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Triple metachronous primary malignancy – case report and literature review

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ABSTRACT

Multiple primary malignancies (MPMs) are defined as more than two synchronous or metachronous cancers in the same individual. Common risk factors for multiple primaries are represented by inherited predisposition to cancer, cancer-promoting aspects of lifestyle, hormonal and environmental factors, history of previously treated primary cancer and increased lifespan of cancer survivors. Herein, we report a single case of a 68-year-old woman with triple metachronous primary neoplasms of the breast, colon and endometrium with three distinct histological patterns. The patient was initially submitted to a supero-external quadrant sectorectomy and axillary lymph node dissection in May 2016, followed by radical sigmoidectomy for perforated sigmoid malignant lesion in December 2018 and respectively by total hysterectomy with adnexectomy and pelvic lymph node dissection for endometrial cancer in September 2021. The histopathological studies confirmed the different histopathological origins for the three lesions. In conclusion, once the lifespan of cancer survivors increased, multiple metachronous malignancies are to be expected.

Keywords: metachronous; multiple primary malignancies; endometrial cancer; breast cancer; colon cancer

Abbreviations
MPM – multiple primary malignancies;
SEER – Surveillance Epidemiology and End Results;
IACR/ IARC – International Association

INTRODUCTION

Multiple primary malignancies (MPMs) are defined as two or more synchronous or metachronous malignant lesions diagnosed in the same patient, the sine qua non condition for a case to be included in this condition being the presence of a histopathological report which demonstrates the different cellular origin of the lesions. Therefore, this condition

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avoids a possible misclassification of multifocal/ multicentric tumours or metastases as MPM (1). When it comes to the incidence of multiple primaries among cancer patients, it ranges between 2% and 17%, being significantly influenced by the follow up period, by the origin of the initial primary and by the type of the first intent treatment (2). Meanwhile, due to the wide implementation of the screening tests for different malignant pathologies such as breast, colon or uterine cervix cancer, such neoplasms are diagnosed in early, curable stages and therefore long term survival is achievable (3,4,5). In this context it is widely understandable why the incidence of MPM is increasingly. When it comes to the most commonly primaries included as part of MPM, it seems that breast, colon and lung cancer are most commonly incriminated, their incidence ranging between 19% and 21% (5-9). Breast cancer patients represents a particular subgroup of patients due to the frequent diagnosis of this malignancy at young ages and in an early stage of the disease; therefore, in such cases curative intent treatment is feasible and consists of surgery in association with chemotherapy and hormone therapy if hormonal receptors are present (9). Although the presence of hormonal receptors is usually considered as a favourable prognostic factor conferring to the patient the chance of another type of treatment besides chemotherapy, it seems that hormonal treatment increases the risk of endometrial, colonic, ovarian and even gastric cancer, the maximum encountered risk being of endometrial cancer after prolonged administration of tamoxifen (7). Meanwhile, patients diagnosed with MPM including breast cancer are usually obese, BRCA1/2 mutation carrier cases and are frequently diagnosed with the second malignancy at five to eight years after the moment of breast cancer diagnosis (7,8).

CASE PRESENTATION

A 68-year-old woman was referred to our hospital for postmenopausal vaginal bleeding and abdominal pain within the last five months. Her past medical and surgical histories showed both breast and colon cancer during a five year period between 2016-2021.

The patient was initially diagnosed in May 2016 with breast cancer and underwent at that moment a right supero-external quadranectomy and axillary lymph node dissection. Before surgery serum levels of cancer antigen 15-3 and 125 (CA15-3 and CA125) as well as the ones of carcinoembrionic antigen (CEA) were normal. At the histopathological and immunohistochemical examination an well differentiated, invasive ductal carcinoma was detected, with positive estrogen receptors (98%) - Allred score 8, weak-positive progesterone receptors (1%) - Allred score 1, HER2 negative, Ki67 positive (3-4%) and no positive lymph node out of the 14 retrieved nodes. The tumour was classified as pT1bN0Mx and therefore the patient underwent 12 sessions of radiotherapy and subsequent hormonal treatment with Letrozole.

In December 2018, the patient was investigated for diffuse pelvic pain, constipation and fever and was diagnosed with a stenotic, perforated sigmoid tumour; at that moment laboratory tests demonstrated normal ranges of CA15-3 and CA 125 and increased levels of CEA (CEA = 10.3 ng/ml) and the patient was submitted to a Hartman sigmoidectomy en bloc with left adnexectomy. Postoperative pathological diagnosis confirmed the presence of a moderately differentiated sigmoidian adenocarcinoma, two of the 14 retrieved lymph nodes presenting metastatic lesions. The tumour was therefore classified as a pT4aN1bMx lesion and the patient was further submitted to nine sessions of fluorouracil, leucovorin, and oxaliplatin (FOLFOX) based adjuvant chemotherapy.Six months after ending the oncological adjuvant treatment the patient was further submitted to a chest computed tomography and abdomino-pelvic magnetic resonance imaging which demonstrated the absence of metastatic lesions.

In September 2021, the patient was referred to our clinic due to lower abdominal pain and vaginal bleeding; the vaginal ultrasound demonstrated the presence of a thickened endometrial mucosa measuring 10 mm while the endometrial biopsy diagnosed the presence of a moderately differentiated endometroid endometrial carcinoma. Furthermore the patient was submitted to an abdomino-pelvic magnetic resonance imaging which demonstrated the presence of an enlarged uterine body measuring 18/15/12 cm due to the presence of multiple tumoral nodules and a thickened endometrial lining measuring 13 mm; meanwhile no separation plane between the uterine tumor and the urinary bladder dome could be identified while multiple pelvic adenopathies were encountered; There were no abnormal cervical growths while the laboratory findings demonstrated normal ranges of CA15-3, CEA and CA72-4 in association with increased serum levels of CA125 (CA125 = 1250 U/ml).

The patient was further submitted to surgery, a total hysterectomy en bloc with right adnexectomy, partial cystectomy, segmental enterectomy with entero-enteral anastomosis and pelvic lymph node dissection being performed (Figures 1-3). The postoperative evolution was favourable, the patient being discharged in the tenth postoperative day; the histopathological studies confirmed the presence of a moderately differentiated endometroid endometrial carcinoma as well as the area of local invasion

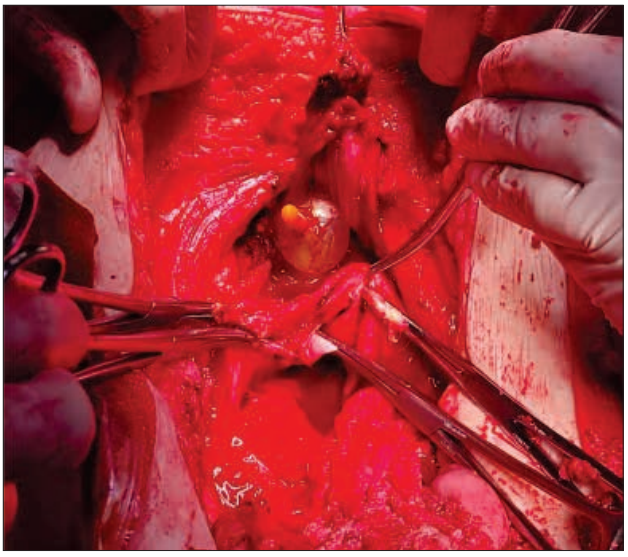

FIGURE 1. Intraoperative aspect – large pelvic tumor invading the urinary bladder – partial cystectomy was associated

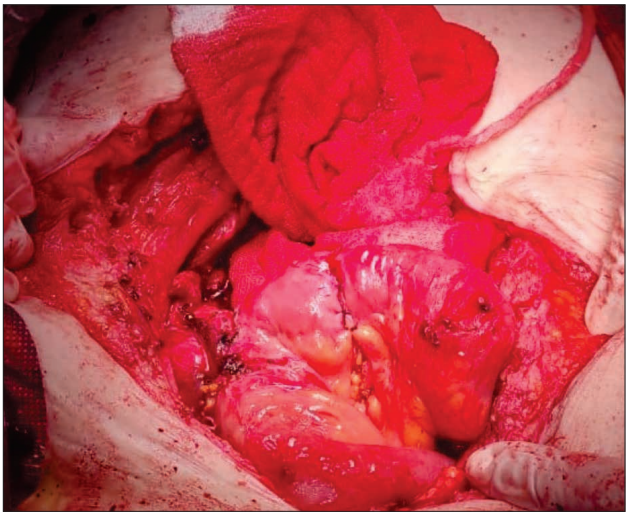

FIGURE 2. Intraoperative aspect after segmental enterectomy – termino-terminal ileal anastomosis was performed in order to re-establish the continuity of the digestive tract

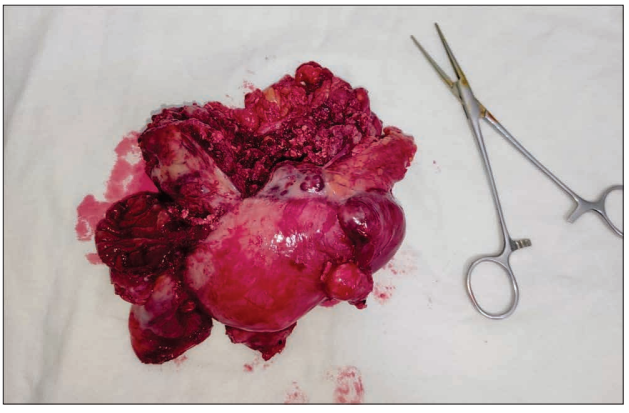

FIGURE 3. The specimen of total hysterectomy en bloc with right adnexectomy, partial cystectomy and segmental enterectomy

at the level of the urinary bladder wall; 14 out of the 21 retrieved lymph nodes presented metastatic deposits. The patient was further confined to the oncology service in order to be submitted to adjuvant treatment and follow up.

DISCUSSIONS

The definitions and understanding of MPM have been submitted to permanent changes over the last decades especially once screening tests for early detection of malignant lesions has been widely implemented. At the current moment, the two most frequently used and agreed definitions are those provided by the Surveillance Epidemiology and End Results (SEER) project and respectively by the International Association of Cancer Registries and International Agency for Research on Cancer (IACR/IARC). The differences between the two definitions are related to the timing of diagnosis between the involved primaries, to the histopathological patterns as well as to the site of the lesion; therefore while in the IACR/IARC guidelines the colon is considered as a single site, in the SEER guidelines each colic segment accounts for an individual site (1,3,9). The European cancer registries generally prefer to use the IACR/IARC definitions, and further suggest that synchronous tumours are considered the lesions diagnosed at an interval of less than six months; meanwhile, lesions diagnosed after a time interval of more than six months are considered as metachronous lesions (3,9).

As mentioned before, progress which has been made in the field of early diagnosis and treatment of cancer patients is causing the increased quality of life and life expectancy and therefore, the probability and possibility of developing second and even a third malignancy increases; however,larger studies are still needed in order to define the magnitude of the problem and to identify which the most significant predisposing factors to its development are (10,11).

The epidemiologic factors accounting for the increasing frequency in MPM are represented by genetics (Caucasian race, Li-Fraumeni or BRCA mutations), index cancer at younger age, hormonal replacement therapies, environmental exposures (geographical, infections or profession associated cancer types) and lower stage at the time of the initial diagnosis; in such cases longer survival is expected and therefore an excessive risk for multiple primary malignancies development is encountered (12-15).

In a recent study by Wang et al., the risks of developing second primary cancers were higher in cancer survivors compared with the general population with a 3.8% higher incidence of metachronous second primary cancers within a median follow-up time of 2.5 years; furthermore, the estimated

10-year cumulative risk of second primary cancers for patients who were firstly diagnosed with cancer aged between 60 and 69 was as high as 13% (16). Compared with a single primary tumor, MPMNs have increased malignant behaviour and worse prognosis (17).

When it comes to breast cancer patients, improvement of the imagistic studies and wide implementation of the screening tests leaded to a higher rate of early diagnostic of this malignancy, conferring therefore an overall good prognostic; meanwhile development of new oncological therapies such as hormonal or immunological therapy increased the chances of achieving long term survival in breast cancer patients. In the meantime the presence of breast cancer in young patients is also frequently associated with germline mutations of BRCA 1and BRCA2 genes (18).

Hormonal treatment of a primary breast cancer increases the risk for endometrial, gastric, colon and ovarian cancers with an excess risk for endometrial cancer, especially after tamoxifen therapy (7). Reproductive/hormonal and genetic factors (eg, BRCA1, BRCA2) as well as obesity are recognised as common risk factors for multiple primaries (19,20). Late toxic effects of radiotherapy and chemotherapy also contribute to the increased risk for a secondary primary tumour after breast cancer.

Stathopoulos studied various differences in gene expression between patients with MPMs and single malignancies and led to the determination of a large number of deregulated genes. Regarding the known biological function, 13 genes had a statistically significant difference in expression between individuals with double primary malignancies compared to individuals with single primary malignancies, defining a direct or indirect relation to cancer development (21).

The combination of MPM with uterus, colon, and breast cancers has been reported in two previous studies, one in which Lee and Ji reported a case of a 63-year-old woman simultaneously diagnosed with uterine carcinosarcoma, breast cancer, and colon cancer (22) and one in which Guanqiao MS reported a case of a 67-year-old woman with a mass in her right breast with a previous history of uterine and colon cancer (23).

The possibility of multiple primary malignancies should always be considered during the treatment and follow-up of cancer patients. This case series could prove helpful to clinicians faced with similar, however, exceedingly rare scenarios. Due to the realistic potential for long-term survival, we recommend aggressive treatment of these patients (24).

It is crucial to differentiate between synchronous / metachronous primary neoplasms and related metastatic diseases, because both management and prognosis vary substantially. The prognosis of a triple neoplasm is largely determined by the neoplasm with the poorest prognosis (25).

CONCLUSIONS

Published data so far revealed an increased risk to develop a secondary, third and even fourth primary cancer especially in younger patients, so there is an obvious need for a good surveillance of the patients. This may not be unreasonable, because the first tumor was probably caused by agents or factors that are more likely still at work. The initiating and promoting agents will not have changed. The incidence of cancer rises with age, including the occurrence of MPMN. Due to an early diagnosis of cancer and radical therapies and as long as the life expectancy is greater, the frequency of persons with multiple cancers will increase.

Fortunately, as a result of well-conducted periodical controls, we will in time discover the new primary, if there is one, and this will offer a good chance for patients to survive.

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