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Primary Anorectal Melanoma: Report of Two Cases and Literature Review from the Radiation Oncology Department of Mohammed VI University Hospital, Marrakech

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Abstract **Case Report**

Primary anorectal melanoma is an extremely rare and aggressive malignancy, accounting for less than 1% of all anorectal cancers and approximately 0.3% of all malignant melanomas. This tumor presents unique diagnostic and therapeutic challenges owing to its rarity and aggressive behavior. We report two cases of primary anorectal melanoma managed at our institution between 2020 and 2023, along with a comprehensive literature review of current diagnostic and therapeutic approaches. Both patients were elderly men (72 and 63 years old) who presented with rectal bleeding as the primary symptom of their disease. Histological diagnosis was confirmed by positive immunohistochemical staining for Melan-A and S-100 proteins. Both patients presented with distant metastases at the time of diagnosis. One patient received palliative chemotherapy and died 9 months after diagnosis, while the other was lost to follow-up. Primary anorectal melanoma has a poor prognosis because of frequent metastasis at diagnosis. Recent advances in targeted therapy and immunotherapy have offered new therapeutic perspectives, although early detection remains crucial for improving patient outcomes.

Keywords: Anorectal melanoma, Diagnosis, Treatment, Prognosis, Immunotherapy.

INTRODUCTION

Primary anorectal melanoma is among the rarest and most aggressive types of malignant melanoma, accounting for about 0.3% of all melanoma cases and less than 1% of all anorectal cancers [1,2]. This unusual tumor arises from melanocytes normally present in the squamous epithelium of the dentate line and the transitional epithelium above the pectinate line [3,4]. The disease predominantly affects elderly patients, with a peak incidence in the sixth and seventh decades of life [5].

The clinical presentation is often nonspecific, leading to delayed diagnosis and poor prognosis. Common symptoms include rectal bleeding, anal pain, and rectal syndrome (tenesmus, straining, terminal constipation, etc.), which can be attributed to more common benign conditions such as hemorrhoids and anal fissures [6]. Characteristic dark pigmentation is present in only approximately one-third of the cases, further complicating early recognition [7].

The aggressive biological behavior of anorectal melanoma, combined with its tendency for early lymphatic and hematogenous dissemination, results in a median survival of approximately 20 months after diagnosis [8,9]. Recent therapeutic advances, particularly in targeted therapy and immunotherapy, have shown promise in improving the outcomes of patients with metastatic melanoma, including rare mucosal variants [10,11].

This report presents two cases of primary anorectal melanoma managed at our institution, accompanied by a comprehensive review of the current diagnostic and therapeutic approaches for this rare malignancy.

Materials and Methods

We conducted a retrospective review of all cases of primary anorectal melanoma diagnosed and managed at the Department of Radiation Oncology, Mohammed VI University Hospital, Marrakech, Morocco, between January 2020 and December 2023. The cases were identified using an institutional tumor registry and pathology database.

The inclusion criteria were histologically confirmed primary anorectal melanoma, immunohistochemical confirmation with positive staining for melanoma markers, complete clinical and imaging documentation, and adequate follow-up data.

The data collected included demographic characteristics, clinical presentation, diagnostic workup, staging investigations, treatment modalities and clinical outcomes.

A comprehensive literature search was performed using the PubMed, EMBASE, and Cochrane databases from January 2000 to December 2023. Search terms included "anorectal melanoma," "anal melanoma," "rectal melanoma," "mucosal melanoma," and "primary anorectal melanoma." Recent clinical guidelines from the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) were also reviewed.

Case Reports

Case 1

A 72-year-old man with no significant medical history or negative HIV status presented with a 6-month history of rectal bleeding associated with anal pruritus and general health deterioration. Physical examination revealed a fixed mass situated 2 cm above the anal margin, extending 4 cm proximally into the rectum that bled upon contact. Sphincter tone was also preserved.

Rectosigmoidoscopy revealed a semi-circumferential budding process extending 2–5 cm from the anal margin, with induration and hemorrhagic appearance. Histological examination confirmed anorectal melanoma, with immunohistochemistry positivity for anti-Melan-A and anti-S100 proteins.

Pelvic magnetic resonance imaging (MRI) revealed a tumor involving the anal canal and lower rectum. Thoracoabdominopelvic computed tomography (CT) revealed multiple hepatic metastases, which were confirmed by hepatic magnetic resonance imaging (MRI), showing scattered parenchymal nodules consistent with metastatic disease.

Owing to financial constraints limiting access to targeted therapy or immunotherapy, the patient received palliative chemotherapy with dacarbazine. After six cycles, radiological evaluation showed local progression with an increase in the primary tumor size and metastatic progression with enlargement of the hepatic lesions and new pulmonary metastases. The patient was transitioned to supportive care and died 9 months after diagnosis.

Case 2

A 63-year-old man with no significant medical history and negative HIV status presented with a 1-year history of rectal bleeding, occasional mass protrusion during defecation, and constipation without any general deterioration. Physical examination revealed an ulcerobudding process located 2 cm from the fixed anal margin, bleeding on contact, and preserved sphincter tone.

Histological examination confirmed anorectal melanoma with positive immunohistochemistry for anti-Melan-A and anti-S100 protein. Pelvic MRI revealed a tumor involving the anal canal and mid-lower rectum, with nodular infiltration of the mesorectum. Thoracoabdominopelvic CT revealed pulmonary nodules suggestive of metastatic disease.

The patient was subsequently lost to follow-up before the initiation of treatment.

Discussion

Primary anorectal melanoma arises from melanocytes in the anal transitional zone, particularly in the squamous epithelium of the dentate line and the transitional epithelium above the pectinate line [3,4].

While historically described with a female predominance, recent large population-based studies have suggested a more balanced sex distribution [12,13]. The disease shows a predilection for Caucasian populations, with a peak incidence in the sixth and seventh decades of life [5,14].

The clinical presentation of anorectal melanoma is nonspecific, contributing to diagnostic delays. The most common presenting symptoms include rectal bleeding (present in 80-90% of cases), anal pain, and changes in bowel habits [6,15]. Characteristic dark pigmentation, while pathognomonic when present, is observed in only 30-40% of cases, with many tumors appearing as amelanotic lesions [7,16].

Both patients in our series presented with rectal bleeding as the primary symptom, which is consistent with the literature. The absence of characteristic pigmentation in many cases emphasizes the importance of histological and immunohistochemical confirmation for a definitive diagnosis.

A definitive diagnosis relies on histological examination and immunohistochemical analysis. The demonstration of melanin pigment using Fontana staining, although supportive, is not always possible [17]. Immunohistochemical markers, including Melan-

A, S-100 protein, HMB-45, and vimentin, are essential for confirming the diagnosis, particularly in amelanotic variants [18,19].

Staging evaluation should include colonoscopy to exclude synchronous lesions, endorectal ultrasound or pelvic MRI for local staging assessment, and thoracoabdominopelvic CT or PET-CT for the detection of regional and distant metastases [20,21]. Both patients in our series underwent comprehensive staging, revealing metastatic disease at presentation, which is consistent with the advanced stage typical of this malignancy at the time of diagnosis.

The optimal treatment strategy for anorectal melanoma remains controversial, reflecting both the rarity of the disease and its aggressive biological behavior. Surgical approaches range from local excision with sphincter preservation to radical abdominoperineal resection (APR).

The historical preference for APR is based on the assumption of improved local control of the disease. However, recent comparative studies have failed to demonstrate superior survival outcomes with radical surgery compared to local excision [22,23]. A systematic review by Matsuda *et al.,* showed that while APR provided better local control, the overall survival was equivalent to that of local excision, leading to increased consideration of sphincter-preserving approaches [24].

Local excision offers several advantages, including reduced operative morbidity, shorter hospital stay, and improved quality of life. Recent reports have described successful endoscopic management using endoscopic mucosal resection or submucosal dissection for selected early-stage lesions [25,26].

Traditional cytotoxic chemotherapy has shown limited efficacy in anorectal melanoma, with response rates typically below 20% [27]. However, recent advances in targeted therapy and immunotherapy have revolutionized the treatment of melanoma, including mucosal variants of the disease.

Targeted Therapy: For patients with BRAF V600E or V600K mutations, combination therapy with dabrafenib and trametinib has demonstrated significant improvement in relapse-free survival and distant metastasis-free survival in stage III melanoma [28,29]. Although specific data on mucosal melanomas are limited, these agents represent an important therapeutic option for appropriately selected patients.

Immunotherapy: Immune checkpoint inhibitors have shown remarkable efficacy in treating advanced melanoma. The combination of nivolumab and ipilimumab has demonstrated a sustained survival benefit compared to ipilimumab monotherapy in advanced melanoma, with 10-year follow-up data confirming durable responses [30]. While mucosal melanomas have historically shown lower response rates to immunotherapy than cutaneous melanomas, significant responses have been documented.

Anti-PD-1 drugs, like nivolumab or pembrolizumab, help lower the chance of cancer coming back in people with stage III skin melanoma after surgery. This is shown in studies like CheckMate-238 and KEYNOTE-054. There isn't much data on mucosal melanomas, but experts suggest using anti-PD-1 therapy for high-risk cases after surgery, based on results from skin melanoma studies.

Adjuvant radiation therapy does not appear to provide a survival benefit compared to surgery alone [31]. However, radiation therapy plays an important palliative role, and when combined with local excision, it may provide local control equivalent to that of APR [22].

Anorectal melanoma has a uniformly poor prognosis, with a median overall survival ranging from 12 to 24 months [8,9]. At presentation, approximately 37% of patients had localized disease, 41% had regional metastases, and 22% had distant metastases [32]. The high propensity for both lymphatic and hematogenous dissemination contributes to poor outcomes.

Prognostic factors include tumor thickness, ulceration, mitotic rate, and disease stage at presentation. However, even patients with apparently localized disease frequently develop metastatic recurrence, reflecting the aggressive biological behavior of this malignancy.

Based on the current evidence, the treatment recommendations include the following:

1. Localized Disease: Local excision with clear margins is preferred over radical surgery for most patients, given the equivalent survival outcomes and reduced morbidity.
2. Advanced Disease: Systemic therapy with immunotherapy or targeted therapy (for BRAF-mutated tumors) represents the standard of care, based on extrapolation from cutaneous melanoma data and limited studies on mucosal melanoma. After treatment, patients should have regular check-ups and scans (CT or MRI) every 3–6 months for the first 2 years because there is a high chance of the disease coming back. After that, the check-ups can be less frequent. It is important for different specialists to work together to catch any recurrence early and improve treatment options.
3. Multidisciplinary Approach: Given the complexity of this rare malignancy, management should involve a multidisciplinary team, including surgical oncology, medical oncology, radiation oncology, and pathology specialists.

This study had some limitations. The small sample size limits the generalizability of our findings. One patient was lost to follow-up, which prevented complete outcome assessment. Additionally, as this was a retrospective case series from a single institution, selection bias may have influenced the results.

CONCLUSION

Primary anorectal melanoma is a rare and aggressive malignancy with a poor prognosis. Early diagnosis requires a high clinical suspicion, particularly in elderly patients presenting with rectal bleeding. Although traditional treatments have offered limited success, recent advances in targeted therapy and immunotherapy have provided new hope for improved outcomes. However, the rarity of this condition necessitates multicenter collaborative studies to better define the optimal treatment strategies.

The cases presented here underscore the importance of maintaining clinical awareness of this rare entity and the need for prompt and comprehensive evaluation when it is suspected. Future research should focus on identifying predictive biomarkers of treatment response and developing treatment protocols specifically tailored for mucosal melanomas.

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Conflict of Interest Statement

The authors declare no conflict of interest.

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