Triple metachronous primary cancer of uterus, colon, and breast cancer
A case report and review of the literature

Guanqiao Li, MS\textsuperscript{a}, Jia Yao, MS\textsuperscript{a}, Tangna Wu, BS\textsuperscript{a}, Yaxiong Chen, BS\textsuperscript{b}, Zhenping Wang, MS\textsuperscript{b}, Yiming Wang, BS\textsuperscript{b}, Fen Wang, BS\textsuperscript{b}, Rui Zhong, MS\textsuperscript{b}, Shiping Yang, MD\textsuperscript{b, a}

Abstract
Rationale: Triple or more primary malignancies are rare, with only 23 previous cases including breast cancer reported in the English language studies between January 1990 and December 2019.

Patient concerns: The patient was a 67-year-old woman with a mass in her right breast. She had a previous history of uterine and colon cancer. Both ultrasonography and mammography revealed a Breast Imaging Reporting and Data System (BI-RADS) category 3 breast lesion, in which proliferative nodules are more likely. Given her previous history of 2 malignancies, her doctors strongly recommended a biopsy.

Diagnosis and interventions: The biopsy pathology suggested intraductal breast cancer. Mastectomy and sentinel lymph node biopsy were performed. The postoperative pathological diagnosis was invasive ductal carcinoma, grade II, stage I. The sample was positive for estrogen receptor and progesterone receptor and negative for cerbB-2. No radiotherapy or chemotherapy was administered except for endocrine therapy. A follow-up at 19 months showed no breast recurrence or distant metastases.

Outcomes: No recurrence or distant metastasis occurred within the 19-month, 11-year, and 20-year follow-ups for breast, colon, and uterine cancers, respectively.

Lessons: To our knowledge, this is the first review of triple or more primary malignancies including breast cancer. These malignancies occur predominantly in older female patients. The most prevalent tumors of triple or more primary malignancies including breast cancer occur in the colon, uterus, and lung. A favorable prognosis is associated with early-stage malignancies.

Abbreviations: BI-RADS = Breast Imaging Reporting and Data System, CT = computed tomography, ER = estrogen receptor, MPM = multiple primary malignancies, PR = progesterone receptor.

Keywords: breast, colon, triple primary cancer, uterus

1. Introduction

Among multiple primary malignancies (MPM), 2 cancers are common, whereas triple or more primary malignancies are rare. According to the time of diagnosis, MPM can be classified as synchronous or metachronous. The reported incidence of MPM in cancer patients ranges from 0.52% to 11.7%[1]. However, there is limited literature regarding treatment and prognosis for MPM.

We reviewed cases of triple or more primary malignancies including breast cancer reported in English in the past 30 years (January 1990–December 2019) and found reports of 23 previous cases of triple or more primary malignancies including breast cancer.

Here, we report a rare case of metachronous triple primary malignant tumors of the uterus, colon, and breast. We also summarized the 23 previous cases and the present case (Table 1)[2-24]. To our knowledge, this is the first report of triple or more primary malignancies including breast cancer. We received written consent from the patient to publish this case report. An approval from the Institutional review committees was not required because this is a case report.

2. Case report

The patient was an older woman who had been diagnosed with 3 different types of cancer in 3 different organs during a 19-year...
Table 1

Previous 23 cases and the present case with triple or more primary malignancies including breast cancer.

| Author                | Publication year | Age, y | Sex | Sites                                                                 | Time of diagnosis          | Outcome of follow-up                                                                 |
|-----------------------|------------------|--------|-----|----------------------------------------------------------------------|-----------------------------|--------------------------------------------------------------------------------------|
| Present case          | —                | 68 F   |     | Breast, uterus, colon                                                | Metachronous 19 mo          | Disease-free                                                                         |
| Jin et al[1]          | 2018             | 57 F   |     | Breast, bilateral lung                                              | Synchronous 30 mo           | Disease-free                                                                         |
| Pantek et al[2]       | 2018             | 73 F   |     | Breast, rectum, kidney                                              | Metachronous                | Dead with retroperitoneal lymphadenopathy progression and renal function failing     |
| Lee and J[3]          | 2018             | 63 F   |     | Breast, uterus, colon                                              | Synchronous                | Bone metastasis progressive, palliative therapy                                        |
| Agoston et al[4]      | 2018             | 70 F   |     | Breast, colon, kidney                                              | Synchronous                | 16 mo (Disease-free)                                                                 |
| Sapalidis et al[5]    | 2018             | 63 F   |     | Breast, tonsill, lung                                              | Metachronous                | —                                                                                    |
| Nyquist et al[6]      | 2018             | 81 F   |     | Breast, uterus, colon melanoma, sarcoma                             | Metachronous                | —                                                                                    |
| Romaniuk et al[7]     | 2017             | 62 F   |     | Breast, thyroid, uterus, bladder                                    | Metachronous                | —                                                                                    |
| Alam et al[8]         | 2017             | 45 F   |     | Breast, ovary, uterus                                              | Metachronous                | —                                                                                    |
| Maruyama et al[9]     | 2015             | 69 F   |     | Breast, lungs, tongue, kidney                                       | Synchronous 5 y             | Disease-free                                                                         |
| Kla Richter et al[10] | 2015             | 74 F   |     | Breast, lung, colon, esophagus                                      | Synchronous 18 mo           | Disease-free                                                                         |
| Williamson et al[11]  | 2015             | 57 F   |     | Breast, melanoma, lymphoma, giant cell tumor                        | Metachronous                | Being treated                                                                        |
| Rastogi et al[12]     | 2014             | 70 M   |     | Breast, esophagus, tongue                                           | Metachronous                | Dead with tongue cancer                                                               |
| Kousaka et al[13]     | 2014             | 41 F   |     | Breast, tongue, thyroid, osteosarcoma                               | Metachronous 3 mo           | Disease-free                                                                         |
| Markakis et al[14]    | 2013             | 67 F   |     | Breast, colon, rectum                                              | Metachronous 18 mo          | Disease-free                                                                         |
| Kim et al[15]         | 2015             | 70 F   |     | Thyroid, breast, pancreas, stomach                                   | Metachronous                | Dead 8 mo after the diagnosis                                                        |
| Demirci et al[16]     | 2015             | 78 F   |     | Bilateral breast, ovarian, retropitoneal neuroendocrine carcinoma   | Metachronous 1–2 y          | Progressive disease with retropitoneal neuroendocrine carcinoma                       |
| Cecato et al[17]      | 2008             | 55 F   |     | Breast, esophagus, tongue                                           | Metachronous 12 y           | Disease-free                                                                         |
| Noh et al[18]         | 2008             | 68 F   |     | Breast, rectum, ovary, uterus                                       | Metachronous                | Chemotherapy after surgery of endometrium and septic shock                          |
| Otrock et al[19]      | 2005             | 65 M   |     | Breast, lung, bladder, prostate                                     | Metachronous 20 mo          | Disease-free                                                                         |
| Baba et al[20]        | 2002             | 64 M   |     | Breast, lung, prostate                                              | Metachronous                | Disease-free                                                                         |
| Frei et al[21]        | 2002             | 62 F   |     | Bilateral breast, ovary                                              | Synchronous 12 mo           | Disease-free                                                                         |
| Nakayama et al[22]    | 1999             | 62 F   |     | Bilateral breast, bile duct, bladder                                | Metachronous                | —                                                                                    |
| Bagrie[23]            | 1991             | 43 F   |     | Breast, colon, fetus, jejunum, stomach, rectum                     | Metachronous                | Two cancers after excision                                                            |

Summary

| Age, y | N | Sex | Sites | N | Time of diagnosis | N | Outcome |
|--------|---|-----|-------|---|-------------------|---|---------|
| 41–50 y| 3 | F   | 21    | Breast | 24 | Metachronous | 15 | Disease-free |
| 51–60 y| 3 | M   | 3     | Colon  | 8  | Synchronous  | 9  | Dead or metastasis or recurrence |
| 61–70 y| 11|     |       | Uterus  | 7  | Known       |     |
| 71–81 y| 7 |     |       | Lung  | 5  | Unknown     | 6  | Disease-free |

= unknown, F = female, M = male, N = number.

period between 1999 and 2018. In November 1999, the patient visited a gynecology department for irregular vaginal bleeding lasting 1 month. The patient was diagnosed with her first malignancy, endometrial cancer, in 1999 at the age of 48 years. Transvaginal ultrasound revealed a regular, mixed echoic mass (15 mm × 10 mm) at the inferior posterior wall of her uterus (Fig. 1A) diagnostic curetaage was performed.

The endometrium pathologic examination showed endometrial cancer. The patient also underwent a radical hysterectomy and pelvic lymphadenectomy. The histopathological examination specimen (Fig. 1B) revealed moderately differentiated endometrioid adenocarcinoma, with tumor invasion of the muscularis and cervical osrice. The surgical margins were negative and none of the 41 axillary lymph nodes excised were positive for malignancy. The postoperative pathological diagnosis was endometrial cancer, grade II, stage II. She received adjuvant radiotherapy for her pelvic cavity after the operation. No recurrence or metastasis had occurred after 20 years of postoperative follow-up.

In July 2008, the patient experienced recurrent right lower abdominal pain for 2 months. She was diagnosed with her second malignancy, colon cancer, in 2008 at the age of 57 years. Abdominal computed tomography (CT) revealed a thickened intestinal wall in the left lower abdominal sigmoid colon and stenosis of the lumen (Fig. 2A). She underwent fiberoptic endoscopy for the suggested ascending colon cancer (photographs of the fiberoptic endoscopy were lost due to the relocation of the endoscopy center). A pathological biopsy revealed a tubular adenocarcinoma. The patient underwent a right hemicolectomy under general anesthesia on July 13, 2008. Postoper-
ative pathology (Fig. 2B) revealed ascending colon papillary adenocarcinoma and moderately differentiated tubular adenocarcinoma with components of mucinous adenocarcinoma, complicated with deep muscle invasion. The surgical margins were negative and none of the 33 axillary lymph nodes excised were positive for malignancy. The tumor was pathologically categorized as stage I. The patient was treated with traditional chemotherapy comprising 6 cycles of oxaliplatin and 5-fluorouracil. She remained free of locoregional recurrence or distant metastases after 11 years of postoperative follow-up.

In June 2018, the patient sought medical advice for possible breast surgery after finding a mass in her right breast for 2 weeks. She was diagnosed with her third malignancy, breast cancer, in 2018 at the age of 67 years. Breast ultrasound and mammography were performed. The ultrasonography (USG) revealed a regular, mixed echoic mass (8.8 mm × 5.0mm) at the 12 o’clock region of her right breast (Fig. 3A) categorized as Breast Imaging Reporting and Data System (BI-RADS) category 3, consideration of proliferative nodules. CT revealed an irregular mass (12 mm × 10mm) behind the nipple of the right breast consistent with the USG findings (Fig. 3B). Mammography (Fig. 3C) revealed a nodular, inhomogeneous, and irregular high-density lesion (20 mm × 18 mm) behind the nipple in the right breast that was categorized as BI-RADS category 3, proliferative nodules are more likely. Although all imaging examinations pointed to a benign nodule, the doctors strongly recommended that the patient undergo a biopsy because of her previous history of multiple cancers. The biopsy pathology suggested intraductal breast cancer. A mastectomy and sentinel lymph node biopsy was performed. Postoperative pathology showed invasive ductal carcinoma of the right breast with a maximum diameter of 1.5 cm, grade II, ductal carcinoma in situ (about 80%) (Fig. 3D), and no sentinel lymph node metastasis (0/2). Immunohistochemistry showed estrogen receptor and progesterone receptor positivity (90% and 3%, respectively). The sample was negative for cerbB-2 but was positive for Ki-67 (5%). No radiotherapy or chemotherapy was administered except for endocrine therapy. A follow-up at 19 months showed no breast recurrence or distant metastases.

3. Discussion
Altogether, 23 previous cases of triple or more primary malignancies including breast cancer have been reported in
English language studies between January 1990 and December 2019.\textsuperscript{1,2–24} According to the summaries of previous reports\textsuperscript{2–24} (Table 1), this type of malignancy occurs predominantly in older female patients, with an average age of 64 years (range 41–81). Our case was 67 years. Fifteen (62.5\%) cases were metachronous and nine (37.5\%) cases were synchronous. The most prevalent tumor was colon cancer (8 cases), followed by uterus cancer (seven cases) and lung cancer (five cases). The follow-up period of most published cases was relatively short. Eight cases experienced death/metastasis or recurrence.\textsuperscript{3,4,13,16,17,19,20,24} The outcomes of cases were not reported.\textsuperscript{6–9,23}

The combination of MPM with uterus, colon, and breast cancers has been reported in 1 previous study, in which Lee and Ji reported a case of a 63-year-old woman simultaneously diagnosed with uterine carcinosarcoma, breast cancer, and colon cancer. However, the time of follow-up was very short in that case and the patient had just finished chemotherapy.\textsuperscript{4}

In these cases, it is important to determine that the second primary cancer is an independent primary cancer rather than a metastasis or recurrence of the first primary cancer as this difference affects staging, treatment, and patient prognosis. In our case, the patient had undergone surgery for endometrium, colon, and breast cancer for which the primary cancers were confirmed by pathology.

There are no guidelines for the diagnosis and treatment of multiple neoplasms; therefore, they are difficult to treat. Yoshino et al.\textsuperscript{25} reported that “the prognosis of patients with multiple primary cancers can be determined independently by the stage of each cancer.” Bae et al.\textsuperscript{26} stated that “one of the most important factors when deciding the best treatment modality for patients with multiple primary cancer is the stage of the cancers.” Primary cancers have much better survival rates than metastatic cases.\textsuperscript{127} When properly managed, patients’ individual circumstances should be considered, including parameters such as disease grade, extent of neoplastic invasion, patient age, and disease type.\textsuperscript{28} The management modalities could include surgical debulking, adjuvant radiotherapy, and adjuvant chemotherapy, as clinically appropriate. More aggressive management modalities may be required for patients with synchronous primary neoplasms, poor histological, higher grade, and advanced stage.

The patient in the present case had been diagnosed with multiple cancers at different times in her life. The primary cancer (endometrial cancer) was diagnosed in December 1999, the second occurrence of cancer (colon cancer) was diagnosed 9 years later in August 2008, and, finally, 10 years after this in 2018, the third cancer (breast cancer) was diagnosed. Due to the long intervals between the cancers, the treatments for all 3 were similar. However, it is curious that the patient received 6 weeks of chemotherapy after an operation for colon cancer and was diagnosed postoperatively as having stage T2N0M0 (stage I) disease. Chemotherapy should not be used in this situation according to National Comprehensive Cancer Network (NCCN)
guidelines. We inquired with the consultant who treated this patient; however, he was unable to recall the treatment because it had happened so long ago and had not saved records from that time. The colon and breast cancer were diagnosed relatively early (stage I), whereas the endometrial cancer was stage II at diagnosis.

This patient had a relatively favorable prognosis associated with early-stage malignancies without lymph node metastases (breast, colon adenocarcinoma, and endometrium adenocarcinoma). After the treatment of the first cancer, patients undergo regular follow-up for early identification of the next primary cancer. This patient's second (colon cancer) and third (breast cancer) primary cancers were both stage I. Due to the early diagnosis and treatment, the patient was able to go on to live a long life. The second or third primary malignancies mostly occur in long-term survivors and may be related to environmental, reproductive, genetic, and lifestyle factors (smoking, drinking, and body mass index).

Reports have indicated that 8% of MPM cases are associated with radiotherapy; the remaining cases were correlated with lifestyle behaviors (eg, smoking), and genetic factors.[28] The patient in the present case had no family history or history of smoking or drinking. She received pelvic adjuvant radiotherapy was performed for endometrial cancer in this case. Thus, we cannot rule out whether the colon cancer was related to radiation. Kumar et al[29] evaluated the association between radiotherapy and subsequent second cancers in endometrial carcinoma survivors.

In this case, the point of early diagnosis in breast cancer was very noteworthy. Both ultrasound and mammography revealed BI-RADS grade category 3. BI-RADS category 3 lesions have a malignancy rate of >2%,[29] and in most diagnostic ultrasound series,[31,32] the patient in the present case had no family history or history of smoking or drinking. She received pelvic adjuvant radiotherapy was performed for endometrial cancer in this case. Thus, we cannot rule out whether the colon cancer was related to radiation. Kumar et al[29] evaluated the association between radiotherapy and subsequent second cancers in endometrial carcinoma survivors.

Barr et al[33] suggested that "as BI-RADS category 3 lesions have a low malignancy rate (0.8%) and only 0.1% of the cancers had suspicious changes at 6-month follow-up and only one (17%) of six malignancies were node-positive at detection (24-month follow-up), a recommendation of 1-year diagnostic follow-up may be appropriate for BI-RADS category 3 lesions detected at screening US."

Graf et al also reported that follow-up USG was an acceptable alternative to biopsy for solid masses with benign morphologic features seen in USG owing to the extremely high negative predictive values (99.8%).[34]

In the present case, the doctors strongly recommended a biopsy because of the patient's previous history of multiple cancers. She apparently benefited from biopsy and received timely diagnosis and treatment. Therefore, for patients with a history of multiple cancers, the possibility of malignancy should be considered for BI-RADS category 3 lesions and positive puncture biopsy should be performed for definitive diagnosis to avoid delayed diagnosis and treatment.

Acknowledgments

The authors are thankful to the patient for her cooperation. The authors also thank Mr Dean Moody for revising our manuscript for mistakes and grammatical errors.

Author contributions

Data acquisition: YS, YJ, WF and WY. Data analysis and interpretation: LG, YJ, and ZR. Radiological analysis of ultrasound and CT images: WT, CY, WZ. Manuscript preparation: LG and YS.

References

[1] Lv M, Zhang X, Shen Y, et al. Clinical analysis and prognosis of synchronous and metachronous multiple primary malignant tumors. Medicine (Baltimore) 2017;96:e7999.
[2] Jin B, Zhang S, Chuang X, et al. Breast cancer and synchronous multiple primary lung adenocarcinomas with heterogeneous mutations: a case report. BMC Cancer 2018;18:1138.
[3] Parekh JD, Kukrety S, Thandra A, et al. Multiple primary malignant neoplasms in an elderly patient. Cureus 2018;10:e2384.
[4] Lee E, Ji Y-I. A case of uterine carcinosarcoma detected simultaneously with breast and colon cancer (triple primary malignant tumor). Case Rep Oncol 2018;11:431–5.
[5] Agoston EI, Somorocza A, Madaras L, et al. Successful treatment of three synchronous primary malignant tumours—reflection on surgical, pathological and oncological aspects and decision making. J Surg Case Rep 2018;2018:ry9041.
[6] Papalidis K, Schiras N, Lazzopoulos A, et al. Multiple metachronous and synchronous malignancies with lung and thorax involvement. Report of two cases. Respir Med Case Rep 2018;24:5–7.
[7] Nygivist J, Persson F, Parris TY, et al. Metachronous and synchronous occurrence of 5 primary malignancies in a female patient between 1997 and 2013: a case report with genome and somatic genetic analysis. Case Rep Oncol 2017;10:1006–12.
[8] Romanuik A, Lyndin M, Snymanov V, et al. Primary multiple tumor with affection of the thyroid gland, uterus, urinary bladder, mammary gland and other organs. Pathol Res Pract 2017;213:574–9.
[9] Alam MS, Perwee R, Saliqqui SA. Triple malignancy involving breast, ovary, and uterine vault: a case report and literature review. J Cancer Res Ther 2017;13:1059–61.
[10] Maruyama T, Nakasone T, Maruyama N, et al. Synchronous quadruple multiple primary cancers of the tongue, bilateral breasts, and kidney in a female patient with a disease-free survival time of more than 5 years: a case report. World J Surg Oncol 2015;13:263.
[11] Clairmont M, Kopkash K, Fauvaza J, et al. Four synchronous primary malignancies of the breast, lung. Colon and Anticancer Res 2015; 35:6159–62.
[12] Williamson CW, Paravati A, Ghassemi M, et al. Five simultaneous primary tumors in a single patient: a case report and review of the literature. Case Rep Oncol 2015;8:432–8.
[13] Rastogi M, Singh S, Singh S, et al. Triple primary malignant neoplasms including breast, esophagus and base tongue in an elderly male: a case report. J Cancer Res Ther 2014;10:1109–11.
[14] Koussaka J, Fuji K, Yorozuya K, et al. A case of quadruple primary malignancies including breast, tongue, and thyroid cancers and osteosarcoma in a young female without karyotype abnormality. Breast Cancer 2014;21:500–3.
[15] Markakis C, Marinis A, Diakos P, et al. Multiple synchronous primary neoplasms of the breast, colon and rectum after surgery for endometrial cancer: a case report. Int J Surg Case Rep 2013;4:293–5.
[16] Kim JS, Chung CY, Park HC, et al. Synchronous quadruple primary tumors of thyroid, breast, pancreas, and stomach: a case report. Anticancer Res 2013;33:2135–8.
[17] Demirci U, Coskun U, Guccion PU, et al. Four different malignancies in one patient: a case report. Cases J 2010;3:53.
[18] Cercato MC, Collella E, Ferrari E, et al. Report of two cases of quintuple primary malignancies and review of the literature. Anticancer Res 2008;28(5B):2953–8.
[19] Noh SK, Yoon JY, Ryoo UN, et al. A case report of quadruple cancer in a single patient including the breast, rectum, ovary, and endometrium. J Gynecol Oncol 2008;19:265–9.
[20] Otrock ZK, Mahfouz RA, Saleem ZM, et al. Four primary tumors of lung, bladder prostate, and breast in a male patient. Southern Med J 2005;98:945–8.
[21] Baba M, Higaki N, Ishida M, et al. A male patient with metachronous triple cancers of small cell lung, prostate and breast. Breast Cancer 2002;9:170–4.
[22] Fert KA, Bonef HM, Forrer P, et al. Primary breast lymphoma, contralateral breast cancer, and bilateral bremer tumors of the ovary. Obstet Gynecol 2002;100:1079–81.
[23] Nakayama H, Masuda H, Ugajin W, et al. Quadruple cancer including bilateral breasts, Vater’s papilla, and urinary bladder: report of a case. Surg Today 1999;29:276–9.
[24] Baigrie RJ. Seven different primary cancers in a single patient. A case report and review of multiple primary malignant neoplasia. Eur J Surg Oncol 1991;17:81–3.
[25] Yoshino K, Asanuma F, Hanatani Y, et al. Multiple primary cancers in the stomach and another organ: frequency and the effects on prognosis. Jpn J Clin Oncol 1985;15 suppl 1:183–90.
[26] Bae JS, Lee JH, Ryu KW, et al. Characteristics of synchronous cancers in gastric cancer patients. Cancer Res Treat 2006;38:25–9.
[27] Phupong V, Khemapech N, Triratanachat S. Triple synchronous primary cervical, endometrial and ovarian cancer with four different histologic patterns. Arch Gynecol Obstet 2007;276:655–8.
[28] Berrington de Gonzalez A, Curtis RE, Kry SF, et al. Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. Lancet Oncol 2011; 12:353–60.
[29] Kumar S, Shah JP, Bryant CS, et al. Second neoplasms in survivors of endometrial cancer: impact of radiation therapy. Gynecol Oncol 2009;113:233–9.
[30] Varas X, Leborgne JH, Leborgne F, et al. Revisiting the mammographic follow-up of BI-RADS category 3 lesions. AJR Am J Roentgenol 2002;179:891–3.
[31] Nam SY, Ko EY, Han BK, et al. Breast imaging reporting and data system category 3 lesions detected on whole-breast screening ultrasound. J Breast Cancer 2016;19:301–7.
[32] Kim EK, Ko KH, Oh KK, et al. Clinical application of the BI-RADS final assessment to breast sonography in conjunction with mammography. AJR Am J Roentgenol 2008;190:1209–15.
[33] Barr RG, Zhang Z, Cormack JB, et al. Probably benign lesions at screening breast US in a population with elevated risk: prevalence and rate of malignancy in the ACRIN 6666 trial. Radiology 2013;269:701–12.
[34] Graf O, Heldich TH, Hopf G, et al. Probably benign breast masses at US: is follow-up an acceptable alternative to biopsy? Radiology 2007; 244:87–93.

Li et al. Medicine (2020) 99:34