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CASE REPORT

MALIGNANT MELANOMA OF ANORECTUM: A REPORT OF FIVE CASES

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Abstract

BACKGROUND: Anorectal melanoma (ARM) is an extremely rare, highly aggressive form of a tumor with the worst prognosis. ARM contributes 0.5% of all melanoma cases. Its presentation is similar to that of adenocarcinoma of the rectum, hemorrhoids, or solitary rectal ulcer, the incorrect clinical diagnosis or delayed diagnosis is often made. The definite diagnosis is only made through histopathology in which immunohistochemical stains positive to S-100, Melan A, and HMB-45 which differentiates it from adenocarcinoma of the rectum.

Because of the limited number of patients and retrospective design of studies to date, there is no proven efficacy of abdominoperineal resection (APR) over local excision (LE) in terms of survival. Furthermore, this neoplasm is quite resistant to chemoradiotherapy. It has a median survival of 18 months and a 5-year survival rate of only 6%.

PRESENTATION OF OUR CASES: Here, we report five rare cases of anorectal malignant melanoma presented to our institute between 2018 to 2022, who were treated with APR and diversion colostomy. The first case is a 27-years old young female with typical complaints, she was diagnosed ARM with locoregional metastasis. Only a diversion colostomy was performed and referred to an oncologist for palliation. Our second case is a 68-years old male with a similar complaint who presented relatively early and was diagnosed with localized disease. Conventional APR was performed and referred for adjuvant chemoradiotherapy, but the patient refused. However, the lump recurred after 6 months of tumor excision. The third case is a 29 years old male again early presentation with a similar complaint labeled as localized diseased. The conventional APR was performed followed by adjuvant chemoradiation; patient presented with metastatic disease after 6 months. The fourth case is a 60-years old male with typical history and diagnosed with localized disease. Conventional Extra-levator APR was performed followed by adjuvant therapy, but patient developed recurrence of disease with mets after 4 months. The fifth case is a 39-years old female diagnosed as ARM, had advance disease and metastatic deposits at the time of presentation, refused any palliative treatment. The study aims to evaluate our experience in treating this neoplasm.

CONCLUSION: Because of the rarity of this neoplasm, no proper trial has been conducted so far. The role of chemoradiotherapy is questionable and the surgical approach varies from radical APR to conservative LE. No surgical approach has been standardized in terms of survival.

Keywords: Anorectal Malignant Melanoma (ARM), Abdominoperineal resection (APR), Local excision (LE).

INTRODUCTION

ARM is a subtype of mucosal melanoma that originates from the sinonasal, anorectal and genitourinary mucosa. Skin and retina are the most common site of malignant melanoma, followed by anorectum which is the third most common site among all melanomas. It has a poorer prognosis than that of skin melanoma.[1] ARM accounts for about 1.5 % of all melanoma cases and has an incidence of about 2.7 patients per 10 million population per year in the USA. However, due to its very low incidence and the lack of clinical information, a standardized treatment for ARM is lacking. ARM is likely to remain unnoticed for a longer period and diagnosed at an advanced stage due to its non-specific symptoms. Therefore, AM has become an aggressive subtype of melanoma, with a 5-year overall survival rate of 14%–20%.[2] Some authors describe the efficacy of immunotherapy and targeted therapy which survival rate. Surgical resection remains the most effective therapy for patients with ARM. However, patients with distant metastases may not significantly gain a survival benefit from surgery alone, and the standard resection and lymph node (LN) dissection are still controversial.

CASE PRESENTATION

CASE 1

A 27-years old female presented in the outpatient department with complaints of progressively increasing perianal mass, bleeding per rectum, and tenesmus for the last one year. On examination hard mass is approximately about 10 x 10cm arising from one end of the anal canal growing outward abutting the right buttock and partially obstructing the lumen. Diagnostic colonoscopy showed mass arising from the dentate line and passed up to 60cm. Multiple biopsies were taken which shows cancerous cells stain positive with S-100 and HMB-45, characteristic of melanoma.

MRI pelvis and Contrast-enhanced CT scan abdomen reveal large fungating mass arising from anal canal involving levator ani, vagina, and perineal body. Multiple lymph nodes are seen in the perirectal, inguinal region, and internal iliac vessels representing metastases.

PET scan shows increased metabolic activity in vertebral bodies, appendicular skeleton, and inguinal lymph nodes.

Because of locoregional metastases, we performed only diversion colostomy. The surgery and postoperative period were uneventful. Later referred a patient to the oncologist for palliative chemoradiotherapy. Unfortunately, the patient died within 3 months.

CASE 2

A 68-years old male patient admitted through the outpatient department with complaints of bleeding per rectum and altered bowel habits for 3 months. On DRE, there was irregular growth starting from the anal verge. Colonoscopy shows polypoidal mass from anal verge up to 16cm. Multiple biopsies were taken. Histopathology revealed cancerous cells stain positive to S-100 and HMB-45, giving the impression of malignant

melanoma. The staging done with an MRI pelvis and a Contrast-enhanced CT scan abdomen which showed localized disease with perirectal lymph nodes.

Conventional abdominoperineal resection was performed. Biopsy shows tumor size of 8 x 7 x 6cm, infiltrating into muscularis propria and perirectal adipose tissue, involvement of lymph nodes, and resection margins free (stage III). Postoperative recovery was uneventful and the patient was referred to an oncologist for further management.

He did not receive any treatment and was admitted again after 6 months with complaints of a lump at the perineal scar site. That lump was excised that shows recurrence of the disease (S-100 positive, HMB-45 negative, Melan A weakly positive). CT scan shows liver metastases and he was referred to hospice care. Unfortunately, the patient died after 5 months.

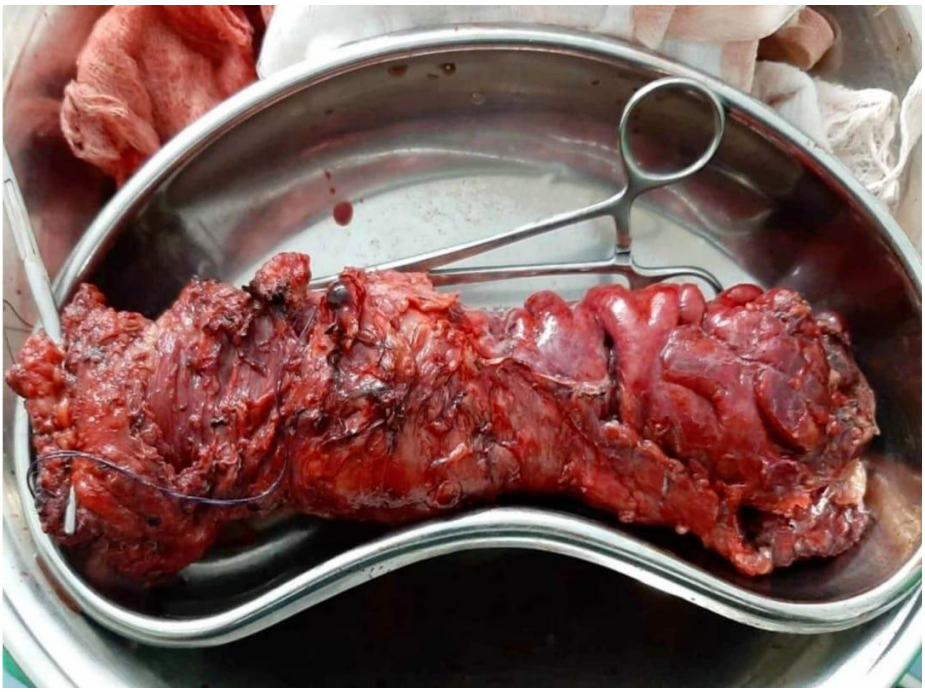

Figure 1: APR SPECIMEN OF CASE 2 ARM

CASE 3

A 29-years old male patient was admitted through the outpatient department with complaints of bleeding per rectum, weight loss, and altered bowel habits for 6 months. There was a growth starting from the anal verge till 15cm on sigmoidoscopy. Contrast-enhanced CT scan abdomen pelvis and MRI pelvis tumor size of about 9 x 7cm and localized disease with perirectal lymph nodes. Histopathology is consistent with malignant melanoma as tumor stains positive to S-100 and HMB-45.

Conventional APR was performed. Biopsy revealed melanoma with free resection margins and out of 13, no lymph node was involved. Patient referred to an oncologist for further management and was on regular follow-ups. Patient was admitted again after 6 months of surgery with SOB, diagnosed with metastatic disease and unfortunately expired after 1 month.

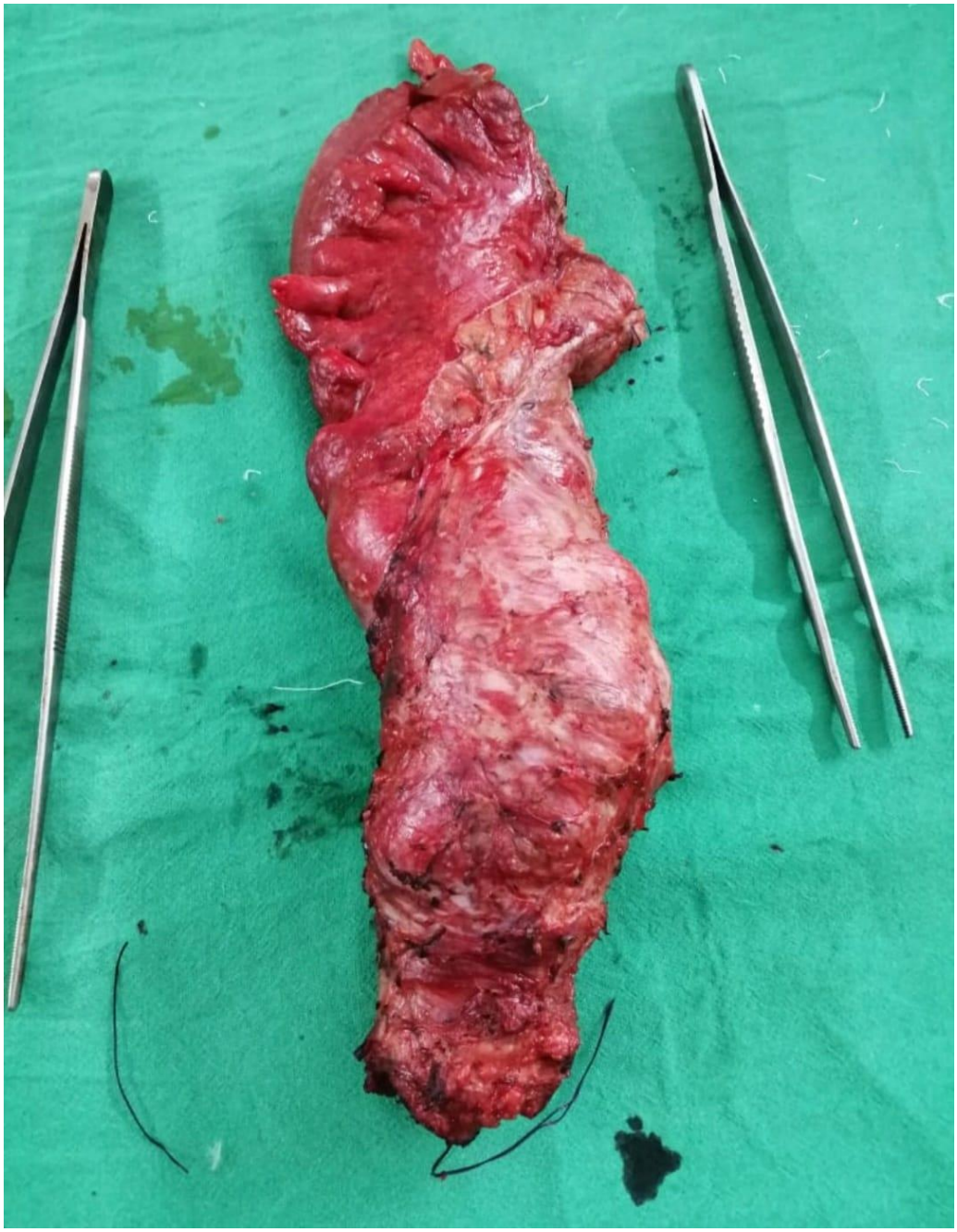

Figure 2: APR SPECIMEN OF CASE 3 ARM

CASE 4

A 60-years old male patient was admitted through the outpatient department with complaints of bleeding per rectum and burning sensation in perianal region for 8 months. On DRE, growth starting from anal verge at 9 o'clock extending internally up to 3cm, hard and pigmented anal verge, fissure at 6 o'clock. Colonoscopy showed growth starting from anal verge extending up to 4cm, multiple biopsies taken. Histopathology revealed cancerous cells stain positive to S-100 and HMB-45, giving the impression of malignant melanoma. The staging done with MRI pelvis and Contrast-enhanced CT scan which showed localized disease with perirectal lymph nodes.

Conventional Extra-levator APR was performed, biopsy showed melanoma with tumor free resection margins (proximal margins 21cm, distal margin 2cm, circumferential resection margin 1.2cm) and out of 11 lymph nodes, 6 were involved. Postoperative recovery was uneventful and the patient was referred to oncologist for further management. Patient was on regular follow-ups and was diagnosed with loco-regional recurrence and metastatic involvement of right inguinal lymph node after 4 months of surgery and died within 6 months.

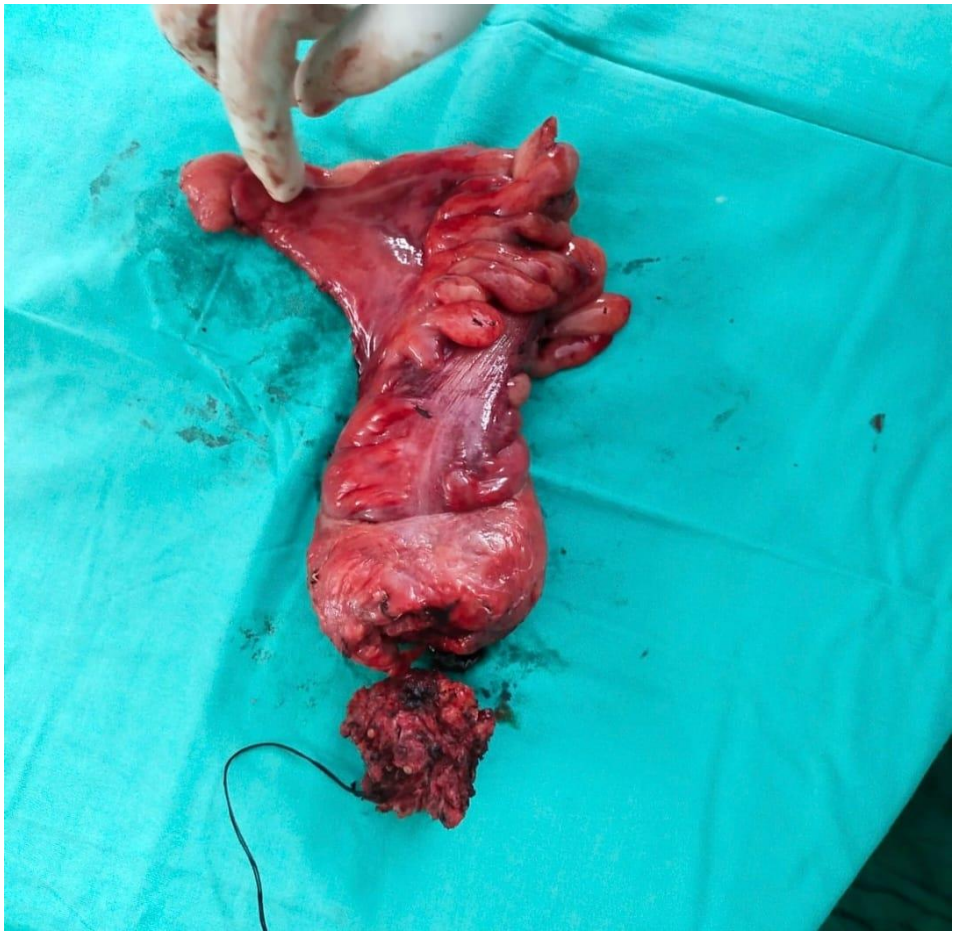

Figure 3: APR SPECIMEN OF CASE 4 ARM

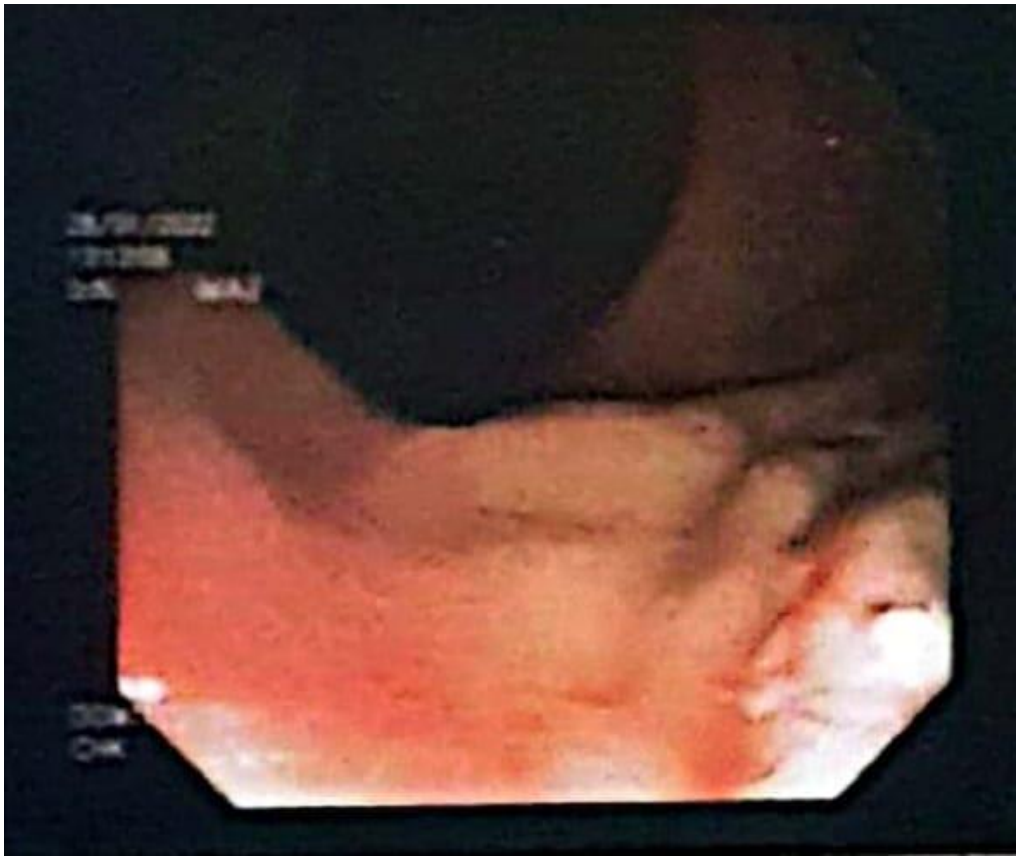

Figure 4: COLONOSCOPIC PICTURE OF CASE 4 ARM

CASE 5

A 39-years old female patient presented in the outpatient department with complaints of bleeding per rectum, painful defecation and altered bowel habits for almost one year. On DRE, irregular growth starting 1cm from anal verge, severely painful. Colonoscopy showed mass starting 1cm from anal verge to 20cm. Contrast-enhanced CT scan and MRI pelvis demonstrated tumor size of about 15×8 cm with involvement of multiple loco-regional lymph nodes, and metastatic deposits in liver, inguinal and internal iliac nodes.

Because of the advance disease, we counseled the patient and family regarding poor prognosis of this disease. Diversion stoma and palliative therapy was offered but the patient refused and lost to follow-up. Patient died after 3 months.

DISCUSSION

Anorectal Malignant Melanoma (ARM) is a rare and lethal malignancy and is the third most common site of primary malignant melanoma. The median age of ARM at diagnosis is 60 years or higher and it occurs slightly more in females.[3] However, in our series two of the patients were in their twenties and two of them were males. No known risk factor for ARM, epidemiologic data suggest that there is a slightly increased risk associated with HIV infection.[4]

The first case of ARM was reported by Moore in 1957, Melanoma is a malignant neoplasm of melanocytes that are derived from neural crest cells and migrated to the anal squamous and transition zone in embryonic life.[5] ARM tends to arise from the melanocytes found near the dentate line.[6] Most anorectal melanomas arise from the dentate line and 65% are located within the anal canal or at the anal verge.[7,8]

Melanocytes produce melanin, a black pigment, which acts as a barrier to ultraviolet radiation thus preventing cutaneous melanoma.[6] The role of melanocytes in mucosal tissue like anal canal is not clear; however, it is thought to play antimicrobial, immune-metabolic, regulation of defensin and other proteins, etc. More than 50% of tumors are amelanotic on histology.[9] Moreover, tumor biomarkers are useful in predicting the risk of metastases and their prognosis.

The signs and symptoms of anorectal melanoma are similar to other benign and malignant disorders like hemorrhoids, adeno-squamous carcinoma, etc.[10] The most common presenting complaints are bleeding, anorectal discomfort or pain, an appreciable anorectal mass, or change in bowel habits. Other symptoms include pruritis, tenesmus, prolapsed hemorrhoid, change in stool habits, and diarrhea. Patients who have metastasis at the time of presentation may additionally have fatigue, weight loss, and anemia.[7,8] Lesions are most commonly found at the anorectum, followed by the anal canal and anal verge.[11] These lesions are often discounted as being benign hemorrhoids or polyps.[12] Moreover, on histopathology, its features resemble Gastrointestinal Stromal Tumor (GIST), Sarcoma, and other undifferentiated carcinomas. Thus, it is very difficult to diagnose only on histopathology. Thanks to immunohistochemical markers S-100, HMB-45, and Melan A which make it possible to diagnose anorectal melanoma. In cases of diagnostic difficulty, which is frequent even on histopathology, the presence of melanin can be helpful, but it is not easily detected in anorectal disease.

In our study, all five patients were positive for S-100 and HMB-45 and only one patient was weakly positive for Melan A. Melanoma antigens S-100, HMB-45, and vimentin are important immuno-histochemical markers. Polyclonal antiserum and monoclonal antibodies to carcinoembryonic antigen can help to distinguish it from a poorly differentiated epidermoid carcinoma.[13] Activating KIT-gene mutations, which are implicated in leukemia and gastrointestinal stromal tumors have also been associated with the pathogenesis of malignant melanoma.[14]

Following histological confirmation of diagnosis, a complete staging workup is mandatory with Contrast Enhanced Computed Tomography (CECT) of the abdomen and chest and a Magnetic Resonance Imaging (MRI) pelvis is necessary to rule out metastatic disease, in addition to ruling out other common primary sites of malignant melanoma.[15]

Anal melanoma is staged on a clinical basis, focusing on loco-regional and distant spread. Stage I is local disease only, Stage II is a local disease with increased thickness and ulcerations, Stage III is local disease with involvement of regional lymph nodes, and Stage IV shows distant metastatic disease.[16]

Most patients with bleeding per rectum in our population seek delayed medical treatment because of social taboo. Thus, being rare, aggressive, and having non-specific symptoms most of the patients had either regional (stage II) or disseminated/advanced disease (stage III/IV) at the time of initial diagnosis.[17] Weinstock reported that at the time of diagnosis only 37% of ARM is confined to the anorectal area, 41% has regional spread and 22% has distant metastasis. In our study, two patients have distant metastases, and three had localized disease at the time of presentation.

Lymphatic spread to the inguinal or inferior mesenteric nodal basins is common. The most common sites for metastases are inguinal lymph nodes, mesenteric lymph nodes, hypogastric lymph nodes, para-aortic lymph nodes.[13] The incidence rates for locoregional lymph node metastases on initial presentation are almost 60%. [13,14] The major sites of distant metastasis are the lung, liver, skin, bone, and brain. At the time of diagnosis, distant metastases are identified in 26-38% of patients.[8,13]

There are many modalities of treatment for ARM like Abdominoperineal Resection (APR), Wide Local Excision (WLE), Endoscopic mucosal resection, diversion colostomy, radiotherapy, immunotherapy, and chemotherapy but none of them have been standardized due to low incidence and lack of evidence. Surgery is considered the mainstay of treatment;[15] chemotherapy has a limited role. The major benefit of radiotherapy is seen only in palliative cases. There has been a debate between APR and WLE as to which one is the superior surgical option.[16] It seems that APR is good in terms of wide resection, and negative resection margins, preventing loco-regional metastases to inguinal and mesenteric lymph nodes. However, due to high perioperative mortality and morbidity like sexual and urinary dysfunction, most authors prefer WLE. Bullard et al reported that APR has no benefit for loco-regional recurrence and systemic recurrence compared to WLE. This means that most recurrences occur systemically regardless of the initial surgical procedure. Local recurrences were more frequent in patients who underwent WLE. But in one of our cases, recurrence occurred within six months despite performing APR. Loco-regional recurrence of ARM occurs more at the inguinal lymph nodes than at the pelvic lymph nodes. Neither APR nor WLE affect any of the inguinal lymph nodes, therefore neither of them offers an advantage in controlling loco-regional recurrence.[17]

There are no standards regarding systemic therapy for disseminated disease. Chemotherapy, radiation therapy, and immune therapy have a limited role. The medications used in adjuvant therapy are cisplatin, vinblastine, dacarbazine, interferon B, and Interleukins IL-2-8. Dacarbazine is the

most commonly used single agent and usually initiates a partial response in 20% of patients in 4-6 months after treatment.[13] Radiotherapy, chemotherapy, and immunotherapy have also been attempted, Targeted therapy and checkpoint inhibitors have an upcoming role but none of them found a good response; therefore, no standard regimen has been established.

CONCLUSION

Malignant melanoma of the rectum is extremely rare, highly aggressive, and difficult to diagnose. Although surgery remains the cornerstone of treatment, the exact procedure remains controversial. Role of adjuvant therapies is minimal. The diagnosis of anorectal mucosal melanoma (ARMM) portends a particularly poor prognosis and a standardized evidence-based treatment approach is not well-defined due to the rarity of this disease.[18]

All five of our patients died within 2 years of diagnosis (three of them died within 1 year and two died after 1 year). Despite the very limited evidence, surgical treatment is widely accepted· WLE for small tumors and APR for large tumors with adjuvant chemo-radiotherapy and immunotherapy. Targeted therapy and checkpoint inhibitors are also an option.[19] Despite all these treatment options, the prognosis is grim and overall survival is dismal as data shows 5 years of survival is 6% to 20% and median survival is 19-26 months.

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INFORMED CONSENT
Written informed consent was obtained from the patients for participation in our study.

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CONFLICT OF INTEREST STATEMENT
The authors have no conflicts of interest to declare.

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AUTHOR CONTRIBUTIONS
All authors contributed substantially to the conceptualization, drafting, and revisions of this manuscript.

DATA AVAILABILITY STATEMENT
All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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