VIA MEDICA

CASE REPORT

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# Synchronous case of cutaneous melanoma and gallbladder cancer in a 74-year-old female patient

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## ABSTRACT

The occurrence of multiple primary neoplasms is not only a diagnostic but also a therapeutic challenge. We aim to present a case of a 74-year-old woman diagnosed with synchronous primary skin melanoma and gallbladder cancer. We showed the diagnostic process, applied treatment, and referenced it to the literature data.

**Key words:** multiple primary tumors, multiple primary neoplasms, personalized medicine, gallbladder cancer, melanoma, cutaneous melanoma

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## Introduction

The incidence of multiple primary neoplasms is 2.4–8%, and it may be even 17% in the case of 20-year follow-up after anticancer treatment. This is a challenge in diagnosis, treatment, and prevention for oncologists [1]. According to the IARC prognosis (International Agency for Research on Cancer), the number of cases of all cancers is expected to double in 2070 compared to 2020 [2].

We aim to present a case of synchronous occurrence of two primary neoplasms: skin melanoma and gallbladder cancer.

## Case report

In June 2021, a 74-year-old woman was admitted to an oncology clinic with a pigmented lesion on the skin of her left foot. On physical examination, apart from the described skin lesion, no abnormalities were found. Her general condition was satisfactory [Eastern Cooperative Oncology Group (ECOG) 1t, visual analog scale (VAS) scale 0].

Excisional biopsy was performed on the pigmented lesion with margins (lateral — 5 mm and 2 mm deep). A histopathological examination showed the presence of nodular melanoma pT3b with infiltration to a depth of 3 mm and ulceration. Blood vessel invasion was also found, while no nerve invasion was revealed. An immunohistochemical examination revealed the lack of broad-spectrum cytokeratin (CKPAN–) expression, the presence of the SOX10 transcription factor (SOX10+), and a high level of Ki-67 (70%).

An abdominal ultrasound examination revealed the presence of heterogeneous vascularization in the area of the gallbladder.

The next stage of treatment was the radicalization of cutaneous melanoma excision accompanied by sentinel lymph node biopsy. In the histopathological examination, no scar infiltration was found, and there were no metastases of melanoma in the sentinel node. Finally, she was diagnosed as pT3bN0.

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A cholecystectomy and peri-gallbladder lymph node biopsy was also performed. The histopathological examination of the gallbladder revealed the presence of MiNEN (mixed neuroendocrine and non-neuroendocrine neoplasm) composed of adenocarcinoma G1 and LCNEC (large-cell neuroendocrine carcinoma) G3. LCNEC included masses in the lumen of the gallbladder, and adenocarcinoma infiltrated the entire thickness of the gallbladder wall and peri-gallbladder tissue (including nerves and blood vessels), but without infiltration of the serosa. Metastasis of adenocarcinoma was found in the surgically removed peri-gallbladder lymph node. Immunohistochemistry of MiNEN showed expression of CAM 5.2 cytokeratin (CK CAM 5.2+), neural cell adhesion molecule (CD56+), chromogranin A (CgA+), synaptophysin (+/–), and cytokeratin 7 (CK7+); however, the transcription factor SOX10 (SOX10-) was not present, cytokeratin 20 was sporadic (CK20 –/+), and the Ki-67 value was 50%.

Then, a part of the liver was resected near the previous location of the gallbladder, and regional lymph nodes and implants (up to 1 mm) on the surface of the 7$^{th}$ segment of the liver were found. The histopathological examination of the lymph nodes showed the presence of metastases of the gallbladder adenocarcinoma component, with infiltration of the nodal capsule. The white implants from the segment VII surface of the liver turned out to be Von Meyenburg complexes (developmental malformation of the intrahepatic bile ducts — hamartoma). The gallbladder cancer stage was defined as cT2N1M0 (stage 3B) and pT2N1.

The diagnosis of the advanced neoplastic process was established. Computed tomography of the thorax, abdominal and pelvic cavity showed no evidence of malignancy.

The patient was qualified for adjuvant treatment with gemcitabine for gallbladder cancer. Currently, the patient continues systemic treatment.

## Discussion

Multiple primary neoplasms are defined as tumors arising in other organs as independent primaries in the same person. Taking into account the criterion of time in diagnosis, we can distinguish synchronous or metachronous. These terms have various definitions [3]. The SEER (Surveillance Epidemiology and End Results) database recommends a 2-month period to distinguish between synchronous and metachronic multiple primary neoplasms. On the other hand, according to the IARC, multiple primary neoplasms with different anatomical locations are classified as synchronous when they are diagnosed within less than 6 months, while if the interval is longer than 6 months, they are considered metachronic [4]. In our case, regardless of which definition we use (melanoma resection was in June, gallbladder cancer resection was in August), we are dealing with synchronous primary neoplasms.

Due to their etiology, multiple primary neoplasms are divided into three groups: (1) neoplasms related to previous treatment, (2) neoplasms associated with disease syndromes of an increased risk of malignancy, (3) neoplasms that may share common etiologic factors, such as genetic predisposition or the same environmental factors. Moreover, multiple tumors can also develop accidentally [5].

Our patient had no genetic tests. However, with advances in molecular biology and especially the increasing availability of genetic tests, patients diagnosed with multiple primary neoplasms will be screened more often for the presence of a predisposition to cancer development [6]. *BRAF* gene mutations appear to be quite common in gallbladder cancers, suggesting that they may play an important role in the pathogenesis of this tumor [7]. Advances in gene sequencing have shown that activated *BRAF* mutations are present in more than 50% of malignant melanomas and contribute to constitutive signals in the MAPK pathway [8]. On the other hand, a mutation in the *BAP1* gene is responsible for an increased risk of uveal melanoma, mesothelioma, kidney cancer, lung adenocarcinoma, meningioma, gallbladder cancer, and cutaneous melanoma [9].

While browsing the PubMed Central databases, we were unable to find similar coexistence cases of gallbladder cancer and melanoma in the publications. However, the occurrence of a hereditary predisposition or familial aggregation is unlikely because the patient became ill at an elderly age and there was no increased incidence of neoplasms in her family history. Most likely, environmental and genetic factors were involved in the etiology, of which the first one played a major role, leading to the new somatic mutations. Probably the incidence of these two cancers was sporadic. The known risk factors for melanoma in the patient were age and, possibly, UV radiation because the lesion was located on the foot. No risk factors for gallbladder cancer were found [10, 11].

The diagnosis of two synchronous primary malignancies is a therapeutic challenge — it is important to select an antineoplastic therapy strategy that will be effective in both types of neoplasms and not be related to intensified toxicity or increased risk of pharmacological interactions [12].

## Conclusions

The predicted increase in cancer incidence and constant progress in the effectiveness of oncological treatment resulting in the prolongation of life make multiple primary neoplasms a significant diagnostic, therapeutic

and prophylactic problem. The postulated development of personalized medicine may help in primary prevention, diagnosis, and treatment of multiple primary neoplasms by increasingly available genetic tests that help to estimate the risk of specific cancer in a specific person, as well as define the patient's metabolic profile due to the drugs used (pharmacogenetics).

## Conflict of interest

Authors declare no conflict of interest.

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