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CASE REPORT
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# METACHRONOUS BREAST AND RECTAL CANCERS: A CASE REPORT OF SUCCESSFULLY TREATED MULTIPLE PRIMARY MALIGNANT TUMORS

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**Abstract**
Genetic predispositions, host characteristics, environmental factors and higher cancer patient survival rates are all contributing to the rising prevalence of multiple primary malignant tumors (MPMTs). The global incidence of MPMTs is as high as 11.7%.
It is uncommon for MPMTs to affect both breast and rectum. Owing to the scarcity of available literature, there is lack of high-quality evidence that can guide clinicians on the management strategies of this complex oncological entity. In our study, we report a case of successfully treated metachronous tumors of the breast and rectum in a 71-year-old woman. The patient was first diagnosed with moderately differentiated invasive ductal carcinoma of left breast in 2019 for which she underwent modified radical mastectomy (MRM) followed by adjuvant chemo and radiotherapy. In 2021, she was diagnosed with adenocarcinoma of the rectum following multiple episodes of per rectal bleeding. The case was discussed in a multidisciplinary tumor board and after ruling out metastasis, a decision of neoadjuvant chemo-radio therapy followed by anterior resection of the tumor was made. The patient remains disease free so far.
In a nutshell, the likelihood of developing a primary second malignancy should always be kept in mind while evaluating a cancer patient. There are no specific guidelines for the management of MPMTs due to the paucity of available data. Therefore, it is imperative that both the patient and the clinician be vigilant for the emergence of new signs and symptoms after the occurrence of index primary malignancy.

**Keywords**: metachronous, multiple primary malignant tumors (MPMTs), breast, rectum

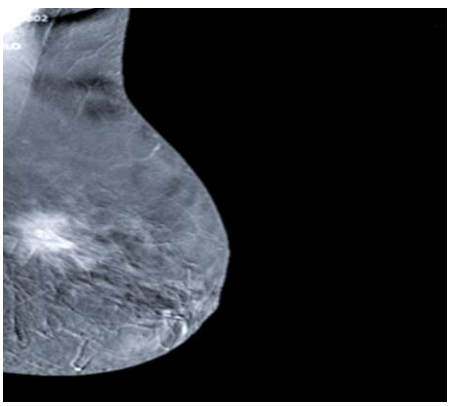
## INTRODUCTION:

Over the past few decades, advancement in breast cancer screening and management due to enhanced awareness & availability of modern diagnostic & therapeutic procedures has increased overall survival rate. (1) As of January 1, 2022, approximately 4 million women are living with a history of invasive breast cancer in the US alone. The 5-year relative breast cancer survival rate has also increased from 75% for patients diagnosed in the mid-1970s to 90% for those diagnosed in 2017. (2) However, increased cancer survivorship has also led to increased risk of developing new primary malignancies. Multiple primary malignant tumors (MPMTs) are defined as the presence of two or more histologically distinct malignancies in one individual (3). These tumors can be detected both synchronously i.e. the second primary cancer is diagnosed within 6 months of detection of the index tumor or metachronously when the second primary cancer is diagnosed after 6 months of detection of the first primary cancer. (3). The relative risk for a second primary malignancy increases by 1.111-fold every month from the detection of the first primary malignancy in any individual.(4) The reported incidence of MPMTs in cancer patients globally ranges from 0.52% to 11.7% (5) The significance of diagnosing multiple primary tumors lies in its impact on treatment strategies, prognosis determination, survival expectancy assessment as well as guiding further management decisions based on specific tumor characteristics.(6) Unfortunately, there is little to none available studies highlighting the occurrence and treatment approach of MPMTs in South Asia, especially in Pakistan. In this study, we report a rare case of successfully treated metachronous tumors of breast and rectum.

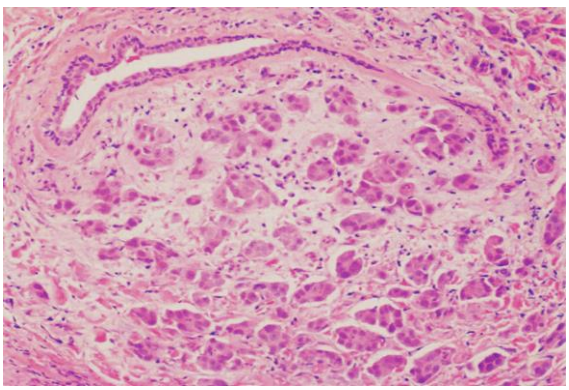
## CASE PRESENTATION:

A 71-year-old postmenopausal female patient presented with left breast lump in 2019 in Shaikh Zayed Hospital, Lahore and was diagnosed with moderately differentiated infiltrating ductal carcinoma (Bloom's Grade 2). Hormone receptor status was positive for both estrogen and progesterone and negative for HER 2 neu. She underwent modified radical mastectomy (MRM) with axillary clearance. Histopathology report showed 4 out of 18 lymph nodes excised positive for metastasis whilst bone scan was unremarkable. MRM was followed by 10 cycles of adjuvant radiotherapy and 6 cycles of chemotherapy from Inmol Hospital, Lahore after which the patient remained symptom free.

Mammogram of left breast showing a suspicious mass with irregular shape and spiculated margins



Histopathological slide depicting moderately differentiated invasive ductal carcinoma, Bloom-Richardson grade: 2 (Tubules: 2, nuclear pleomorphism: 2, mitosis:2)



She then presented in 2021 with on and off episodes of fresh bleeding per rectum associated with constipation and lower abdominal pain. An abdominal and digital rectal examination was

insignificant with no evidence of visceromegaly, lymphadenopathy or palpable growth. Keeping in view her past surgical history, an examination of her left mastectomy scar, right breast and bilateral axillae was also performed which turned out to be unremarkable. Relevant investigations like CT chest, abdomen and pelvis, MRI pelvis and colonoscopic biopsies in addition to the clinical examination were planned to accurately stage the disease.

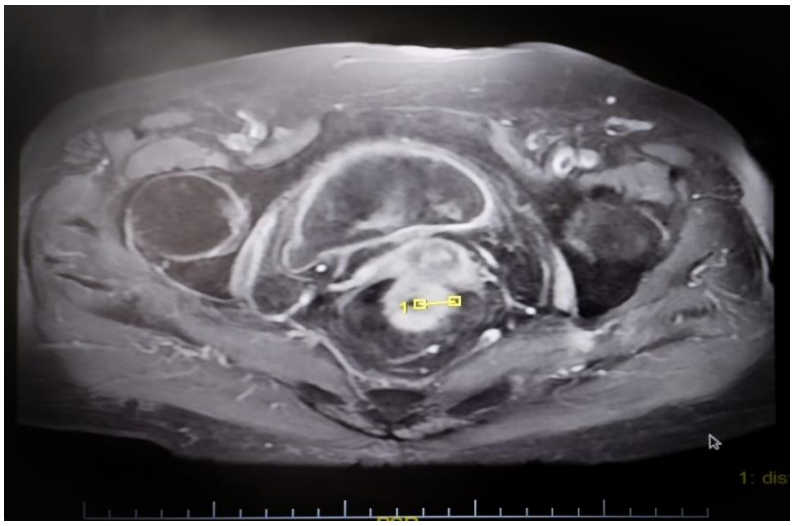
## LABORATORY RESULTS ON PRESENTATION

| COMPLETE BLOOD COUNT | RESULT | RANGE |
|---|---|---|
| White blood cell | 5.4 | 4.0-11.0 x $10^9$/L |
| Red blood cell | 3.76 | 4.00-5.50 x$10^{12}$/l |
| Hemoglobulin | 12.0 g/dL | 12.0–16.5 g/dL |
| Hematocrit | 33.8 | 36-48% |
| Platelets | 281 | 150-450 x $10^9$/L |

| COMPLETE METABOLIC PANEL | RESULT | RANGE |
|---|---|---|
| Potassium | 3.7 | 3.5-5.0 mmol/L |
| Sodium | 148 | 135–148 mmol/L |
| Calcium | 8.6 | 8.8-10.5 mg/dL |
| Bilirubin (total) | 0.5 | 0.0-1.0 mg/dL |
| Aspartate aminotransferase | 34 | <37 U/L |
| Alanine aminotransferase | 19 | <63 U/L |
| Albumin | 2.5 | 3.5-5.0 g/Dl |
| Alkaline Phosphatase | 100 | 50-136 U/L |
| Blood urea nitrogen | 14 | 7-18 mg/dL |
| Creatinine | 1.1 | 0.6-1.30 mg/dL |

| TUMOR MARKERS | RESULT | RANGE |
|---|---|---|
| Serum CEA | 64.61 | <3.8 ng/mL |

MRI Pelvis showing a circumferential wall thickening measuring approximately 13.8 mm in the proximal rectum with surrounding haze and para-rectal fat stranding.



Colonoscopy showed a friable, bleed to touch tumor at 12 cm from the anal verge in the proximal rectum with an otherwise normal colon. The histopathological examination revealed a moderately differentiated adenocarcinoma of rectum. (shown below)

(A) Colonoscopy showing growth at 12 cm from anal verge beyond which scope passed easily.
(B) Histopathology showing infiltration of tumor cells beyond submucosa


The case was presented in the multidisciplinary tumor board of Shaikh Zayed Hospital, Lahore and a unanimous decision was made to run ER PR and GATA 3 immunohistochemical tests on the biopsy sample to conclude whether the second tumor was primary or metastatic in nature. The rectal specimen turned out to be positive for both estrogen and progesterone receptors but negative for GATA 3. Since ER PR expression has been ascertained with individual colorectal cancers and the GATA 3 immunohistochemical stain is strongly positive (and hence sensitive) for breast metastasis, it was concluded that adenocarcinoma of the rectum was indeed a primary one. Following this, the patient was re-discussed in the tumor board and this time, a decision of neoadjuvant chemoradiotherapy followed by anterior resection of the tumor was made. The patient underwent 5 cycles of radiotherapy followed by 6 cycles of chemotherapy. She was restaged for her disease and after considering her clinical and radiological parameters as well as normal serum CEA levels, anterior resection was planned. Intra operative findings included an 8x7 cm growth in the proximal rectum with no evidence of ascites or lymph nodes. The patient's post operative recovery period was uneventful. Biopsy report of the specimen revealed all resected margins including proximal margin, distal margin and mesenteric margins negative for tumor involvement. 2 lymph nodes were identified which were also negative for malignancy. This patient is on regular follow ups and remains disease free so far.

## DISCUSSION

MPMTs are often challenging because each tumor requires an intensive evaluation and treatment strategy is planned after employing a multi-disciplinary approach. Currently, the Warren and Gates classification is used to diagnose MPMTs and is as follows: 1) Each tumor must be confirmed by histopathology. 2) Each tumor must be anatomically distinct from the other with a normal mucosal barrier between the two. 3) The probability of one lesion being metastatic of the other must be excluded. (7). Although the exact mechanism is unknown, the National Comprehensive Cancer Network (NCCN) Guidelines postulates various risk factors for the development of MPMTs. These include genetic predispositions, lifestyle (e.g., tobacco use or excessive alcohol intake), late effects of cancer treatments (e.g., cytotoxic, radiation or hormonal therapies and increased life expectancy secondary to cancer survival. (8)

A study conducted in Libya demonstrated that second primary malignant tumors occurred in 1.14% of the cases, with a higher incidence in females. The most common index primary tumors were found in breast, ovary & urinary bladder whilst the most frequent second metachronous tumors were found in gastrointestinal tract (9). Another study published in Korea revealed that MPMTs occurred

in 4.1% of patients of breast cancer with significantly increased relative risk of developing thyroid (41.7%) and gastric cancer (14.8%) after treatment of breast cancer. (10) This implies that neoplasms of breast ought to be monitored for a duration greater than the conventional 5-year disease free period.

It is important to distinguish whether subsequently developing tumors are independent primary neoplasms or metastatic of the index tumor because treatment and prognosis radically differs between the two. This differentiation can be established by rigorous histopathology, radiology, genetic testing and immunohistochemistry. (11) Schwarz et al have recommended making a histopathologic and immunohistochemical comparison between primary breast and primary gastrointestinal tumor to differentiate the second primary malignancy from metastasis. Traditionally, commonly utilized immunohistochemical markers have been ER and PR. When the gastrointestinal tumor is ER/PR negative and the main breast tumor is ER/PR positive, the diagnosis is made easily. (12). However, recent studies have also shown a positive correlation between colorectal carcinoma (CRC) pathogenesis with sex steroid hormones such as ER and PR. This demonstrates the probability of ER PR expression in primary malignant colorectal tumors as was consistent with our case. (13) Hence, ER PR positivity in colorectal mucosa warrants additional testing to confirm the primary nature of the tumor. One of these include GATA 3 analysis. GATA 3, a transcription factor involved in cell development and differentiation, is particularly expressed in breast epithelial and urothelial neoplasms, and is often used to distinguish these tumors from other malignancies. (14)

It has been observed that subsequently developing MPMTs tend to be more aggressive and resistant to treatment possibly owing to tumor genetics and the fact that affected patients are already immunocompromised with depleted physiological reserves. (5) This is a dilemma for oncologists who not only have the responsibility of identifying and eliminating modifiable risk factors but also must keep treatment of primary tumor (such as concurrent chemotherapy and radiation doses and fields) in mind whilst planning management of the second malignancy. (15)

Optimal treatment strategy for MPMTs of the breast and rectum remains unclear due to the limited number of cases and heterogeneity in treatment approaches reported in the literature (16). Thus, the authors recommend a multidisciplinary approach for individual cases keeping in view the patient's physiological status and tumor characteristics. The prognosis for patients with MPMTs of the breast and rectum is generally poor. The overall survival rates reported in the literature range from 20% to 50% at five years. However, it is important to note that these estimates are based on small case series and retrospective studies, limiting the generalizability of the findings.

## CONCLUSION:

MPMTs involving both the breast and rectum is a rare entity. The clinical presentation, pathological characteristics, treatment approaches and prognosis of MPMTs of the breast and rectum vary among reported cases. Optimal timing of surgery, the use of neoadjuvant and adjuvant chemotherapy and the role of radiation therapy are areas of ongoing debate. Based on the available evidence, a multidisciplinary approach involving a tumor board discussion is recommended to individualize treatment decisions for these patients. Due to the scarcity of data, there is currently no consensus on a uniform management strategy for these patients. Further research, including prospective studies with larger sample sizes, is needed to better understand the characteristics and outcomes of MPMTs of the breast and rectum.

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