—Case Reports—

A Case of Rectal Malignant Melanoma Showing Immunohistochemical Variability in a Tumor

Tomoko Seya[1,2], Noritake Tanaka[1,2], Seiichi Shinji[1,2], Emi Shinji[1,2], Kimiyoshi Yokoi[1,2], Koji Horiba[1,2], Yoshikazu Kanazawa[1,2], Takeshi Yamada[1,2], Yoshiharu Oaki[3] and Takashi Tajiri[1]

[1]Surgery for Organ Function and Biological Regulation, Graduate School of Medicine, Nippon Medical School
[2]Department of Surgery, Nippon Medical School Chiba Hokusoh Hospital
[3]Department of Pathology, Nippon Medical School Chiba Hokusoh Hospital

Abstract

We report on a patient with rectal malignant melanoma. The patient was a 40-year-old man who complained of anal bleeding. His grandmother had died of pancreatic cancer and his mother had been operated for rectal cancer. Physical examination revealed a hard mass at the 12 o'clock position, 2 cm from the anal verge. A colonoscopic examination revealed an irregular surface mass, approximately 4.0 cm in size, located on the anterior wall of the lower rectum. A biopsy of the rectal tumor showed the proliferation of epithelioid cells with pleomorphic features. Immunohistochemical analysis was performed. S-100 protein, CD-56, and KIT expression were positive, but HMB-45 expression was negative. Abdominopelvic computed tomography (CT) revealed multiple liver and lymph node metastases. With the diagnosis of neuroendocrine carcinoma of the rectum, abdominoperineal resection was performed. After the operation, the serum lactate dehydrogenase level had rapidly increased. An abdominal CT showed progressive liver metastases. Thirteen days after the surgery, abdominal angiography was performed, which showed multiple hypervascular tumor stains in the liver. The reservoir was implanted transcutaneously with the aid of angiography and the catheter was fixed to the proper hepatic artery. Neoadjuvant chemotherapy using cisplatin and irinotecan via the subcutaneous reservoir port was performed and a partial response was obtained. However, the final pathological diagnosis of the surgically resected specimen was malignant amelanotic melanoma of the rectum. Immunohistochemical expression differed between rectal biopsy specimens and surgically resected specimens. HMB-45 expression was positive and KIT expression was negative in the resected specimen. As preoperative pathological diagnosis showed rare rectal tumor, we measured the chemosensitivity of the rectal tumor using the collagen gel droplet-embedded culture drug sensitivity test (CD-DST) to determine the most appropriate chemotherapy regimen for the patient. However, there were no anticancer drugs tested by CD-DST for malignant melanoma. With informed consent, the patient received two cycles of immunochemotherapy consisting of dacabazine, nimustine hydrochloride, vincristine sulfate, and interferon -beta. Although the patient was treated with immunochemotherapy for metastatic liver tumor, he died because of progression of metastases.
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Key words: malignant melanoma, rectum, immunohistochemistry, collagen gel droplet-embedded culture drug test

Correspondence to Tomoko Seya, MD, PhD, Department of Surgery, Nippon Medical School Chiba Hokusoh Hospital, 1715 Kamagari, Imba-mura, Imba-gun, Chiba 270–1694, Japan
E-mail: seya@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

Introduction

Anorectal melanoma is a rare tumor with poor prognosis[1–6], which was first reported in 1857 by Moore[4]. Owing to its rarity and histological variability, misdiagnosis as lymphoma, carcinoma, or sarcoma is common[5,6]. Sometimes KIT expression is observed, which may lead to confusion with gastrointestinal stromal tumors (GISTs)[7]. There are few guidelines for the optimal management of anorectal malignant melanoma[2]. The collagen gel droplet-embedded culture drug sensitivity test (CD-DST), which was first developed by Yang et al.[8], has been a useful tool for designing tailor-made chemotherapy regimens[9,10]. Here, we present a case of rectal malignant amelanotic melanoma, which could not be diagnosed preoperatively. Diagnosis was established using surgically resected specimens, which showed immunohistochemical expressions that were different from those of rectal biopsy specimens. CD-DST was performed on surgical specimens, whose results were regrettably not used, because of the lack of tested antimelanoma drugs.

Case Report

A 40-year-old man was admitted to our hospital with the chief complaints of anal bleeding. His grandmother had died of pancreatic cancer and his mother had been operated for rectal cancer. Laboratory data revealed low hemoglobin and hematocrit levels. The serum lactate dehydrogenase (LDH) level was 331 U/L (normal range, 120～245 U/L). The patient's serum carcinoembryonic antigen and CA19-9 levels were normal, but the neuron-specific enolase level was elevated to 16.2 ng/mL (reference range, <10.0). Physical examination revealed a hard mass at the 12 o'clock position, 2.0 cm from the anal verge. Barium enema revealed an irregular mass in the lower rectum. Colonoscopic examination revealed an irregular surface mass of approximately 4.0 cm in diameter, located on the anterior wall of the lower rectum.

Biopsy of the rectal mass was performed and showed the proliferation of round to polygonal cells with large nuclei, and mitotic figures were found with bleeding and necrosis (**Fig. 1a**). Immunohistochemical analyses using cytokeratin, synaptophysin, LCA, HMB45, CD56 and S-100 were performed on the rectal biopsy specimen. The results are shown in **Table 1**. HMB-45 expression was negative (**Fig. 1b**), but CD56, S-100 protein and KIT expression were positive (**Fig. 1c**). Neuroendocrine carcinoma was highly suspected, but GIST and gastrointestinal autonomic nerve tumor could not be ruled out on the basis of the results.

Abdominopelvic computed tomography (CT) showed enlarged lymph nodes along the inferior mesenteric artery and on the posterior side of the lower rectum. Multiple liver metastases were also detected. Magnetic resonance imaging of the pelvis showed a mass (4.0 cm × 5.0 cm) in the lower rectum invading with the adventitia. Multiple metastastic lymph nodes (8～12 mm) were detected in the pararectal fatty tissue and along the right internal iliac artery.

In February 2005, with the diagnosis of neuroendocrine carcinoma of the rectum, abdominoperineal resection (APR) with dissection of the third group of the lymph nodes, according to the classification of the Japanese Research Society for Cancer of the Colon and Rectum[11], was performed. After the operation, the serum LDH level rapidly increased. With suspicion of progressive liver metastases, abdominal CT was performed. The results revealed enlarged multiple liver metastases. Thirteen days after the surgery, abdominal angiography was performed and revealed multiple hypervascular lesions in the liver.

After the anterior and posterior superior pancreaticoduodenal arteries and right gastric artery that branched from the common hepatic artery were selectively occluded with microcoils to prevent gastroduodenal injury from the anticancer drugs, the catheter was fixed to the proper hepatic artery. Then a reservoir was implanted at a subcutaneous site for locoregional chemotherapy. An alternative adjuvant chemotherapy was carried out with cisplatin (50 mg/day) + irinotecan (60 mg/day)[12] via the subcutaneous reservoir port under the

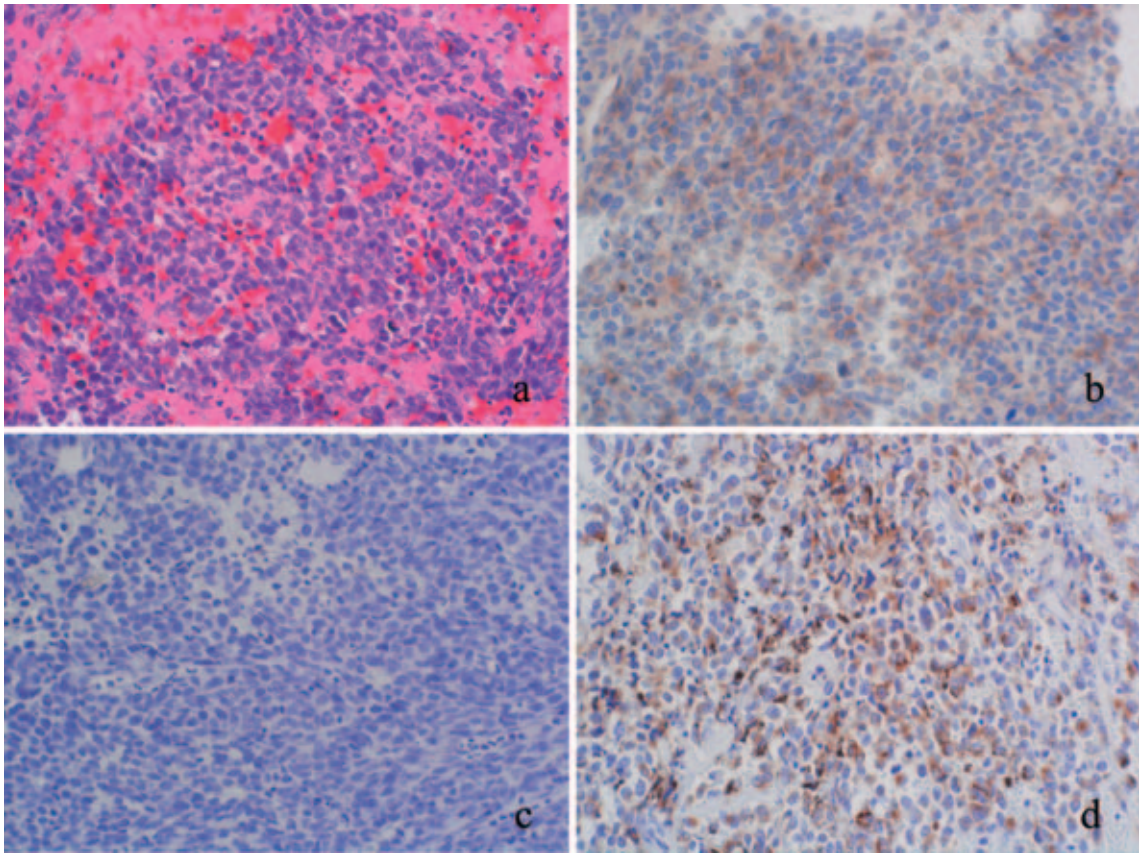

Fig. 1 **a**: The proliferation of round to polygonal cells with large nuclei, and mitotic figures were found in HE stain (×200). **b**: HMB-45 expression was negative in the rectal biopsy specimen (×200). **c**: KIT expression was positive in the rectal biopsy specimen (×200). **d**: HMB-45 expression was positive in the resected specimen (×200).

Table 1 The differences of immunohistochemical analysis between rectal biopsy and surgical specimen

	HMB-45	S-100	CD56	CK	KIT	LCA	SP
biopsy	(−)	(+)	(+)	(−)	(+)	(−)	(−)
surgical specimen	(+)	(+)	(+)	(−)	(−)	(−)	(−)

CK: cytokeratin, KIT: c-kit (CD117), LCA: leucocyte common antigen,
SP: synaptophysin

diagnosis of rectal neuroendocrine carcinoma. After the chemotherapy, the patient showed a partial response to chemotherapy.

However, based on immunohistochemical analysis, the final pathological diagnosis of the surgically resected specimen was malignant amelanotic melanoma of the rectum (**Table 1**). Immunohistochemical expression differed between rectal biopsy specimens and surgically resected specimens. In the resected specimen, HMB-45 expression was positive and KIT expression was negative (**Fig. 1d**). As the preoperative pathological diagnosis revealed a rare rectal tumor, we measured the chemosensitivity of rectal tumor using CD-DST to determine the most appropriate chemotherapy regimen for the patient. The results of the analysis are shown in **Table 2**. However, there were no anticancer drugs for malignant melanoma tested by CD-DST. With informed consent, the patient received two cycles of immunochemotherapy for malignant melanoma consisting of 200 mg of dacabazine (days 1–5), 100 mg of nimustine hydrochloride (day1), 1 mg of vincristine sulfate (day1), and 30×10^6 IU of interferon -beta (days 1–5)

Table 2 Drug sensitivities assessed by CD-DST in rectal tumor and metastatic LN

	Primary lesion (%)	metastatic LN (%)
CDDP	36.9	34.4
TXL.PAC	73.3	74.9
TXT.DOC	41.6	43.4
CBDCA	29.9	21.4
GEM: 8.0/1h	83.8	85.3
VP-16		34.4
SN-38: 30 ng	27.8	29.1
SN-38: 300 ng	64.1	56.5
5-FU: 10.0/24h	4.2	13.4

CD-DST: collagen gel droplet-embedded culture drug sensitivity test, LN: lymph node CDDP: cisplatin, TXL.PAC: paclitaxel, TXT.DOC: docetaxel, CBDCA: carboplatin, GEM: gemcitabine, VP-16: etoposide, SN-38: irinotecan, 5-FU: 5-fluorouracil

per cycle (DAV-feron therapy)[13]. By the time the patient showed remission of the metastatic liver tumor by this immunochemotherapy, he died because of progressive liver disease three months after the surgery. This study was performed in accordance with the principles of the Declaration of Helsinki.

Discussion

Anorectal melanoma is a rare condition accounting for 0.2% to 3% of all melanomas, and 0.1% to 4.6% of all malignant tumors of the rectum and anus[3]. Long-term survival is very low; because of early systemic spread, only 6.7% to 12% of patients are reported to be free of the disease 5 years after the operation[1,2]. The symptoms of anorectal melanoma are often mistaken for those of hemorrhoids. Clinical diagnosis may be incorrect in 80% of all cases[14]. The histology often mimics that of other malignancies, because anorectal melanomas exhibit considerable variability in cell size and shape.

Therefore, immunohistochemical studies are said to be useful in establishing the correct diagnosis[15,16]. The diagnosis has been mainly confirmed by the expressions of S-100 protein and HMB-45[15]. The rectal biopsy specimen in our case showed positive expression of S-100 protein but negative expression of HMB-45. Furthermore, the positive expressions of CD56 and KIT caused confusion in the histological diagnosis. Chute et al. reviewed 17 cases of anorectal malignant melanoma and reported that rates of immunohistochemical expressions for the S-100 protein, HMB-45, Melan-A, and KIT were 100%, 94.1%, 93.3%, and 75.0%, respectively. They reported that the KIT is frequently expressed, even though HMB-45 and Melan-A, which are said to be melanoma markers, are not always expressed in anorectal melanoma[7]. The surgically resected specimen showed expression of HMB-45 but not of KIT, which is differed from the biopsy specimen. After additional staining, Melan-A was found to be positive in both rectal biopsy and resected specimens, which confirmed the diagnosis of rectal amelanotic melanoma. The confusion in the diagnosis might be attributed to the variability of anorectal melanoma. The tumor in our case showed different immunoreactivities in a tumor. The differences in immunohistochemical staining between the rectal biopsy and the surgical specimen may be due to the heterogeneity of the tumor, malignant characteristics of tumor cells, or the state of fixation for the specimens. Immunohistochemical analysis must be performed as many times as possible so that biopsy specimens can be correctly diagnosed.

There are two opinions concerning the surgical treatment of anorectal malignant melanoma. First, wide local excision (WLE) should be considered a procedure of choice, because of the high mortality rate and lack of survival advantage of associated with APR[17,18]. Second, APR can improve locoregional control rates[3,19], which can maintain the quality of life, and improve the good prognosis[20]. In our patient, APR was performed because WLE was not expected to completely remove the rectal tumor totally. Then adjuvant chemotherapy had been selected to reduce the metastatic tumor. As the preoperative diagnosis was neuroendocrine carcinoma of the rectum, which is also a rare tumor of the rectum, the surgically resected specimen was examined by CD-DST and was cultured in the laboratory. CD-DST is a useful tool with which to design tailor-made chemotherapy regimens using the most suitable agents, doses, and schedules of administration[10], particularly in cases of rare tumors, for which a standard chemotherapy regimen has not

been established. The antitumor effect was determined from the inhibition ratio, which was calculated from the total volume of the colony that was in contact with the drug (T) and total volume of the colony that was not in contact with the drug (C), according to the following formula: (1-T/C) × 100%. A value of more than 50% is indicative of drug sensitivity. Paclitaxel, gemcitabine, and irinotecan showed high sensitivity for the rectal tumor **(Table 2)**. However, there are no anticancer drugs tested by CD-DST for malignant melanoma. There have been no reports of anorectal malignant melanoma treated with the chemotherapy regimen based on the results of CD-DST. After the trial of DAV-feron therapy for cutaneous melanomas commenced in 1988 with excellent results in terms of 5-year survival rates [13], this modified adjuvant chemotherapy was introduced in Japan to improve the therapeutic effect of anorectal melanoma. There have been a few reports on the success of this immunochemotherapy regimen for anorectal melanoma after surgery[18]. Two cycles of modified DAV-feron therapy was carried out with informed consent without using the results of CD-DST. In the future, we believe that the optimal treatment for anorectal malignant melanoma will be established using CD-DST.

Here, we have presented a case of rectal malignant amelanotic melanoma, which was not diagnosed preoperatively. The immunohistochemical expression differed between the rectal biopsy specimens and the surgically resected specimens. CD-DST was performed for the surgically resected specimens, but the results were not used to select the therapy.

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