DOI: 10.7860/JCDR/2022/59796.17174

Case Series

Pathology Section

Rare and Aggressive Primary Amelanotic Melanoma in Anorectal Region: A Case Series

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ABSTRACT

Anorectal amelanotic melanoma is a rare and aggressive disease with high morbidity and mortality. A conclusive diagnosis of anorectal amelanotic melanoma poses a challenge to pathologists and clinicians due to the protean nature of this entity, be it in its initial clinical assessment appearing as non pigmented polypoidal growths usually mistaken for haemorrhoids or anorectal polyps. Histomorphologically, these entities get categorised in bewildering array of diagnoses like spindle cell carcinoma, Gastrointestinal Stromal Tumour (GIST), High grade sarcomas and even lymphoma. Thus Immunohistochemistry (IHC) remains a vital tool for conclusive diagnosis. The purpose of the present case series is to discuss in detail about the three patients all aged above 55 years and clinically assessed with anorectal polypoidal growths. All three cases on histopathological evaluation were diagnosed as spindle cell neoplasm with no discernible melanin pigments. The IHC performed on all three cases turned positive for S-100 and Human Melanoma Black 45 (HMB 45). This case series highlights the challenging and bewildering nature of presentation of anorectal amelanotic melanomas, by virtue of its rarity and hence justifies the need for it to be considered as a possible differential diagnosis.

Keywords: Abdominoperineal resection, Immunohistochemistry, Malignant

INTRODUCTION

Malignant melanoma is the tumour arising from melanocytes in the skin and rarely these tumours are arising from mucosa and melanocytes from gastrointestinal tract, central nervous system and other internal organs [1]. Malignant melanoma is clinically subtyped into superficial spreading melanoma, nodular melanoma, amelanotic melanoma, lentigo malignant melanoma, spitzoid melanoma and desmoplastic melanoma. Among the subtypes, amelanotic melanoma is considered to be a rare and aggressive variant and the incidence is around 2 to 20 percentage. Malignant melanoma in the anorectal region is extremely rare and it constitutes around 0.8 to 1% of all the malignancies occurring in anorectal region [2]. And the incidence of the variant that is amelanotic variant in the anorectal region is still exceedingly rare and only few reported cases are there in the literature [3,4].

Most of the patients with anorectal melanoma are presented with non specific symptoms such as mass descending per anal canal, bleeding and sometimes with anal pain. These symptoms were often neglected by the patients and are usually presented as an advanced stage at the time of diagnosis.

In addition to that, there is a higher chance of misdiagnosis on physical examination especially when the lesions are polypoidal and without melanin pigments, because most of the polypoidal lesions are clinically diagnosed as haemorrhoids or anorectal polyps. Hence, the absence of early clinical manifestation and lack of clinical suspicion contribute to delayed diagnosis and therefore the morbidity and mortality are very high for this disease.

Histomorphologically also amelanotic melanoma in the anorectal region are often mistaken for spindle cell carcinoma, gastrointestinal stromal tumour, high grade sarcomas and sometimes as lymphoma. Therefore, immunohistochemistry study may be essential to diagnose this condition [3].

Hereby, authors report three cases of primary anorectal amelanotic melanoma presented as non pigmented polypoidal mass with bleeding per rectum. This series of cases will bring us awareness about the rare presentation and diagnostic difficulties associated with anorectal amelanotic melanoma.

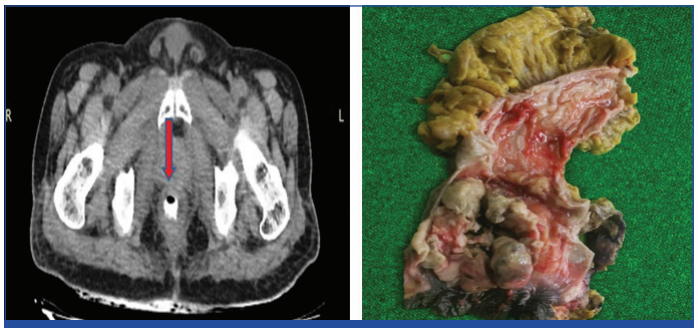
CASE SERIES

The study was carried out in the Department of Pathology. A total of three cases collected over a period of 11 months from 1st August 2021 to 1st July 2022 who underwent surgery for anorectal mass and were diagnosed as primary anorectal melanoma by histopathological examination were included in the study. The age, sex, relevant clinical and radiological details were recorded for each case. The specimen was processed as per standard procedure. The sections were cut on microtome and stained by hematoxylin and eosin stain. The stained slides were studied and an Immunohistochemistry panel was done for confirmation. Out of three cases, case 1 was provisionally diagnosed as malignant lesion with multiple liver metastasis. Haemorrhoids and rectal prolapse were the differential diagnoses for cases 2 and 3, which were tentatively identified as rectal adenomatous polyp and anal fibroepithelial polyp respectively.

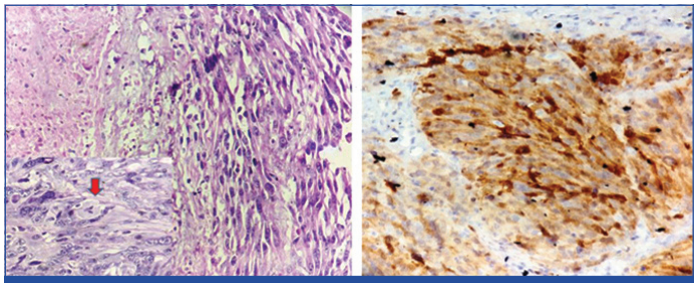
Case 1

A 57-year-old male presented with loss of weight of more than 5 kgs within three months and pain during defecation. Per rectal examination showed perianal growth extending from the anal canal into rectum. Contrast-Enhanced Computed Tomography (CECT) abdomen reported as anal malignancy with multiple nodules of varying sizes in both lobes of the liver and few subcentric bilateral inguinal groups of lymphnodes [Table/Fig-1]. Colonoscopic biopsy was sent for histopathological evaluation and diagnosed as malignant spindle cell neoplasm. Abdominoperineal resection was done. On cut surface there is grey white, ulcerated polypoidal growth measuring 6×3×2.5 cms involving the anorectal mucosa [Table/Fig-2]. Pericolic fat revealed one lymph node measuring 0.5 cm. On microscopic examination, tumour cells are arranged in sheets and infiltrate into muscularis propria. Individual cells are spindle shaped with marked nuclear atypia and prominent nucleoli. Melanin pigments are not

appreciated. Many mitotic figures are also noted [Table/Fig-3]. Immunohistochemistry was done to subcategorise the malignant lesion and the tumour cells were positive for S100 [Table/Fig-4]; HMB45 [Table/Fig-5] and negative for vimentin, CD 117, CD 45 and cytokeratin. Final diagnosis of anorectal amelanotic melanoma was made. Patient received three cycles of adjuvant chemotherapy (cisplatin and epirubicin). Each cycle was taken with a three week interval period. The patient defaulted from the 4th chemotherapy cycle. After three months, the patient came with the complaints of difficulty in breathing, vomiting and haemoptysis. After the onset of these complaints, surveillance CT chest was taken and it revealed multiple varying sized lesions in bilateral lung fields with the largest nodule visualised measuring 21 mm in size. The CT scan features were favouring the diagnosis of pulmonary metastasis. No other lesions were noted elsewhere in the body on clinicoradiological evaluation. Hence the patient was advised biopsy from the lung lesion for confirmation, for which the patient was not willing. So, the patient was referred to Medical Oncologist for further management by palliative chemotherapy.



[Table/Fig-1]: CT of the Abdomen and Pelvis revealed polypoidal intraluminal mass in anal canal (arrow). **[Table/Fig-2]:** Gross examination of the specimen after abdominoperineal resection showing ulcerated polypoidal growth. (Images from left to right)

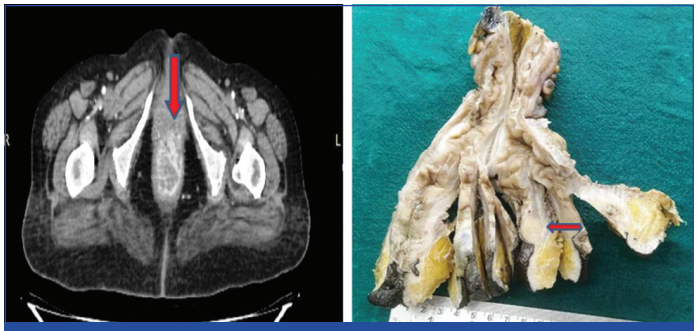


[Table/Fig-3]: Photomicrograph showing tumour cells are arranged in sheets with areas of necrosis. Insert shows atypical mitosis (arrow) (Hematoxylin and Eosin stain; 400X). **[Table/Fig-4]:** Photomicrograph showing tumour cells are immunoreactive for S100 (IHC; 400X). (Images from left to right)

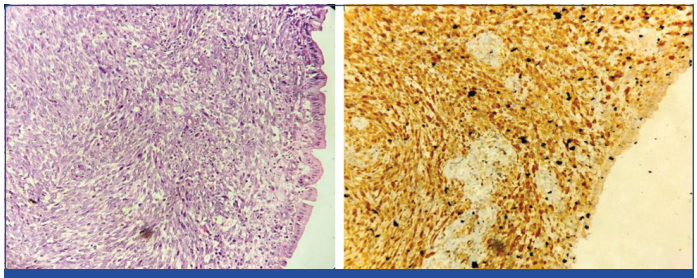
[Table/Fig-5]: Photomicrograph showing tumour cells are immunoreactive for HMB 45 (IHC: 400X).

Case 2

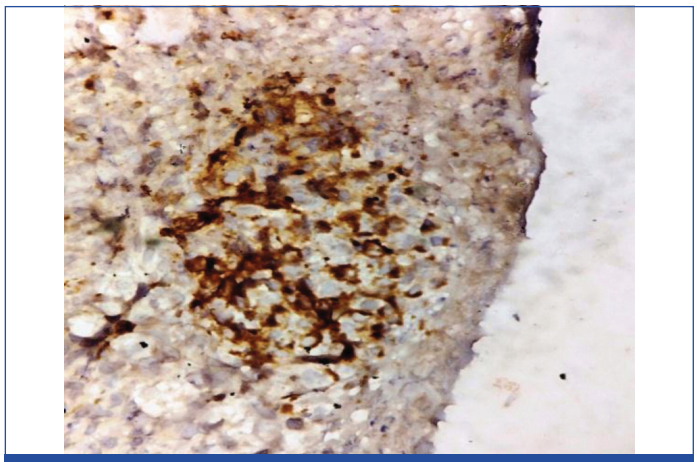
A 55-year-old female presented with constipation on and off for 6 months and history of bleeding per rectum for 2 months. She was a known case of hypertension. On per rectal examination, there was a mass felt at anal verge. Rectosigmoidoscopy showed a polypoidal growth extending to 4 cm from the anal verge. Computed Tomography (CT) abdomen showed a polypoidal growth involving the anorectal region [Table/Fig-6]. Colonoscopic biopsy was done and was diagnosed as malignant tumour in which tumour cells are oval to spindle shaped and cells are arranged in sheets and fascicles exhibiting marked nuclear pleomorphism. Abdominoperineal resection done and the diagnosis of poorly differentiated malignant tumour has been made [Table/Fig-7,8]. To differentiate this lesion from various undifferentiated tumours, immunohistochemistry was done and tumour cells showed positivity for S100 [Table/Fig-9] and HMB45 [Table/Fig-10] and negative for CD 117, cytokeratin and vimentin. Based on morphological features and immunohistochemical findings the diagnosis of anorectal amelanotic melanoma was made. On postoperative day 4, patient developed deep vein thrombosis with respiratory distress and got discharged against medical advice. Hence, thepatient has lost to follow-up.



[Table/Fig-6]: CT of the Abdomen showed polypoidal growth involving anorectal region (arrow). **[Table/Fig-7]:** Abdominoperineal resection showing grey white polypoidal and infiltrating growth in anorectal region (arrow). (Images from left to right)



[Table/Fig-8]: Photomicrograph showing polypoidal mass lined by columnar cells (rectal mucosa) and subepithelium shows oval to spindle shaped tumour cells are arranged in sheets and fascicles (Hematoxylin and Eosin stain; 200X). **[Table/Fig-9]:** Photomicrograph of immunohistochemical analysis of the lesion showing tumour cells are immunoreactive for S100 (IHC: 200X). (Images from left to right)

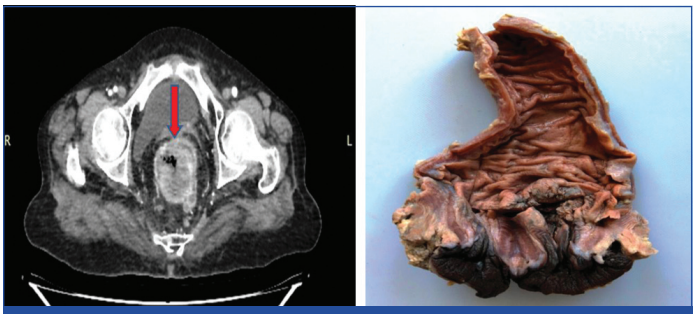


[Table/Fig-10]: Photomicrograph of Immunohistochemical analysis showing tumour cells are immunoreactive for HMB 45 (IHC; 200X).

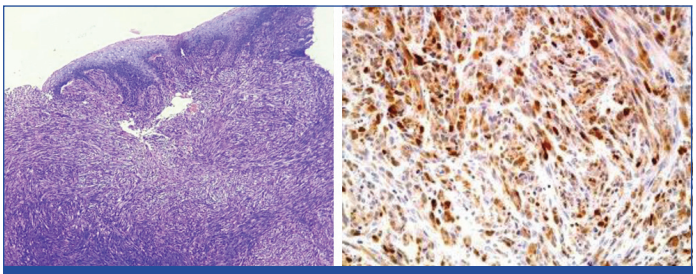
Case 3

A 56-year-old female presented with a 7 months history of bleeding per rectum and mass coming out. On per rectal examination, an obstructed polypoidal mass was felt at anal verge. CT abdomen showed a heterogeneously enhancing intraluminal polypoidal lesion

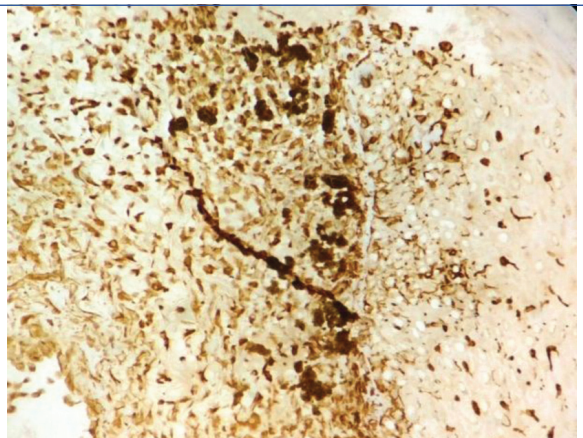
of size 5×4×3 cm at the anal verge [Table/Fig-11]. Abdominoperineal resection was done. On gross examination a polypoid lesion measuring about 5×4×3 cm in anorectal region [Table/Fig-12]. On histopathological examination, tumours are arranged in nests. These tumour cells are spindle shaped with moderate nuclear atypia and prominent nucleoli. Histomorphologically this tumour has been diagnosed as malignant spindle cell tumour [Table/Fig-13]. Immunohistochemistry was done and tumour cells showed positivity for S100 [Table/Fig-14] and HMB45 [Table/Fig-15] and negative for Vimentin and CD 117. Final Diagnosis of anorectal amelanotic melanoma was made. A staging positron emission tomography was performed which showed multiple metastasis in liver and bilateral ilioinguinal lymphnodes. Patient was referred to the higher center for further management.



[Table/Fig-11]: CT Abdomen showed a heterogeneously enhancing polypoidal lesion at anal verge (red arrow). **[Table/Fig-12]:** Abdominoperineal resection showing Ulcerated polypoidal mass at anal verge. (Images from left to right)



[Table/Fig-13]: Photomicrograph showing polypoidal mass lined by stratified squamous epithelium (anal mucosa) and subepithelium shows sheets of spindle shaped tumour cells (Haematoxylin and Eosin stain; 200X).
[Table/Fig-14]: Photomicrograph of immunohistochemical analysis of the tumour showing nuclear positivity for S100 immunostain (IHC; 400X). (Images from left to right)



[Table/Fig-15]: Photomicrograph of Immunohistochemical analysis showing tumour cells are immunoreactive for HMB 45 (IHC; 400X).

DISCUSSION

Anorectal melanoma or otherwise called anorectal mucosal melanoma is a rare and aggressive malignancy accounting for 0.1 to 4.6% of all malignant lesions of the anorectal region [4]. Anorectal mucosal melanoma usually originates from the melanocytes near the dentate line. The incidence of melanoma in anorectal region has rapidly increased over the last decades. Even though many factors such as family history of melanoma, presence of dysplastic nevus and exposure to ultraviolet radiation have been proposed for melanoma of the skin. No such risk factors are associated with anorectal melanoma. Many theories have been proposed such as mutation associated with CDKN2a to and BRAF and Tumour rotein p53 (TP53) for malignant cutaneous melanoma [5]. The available material on mutation theory of anorectal melanoma are very limited in the literature field [6].

Usually anorectal melanoma commonly affects the female and the common clinical presentation is rectal bleeding [7]. Most of the patients generally ignore those symptoms. Because of the abundant lymphatics and rich vascular network in this area promotes lymphatic spread to inguinal lymph nodes and haematogenous spread to systemic organs. Hence, the the mortality and morbidity of anorectal melanoma is very high as compared to many vital diseases. The present case series showed two of the patients were presented with bleeding per rectum and one of the patients had loss of weight with pain on defecation. Similar to the present case series findings, Kumar U et al., and Van Pham B et al., reported bleeding per rectum as the commonest presentation of anorectal melanoma [7,8]. Zhang MD et al., also reported painless rectal bleeding is a most common symptom followed by loss of weight [9]. In addition to that the majority of lesions are grossly polypoidal which further leads to misdiagnosis of anorectal melanoma as haemorrhoids or rectal polyp. So, ignoring symptoms by the patients and because of many clinical mimics of melanoma, the patients usually present at the advanced stages. In the current case series, there was no clinical suspicion of melanoma due to the polypoidal nature of the growth at the time of presentation. Instead, the differential diagnosis included haemorrhoids, rectal prolapse, adenomatous polyps, fibroepithelial polyps, and malignant lesions. In a study conducted by Kumar U et al., and Nguyen MT et al., similar results were discovered. A instance of anorectal melanoma was clinically misinterpreted as haemorrhoids or an anorectal polyp in each study, according to the authors [7,10].

Histopathologically the classical malignant melanoma will have either plasmacytoid or spindle shaped or epithelioid morphology with abundant cytoplasmic melanin pigments. For a pathologist, it is going to be a straight forward diagnosis of malignant melanoma only if the above said histomorphological findings are present. Once the tumour cells are not having the cytoplasmic melanin pigment then it is going to be a very difficult task for the pathologist for diagnosing malignant melanoma based only on histomorphology. The subvariant form of malignant melanoma is called amelanotic melanoma in which the tumour cells are usually devoid of cytoplasmic melanin pigments. This amelanotic melanoma is often misdiagnosed as lymphoma, carcinoma or sarcoma [11]. Since, these kinds of tumours can be subtyped and diagnosed only based upon the Immunohistochemical study. Immunohistochemical markers are extremely useful for diagnosing amelanotic variant of malignant melanoma. In the present case series, the cytoplasmic melanin pigment and atypical epidermoid cells next to the tumour focus were completely absent; therefore the diagnosis was based on immunohistochemistry results that the tumour cells are immunoreactive for HMB45 and S100. Similar findings were seen in a study by Serra M et al., where the diagnosis of malignant melanoma was only possible with the use of an immunohistochemistry examination because there were no typical histopathological characteristics present [12]. Khan M et al., and Urbani M et al., also diagnosed a case of anorectal melanoma based on histomorphological and immunohistochemical markers such as S100 and HMB45 [13,14]. Using TNM pathologic staging classification malignant melanoma is grouped into four stages:

Stage I: Tumour thickness is <2 mm or <1 mm thickness with ulceration and no regional lymph node metastasis.

Stage II: Tumour thickness is >2 mm or >1 mm thickness with ulceration and no regional lymph node metastasis.

Stage III: Tumour of any size with regional lymph node metastasis.

Stage IV: Melanoma cells have spread elsewhere in the body, away from the primary site [15].

For the treatment of anorectal melanotic melanoma, options range from local excision to radical abdomino perineal resection. Other modes of treatment such as adjuvant chemotherapy, immunomodulators like Interferon, Alpha interleukin 2 and adjuvant radiotherapy following promising results [16]. However, definite assessment of the efficacy of the adjuvant therapy requires further studies and individualised approach according to the stage of the disease. Overall anorectal amelanotic melanoma carries poor prognosis as compared to many other tumours. A summary of this study findings with various authors are depicted in [Table/Fig-16,17].

Author name	Year and place of study	Clinical findings	Radiological findings
Present study	Tamil Nadu, 2022	Polypoidal mass (Case 1,2,3)	Polypoidal intraluminal mass (Case 1,2,3)
Yadav S et al.,[3]	Maharashtra, 2018	Brownish black mass	NA
Kobakova I et al., [4]	Bulgaria, 2018	Polypoidal mass	NA
Kumar U et al., [7]	Delhi, 2017	Polypoidal mass	Circumferential thickening
Van Pham B et al., [8]	Korea, 2020	Polypoidal mass (Case 1,2)	No lymphnode or distant metastasis (case 1), NA (case 2)
Zhang MD et al., [9]	Philadelphia, 2016	Firm haemorrhoid like mass (Case 1,2,3)	NA (case 1,2,3)
Nguyen et al., [10]	Vietnam, 2020	Large pigmented polyp	Lesion limited to Submucosa
Serra M et al., [12]	Portugal, 2019	Prolapsed mass	NA
Khan M et al., [13]	Chicago, 2014	Non obstructive firm mass	Mass lesion with marked metabolic activity
Urbani M et al., [14]	Italy, 2016	Blackish fragile lesion	NA

[Table/Fig-16]: Comparison of clinicoradiological findings of anorectal melanoma with various studies [3,4,7-10,12-14].
NA: Not applicable

Author name	Year and place of study	Histomorphological diagnosis	Positive IHC markers	Follow-up details
Present study	Tamil Nadu, 2022	Amelanotic malignant melanoma (case 1,2,3)	S-100, Human Melanoma Black 45 (HMB 45) (case 1,2,3)	Referred for palliative chemotheraphy (case 1), Lost to follow-up (case 2) and Referred to higher center (case 3)
Yadav S et al., [3]	Maharashtra, 2018	Malignant melanoma	HMB 45	NA
Kobakova I et al., [4]	Bulgaria, 2018	Malignant melanoma	S100, HMB45, Melan A, Vimentin, CD117	NA
Kumar U et al., [7]	Delhi, 2017	Malignant melanoma	HMB45	PET CT showed multiorgan metastasis and then lost to follow-up
Van Pham B et al., [8]	Korea, 2020	Malignant melanoma (case 1,2)	HMB45, Melan A (case 1), HMB45 45 (case 2)	Received Adjuvant chemotherapy (case 1), Radiotherapy was initiated (case 2)
Zhang MD et al., [9]	Philadelphia, 2016	Malignant melanoma (case 1,2,3)	S100, HMB45 (case 1,2,3)	Surveillance chest radiography revealed lung metastasis (case 1), Intracerebral metastasis after symptom free interval for 2 years (case 2) and No distant spread (case 3)
Nguyen et al., [10]	Vietnam, 2020	Malignant melanoma	S-100, HMB45, Vimentin	NA
Serra M et al., [12]	Portugal, 2019	Amelanotic malignant melanoma	S-100, CD 117, HMB45	Patient died
Khan M et al., [13]	Chicago, 2014	Malignant melanoma	S-100, HMB45, Vimentin	Scheduled for chemotherapy
Urbani M et al., [14]	Italy, 2016	Malignant melanoma	S-100	Received adjuvant immunotherapy

[Table/Fig-17]: Comparison of Histomorphological and IHC Findings of Anorectal Melanoma with various studies [3,4,7-10,12-14].
PET CT: Positron emission tomography and computed tomography

CONCLUSION(S)

Anorectal amelanotic melanoma is a very rare and aggressive disease with high morbidity and mortality. Diagnosing anorectal amelanotic melanoma is challenging. This is the cancer that may be misdiagnosed as an anorectal polyp or refractory haemorrhoids. Histologically, anorectal amelanotic melanoma can resemble cancers such as lymphoma, sarcoma, and carcinoma. Therefore, melanoma diagnosis is very challenging without immunohistochemical analysis and clinicopathological suspicion. The clinician and pathologist should consider amelanotic melanoma as a differential diagnosis for lesions involving the anorectal region even if it is a rare occurrence. Therefore, through this case series, the awareness of this rare entity is highlighted.

Acknowledgement

The authors are grateful to Prof. Dr. T. Gomathy, Department of Pathology, Dr. Ravi Iyengar, Surgical Oncologist and Department of Radiology, Dhanalakshmi Srinivasan Medical College and Hospital, Perambalur for their support throughout the study.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 03, 2022
- Manual Googling: Sep 26, 2022
- iThenticate Software: Oct 03, 2022 (5%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Aug 22, 2022**
Date of Peer Review: **Sep 12, 2022**
Date of Acceptance: **Oct 04, 2022**
Date of Publishing: **Nov 01, 2022**