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Laparoscopic Treatment of Primary Colon
Melanoma: A Case Study

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Financial support: This research was supported by University Hospital "Sofiamed"- Sofia and Institute of Biophysics and Biomedical Engineering – Bulgarian Academy of Sciences
Conflict of interest: None declared**Patient:** Female, 35-year-old
Final Diagnosis: Primary melanoma of the descending colon
Symptoms: Nausea without vomiting, abdominal swelling and pain, difficult and irregular defecation
Clinical Procedure: —
Specialty: Laboratory Diagnostics • Gastroenterology and Hepatology • Oncology • Surgery**Objective:** Rare disease**Background:** Gastrointestinal tract melanomas are usually of metastatic origin, with primary melanomas being relatively rare. Controversy arises about the existence of primary melanoma in the gastrointestinal tract except in areas where melanocytes exist. The appearance of primary colon melanoma is rare due to the embryological absence of melanocytes in the large intestine, with some authors denying its existence at all.**Case Report:** We present a clinical case of a female patient with a primary melanoma of the descending colon. The patient came to the clinic with nausea without vomiting, abdominal swelling and pain, difficult and irregular defecation, and data on a tumor process of the left colon from the performed colonoscopy. Laparoscopic left hemicolectomy with lymphatic dissection was performed. The conclusion to be drawn from histological results was that the malignancy is poorly-differentiated adenocarcinoma. However, the immunohistochemical examination showed colon melanoma. Postoperative complete dermatological and ophthalmic examinations showed no evidence of a cutaneous or an ocular primary lesion, so we decided that this could be a primary colon melanoma.
Conclusions: Because of the colonoscopy we were able to make a detailed histological examination of the tumor, which allowed us to differentiate it from common colon adenocarcinomas. Surgical treatment is important in the removal of the primary tumor. The method of choice, with excellent postoperative results, is laparoscopic left hemicolectomy with selective cut-off of the colic vessels at the site of separation and removal of the affected segment together with the mesentery-bearing regional lymphatic basin.**Keywords:** Nevi and Melanomas • Histology, Comparative • Colorectal Surgery • Colonoscopy
Abbreviations: MUP – melanoma of unknown primary; ENT – examination-inspection of the face, ears, nose, throat and neck; GIST – gastrointestinal stromal tumor; EPMNST – epithelioid malignant peripheral nerve sheath tumor; CT – computed tomography; CEA – carcinoembryonic antigen; CA 19-9 – carbohydrate antigen; PET/CT – positron emission tomography/computed tomography; HPF – high-power field**Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/938914> 1826 — 4 23

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1 Background

Skin melanomas are the most common of all melanomas, followed by ocular forms, leptomeninges melanoma, oral cavity, nasal mucosa, pharynx, bronchi, esophagus, vaginal, and ano-rectal mucosa [1]. Only 20% of non-cutaneous melanomas are of mucosal origin, representing 3-4% of all melanomas per year [2]. However, the appearance of primary colon melanoma is extremely rare due to the embryological absence of melanocytes in the large intestine [3], and some authors deny its existence.

The existence of potentially metastatic colon melanoma with an unclear primary lesion – melanoma of unknown primary (MUP) – can be explained by the tumor regression model. The regression theory first proposed by Smith and Stehlin in 1965 attributes the disappearance of primary melanoma to spontaneous regression after metastasis has occurred [4]. Changes in immunological status, such as infection or pregnancy, may be associated with spontaneous regression of melanoma at its primary site. A study of 437 skin melanomas showed that 12.3% had at least partial regression [5], but total regression of melanomas is rare.

The occurrence of primary colonic melanoma can be explained by the following factors. The cells developed from neural crest during embryogenesis are common in the intestine, but factors released from branchial arches deprive these cells of potential melanocyte differentiation. This explains why the colon is a rare site for primary melanoma [6]. The possible origin of primary colon melanomas may include the concept of ectodermal differentiation, such as the ability of ectodermal cells to differentiate into multiple cell lines and to migrate into the colon during embryogenesis [7]. Ductus omphaloentericus may provide a potential pathway for the transfer of such cells [8]. This process may be associated with the migration of melanoblasts from the anal region to the distal colon, and primary stem cells located in the intestinal wall may initiate the development of heterotropic melanocytes in the colon [9]. Another argument is that apparently unrelated endocrine cells might be responsible for the development of primary colon melanoma, because they can differentiate into melanocytes [10]. Despite these different hypotheses, the true pathogenetic cause of melanocytes arising in the intestinal wall remains unclear.

When a seemingly primary melanoma is found in an atypical site, such as the colon, extensive clinical examination should be performed to rule out the possibility of metastatic disease. First, skin and eye forms, which are most common, should be excluded. Gynecological examination, proctoscopy, ENT examination, and ophthalmologic examination should be used if diagnostic ambiguities are present. However, there are no firm recommendations for the routine application of all the studies mentioned. Compared to metastatic colonic melanoma, primary

melanoma is more difficult to diagnose due to the absence of anamnestic data. Colonoscopy is a very safe method with high sensitivity and specificity for diagnostics of different colon malignancies, including colon melanoma. Moreover, it allows histological confirmation of the diagnosis [11].

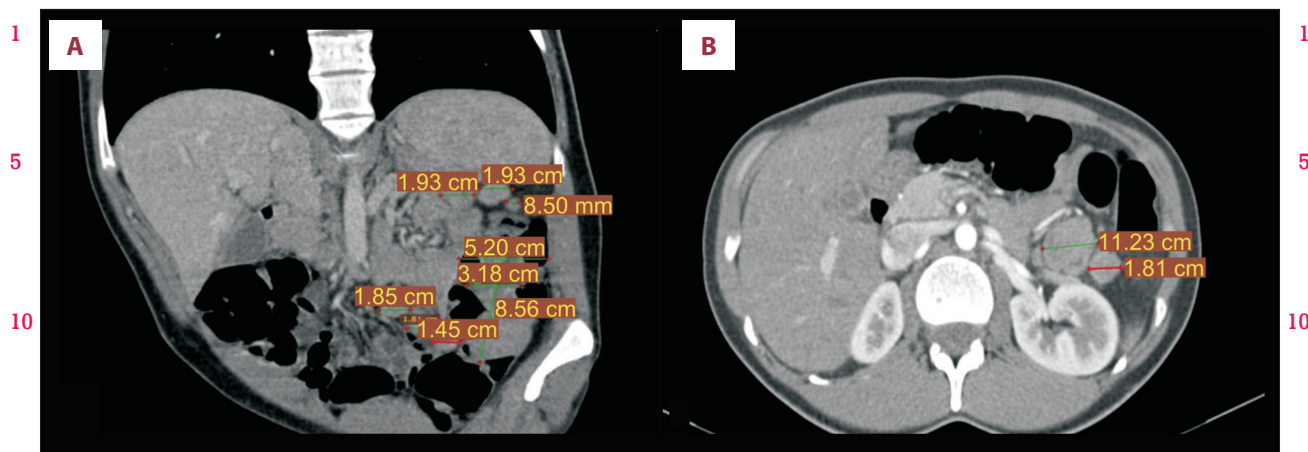
Histopathologically, melanoma tumor cells are represented by varying ratios of epithelioid zones and spindle cell zones. Cells may show either an abundance of melanin pigment or be completely amelanotic [12]. The use of immunohistochemical dyes can help with diagnosis. Immunohistochemical examination showed that most melanoma cells are positive for S-100 protein (highly sensitive for melanocytic differentiation), HMB-45, Melan A, vimentin, CD38, and Ki-67 (which suggests a mitotically active tumor). S-100 is sensitive to the detection of melanomas with 90% sensitivity. HMB-45 is also a specific marker for demonstrating this neoplasm, but may be negative for undifferentiated amelanotic neoplasms [12].

Nevertheless, there are 3 major nosological units that show histological and immunohistochemical similarities to colon melanoma: 1) A gastrointestinal stromal tumor (GIST) that can positively be labeled for S-100 in up to 10% of cases may be mistaken for melanoma. In turn, up to 55% of melanomas are capable of being positive for CD-117, which is a specific GIST marker [13,14]. 2) Confusion can also occur with soft-tissue sarcoma, which, like melanoma, can positively affect S-100. If in doubt, their histological views should be compared, which is usually sufficient to distinguish these 2 malignancies. 3) Epithelioid malignant peripheral nerve sheath tumor (EPMNST), which shows diffuse S-100 positivity, can also be mistaken with melanoma diagnosis [13].

Aggressive surgical resection is considered the criterion standard treatment of most melanomas that do not have dissemination data at diagnosis. There are suggestions that surgery not only decreases the overall tumor heaviness, but also decreases the extent of immunosuppression, allowing anti-tumor immunity to develop [15]. This may be followed by adjuvant radiation, chemotherapy, and immunotherapy at persistence or positive nodal status [16,17]. Surgical intervention may be warranted even with metastatic bowel melanoma, as it is not only palliative but may also affect long-term prognosis [17,18]. Up to 80-90% of incurable gastrointestinal melanoma cases experience symptomatic improvement after palliative resection [11].

Case Report

A 35-year-old female patient, without concomitant diseases, was admitted to the clinic with abdominal pain (more in the lower abdominal floor and left abdominal half), with nausea



15 Figure 1. Preoperative CT – (A) – frontal reconstruction. Polypoid formation, obturating to a significant extent the lumen of the intestine with a length of 8.56 cm. Enlarged mesenteric lymph nodes; (B) – transverse reconstruction. Polypoid formation, obturating to a significant extent the lumen of the intestine with a diameter of 3.23 cm. Enlarged mesenteric lymph node.

but no vomiting. She reported weight gain and swelling of the abdomen for several months, but within days these intensified. For this reason, a computed tomography (CT) scan of the pelvis (Figure 1A) and abdomen (Figure 1B) was performed, in which a tumor formation of the descending-sigma transition and locoregional lymphadenomegaly was established. A polypoid neoplasm was detected at 65 cm from the linea ano-

rectalis by the performed fibro-colonoscopy, preventing the apparatus from passing proximally. The biopsy taken in the study showed necrotic fragments with leukocyte infiltration.

Unfortunately, the paraclinical picture showed no significant deviations from the norm, and the tumor markers specific carbohydrate antigen 19-9 (CA 19-9) and common carcinoembryonic antigen (CEA) were within the reference range. The patient was prepared for surgery. Pneumoperitoneum was established with a Veress needle. We placed the working trocars. During revision of the abdominal cavity, the following was found. Tumor formation of the large intestine was down to 6-7 cm after the left flexion, measuring about 7-8 cm, with non-infiltrating serosa of the intestine. Regional enlarged lymph nodes were found, single and in groups. The rest of the abdominal organs were normal. A left hemicolectomy was performed according to a standard technique without intraoperative complications. The postoperative period went smoothly, without complications. The patient was fed and moved on time and discharged on the 7th day after surgery.

No evidence of residual metabolically active tumor on whole-body positron emission tomography/computed tomography (PET/CT) was detected 30 days after (Figure 2).

Histological examination revealed infiltration of the colon wall to the submucosa by diffusely proliferating epithelioid-like

neoplastic cells with moderate atypism, pink, rarely light cytoplasm, and large vesicular nuclei with protruding nucleoli. Up to 3 mitotic figures were found per field (50x high-power field (HPF) microscopy) (Figure 3).

The resection lines were free of tumor invasion. In 13 of the 19 lymph nodes examined, macrometastases from the same tumor were found. The staging of the tumor was as follows: pT1; N2; M0; G3 (the staging was consistent with cutaneous melanoma). Due to doubts about the type of formation, additional immunohistochemical and genetic studies were performed.

Immunohistochemical examination revealed evidence of heterogeneous malignant melanoma: Melan A Clone A 103 – (1+) weakly positive (Figure 4A); Melanosome Clone HMB 45 – (2+) moderately positive (Figure 4B); S 100 – (2+) moderately positive (Figure 4C); Ki-67 – (1+) 15% weakly positive (Figure 4D); and PD-L1/22C3 – weakly positive 8% (Figure 4E). Negative markers tested were Cytokeratin AE1/AE3, Cytokeratin7, MUC2, Desmin, CD8, CD45, CD68, CD117, DOC1, CD34, Chromogranin A, NSE, and Synaptophysin (results not shown).

Materials for analysis were sent to Gratz Medical University. The analysis was carried out using next-generation sequencing on an Ion Torrent Sequencer (Thermo Fisher Scientific) using the Core cancer panel V10. The following mutations were analyzed: *KRAS* (G12, G13, A59-Q61, K117, A146), *NRAS* (G12, G13, A59-Q61, K117, A146), *HRAS* (G12, G13, A59-Q61, K117, A146), *BRAF* (exon 11 and D594-K601), *KIT* (exon 8, 9, 11, 13, 17, 18, 20), *PDGFRA* (exon 12, 14, 18), *JAK2* (V617, exon 14 and 12), *MYD88* (L265), *MPL* (W515), *CALR* (exon 9), and *CSFR3* (T618). No mutations in any of the above genes were found in the tissue examined.

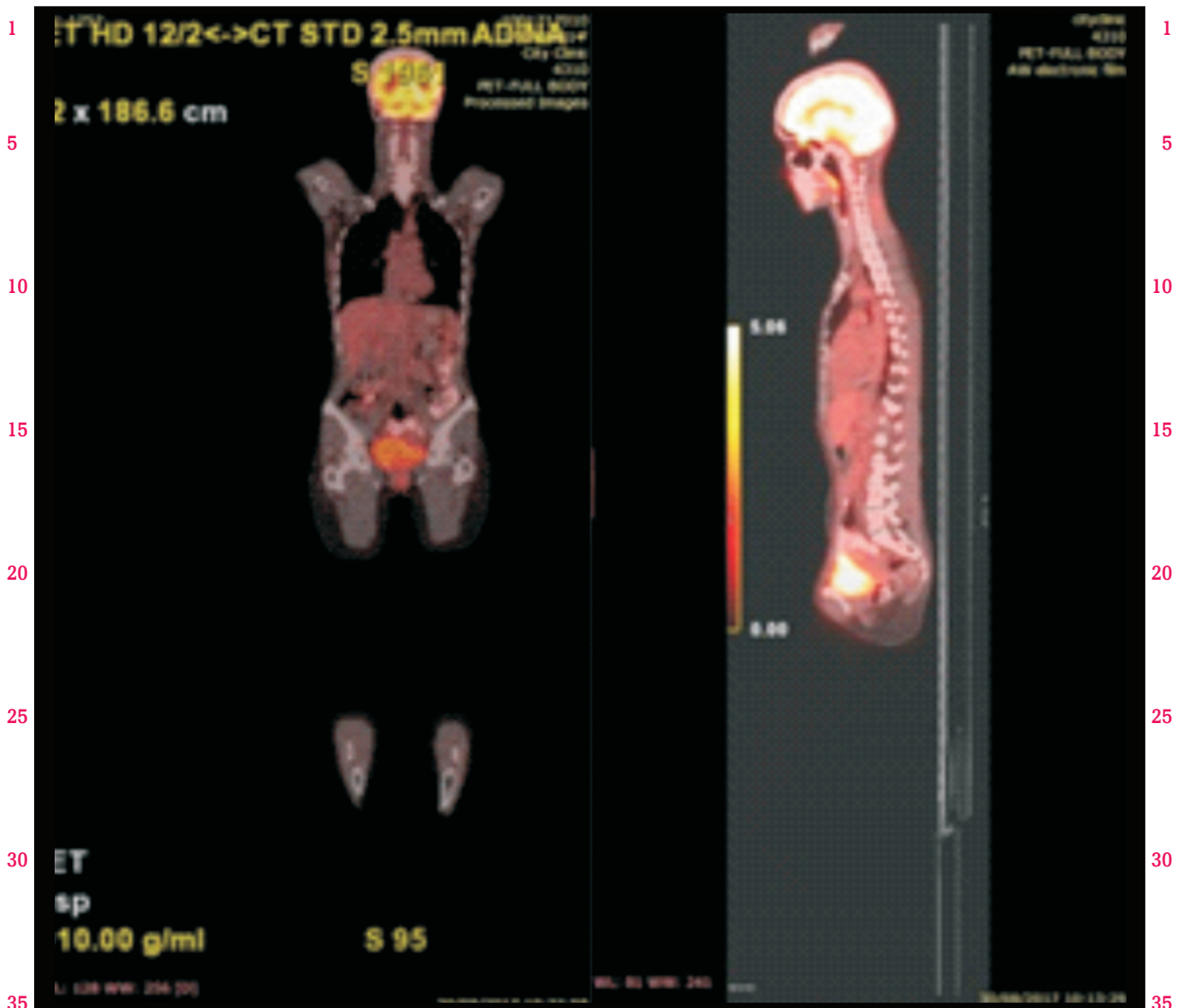


Figure. 2. Postoperative PET/CT.

In addition to the clinical evidence, it is relevant that the patient's father died of malignant melanoma.

Discussion

The medical database in PUBMED describes only 17 cases of primary colonic melanoma to date, its clinical manifestations, diagnosis, and treatment [19,20] (including these 2 publications). According to a recent publication of Endo et al in 2021, the number of published cases increased up to 37. Nevertheless, cases of primary melanoma of the colon account for only 0.9% of all gastrointestinal primary melanomas [21]. Because of this rarity, there are no criteria developed for diagnosing primary colonic melanoma, and we used 6 criteria developed for primary bronchial mucosal melanoma diagnostics: 1) the lesion

must be solitary in the surgical specimen; 2) there must be no previously excised skin melanoma; 3) no previous or concurrent ocular tumor is present; 4) the morphology must be compatible with that of a primary tumor; 5) there must be no other demonstrable melanoma at the time of surgical exploration; 6) the findings should be confirmed by a careful autopsy for patients who died of the disease [22]. The melanoma of our patient met 5 of the 6 criteria, as the sixth one can only be applied postmortem.

After histological examination, an initial working diagnosis of colon adenocarcinoma was made. After a more detailed immunohistochemical study, the neoplasm was found to be positive for Melan A, HMB 45, and S-100, which are characteristic markers of melanoma; therefore, the diagnosis was changed to heterogeneous malignant melanoma. GIST was rejected because

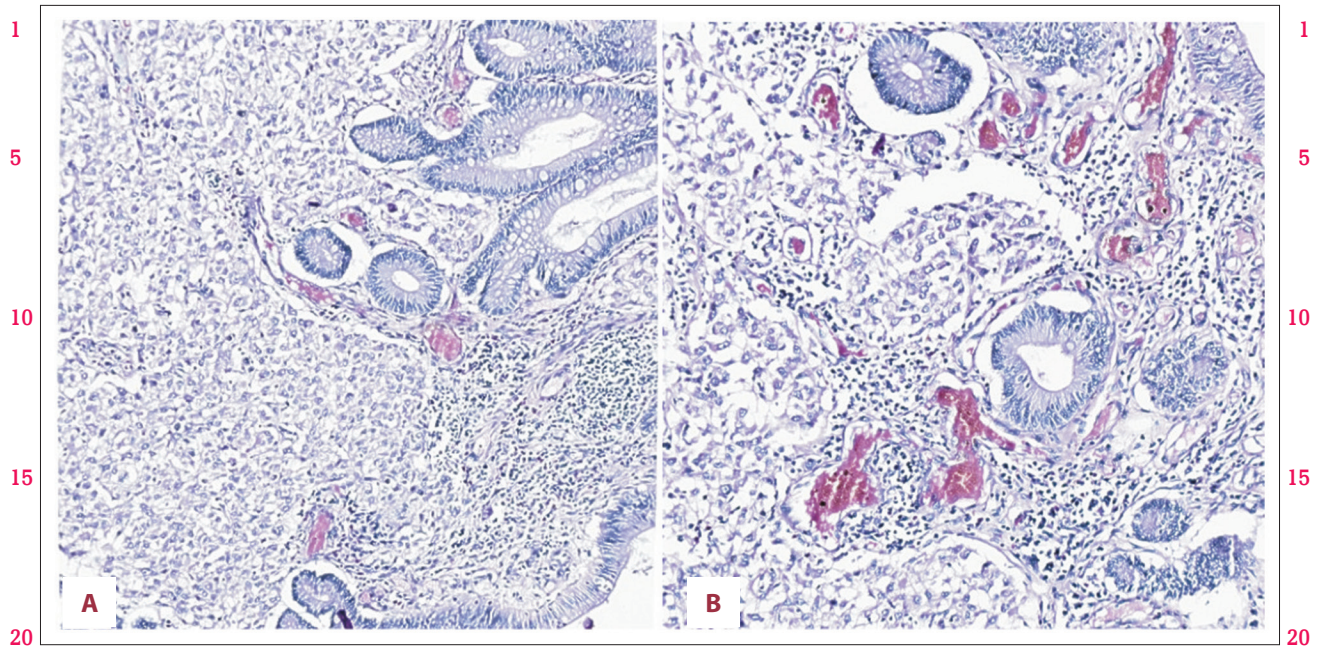


Figure 3. Representative image of hematoxylin and eosin staining of the tumor (scanning microscopy). (A, B) Stromal infiltration of polygonal tumor cells with pronounced cohesion, invading the colorectal mucosa.

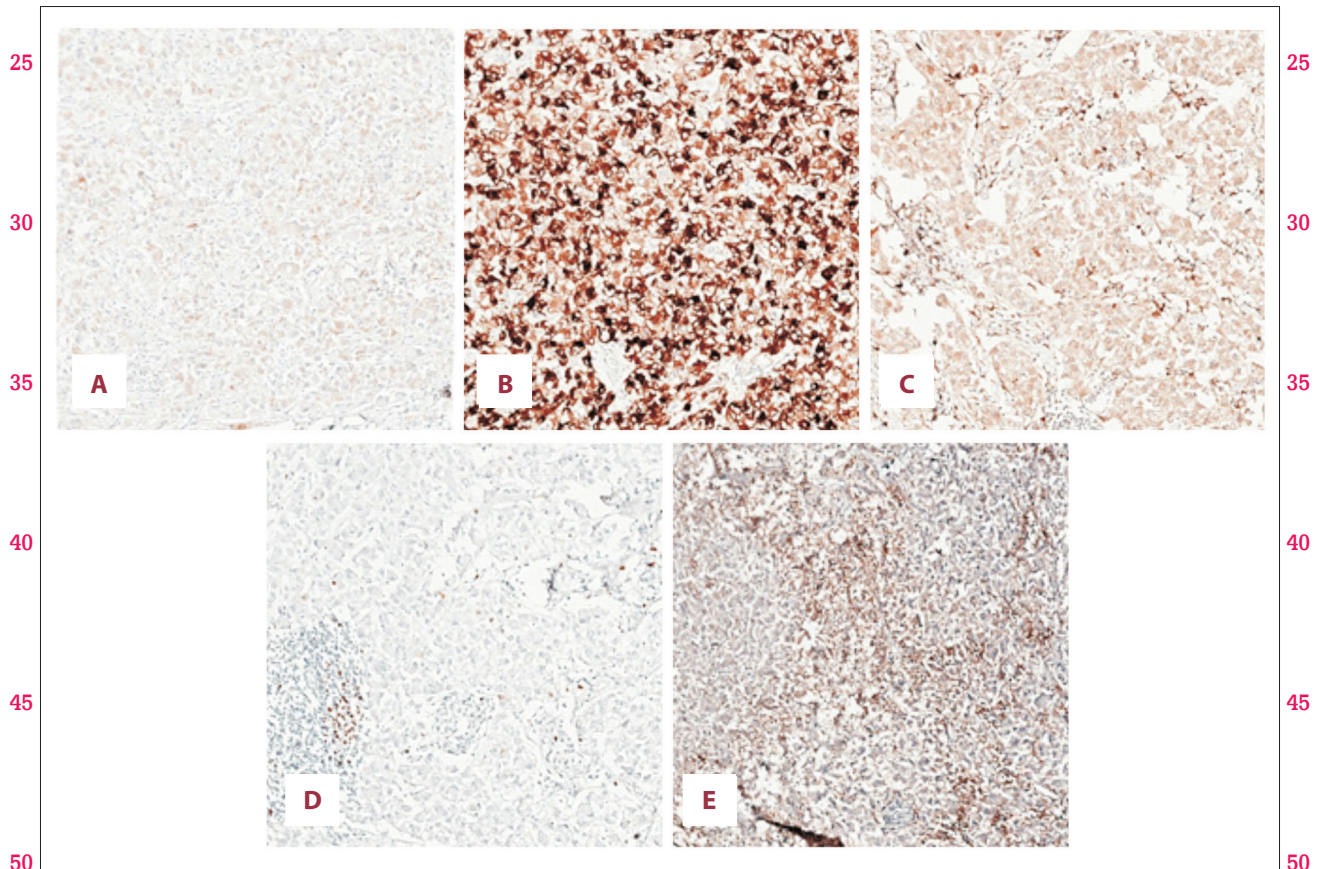


Figure 4. Immunohistochemical examination of a material taken from the formation of the colon during colonoscopy (paraffin block № 11256/17). (A) Cells are stained for Melan A; (B) cells are stained for HMB 45; (C) cells are stained for S 100; (D) cells are stained for Ki-67; (E) cells are stained for PD-L1.

1 of the negative staining for CD 117, and soft-tissue sarcoma was rejected histologically. Genetic testing did not show mutations characteristic of UVR-sensitive melanomas [23]. All this, as well as a thorough ENT, eye, skin, gynecological, and ano-
5 rectal examination, and the CT, led us to believe that the formation was a primary mucosal melanoma of the colon.

Conclusions

10 In conclusion, it is very important to differentiate gastrointestinal melanoma from other neoplasms. This is the basis of the subsequent adequate surgical treatment, chemo-targeted radiation and immunotherapy. Due to the low incidence of primary
15 melanoma of the colon, there is no established algorithm for treatment of this disease. Documentation and long-term follow-up are needed to assess the safety profile and effect on survival of different therapeutic approaches.

20 The treatment of this disease should be complex, starting with surgical treatment, followed by chemotherapy and hormone therapy.

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Ethic statement

This study was approved by the Ethics Committee of the University Hospital "Sofamed", Sofia, Bulgaria.

Institution Where Work Was Done

The work was done in the University Hospital "Sofamed", Sofia, Bulgaria.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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