

A CASE REPORT OF A PATIENT WITH FOUR METACHRONOUS CANCERS

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Multiple primary malignant neoplasms (MPMNs) are two or more histopathologically distinct malignancies in one or more organs such that one tumor is not a recurrence or metastasis of the other. Although there are well-known genes associated with hereditary cancers, sometimes it is not possible to find a genetic link between neoplasms. Our patient had four metachronous primary malignancies: breast cancer (BC), rectal cancer (RC), parotid cancer, lung cancer (LC), and highly suspected contralateral BC, over a 28-year period. We presented the challenges in diagnosis and therapeutic approach and highlighted the importance of genetic counseling and testing in these patients. To achieve better treatment, we need to find out which patients are at risk for MPMNs, and which tumors are more likely to occur synchronously or metachronously and enroll these patients in clinical trials.

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Key words: *neoplasms, multiple primary, neoplastic syndromes, hereditary, genetic testing*

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rectal cancer, parotid cancer, lung cancer, and highly suspected contralateral BC) over a 28-year period, explains the challenges in diagnosis and therapeutic approach, and highlights the importance of genetic counseling and testing in these patients.

Case report

The female patient had a verified ductal invasive right BC as her first malignancy at the age of 33. Immunohistochemical examination of receptor status was not performed in the 1990s, and she was treated with preoperative radiotherapy (RT) followed by radical mastectomy in October 1994 at the Institute of Oncology and Radiology of Serbia. Thereafter, she underwent regular follow-up. In May 2004, after a colonoscopy with biopsy, she underwent anterior and inferior rectal resection with total mesorectal excision and coloanal anastomosis. Histopathologically, it was a villous adenocarcinoma of the rectum, Dukes B, Astler-Coller B2, without lymph node invasion, classified as T1N0Mx. Accordingly, in stage I, the patient underwent follow-up. In December 2018, after palpating a nodule in her right parotid gland, she underwent a subtotal parotidectomy with preservation of the right facial nerve and was diagnosed with parotid gland cancer. Local recurrence occurred after 2 years and was confirmed after extirpation. Due to frequent epi attacks, severe right-sided weakness, and severe motor dysphasia, a brain magnetic resonance imaging (MRI) was performed, which showed an expansive change in the left

Introduction

Multiple primary malignant neoplasms (MPMNs) are two or more histopathologically (HP) distinct malignancies in one or more organs, such that one tumor is not a recurrence or metastasis of the other (1). They may be synchronous or metachronous, depending on the time of occurrence. Risk factors include genetic predisposition, exposure factors (tobacco, alcohol, hormones, immunodeficiency, infections), and carcinogenic effects of cancer treatment. The incidence (2.4%–8%) is low, tending to increase with longer survival and early detection. It depends on the primary cancer and prior treatment. In patients with breast cancer (BC), the incidence of MPMNs is approximately 4.1% to 16.4% (2). MPMNs occur in hereditary syndromes. Although there are well-known genes associated with hereditary cancers (3), sometimes it is not possible to find a genetic link between neoplasms.

This article presents the case of a patient with four metachronous primary malignancies (BC,

temporoparietal lobe. Complete tumor extirpation was performed in September 2019 at the Neurosurgery Clinic of the University Clinical Center Niš. Based on the immune profile, it was a metastasis of lung adenocarcinoma with papillary growth. She underwent palliative RT to the brain with 30 Gy TD in 10 sessions. There was no evidence of recurrence at the last endocranial MRI in December 2021. She had no respiratory symptoms until November 2021, and this was the first time she saw a pulmonologist. She presented with a cough with yellowish sputum, dyspnea, and fatigue without fever. Multi-slice computed tomography (MSCT) of the chest showed a 60 mm pleural effusion on the right side, an irregular lung tumor lesion of 53 x 43 x 64 mm, a reduction of the tracheal lumen ipsilateral to the main bronchi, and secondary deposits of both adrenal glands of 53 x 21 mm and 40 x 36 mm. A bronchological examination was indicated to clarify the etiology of the lung changes, but it was not performed because the patient was not motivated. Treatment for the lung cancer was limited to symptomatic therapy due to the patient's poor Eastern Cooperative Oncology Group performance status (ECOG PS) 3. In February 2022, she presented to the breast multidisciplinary (MTD) with a highly suspicious 60 x 40 mm left BC and marked lymphedema on the right hand. According to the Breast Imaging Reporting and Database System, the change was graded as BI-RADS 5. The MDT recommended a CORE biopsy for possible hormone therapy in case of hormone receptor-positive disease.

The patient is a non-smoker and denies hereditary diseases.

Discussion

This is a rare case of a patient with a metachronous cancer quartet that includes the breast, rectum, parotid gland, and lung. In such a case, it is important to determine whether the tumor is hereditary. Our patient met some of the criteria (4): first cancer at age 33, MPMNs, but negative family history, and searching the literature we could not find a specific syndrome for this quartet. An Asian study showed that patients with MPMNs were more likely to be carriers of pathogenetic variants, most frequently in BRCA 1 and BRCA 2 and mismatch repair genes and less frequently in APC, ATM, MUTIH, PALB2, RAD50, and TP53 (5).

While a Turkish study described BC with gynecologic carcinoma as the most common pair

of primary cancers in women (6), Halamkova J. et al. showed that in 32.7% of cases and with a mean time of 8.9 years, the second was colorectal carcinoma (CRC), consistent with our case. This association may be sporadic or germinal. Older patients, with early-stage disease and without recurrence have a higher risk of secondary cancer (7, 8). We can establish a link between LC and preoperative BC RT (2) or the fact that BC is the most common cancer in women, LC the second most common primary cancer, and that patients' lives have been prolonged thanks to better screening and advanced therapies (8). The risk of contralateral BC cancer is five times higher in patients who have had this cancer before (9), which supports our suspicion. There is an association with lobular cancer and family history.

The treatment decision is multidisciplinary and based on the characteristics of the cancer, the patient and the drugs. These patients are usually excluded from clinical trials, so there are no specific guidelines for their treatment. Because of the marked neurological symptoms and poor PS, our patient underwent tumor extirpation in the brain, followed by palliative RT. She was not a candidate for specific oncological treatment for LC, so she received only symptomatic therapy. In the case of BC, she could be a candidate for hormonal therapy in hormone receptor-positive disease.

Genetic counseling and testing are very important in these patients because of therapeutic options (e.g., BRCA, PALB2 mutation) and investigation of predisposition to other cancers in the carrier of a particular mutation or first-degree relatives. Previously, genetic testing was expensive and time-consuming, but now next-generation sequencing (NGS) allows the investigation of a whole range of genes at a lower cost and with faster testing speed (10).

Conclusion

This quartet of cancers may occur sporadically, due to immunodeficiency or previous therapies, or in the context of hereditary syndromes. Therefore, it is necessary to perform genetic testing in patients with MPMNs, for themselves but also for their family members. The incidence of MPMNs will tend to increase in the future. To achieve better treatment, we need to find out which patients are at risk for MPMNs, which tumors are more likely to occur synchronously or metachronously and enroll these patients in clinical trials.

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Prikaz bolesnika

UDC: 616-006.6-055.2:575.1
doi: 10.5633/amm.2024.0112**PRIKAZ SLUČAJA BOLESNICE SA ČETIRI METAHRONA
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Multiple primarne maligne neoplazme (MPMN) predstavljaju pojavu dvaju ili više histopatološki različitih maligniteta u jednom organu ili u više organa, i to tako da jedan tumor nije recidiv ili metastaza drugog. Iako su dobro poznati geni udruženi sa hereditarnim karcinomima, ponekad nije moguće pronaći genetsku vezu između neoplazmi. Prikazan je slučaj bolesnice koja je u periodu od 28 godina imala četiri metahrona primarna maligniteta: karcinom dojke, karcinom rektuma, karcinom parotida, karcinom pluća i vrlo sumnjiv kontralateralni karcinom dojke. U radu su predstavljeni izazovi na koje smo naišli u dijagnostici i terapijskom pristupu. Takođe, istaknut je značaj genetskog savetovanja i testiranja ovakvih bolesnika. Da bi se postigao bolji tretman, mora se saznati koji su bolesnici u riziku od pojave MPMN-a, kao i kod kojih tumora postoji veća verovatnoća da će se pojaviti sinhrono ili metahrono. Osim toga, potrebno je uključiti ove bolesnike u klinička ispitivanja.

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Ključne reči: neoplazme, višestruki primarni, neoplastični sindromi, nasledni, genetsko testiranje

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