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**Case Report / Приказ болесника**

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**Metastatic melanoma of the gallbladder**

Метастатски меланом жучне кесе

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## Metastatic melanoma of the gallbladder

### Метастатски меланом жучне кесе

#### SUMMARY

**Introduction** Malignant melanoma (MM) is a tumor of the melanocytes and is one of the most aggressive tumors. In most cases, the first symptoms appear in the metastatic phase of the disease. In clinical practice, malignant melanoma very rarely metastasizes to the gallbladder. Modern diagnostic methods include 18F-fluorodeoxyglucose positron emission tomography, new computed tomography protocols, new nuclear magnetic resonance for melanoma protocols, and contrast-enhanced ultrasound. The article aims to emphasize the necessity of radical surgical treatment of metastatic melanoma of the gallbladder.

**Case report** We present a rare case of metastatic malignant melanoma of the gallbladder, which was treated with cholecystectomy and radical surgical excision of all metastatic lesions.

**Conclusion** All patients with a positive anamnesis for malignant melanoma require to be checked for the spread of the disease to the gallbladder and subsequent surgical treatment.

**Keywords:** malignant melanoma; gallbladder; metastasis; surgical treatment

#### САЖЕТАК

**Увод** Малигни меланом (ММ) је тумор меланоцита и спада у један од најагресивнијих тумора. У већини случајева први симптоми се јављају у метаастатској фази болести. У клиничкој пракси веома ретко се виђа метастазирање ММ у жучну кесу. Савремене дијагностичке методе су 18Ф-флуороеоксиглукоза позитрон емисиона томографија, нови протоколи компјутеризоване томографије и нуклеарне магнетне резонанце за меланом и ултразвук са контрастом. Циљ рада је истаћи неопходност радикалног хируршког лечења метаастатског меланом жучне кесе.

**Приказ болесника** Представимо случај ретке метаастатске болести ММ у жучној кеси који је лечен холецистектомијом и радикалном хируршком ексцизијом свих метаастатских промена.

**Закључак** Сви пацијенти са позитивном анамнезом малигног меланом захтевају и проверу раширености болести у жучну кесу а потом и хируршко лечење.

**Кључне речи:** малигни меланом; жучна кеса; метастаза; хируршко лечење

#### INTRODUCTION

Malignant melanoma (MM) is caused by the malignant proliferation of melanocytic cells. Most commonly, primary MM occurs in the skin, and less commonly in the eyes, gastrointestinal tract, genitourinary system, lymphatic system, and soft tissues [1, 2, 3]. Metastases most often occur in the lymph nodes, lungs, liver, and brain [4, 5]. According to the literature, primary and secondary malignant melanoma of the gallbladder has been diagnosed only in 58 patients so far [6]. Weiting and Hamdi reported the first case of MM metastasizing to the gallbladder in 1907 [7]. About 50% of gallbladder metastases are attributed to MM [8]. Apart from the embryological origin, one of the explanations may be that malignant melanoma often spreads hematogenously [9]. For most patients, the primary tumor is asymptomatic until metastatic disease is diagnosed [10,11,12]. Namely, diffuse metastatic disease involves other

intra-abdominal organs in 60% of cases [13]. Preoperative diagnosis of malignant melanoma of the gallbladder is challenging [14]. In addition to clinical presentation, other diagnostic procedures such as ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) of the abdomen, and 18F-fluorodeoxyglucose positron emission tomography (FDG PET-CT) could be performed, enabling the differentiation of a malignant from a benign gallbladder tumor [15]. However, pathohistological and immunohistochemical examination is the gold standard. Surgical treatment is the preferred method of treatment.

In this article, we present a rare case of metastatic malignant melanoma of the gallbladder.

### **CASE REPORT**

A 35-year-old man was admitted to our department due to pain in right hypochondrium and nausea. A year earlier, the patient underwent left pneumonectomy due to large cell lung cancer. He had no other comorbidities. The tumor markers were within the normal ranges. US, CT, and MRI examinations of the abdomen and pelvis revealed a tumor in the lumen of the gallbladder, 64 x 39 mm in diameter. Also, several soft tissue nodular lesions were detected in other locations: one lesion in the greater omentum, 8 x 8 mm; two lesions in the front abdominal wall at the level of the right rib arch, 40 x 30 mm in size, and suprapubically, 8 x 6 mm in size; one lesion in the right inguinal region, 25 x 20 mm in size; and one lesion in the subcutaneous region of right shoulder measuring 18 x 15 mm (Figure 1).

During the same surgical procedure, cholecystectomy, excision of the tumorous lesion from the greater omentum, and lymphadenectomy were performed. Two nodular lesions were excised from the anterior abdominal wall, one was removed from the right groin area, and one was excised from the right shoulder region (Figure 2a). Complete surgical exploration found no other tumorous lesions in the abdomen and pelvis.

Definitive histopathological and immunohistochemical findings confirmed metastatic melanoma of the gallbladder, the greater omentum, and subcutaneous tissue of the subcostal, shoulder, and right inguinal regions (Figure 2b). All of the examined tissue samples showed nodular metastatic tumor deposits, of whom most showed clear borders and had free margins, indicating R0 resection. All tumor cells showed clear diffuse cytoplasmic immunoreactivity, positive for Vimentin, HMB-45, S-100, while a part of the tumor cells were positive for Melan A and Synaptophysin, and focally for epithelial membrane antigen (EMA) (Figure 2c). The Ki-67 proliferative index was 80%.

Note: The article was approved by the ethics committee of the University of Belgrade Medical Faculty (No. 1038/7)

## DISCUSSION

Malignant melanoma is a very aggressive tumor with a high metastatic potential and a high mortality rate. Men and women are affected almost equally. The pathogenesis of metastases has not yet been fully elucidated. The migration of melanin-producing cells from the neural crest to derivatives of the endoderm during embryonic development might explain the presence of melanocytes within their mucosa. This could explain the possibility of the development of primordial melanoma in these organs [16]. Malignant melanoma of the gallbladder makes up 50% to 67% of all gallbladder tumors [17]. According to autopsy findings, gallbladder and biliary tract metastases occur in approximately 15% of patients with MM metastases in the gastrointestinal tract. However, there are significant statistical discrepancies in the scientific literature [18] regarding this issue. In some cases, patients are asymptomatic or have symptoms such as are pain under the right rib cage, nausea and vomiting, food intolerance, weight loss, and diarrhea [11]. Jaundice can develop due to the infiltration of the bile ducts by the tumor or as the result of their compression. Rarely, a biliary fistula may

develop and hemobilia may occur [12]. We must always bear in mind the differential diagnosis, such as primary malignant tumors of the gallbladder, benign polyps, and adenomyomatosis. Preoperative diagnosis is established based on US, CT, MRI, or PET/CT examinations. A definitive diagnosis is often established by combining multiple imaging modalities. However, it is very difficult to distinguish preoperatively between gallbladder metastases and primary gallbladder tumors. Ultrasound can be the initial examination for evaluating metastasis of melanoma in the gallbladder. Contrast-enhanced ultrasound is useful in differentiating between solid wall lesions and tumefactive biliary sludge, but it is not possible to make a differential diagnosis between adenocarcinoma and gallbladder metastases. Compared with contrast-enhanced ultrasound, CT is the method of first choice and the most commonly used method for staging and monitoring therapeutic response in melanoma patients. CT examination of the gallbladder is based on the detection of tumor localization (fundus, body, neck, cystic duct, diffuse), tumor morphology (infiltrative, polypoid, mass-forming), degree and pattern of enhancement, depth of invasion and signs of concurrent cholecystitis. The MRI protocol for gallbladder examination should include thin slices (< 5 mm) axial T1/weighted images, coronal and axial T2/weighted, 3D-cholangiopancreatic images, axial dynamic contrast-enhanced (DCE) images, after intravenous injection of gadolinium contrast agent [19]. CT and MRI can reveal single or multiple exophytic masses or polyps arising from the gallbladder wall or infiltrative lesions invading the mucosal, muscular, or serous layers of the gallbladder. MM metastases are generally larger than 1 cm and attached to the gallbladder wall. If the mass involves the biliary tree, ductal dilatation and intraluminal masses may be visualized. The presence of melanin results in hyperdensity in unenhanced CT images and hyperintensity in T1-weighted MRI, facilitating the differential diagnosis of MM from other primary or secondary gallbladder lesions [7]. Endoscopic retrograde cholangiopancreatography (ERCP) and magnetic retrograde cholangiopancreatography (MRCP) are also helpful, as they can

identify biliary obstruction. PET/CT is very useful in detecting MM metastases throughout the body, as well as for evaluating response to treatment. The sensitivity and specificity of FDG PET/CT in the detection of distant metastases are reported to be 92% and 90%, respectively. FDG PET/CT is being developed as a standard diagnostic imaging method in melanoma patients [20]. If radical surgical treatment of malignant melanoma of the gallbladder is performed, one-year survival is possible in 100% of patients, while it is 0% in non-operated patients [11]. Surgical treatment reduces symptoms and prevents the further spread of the tumor. The effect of adjuvant and immunotherapy has not yet been determined. According to some studies, the application of Interleukin-2 leads to tumor remission in 15% of patients, with a significant effect in the early stages of the disease. However, its use is very limited due to its toxicity [21]. The most important prognostic factor is tumor biology, as demonstrated by numerous retrospective survival studies of patients with metastatic disease [10].

Malignant melanoma entails poor prognosis, as few patients survive two years past diagnosis. All patients with a positive anamnesis for malignant melanoma should be evaluated for gallbladder disease spread if the clinical presentation points to biliary involvement.

**Conflicts of interest:** None declared.

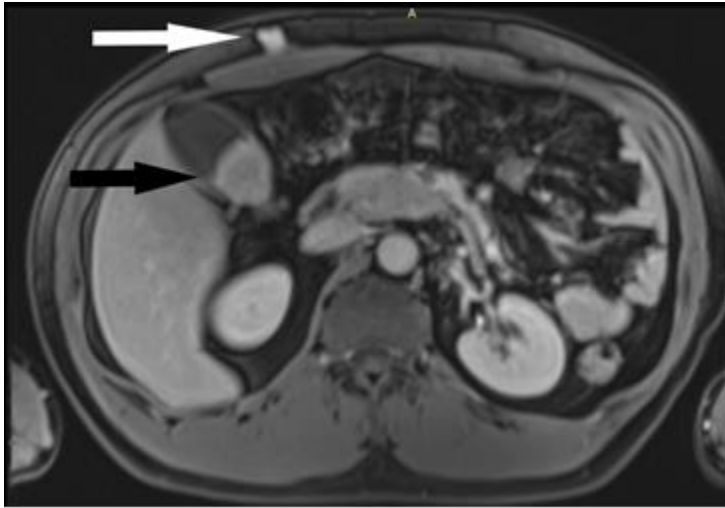
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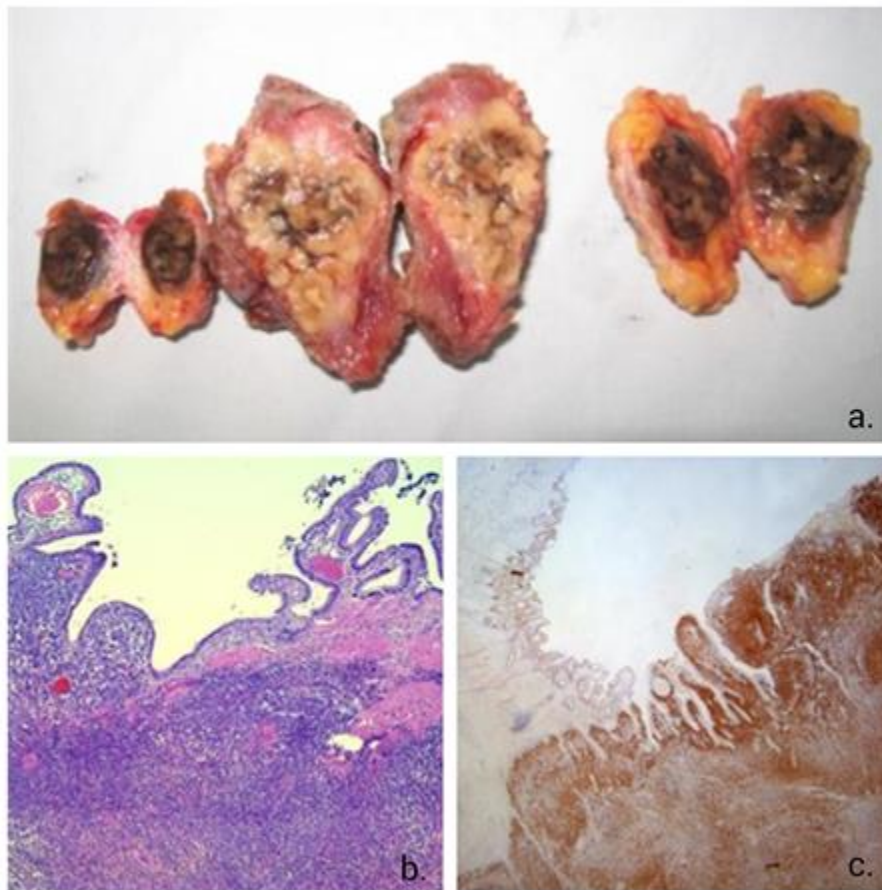
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**Figure 1.** Magnetic resonance imaging scan: axial postcontrast T1-weighted image in the portal venous phase clearly depicts an intraluminal viable tumorous lesion of the gall bladder (black arrow), and also an opacified nodular lesion, subcutaneously in the right anterior abdominal wall (white arrow)



**Figure 2.** a – macroscopic image: solid and black-pigmented tumorous lesions were verified by cutting out the lesions from the subcutaneous fatty tissue; b – insular and solid/trabecular histological organization of melanoma cells with areas of hyperpigmentation; c – tumor cell showed strong cytoplasmic immunorexpression of HMB-45