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CASE REPORT

Rectal malignant melanoma: A second primary malignancy in a Filipino adult male - A case report

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ABSTRACT

Introduction: Malignant melanoma is most commonly found on the skin and rarely occurs in the rectal region. This case illustrates that rectal melanoma can be misdiagnosed as hemorrhoids. It also aims to add knowledge to possible treatment options for rectal melanoma.
Case Presentation: We report a case of a 77-year-old Filipino adult presenting with rectal bleeding for three weeks. He underwent sigmoidoscopy that showed thrombosed hemorrhoids; however, subsequent surgical excision biopsy histopathology and immunohistochemistry revealed features compatible with malignant melanoma (HMB45, Melan A, and Cytokeratin positive; CDX2 negative). Staging workup done, including abdominal magnetic resonance imaging (MRI) with IV contrast and chest computed tomography (CT), showed distant metastases. He was then started on pembrolizumab but follow up imaging showed recurrence of the rectal melanoma and progression of metastases. Molecular testing done revealed c-KIT / CD117 positive results, hence, treatment was shifted to imatinib.
Discussion and Recommendation: It was seen that rectal melanoma is an aggressive disease; therefore, multidisciplinary management is crucial to yield the best possible outcome, despite its poor prognosis. Such as in this case, using immunotherapy (Pembrolizumab) and targeted therapy (Imatinib) still have inconsistent outcomes, thus, further studies should be pursued. In this patient, both pembrolizumab and imatinib post-surgery resulted to recurrence of the rectal tumor and progression of hepatic and osseous metastases.

Introduction

Anorectal cancer, a rare disease, has increased by 2 to 3% within the past years. It commonly presents as gastrointestinal bleeding (45%), sensation of a mass (30%), changes in pattern of defecation, or anal pain. One of the less common histopathologies of anorectal cancer is melanoma (1%) [1,2]. Rectal melanoma occurs more commonly in women. It is often misdiagnosed as a benign lesion such as hemorrhoids [3]. Rectal melanoma is an aggressive disease, requiring biopsy and immunohistochemistry for diagnosis and possible therapeutic options [4].

Due to its rarity, there is still no consensus guidelines for its management, leading to poor prognosis. Different treatment modalities are offered to patients depending on each case. Surgical resection is often considered but the extent and type of surgery is still in question. Moreover, there is still no guideline for systemic therapy for rectal melanoma. Chemotherapy is used in some patients (cisplatin, vinblastine, dacarbazine, IFN-α, and interleukin-2) but response is poor. Radiotherapy is often used for palliation in unresectable tumor or used as adjuvant therapy following local excision. Some cases appeared to be resistant to radiotherapy while others decrease local recurrence [5,6]. Case reports exist regarding rectal melanoma, its diagnosis and management options; however, none yet in the Philippines.

We report a case of a Filipino male diagnosed with rectal melanoma, occurring as his second primary malignancy, being treated with systemic therapies.

Patient Information

A 77-year-old Filipino male, diagnosed case of colon adenocarcinoma stage I in 2009 status post left hemicolectomy with end-to-end anastomosis, who presented with blood in stools. This was accompanied by intermittent pain on defecation for 3 weeks and the hematochezia did not resolve with diosmin/hesperidin. He denied weight loss, decrease in caliber of stools, constipation, and loss of appetite. He is also hypertensive, dyslipidemic, and diabetic. He was a previous smoker, but there was no family history of cancer nor did he have a significant sexual history.

2.1 Clinical Findings

His vital signs were within normal limits and abdominal physical examination was unremarkable. Digital rectal examination revealed a palpable polypoid mass at the 1 o clock position with its base 2.0 cm from the anal verge.

2.2 Diagnostic Assessment

Flexible sigmoidoscopy was performed with findings of thrombosed internal hemorrhoids, described as 3.0 cm bluish-gray circumferential mass. Further probing of the mass showed its stalk continuous with the hemorrhoids (Figure 1). Of note, a previous surveillance colonoscopy done 15 months ago was unremarkable.

He underwent excision biopsy of rectal mass, with findings of an irregularly shaped, friable, pedunculated, polypoid thrombosed hemorrhoids versus rectal mass, measuring 2.0 x 3.2 cm, at the 1 o clock position with hematoma. It had a wide base stalk with grossly normal mucosa, measuring 3.0 cm, 1.0 cm above the dentate line.

On histopathology, the rectal mass was a poorly differentiated tumor. The parenchyma almost completely infiltrated by tumor (approximately 0.8 cm in depth). No definite lymphovascular space invasion is noted. The base of

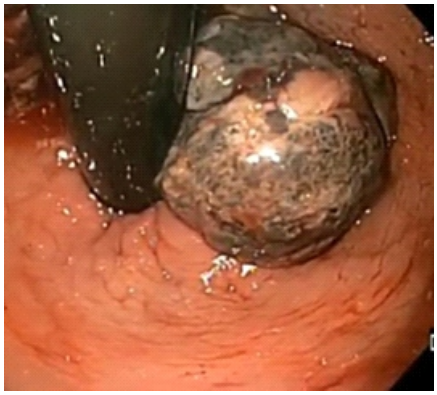

Figure 1. Sigmoidoscopy image of a 3.0 cm bluish-gray rectal mass above the dentate line, with its stalk continuous with the hemorrhoids

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Timeline

2009	Colon adenocarcinoma stage I s/p left hemicolectomy with end-to-end anastomosis
November 2021	Surveillance colonoscopy: internal hemorrhoids grade 1
November 2022	Follow up PET scan: unremarkable
January 2023	Hematochezia, anal pain Sigmoidoscopy: thrombosed hemorrhoids (Figure 1)
February 2023	Excision biopsy of rectal mass Pathology & immunohistochemistry: CDX2 positive in normal rectal epithelium; while in tumor cells positive for: Cytokeratin, Melan A, HMB45; consistent with rectal malignant melanoma Chest CT & Whole abdominal MRI with contrast: lung, liver, mesorectal lymph nodes, L5 metastases
March 2023	Pembrolizumab
April 2023	Follow up chest CT & whole abdominal MRI with contrast while on Pembrolizumab: recurrence of rectal mass & progression of metastases Molecular tests: c-KIT/ CD117 positive
May 2023	Pembrolizumab stopped Imatinib started
June 2023	Hematochezia Follow up whole abdominal MRI with contrast: progression of rectal mass & progression of metastases (Figure 2) Colonoscopy: no active bleeding in rectal mass

resection was negative for tumor and the nearest distance was noted to be 0.2 cm. Immunohistochemistry testing done showed features more compatible with malignant melanoma (HMB45, Melan A, and Cytokeratin positive but CDX2 negative).

A positron emission tomography (PET) scan done for follow up 3 months prior to consultation was normal. After biopsy, contrast-enhanced chest CT scan revealed bilateral pulmonary nodules, worrisome for metastasis. A whole abdominal MRI with contrast showed hepatic metastasis; lymph nodes in the left mesorectal fat and left L5 vertebral body, with consideration for metastasis; and mild wall thickening and enhancement in the mid- to low rectum, which may be secondary to inflammation/colitis. A diagnosis of rectal malignant melanoma stage IV was then established.

2.3 Therapeutic Intervention and Follow up / Outcomes

As a consensus with a multidisciplinary team (composed of a gastroenterologist, surgeon, and oncologist), the patient was given pembrolizumab 200mg intravenously once every week for 3 cycles.. However, follow-up chest CT scans showed progression of pulmonary nodules. Also, an MRI of the whole abdomen with contrast showed recurrence of a rectal mass measuring 1.3 x 1.3 x 1.9 cm (AP/T/CC) cm, involving the anterior low rectal wall, 4.4 cm above the anal verge. This was accompanied by a 2.4 x 1.8 x 2.1 cm nodular left mesorectal mass, intimately related to the left rectal wall, 7.0 cm above the anal verge, likely representing progressing metastatic lymphadenopathy or enlarging tumor implant; enlarging hepatic metastatic nodules; and progressing osseous metastasis now also involving T12 vertebral body.

Due to recurrence of rectal melanoma and metastatic progression, pembrolizumab was stopped. The patient's biopsy specimen was sent for further molecular tests revealing: c-KIT / CD117 positive, no detectable mutation in KRAS/NRAS gene, Pan Lung Cancer PCR panel all not detected. He was then started on imatinib 400mg tablet 1 tablet once daily. He was adherent to imatinib, however, developed generalized crampy abdominal pain accompanied by loose watery stools, malaise, and anorexia.

On further follow-up, four months post-excision biopsy of the rectal mass the patient presented with hematochezia and was admitted. Whole abdominal MRI with contrast revealed an increase in size of the previously seen anterior low rectal mass 4.4 cm. above the anal verge, measuring 2.3 x 2.7 x 1.8 cm. (previously 1.3 x 1.9 x 1.4 cm.) and increase in size of the partially exophytic left low to mid rectal mass, measuring 4.0 x 3.4 x 3.4 cm. (previously 2.4 x 1.8 x 1.8cm). There was an increase in size of metastatic hepatic nodules and T12 osseous metastasis. There were also new osseous lesions involving the left iliac bone and left femoral neck and a rim-enhancing T2 hyperintense perianal signal abnormality with marked restricted diffusion measuring 2.0 x 0.9 x 2.6 cm., involving the anal mucosa at 7 o'clock and extending to the anal verge, probably a new perianal abscess (Figure 2). For possible control of bleeding, colonoscopy done revealed a bluish gray, irregular, friable mass, approximately 2.0 cm in size, with no active bleeding. Imatinib was then temporarily stopped and the perianal abscess was treated with antibiotics.

Discussion

In current reports on rectal melanoma, recognition and diagnosis were emphasized. Few studies exist on the outcome of different treatment

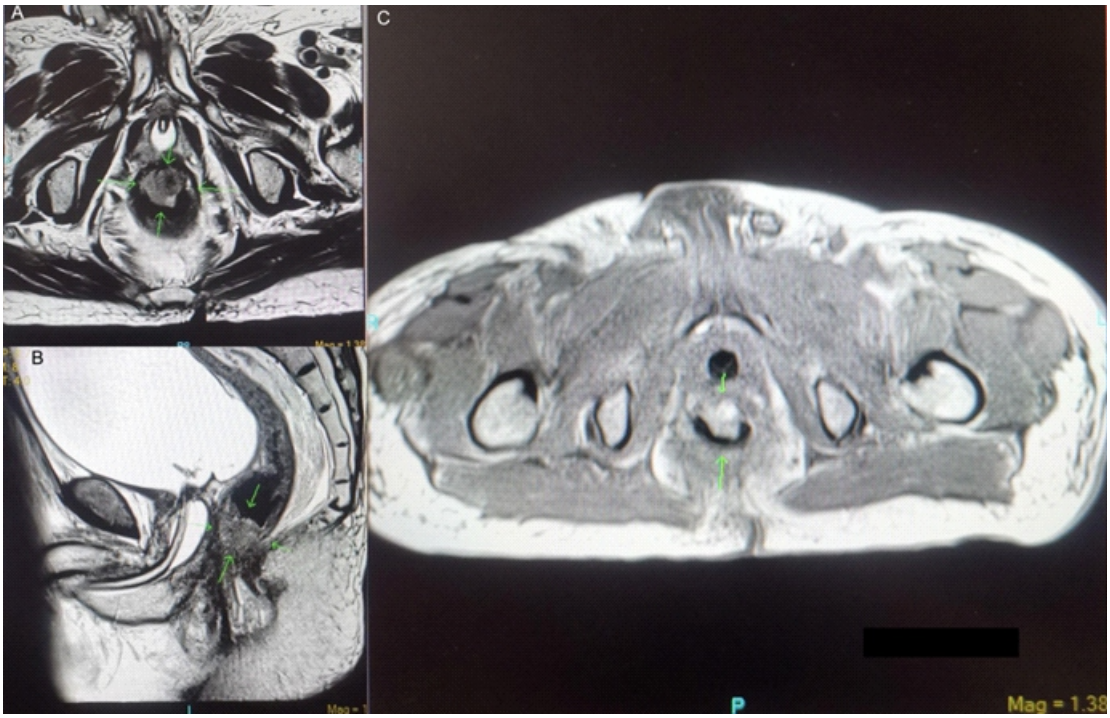

Figure 2. Whole abdominal MRI with contrast four months post surgery revealed (A) on axial view, an increase in size of the previously seen anterior low rectal mass measuring 2.3 x 2.7 x 1.8 cm. (previously 1.3 x 1.9 x 1.4 cm.) and increase in size of the partially exophytic left low to mid rectal mass, measuring 4.0 x 3.4 x 3.4 cm. (previously 2.4 x 1.8 x 1.8cm); (B) on sagittal view; (C) A rim-enhancing T2 hyperintense perianal signal abnormality with marked restricted diffusion measuring 2.0 x 0.9 x 2.6 cm., involving the anal mucosa at 7 o'clock and extending to the anal verge, probably a new perianal abscess

modalities, especially systemic therapy. Some patients underwent surgery, palliative radiotherapy, and few had systemic therapy. In this case report, we discuss a patient who did not undergo surgery nor radiotherapy. It is shown that he had failure of response to pembrolizumab (immunotherapy); however, long term outcome is still be determined with imatinib (targeted therapy).

Rectal melanoma is a rare malignancy, accounting for 0.5-2% of melanomas. The median age at diagnosis is the sixth decade for men and seventh decade for women, with higher incidence in females. Most rectal malignant melanomas are located near the anal canal or anal verge, presenting as hematochezia or anal mass. Several risk factors are known to increase the likelihood of skin melanoma; however, the risk factors for rectal melanoma are not known. Approximately 30% is amelanotic, resulting to misdiagnosis of a benign lesion [3,5].

Diagnosis relies on biopsy and immunohistochemistry - positive staining for melanocyte markers including S100, HMB-45, Vimentin, melan-A and tyrosinase. Computed tomography and ultrasonography are used for staging and follow-up to assess regional disease and recurrence. Other modalities such as endoscopic ultrasound may also be used to assess tumor depth, and MRI to evaluate the depth, nodal status and local involvement. Moreover, PET scan is also useful for evaluation of indeterminate lesions [4,7]. In this case, investigation of the possible cause of hematochezia in a Filipino male adult initially led to findings of thrombosed hemorrhoids grossly. On histopathology and immunohistochemistry, the rectal biopsy specimen was positive for HMB45 and melan-A. Together with a contrast-enhanced chest CT scan and abdominal MRI with contrast, the diagnosis of rectal melanoma stage IV with lung, liver, lymph node metastases was established.

Because of its rarity, there is no standard guidelines for treatment. Current strategies have not been consistent because of the lack of clinical trials. Case reports of rectal or anorectal melanoma have shown patients who had good and poor response to different types of management.

In a study by Songtanin, *et al.* (2022), a patient was diagnosed as a case of rectal melanoma stage IV with mutation studies negative for BRAF, V600E, and KIT, hence, given and tolerated nivolumab and ipilimumab [3]. Another case by Saadaat, *et al*. (2023) was a 48 year-old man, diagnosed with primary rectal melanoma stage II. He underwent abdomino-perineal resection with colostomy and follow up with a Computed Tomography (CT) excluded local, regional, and distant metastasis. After 8 months, he was found in good health [6].

On the other hand, an 81-year-old woman studied by de Meira Júnior, *et al*. (2021) was found to have anorectal melanoma with adrenal, lymphatic and hepatic metastases. A wide local excision of the tumor was performed, with immunohistochemistry findings of positive results for S-100 and HMB-45. However, due to multiple factors such as poor performance status, chemotherapy was deferred. After 5 months, radiation therapy (800 cGy) for palliation was done due to bleeding recurrence. The patient expired 10 months after, due to liver failure related to multiple liver metastases [8]. Also, according to a case report by Apostu, *et al.* (2021), his patient diagnosed with anorectal melanoma stage III tolerated total mesocolic and mesorectal excision. A month post operation, her PET CT scan revealed pulmonary metastases; therefore, she was given immunotherapy. Five months after, there was noted recurrence of mass at the perineal area [9].

To aid with treatment, molecular testing is recommended at the time of the diagnosis. Triple-negative melanomas (no Braf, c-Kit, or RAS mutation) can benefit from novel anti-CTLA-4 (cytotoxic T-lymphocyte associated antigen) and anti-PD-L1 (programmed cell death ligand 1) immunotherapy. Anti CTL-4 such as ipilimumab has demonstrated long-term survival success in 20% of treated patients, hence, it was the first anti-CTLA-4 agent approved for treating advanced melanoma, followed by nivolumab and pembrolizumab (anti-PD-1 antibodies). There are no randomized clinical trials using anti-PD-1 inhibitors for rectal melanoma, but a response rate of 23% has been demonstrated in a few case reports. One study reported a response rate to pembrolizumab of 19% with a median overall survival of 11.3 months. The use of a single-agent antiPD-1 inhibitor is recommended for stage III or IV unresectable disease. With nivolumab, a significant reduction in liver and bone metastasis without recurrence 17 months after treatment has been seen. Targeted therapies such as sunitinib, a tyrosine kinase inhibitor, had a response rate of 23-54% in some randomized trials [8-10]. In this case, the patient's metastases still progressed despite administering pembrolizumab, hence molecular testing done led to initiating imatinib. Even with imatinib, there was noted progression of the tumor, liver and bone metastases and development of perianal abscess.

Rectal melanoma is an aggressive malignancy, often having regional metastasis at the time of diagnosis. Common metastasis sites include the lung and liver, occurring in 27% of cases at diagnosis. It has poor prognosis, having a current 5-year survival rate of 10-16 %, with median survival rate of 14 to 19 months [7, 9].

Conclusion

Most research discussing rectal melanoma are case reports, none of which document any such case in the Philippines. Because of its similarity in presentation with hemorrhoids, they are often recognized late in their disease course. Once recognized, further investigation should be pursued for staging, to determine possible treatment options, and for follow up. In this case, despite prompt diagnosis, both pembrolizumab and imatinib post-surgery resulted to recurrence of the rectal tumor and progression of hepatic and osseous metastases. This case demonstrates that a multidisciplinary approach is essential in patients with rectal melanoma.

Patient perspective

According to the patient's daughter, the patient was able to tolerate imatinib in the first few days but eventually had abdominal pain, loose watery stools, and anorexia that made him weak, hence, he was admitted for hydration and fluid replacement.

Informed consent

The authors declare that a written informed consent from the person involved was granted for the publication of this case report and accompanying images. Moreover, strict anonymity will be maintained.

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