Multiple primary malignant neoplasms and long-term survival: A case report

BIAO XIE, KE HUANG and SHUIBO ZHU

Department of Thoracic Cardiovascular Surgery, General Hospital of Central Theater Command, Wuhan, Hubei 430070, P.R. China

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Abstract. At present, morbidity rates in patients with multiple primary malignant neoplasms (MPMNs) are continually improving as tumor diagnosis and treatment technology progress. The present study aimed to describe the rare case of a patient with MPMNs. Following initial detection of the first primary malignant tumor, the patient underwent six surgical interventions. The medical history showed that the patient had been sequentially diagnosed with seven types of primary tumors over a period of 38 years. These included sigmoid colon cancer, thyroid cancer, ileocecal adenocarcinoma, left lung invasive adenocarcinoma, bilateral breast invasive cancer and right lung invasive adenocarcinoma. Although this clinical presentation of MPMN is exceptionally uncommon, timely detection and consistent medical interventions have led to an increased survival period for affected patients. Therefore, the present study aimed to describe the diagnostic and therapeutic strategies used for the current patient, and to offer novel insights for the clinical management of similar conditions.

Introduction

Multiple primary malignant neoplasms (MPMNs) denote the concurrent or sequential development of at least two distinct primary malignant tumors within the body, which may arise from the same organ, paired organs, different regions of the same system, or various organs across different systems. Based on the time interval between tumor occurrences, MPMNs are categorized into two sub-types, namely, simultaneous MPMNs (sMPMNs), with an interval of ≤6 months, and metachronous MPMNs (mMPMNs), with an interval of >6 months (1). The morbidity of MPMNs is steadily increasing, with reported rates in China ranging from 1.02 to 37.25% over the past 5 years (2). Cases with double primary tumors are the most common, while cases with three or more primary tumors are rare (3). Medical advancement has led to a notable increase in the number of long-term survivors of initial primary tumors, consequently leading to an increased number of patients with MPMNs. The present study describes the case of a patient diagnosed with seven primary malignant tumors that spanned a 38-year period.

Correspondence to: Professor Shuibo Zhu, Department of Thoracic Cardiovascular Surgery, General Hospital of Central Theater Command, 627 Wuluo Road, Wuchang, Wuhan, Hubei 430070, P.R. China
E-mail: whzyyzsb@126.com

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Case report

Current presentation. A 68-year-old female patient with bilateral pulmonary nodules first identified on a routine health check-up in July 2021, was admitted to the Department of Cardiothoracic Surgery at the General Hospital of Central Theater Command (Wuhan, China) in January 2024, following the detection of an enlarged nodule in the right lung. At the request of the patient, a breast ultrasound was conducted, revealing a solid hypoechoic nodule of ~0.5x0.5 cm at the 8-9 o'clock position, 3-4 cm away from the right nipple, with clear borders and uneven internal echoes. In the left breast, a solid hypoechoic nodule of 1.2x0.8 cm was identified at the 2-3 o'clock position, 3-4 cm away from the nipple, with indistinct borders and uneven internal echoes. Following discussions with the patient and their family, it was decided that the breast nodules should be removed. With reference to the Guidelines for Breast Cancer Diagnosis and Treatment by China Anti-Cancer Association (2024 edition) (4), the patient and their family were informed of the survival rate and incidence of distant metastasis in patients with early-stage breast cancer, as these rates are comparable between those that undergo breast-conserving therapy and those that undergo total mastectomy. Notably, breast-conserving therapy includes both breast-conserving surgery and post-operative adjuvant radiotherapy. Considering the age of the patient, their history of multiple tumors and their financial situation, the patient ultimately opted against breast-conserving therapy. During surgery, a bilateral breast nodulectomy was initially performed, and the intraoperative frozen pathology indicated bilateral breast invasive carcinoma. Consequently, a bilateral simple mastectomy and bilateral sentinel lymph node biopsy were subsequently performed. Postoperative pathology (Fig. 1D and E) revealed invasive breast cancer on

the right side, with a tumor diameter of 2 mm, and without nerve invasion or intravascular cancer embolism. Results of the immunohistochemical analysis (Fig. 2A and B) of the right breast specimen revealed the following expression results: Estrogen receptor (ER)(+) (moderate to strong, 95%), progesterone receptor (PR)(+) (moderate to strong, 80%), human epidermal growth factor receptor 2 (HER-2) (-), GATA binding protein 3 (GATA-3)(+), E-cadherin(+) (membrane), P120(+) (membrane), cytokeratin (CK)5/6(-), tumor protein p63 (p63)(-), transcription factor SOX-10 (SOX-10)(-), calponin(-), gross cystic disease fluid protein-15 (GCDFP-15)(+), mammaglobin(+), Ki-67(+) (5%) and p53 (wild-type) (data not shown). Subsequently, the patient was diagnosed with breast carcinoma on the left side with three foci (1, 3 and 4 mm in diameter, respectively). Notably, there was no nerve invasion and no intravascular cancer thrombi were observed; however, breast carcinoma was accompanied by low-grade ductal carcinoma *in situ*, including cribriform and papillary types. Results of additional immunohistochemical analysis (Fig. 2C and D) of the left breast specimen revealed expression levels as follows: ER(+) (moderate to strong, 80%), PR(+) (moderate to strong, 60%), HER-2(0), GATA-3(+), E-cadherin(+) (membrane), P120(+) (membrane), CK5/6(-), p63(-), SOX-10(-), calponin(-), GCDFP-15(+), mammaglobin(+), Ki-67(+) (10%) and p53 (wild-type) (data not shown). Notably, no metastases were detected in the bilateral sentinel or axillary lymph nodes. Following surgery, the patient was discharged without any complications and received oral letrozole for endocrine therapy. Daily letrozole (2.5 mg) was continued for a duration of 5 years, until the time of disease recurrence. Following 3 months of rest, the patient was instructed to return to the hospital to address the right pulmonary nodule. In April 2024, follow-up chest CT scans (Fig. 3C and D) revealed an increase in the size of the right lung nodule. Surgical intervention was planned to confirm the pathological diagnosis, but it was postponed due a recent cerebral infarction experienced by the patient and a high surgical risk. During post-operative follow-up, the patient, who underwent radical resection of cancer in the right lower lung at the Tongji hospital (Wuhan, China) in November 2024, exhibited invasive adenocarcinoma that was moderately differentiated with an acinar growth pattern, with no lymph node metastasis. Immunohistochemical analysis revealed the following expression results: TTF-1(+), CD56(+), synaptophysin(+), chromogranin A(+), insulinoma-associated protein 1(punctate +), PCK(-), epithelial membrane antigen(-), CK8/18(-), p63(-), p40(-), Somatostatin receptor 2(-), PR (1E2)(-), S-100(-), SOX10(-) and Ki-67 (~1%) (data not shown).

Patient history. The patient presented with a history of hypertension lasting >10 years. In July 2021, a coronary angiography at the Department of Cardiothoracic Surgery at the General Hospital of Central Theater Command revealed moderate-to-severe stenosis in the proximal left anterior descending artery. In April 2022, the patient experienced cerebral infarction, and in 2023, the patient was diagnosed with type 2 diabetes. The patient reported no history of food or drug allergies, no history of smoking or drinking, no family history of tumors and maintained healthy lifestyle habits. Notably, the parents of the patient died due to unknown causes.

In February 1987, the patient had presented to the Department of General Surgery at the General Hospital of Central Theater Command with a 10-month history of fecal occult blood. The patient underwent radical resection of sigmoid colon cancer and removal of rectal polyps. Postoperative pathology revealed a papillary adenocarcinoma of the protruding type in the sigmoid colon, which had invaded the muscular layer, with no metastasis to the mesenteric lymph nodes. The rectal polyp was identified as an inflammatory polyp. In 2014, the patient was again admitted to the Department of General Surgery following the discovery of thyroid nodules. In October 2014, the patient underwent a bilateral thyroid and isthmus resection, in addition to a left central compartment lymph node dissection. Postoperative pathology (Fig. 1A) revealed a left thyroid papillary microcarcinoma measuring ~0.6 cm, an isthmus papillary microcarcinoma measuring ~0.3 cm and one parathyroid lymph node with an inflammatory lesion. In July 2017, the patient was diagnosed with ileocecal adenocarcinoma at the Hubei Jianghan Oilfield General Hospital (Qianjiang, China) and was subsequently admitted to the Department of General Surgery at the General Hospital of Central Theater Command. The patient underwent a right hemicolectomy and cholecystectomy. Post-operative pathology (Fig. 1B) revealed a poorly-to moderately-differentiated adenocarcinoma, with some mucinous adenocarcinoma, infiltrating the serosa. No metastasis was detected in the ileocecal or pericolonic lymph nodes; however, one tumor nodule was observed in the ileocecal mesentery. In addition, a tubular adenoma was identified in the colon. Immunohistochemistry results revealed expression levels as follows: CK7(-), CK20(+), villin(+), Ki-67(+) (50%), DNA mismatch repair (MMR) protein Msh6 (MSH6) (+), DNA MMR protein Mlh1 (MLH1)(+), MMR endonuclease PMS2 (PMS2)(+) and MSH2(+). Following surgery, the patient received one course of chemotherapy locally (specific drug names unspecified by the hospital). In 2021, chest computed tomography (CT) scans identified partially solid nodules in the upper lobe of the left lung (Fig. 3E and F) and the lower lobe of the right lung (Fig. 3A and B) that were 23x15 and 10x7 mm in size, respectively, displaying lobulation, spiculation, vacuoles and cavities. The morphology of the nodules indicated a high likelihood of early-stage malignant tumors in the lungs. Due to multiple comorbidities and limited tolerance of the patient, surgery was initially performed on the left pulmonary nodule. Post-operative pathology (Fig. 1C) revealed invasive adenocarcinoma of the left upper lung, comprising 70% acinar, 25% lepidic and 5% micropapillary types, with no evidence of nerve invasion, intravascular cancer embolism or lymph node metastasis. Immunohistochemical analysis revealed expression levels as follows: Pan-cytokeratin (PCK)(+), CK7(+), NapsinA(+), Thyroid transcription factor-1 (TTF-1)(+), Ki-67 (3-5%), smooth muscle actin(+), CK5/6(-), S-100(partially +), CD34(+) (blood vessels) and D2-40(+) (vascular channels).

Histological examination

Frozen section histopathology. Tissue samples were embedded, frozen at -20 to -25°C, and sectioned at 4-6 μm. Sections were mounted on glass slides and immediately fixed in 95% ethanol for 30 sec. H&E staining (cat. no. G1120;

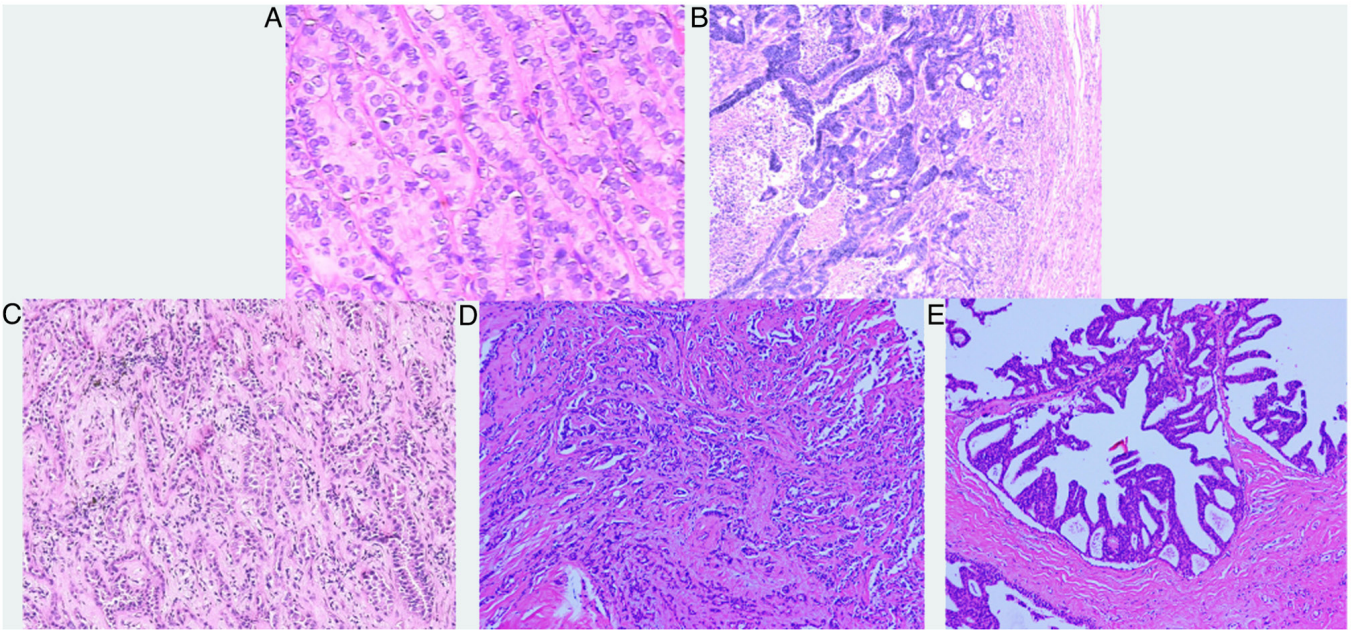

Figure 1. Photomicrographs of hematoxylin and eosin-stained specimens obtained from the various carcinomas in the patient. (A) Microscopic papillary thyroid cancer observed in October 2014 (magnification, x400). (B) Adenocarcinoma of the ileocecal region observed in July 2017 (magnification, x40). (C) Invasive adenocarcinoma of the left upper lung observed in August 2021 (magnification, x200). (D) Invasive carcinoma of the right breast observed in January 2024 (magnification, x40). (E) Invasive carcinoma of the left breast observed in January 2024 (magnification, x40).

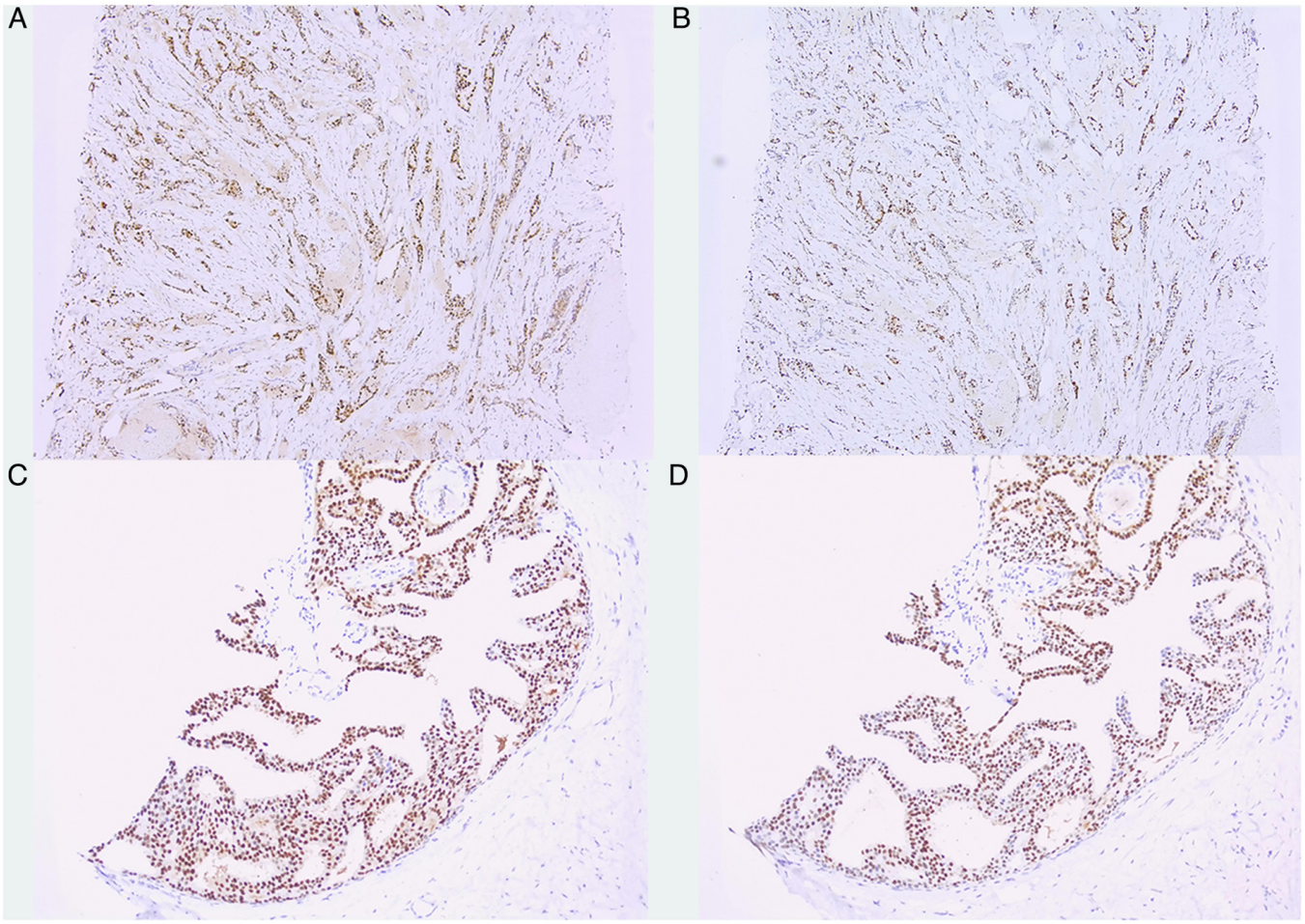

Figure 2. Immunohistochemical staining. Strong positivity was confirmed for ER and PR of the invasive carcinoma of the (A and B) right and (C and D) left breast. (A) ER-positive, with 95% of cell nuclei recorded as positively stained. (B) PR-positive, with 80% of cell nuclei recorded as positively stained. (C) ER-positive, with 80% of cell nuclei recorded as positively stained. (D) PR-positive, with 60% of cell nuclei recorded as positively stained (magnification, x200). ER, estrogen receptor; PR, progesterone receptor.

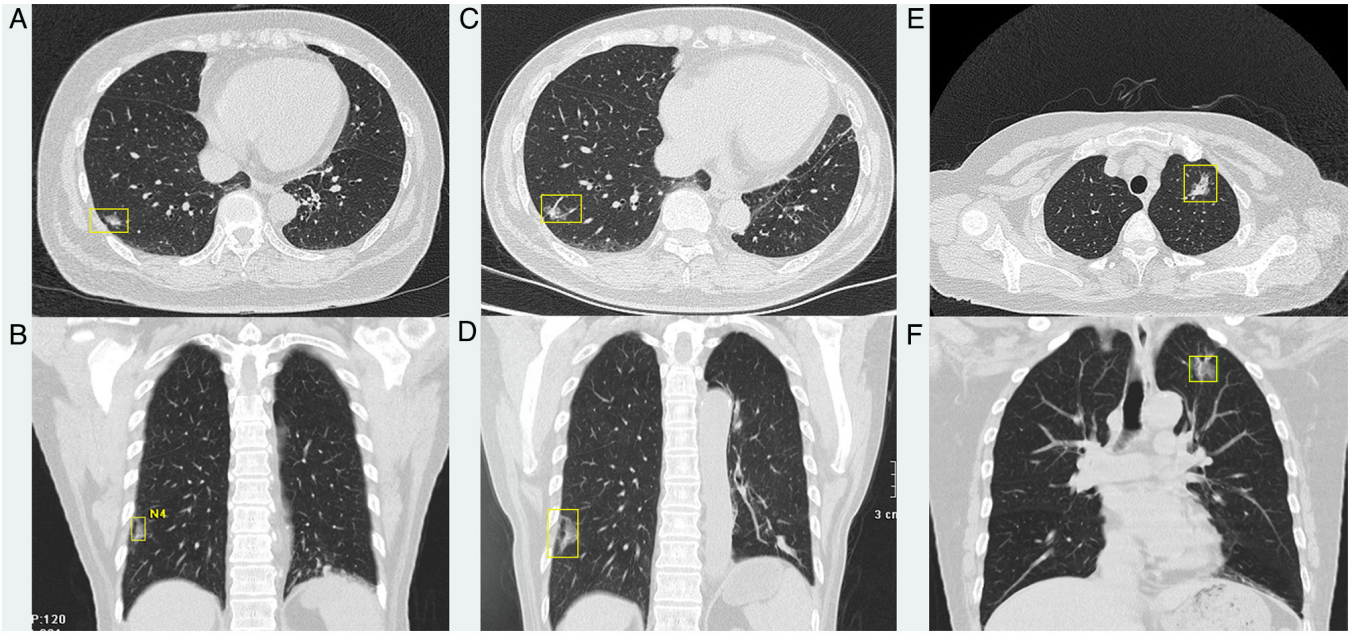

Figure 3. Chest computed tomography scan. (A and B) Partially solid nodule in the lateral basal segment of the lower lobe of the right lung, observed in July 2021. (C and D) Partially solid nodule in the lateral basal segment of the lower lobe of the right lung, observed in April 2024. (E and F) Partially solid nodules in the apical and posterior segments of the left upper lobe, observed in July 2021.

Beijing Solarbio Science & Technology Co., Ltd.) was performed at room temperature with hematoxylin for 30 sec and eosin for 10 sec.

Conventional histopathology. Specimens were fixed in 10% neutral buffered formalin at 4˚C for 24 h, dehydrated through a graded ethanol series, paraffin-embedded and sectioned at 4-5 μm. Sections were H&E-stained at room temperature with hematoxylin for 5 min and eosin for 10 sec. All stained sections were examined using an Olympus BX53 light microscope (Olympus Corporation).

Immunohistochemistry. Paraffin-embedded sections (4 μm) were deparaffinized and rehydrated. Following deparaffinization and rehydration, antigen retrieval was conducted using citrate buffer (95˚C for 20 min). Endogenous peroxidase activity was quenched with 3% H_2O_2 for 10 min at room temperature. Non-specific binding sites were blocked with normal goat serum (20 min at room temperature). Sections were then incubated overnight at 4˚C with primary antibodies against ER (1:100; cat. no. RMA-1065), PR (1:100; cat. no. RMA-0896), HER-2 (1:100; cat. no. RMA-1022), GATA-3 (1:100; cat. no. RMA-1022), E-cad (1:100; cat. no. MAB-0738), P120 (1:100; cat. no. MAB-1077), CK5/6 (1:100; cat. no. RMA-1144), p63 (1:100; cat. no. RMA-1152), SOX-10 (1:100; cat. no. RMA-1058), calponin (1:100; cat. no. MAB-0712), GCDFP-15 (1:100; cat. no. MAB-1035), mammaglobin (1:100; cat. no. RMA-1133), Ki-67 (1:100; cat. no. RMA-0542) and p53 (1:100; cat. no. MAB-0674) (all Fuzhou Maixin Biotech. Co., Ltd.). After washing, sections were incubated with an HRP-conjugated goat anti-mouse secondary antibody (1:500; cat. no. ab6789; Abcam) for 30 min at room temperature. Signal detection was carried out using a DAB substrate (cat. no. kit-0038; MXB Biotechnologies), followed by counterstaining with hematoxylin. All sections were examined under an Olympus BX53 light microscope (Olympus Corporation).

Discussion

The diagnostic criteria for MPMNs were established by Warren (5) in 1932, requiring each tumor to be pathologically confirmed as malignant, occur independently without mutual metastasis and be located in different sites. The patient described in the present case underwent six surgeries under general anesthesia (Table I), all of which were pathologically and immunohistochemically consistent with the diagnosis of a primary malignant tumor. One limitation of the present study is that the results described in the manuscript are based on pathology reports rather than retrievable image files.

Prior research has indicated a typical 5- to 10-year time lapse between the emergence of the initial primary tumor and the subsequent primary tumor (6). Other studies have revealed that the peak occurrence of secondary primary tumors falls within 1 to 3 years following the onset of the first primary tumor, with a notably higher morbidity observed in the initial year (7,8). In Western countries, such as Europe and the United States, MPMNs often manifest in organs such as the skin, bladder, prostate and thyroid (9). By contrast, in Asian countries, such as China and Japan, MPMNs are more prevalent in gastrointestinal malignancies, particularly in esophageal, gastric and colorectal cancer (10). Zhang *et al* (11) conducted a study involving 557 patients, and identified colorectal, breast and thyroid cancer as the most frequently encountered MPMNs. Notably, the patient described in the present study was diagnosed with sigmoid carcinoma as the primary malignancy 38 years prior to study inclusion, aligning with the predisposition of Asian populations towards gastrointestinal tumors as initial malignancies. However, the discovery of the second primary malignancy occurred after a notably prolonged interval of 27 years, highlighting relatively uncommon circumstances.

Table I. Summary of the tumor diagnosis and treatment of the patient.

Date	Age at diagnosis, years	Indication	Treatment	Dosage
February 1987	31	Papillary adenocarcinoma of the sigmoid colon	Radical surgery for sigmoid colon cancer	NA
October 2014	59	Microscopic papillary thyroid cancer	Bilateral thyroid and isthmus resection	NA
July 2017	62	Adenocarcinoma of the ileo-cecal region	Right hemicolectomy	No data
August 2021	66	Invasive adenocarcinoma of the left upper lung	Radical surgery for left upper lung cancer	NA
January 2024	68	Invasive carcinoma of the left and right breasts	Bilateral simple mastectomy + sentinel lymph node biopsy	Letrozole, 2.5 mg daily
November 2024	69	Invasive adenocarcinoma of the right lower lung	Radical surgery for left lower lung cancer	NA

NA, no relevant treatment in the later stage; no data, unknown later treatment.

The pathogenic factors of MPMNs remain largely undefined. Scholars have proposed the multifactorial origin encompassing environmental influences, lifestyle choices, such as smoking, excessive alcohol use and obesity, endocrine factors, genetic predispositions, cancer treatments, such as radiotherapy and chemotherapy, and age (12). The patient described in the present study was diagnosed with sigmoid colon cancer in 1987 and ileocecal adenocarcinoma in 2017, indicative of metachronous multiple primary colorectal cancer. Genetic conditions, such as Lynch syndrome (LS) and familial adenomatous polyposis should also be considered. LS, or hereditary non-polyposis colorectal cancer, is an autosomal dominant disorder caused by mutations in DNA MMR genes, namely, MLH1, MSH2, MSH6 and PMS2, leading to microsatellite instability in the tumor and a lack of expression. Individuals with LS exhibit a heightened risk of various cancer types, including colorectal, gastric and endometrial cancer. In addition, the risk of colorectal cancer may reach 80%, making it the most prevalent hereditary familial tumor syndrome (13,14). LS was effectively ruled out in the present study due to the absence of colorectal cancer among the patient's close relatives and positive immunohistochemical results for MMR protein levels. Moreover, extracolorectal MPMNs are not often observed in cases of colorectal cancer. Lee *et al* (15) conducted a retrospective analysis of 758 patients with colorectal cancer, including 33 patients with extracolorectal MPMNs. Of these, 36.4% presented with gastric cancer, 15.1% presented with thyroid cancer, 15.1% presented with prostate cancer and 6.0% presented with esophageal cancer. The patient described in the present study presented with a second primary tumor that was papillary microcarcinoma in the left lobe and isthmus, while the fifth and sixth primary tumors were invasive carcinomas of the left and right breasts, respectively. According to the Chinese Expert Consensus on Diagnosis and Treatment of Multiple Primary Neoplasms (2024 Edition) (16), the diagnostic criteria for bilateral primary breast cancer stipulate that when the histopathological types of the bilateral breast cancers are identical, the primary tumor on the first side must not exhibit local recurrence, lymph node metastasis or any distant metastases. In this case, the patient demonstrated no metastasis in the sentinel lymph nodes or the axillary lymph nodes. Coupled with immunohistochemical results and a tumor interval time of <6 months, the patient was diagnosed with synchronous bilateral primary breast cancer. Studies have noted that the coexistence of breast and thyroid cancer is the most prevalent among patients with multiple primary cancers (17,18). A family history of breast cancer, ER positivity, PR positivity and thyroid hormone positivity are associated with thyroid and breast tumor development (19). The breast cancer pathology of the present patient revealed positive ER and PR expression patterns, indicating its suitability for endocrine therapy. Consequently, oral letrozole was recommended to the patient for endocrine treatment during the post-operative period.

The patient's fourth and seventh primary malignant tumors were invasive adenocarcinomas of the left and right lungs, respectively. Van Rens *et al* (20) demonstrated that p53 gene mutation analysis may differentiate metastatic lung cancer from multiple primary lung cancers. By comparison, Iwata *et al* (21) revealed that EGFR and KRAS gene mutation analysis is conducive to distinguishing multiple primary lung cancers from intrapulmonary metastases. Mutations in EGFR, KRAS and TP53 genes may be associated with MPMNs. Despite a healthy lifestyle and no history of smoking or drinking, the patient's condition may be associated with factors such as endocrine influences, proto-oncogene amplification, tumor suppressor gene mutations or MMR gene defects. Due to financial constraints, the patient in the present study did not undergo genetic testing to verify gene mutation-related etiology, which is a limitation of the present case report. The p53 immunohistochemical assay primarily reflects the expression status of the p53 protein, and its various expression patterns can indirectly infer mutations or other abnormalities in the TP53 gene. Although further genetic

testing has not been conducted, the relatively inexpensive p53 immunohistochemical assay may still hold value.

A unified treatment protocol for MPMNs remains elusive, largely influenced by tumor stage, underlying conditions, patient age and complications. Personalized treatment necessitates a multidisciplinary team approach. Surgery is crucial in managing multiple primary solid tumors (22). Adebonojo *et al* (23) revealed that active surgical intervention is generally preferable for the majority of patients with MPMNs. The patient described in the present study underwent six surgeries under general anesthesia since the onset of the disease, with precise timing and successful post-operative recovery. The patient receives follow-up phone calls every 3 months to assess their physical condition. As of the latest submission, they are reported to be in generally good health.

Research indicates that the prognosis for patients with MPMNs is influenced by multiple factors, such as tumor stage, differentiation, site distribution, interval between tumor occurrences, treatment method and patient age (24). Amer (25) discovered that patients with multiple primary malignant tumors exhibit a higher survival rate than those with a single tumor, and the life expectancy of patients with three or more primary tumors aligns with that of age- and sex-matched healthy populations. Moreover, a prolonged interval between the first and second primary cancers may be associated with an improved prognosis. Oeffinger *et al* (26) revealed that patients with mMPMNs exhibited an improved prognosis compared with those with sMPMNs. Jiang *et al* (13) documented the case of a male patient with LS who was diagnosed with a total of eight primary malignant tumors and survived for >41 years. Similarly, Zhao *et al* (27) reported the case of a female patient with eight primary malignant tumors who exhibited a lifespan of >32 years. Long-term survival of the patient described in the present study is attributed to early disease detection, as well as timely and effective treatment. The majority of the tumors were diagnosed at an early clinical stage, allowing for successful surgical intervention. In addition, the extended intervals between tumor occurrences may contribute to prolonged survival.

Patients with multiple primary malignant tumors require diligent post-operative follow-up. Educating patients to enhance their awareness is crucial for early detection, diagnosis and treatment, thereby optimizing outcomes. The present patient exhibited post-operative psychological stress during the follow-up period, highlighting the requirement to address psychological well-being. In addition, counseling to alleviate any anxiety experienced by the patient is crucial for optimal medical management.

In conclusion, the pathogenesis of MPMNs remains to be fully elucidated. Immunohistochemistry and molecular genetic testing are crucial for diagnosis and etiological identification. Notably, the treatment and prognosis predictions for MPMNs differ from those of metastatic and recurrent cancers. Early diagnosis and intervention are vital, and radical surgery may be curative. For patients who are ineligible for surgical intervention, personalized treatment plans may be used to prolong survival and improve prognosis.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

BX and KH acquired the data. BX, KH and SZ analyzed and interpreted the data, and confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report.

Competing interests

The authors declare that they have no competing interests.

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