A CASE REPORT

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Metachronous Multiple Primary Malignancies (endometrium and breast)

Ketut Suega,* Prayuda

ABSTRACT

Introduction: Advanced progression the field of diagnosis and treatment of cancer patients causes increased survival of patients. Increasing life expectancy can lead to new health problems, including Multiple primary malignancies (MPM). Although the incidence of MPM is increasing, the diagnosis of MPM remains very rare. Based on the interval between tumor diagnosis, MPM can be divided into synchronous MPM and metachronous. Studies of MPM may provide useful information not only for clinical purposes but also can provide clues about etiology and management of this type of cancer. This case report was a woman with metachronous MPM (endometrium-breast).

Case: A 60-year-old female presented with a lump on the right breast since 2 months before admission. Patients also complained multiple marble sized lumps on the right armpit and right neck since 1 ½ months ago. From previous medical record data (5 years ago), the patient was diagnosed with endometrial carcinosarcoma stage IV. On physical examination on neck showed supraclavicula lymph nodes enlargement. Examination of right mammary region showed Peau d'orange skin with hyperemic colour, and a palpable solid mass. On right axillary region, there was lymph nodes enlargement. Mammae and axilla Ultra Sonography (USG) showed solid malignant in right upper-lateral quadrant breast with diffuse skin edema and multiple solid nodules in right axilla. Mammae histopathologic biopsy results conclusion is invasive carcinoma of no special type grade 3.

Conclusion: Our case was a woman with a metachronous MPM endometrial and breast, with the first malignancy was endometrial carcinosarcoma stage IV (type II endometrial carcinoma) followed by the appearance of second malignancy as a breast cancer dextra grade 3 stage IIIC. Time interval between these malignancies more than 6 months (5 years).

Keywords: endometrial carcinosarcoma, breast cancer, metachronous MPM

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Medical Hematology and Oncology Division, Department of Internal Medicine, Faculty of Medicine Udayana University/ SanglahGeneral Hospital, Denpasar

INTRODUCTION

Advanced progress in the field of diagnosis and treatment of cancer patients causing the increased quality of life and life expectancy of patients. Increasing life expectancy in cancer patients can lead to new health problems, including the emergence of other de novo malignancies.

Patients that already diagnosed with cancer are at risk for other de novo malignancies depending on various risk factors, congenital, environmental and iatrogenic condition. Multiple primary malignancy (MPM) are primary malignant tumors originating from a different histological source in single patient.[1]

Although the incidence of MPM is increasing, the diagnosis of MPM remains very rare. The incidence rate of MPM ranged between 0.7% and 11.7%.[2] Prevalence of MPM in China is reported between 0.4-2.4%.[3] Schoenberg et al. showed that patients with cancer had a risk of 1.29 times to develop new malignancy compared with those who never diagnosed cancer previously.[4] According to the National Cancer Institute's (NCI) & Surveillance, Epidemiology and End Results (SEER) data in 2007, the number of patients with MPM progressively increased with an incidence 16% (one in six) of primary cancer patients.[5]

Based on the interval between tumor diagnosis, MPM can be divided into two categories: synchronous MPM that occurs either simultaneously or within 6 months after the diagnosis of first malignancy and metachronous MPM that diagnose after 6 months from the first malignancy.[6]

There was a balanced incidence rate among male and female based on analysis of patients with MPM treated at the Cluj-Napoca Institute of Oncology between 2001 and 2004. Most of the patients are diagnosed between the 6th and 8th decades of life. Tumors occur earlier (mostly 10 years) in female patients than in male patients. Most of the patients are diagnosed with metachronous MPM type (41:22).[7] Studies of MPM may provide useful information not only for clinical purposes, but also can provide clues about etiology and management of these cancer types.[8]

This case report was a woman with metachronous MPM(endometrium-breast). The MPM is a rare case, so we could improve understanding of epidemiology, risk factors, diagnosis, and comprehensive MPM management by presented this case.

*Correspondence to: Ketut Suega, Medical Hematology and Oncology Division, Department of Internal Medicine, Faculty of Medicine Udayana University/SanglahGeneral Hospital, Denpasar
ksuega@yahoo.com

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CASE REPORT

A 60-year-old female presented with lump on the right breast since 2 months prior to admission, The lump was about the size of a quail egg with solid and hard consistency. The skin around the breast lump was rough and slightly hardened. Patients also complained right breast pain since 2 weeks, the pain was felt persistent, but didn't interfere patient's daily activities. Discharge from the nipple was denied. Patients also complained multiple marble sized lumps with rubbery consistency and not felt warm or painful on the right armpit and right neck since 1 ½ months ago.

Complaints of fever, cough, shortness of breath, weight loss, and night sweats were denied. Complaints of lumps on the stomach, vaginal discharge, and vaginal bleeding are denied. Patients experience first menstruation at age 16 years old. Patients experienced menopause at age 44 years old. The patient was pregnant 3 times and had 3 children, first pregnancy at the age 19 years.

From previous medical record data (5 years ago), patient was diagnosed with endometrial carcinosarcoma stage IV (omentum metastase), treated with total abdominal hysterectomy bilateral salphingo oovorectomy + omentectomy + debulking surgery followed by chemotherapy with cyclophosmide, doxorubicin, and cisplatin regimens for 6 cycles. There is no uterine cancer-related complaints had been experienced and the evaluation of ca-125 tumor markers within normal limits in post-treatment evaluation for 5 years.

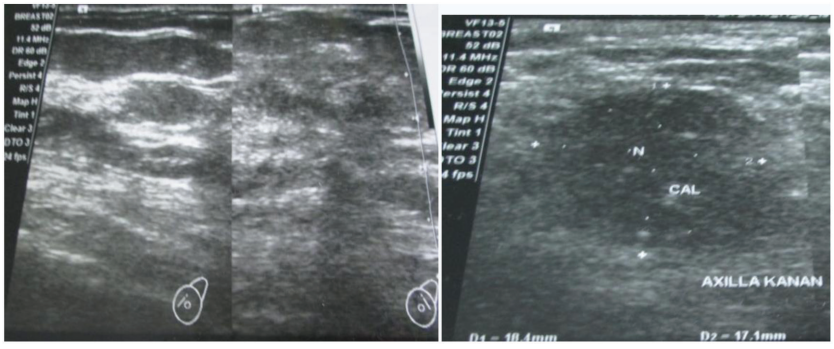

Figure 1 Mammae and Axilla USG

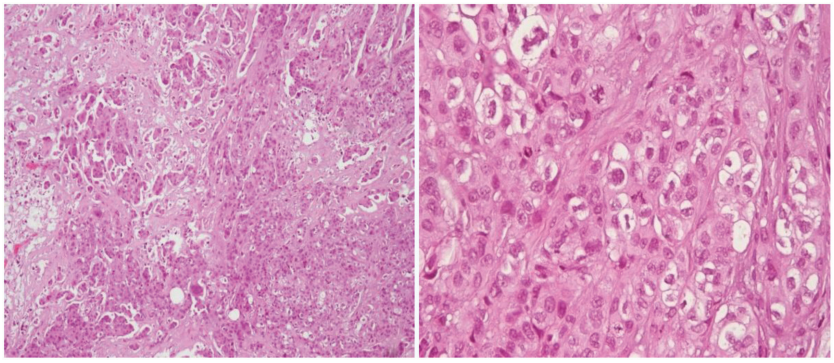

Figure 2 Histopathologic of Breast Biopsy

On physical examination of patients, level of consciousness was compos mentis, blood pressure 120/80 mmHg, pulse rate 92 ×/minute regular, axilla temperature 37° C, respiratory rate 18 ×/minute. Patient has normal body mass index (21.96 kg/m^2). Examination on neck showed supraclavicula lymph nodes enlargement (size 2×2 cm), soft consistency, fixed, no tenderness. Lung and heart examination within normal limit.

Inspection at the right mammary region showed Peau d'orange skin with hyperemic colour, inverted nipple (-), discharge (-), there was a palpable solid mass with size 3×2 cm, solid consistency, fixed, tenderness (+) on upper outer quadrant. On right axillary region, there was lymph nodes enlargement (2×2cm) with soft consistency, mobile, no tenderness. Abdominal examination showed scar from epigastric region to supra symphysis, the other abdominal examination within normal limit.

Laboratory examination showed hemoglobin 12,27 gr / dL; Hematocrit 40.92%; MCV 97,90 fL; MCH 29.35; MCHC 29.98 pg; Leukocyte 9.9 × 103 / µL; Platelets 355 × 103 / µL, AST 19.2 U/L, ALT 9.01 U / L, albumin 3.8 g / dL, BUN 12.10 mg / dL, creatinine 0.79 mg / dL, glucose 93 mg / dL, sodium 140 mmol / L, potassium 4.45 mmol / L.

Mammae and axilla Ultra Sonography (USG) showed: right mammae: there is a diffuse skin thickening, increasing mamae echoparenchym, and lobulated, inhomogeneous hypoechoic nodules with irregular border in upper outer quadrant, size about 31 mm × 24.7 mm; Right Axilla: multiple round hypoechoic nodules, regular border, with calcification, size about 18.6-29.4 mm. The Conclusion are: solid malignant nodule (31 mm × 24.7 mm) in right upper-lateral quadrant breast with diffuse skin edema and multiple solid nodules in right axilla (figure 1). Examination of liver and paraaorta USG does not indicate the presence of metastatic nodules. Postero-Anterior thorax x-ray shows no metastatic nodules in both hemithorax with sharp left and right pleural sinuses.

Mammae histopathologic biopsy results conclusion is invasive carcinoma of no special type grade3 (figure 2). Immunohistochemistry of estrogen receptor (ER), progesterone receptor (PR), and HER2 were negative. Ki-67 staining showed positive results in 40% of tumor cells.

Patients was diagnosed with breast cancer stage IIIC (T4bN3cMo) grade 3 with karnofsky score 70%. Patients was given 3-series Cyclophosphamide, Doxorubicin, 5-Fluorouracil chemotherapy

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regimen. Restaging evaluation after 3 series of chemotherapy showed there was a progression to stage IV (T4cN3cM1) with pulmonary metastases (right hemorrhagic pleural effusion). Chemotherapy followed by paclitaxel doxorubicin regimen for 3 series. Results of post-chemotherapy evaluation: no right pleural effusion; mammae, axilla, and abdominal ultrasound showed no nodules appear in both mammae and axilla, liver and paraaorta.

DISCUSSION

A study of 1,104 269 cancer patients showed the prevalence of MPM was between 0.73% and 11.7%. Improvement in survival rate of patients with neoplastic disease due to early diagnosis and advanced therapeutic progress allows more patients to survive long enough to experience subsequent malignancy.[9] The cancer prevalence ratio between male female in the Regional Cancer Institute between 2009 and 2012 was 0.8: 1, while the analysis performed on patients with MPM showed inverse ratio about 1.56: 1.[1] Most patients (65.85%) were diagnosed at 5th-6th decade of life.[1] Prevalence ratio between metachronous and synchronous MPM was 41:22. This MPM occur earlier (mostly 10 years) in female than male patients.[7]

Multiple primary malignancy is primary malignant tumors originating from different histological sources in same patient. The MPM diagnosis criteria according to Warren and Gates must meet all 3 criteria: (1) Confirmation of malignant histology on index and secondary tumor; (2) There should be minimum 2 cm distance of normal mucosal between tumor. If the tumor appears in the same location, the diagnostic interval must be five-year apart; (3) The probability that one of the tumor is metastasized from the other must be excluded.[1]

The definition and classification of MPM by Moertel in 1977 is still adopted until now. Classification of MPM is divided into 3 groups. Group I is MPM that occurs in organs with the same histology, group II is MPM that originating from different tissues and group III is formed from cancer originating from different tissues and organs. Group I is subdivided into group A which includes cancer occurring in the same tissues and organs; Group B that includes cancers from different tissues and organs; Group C, which includes cancer in the bilateral organ.[10]

The classification of MPM based on the time of diagnosis of the tumor is divided into two broad categories: synchronous and metachronous. If the tumor is diagnosed simultaneously or within 6 months intervals is called synchronous. If the diagnosis interval between malignancy more than 6 months is called metachronous.[11]

Our case is a 60-year-old female patient (6^{th} decade) diagnosed with breast cancer dextra (invasive carcinoma of no special type grade 3) stage IIIC, 5 years ago the patient was also diagnosed with endometrial carcinosarcoma stage IV (omentum metastatic) received surgical therapy and adjuvant chemotherapy with complete response at the end of treatment. Our case can be concluded as metachronous MPM based on Warren and Gates criteria. Our case fulfills all the criteria such as: (1) confirmation of malignant histology on index tumor and secondary tumor; (2) There is a minimum 2 cm distance of normal mucosal between tumors; (3) The possibility of one of the tumors being a metastasis from another has been excluded from different histopathological results. The interval between first and second malignancy diagnosis is more than 6 months (5 years)

Exact mechanisms that involved in the occurrence of MPM are not fully understood. Innate predisposing factors may be involved in several MPM, such as the presence of an association between hereditary nonpolyposis colorectal cancer and an increased risk of ovarian cancer or endometrial and small intestine cancer.[7] In addition to genetic susceptibility, the carcinogenic effects of radiotherapy / chemotherapy have been widely proposed as factors that contribute to the emergence of metachronous MPM. People with families who have cancer will inherit a genetic susceptibility to the occurrence of cancer as a risk factor. This risk will increase if the patient is getting therapy and can survive from its previous cancer. In addition, the treatment used for primary malignancy has resulted in the deterioration of the specific region of DNA that responsible for carcinogenesis process. The presence of Microsatellite instability (MSI) is more common in cases of MPM than in sporadic cancers.[12]

The development of secondary cancers after chemotherapy was first reported in 1970 by Kyle et al. Kyle et al reported Acute Myeloblastic Leukemia (AML) diagnosed after an alkylating agent for multiple myeloma disease. Treatment-related leukemia opens up a new paradigm for malignancy research induced by chemotherapy. In contrast, solid malignancy induction after chemotherapy has not been adequately established. Alkylating agents known or suspected to have leukemogenic effects on humans are mechlorethamine, chlorambucil, cyclophosphamide, melphalan, semustine, lomustine, Carmustine, procarbazine, prednimustine, busulfan, and a platinum-based chemotherapeutic

agents.[1] Secondary solid cancer of breast often occurs in patients who undergo radiation therapy in the chest area. The risk of breast cancer-related radiation is higher in patients who get radiation therapy at age less than 40 years.[13] Platinum-based agents are cytotoxic drugs that widely used for the treatment of various types of cancer including ovarian and testicular cancer. Like other alkylating agents, these platinum-based agents can cause defect of DNA.[1] Topoisomerase II inhibitor such as epipodophyllotoxins (eg, etoposide), anthracycline (eg. epirubicin) and anthracenediones (eg. mitoxantrone) have a simple mechanism of carcinogenesis by inducing formation of chimeric fusion genes which in some cases is sufficient to cause transformation, although additional mutagenic events may also be necessary.[1]

Risk factor that contributes to the occurrence of MPM in our case is chemotherapy that can cause damage to specific regions of DNA that can trigger the process of carcinogenesis. Chemotherapy agents used in this case are alkylating agents (cyclophosphamide), anthracycline which is a topoisomerase II inhibitor (doxorubicin) and a platinum-based alkylating agent (cisplatin). Platinum and non-platinum based agents can cause lesions in DNA because of their ability to form cross-links in DNA, but it may also induce microsatellite instability which is a form of genomic instability characterized by expansion or retraction of repetitive DNA sequences. Topoisomerase inhibitor chemotherapeutic agents may trigger secondary malignancies by forming chimeric fusion genes that cause transformation. Mechanisms of carcinogenesis by these chemotherapy agents has been extensively studied in treatment-related leukemia. However, recent research developments have begun to show a link between specific cytotoxic drugs and solid tumors.[1,12]

For several decades, endometrial carcinoma has been classified into two major groups based on epidemiological, pathological and clinical manifestation factors. The classification of this dualistic model consists of: (1) type I endometrial carcinoma with the most common type is endometrioid histotype which is the majority of all endometrial cancers. This type is associated with hyperestrogenic conditions, clinical manifestations are predominantly limited to uterine lesions, and are generally associated with better prognostic.[14] This type of carcinoma is 75-85% of all endometrial carcinomas, often diagnosed at stage I or II and confined to the uterus and cervix;[15] (2) type II endometrial carcinoma: more heterogeneous and usually has inversely clinical manifestation than type endometrial carcinoma. Endometrial serous carcinoma, clear cell carcinomas and carcinosarcomas are classified as type II carcinomas. This type of carcinoma often manifests outside the uterus (stage III or IV) and prone to recur after primary therapy. The associated risk factors are not fully understood, including white race, older menarche age, multiparity, older age and non-obesity. The most common sites of metastases in this type of cancer are pelvic/paraaortal lymph nodes, vagina, lung, liver, peritoneum, brain and bone.[14,15]

Several recent researches have showed the possible association between breast cancer and type II endometrial carcinoma.[14] Study of Geisler et al evaluating medical records of 592 patients diagnosed with endometrial carcinoma. This study concluded 25 patients (4.2%) were diagnosed with either synchronous or metachronous breast cancer and most of them with type II endometrial carcinomas. Endometrial cancer as predisposition factor of breast cancer suspected as a result of similar risk factors such as: similar environmental risk factors, genetic risk factors, iatrogenic factors, or some combination of these risk factors.[12] Some of the same risk factors between type II endometrial carcinoma and breast carcinoma are broad and non-specific including sex, age, and family history of breast cancer. Several initial evidences suggest that breast cancer that appears after endometrial carcinoma is more likely to be type II endometrial cancer compared with type I endometrial cancer. The association between type II endometrial cancer and breast cancer may have a multifactorial basis with one of the contributing factor is mutation BRCA 1/2 genes.[7]

In our case, the patient first malignancy was endometrial carcinosarcoma stage IV which is a type II endometrial carcinoma that often manifests outside the uterus (stage III or IV). Risk factors for endometrial type II carcinoma in these patients are multiparity, older age and non-obesity. The second primary malignancy of our patient was breast cancer dextra grade 3 stage IIIC (T4bN3cMo). From several studies in the United States showing an association between synchronous and metachronous MPM breast cancer with type II endometrial carcinoma. The association between breast cancer and type II endometrium may have a multifactorial etiology with one of the contributing factor is BRCA 1/2 gene mutation, but we didn't examine BRCA 1/2 gene mutation.

Possibility of MPM should always be considered during pre-therapy evaluation. The screening procedure is particularly useful for early detection of MPM before clinical manifestations occur. There is some evidence that screening will improve treatment outcomes in patients with possibility to

experience metachronous MPM. With close monitoring, MPM can be detected earlier and followed by appropriate intervention can maintain patient survival rate.[16] Women with endometrial carcinoma have a risk for experience breast and colorectal cancer.[17] During control and evaluation, we should advise the patient to counsel and perform secondary cancer prevention strategies with mammography methods for breast cancer and stool examination for occult blood detection or colonoscopy for colon cancer. Based on research conducted in Canada, high economic status is associated with high rates of breast and colorectal cancer screening.[18]

Recent recommendations for breast cancer screening in the general population is mammography every 1-2 years at age over 40 years. Fecal occult blood every 2 years or colonoscopy every 10 years after age 50 are the methods for colorectal cancer screening. All of these strategies are expected to maximize life expectancy in patients with endometrial cancer.[19] In our case, routine evaluation for endometrial cancer recurrence is performed by the patient, but possibility of MPM occurring in other organs is not evaluated.

CONCLUSION

Increasing life expectancy in cancer patients can lead to new health problems, including the emergence MPM. Although the incidence of MPM is increasing, the diagnosis of MPM remains very rare. Knowledge about epidemiology, risk factors, diagnosis, and comprehensive management especially early diagnosis and prompt treatment of MPM will improve treatment survival of the patients.

Our case was a woman with a metachronous MPM endometrial and breast, with the first malignancy was endometrial carcinosarcoma stage IV (type II endometrial carcinoma) followed by the appearance of second malignancy as a breast cancer dextra grade 3 stage IIIC. Time interval between these malignancies diagnosis is more than 6 months (5 years).

REFERENCES

1. Bagri PK, Singh D, Singhal MK, Singh G, Mathur G, Jakhar SL, *et al*. Double Primary Malignancies: A Clinical & Pathological Analysis Report from a Regional Cancer Institute in India. Iran J Cancer Prev. 2014; 2:66-72.
2. Chowhan AK, Jena A, Kinnera SB, Patnayak R, Reddy OM, Reddy KM. Dual malignancy: An interesting concurrent mixed epithelial ovarian tumor with esophageal carcinoma. Indian J Cancer. 2011; 48: 361-2.
3. Zhu YR. Multiple primary malignant tumors. The J Med Theory Practical. 2006; 19(11):1249–1250.
4. Reddy PA, Harinarayan CV, Suresh V, Jena A, Chandrasekhar SL, Rashmi P, *et al*. An unusual case of virilizing ovarian tumor associated with carcinoma *in situ* of cervix. Int J EndocrinolMetab. 2009; 4: 255-8.
5. Lois B, Travis, Bhatia S, James M, Allan M, Kevin C, *et al*. Second Primary Cancers. In: DeVita VT, Lawrence TS, Rosenberg SA., eds. Cancer Principles & Practice of Oncology. 9th. Philadelphia:Lippincot Williams & Wilkins; 2011. 5141-5180.
6. Suzuki T, Takahashi H, Yao K, Inagi K, Nakayama M, Makoshi T, et al. Multiple primary malignancies in the head and neck: a clinical review of 121 patients. Acta Otolaryngol Suppl. 2002; (547):88-92.
7. Irimie A, Cadariu PA, Burz C, Puscas E. Multiple Primary Malignancies – Epidemiological Analysisat a Single Tertiary Institution. J Gastrointestin Dis. 2010; 19(1): 69-73.
8. Jena A, Patnayak R, Lakshmi AY, Manilal B, Reddy MK. Multiple primary cancers: An enigma. South Asian Journal of Cancer. 2016; 5(1): 29-32
9. Chaturvedi AK, Engels EA, Gilbert ES. Second cancers among104.760 survivors of cervical cancer: evaluation of long-term risk. JNatl Cancer Inst. 2007; 99: 1634-1643.
10. Moertel CG, Dockerty MB, Baggenstoss AH. Multiple primary malignant neoplasms. Introduction and presentation of data. Cancer 1961;14:221-30.
11. Aydiner A, Karadeniz A, Uygun K. Multiple primaryneoplasms at a single institution: differences between synchronous and metachronousneoplasms. Am J ClinOncol. 2000;23:364-70.
12. Horii A, Han HJ, Shimada M, Yanagisawa A, Kato Y, Ohta H, *et al*. Frequent replication errors at microsatellite loci in tumors of patients with multiple primary cancers. Cancer Res. 1994; 54(13): 3373-3375.
13. Andrea K, Kenney LB, Gilbert ES, Travis LB. Secondary malignancies across the age spectrum. SeminRadiatOncol. 2010; 20(1): 1-20.
14. Vaslamatzis M, Alevizopoulos N, Petraki. Second primary neoplasms (SPN) in cancer patients. Proc ASCO. 2003; 22: 3581.
15. Diver EJ, Foster R, Rueda BR, Growdon WB. The Therapeutic Challenge of Targeting HER2 in Endometrial Cancer. The Oncologist. 2015; 20: 1058-1068.
16. Vogel VG. Identifying and screening patients at risk of second cancers. Cancer Epidemiol Biomarkers Prev. 2006; 15(11): 2027-2032.
17. Re A, Taylor TH, DiSaia PJ, Anton-Culver H. Risk for breast and colorectal cancers subsequent to cancer of the endometrium in a population-based case series. GynecolOncol. 1997; 66: 255–257.
18. Katz SJ, Zemencuk JK, Hofer TP. Breast cancer screening in the United States and Canada, 1994: socioeconomic gradients persist. Am J Public Health. 2000; 90: 799–803.
19. Smith RA, Cokkinides V, Brawley OW. Cancer screening in the United States, 2008: a review of current American Cancer Society guidelines and cancer screening issues. CA Cancer J Clin 2008;58:161–79.