

**RARE METASTASES OF MALIGNANT MELANOMA**

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Melanomas are malignant neoplasms that originate from melanocytes. The most common are on the skin and mucous membranes. Choroidal melanomas are quite different from cutaneous melanomas with regard to presentation, metastases, and treatment.

We report two cases of metastatic gastric malignant melanoma of the eye and skin, with reference to the literature. The first patient was a woman aged 23 years, who underwent gastrectomy 22 months after enucleation of the eye due to malignant choroid melanoma. The second patient was a man, 72 years old, who underwent surgery 28 months before because of malignant melanoma of the skin of the forehead. Paraffin sections, 4 µm thick were stained using a classic method, as well as immunohistochemical DAKO APAAP method, using a specific S - 100 antibody and Melan A antibodies.

The stomach is considered a rare place for the development of metastases. Metastases in the stomach are often limited to the submucosal as well as the serous-muscular layer, as noted in one of our patients. Metastatic melanoma of the gastrointestinal tract should be suspected in any patient with a history of malignant melanoma and new gastrointestinal symptoms. Because of the similarity between certain common histopathological types of malignant melanoma, primarily achromatic, and types of primary cancers of the stomach, the following immunohistochemical studies are needed: Melan A and S - 100 protein ( markers of malignant melanoma ), as well as mucins: MUC5AC, MUC2 and CDX2 ( markers of different types of primary gastric carcinoma). *Acta Medica Medianae 2014;53(3):58-62.*

**Key words:** *malignant melanoma, metastases, localization, histopathology, immunohistochemistry*

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**Introduction**

Melanomas are malignant neoplasms that originate from melanocytes. The most common are on the skin and mucous membranes. Choroidal melanomas are quite different from cutaneous melanomas with regard to the presentation, metastases, and treatment (1-5).

Melanomas of the gastrointestinal tract may be primary or secondary i.e. metastases. Primary gastrointestinal melanoma is a rare, and even rarer in the stomach (6). Metastatic malignant tumors of the stomach originate most often from breast cancer (27.9%), lungs (23.8%), esophagus (19.1%), renal cell carcinoma (RCC ; 7.6%) and malignant melanoma (7,0%) (7). Metastatic malignant mela-

noma is also rare in the gastrointestinal tract but most commonly affects the small intestine. Less than 5% of patients with metastases in the gastrointestinal tract are diagnosed postmortem. Metastases in the gastrointestinal tract may be present at the time of establishing the primary diagnosis or years later, as the first sign of recurrence (8,9). The clinical presentation may be acute abdominal pain due to the obstruction of the intestines, intussusception, bleeding and perforation, dysphagia, hematemesis, melena, or the symptoms of the chronic form of the loss of weight, abdominal pain and anemia (10,11). Melanoma of the stomach has a distinctive endoscopic appearance. Differentiation of primary from secondary melanoma is possible based on localization and clinical behavior (7,12).

Malignant melanoma of the uveal tissue is the most common malignant tumor of the eye in adults. Fifty percent of the tumors will eventually metastasize, and except for enucleation of the eye there is no effective treatment for them (13, 14).

Melanomas of the conjunctiva have many similarities with the skin melanomas. In both cases, the regional lymph nodes are the most common sites of metastases which may be isolated and

distant. Gastric metastases are more common in skin melanoma (15,16).

### Aims

We report two malignant melanomas of the eye and skin, with extremely rare metastases in the stomach.

### Case reports

We report two patients with melanoma of the eye and facial skin, with metastases in the gastric wall, with a review of the literature. The first patient was a woman aged 23 years, who underwent gastrectomy 22 months after enucleation of the eye due to malignant choroid melanoma. The second patient was a man, 72 years old, who underwent surgery 28 months before because of malignant melanoma of the skin of the forehead. Metastatic melanoma of the eye in the stomach was discovered in the removed tissue after total gastrectomy because of "stomach cancer". Metastatic skin carcinoma was detected during gastric endoscopy.

Surgical and endoscopic biopsy material from the stomach was fixed in buffered formaldehyde and routinely processed in the autotehnicon. Paraffin sections, 4  $\mu$ m thick, were stained with HE conventional method, and the APAAP (Alkaline Phosphatase Anti-Alkaline Phosphatase) Kit DAKO immunohistochemical methods, using the specific markers for malignant melanoma: S-100 protein and Melan A.

#### Macroscopic appearance

Gastric metastases were multiple in both cases, localized throughout the wall (first patient) and in the mucosa (second patient). Intramucous metastases were seen as nodules covered by normal mucosa, sometimes with central ulceration and with small black spots on the mucosa. The mucosa was rough, lifted and thickened, dark brown and black in the second patient. At the intersection, the wall was thickened and interspersed with black multiple fields of different sizes and shapes. Regional lymph nodes (at the small and the large curvature of the stomach) were enlarged, with the normal structure at the intersection, of gray and white colors.

#### Histopathological appearance

In both patients, the localization of malignant melanoma was transmural; the thick, often confluent nests, composed of large cells epithelioid-cell type and atypical hyperchromic nuclei with an increased number of mitoses, were present in the mucosa and submucosa on endoscopic biopsies; on the surgical biopsy, nests of malignant cells were observed in the whole wall. The cytoplasm of these cells was full of dense deposits of melanine pigments black in

color (Figure 1), which was confirmed by an intense immunohistochemical reaction, detected with S-100 protein (Figure 2). The angiogenesis was discovered in the stroma of metastatic field. The regional lymph nodes were reactively hyperplastic, without malignant cells.

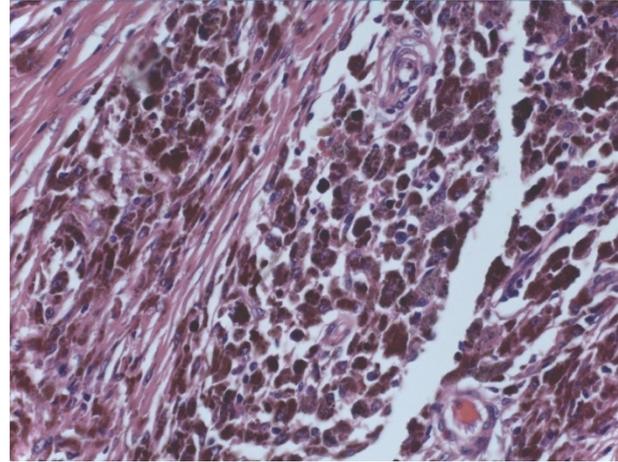


Figure 1. Disintegration and destruction of the tunica muscularis with fields of malignant melanoma. HE x 300

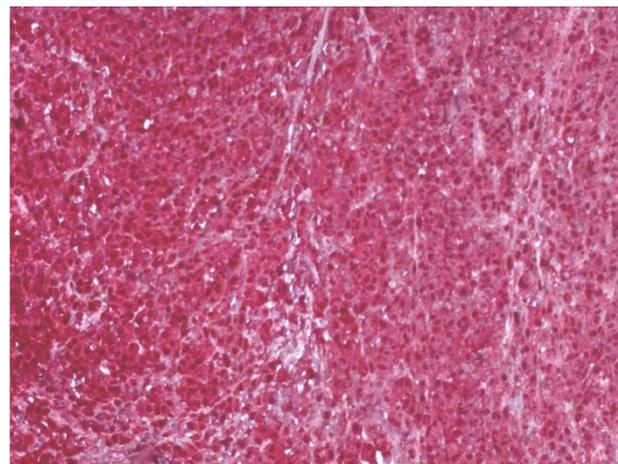


Figure 2. Intensive expression of melanin with dark red color in the cell cytoplasm of malignant melanoma. APAAP x 200

### Discussion

Gastric carcinomas represent a biologically and genetically heterogeneous group of tumors with multifactorial etiologies, both environmental and genetic. Gastric cancer accounts for 7.8% of cancers worldwide (17). Areas where incidence is high >60 per 100.000 males include Korea, Japan, eastern Europe, and central and Latin America (17).

The rate of patients in the world with confirmed metastatic disease of the abdominal cavity reaches only 2%. In contrast, 60% of patients who have died with the diagnosis of malignant melanoma were detected at autopsy with the metastases in the gastrointestinal tract

(18). Metastases cause gastric symptoms in half of these patients (19).

The stomach is considered a rare place for the development of metastases. Macroscopically, gastric mass is usually considered as the primary gastric cancer. However, the stomach may be affected by metastatic malignant melanoma. In addition to possible macroscopic misdiagnosis, metastatic gastric melanoma can also be microscopically misdiagnosed, especially achromatic type. This makes the diagnosis of gastric metastatic melanoma a challenge in certain cases (20).

Metastases in the stomach are often limited to the submucosal serous-muscular layers, as noted in one of our patients (19). In this case, the endoscopic findings are often normal. The most common endoscopic gastric metastases present as nodules similar to the tumor of the submucosa, smooth surface with a central depression, or ulceration. Significant role in diagnosis using radiological methods such as computed tomography (CT), ultrasonography and endoscopy is to show pathological thickening of the gastric wall.

In the case of the involvement of mucosa, the differentiation of primary cancer is difficult. Immunohistochemical analysis assists in differentiation of primary gastric cancers from metastatic melanoma (19). This analysis is justified if one keeps in mind that the majority of primary gastric cancer were positive for keratin 7, MUC5AC, MUC2 and CDX2, and metastatic melanomas were positive for Melan A and S-100 protein, which is highlighted in our results.

Malignant melanoma, depending on the localization, invades the environment, by spreading through lymphatics and hematogenously. Metastatic melanoma of the forehead skin and the eye presented in our patients most likely originates from hematogenous dissemination, as evidenced by angioinvasion stromal metastases, as pointed out by other authors (21-26).

Ocular malignant melanoma mainly metastasizes to the liver. Lorigan et al. (27) studied metastases in 110 patients with metastatic ocular

melanoma. After the initial diagnosis, metastases were studied in the next 2 months to 36 years. Ninety-five percent of patients in this study died between 1 month and 38 months after the start of metastatic disease. Hepatic metastases have developed in 101 patients (92%), and in 60 patients (55%) the liver was the only organ affected by metastatic disease. Lungs, subcutaneous tissue, bones (primarily the spine), lymph nodes, brain and adrenal glands are the other places affected by metastases (24,27).

In contrast to statements in the literature that gastric metastases are late, i.e. disseminated stage of the disease of the patient, these two patients had metastases in the stomach without disseminated metastases in other organs (19).

### Conclusion

Metastatic melanoma of the gastrointestinal tract should be suspected in any patient with a history of malignant melanoma and the new gastrointestinal symptoms. Diagnosis requires careful endoscopy and mucosal inspection for the metastatic lesions. If there are negative endoscopic findings, i.e. if metastases of malignant melanoma are present with transmural localization, radiological methods are necessary: CT, NMR, especially ultrasonographic gastroscopy.

Because of the similarity of certain common histopathological types of malignant melanoma, primarily achromatic with the types of primary gastric cancer and accurate differential diagnosis, the following immunohistochemical studies are needed: Melan A and S-100 protein (markers of malignant melanoma), as well as mucins: MUC5AC, MUC2 and CDX2 (markers of different types of primary gastric carcinoma). Surgical intervention for patients with metastatic malignant melanoma of the stomach can significantly alleviate the pain and other symptoms, improve quality of life and may allow better survival of these patients.

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## RETKE METASTAZE MALIGNOG MELANOMA

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Melanomi su maligne neoplazme koje vode poreklo od melanocita. Najčešći su na koži i sluzokoži. Horoidalni melanomi se prilično razlikuju od kožnih melanoma u odnosu na prezentaciju, metastaze koje daju i način lečenja.

Saopštavamo dva slučaja metastaza u želucu malignog melanomom oka i kože, sa osvrtom na literaturu. Prvi slučaj je žena, starosti 23 godine, kojoj je rađena gastrektomija 22 meseca nakon enukleacije oka zbog malignog melanoma horoidee. Drugi slučaj je muškarac, 72 godine starosti, operisan od malignog melanoma kože čela 28 meseci pre oftalmološkog pregleda. Parafinski preseci debljine 4 µm bojeni su klasičnom HE metodom, kao i imunohistohemijskom DAKO APAAP metodom, korišćenjem specifičnog S - 100 antitela i Melan A antitela.

Želudac se smatra retkim mestom za razvoj metastaza. Metastaze u želucu su često ograničene na submukozu i serozno-mišićne slojeve, što je istaknuto i kod jednog našeg bolesnika. Na metastatski melanom gastrointestinalnog trakta treba posumnjati kod svakog bolesnika sa istorijom malignog melanoma i novim gastrointestinalnim simptomima. Zbog česte patohistološke sličnosti pojedinih tipova malignog melanoma sa tipovima primarnog karcinoma želuca, neophodna su sledeća imunohistohemijska ispitivanja: Melan A i S- 100 protein (markeri malignog melanoma), kao i mucini MUC5AC, MUC2 i CDX2 (markeri različitih tipova primarnog želudačnog karcinoma). *Acta Medica Medianae 2014;53(3):58-62.*

**Ključne reči:** *maligni melanom, metastaze, lokalizacija, histopatologija, imunohistohemija*