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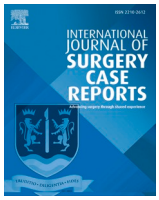

Case report

Primary malignant melanoma of rectum: A rare case report

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ABSTRACT

Introduction: Malignant melanoma of the gastrointestinal tract is an extremely rare event of which 50 % occurs in anorectal region. The lesion can easily be misdiagnosed as rectal-carcinoma, which comprises >90 % of rectal tumors and has a different treatment. The behavior of the anorectal melanoma is very aggressive and has very poor prognosis with fatal outcome.

Presentation of case: A 48-year-old man presented complaining of rectal bleeding of two months' duration, without any other significant history. Colonoscopy showed a polypoidal mass in the rectum that was in favor of adenocarcinoma. The microscope examination of biopsy tissue showed sheets of poorly differentiated malignant neoplasm. Immuno-histochemical (IHC) staining showed negativity of pan Cytokeratin and CD31. IHC for HMB45 showed diffuse and strong positivity in neoplastic cells, confirming the diagnosis of malignant melanoma.

Clinical discussion: According to a report by the National Cancer Database of the United States, primary rectal melanoma is very rare. Mucosal surface of the body is third most common site for primary melanoma after skin and eye. The first case of anorectal melanoma was reported in 1857. Histopathological examinations are gold standard for diagnosis, but histopathology examination without immunohistochemistry will misdiagnose some cases as poorly differentiated adenocarcinoma which has completely different treatment. Surgical resection has been reported as the most useful treatment option.

Conclusion: Malignant melanoma of the rectum is extremely rare and difficult to diagnose in low resources settings. Histopathologic examination with IHC stains can differentiate poorly differentiated adenocarcinoma from melanoma and other rare tumors of anorectal region.

1. Introduction

Malignant melanoma of the gastrointestinal tract is an extremely rare event, in which 50 % occurs in anorectal region [1]. It comprises 1 % of all malignant neoplasms of anorectal region and constitute only 0.3–1 % % of all malignant melanomas [2]. The behavior of the anorectal melanoma (AM) is very aggressive and has very poor prognosis with a fatal outcome [1]. Demographically, women have 1.6-folds higher risk to be affected by rectal melanoma than men and the average age during diagnoses has been reported to be 71-years [2]. Due to the location of AM, it can cause symptoms such as rectal bleeding, mass effect and change in bowel habit, that can also be the symptoms in patients with hemorrhoid, therefore, the diagnosis can be delayed [3]. According to epidemiological studies, melanomas occur more commonly in the rectum as compared to the anus and with a rapid progression than anal region, however, these two entities are frequently studied together [4]. Generally, the choice of primary treatment for rectal melanoma is surgery either wide local excision or transabdominal approaches, whereas the choice of surgical approach and the effectiveness of the approach for individual patients is still under debates [2]. Here we report a rare case of rectal primary melanoma. Our work has been reported in concordance with the SCARE criteria [5].

Abbreviations: IHC, immunohistochemistry; AM, anorectal melanoma; H&E, Hematoxylin & Eosin; HMB45, human melanoma black 45; CK, cytokeratin; WLE, wide local excision; APR, abdominoperineal resection.

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2. Presentation of case

A 48-year-old Hazara man living in Kabul city with job of being a shopkeeper presented to a private clinic complaining rectal bleeding for two months, sometime associated with mild painful defecation. The bleeding was fresh and admixed with stool but no mucus or tenesmus. Patient did not have weight loss, anorexia or other significant symptoms and signs. On laboratory examination, the hemoglobin level was within normal limits (15.5 g/dl) and similarly, electrolytes including sodium, potassium, chloride and bicarbonate were also within normal range. Liver function tests and renal function tests were normal. In the past history, patient revealed to have undergone appendectomy 15 years back, for which pathological examination was not done. No other significant disease was noted. Colonoscopy was performed that showed an ulcerated polypoid mass in rectum, 5 cm from the anal verge and in lateral wall. Colonoscopic findings were in favor of malignancy, thus endoscopic biopsy of the mass was taken during colonoscopy and sent for histopathologic examination. We received the biopsy in multiple small gray-dark tissue fragments, measuring 0.6 × 0.4 cm in total aggregations at the department of pathology and clinical laboratory, French Medical Institute for Mothers and Children (FMIC). The biopsied tissue was processed and stained with Hematoxylin and Eosin (H&E). The slides were examined under light microscope that demonstrated presence of sheets of poorly differentiated malignant atypical cells with enlarged hyperchromatic nuclei, visible nucleoli and many mitotic figures associated with increased number of vascular channels in the background. These findings lead to the suspicion of vascular tumor, carcinoma, melanoma or metastatic malignant neoplasms including sarcoma. Parts of slide also showed foci of normal rectal mucosa with benign columnar epithelial lining, shown in Fig. 1A. Immunohistochemical (IHC) staining was done which showed negativity for pan Cytokeratin (CK) and CD31 which ruled out possibility of carcinoma/adenocarcinoma and of vascular lesion. Human melanoma black 45 (HMB45) IHC was performed that showed diffuse and strong positivity in neoplastic cells, that favored the diagnosis of malignant melanoma (Fig. 2). To exclude the possibility of metastatic malignant melanoma, the patient was re-examined for any skin lesion and no lesions were found. Similarly, the patient was also asked about any previous skin surgery, which he denied. Based on the above evaluation, diagnosis of primary rectal melanoma was made. Due to lack of oncology center in our country, patient went to one of the neighboring countries for treatment and abdomino-perineal resection with colostomy was done for him. A polypoidal tumor in middle part of rectum was seen that reached to submucosa and histopathology examination of whole mass also confirmed the diagnosis of malignant melanoma. Unfortunately, surgical resection was done outside of the country and therefore, we do not have the images of the resected bowel segment. It should also be mentioned that prior to surgery a Computed Tomography (CT) scan was also performed for the patient that excluded local, regional as well as distant metastasis. Patient was followed up 8 months after the surgery whence he was having colostomy, using colostomy bag, otherwise he was in good health.

3. Discussion

Colorectal cancer is the fifth most common cancer and third leading cause of cancer related death in the United States. It is the frequently diagnosed cancer in gastrointestinal tract and rectal cancer is the second most common cancer of large intestine after proximal colon cancer. The majority of these cancers are adenocarcinoma that arises from columnar

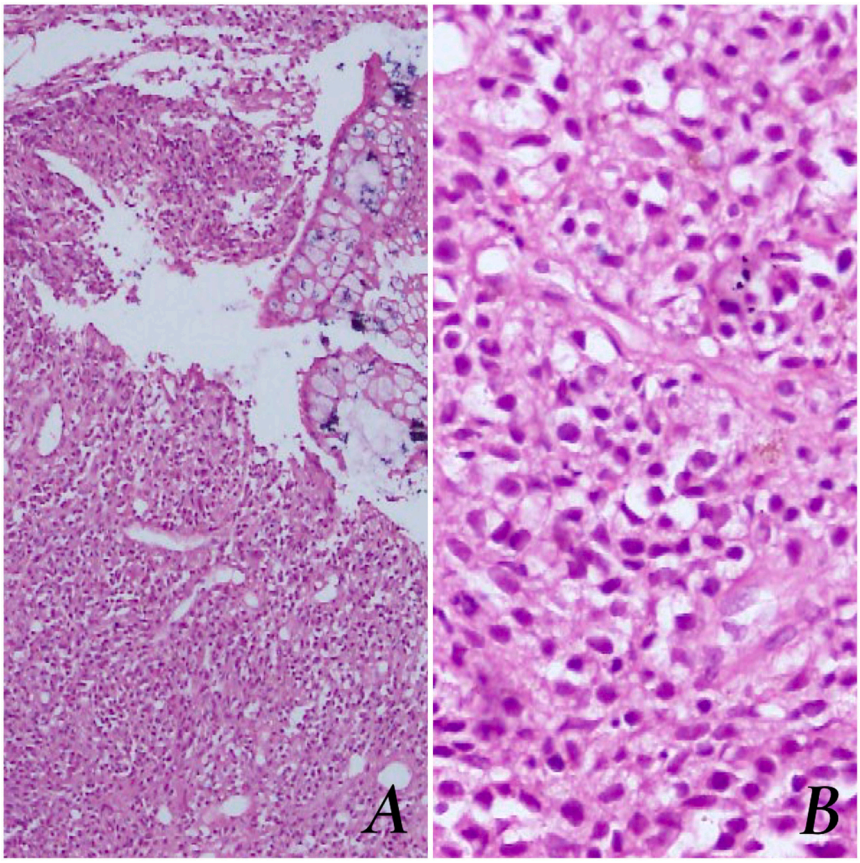

Fig. 1. H&E staining of the tissue. 10× magnification Shows large bowel mucosa and a neoplasm arranged in sheets and nests (A). 40× magnification, the neoplastic cells are large pleomorphic having abundant eosinophilic cytoplasm with brown melanin pigmentation, hyperchromatic pleomorphic nuclei. Increased number of mitosis seen (B).

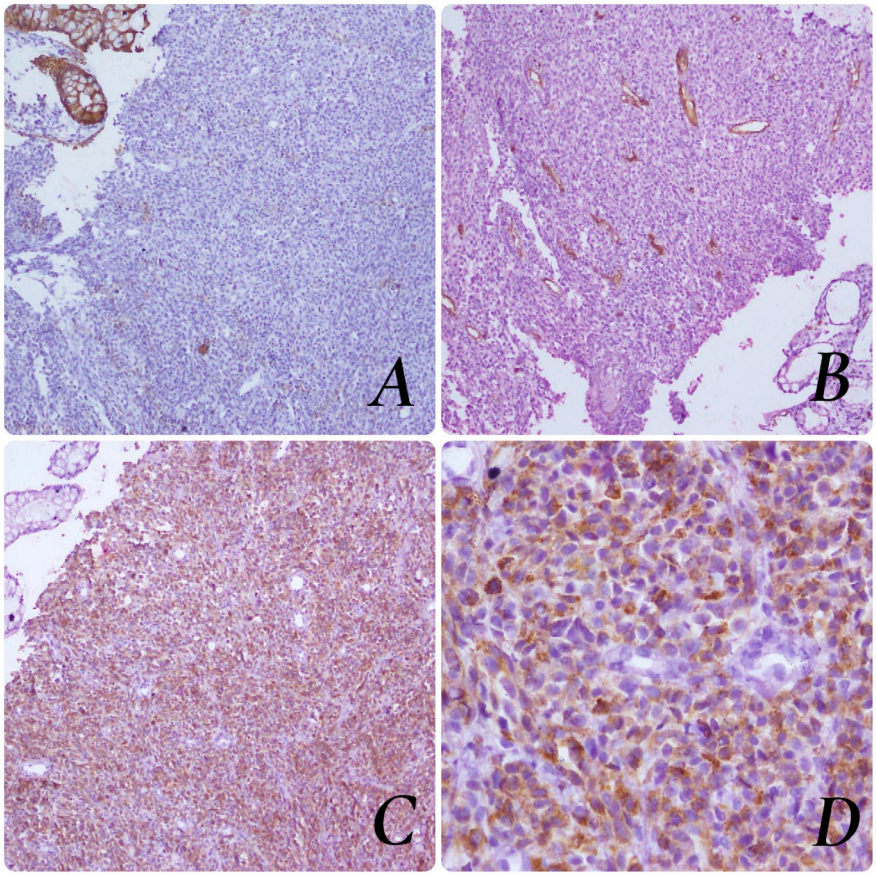

Fig. 2. Immunohistochemical staining results in neoplastic cells; Cytokeratin which shows positivity in normal rectal epithelium but negative in neoplastic cells (A). CD34 which is negative in neoplastic cells and positive only in vascular endothelial cells (B). HMB45 Positive in neoplastic cells, shown in 10× magnification (C). HMB45 Positive in neoplastic cells, shown in 40× magnification (D).

epithelial lining cells of the rectal mucosa [6,7]. Other rare types of tumors of rectum include carcinoid tumor, sarcomas and melanoma. Carcinoid tumor originates from neuroendocrine cells located in colorectal area. Among sarcomas, leiomyosarcoma make >50 % of cases [7]. Primary rectal melanoma is also very rare. According to the report by National Cancer Database of the United States, mucosal surface involvement constitutes the third most common site for primary melanoma after skin and eye [1]. The first case of anorectal melanoma was reported in 1857 by Moore [8].

Tumor thickness, ulceration, high tumor mitotic rate, satellite lesions and lymphovascular invasion are established adverse prognostic factors for rectal melanoma. Studies have estimated that 85 % of AM were stage T1 or T2 and the mean number of mitotic figures were fewer in thin tumors [9,10].

Melanoma arises from melanocytes which embryologically are the cells that migrate from neural crest or mucocutaneous junction to skin. The main function of melanocytes in skin is to form melanin pigment, while in mucosal surfaces its function is to contribute in the regional immune response and antioxidant activity [11–13]. Melanocytes are commonly present in the anal squamous zone and sporadically in transition zone. This localization can be related to the presence of melanocytes in dentate line epithelium which extends to the rectum. The malignant transformation of melanocytes in anorectal mucosa is thought to be linked to oxidative stress as well as immunosuppression [11–13].

Considering the genetic alteration in melanomas, there are differences in mucosal melanoma and skin melanoma. In a series of 13 cases, Edwards et al. reported that exon 15 BRAF mutation was not detected in mucosal melanomas [14], however the occurrence of this mutation was reported in 33 % of skin melanomas [15]. These findings raises the concern about the role of BRAF e600 mutation and development of melanoma in specific anatomical sites, as more commonly associated with melanoma of the skin rather than mucosal probably due to sun exposure to these sites [14]. In addition, medication such as vemurafenib and dabrafenib which are inhibitor of BRAFe600 would not be effective in primary mucosal melanoma [16].

KIT mutation has been reported in 40 % of AM which is higher than reported in head and neck melanomas [15]. Higher genomic instability in primary mucosal melanoma resulting from Human Papilloma Virus (HPV) and causing degradation of the p53 protein has also been postulated. But in a study, which was conducted on 15 AM cases, who were also investigated for HPV DNA by PCR, HPV was not detected [17].

The surgery has been reported as most useful treatment for AM and wide local excision (WLE) and abdominoperineal resection (APR) are the two most common types of surgery. Studies have elucidated that APR did not result in survival improvement over local excision, whereas, APR showed better disease-free survival with major control of locoregional disease in primary rectal melanoma but not in metastatic melanoma. Wide surgical approach did not show any long-term better outcome for patient, where-as in many cases local excision was suggested in order to improve quality of life of the patients [18,19]. In a study that was aimed to evaluate the effectiveness of the two surgery procedure including 143 AM patients, reported no survival differences between the above mentioned two types of surgeries [19]. Another less invasive procedure to treat AM is Endoscopic Mucosal Resection (EMR), that can only remove mucosal and superficial submucosal tumors and it's also appropriate procedure for frail older patients, who cannot tolerate the WLE or APR [20]. Small size tumors with shallow dept. invasion of tumor can have long term survival with EMR. Magnetic

resonance (MRI) is a diagnostic modality of choice for determining the depth of tumor invasion in AM [20]. Therefore, MRI is useful for pre-operative staging in AM patients and for detection of metastasis. For our patient MRI was not done and instead Computed Tomography (CT) scan was done and showed no regional and distant metastasis.

For our patient APR procedure with colostomy was done with no chemotherapy. Combination of chemotherapy or radiotherapy with surgery have been reported to show benefits for patient, however, chemotherapy and radiotherapy without surgery have not been widely proposed for treatment of AM [2]. Clinically tolerable high dose of immune mediators, such as interferon-α and interleukin-2 (IL-2) have shown good response in metastatic cutaneous melanoma. Indeed, recently, IL-2 combined with ipilimumab (at 3 mg/kg) showed effectiveness in AM patients with unresectable disease [1]. Therefore, taking in consideration the different therapeutic modalities for different types of tumor, an accurate histopathological diagnosis and clinical and radiological correlation is vital. AM in small endoscopic biopsy will be misdiagnosed as poorly differentiated adenocarcinoma in particularly when there are no melanin pigments. Rectal carcinoma will have completely different chemotherapy and therefore IHC staining is mandatory and crucial in such cases. In addition, a careful clinical history and evaluation is very important to see the presence of skin lesion or previous surgery for skin nodules, to exclude the possibility of cutaneous melanoma metastasizing to rectum.

4. Conclusion

Malignant melanoma of the rectum is extremely rare, highly aggressive, and difficult to diagnose in low resources settings. Although surgery remains the cornerstone of treatment, the therapeutic modality of choice still remains controversial. The role of adjuvant therapies is minimal. Survival can be prolonged only by early diagnosis and intervention.

Patient perspective

The patient stated that it would be useful to publish and share this case with other healthcare workers, to enable better understanding and correct diagnosis of such rare cases that would cause a specific treatment and follow up.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Provenance and peer review

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CRediT authorship contribution statement

RS convinced the idea. JAG, RS and EE diagnosis the case. RS was involved in literature review and drafted the manuscript. RS, MAA and S helped to collect clinical and follow-up data of the cases. AMH participated in reviewing the drafted manuscript. RS participated with the corresponding, editing the drafted manuscript as per journal policy, and submission of the article. All authors read and approved the final manuscript.

Conflict of interest

It is declared that all authors have no conflict of interest.

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