



Malignant melanoma metastasis in the ileum – two case reports

Metastaza malignog melanoma u ileum

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Abstract

Introduction. Malignant melanoma is a tumor that develops from melanocytes, so this type of tumor can occur in any part of body containing the cells. Melanoma is less common than other skin tumors. It is very aggressive type of skin tumor with very early metastases and accounts for 75% of cases of death due to skin tumor. In the initial phase the tumor growth is horizontal. Early detection of changes is very important. Over time, as the tumor gets the vertical growth phase, occurrence of metastases depends on the depth of invasion (Breslow). Malignant melanoma metastasizes to regional lymph nodes, but also in the liver, lung, brain and almost any place that can be populated by the hematogenous route. **Case report.** We reported two cases of patients who were urgently surgically treated in the Emergency Center of Vojvodina, Serbia, with the clinical signs and symptoms of ileus. In both cases, the ileum resection was performed with terminal ileostomy. Histological analysis was performed and through morphology and immunohistochemical profile, in both cases, the diagnosis was metastatic malignant melanoma in the ileum. **Conclusion.** In patients with diagnosed malignant melanoma of the skin with symptoms of abdominal pain and/or anemia, application of modern imaging techniques is imperative in order to obtain an early diagnosis of gastrointestinal metastases of this tumor, because the rapid detection and radical resection may contribute to the overall survival of these patients.

Key words:

diagnosis; immunohistochemistry; ileus; melanoma; neoplasm metastasis; surgical procedures, operative; treatment outcome.

Apstrakt

Uvod. Maligni melanom je tumor koji se razvija od melanocita, ćelija koje proizvode pigment melanin, te se ovaj tip tumora može razviti u bilo kom delu tela koji sadrži ove ćelije. Melanom je ređi od drugih tumora kože, ali predstavlja uzuzetno agresivan tip tumora kože koji vrlo rano daje metastaze i pripisuje mu se oko 75% slučajeva smrtnog ishoda zbog tumora kože. U početnoj fazi tumor ima horizontalan rast, te je vrlo značajno što ranije dijagnostikovanje promene. Vremenom tumor dobija i vertikalnu fazu rasta, te upravo od dubine invazije (Breslow) zavisi pojava metastaza. Tumor metastazira ne samo u regionalne limfne čvorove, već i u jetru, pluća, mozak i skoro svako mesto koje može biti naseljeno hematogenim putem. **Prikaz bolesnika.** U radu su prikazana dva bolesnika koja su hitno hirurški zbrinuta u Urgentnom centru Vojvodine zbog kliničkih simptoma i znakova ileusa. U oba slučaja urađene su resekcije ileuma sa terminalnom ileostomijom. Učinjena je patohistološka analiza i na osnovu imunohistohemije i morfološke slike u oba slučaja je postavljena dijagnoza metastaze malignog melanoma u ileum. **Zaključak.** Kod bolesnika kojima je dijagnostikovani maligni melanom kože sa simptomima bolova u stomaku i/ili anemijom, primena modernih imidžing tehnika je imperativ u cilju postavljanja rane dijagnoze gastrointestinalnih metastaza tog tumora. Brza detekcija i radikalna resekcija mogu doprineti dužini preživljavanja ovih bolesnika.

Ključne reči:

dijagnoza; imunohistohemija; creva, opstrukcija; melanom; neoplazme, metastaze; hirurgija, operativne procedure; lečenje, ishod.

Introduction

Malignant melanoma is a tumor that develops from melanocytes, so this type of tumor can occur in any part of

body containing the cells. Melanoma is less common than other skin neoplasm, but it is the most serious type of skin tumor and accounts for 75% of cases of death due to skin tumors. This neoplasm is more common in people whose

family history provides information about the existence of skin tumors^{1, 2}, prominent moles, astrocytoma, pancreatic cancer, changes in previously normal naevus, as well as information about exposure to the sun, especially early in life. In females, the most common localization of melanomas are legs, while in men those are usually present on the back^{3, 4}. Melanomas of the skin are usually clinically asymptomatic, but the most important clinical signs are change in color or size of pigmented lesions. The main clinical warning signs we can see using alphabet of melanoma – Asymmetry, Border (edges), Color, Diameter (≥ 6 cm), Evolution⁵. There are four basic types of the growth of malignant melanoma: the superficial spreading malignant melanoma (in about 75% of cases), nodular melanoma, lentigo malignant melanoma and acral lentiginous melanoma⁶. It is crucial to detect this change in the early phases of melanoma. Malignant melanoma shows the initial inclination of the radial growth. Radial growth is horizontal growth within the dermis (*in situ*) and the superficial layers of the dermis when the cells have the ability to metastasize and there is no evidence of angiogenesis^{7, 8}. Over time, the growth acquires a vertical component, melanoma grows down into the deeper layers of the dermis^{7, 8}. Based on the thickness of the invasive vertical growth phase measured in millimeters is what determines the likelihood of metastasis. According to the Breslow there are five stages of depth of malignant melanoma in the skin: stage I - depth is less or equal of 0.75 mm; stage II - depth is between 0.76–1.5 mm; stage III - depth is between 1.51–2.25 mm; stage IV - depth of tumor is between 2.26–3.0 mm; stage V - depth is greater than 3 mm⁹. Other indicators of metastatic potential are density of lymphatics, the number of mitosis and ulceration over the tumor. The tumor metastasizes to regional lymph nodes, but also in the liver, lung, brain and almost any place that can be populated by the hematogenous route¹⁰. Treatment of malignant melanoma is a surgical removal of the tumor. Sentinel lymph node biopsy provides additional information about the biological aggressiveness of the tumor^{11, 12}. According to international guidelines histopathological analysis of the sentinel node (the first lymph node on the way of lymph after tumor) helps in decision to avoid early unnecessary elective lymphadenectomy. Early elective lymphadenectomy did not show better survival after surgery of malignant melanoma, but surely it can make a patient mo-

re difficult to recover^{13, 14}. Although most of the lesions occur in the skin, they can also be found in other rare localities, including oral genital mucosa, esophagus, meninges, eye, etc. If the tumor is smaller and comprises a thin layer of skin, by surgical removal of the tumor, chances for cure are definitely great. Since the probability of the recurrence of malignant melanoma depends on the depth of invasion of cancer cells (in such cases they are also spread), the treatment includes surgical removal of the tumor, as well as chemotherapy, radiotherapy and immunotherapy^{3, 4}.

Case report

Case I

Male patient, aged 43, was presented in the Emergency Room of Vojvodina, Serbia with the clinical picture of ileus. The patient had abdominal pain and bloating feeling, lack of gas and stool for a period of 4 days, and repeatedly vomited. He denied other symptoms, as well as diseases of the importance of heredity. After clinical examination, laboratory and radiological examinations, the ileus diagnosis was made, and urgent surgical treatment was indicated. The Laboratory of the Centre for Pathology and Histology received the surgical specimen. Small bowel length of 20 cm, on which the mucosa was changed in size 5 x 3 x 1 cm, dark brown, with wide base attached to the intestinal mucosa (Figure 1).

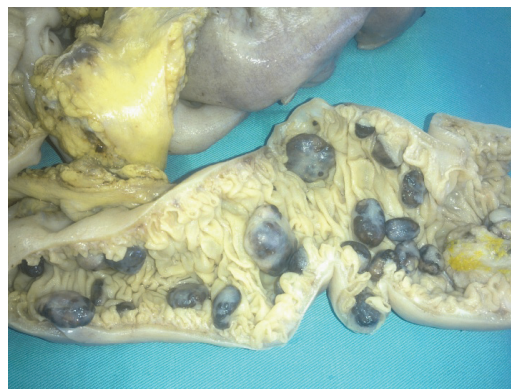
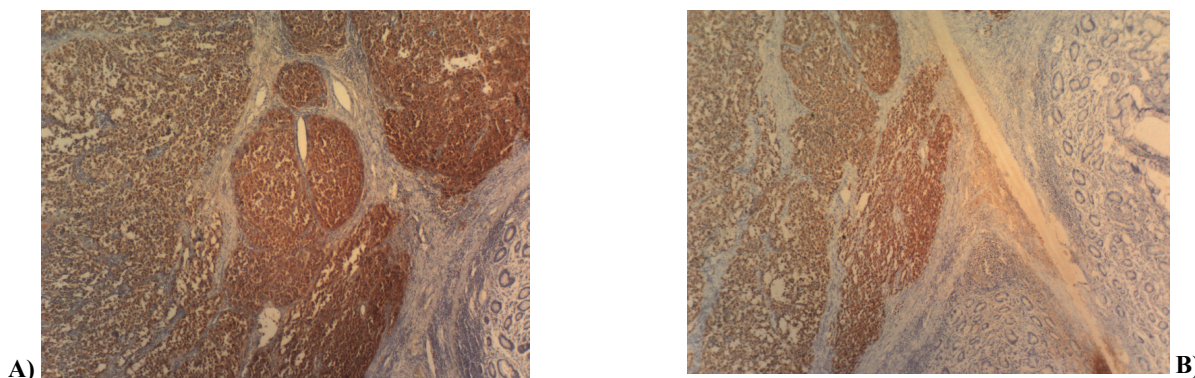


Fig. 1 – Macroscopic appearance of changes in the small intestinal mucosa (the first patient).



**Fig. 2 – Immunohistochemical examination of the surgical specimen (the first patient):
A) S100; $\times 100$; B) HMB45 stain, $\times 400$**

Detailed histopathological examination verified the polygonal and spindle cells hyperchromatic and vesicular nuclei, prominent acidophilic nucleoli in places, medium abundant acidophilic cytoplasm arranged in solid beach and partly in the swirling structure with fibrotic-vascular stroma. Described tumor infiltrating all layers of the wall of the ileum extending to the surrounding connective and fatty tissue, and in some places were present areas of necrosis. Special immunohistochemical stainings were made: S-100 + (Figure 2A), Melan A +, HMB + (Figure 2B), AE1/AE3 -, Desmin -, Vimentin + / -, and based on histological and immunohistochemical description of the tumor, the diagnosis of metastatic malignant melanoma in the ileum was made. In the examined lymph nodes, which were received with a portion of the small intestine, the reactive changes were found.

Case II

The patient, aged 34 years, was admitted in the Emergency Room of Vojvodina, Serbia with abdominal pain which lasted for a month. Disease history stated that there was a surgery of malignant melanoma on his right hand when metastases in the lymph nodes were found. He denied the existence of diseases of importance to heredity. Having applied clinical, laboratory and radiological examinations,

the patient was hospitalized in the Semintensive Department of Emergency Room (ER) of Vojvodina with clinical signs of ileus. The Laboratory of the Centre for Pathology and Histology received the surgical specimen. Small bowel length of 25 cm, on which the mucosa had vegetative change dimensions 6 x 3 x 5.5 cm, of a yellowish color, which impressed on the serial sections that infiltrated the intestinal wall. By detailed histopathological examination of preparations, atypical polygonal and round cells were observed with hyperchromatic and vesicular nuclei, some bizarre-looking with two nucleoli and in places with prominent acidophilic nucleoli. Tumor cells were spread into the alveolar structure, papillary formations and the less solid beaches, whereby the surface of the tumor was mainly ulcerated and permeated with necrotic tissue. The tumor stroma was abundant and connective-vascular. Tumor infiltrated the mucosa, submucosa, and muscle layer of the wall of the small intestine. Special immunohistochemical stainings were made: Vimentin + + Melan A + (Figure 3A), HMB45 (Figure 3B), CK7 -, CK20 -, AE1/AE3 -, S100 + (Figure 3C), Tropomyozin -, Desmin -, and diagnosis of metastatic melanoma in the small intestine was made. In the examined lymph nodes, which were received with a portion of the small intestine, the reactive changes were found.

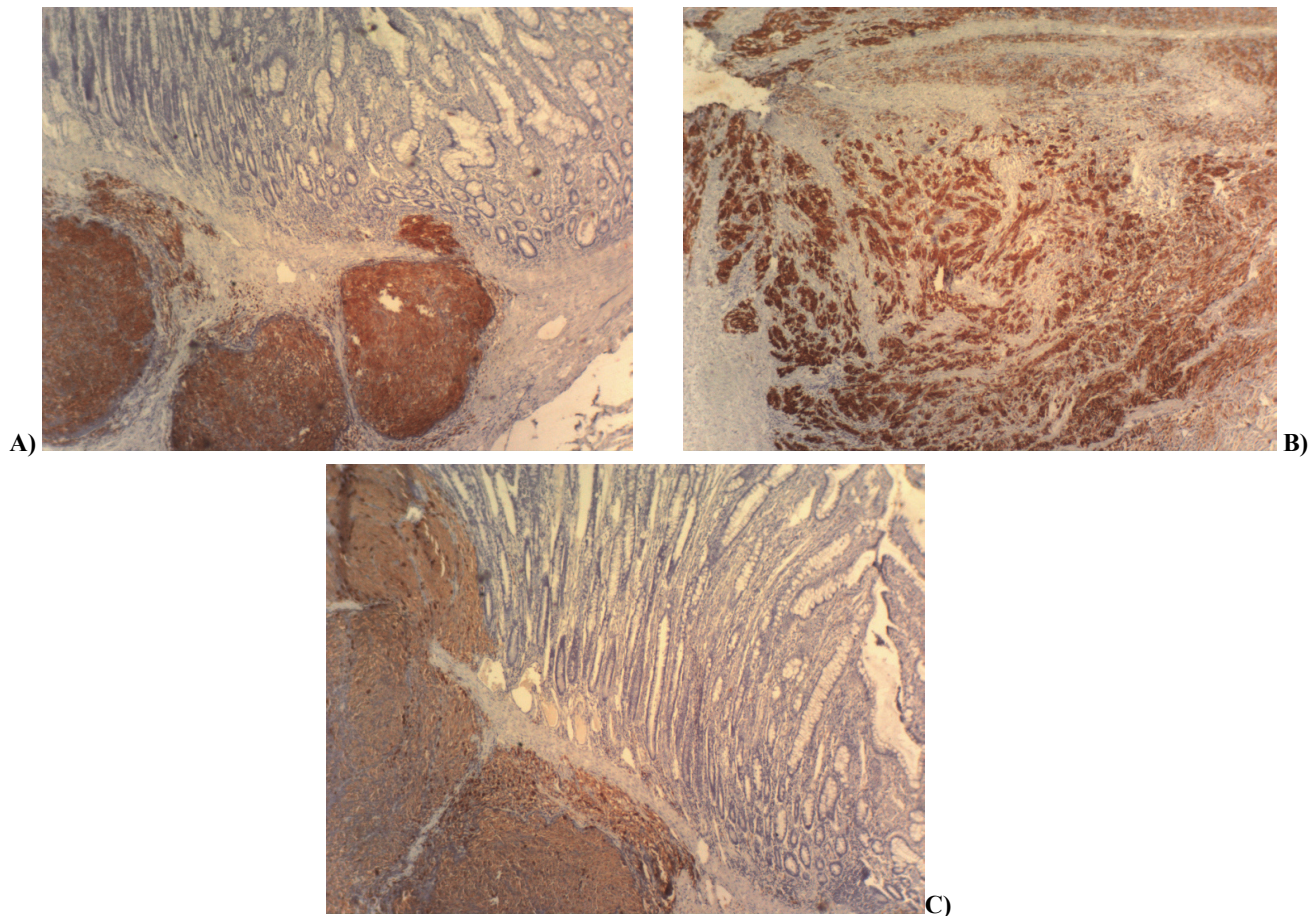


Fig. 3 – Special immunohistochemical stainings of the surgical specimen (the second patient):
A) Melan A stain, ×400; B) HMB45 stain, ×400; C) S100 stain; ×400.

Discussion

Primary malignant melanoma of the gastrointestinal tract is extremely rare, compared to the metastasis of this tumor in the small intestine¹⁵. Malignant melanoma counts 1% to 3% of all malignant lesions of the gastrointestinal tract¹⁶, and as noted above, the majority of these tumors are metastatic spread of the primary tumor, mainly from the skin, but can also have the origin from the retina, the anus or nail plate¹⁷. Routine barium mash-ray examination and computed tomography (CT) examinations have limited options, but fluorodeoxyglucose (FDG) positron emission tomography (PET) CT imaging can demonstrate the existence of metastatic malignant melanoma in the small intestine. PET CT imaging is highly sensitive identification of changes in human body which is carried out by measuring the biochemical activity of tumor cells that is extremely high in malignant tumors. Metastatic disease may be suspected in all patients with gastrointestinal complaints and a personal history of previous treatment of malignant melanoma of the skin¹⁵. The period between diagnosis of primary malignant melanoma and identification of metastases in the gastrointestinal tract varies from 2 to 180 months, and most of them are the findings at the autopsy¹⁸. Melanoma of the small intestine is often asymptomatic. If there are symptoms, they could be vague and nonspecific, and may be very different – from chronic pain in the abdomen (17%–64%), the occult or manifest bleeding (26%–84%) and body weight loss (10%–47%)¹⁸. As a nonspecific clinical picture, it is necessary to exclude other causes of abdominal discomfort for the safety of diagnosing metastases of malignant melanoma. Sometimes, melanoma of the small intestine is manifested with the clinical picture of the emergency state due to intestinal obstruction or intussusceptions and, rarely, intestinal perforation. Up to now only six cases of the intestinal perforation and metastases of malignant melanoma have been described^{19–23}, and 20 cases of minor intussusceptions of the small intestine²⁴. Metastatic malignant melanoma is usually polypoid, multinodular, and depending on the size can cause obstruction, as in our case. The primary localization is most common previously diagnosed skin lesion. In 4%–12% of the intestinal metastasis of melanoma, it is impossible to determine the nature and localization of primary lesion²⁵. Gutman et al.²⁶ published a study of indications for surgical treatment of metastatic malignant melanoma of the gastrointestinal tract. Half of the patients in this study were considered for elective

surgical treatment, and 22% of patients required urgent surgical treatment for intestinal obstruction or overt gastrointestinal bleeding. Olila et al.²⁷ have published the results of their research which show statistically significant prolongation of survival in surgically treated patients particularly those who had complete resection. Surgical treatment provides better survival compared to pharmacological or palliative ones^{24–31}. Kadakia et al.³² published the results of studies in which 70% of anemia were present, as well as acute bleeding from the upper gastrointestinal tract, which was present in 50% of observed cases with metastasis of malignant melanoma in the gastrointestinal tract, while the others registered abdominal pain (60%), intestinal obstruction (47%), nausea and vomiting (41%), and gastrointestinal bleeding (30%). Abdominal masses were recorded in only 10% of patients. The histological picture of malignant melanoma showing different relations of spindle cells and areas of epithelial proliferation with large nuclei and abundant eosinophilic cytoplasm³³. Tumor cells may indicate melanin pigment within the stromal macrophages, but they can be completely amelanotic. Immunohistochemical staining for melanoma that does not depend on the melanin pigment includes: vimentin, S 100 protein and the more specific HMB 45 and melan A. Melan A antibody is high specific for melanocytic tumors in the skin, with positivity in benign and malignant tumors, but in neoplasm in intestine it shows high specificity for malignant melanoma. In patients who died due to metastatic spread of melanoma the intestinal metastases were found in 43.5% to 86.3% of the cases.

Conclusion

Primary malignant melanoma of the small intestine occurs rarely. It is always metastatic lesion of treated or untreated skin melanoma. Diagnosis is often very late set, and these patients are considered for urgent surgical treatment. Due to high incidence of gastrointestinal metastases in patients with a personal history of malignant melanoma of the skin, manifested as abdominal pain and/or anemia, the use of modern imaging techniques is imperative in order to obtain an early diagnosis of gastrointestinal metastases of this tumor and timely undertake radical surgical resection in order to improve overall survival in this group of patients. Among diagnostic methods, histopathological analysis is golden standard in diagnosis of malignant melanoma.

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