Breast Cancer: Targets and Therapy

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CASE REPORT

Diagnosis and Individualized Treatment of Three Primary Malignant Tumors: A Case Report

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Abstract: Continuous optimization of diagnosis and treatment of malignant tumors has led to significantly prolonged survival in cancer patients. Despite the recent increase in the incidence of multiple primary malignant tumors (MPMT), it remains rare in clinical practice; therefore, normative guidance on its etiology, diagnosis, and treatment is insufficient. Here we describe the case of a patient with three primary malignant tumors, namely breast cancer, diffuse astrocytoma, and hepatic malignant perivascular epithelioid cell tumors (PEComa) and discuss relevant literature.

Keywords: multiple primary malignant tumors, breast cancer, diffuse astrocytoma, liver malignant PEComa, etiology, prognosis

Introduction

Two or more primary malignant tumors occurring simultaneously or successively anywhere in the body are diagnosed as multiple primary malignant tumors (MPMT). MPMT is rare. Despite the continuous advancements in cancer diagnosis and treatment and the extension of the treatment time of patients, the incidence of the disease has been gradually increasing. The diagnosis of MPMT mainly relies on pathological biopsy. Although its causes remain unclear, endogenous, exogenous, hereditary, and therapeutic factors may be involved. At present, a comprehensive treatment method based on surgery, radiotherapy, and chemotherapy is mainly selected according to the tumor location, pathological stage, and systemic conditions. This article will describe the diagnosis and treatment of a patient with three primary malignancies and review the relevant literature based on this case. Currently, this patient's condition is stable and she agreed for the collection and publication of her case's details.

Case Presentation

A 30-year-old female presented to our hospital on December 4, 2017 due to a 4-month-old mass on her left breast. She did not complain of pain, dizziness, headache, or any other discomfort, and did not report any relevant family history. Physical examination revealed a palpable mass, 6×5 cm in size, at 3 o'clock on the left breast. No enlarged lymph nodes were palpable in the armpit. Ultrasound light scattering breast examination revealed a hypoechoic nodule, approximately 3.68×2.77 cm in size, in the outer quadrant of the left areola and an areola with indistinct borders. Multiple, enlarged, left axillary lymph nodes were also observed and the tumor was graded as 4C according to the breast imaging reporting and data

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Received: 22 May 2021
Accepted: 21 August 2021
Published: 9 September 2021

system (BI-RADS). No obvious abnormalities were observed in the right breast. A needle biopsy of the mass in the left breast was performed on December 18, 2017 and pathological analysis revealed that it was an invasive carcinoma (non-special type III) (Figure 1) that was HER-2 2+, ER 10%, PR 5%, Ki-67 30%, and FISH test positive. Therefore, further whole body assessment was performed, and computed tomography (CT) scans of the chest and head (Figure 2A) revealed a mass with abnormal density or shadows in both breasts, with bilateral multiple enlarged axillary lymph nodes and circular low-density plaques with a diameter of about 3 cm in the right frontal lobe. Moreover, because head magnetic resonance imaging (MRI) (Figure 2B) showed that the right frontal lobe was abnormally enhanced and occupied, the possibility of metastasis was considered based on her medical history. Further, needle biopsy of the tumor on the right breast and pathological test results revealed the absence of cancerous tissue. Other related tests such as bone scan and abdominal CT did not reveal any remarkable results. Based on the above observations, she was diagnosed with HER-2 positive breast cancer (left) according to the eighth edition of the American Cancer Society (AJCC) standard diagnosis. Meanwhile, the cancer was staged as T3N2M1 stage IV. As the patient was young and had no history of childbirth, Goserelin (3.6 mg, subcutaneous injection) was immediately initiated with a 28-day cycle. She also underwent four cycles of AC (cyclophosphamide + pirarubicin) chemotherapy on January 6 and 28, and February 10 and 26, 2018. Next, she was administered three cycles of TH (trastuzumab + docetaxel) chemotherapy on March 14, April 7, and April 29, 2018, along with antiemetic, white blood cell elevators, and other comprehensive treatments. Chemotherapy progressed without complications, and after seven cycles of chemotherapy, the mass in the upper outer quadrant of the left breast was found to be significantly smaller than before (2 × 1 cm) upon physical examination. CT scans of the chest (Figure 2C) suggested that the axillary lymph nodes and abnormal mass in the left breast had reduced in size. The patient underwent a modified radical mastectomy for left breast cancer on May 15, 2018, in the breast surgery department of our hospital and evaluation of resected tissue (Figure 3) showed an invasive carcinoma (non-special type, grade III). Immunohistochemically, the tissue was typed as ER 20%, PR 10%, HER-2 (2+ −3+), and Ki-67 40%, and no FISH test performed. HP (Trastuzumab + Pertuzumab) regimen targeted therapy was given on May 24, 2018 and tamoxifen 20 mg, once a day, was prescribed as endocrine therapy from July 2018 onwards. Radiation therapy was initiated on July 28, 2018, and the sites were left chest wall, left upper and lower clavicle, and

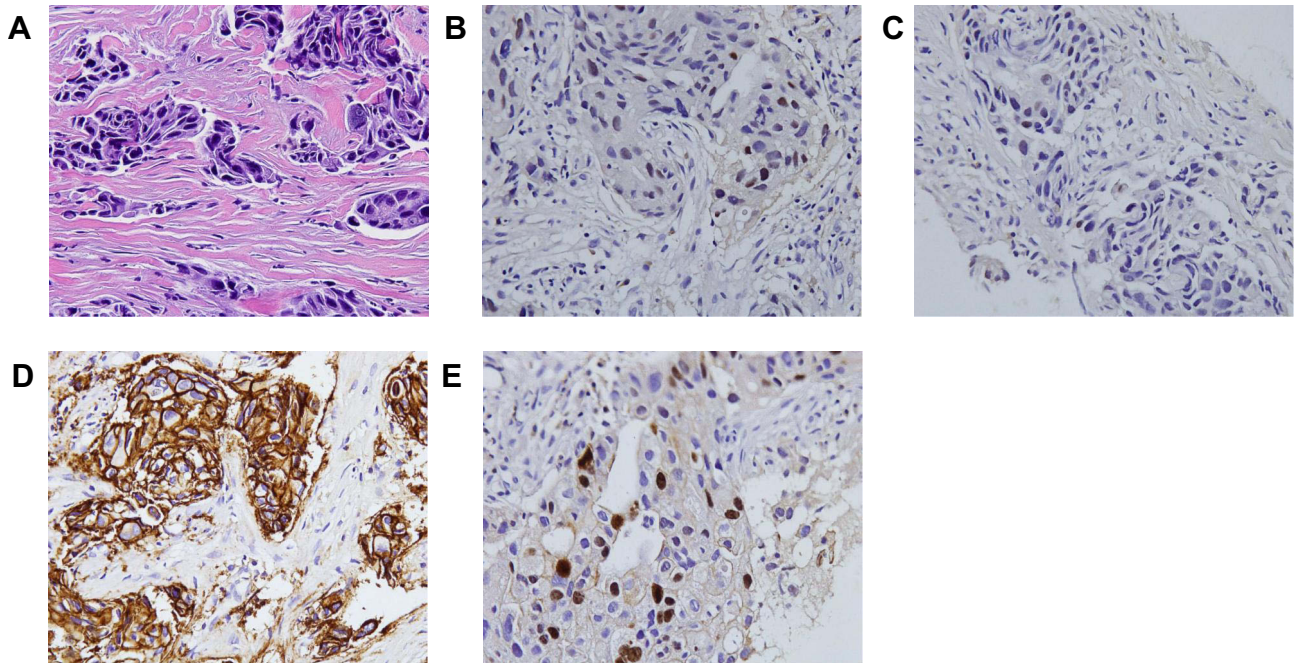

Figure 1 Pathological results of the breast. Haematoxylin–eosin (H&E) staining of biopsy samples (40×) magnification. (**A**) Immunohistochemical staining results of breast showed ER 10% (**B**) and PR 5% (**C**) and HER-2 2+ (**D**) and Ki-67 30% (**E**).

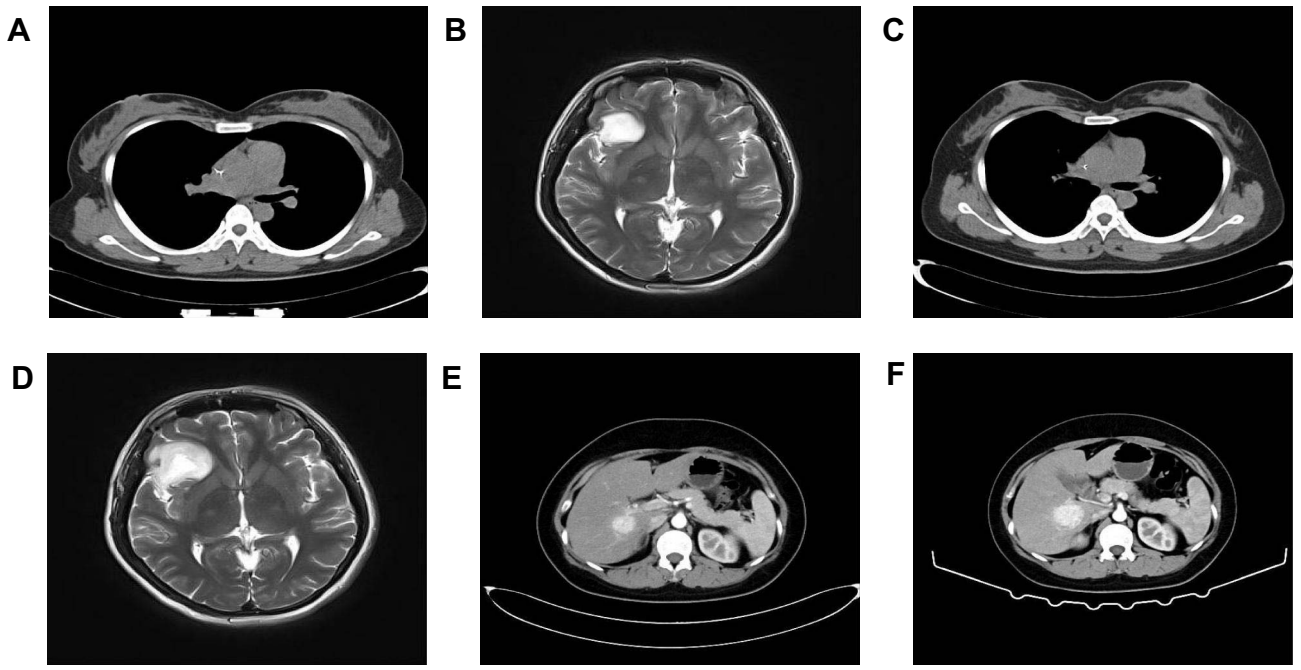

Figure 2 Computed tomography of the chest and breast before treatment. (**A**) First whole body assessment. Abnormal high-density shadows can be seen on magnetic resonance imaging of the head. (**B**) Computed tomography before modified radical mastectomy of left breast cancer. (**C**) Magnetic resonance imaging of the second intracranial mass before surgery. (**D**) First computed tomography image revealing the hepatic space-occupying lesions. (**E**) Computed tomography image of the hepatic mass before biopsy (**F**).

left axilla. PTV was set at DT5000cGy/25f with a dose separation of 200 cGy/session, five times a week. The patient complained of headaches, mostly located on the right side, with intermittent dull pain in October 2018, and MRI of the head showed no change in abnormal enhancement of the right frontal lobe. Therefore, she was transferred to the neurosurgery department of our hospital and an intracranial mass was resected on October 23, 2018. Postoperative analysis of the resected tissue (Figure 4) showed that the tumor cells were small sized, arranged tightly, and localized, with significant proliferation of small blood vessels. Immunohistochemically, the tissue was ckp (-), GFAP (3+), Ki-67 (<5%), p53 (-). Morphology and immunohistochemistry supported glial cell proliferation, consistent with a localized glioma (WHO Grade I). The patient was regularly followed-up after surgery and her condition remained stable during this period. Further, during follow-up consultation on May 6, 2020, she did not complain of dizziness or headache. However, a repeat head MRI showed (Figure 2D) that the right frontal lobe was abnormally enhanced and that it was slightly larger than before. Therefore, a frontal lobe tumor resection was performed again in the neurosurgery department on May 14, 2020. Postoperative examination of the tissue (Figure 5) showed that the tumor cells were extremely diverse, ie, they were oval, fusiform, or star-shaped, and both sparse or dense with some having less cytoplasm and others having more. Some tumor cells were atypical, a few had large and darkly stained nuclei with visible nucleoli and occasional mitotic structures, while others showed hypertrophy or an offset nucleus, or were rich in cytoplasm or interstitial blood vessels. However, no clear necrosis was seen. Immunohistochemically the resected tissue was S-100 (3+), sox10 (mildly +), Ki-67 (5%, local 5–10%), p53 (mildly +), CD34 (vascular endothelium +), ckp (-), GFAP (small part +), and NSE (-), and when combined with morphology, these findings supported a diagnosis of diffuse astrocytoma (WHO grade II). CT imaging of the chest and abdomen performed (Figure 2E) at follow-up on November 23, 2020 revealed expected postoperative changes in the left breast with no obvious abnormal masses or shadows. However, an abnormally enhanced shadow, approximately 20×20 mm in size, was observed on the liver (S6 segment). Given the patient's disease progression, liver metastasis was diagnosed and she underwent two cycles of chemotherapy with pyrotinib and capecitabine. Repeat chest and abdominal CT performed on January 13, 2021 showed abnormal enhancement and enlargement of the right lobe of the liver. Hence, two cycles of TPH (trastuzumab + docetaxel +

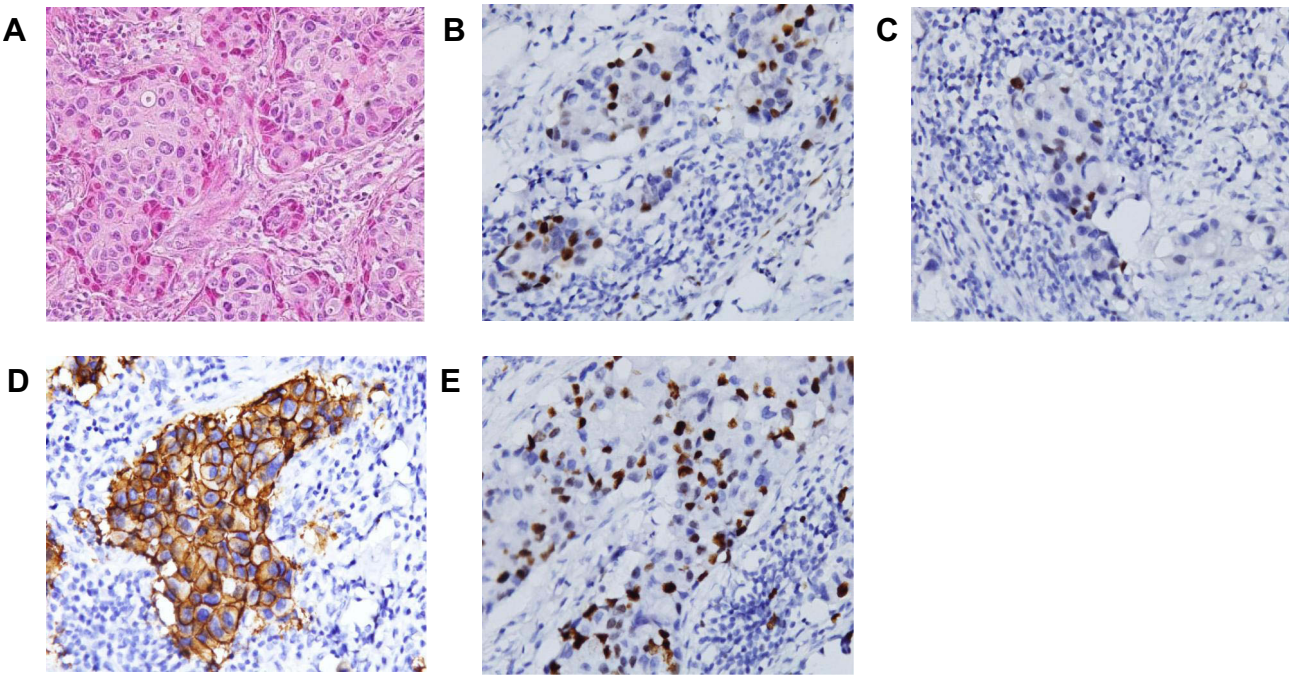

Figure 3 Pathological results after breast cancer surgery. Haematoxylin–eosin (H&E) staining of biopsy samples (40×) magnification). (**A**) Immunohistochemical staining results after breast cancer surgery: ER 10% (**B**), PR 20% (**C**), HER-2 2+-3+ (**D**), Ki-67 40% (**E**).

cisplatin) chemotherapy were administered on January 22, 2021 and February 17, 2021. A whole abdomen enhanced CT on March 11, 2021, revealed (Figure 2F) that the abnormal enhancement of the lobe was about 35×26 mm in size and larger than that seen previously. A liver biopsy was performed and pathology reported (Figure 6) that the tissue was relatively fragmented with little liver tissue seen in some areas. The tumor tissue was composed of short spindle or oval cells arranged in diffuse sheets with abundant blood vessels and a small amount of chronic inflammatory cell infiltration. Immunohistochemically the tissue was ckp (-), Her-2 (-), vimentin (+), Ki-67 (15%), SMA (-), Desmin (-), CD34 (vascular +), CD31 (vascular +), Hepatocyte (-), GPC-3 (-), CK19 (-), HMB45 (+), Melan-A (+), GFAP (-), sox10 (-), S-100 (-), GATA- 3 (-), ER (-), PR (-), and CD117 (focal 1+); therefore, a vascular tumor was suspected and the patient was transferred to the General Surgery Department of our hospital, where she underwent laparoscopic resection of the liver lesions on March 24, 2021. No tumor tissue was seen at the resection margin of the liver and the patient recovered well after surgery. Postoperative pathological report (Figure 7) described the liver structure as destroyed with unclear tumor tissue boundaries and no capsules. Tumor cells were spindle shaped with visible pathological mitoses and the nucleus was fusiform or polygonal with an

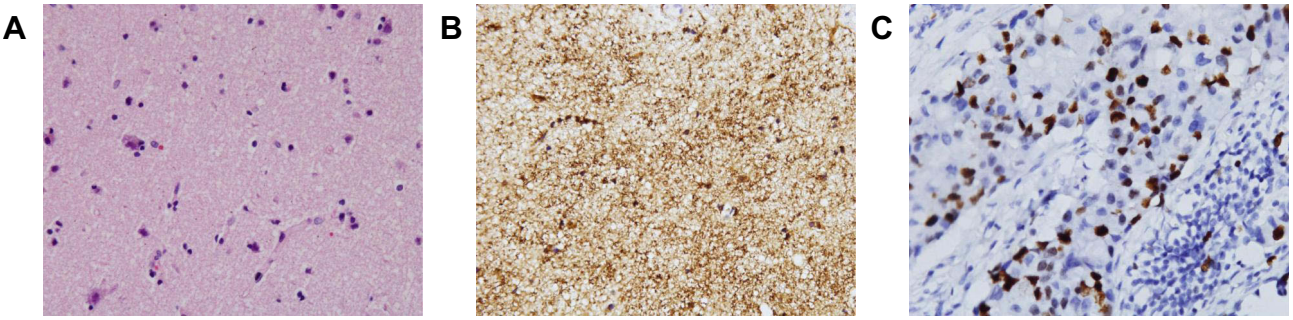

Figure 4 Postoperative pathological results of the initial intracranial space-occupying lesion. Haematoxylin–eosin (H&E) staining of biopsy samples (40×) magnification. (**A**) Postoperative immunohistochemical staining results of the initial intracranial space-occupying lesion showed GFAP 3+ (**B**), Ki-67 <5% (**C**).

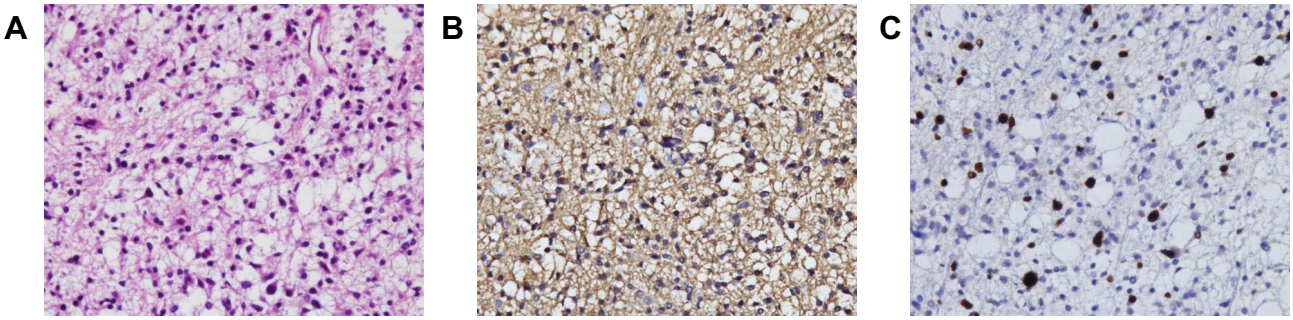

Figure 5 Pathological results of the intracranial space-occupying lesion after the second operation. Haematoxylin–eosin (H&E) staining of biopsy samples (40×) magnification). (**A**) Immunohistochemical staining results of the intracranial space-occupying lesion after the second operation showed GFAP (small part +) (**B**), ki-67 (5%, partial 5–10%) (**C**).

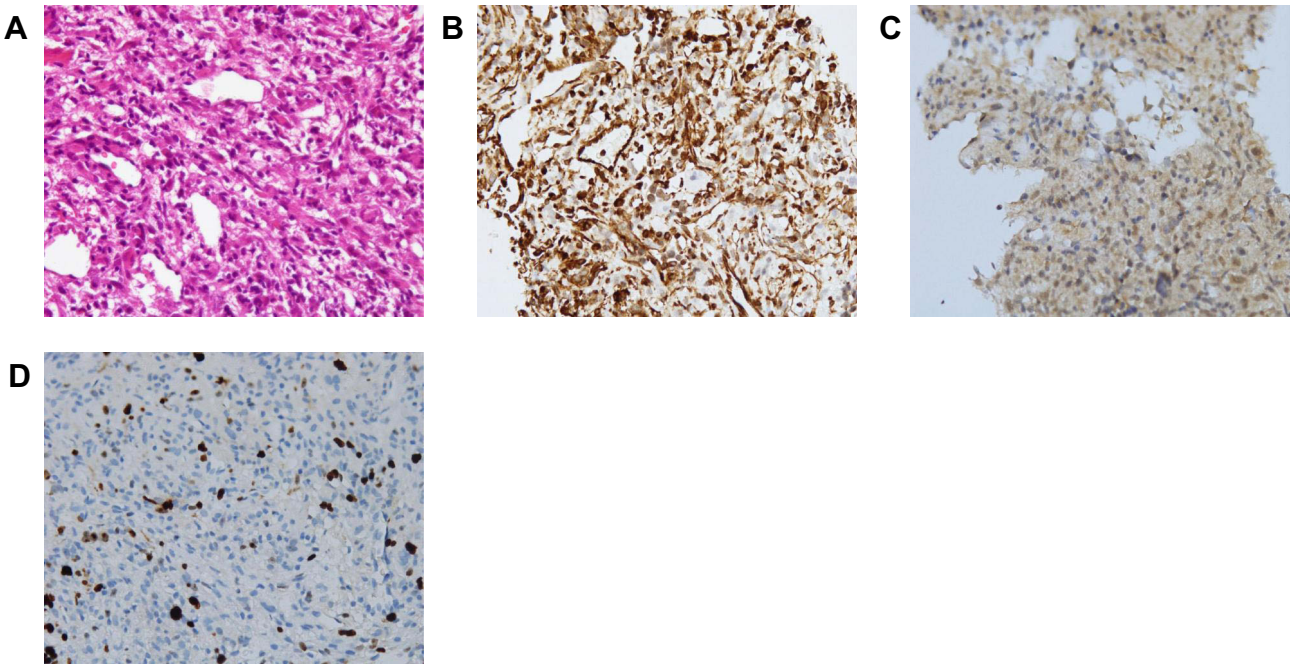

Figure 6 Pathological results of the puncture of the space-occupying liver lesions. Haematoxylin–eosin (H&E) staining of biopsy samples (40×) magnification. (**A**) Immunohistochemical staining results of the puncture of the space-occupying liver lesions: vimentin + (**B**), HMB45 + (**C**), ki-67 15% (**D**).

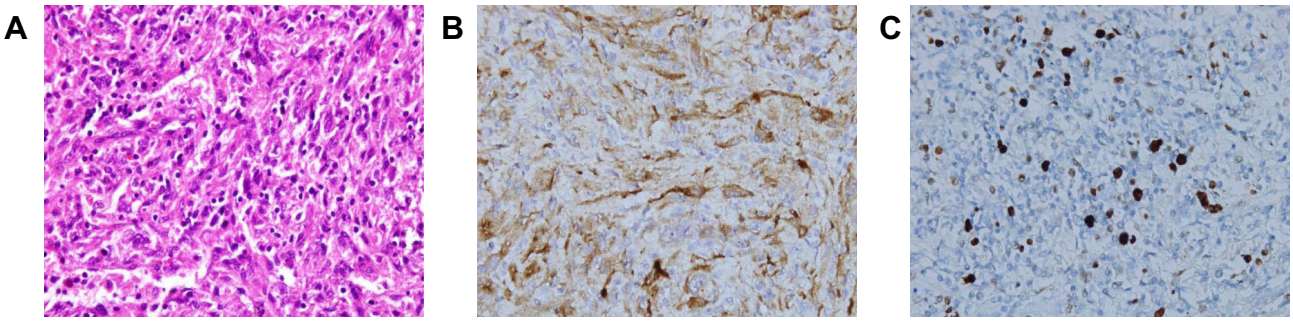

Figure 7 Pathological results of hepatic space-occupying lesions after surgery. Haematoxylin–eosin (H&E) staining of biopsy samples (40×) magnification. (**A**) Immunohistochemical staining results of hepatic space-occupying lesions after surgery: Melan A + (**B**), ki-67 10% (**C**).

increase in both cell number and volume. The ratio of nucleoplasm was also greater with more megakaryocytes and strange nuclei that were arranged in strips or were diffuse. Additionally, infiltrating growth, bleeding, and small lamellar necrosis, tissue congestion, edema, and lymphocyte infiltration were visible. The tissue was immunohistochemically characterized as Desmin (-), H-caldesmon (-), D2-40 (-), NSE (-), inhibitor-α (-), Syn (-), ckp (-), EMA (-), CD31 (vascular +), CD34 (vascular +), fli-1 (vascular +), ERG (vascular +), Ki-67 (10%), p53 (-), S-100 (-), Melan-A (+), HMB45 (-), CD117 (-), Hepatocyte (liver cell +), and CD68 (histocyte +). Morphological and immunohistochemical results were consistent with a malignant perivascular epithelioid cell tumor (PEComa). After discharge from the hospital, goserelin once/28 days and letrozole 2.5 mg once/day were prescribed for treatment. The patient has been currently instructed to undergo chest and abdominal CT and head MRI every 3 months. At present, the patient's overall condition is good and she remains stable However, she refused to undergo genetic testing owing to economic reasons.

Discussion

The incidence of MPMT in China (0.4–2.4%) is significantly lower than that reported by other countries (0.73–11.7%),[1] and may be related to a lack of understanding of the disease or its misdiagnosis as metastasis or recurrence. Clinically, MPMT is often confused with recurrence or metastasis of malignant tumors. The diagnosis of MPMT mainly relies on pathological analysis of biopsy specimens and the current widely recognized diagnostic criteria for MPMT are based on those described by Warren and Gates, viz., each tumor has a clear pathological result; the location of each tumor is different and their pathology independent of each other; and the possibility of mutual metastasis is excluded. Moertel has defined simultaneous malignant tumors as two or more malignant tumors occurring within 6 months, while metachronous malignant tumors refer to those occurring more than 6 months apart.[2] Thus, our patient displayed three primary malignant tumors that were both simultaneous and metachronous.

Liu reported that breast tissue and digestive and respiratory systems are common sites for the occurrence of MPMT.[1] Utada stated that esophageal cancer, laryngeal cancer, ovarian cancer, and oral/pharyngeal cancer are the most common primary cancers. Further, a second primary cancer is most common in thyroid cancer, followed by esophageal cancer.[3] Corso conducted a statistical analysis of patients whose first cancer was breast cancer and found that digestive tract cancer was the most common second tumor, followed by tumors in the gynecological, hematological, or pulmonary systems, and thyroid cancer.[4] Thus, according to available literature, the most common first, second, and third primary cancers are those of the digestive, urinary and respiratory systems, in that order, and that among them, breast and gynecological cancers are more common in women. Importantly, studies have proved that the risk of other primary malignant tumors is higher among cancer patients,[5] which may be related to the patient's long-term carcinogenic state.

Breast cancer is the most common cancer and the main cause of death among women worldwide.[6] Gliomas account for nearly 80% of all primary malignant brain tumors and they are more common in women than in men.[7] When the second primary malignant tumor is a glioblastoma, the most common first tumor in women is breast cancer, followed by melanoma and lung cancer, and this pattern may be related to hormone levels.[8]

PEComa is a mesenchymal tumor characterized by histological and immunological phenotypes in perivascular epithelioid cells. It is more common in middle-aged women than in other populations and typically occurs in the uterus, posterior peritoneum, and mesentery. PEComa in the liver is very rare, and although most PEComas are benign, some can potentially become malignant or show malignant characteristics. Folpe et al (2005) proposed an evaluation standard for malignant PEComa using the following six criteria–tumor maximum diameter >5 cm; invasive growth; high nuclear atypia; nuclear division ≥1/50 HPF; tumor coagulation necrosis; and vascular invasion. According to this system, tumors that meet one of the above criteria are potentially malignant while those that conform to ≥ 2 criteria are diagnosed as malignant.[9] Bleeker et al have suggested updating this classification as they have shown that only tumors ≥5 cm with mitosis ≥1/50 HPF are significantly related to potential malignant behavior and recurrence.[10] Thus, according to these criteria, our patient had a malignant liver PEComa.

The etiology of MPMT remains unclear and it is currently divided into four types. The first is endogenous factors, such as abnormal embryonic development, immune-related diseases, and endocrine diseases that are sensitive to carcinogens, along with innate and acquired immune surveillance, for eg, loss of immune defenses increases the possibility of developing MPMT.[11]

The second comprises exogenous factors, represented by environmental factors and lifestyle, including long-term effects of radiation and industrial pollution, smoking, and alcohol abuse. The third group includes genetic factors as studies have shown that family members with *BRCA* gene mutations have an increased risk of early breast cancer and ovarian cancer.[12] The fourth group lists therapeutic factors, such as radiotherapy and chemotherapy, because radiotherapy can lead to DNA damage and oncogene activation. Patients with breast cancer are prescribed a variety of chemotherapy and hormone therapy treatments that may suppress the immune system, and thereby increase the possibility of cancer development. For eg, a study by Bazire et al found that the risk of second malignant tumors was significantly higher in patients who had undergone breast cancer treatment.[13] Furthermore, underlying etiologies for breast cancer and glioma may be related to hormone levels as estrogen and progesterone may promote the occurrence and development of glioma. Mezencev found that among individuals under 40 years of age who were diagnosed with breast cancer, female patients had a higher risk of glioma compared to those over 40 years of age.[14] On the other hand, greater risk of glioma among young breast cancer patients is likely to be related to genetic factors, such as TP53 (Li-Fraumeni synthesis) or germline pathogenic mutations in BRCA1 and BRCA2 genes, which are related to early-onset breast cancer and glioma.[15] The primary brain tumor in this patient was a glioma (WHO grade I), and the second postoperative examination after intracranial mass resection revealed diffuse astrocytoma (WHO grade II) owing to the low grade. In the process of cell proliferation, gliomas may "accumulate" new mutations, thereby resulting in them becoming high-grade gliomas (malignant transformation). Hepatic PEComa is more common in middle-aged women, and its occurrence and development are also related to the hormone levels in the patient. Studies have found that PEComa is associated with changes in the TSC1 or TSC2 genes, which leads to the activation of the mTOR pathway and promotes excessive cell proliferation, occurrence, and development of tumors. An interaction between the mTOR pathway and estrogen has also been demonstrated.[16]

Currently, there are no relevant guidelines for the management of MPMT. Treatment is mainly based on tumor location, pathological staging, and general conditions, and involves a combination of surgery, radiotherapy, and chemotherapy. Further, individualized treatment is decided after multidisciplinary consultation and discussion. For local cancers, surgery, radiotherapy, and chemotherapy can be used to treat coexisting tumors, but the choice of anti-tumor therapy is difficult in advanced cancer, and systemic chemotherapy is the main treatment strategy.[17] In simultaneous MPMT, malignant tumors with a high degree of malignancy, rapid progress, and poor prognosis should be treated first, while treatment is based on the sequence for metachronous MPMT because the interval between each tumor is longer. Thus, while guidelines for the management of breast cancer and diffuse astrocytoma are available, malignant PEComa is a rare clinical tumor with no clear treatment recommendations and radical surgery is the main treatment method. However, based whether or not mTOR is activated in PEComa, a few studies have found that the use of mTOR inhibitors to treat PEComa can provide patients with clinical benefits.[18] A retrospective analysis of 40 PEComa patients prescribed mTOR inhibitors, including sirolimus (80%), everolimus (12.5%), or temsirolimus (7.5%) revealed a remission rate of 40% and a PFS of 9 months. Furthermore, PFS among patients who responded to mTOR inhibitor treatment was 15.4 months, and it was found that the response rate of extrauterine PEComa to mTOR inhibitors was higher than that of uterine PEComa, but there was no statistical difference between the two PFS durations.[19] As multiple studies have confirmed an interaction between estrogen and mTOR, Sanfilippo et al retrospectively analyzed data from seven patients with PEComa who were treated with sirolimus and exemestane after the cancer progressed when they were treated with sirolimus alone. The results showed that the total effective rate was 43%, disease control rate was 86%, median PFS was 7 months, and that median time to remission was 11.1 months. Importantly, that study proved that anti-estrogen therapy was effective in patients who are resistant to mTOR inhibitors.[16]

Notably, prognosis in MPMT does not appear to be different from that of the more common single malignant tumors. Specifically, studies have found that the prognosis of patients with thyroid cancer after breast cancer is not different from that of patients with only breast cancer.[20] In contrast, while Zhang demonstrate that MPMT patients have a worse prognosis than patients with breast cancer alone, which may be the result of differences between the analyzed groups,[21] Hamza report no significant difference in overall survival or PFS between patients with only malignant glioma and those

with simultaneous non-central nervous system primary tumors.[22] Nevertheless, many studies have also demonstrated that prognosis in concurrent malignancies is worse than that of metachronous malignancies,[20,23] and as there are only a few studies on the prognosis in MPMT, more relevant studies are needed for meaningful statistical analysis.

Our patient displayed a unique presentation in that she had three primary malignant tumors, namely breast cancer, diffuse astrocytoma, and liver malignant PEComa, which were both simultaneous and metachronous. Specifically, she was first diagnosed with breast cancer at the age of 30 and provided comprehensive treatment that included chemotherapy, surgery, radiotherapy, targeted therapy, and endocrine therapy. Subsequently, diffuse astrocytoma and hepatic PEComa were diagnosed at 10 and 35 months after the diagnosis of breast cancer, and both were managed by radical surgery. During the initial visit for a systemic evaluation, we found that the diagnosis of diffuse astrocytoma and hepatic PEComa had been delayed due to interference from breast cancer. The Immunohistochemical staining of the breast cancer in this patient after surgery was hormone-receptor positive; therefore, tamoxifen was administered as an endocrine therapy. A report by Karthik et al showed that tamoxifen can induce mTOR activation in breast cancer stem cells, and that this process can be antagonized by mTOR inhibitors.[24] Thus, as the PEComa in our patient showed activation of the mTOR pathway, it is possible this may be related to the long-term use of tamoxifen. However, currently, it is not possible to confirm such induction of mTOR activation in other cells due to paucity of data. At present, the overall condition of our patient is good and she remains stable, which may be related to the patient's regular physician follow-ups, clinical staging of each tumor, and active comprehensive treatment. Additionally, primary cancer improves the body's immune clearance of tumor cells and can thereby help delay tumor progression.[25]

In summary, MPMT is a rare clinical condition and clinicians must be able to distinguish between recurrence and metastasis of the first malignant tumor at the time of diagnosis, to reduce misdiagnosis and missed diagnosis of MPMT. At present, the etiology of MPMT remains unclear, and further data is needed. MPMT treatment is based on the type, pathology, and location of the tumor, and depending on the overall situation of the patient, an individualized treatment plan that combines surgery, radiotherapy and chemotherapy, and molecular targeted therapy can be designed. Vigilance against multiple primary tumors during the follow-up period and improved ability to distinguish between tumor recurrence and metastasis are also needed. It is necessary to continuously optimize and improve cancer treatment programs, control endocrine and metabolic diseases, smoking and alcoholism, and other high-risk factors, and enhance the ability to screen for precancerous lesions. At the same time, these approaches must be supplemented with psychological counseling to enable patients to obtain greater clinical benefits.

Ethics Statement

Written informed consent was obtained from the included patient, and the patient agreed to publish the details of her case and any accompanying pathological images. This study and the publication of the case's details were approved by the ethics committee of the First Hospital of Lanzhou University.

Funding

There is no funding to report.

Disclosure

The authors declare no conflicts of interest.

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