

80709_Auto_Edited.docx

Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 80709

Manuscript Type: CASE REPORT

Synchronous multiple primary malignant neoplasms in breast, kidney, and bilateral thyroid: a case report

Multiple primary malignant neoplasms

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Abstract

BACKGROUND

Multiple primary malignant neoplasms (MPMNs) are rare, while synchronous MPMNs (SMPMN) are even less common. Owing to the progression of medical technology and the extension of life expectancy, its incidence is gradually increasing.

CASE SUMMARY

Although reports of breast and thyroid dual cancers are common, cases of an additional diagnosis of kidney primary cancer within the same individual are rare.

CONCLUSION

We present a case of simultaneous MPMN of three endocrine organs, reviewing the relevant literature to enhance our understanding of SMPMN while emphasizing the increasingly important need for accurate diagnosis and multidisciplinary management whenever this challenging situation arises.

Key Words: synchronous, multiple primary malignant neoplasms, breast cancer, kidney cancer, bilateral thyroid cancer, tumor neoplasm

Jia M, Yang B, Ding C, Yao Y, Guo J, Yang H. Synchronous multiple primary malignant neoplasms in breast, kidney, and bilateral thyroid: a case report. *World J Clin Cases* 2023; In press

Core Tip: Multiple primary malignant neoplasms (MPMNs) are rare, while synchronous MPMNs (SMPMN) are even less common. Owing to the progression of medical technology and the extension of life expectancy, its incidence is gradually increasing. Although reports of breast and thyroid dual cancers are common, cases of an additional diagnosis of kidney primary cancer within the same individual are rare.

INTRODUCTION

5 Multiple primary malignant neoplasms (MPMNs) are generally defined as the occurrence of two or more pathologically diagnosed primary malignant tumors in ≥ 1 organ or tissue in the same person [1]. Although inconsistent among various studies, an additional diagnosis that occurs within six months of the primary tumor diagnosis is defined as synchronous MPMN (SMPMN); otherwise, they are classified as metachronous cancers (MMPMNs) [2].

The number of confirmed cases of MPMNs is increasing, accompanied by increasing availability of screening, diagnosis, and treatment. Most of these are diagnosed as dual primary cancers, while triple is relatively rare, and triple SMPMNs are even rarer. However, a kidney cancer that occurs concurrently with breast and thyroid cancers has rarely been described in the literature. Therefore, we report a case of SMPMNs to further understand its diagnosis and management.

CASE PRESENTATION

Chief complaints

2 A 48-year-old female patient was admitted to our department of breast surgery at a tertiary hospital, presenting with "the right breast mass and pain for more than four months" on April 20, 2020. With a BMI of 22.8,

History of present illness

4 the patient had no previous medical history,

History of past illness

no adverse health habits such as smoking and alcohol,

Personal and family history

and no family disease history. We did not palpate any other positive signs except for the right breast mass.

Physical examination

We performed an imaging evaluation, and breast ultrasound revealed a mass in the gland approximately $2.0 \times 1.3 \times 1.7$ cm in size, positioned at 12 o'clock in the right breast, 1.8 cm away from the nipple. The mass had an unclear border and an angled edge and was classified into five categories according to the breast imaging reporting and data system (BI-RADs) (Figure 1). No abnormal enlargement of lymph nodes was observed in the axillary, supraclavicular, or infraclavicular regions. Both mammogram and breast magnetic resonance imaging (MRI) indicated that the mass was malignant. In addition, no other abnormal changes were observed in the patient's bilateral breasts. Immediate ultrasound-guided core needle biopsy confirmed the presence of invasive ductal carcinoma of the breast by pathology (Figure 2).

Laboratory examinations

Therefore, we performed a further systemic evaluation to rule out metastatic disease and found thyroid- and kidney-occupying lesions. Thyroid ultrasound revealed solid nodules in the middle and upper of the thyroid right lobe, the inferior proximal isthmus, and the middle of the left lobe with sizes of approximately 0.7×0.6 , 0.8×0.5 , and 1.0×0.8 cm, respectively (Figures 3, 4, and 5). With unclear boundaries, multiple-sized calcification foci were observed in the nodules and classified as category 4c according to the thyroid imaging reporting and data system (TI-RADs). In the IV area of the left neck, an enlarged lymph node with a size of 1.8×0.6 cm and uneven cortical thickening can be seen.

Imaging examinations

In addition to this, an abdominal ultrasound revealed a 6.4×5.9 cm solid hypoechoic mass on the upper pole of the right kidney and an uneven internal echo. Furthermore, computed tomography (CT) of the urinary system displayed that the lesion was cystic low-density, with massive calcification and shadows of flocculent soft

tissues, which appeared slightly thickened on an enhanced scan and was therefore considered to be cystic kidney cancer (Figure 6).

MULTIDISCIPLINARY EXPERT CONSULTATION

After a multidisciplinary team discussion, the decision was made to temporarily exclude metastasis because of the earlier manifestations of the patient's various examinations. Surgical indications were clear. At the request of the patient and family members and considering the patient's tolerance, separate surgeries were performed.

FINAL DIAGNOSIS

Owing to the variety of breast cancer treatments available, this surgery was performed in advance. Second, kidney surgery was advised as soon as possible to reduce the tumor burden. Considering the inertia of thyroid cancer, thyroid surgery was performed.

TREATMENT

Breast-conserving surgery was performed; however, the patient refused surgery. Thus, a right radical mastectomy was performed on April 28, 2020. Postoperative pathology revealed moderately differentiated invasive ductal carcinoma (Figure 7), with a tumor volume of $2 \times 1.5 \times 1.2$ cm, where the vessels and nerves were not invaded. The margins were negative. Immunohistochemistry revealed the following results: ER (+, medium intensity, approximately 80%, 1604/2000cells), PR (+, medium-strong intensity, approximately 80%, 1596/2000cells), CerbB-2 (1+), and Ki67 (approximately 30%+) (Figure 8). A 0.2 mm metastasis (1/5) was detected in the sentinel lymph node, while (0/23) no cancer cells were detected in the axillary lymph node dissection. According to the AJCC version 8.0, the pathological stage was pT1N0 (i+). Therefore, six cycles of EC regimen chemotherapy were delivered postoperatively per NCCN guidelines for breast cancer, followed by endocrine therapy with tamoxifen.

A radical nephrectomy was performed at our hospital on June 2, 2020. Right kidney pathological revealed (Figure 9) renal cell carcinoma grade 3, with a mass of $6.5 \times 6 \times 5$ cm. Combined with immunohistochemistry, it was found prone to type 2 papillary renal cell carcinoma. The vessels, nerves, renal sinuses, and perirenal fat sacs are clear. No tumor was found in the severed ureters or blood vessels. The pathological result was pT1bN0, and no medication was administered following surgical excision.

Due to personal reasons, thyroid surgery was postponed to December 24, 2020. Postoperative pathology found that the left, right, and isthmus tumors of the thyroid were all papillary carcinoma (Figure 10), each with a diameter of about 1, 0.9, and 0.6 cm, consistent with the imaging results observed eight months prior. The remaining cancer tissue invaded the thyroid capsule and reached the striated muscle tissue, and a tumor thrombus was observed in the vessel without lymphatic complications. No lymphovascular invasion was observed in the right lobe. Lymph node infiltration was observed around the thyroid (1/1), right IV (1/3), and left III (1/8) areas. I¹³¹ and levothyroxine sodium tablets were administered postoperatively.

OUTCOME AND FOLLOW-UP

Thus far, SMPMNs of the breast, kidney and bilateral thyroid have been diagnosed if surgery is performed as planned. (Table 1) The patient followed the doctor's advice for the treatment, and no evidence of recurrence or metastasis has been observed in the follow-ups to date. Both the doctors' team and patients were satisfied with the treatment results.

DISCUSSION

In 1889, Billroth first described dual primary cancers of the thyroid and breast [3]. The situation has gradually increased since then in the case presented herein. MPMNs were later defined by Warren and Gates in 1932 [1]. Increasing evidence has demonstrated that progress in medicine has contributed to the detection rate of MPMNs

in this aging population era. However, the morbidity of MPMNs varies greatly among different cancer types, ranging from 0.73% to 20% abroad ^[1,2], which is significantly higher than China's 0.4% to 2.4% ^[3]. This discrepancy could be attributed to medical level and financial factors. SALEM *et al* ^[4] reported that the morbidity rates of MPMNs were 2.3%, and triple cancer was only 0.16%, respectively. ROSSO *et al* ^[5] found that MPMNs accounted for 6.3%, of which 2%–12% were triple cancer and above. In addition, SMPMNs, accounting for 18.4%–30.1% of MPMNs ^[6,7], are associated with a lower incidence than MMPMN. Therefore, the three synchronous primary cancers are extremely rare.

Early diagnosis and proper treatment are essential for obtaining the best prognosis. Based on postoperative proprietary pathological features and immunohistochemistry to exclude mutual metastasis, our patient was confirmed to have SMPMN following Warren and Gates's criteria ^[1,2]. Early staging further strengthens the diagnostic evidence. With a breast and kidney cancer diagnosis within two months, if treated as planned, the patient will be diagnosed simultaneously with bilateral thyroid cancer. Clinical data have demonstrated that MPMNs are more likely to occur in the same organ, system or pairs of organs, such as the lung, breast, thyroid, and kidney ^[8]. Interestingly, SMPMN occurred in three pairs of organs.

However, the pathogenesis of MPMNs remains unclear. Compared with the general population, the increased risk appears to be complicated by genetics, host autoimmune and hormonal, external environment, and living habits (smoking, alcohol abuse, and excessive fat intake). Therefore, some patients have increased susceptibility to tumors. In addition, carcinogenic factors, such as radiation and cytotoxic drugs, contribute to the prolonged survival of patients. Thyroid cancer is commonly observed in breast cancer patients. A large retrospective study in South Korea demonstrated that the most common malignant tumor is thyroid cancer in breast cancer patients ^[9,10]. The breast and thyroid glands are controlled by the hypothalamic-pituitary endocrine axis. There are certain commonalities in the absorption of sex hormones, iodine, and thyroid hormones, which can potentially develop MPMNs ^[11,12]. Several studies have depicted

that breast, thyroid, and renal cancers have bidirectional associations, likely shared genetic and environmental risk factors, and treatment effects [13,14]. Gordon syndrome is an autosomal dominant inherited disease caused by mutations in PTEN, which often accompanies thyroid and breast cancers [15]. In addition, papillary renal cancer is increased in individuals with PTEN mutations [16,17]. The reasons for this remain unknown based on available data. Many studies have revealed that obesity is related to these three cancer types [18,19]; however, as stated, the patient's BMI was not high. Moreover, they had no family history of tumors or unhealthy habits. Concurrent suffering from breast, thyroid, and kidney cancers may be closely related to gene mutations, immunodeficiency, and hormones. Unfortunately, the patient declined genetic testing for financial reasons. The pathogenesis and risk factors of MPMNs require further exploration.

As completely different treatment options exist, it is particularly important to distinguish primary lesions from metastatic lesions. Advances in imaging technology have contributed to the MPMNs diagnosis rate, and genetic testing has further improved its accuracy. On imaging, metastasis is often multiple, and MPMNs are often singular. When there is no peripheral lymph node metastasis in the first malignant tumor or other tumors, we should be aware of the presence of MPMNs. In addition, most patients only undergo traditional primary cancer imaging examinations and ignore MPMNs, which leads to missed diagnosis, delays in treatment, and affects prognosis. Recently, whole-body MRI (WB-MRI) [20] and positron-emission tomography-computed tomography (PET/CT) [21] are highly sensitive in discovering new cancer foci and observing the progression of the disease in asymptomatic carriers, which has great consequences for diagnosis. In addition, accuracy can be ensured by increasing the number of inspection methods.

It is difficult to identify SMPMN and metastasis; however, it affects treatment and prognosis in sequence. Treating MPMNs is similar to that of early single primary cancers and tends to be a comprehensive treatment based on surgery, while recurring and metastatic tumors lose the opportunity for surgery based on comprehensive

treatment. Currently, recommendations for the treatment of MPMN are limited. A multidisciplinary team discussion is optimal, following the principles of individualized and comprehensive treatment [22]. Almost all literature reports support the selection of radical surgery resection based on tumor location, pathological characteristics, staging, and the patient's system conditions. Subsequent treatments should be performed separately for each MPMN tumor. If the situation permits, simultaneous surgery is recommended, especially for young and healthy patients. Otherwise, in principle, the treatment of highest malignant degree should be undertaken first, followed by an appropriate interval that is beneficial for observing the treatment effect and rehabilitation [23]. Therefore, independent staging of each tumor should be performed as soon as possible after diagnosing MPMNs [24]. Inoperable patients should be actively administered chemotherapy, targeted therapy, and other treatment methods to improve their quality of life and prolong survival as much as possible. The advantages and disadvantages must be weighed because of the risk of secondary radio-induced, chemo-induced, and endocrine-induced cancers [23]. After multidisciplinary team discussion, we performed sequential surgery based on the above principles in combination with the patient's situation and provided corresponding postoperative adjuvant treatment.

As we all know, primary cancer has a significantly better prognosis than recurrence or metastasis. For MPMNs, prognosis based on the patient's physical condition is mainly related to cancer characteristics, radical resection, and the interval between different tumors. The shorter the interval between the second and first primary cancers, the worse the prognosis [9]. Multiple cancers that occur simultaneously in the same system generally progress quickly and have a poor prognosis [25,26]. However, there are also reports that a second primary cancer does not affect the disease-free survival and overall survival of patients with a single primary cancer [9,27]. For such patients, early detection, diagnosis, and provision of reasonable and effective treatment are key to improving survival rates and prognosis. In addition, compared with single primary cancers, patients with MPMNs experience more psychological pain, financial stress, and

worse treatment compliance, which has a negative impact on the outcome [28]. Therefore, it is necessary to pay attention to the psychological burden of these patients.

CONCLUSION

Herein, we report a rare case of early SMPMNs in the breast, kidney, and bilateral thyroid, where early recognition and management of this disease is important. Early-stage malignant tumor symptoms are subtle and difficult to diagnose. Therefore, careful physical examination can help to identify tumors located elsewhere. When it is difficult to distinguish between primary and metastatic tumors, immunohistochemistry and genetic analysis may aid the diagnosis. Second, a highly individualized and comprehensive treatment plan should be developed for every MPMN patient, preferably by multidisciplinary joint diagnosis and treatment, with an urgent need to establish evidence-based methods for managing them. Finally, the patient is encouraged to abandon unhealthy lifestyles, such as smoking, drinking, and excessive fat intake, to aid in successful prevention and recovery. Appropriate follow-up cannot only detect the recurrence and metastasis of the first primary cancer earlier but also other primary cancers simultaneously, which can ultimately improve patient outcomes.

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