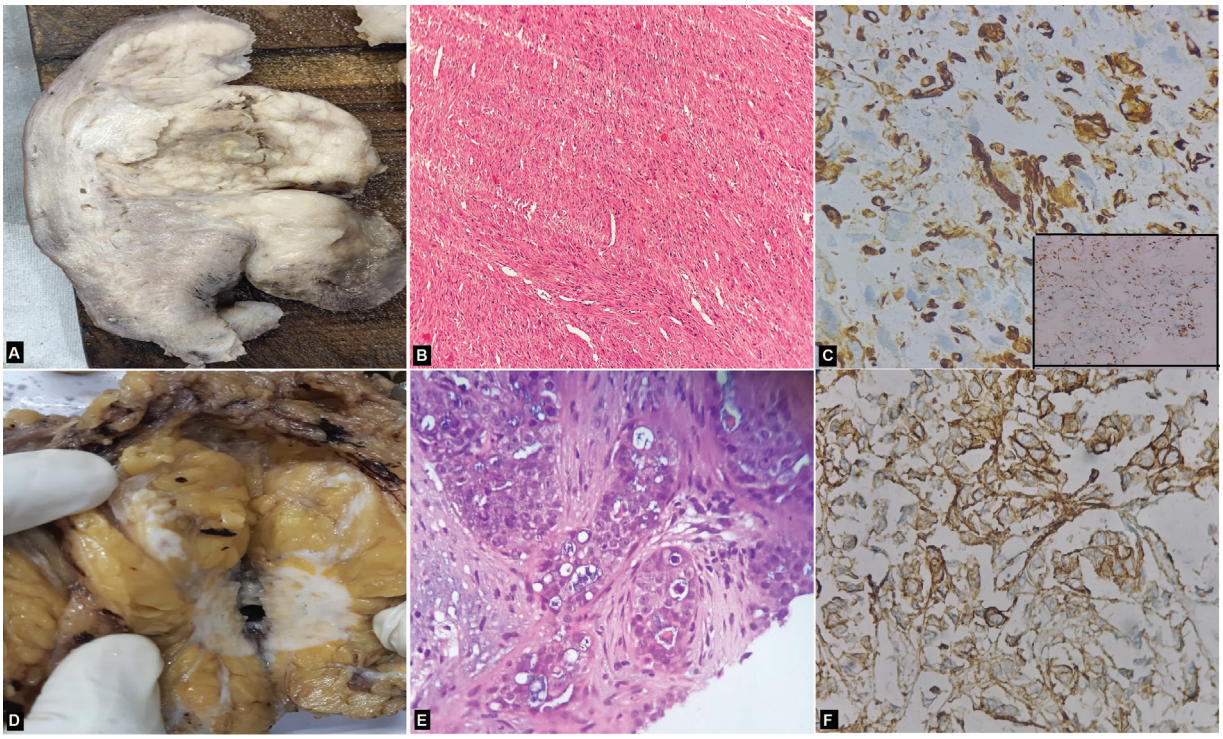

Fig. 2 Case 2: (**A**) Gross image of the uterus showing a polypoidal tumor projecting into the endometrial cavity and infiltrating into the myometrium. (**B**) Leiomyosarcoma—Malignant spindle cells arranged in sheet and fascicular growth pattern (hematoxylin and eosin [HE] 40 ×). (**C**) Immunohistochemistry (IHC): smooth muscle actin (SMA) positive (100 ×) (inset showing desmin positive [40 ×]). (**D**) Cut surface of breast showing a tumor with well-circumscribed borders. (**E**) Invasive breast cancer—Tumor cells arranged as solid nests (HE 100 ×). (**F**) IHC: Her2neu 3+ positive (100 ×).

nuclear pleomorphism; mitosis > 20/10 hpf) (►**Fig. 2E**). Ki67 proliferative index was 50 to 60%. The tumor cells were positive for ER, PR, Her2neu, and Ki67 was 70 to 80% (►**Fig. 2F**). Thus, a final diagnosis of synchronous leiomyosarcoma of uterus and invasive breast carcinoma was given.

Case 3

A 67-year-old male patient presented with complaints of constipation and hematuria on and off for the past 8 to 9 months. He also complained of indigestion, loss of weight, and decreased appetite in the last 3 to 4 months. Contrast-enhanced computed tomography of abdomen showed an irregular polypoidal mass lesion of 4 × 4 cm involving the right and posterior wall of bladder. Another lesion measuring around 4 × 4 × 1 cm involving the distal wall of rectum with seen. Rectal biopsy and transurethral resection of bladder tumor was done which confirmed presence of adenocarcinoma, rectum, and low-grade papillary urothelial carcinoma, and urinary bladder, respectively. Radical cystoprostatectomy along with low anterior resection was done. A polypoidal growth of 4 × 4 cm was noted in the right and posterior bladder wall, adjacent to right ureteric opening (►**Fig. 3A**). Rest of the urinary bladder wall appeared normal. Histological examination showed long branching papillae, with cells showing loss of nuclear polarity and moderately pleomorphic nuclei (►**Fig. 3B, C**). Although, no invasion into the muscular wall was noted. Grossly, an ulceroproliferative circumferential hard growth measuring around 4 × 4 cm was observed proximal to the anorectal junction (►**Fig. 3D**). Rest of the bowel and viscera appeared unremarkable. The rectal tumor showed well-formed glands, arranged in back-to-back manner (►**Fig. 3E**). The malignant cells showed moderate nuclear pleomorphism along with conspicuous nucleoli (►**Fig. 3F**). Based on morphological features, diagnosis of synchronous low grade noninvasive papillary urothelial carcinoma and moderately differentiated adenocarcinoma of rectum was rendered.

Discussion

Patients developing more than one malignancy in their lifetime are quite rare and happen only in a subset of patients, where in course of detection and management of the primary malignancy, another tumor is detected, mostly with the use of advanced imaging modalities. Warren and Gates have defined the criteria for classifying a tumor as "second primary malignancy." Diagnostic criteria require each cancer to be proven malignant by histopathological examination, and there should be at least 2 cm of normal mucosa between the tumors, if they are in same location. They should also be separated in time by at least 5 years and the possibility of metastasis should be excluded.[3] Zhai et al, in their retrospective analysis of 15,321 patients with malignant tumors, found 167 patients (1.09%) with multiple primary malignant tumors, which included 144 double primaries and 23 triple primaries.[4]

Tumorigenesis involves successive "hits," leading to a cascade of events, thus culminating into neoplastic transformation of the cells. Genetic susceptibility, smoking, occupational hazards, dietary intake, and aging are the known

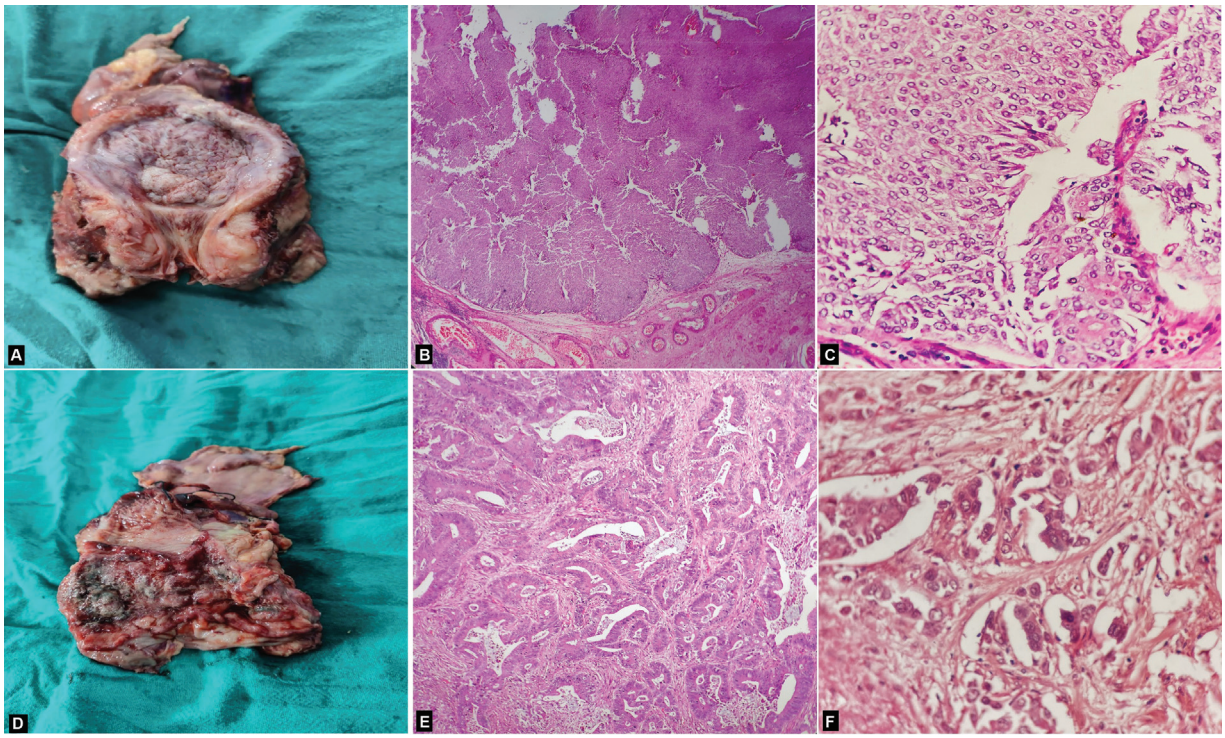

Fig. 3 Case 3: (**A**) Gross image of the urinary bladder showing polypoidal growth involving the right and posterior wall. (**B**) Noninvasive papillary urothelial carcinoma—Tumor cells arranged in long branching papillae (hematoxylin and eosin [HE] 40 ×). (**C**) Urothelial cells showing loss of nuclear polarity and moderately pleomorphic nuclei (HE 400 ×). (**D**) Low anterior resection specimen showing an ulceroproliferative circumferential growth proximal to the anorectal junction. (**E**) Rectal adenocarcinoma—Glands arranged in back to back manner (HE 40 ×). (**F**) Tumor cells showing moderate pleomorphism with conspicuous nucleoli (HE 400 ×).

factors which are intricately linked to each other, thus playing interacting roles in the development of various cancers like breast, gallbladder, pancreatic, colon, and rectal cancers. Development of MPMs is a multifactorial process, and the likely possible mechanisms involved are defective immune surveillance systems, inherent faulty gene expression, tumor suppressor genes, and many other possible etiologies. It has been observed that MPMs share a common underlying oncogenic predisposition for the primary and the subsequent malignancies. Indeed, time factor also plays an instrumental role, as supported by the fact that elderly patients are more likely to develop MPMs.

Detection of successive malignancies is crucial for both clinicians and pathologists, requiring vigilant examination of the organ system involved, for example, it is quite reasonable for a urologist to expect the possibility of prostate cancer along with concomitant bladder or renal malignancy. A gynecologist is always on a look out for the possibility of cervical, endometrial, or ovarian malignancy after the diagnosis of any one of the primaries. But, the detection of other primary cancers "outside" the organ system with which the specialist doctor is primarily concerned is usually masked during preoperative evaluation. MPMs are more commonly seen in gastrointestinal tract followed by genitourinary system.[5] Among the gynecologic MPMs, breast cancers have been commonly associated with ovarian, endometrial, or cervical cancer. Due to common mutations and pathogenic pathways, there is always an increased probability of developing additional primary cancers. It is well know that carriers of the *BRCA-1* mutation are more likely to develop breast and ovarian cancer. Lu et al after performing whole-exome sequencing on 11,416 patients, found out few addition genes, namely, *MSH6* and *ATM*, that may increase the susceptibility to develop breast and ovarian cancer.[6] *CDKN2A* mutations have also been detected in both cancers. Few of the pathogenic pathways which have gained attention with respect to their association to MPMs are tumor-associated macrophages (TAMs). They have a common association in breast, renal, and colorectal carcinoma patients. In the published studies, it has been proven that TAMs facilitate angiogenesis, by hampering antitumor immune responses, thus promoting tumor growth and metastasis.[7] Dietary fat and obesity can enhance procreation of hormone-sensitive tumors, such as endometrial, ovarian, prostatic, and breast malignancy as adipose tissue consists of triglycerides and cholesterol and form elementary blocks for estrogen and testosterone. Genetic syndromes like hereditary nonpolyposis colorectal cancer syndrome, confer an increased risk of colon cancer as well as extracolonic tumors of uterus, ovaries, stomach, biliary tree, urinary bladder, renal pelvis, and ureter. Calderwood et al in their retrospective cohort of 3,57,597 colorectal cancer patients, observed 3,026 patients which subsequently developed urologic cancer on follow-up.[8] It has also been found that development of second cancers could be treatment-related to the primary cancer. This has been observed in patients undergoing treatment with highly selective RAF inhibitors (for melanomas), becoming prone to develop cutaneous squamous tumors.[9]

MPMs are often misdiagnosed as recurrence or metastasis of the original malignancy, which may result in inappropriate treatments, thus inevitably may lead to adverse effects on the patient's prognosis. One of the frequent challenges encountered by the oncologist is to find an anticancer treatment protocol that covers both malignancies without chances of increased toxicity or any pharmacologic drug interaction or any mishap that maybe incur deleterious impact on the overall outcome. Thus, there is no universal protocol for the treatment of multiple malignancies. When multiple primary malignant tumors are pathologically confirmed, each tumor should be evaluated and staged as an independent tumor. In general, the pragmatic solution is to treat the more aggressive tumor which would be more detrimental to the patient's survival or quality of life. If patient is fit for surgery, resection for both tumors should be prioritized and could be combined with chemo- or radiotherapy. Preoperative risk assessment, postoperative monitoring, and long-term follow-up are indispensable and should be strictly followed in such cases.

Conclusion

Strong clinical acumen and suspicion is required to identify malignancies with a synchronous presentation and its differentiation from metastatic disease is pivotal as metastatic disease indicates disease progression and a poor prognosis. A regular follow-up increases the chances of early detection of synchronous or metachronous malignancies, thus improving the overall survival. During follow-up, cancer patients should be informed about the role of preventive medicine and should be encouraged of the various screening methods.

Guarantor of Submission

The corresponding author is the guarantor of submission.

Declaration of Patient Consent

The authors certify that they have obtained the appropriate consent from the patient's parents. The parents have given their consent for the images and other clinical information to be reported in the journal. The parents understand that the name and initials will not be published.

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Conflict of Interest

None declared.

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