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Case Report

Metachronous Sporadic Sextuple Primary Malignancies Including Bilateral Breast Cancers

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ABSTRACT

Multiple primary malignancies are defined as the presence of more than one malignant neoplasm with a distinct histology occurring at different sites in the same individual. They are classified as synchronous or metachronous according to the diagnostic time interval of different malignancies. Diagnosis of multiple primary malignancies should avoid misclassification from multifocal/multicentric tumors or recurrent/metastatic lesions. In multiple primary malignancies, with increase in the number of primary tumors, the frequency rapidly decreases. Here, we report an exceptionally rare case of a woman who was diagnosed with metachronous sporadic sextuple primary malignancies including bilateral breast cancers (gastric cancer, ovarian Sertoli-Leydig cell tumor, left breast cancer, thyroid cancer, right breast cancer, and rectal neuroendocrine tumor). The sextuple primary malignancies in this case involved 5 different organs: the stomach, ovary, thyroid, rectum, and bilateral breasts. Further studies are needed to elucidate the current epidemiologic status of patients with multiple primary malignancies.

Keywords: Breast neoplasms; Neoplasms, multiple primary; Neoplasms, second primary

INTRODUCTION

Multiple primary malignancies are defined as the presence of more than one malignant neoplasm with a distinct histology occurring at different sites in the same individual [1-3]. Multiple primary malignancies are classified as synchronous or metachronous according to the diagnostic time interval of different malignancies [2,4]. Although the incidence of multiple primary malignancies is increasing, cases of quadruple or more primary malignancies remain extremely rare [2,3].

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Conflict of Interest
The authors declare that they have no competing interests.

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Herein, we report an exceptionally rare case of a woman who was diagnosed with metachronous sporadic sextuple primary malignancies including bilateral breast cancers (gastric cancer, ovarian Sertoli-Leydig cell tumor, left breast cancer, thyroid cancer, right breast cancer, and rectal neuroendocrine tumor). The sextuple primary malignancies of this case involved 5 different organs (stomach, ovary, thyroid, rectum, and bilateral breasts), with multiple liver metastases from a rectal neuroendocrine tumor.

CASE REPORT

In November 2004, a 54-year-old woman was referred to the breast cancer center of our hospital due to microcalcification in the left breast, which was incidentally detected by mammography during routine breast cancer screening. Ultrasonography showed a hypoechoic lesion with an irregular margin in the left breast (**Figure 1**). A vacuum-assisted breast biopsy of that lesion revealed a microinvasive ductal carcinoma. She underwent subcutaneous mastectomy with axillar lymph node dissection and immediate implant insertion. Pathology results revealed a T1miN0M0 invasive ductal carcinoma (**Figure 2**). Immunohistochemistry results indicated estrogen receptor negative, progesterone receptor positive (50%), borderline cerbB2 (2+/3), and 5% Ki67 positivity (**Figure 3**). She completed endocrine therapy with anastrozole medication for 5 years. She was regularly followed up at the breast cancer center and underwent appropriate tests including mammography and breast ultrasonography every 6 to 12 months.

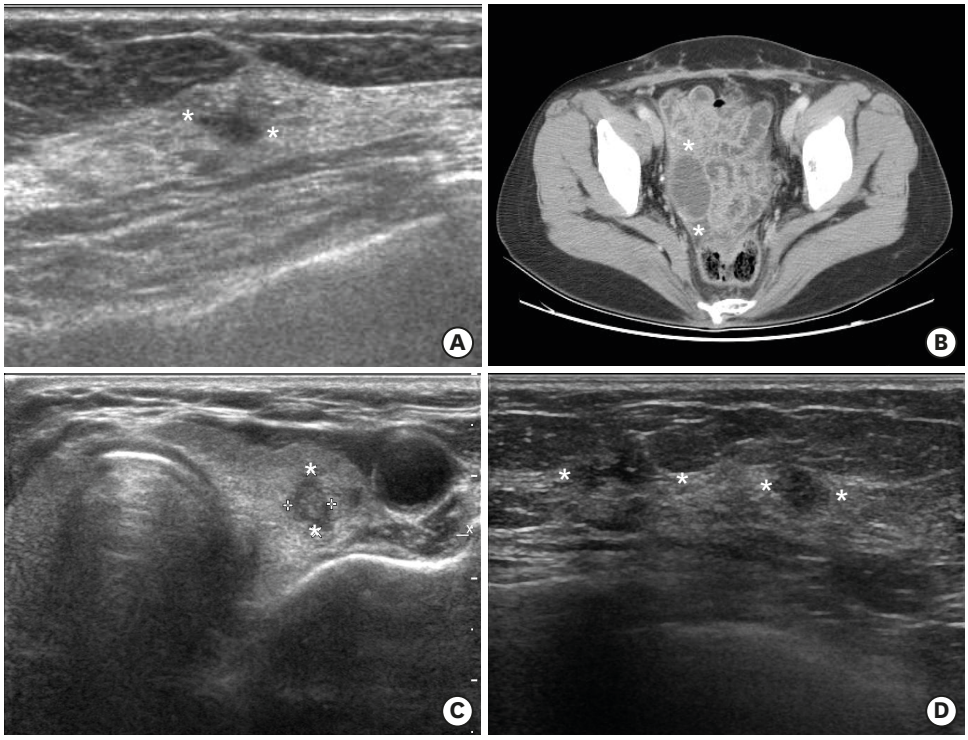

Figure 1. Ultrasonography findings of the lesions in the ovary, breasts, and thyroid. (A) Ultrasonograph of a left breast lesion. (B) Computed tomography of a right ovarian tumor. (C) Ultrasonograph of a left thyroid lesion. (D) Ultrasonograph of right breast lesions.
*Indicates the lesion in each organ.

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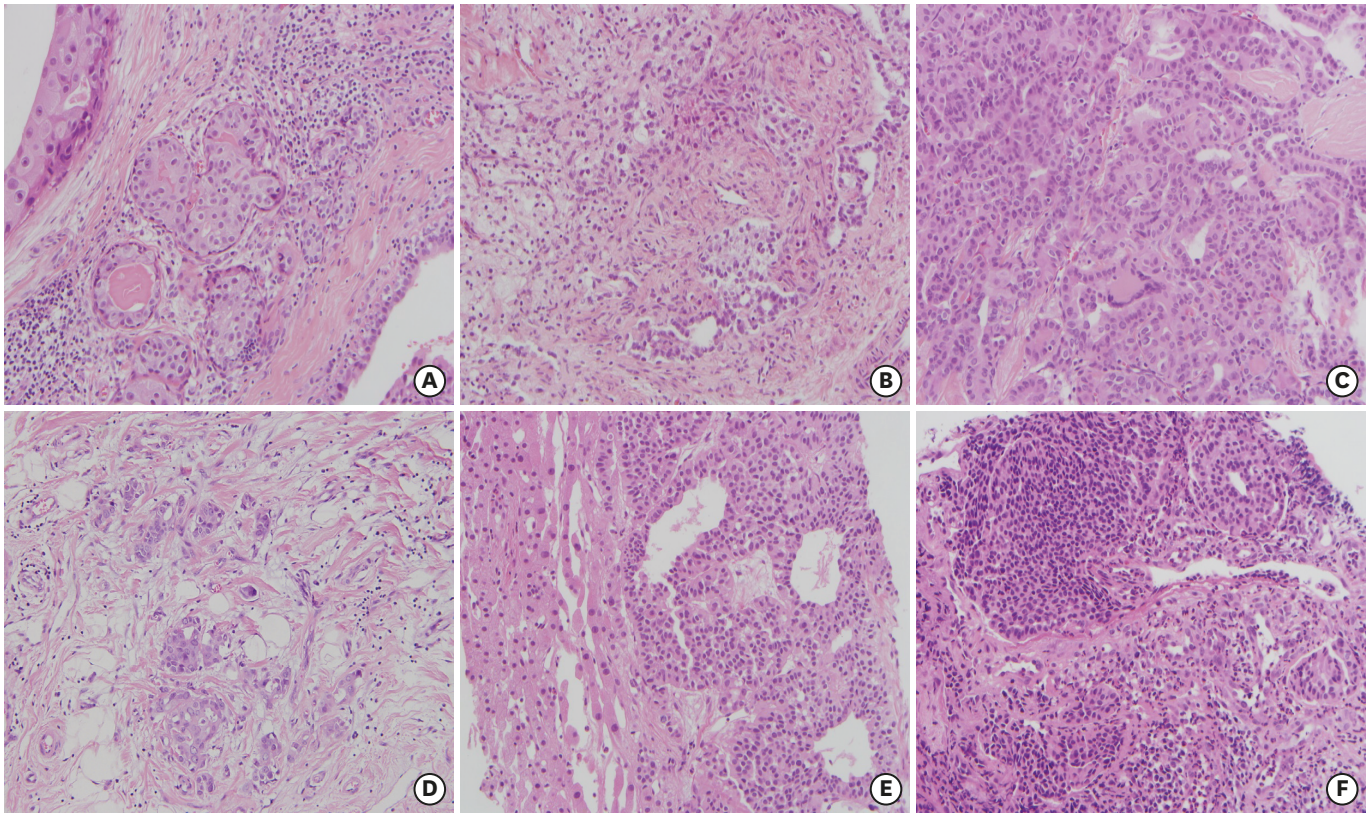

Figure 2. Pathologic findings for each tumor (hematoxylin and eosin stain, magnification ×200). (A) Left breast cancer. (B) Right ovary tumor. (C) Left thyroid cancer. (D) Right breast cancer. (E) Neuroendocrine tumors of the liver. (F) Neuroendocrine tumor of the rectum.

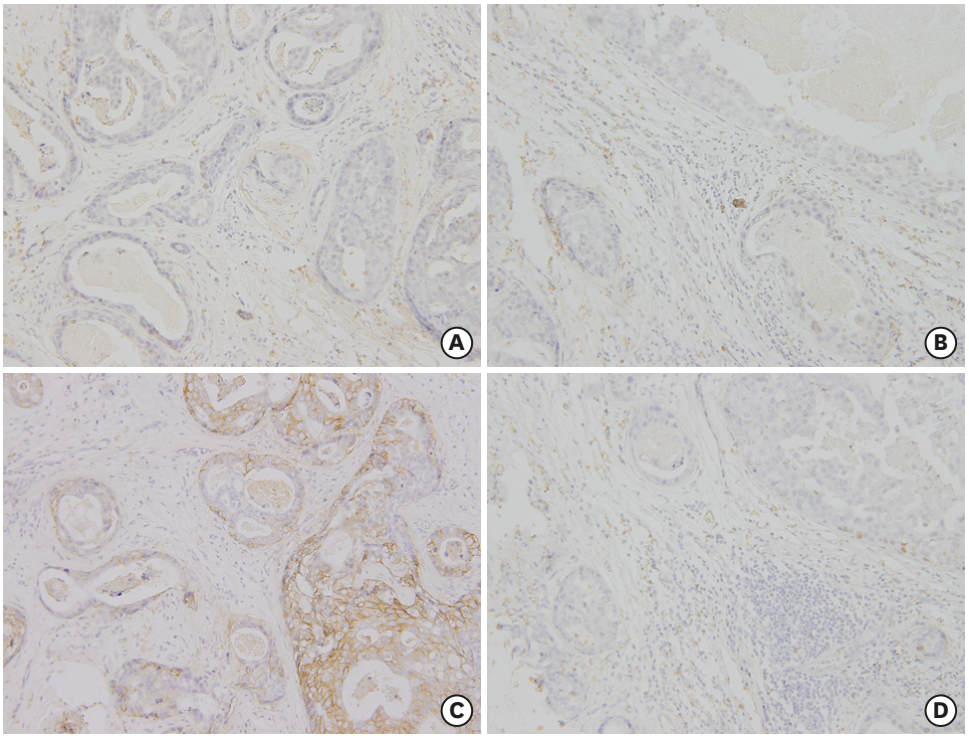

Figure 3. Immunohistochemistry of left breast cancer (magnification ×200). (A) Estrogen receptor. (B) Progesterone receptor. (C) CerbB2. (D) Ki67.

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The patient had histories of gastric cancer and Sertoli-Leydig cell tumor of the right ovary. Fifteen years ago (1989), she was diagnosed with advanced gastric cancer at the age of 39 years. She underwent radical subtotal gastrectomy at another hospital and then received adjuvant chemotherapy for 6 months. Ten months ago (2004 January), a 4-cm right ovarian mass was incidentally detected by computed tomography (**Figure 1**). Serum carcinoembryonic antigen, carbohydrate antigen 125, and carbohydrate antigen 19-9 levels were within the normal limit. She underwent bilateral salphingo-oophorectomy. Pathology results revealed a Sertoli-Leydig cell tumor with moderate differentiation (**Figure 2**). She had a history of receiving total abdominal hysterectomy due to a uterine leiomyoma 2 years ago. Twelve years ago, she was diagnosed with pulmonary tuberculosis, which was cured under medication for 1 year. She reported having no other past medical histories and any family history of malignancies. She regularly visited a family medicine clinic for routine health check-ups that included tests such as gastroscopy. She also regularly visited a gynecology clinic for routine gynecological examinations.

In August 2010, a sub-centimeter-sized nodule was incidentally detected in the left thyroid. Malignant cells of the suspected papillary carcinoma were diagnosed by fine-needle aspiration cytology. She underwent total thyroidectomy (**Figure 1**). Pathology results showed T1aN0M0 papillary thyroid cancer (**Figure 2**). She was regularly followed up for thyroid cancer with a 6-month interval, receiving appropriate tests that included neck ultrasonography. In August 2016, several hypoechoic masses with an extent of 2.8 cm were incidentally detected in the right breast by routine follow-up ultrasonography (**Figure 1**). A core needle biopsy revealed a high-grade ductal carcinoma in situ. She received a mastectomy with a sentinel axillar lymph node biopsy. Final pathology results revealed a T1miN0M0 invasive ductal carcinoma (**Figure 2**). Immunohistochemistry revealed estrogen receptor negative, progesterone receptor negative, borderline cerbB2 (2+/3), and 30% Ki67 positivity (**Figure 4**). She did not receive any adjuvant therapy for her right breast cancer. Mutation tests on *BRCA1* and *BRCA2* showed no clinically significant mutations, although unclassified heterozygous variants (851T>G [c.623T>G], p.Val208Gly) were detected for *BRCA2*. She was regularly followed up at the breast cancer center with a 3-month interval.

In February 2017, multiple liver masses were incidentally detected by computed tomography (**Figure 5**). Further evaluation revealed an additional 2-cm rectal mass by computed tomography and colon fibroscopy (**Figure 5**). The serum carcinoembryonic antigen level was within the normal limit. Biopsies for liver and rectal masses led to the diagnosis of grade 2 neuroendocrine tumors for both the liver and rectal masses (**Figure 2**). She was diagnosed with a primary neuroendocrine tumor of the rectum with multiple metastases to the liver. She was 66 years old at that time. She refused further evaluation and treatment at this hospital. She decided to visit another hospital, and further follow-up was lost. She died in August 2017. The types of organs involved in this case are summarized in **Table 1**.

This case report was approved by the Institutional Review Boards of Seoul Metropolitan Government Seoul National University Boramae Medical Center (20-2019-2) with a waiver of informed consent.

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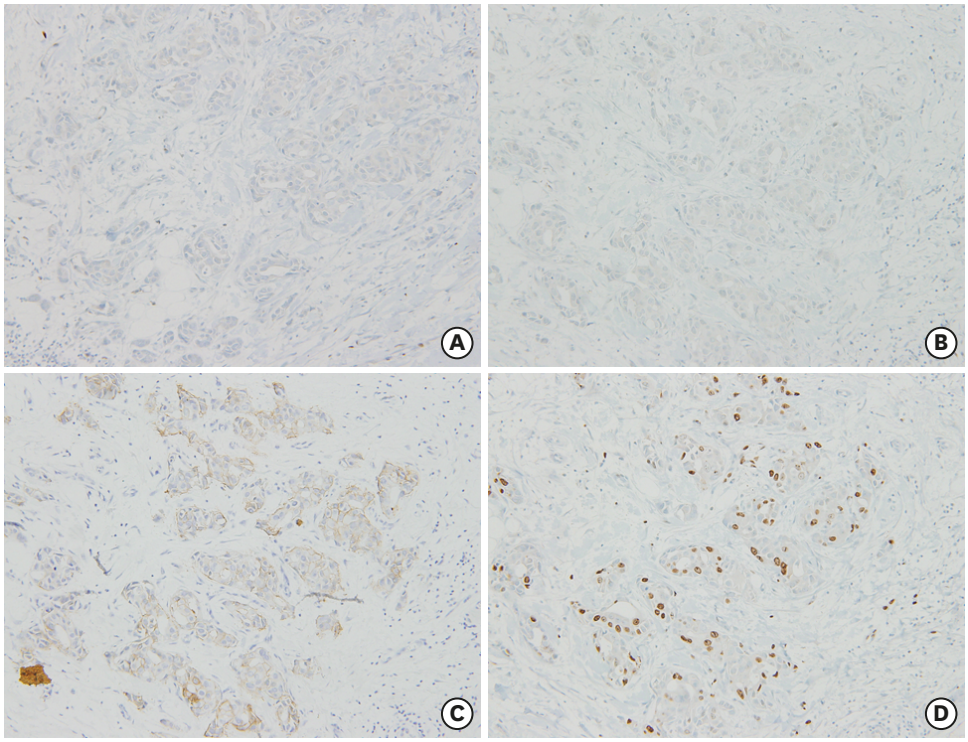

Figure 4. Immunohistochemistry of right breast cancer (magnification ×200). (A) Estrogen receptor. (B) Progesterone receptor. (C) CerbB2. (D) Ki67.

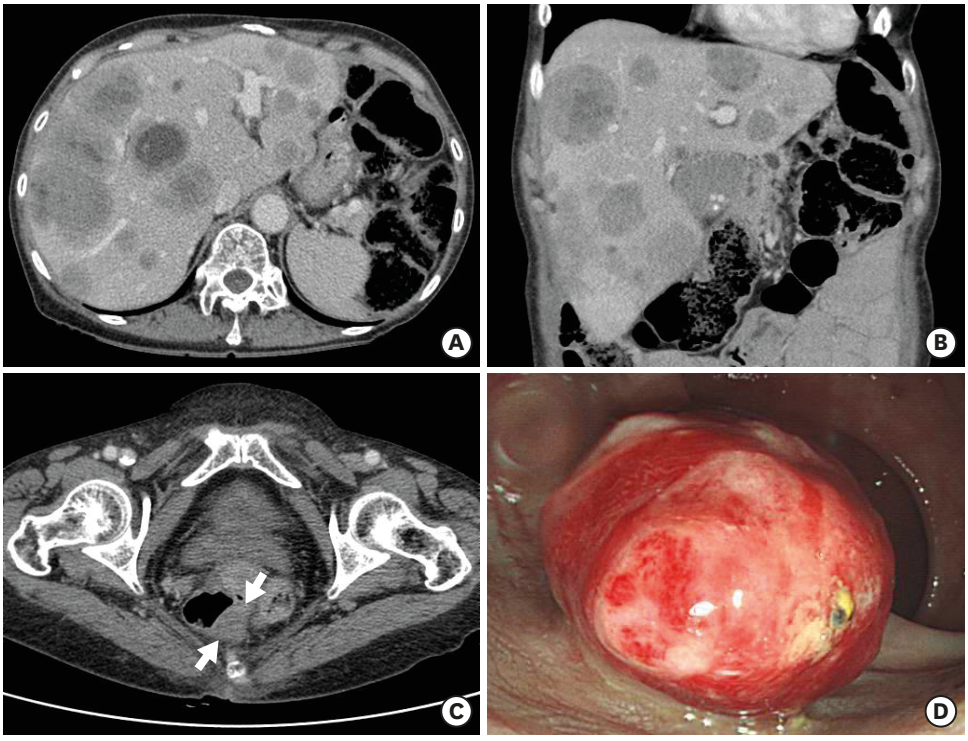

Figure 5. Image and gross findings of neuroendocrine tumors of the liver and rectum. (A) Computed tomography image of liver lesions in the axial view. (B) Computed tomography image of liver lesions in the coronal view. (C) Computed tomography image of the rectal lesion in the axial view (arrows). (D) Gross finding of the rectal mass by colon fibroscopy.

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Table 1. Case summary according to the organs involved

Organ (site)	Diagnosis	Histology	Time of diagnosis	Age at diagnosis	Stage*	Surgery	Adjuvant Treatment
Stomach	Gastric cancer	Adenocarcinoma	1989	39	Unknown	Radical subtotal gastrectomy	Chemotherapy
Ovary (right)	Sertoli-Leydig cell tumor	Moderately differentiated Sertoli-Leydig cell tumor	January, 2004	53	T1aN0M0, stage I	Bilateral oophorectomy	None
Breast (left)	Breast cancer	Invasive ductal carcinoma	December, 2004	54	T1aN0M0, stage I	Mastectomy	Anastrozole for 5 years
Thyroid (left)	Thyroid cancer	Papiilary carcinoma	October, 2010	59	T1aN0M0, stage I	Total thyroidectomy	None
Breast (right)	Breast cancer	Invasive ductal carcinoma	August, 2016	65	T1miN0M0, stage I	Mastectomy	None
Rectum	Neuroendocrine tumor	Neuroendocrine tumor	February, 2017	66	Stage IV (primary lesion)	No	Unknown
Liver	Neuroendocrine tumors†	Neuroendocrine tumor	February, 2017	66	Stage IV (metastatic lesions)	No	Unknown

*Cancer Staging Manual of the American Joint Committee on Cancer (Eighth edition); †Metastatic tumors from the rectal neuroendocrine tumor.

DISCUSSION

Multiple primary malignancies were first reported by Billroth [5] in 1889. Warren and Gates [1] have used the following criteria to define multiple primary malignancies: 1) each tumor must present a definite picture of malignancy; 2) each must be distinct; and 3) the probability of one being a metastasis of the other must be excluded. Currently, the following modified criteria are widely accepted for the definition of multiple primary malignancies: 1) each tumor is malignant; 2) each tumor has its own pathological features; 3) tumors occur in different parts of the organs, not continuous with each other; and 4) each tumor has its own metastatic pathway without the diagnosis of metastatic or recurrent tumors [3]. Diagnosis of multiple primary malignancies should avoid misclassification from multifocal/multicentric tumors or recurrent/metastatic lesions. The first malignant lesion without any other prior malignant neoplasm is referred to as the index cancer of multiple primary malignancies. Overall, the frequency of multiple primary malignancies among the cancer population is reported to be 2%–8%, up to 17% within 20 years of follow-up duration [2]. This frequency could vary according to the definition of multiple primary malignancies, the study population, and follow-up duration. The occurrence of multiple primary malignancies is increasing due to several factors, including an increasing number of cancer survivors, an increasing number of older people, widespread screening programs, improved diagnostic methods, and advanced treatment methods [2,6]. Of multiple primary malignancies, double primary tumors account for the majority. As the number of primary tumors increases, the frequency rapidly decreases [4]. Depending on the diagnostic time interval of different malignancies, multiple primary malignancies could be classified as synchronous or metachronous, usually with a cut-off value of 6 months [2,4]. Metachronous tumors are more common than synchronous tumors. The ratio of metachronous tumors to synchronous tumors has been reported to be 2.7:1 [3]. In the present study, we reported an exceptionally rare case of metachronous sporadic sextuple primary malignancies including gastric cancer, Sertoli-Leydig cell tumor, thyroid cancer, neuroendocrine tumor of the rectum, and bilateral invasive breast cancers. Six different primary malignancies developed from 5 different organs: the stomach, ovary, thyroid, rectum, and bilateral breasts.

Multiple primary malignancies are often associated with hereditary cancer syndromes. Diagnosis of bilateral breast cancers led us to suspect an association with hereditary breast/ovarian cancer syndrome affected by *BRCA1/2* genes [7]. Increased risk of breast cancer is also associated with 2 very rare hereditary cancer syndromes, namely, Li-Fraumeni

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syndrome and Cowden syndrome, which affect *TP53* and *PTEN*, respectively [8,9]. Mutations in *BRCA1/2* are mainly associated with serous adenocarcinoma of the ovary. Non-epithelial ovarian malignancies are not significantly associated with *BRCA1/2* mutations [10]. Ovarian Sertoli-Leydig cell tumor is one kind of sex cord–stromal tumor that has been reported to be associated with Peutz-Jeghers syndrome or *DICER1*-related disorders, affect *STK11* or *DICER1*, respectively [11,12]. In the present case, we could not obtain any definite clinical evidence supporting the hereditary cancer syndromes mentioned above. Mutation tests for *BRCA1/2* reported no clinically significant mutations. Other genetic tests regarding *TP53*, *PTEN*, *STK11*, and *DICER1* were not performed.

Several previous studies have reported cases of multiple primary malignancies with high numbers of primary malignancies. A previous study reported a case of 8 primary malignant neoplasms in a woman [13]. The reported case was a 61-year-old Chinese woman with 5 adenocarcinomas of the colon (during 32 years of follow-up period), an adenocarcinoma of the endometrium, a papillary carcinoma of the right breast, and a mucinous adenocarcinoma of the small intestine. Six of eight malignancies, from the first to sixth, were metachronous; the seventh and eighth malignancies were synchronous. The authors reported that the 5 colonic malignancies originated from different sites of the colon; 4 different organs (colon, endometrium, right breast, and small intestine) were involved in that case. Another previous study reported a case of sextuple primary malignancies [14]. In that case, a 53-year-old Caucasian man was diagnosed with multiple primary malignancies involving the jejunum, transverse colon, sigmoid colon, rectosigmoid colon, urinary bladder, and skin. Four tumors from the intestinal tract were diagnosed within 5 months; the other 2 tumors were metachronous lesions. Three different organs were involved: the small intestine, colon, and skin. Another paper reported a case of 61-year-old woman diagnosed with metachronous sextuple primary malignancies with Lynch syndrome II [15]. In that case, all 6 malignancies involved the gastrointestinal tract, including the jejunum, rectum, stomach, colon, ileum, ascending colon, and cecum. Molecular genetic analysis revealed a pathological mutation of the *MSH2* gene in the 12th exon. Our case had metachronous sextuple primary malignancies involving 5 different organs (stomach, ovary, thyroid, rectum, and bilateral breasts) without showing an association with familial or hereditary cancer syndromes. To the best of our knowledge, our case had the largest number of organs affected with primary malignancies. This is the first case report of metachronous sporadic sextuple primary malignancies affecting 5 different organs, including bilateral breast cancers.

In this study, the patient was diagnosed as sextuple primary malignancies during 28 years (from 1989 to 2017). All lesions were incidentally detected except gastric cancer. The details of gastric cancer could not be checked in the medical records because it was diagnosed and treated at another hospital a long time ago. Most malignancies were diagnosed at the early stages except for the neuroendocrine tumors: moderately differentiated Sertoli-Leydig cell tumor, stage I bilateral breast cancer, and stage I thyroid cancer. She received appropriate treatments, including surgery and adjuvant therapies, for these early-staged malignancies, and there was no recurrence. Although the neuroendocrine tumors of the rectum and liver were incidentally detected, multiple liver lesions were inferred to be metastatic lesions from the rectal lesion. Early-stage diagnosis and appropriate treatment for the previous 5 metachronous primary malignancies could partly explain this exceptionally rare case of sextuple primary malignancies. A previous study reported that patients with metachronous multiple primary malignancies have better prognoses than patients with synchronous multiple primary malignancies or a single primary tumor [4]. Patients with metachronous

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multiple primary malignancies tend to have less aggressive malignancies, present at earlier stages and have an indolent clinical course with longer survival rates [4].

In conclusion, we herein report an exceptionally rare case of metachronous sporadic sextuple primary malignancies including bilateral breast cancers. Further studies are needed to elucidate the current epidemiologic status of patients with multiple primary malignancies. As detection of early-stage breast cancer is increasing, long-term breast cancer survivors are also increasing. Accordingly, patients with multiple primary malignancies including breast cancer, are expected to increase more and more, and clinicians need to be aware of the appropriate management of these patients. Establishment of guidelines on diagnosis and management for patients with multiple primary malignancies would be helpful to both clinicians and their patients.

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REFERENCES

1. Warren S, Gates O. Multiple primary malignant tumors: survey of the literature and a statistical study. Am J Cancer 1932;16:1358-414.
2. Vogt A, Schmid S, Heinimann K, Frick H, Herrmann C, Cerny T, et al. Multiple primary tumours: challenges and approaches, a review. ESMO Open 2017;2:e000172.
PUBMED | CROSSREF
3. Wang DD, Yang Q. Synchronous quadruple primary malignancies of the cervix, endometrium, ovary, and stomach in a single patient: a case report and review of literature. World J Clin Cases 2019;7:3364-71.
PUBMED | CROSSREF
4. Amer MH. Multiple neoplasms, single primaries, and patient survival. Cancer Manag Res 2014;6:119-34.
PUBMED | CROSSREF
5. Billroth T. Die allgemeine chirurgische pathologie and therapie. In: Reimer G, editor. 51 Vorlesungen-Ein Handbuch fur Studierende and Artze, 14. Berlin: Auflage; 1889.
6. Soerjomataram I, Coebergh JW. Epidemiology of multiple primary cancers. Methods Mol Biol 2009;471:85-105.
PUBMED | CROSSREF
7. Blackwood MA, Weber BL. BRCA1 and BRCA2: from molecular genetics to clinical medicine. J Clin Oncol 1998;16:1969-77.
PUBMED | CROSSREF
8. Li FP, Fraumeni JF Jr, Mulvihill JJ, Blattner WA, Dreyfus MG, Tucker MA, et al. A cancer family syndrome in twenty-four kindreds. Cancer Res 1988;48:5358-62.
PUBMED

9. Lloyd KM 2nd, Dennis M. Cowden's disease. A possible new symptom complex with multiple system involvement. Ann Intern Med 1963;58:136-42.
PUBMED | CROSSREF

10. Werness BA, Ramus SJ, DiCioccio RA, Whittemore AS, Garlinghouse-Jones K, Oakley-Girvan I, et al. Histopathology, FIGO stage, and BRCA mutation status of ovarian cancers from the Gilda Radner Familial Ovarian Cancer Registry. Int J Gynecol Pathol 2004;23:29-34.
PUBMED | CROSSREF

11. Clements A, Robison K, Granai C, Steinhoff MM, Scalia-Wilbur J, Moore RG. A case of Peutz-Jeghers syndrome with breast cancer, bilateral sex cord tumor with annular tubules, and adenoma malignum caused by STK11 gene mutation. Int J Gynecol Cancer 2009;19:1591-4.
PUBMED | CROSSREF

12. Goulvent T, Ray-Coquard I, Borel S, Haddad V, Devouassoux-Shisheboran M, Vacher-Lavenu MC, et al. DICER1 and FOXL2 mutations in ovarian sex cord-stromal tumours: a GINECO group study. Histopathology 2016;68:279-85.
PUBMED | CROSSREF

13. Zhao J, Tan Y, Wu Y, Zhao W, Wu J, Ji M, et al. A rare case of eight multiple primary malignant neoplasms in a female patient: a case report and review of the literature. Oncol Lett 2015;9:587-90.
PUBMED | CROSSREF

14. Ettinger J, Massell TB, Wilkins FB. Six primary carcinomas in one patient. Am J Surg 1949;78:894-7.
PUBMED | CROSSREF

15. Danys D, Stratilatovas E, Cereska V, Poskus T. Lynch syndrome and sextuple primary malignancies. Acta Chir Belg 2018;118:326-30.
PUBMED | CROSSREF