Case Report

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Multiple Primary Metachronous Malignancies, Namely Kidney, Colon, Uterus, and Breast Cancer: A Case Report

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ABSTRACT

The incidence of multiple primary malignancies (MPMs) has risen in clinical practice; however, cases involving three or more primary cancers remain rare. A 56-year-old postmenopausal female with a significant familial cancer history developed four primary malignancies: papillary renal cell carcinoma, endometrial stromal sarcoma, colon adenocarcinoma, and invasive ductal carcinoma of the breast. The patient passed away after one year of receiving palliative treatment for her metastatic breast cancer. This study reviews 33 cases of MPMs, primarily involving breast, colon, and uterine cancers, mostly in women over 60. Genetic predisposition plays a significant role, with 35.5% having hereditary cancer syndromes.

This report emphasizes the importance of considering new masses in cancer patients as potential new malignancies. Early detection using fluorodeoxyglucose positron emission tomography (FDG-PET), implementing genetic testing, and timely cancer screenings in high-risk families significantly improve patient outcomes and management.

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Introduction

The work has been reported in line with the SCARE criteria [1]. MPMs are described as two or more malignant tumors emerging separately in the same or different organs while metastasis of the primary malignancy is excluded. The detection of MPMs is on the rise mainly due to a significant upsurge in new cancer cases, increased longevity, and improved cancer survival rates on account of advancements in cancer treatment and diagnostic procedures [2]. In previously published reviews, the incidence of multiple primaries was reported between 2.4% and 8% depending on the cancer population, while in patients with breast cancer the incidence of multiple primaries was approximately 4.1% [3]. However, most are double primary cancers, and quadruple cancer in a single patient is rare, about <0.1% [4]. In the literature, the reported frequency of triple primary malignancies ranges between 0.04% and 0.81% [5–10].

We herein present a 56-year-old postmenopausal woman with metachronous renal cell carcinoma, endometrial stromal sarcoma, sigmoid adenocarcinoma, and invasive ductal carcinoma (IDC). We also review the previously reported cases of triple or more primary cancers including breast cancer.

Case presentation

The subject is a 56-year-old postmenopausal female with a medical history of four distinct primary cancers diagnosed at separate intervals (Table 1). Her familial history is significant, as it includes three brothers and her mother who succumbed to colon cancer, as well as a sister who passed away due to a brain tumor.

The patient, a housekeeper, had no history of smoking or alcohol consumption, and her medication history was unremarkable. Her medical history included minor thalassemia and a cholecystectomy performed due to acute cholecystitis. In 2013, she underwent a total left nephrectomy for renal cell carcinoma of the left kidney at another hospital. She had presented to that hospital with brief pain in the left upper back region. An abdominal and pelvic CT scan with intravenous contrast revealed a 3.2 × 2.7 cm complex cyst in the left kidney, characterized by an irregular wall, thick septa, and enhancing soft tissue components, without involvement of regional lymph nodes, the inferior vena cava, or the renal vein (Bosniak category IV). Pathology of the resected kidney confirmed a diagnosis of papillary renal cell carcinoma, confined to the kidney without capsular or other structure involvement (T1N0M0).

In August 2017, the patient presented with a pale appearance and a hemoglobin level of 8.6 g/dL. Abdominopelvic ultrasonography (US) revealed an enlarged uterus measuring 112 × 57 mm, with a transmural myoma (59 × 62 mm) located in the upper part of the fundus (Figure 1A). Diagnostic curettage was performed, and complex endometrial hyperplasia with atypia was reported. Subsequently, the patient underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO), followed by adjuvant chemotherapy. Postoperative pathological analysis confirmed a diagnosis of stage II (T2aN0M0) endometrial stromal sarcoma (Figure 1B). We planned for the patient to undergo an FDG-PET scan to evaluate other possible cancer sites, but it was not done due to financial limitations and lack of access to the scan. Postoperative follow-up showed no evidence of recurrence or metastasis.

Approximately three years after undergoing TAH-BSO surgery, in December 2020, the patient presented with abdominal pain. Colonoscopy was performed, which revealed a sigmoid mass and multiple sigmoid polyps (Figure 2A). Histopathologic analysis of the biopsy specimens confirmed malignancy. Chest

Table 1. Case summary timeline of the patient

Date	Event/Diagnosis	Treatment	Outcome
2013	Papillary Renal Cell Carcinoma (Stage I, T1N0M0)	Total left nephrectomy	Successful surgery, no recurrence noted
August 2017	Endometrial Stromal Sarcoma (Stage II, T2aN0M0)	TAH-BSO + chemotherapy (Gemcitabine & Paclitaxel)	No recurrence observed during follow-up
December 2020	Colon Adenocarcinoma (pT3N1M0)	Left hemicolectomy; patient refused adjuvant chemotherapy	No recurrence observed; standard follow-up evaluations performed
July 2021	Invasive Ductal Carcinoma (IDC) (Stage IIIB, cT4bN1M0)	After one session of neoadjuvant chemotherapy, refused to continue chemotherapy => right modified mastectomy	Patient's failure to follow-up after treatment
Mar 2022	Recurrence Breast Cancer (Stage V)	Palliative therapy	Death after one year of palliative therapy for her distant metastasis

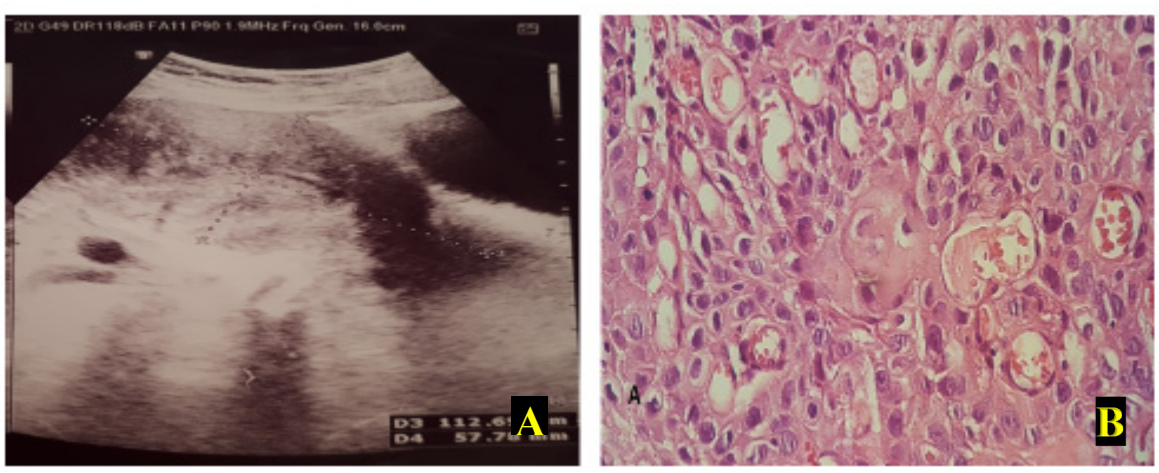

Fig. 1. A 112 mm × 57 mm uterus is seen along with a transmural myoma (59 mm × 62 mm) in the upper part of the fundus (A). The postoperative pathological evaluation shows endometrial stromal sarcoma (B).

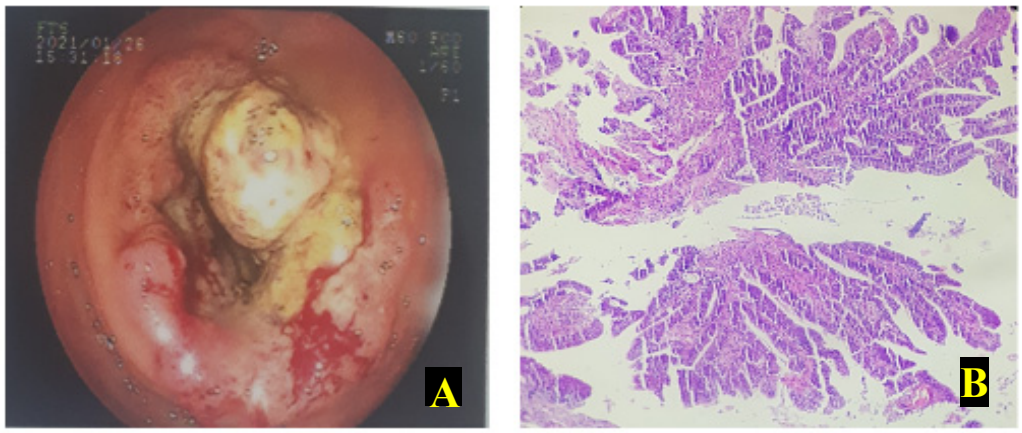

Fig. 2. The colonoscopy shows a sigmoid mass and several sigmoid polyps (A). The post-operative histopathology reveals moderate to poorly differentiated adenocarcinoma (B).

and abdominopelvic CT scan showed thickening of the intestinal wall in the transverse colon, without additional significant abnormalities. The patient underwent a left hemicolectomy; however, she declined adjuvant chemotherapy based on personal preference. Postoperative histopathological evaluation revealed moderately to poorly differentiated adenocarcinoma (Figure 2B), with tumor invasion into the subserosa and metastatic involvement of 3 out of 11 lymph nodes (pT3N1M0). Genetic testing was recommended to investigate hereditary cancer syndromes, such as Lynch syndrome; however, this evaluation was not performed due to the patient's lack of consent and existing constraints.

In July 2021, one year after her hemicolectomy surgery, the patient was referred to our department with a core needle biopsy (CNB) result consistent with breast malignancy.

On physical examination, a large, fixed, irregular, painless mass was observed on the right breast, accompanied by palpable pathological axillary lymph nodes and an evident ulceration on the overlying skin. Breast US and mammography revealed a sizable hypoechoic lesion measuring 103 × 76 mm in the right breast and pathological lymph nodes in the right axilla measuring 16 × 36 mm (Figure 3A). A metastatic workup using abdominopelvic CT showed no evidence of distant metastases. CNB histopathology confirmed invasive ductal carcinoma (IDC) (Figure 3B), and the clinical TNM stage was determined to be cT4bN1M0 (stage IIIB).

Neoadjuvant chemotherapy was initiated, but the patient voluntarily discontinued treatment after receiving one session of chemotherapy and chose to undergo breast surgery at another center. Right modified mastectomy was performed by a general surgeon, and postoperative pathological analysis indicated IDC with a maximum tumor diameter of 14 cm (grade III). The tumor demonstrated positive

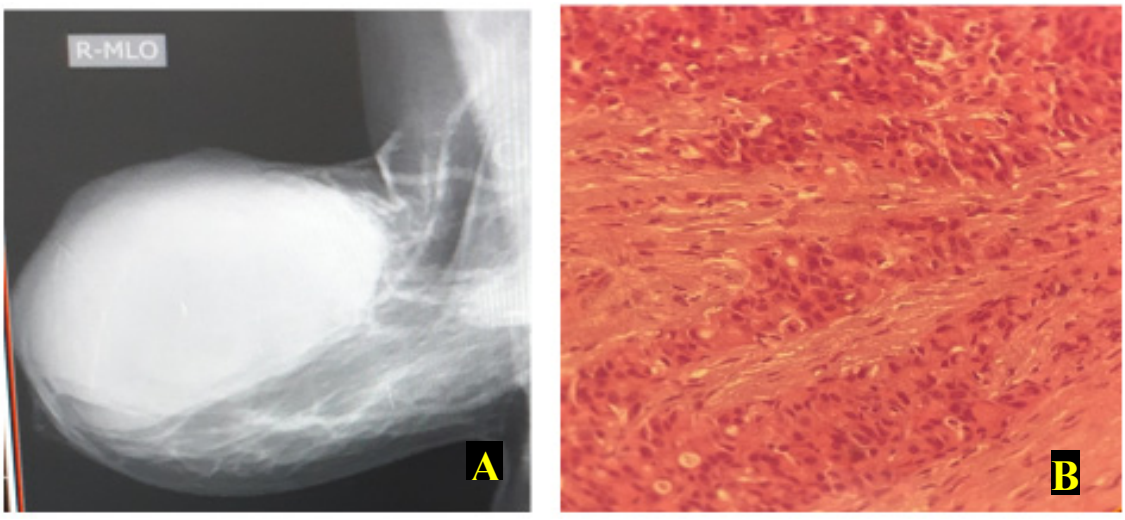

Fig. 3. The mammography shows a massive hypoechoic lesion in size of 103 mm × 76 mm on the right breast (A). CNB histopathology demonstrates invasive ductal carcinoma (B).

lymphovascular and perineural invasion, direct skin involvement with ulceration (T4b), and tumor-free surgical margins, although the deep margins were close and nodal status was not determined (Nx).

Six months later, the patient returned to our department. Immunohistochemistry (IHC) revealed that the tumor cells were positive for estrogen and progesterone receptors and negative for human epidermal growth factor receptor-2 expression. Updated metastatic evaluation with CT scans and whole-body bone scans confirmed supraclavicular lymph node and bone metastases. The patient passed away after one year of receiving palliative treatment for her metastatic breast cancer.

Discussion

The etiology of MPMs remains poorly understood; however, various factors such as aging, chemoradiation for previous cancers, genetic predisposition, environmental influences, and immunosuppression are known to contribute to their development [11]. Bychkovsky et al. conducted an analysis involving 9,714 patients with multiple primary cancers, demonstrating that the prevalence of germline pathogenic variants increased with the number of primary cancers [12]. Mutations in tumor suppressor genes and proto-oncogenes have been proven to cause syndromic presentations of secondary primary cancers [13]. Based on current studies, genetic testing can play a pivotal role in the screening of family members and future generations. Unfortunately, the absence of genetic testing in the present study represents a notable limitation. A review of the literature reveals that most cases of MPMs, including breast cancer, involve colon and uterine malignancies. The majority of affected patients are women over the age of 60; however, it is notable that men constitute a significant proportion of cases (13.7%) (Supplementary table).

The occurrence of MPMs encompassing uterine, colon, and breast cancers has been reported in two previous cases. In 2018, Lee and Ji [14] described a 63-year-old woman with synchronous involvement of these malignancies. In 2020, Li and colleagues [15] reported a similar case involving a 67-year-old woman, but in a metachronous presentation. This patient exhibited no recurrence or distant metastasis for breast, colon, and uterine malignancies during follow-ups spanning 19 months, 11 years, and 20 years, respectively.

At present, no standardized consensus exists regarding the diagnosis and management of MPMs. Future research should focus on designing a reliable algorithm for evaluating patients presenting with primary cancers and risk factors, such as a strong family history of malignancies.

Primary cancers are generally associated with a higher survival rate compared to metastatic cancers [16]. As evidenced in previously reported cases, the majority of patients achieved disease-free status following treatment and regular follow-up; however, seven patients either succumbed to the disease or developed metastatic lesions. Consistent with the present case, most of the previously reported cases involved metachronous multiple malignancies. This observation underscores the importance of considering the emergence of a new mass following the treatment of a malignant tumor as a potential

multiple primary cancer, rather than metastasis. Consequently, performing biopsies is vital for the early diagnosis of possible new malignancies [15].

Regular follow-up and early detection play an essential role in achieving optimal outcomes for patients with multiple primary cancers. Studies have demonstrated the utility of FDG-PET in identifying secondary malignancies. In the case presented here, if FDG-PET had been performed at the time of endometrial cancer diagnosis, breast cancer might have been identified at earlier stages, potentially leading to improved clinical outcomes. However, a reliable framework for determining the sequence of FDG-PET in individuals with specific risk factors has not yet been established. Further studies are recommended to explore its sequencing in clinical practice [17].

Conclusion

Based on prior studies and comparisons with similar cases, we conclude that the appearance of a new mass in a cancer patient is likely indicative of a new malignancy. The utilization of FDG-PET can facilitate the early detection of secondary cancers, thereby improving patient outcomes. Moreover, in families with a history of multiple cancer occurrences, genetic testing is instrumental in identifying individuals at increased risk for multiple cancers. Implementing timely and appropriate cancer screening protocols in such cases can significantly enhance prognosis and patient management.

Ethical Considerations

Ethical approval

Ethical approval for this case report was obtained from the ethical principles and the national norms and standards for conducting medical research in Iran (Approval ID: IR.LUMS.REC.1403.502).

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Conflict of Interests

The authors declare that they have no conflict of interest.

Consent

Written informed consent was obtained from the patient for publication of this case report.

Data availability

The data shown in this report are available from the corresponding author on reasonable request.

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