

A rare case of a primary malignant anorectal melanoma

Andrei Văcărașu¹, Razvan Iosifescu^{2,3}, Marius Zamfir^{1,2}, Mara Mardare^{1,2}, Irina Bondoc¹, Camelia Călin³, Leila Ali³, Bianca Galateanu⁴, Taxiarchis K. Nikolouzakis^{5,6}, Maria Tolia⁷, Octav Ginghină^{1,2}

AFFILIATION

- 1 Surgery 3 Department, Institute of Oncology 'Prof. Dr. A. Trestioreanu', Bucharest, Romania
- 2 Faculty of Medicine, University of Medicine and Pharmacy 'Carol Davila', Bucharest, Romania
- 3 General Surgery Department, Emergency Clinical Hospital 'Sf. Ioan', Bucharest, Romania
- 4 Department of Biochemistry and Molecular Biology, University of Bucharest, Bucharest, Romania
- 5 Department of General Surgery, University General Hospital of Heraklion, Greece
- 6 Laboratory of Toxicology, Medical School, University of Crete, Heraklion, Greece
- 7 Department of Radiotherapy, School of Medicine, University of Crete, Heraklion, Greece

CORRESPONDENCE TO

Mara Mardare. Surgery 3 Department, Institute of Oncology 'Prof. Dr. A. Trestioreanu', 252 Fundeni Avenue, 022328, district 2, Bucharest, Romania.
E-Mail: mara_mardare@yahoo.com

KEYWORDS

anorectal melanoma, abdominoperineal resection, case report

Received: 28 December 2022, **Revised:** 7 January 2023, **Accepted:** 9 January 2023
Public Health Toxicol. 2023;3(1):1
<https://doi.org/10.18332/pht/159114>

ABSTRACT

Anorectal melanoma (ARM) is an extremely rare and aggressive malignancy. There is no standard therapeutic management, mainly due to scarcity of data and randomized control trials regarding the optimal surgical strategy.

We present the case of a male patient aged 65 years in our hospital, presenting perineal pain and rectal bleeding. Patient's performance status (PS) was good. Hematological analysis revealed normocytic normochromic anemia. In the rectoscopy, an anal canal tumor formation was identified. The diagnosis of ulcerated melanoma was confirmed at the histopathological examination. The pelvic MRI detected a circumferential parietal thickening, posteriorly accentuated

at the level of the anal canal, about 4.4 cm long, situated 2 cm from the external anal orifice, causing a subtotal lumen stenosis. The patient underwent abdominoperineal resection (APR). Postoperative course was favorable and the patient was discharged on the 13th postoperative day, with no complications.

A multidisciplinary cancer care team will prove to be of substantial value, because it may develop a personalized treatment plan for this unusual tumor. Although the therapeutic approach is still controversial, surgery is considered the mainstay therapy.

INTRODUCTION

Anorectal melanoma (ARM) is an extremely rare and highly aggressive malignant lesion. It presents a low incidence, comprising between 0.05% and 4.6% (depending on the geographical area)¹. Most ARM patients are caucasian females, aged 60–90 years. The most common symptoms described include abdominal pain, anal bleeding and constipation¹. Non-specific symptoms can lead to a difficult differential diagnosis, since 25% of the ARMs have an amelanotic histological appearance (lack of pigmentation) and can be easily misdiagnosed as a benign polyp, adenocarcinoma, or clinically as hemorrhoids².

The current available data are inconclusive and do not

allow the formulation of guidelines regarding the optimal treatment strategy. Although no therapeutic consensus exists, wide local excision (LE) and abdomino-perineal resection (APR) are considered as the main therapies, with no difference in survival rates³⁻⁵. If technically feasible, wide local excision may represent a less invasive surgical procedure, maintaining the anal sphincter and patient's quality of life^{4,5}.

CASE PRESENTATION

A patient aged 65 years in a good general condition was presented complaining of a specific clinical symptomatology, with episodic perineal pain, discomfort and rectal bleeding.

Figure 1. Hematoxylin-eosin staining of colonic tissue biopsy showing: a) epithelioid cells with eosinophilic cytoplasm, intracytoplasmic granular brown pigment deposits, vesicle nuclei with eosinophilic macronucleoli (OB 10X), and b) granulation tissue, overlying fibrinemat and neutrophilic exudate (OB 20X)

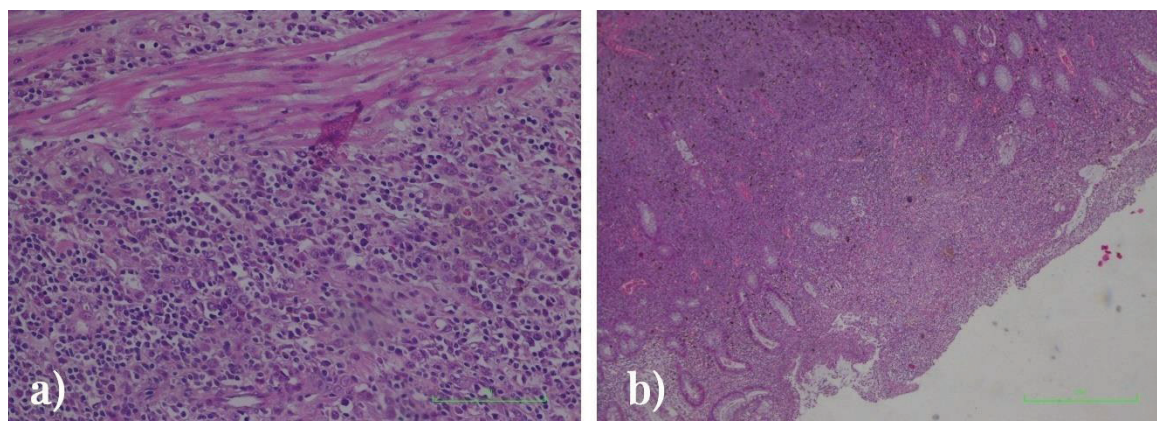


Figure 2. Pelvic MRI: a) transversal view, arrow indicating anal tumor partially stenotic, and b) frontal view, cranio-caudal grown anal tumor

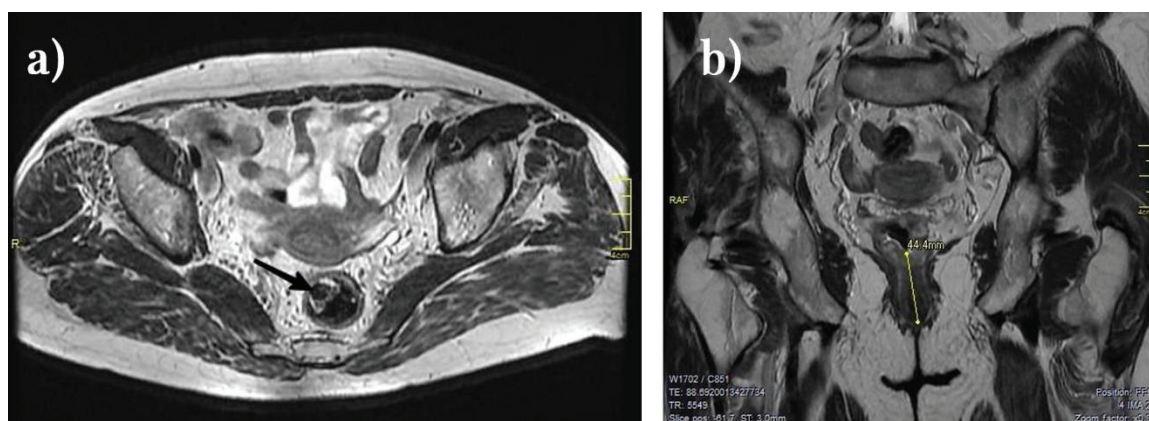
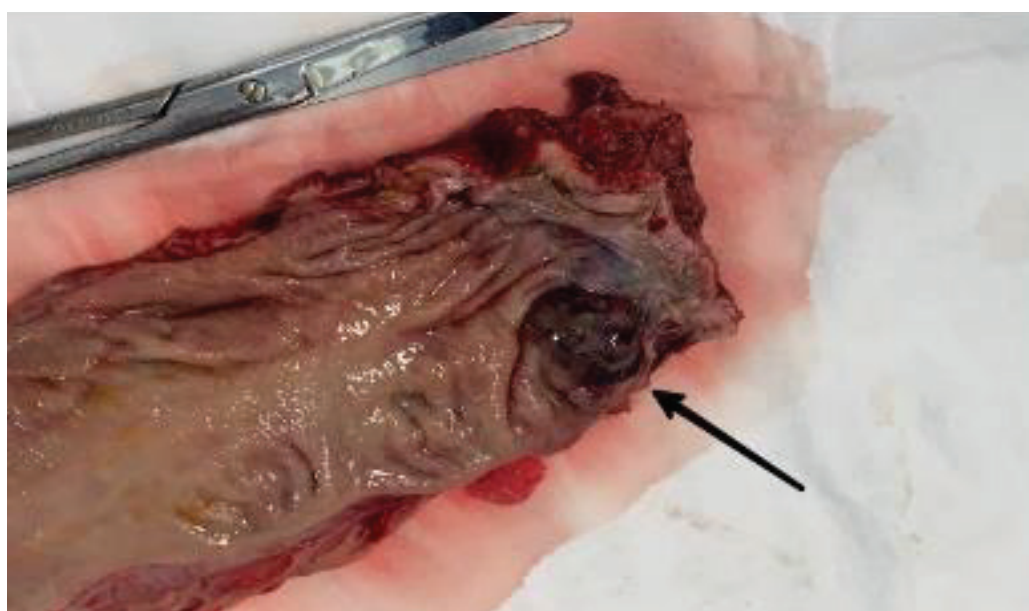


Figure 3. Sliced open rectal amputation specimen, arrow indicating the tumor at 2 cm from the external anal orifice



A rectoscopy was carried out revealing an anal canal tumor mass that was biopsied. After a detailed dermatological examination, no other skin lesions were found, suggesting that the anorectal localization was the only primary site of the tumor. The pathological examination revealed a proliferation with granulation tissue, overlying fibrinematous and neutrophilic exudate, solid pattern consisting of large epithelioid cells with eosinophilic cytoplasm, intracytoplasmic granular brown pigment deposits, vesicle nuclei with eosinophilic macronucleoli and frequent atypical mitosis, an aspect compatible with the diagnosis of ulcerated malignant melanoma (Figure 1).

The analysis of haematological and biochemistry analytes indicated a normochromic normocytic anemia. There were no signs of locoregional or presence of distant metastasis on the performed staging workup, including staging MRI and CT scans. The MRI of the pelvis detected a circumferential parietal thickening of approximately 19 mm, posteriorly accentuated at the level of the anal canal about 4.4 cm long, at 2 cm from the external anal orifice, causing the subtotal obstruction, with no serosa or levator muscles' infiltration (Figure 2).

The patient underwent an APR with an R0-resection (Figure 3). Consequently, the postoperative course was favorable with fast recovery and no complications. The patient regained normal bowel movements on the 13th postoperative day. Two years later, no complications occurred and the patient is still followed up regularly (every 6 months, with imaging, hematological and biochemical tests), with no signs of local or distant tumor recurrence.

DISCUSSION

ARM therapeutic management strategies have not been well established, due to the lack of available randomized control trials. The treatment of ARM is mainly surgical, but the optimal approach is still debatable. The principal surgical procedure can be either APR or LE.

Brady et al.⁶ reviewed retrospectively a total of 85 cases and found that the overall survival for these patients was very poor (17% at 5 years; median, 19 months). The authors showed that APR can be considered as the preferred surgical approach for localized ARM. Long-term survival was better in the APR group versus local surgical procedures (27% vs 5%; $p=0.11$).

The invasion of the submucosa allows tumor cells to gain access to lymphovascular pathways, accelerating tumor growth. As a result, the depth of the tumor invasion determines the chances of lymphatic dissemination, rather than the thickness of the lesion, similar to the behavior of adenocarcinomas⁷. The presence of lymph node involvement is a negative prognostic factor and it is associated with a high mortality rate, especially in case of mesenteric lymphadenopathy. Perez et al.⁸ found a higher disease-specific survival in cases with clinically negative inguinal lymph nodes. The investigators concluded that

lymphadenectomy should be reserved only for gross symptomatic disease. Another negative powerful prognostic factor is the presence of tumor perineural invasion (PNI). Perez et al.⁸ indicated that PNI was significantly correlated with recurrence-free survival because in their study all PNI patients experienced recurrence 2 years after surgery ($p=0.002$).

The surgical treatment decision (LE vs APR) should be individualized^{9,10}. Temperley et al.⁹ performed a meta-analysis that included 10 studies and 303 patients. The main aim of the review was to compare LE and APR outcomes. The review included a total of 303 patients. The authors observed that despite the slightly better 5-year survival rate of LE (32% vs 23%), a statistically significant reduction in recurrence was found in APR group (OR=0.15; 95% CI: 0.08–0.28, $p<0.00001$)⁹. Lei et al.¹¹ analyzed 795 ARM patients from the USA Surveillance, Epidemiology, and End Results (SEER) database. A nomogram based on a multivariate Cox regression model was generated to predict ARM-Specific Survival. The nomogram C-index was 0.74 (95% CI: 0.71–0.77) on internal verification, and in the validation cohort the nomogram C-index was 0.72 (95% CI: 0.68–0.76). The propensity score matching analysis results showed that patients who underwent surgery achieved a statistically significant overall survival (log-rank=17.41, $p<0.001$; ARM-Specific Survival: log-rank=14.55, $p<0.001$). Patients were stratified into LE and extended surgery (ES) groups, but the results were not statistically significantly different between the two subgroups (all $p>0.05$) and ES may not improve ARM-Specific or Overall Survival¹¹. A recent systematic review and meta-analysis by Jutten et al.^{12–14} identified 347 studies and included 34 studies, with a total of 1858 ARM patients. They found that, regardless of stage, no significant difference in overall survival was found between the two surgical approaches (LE or ER). The authors found: in stage I, odds ratio 1.30 (95% CI: 0.62–2.72, $p=0.49$); in stage II, odds ratio 1.61 (95% CI: 0.62–4.18, $p=0.33$); and in stages I-III, odds ratio 1.19 (95% CI: 0.83–1.70, $p=0.35$)^{12–14}.

Surgery is beneficial in cases without evidence of metastatic disease. In case of stage IV, a survival benefit was found because of immunotherapy and targeted therapies¹⁵. Treatments that inhibit the activity of type III transmembrane receptor tyrosine kinase KIT have been investigated by using imatinib mesylate and very good clinical responses were obtained, but only in the case of malignancies with demonstrated functional KIT mutations as demonstrated by Kim et al.¹⁵ and Carvajal et al.¹⁶. The study led by Taylor et al.¹⁷ affirms that the 2-year survival of ARM patients treated with immunotherapy increased, without any influence of their survival at 5 years though. Thus the research of new molecules is encouraged to change the treatment from a palliative to a curative one.

The most appropriate treatment strategy for ARM remains controversial regarding both the use and timing of radiotherapy (RT) in neoadjuvant or adjuvant setting.

Patients who underwent LE with adjuvant chemotherapy and/or RT had a similar cancer-specific survival compared to those who underwent only ES¹⁸. In two single center studies, Ballo et al.¹⁹ and Kelly et al.²⁰ evaluated 23 and 54 patients, respectively, who underwent LE, nodal dissection, and adjuvant RT and both have shown that the regimen has adequate local-regional disease control and is well tolerated. Ballo et al.¹⁹ reported a 5-year local and regional nodal control with rates of 74% and 84%, respectively, and Kelly et al.²⁰ achieved a 5-year local control rate of 82%. Neoadjuvant chemo-irradiation (CRT) was performed in order to achieve a pathological response, a negative margins excision and render a sphincter preservation feasible^{21,22}.

CONCLUSION

ARM is an exceptionally rare disease with poor survival. Although the optimal therapeutic approach has not yet been established, surgery remains the only effective therapy^{23,24}. The role of RT is still controversial, while new immunotherapeutic treatments are being developed. The main prognostic factors are tumor extent/stage, presence of perineural invasion and/or lymphodal metastasis. LE is sufficient when free resection margins may be achieved, because ARM disseminates along the submucosal planes. In case of larger tumors or sphincter infiltration, an APR is required with curative intent²⁵. Regional lymphadenectomy is advised when regional lymph node metastases are present. Palliative surgery may be warranted in case of distant metastases presence (metastasectomy) and in cases of refractory pain or incontinence.

REFERENCES

- de Meira Júnior JD, Sobrado LF, Guzela VM, Nahas SC, Sobrado CW. Anorectal Mucosal Melanoma: A Case Report and Literature Review. *Am J Case Rep.* 2021;22:e933032. doi: 10.12659/AJCR.933032
- Malaguarnera G, Madeddu R, Catania VE, et al. Anorectal mucosal melanoma. *Oncotarget.* 2018;9(9):8785-8800. doi:10.18632/oncotarget.23835
- Reina A, Errasti J, Espín E. Anorectal melanoma. An update. *Cir Esp.* 2014;92(8):510-516. doi: 10.1016/j.ciresp.2013.07.004
- Droesch JT, Flum DR, Mann GN. Wide local excision or abdominoperineal resection as the initial treatment for anorectal melanoma?. *Am J Surg.* 2005;189(4):446-449. doi:10.1016/j.amjsurg.2005.01.022
- Nilsson PJ, Ragnarsson-Olding BK. Importance of clear resection margins in anorectal malignant melanoma. *Br J Surg.* 2010;97(1):98-103. doi: 10.1002/bjs.6784
- Brady MS, Kavolius JP, Quan SH. Anorectal melanoma. A 64-year experience at Memorial Sloan-Kettering Cancer Center. *Dis Colon Rectum.* 1995;38(2):146-51. doi: 10.1007/BF02052442
- Ferrer Márquez M, Velasco Albendea FJ, Belda Lozano R, Berenguel Ibáñez Mdel M, Reina Duarte Á. Adenocarcinoma del canal anal. Revisión de conjunto. Adenocarcinoma of the anal canal. Narrative review. *Cir Esp.* 2013;91(5):281-286. doi:10.1016/j.ciresp.2013.01.002
- Perez DR, Trakarnsanga A, Shia J, et al. Locoregional lymphadenectomy in the surgical management of anorectal melanoma. *Ann Surg Oncol.* 2013;20(7):2339-2344. doi:10.1245/s10434-012-2812-6
- Temperley HC, O'Sullivan NJ, Keyes A, et al. Optimal surgical management strategy for treatment of primary anorectal malignant melanoma-a systematic review and meta-analysis. *Langenbecks Arch Surg.* 2022;407(8):3193-3200. doi:10.1007/s00423-022-02715-1
- Kuka WP, Gatheru J, Mwanzi S, Onyango N, Rajula A. Primary rectal melanoma in an African female: a case report. *Pan Afr Med J.* 2022;41:286. doi: 10.11604/pamj.2022.41.286.33128
- Lei X, Qingqing L, Weijie Y, et al. Effect of surgical treatment for anorectal melanoma: a propensity score-matched analysis of the Surveillance, Epidemiology, and End Results programme data. *BMJ Open.* 2022;12(4):e053339. doi: 10.1136/bmjopen-2021-053339
- Jutten E, Kruijff S, Francken AB, et al. Surgical treatment of anorectal melanoma: a systematic review and meta-analysis. *BJS Open.* 2021;5(6):zrab107. doi:10.1093/bjsopen/zrab107
- Kazi M, Chatterjee A, Saklani A. Comment on: Surgical treatment of anorectal melanoma: a systematic review and meta-analysis. *BJS Open.* 2022;6(1):zrac015. doi:10.1093/bjsopen/zrac015
- Jutten E, Kruijff S, Francken AB, et al. Author response to: Surgical treatment of anorectal melanoma: a systematic review and meta-analysis. *BJS Open.* 2022;6(1):zrac016. doi: 10.1093/bjsopen/zrac016
- Kim KB, Eton O, Davis DW, et al. Phase II trial of imatinib mesylate in patients with metastatic melanoma. *Br J Cancer.* 2008;99(5):734-740. doi:10.1038/sj.bjc.6604482
- Carvajal RD, Antonescu CR, Wolchok JD, et al. KIT as a therapeutic target in metastatic melanoma. *JAMA.* 2011;305(22):2327-2334. doi: 10.1001/jama.2011.746
- Taylor JP, Stem M, Yu D, et al. Treatment Strategies and Survival Trends for Anorectal Melanoma: Is it Time for a Change?. *World J Surg.* 2019;43(7):1809-1819. doi:10.1007/s00268-019-04960-w
- Kahl AR, Gao X, Chioreso C, et al. Presentation, Management, and Prognosis of Primary Gastrointestinal Melanoma: A Population-Based Study. *J Surg Res.* 2021;260:46-55. doi:10.1016/j.jss.2020.11.048
- Ballo MT, Gershenwald JE, Zagars GK, et al. Sphincter-sparing local excision and adjuvant radiation for anal-rectal melanoma. *J Clin Oncol.* 2002;20(23):4555-4558. doi:10.1200/JCO.2002.03.002
- Kelly P, Zagars GK, Cormier JN, Ross MI, Guadagnolo BA. Sphincter-sparing local excision and hypofractionated radiation therapy for anorectal melanoma: a 20-year experience. *Cancer.* 2011;117(20):4747-4755. doi:10.1002/cncr.26088
- Su M, Zhu L, Luo W, Wei H, Zou C. Primary anorectal malignant melanoma treated with neoadjuvantchemoradiotherapy

- and sphincter-sparing surgery: A case report. *Oncol Lett.* 2014;7(5):1605-1607. doi: 10.3892/ol.2014.1925
22. Uner A, Kilic D, Menten BB, Egehan I, Dursun A. Neoadjuvant radiotherapy in anorectal malignant melanoma. *Int J Clin Pract.* 2003;57(1):65-67. Accessed January 7, 2023.
23. Glowka TR, Keyver-Paik MD, Thiesler T, Landsberg J, Kalff JC, Pantelis D. Das anorektale maligne Melanom: Eine Therapieempfehlung. Anorectal malignant melanoma: Treatment recommendations. *Chirurg.* 2016;87(9):768-774. doi:10.1007/s00104-016-0242-x
24. Nafees R, Khan H, Ahmed S, Ahmed Samo K, Siraj Memon A. Primary Rectal Amelanotic Malignant Melanoma: A Rare Case Report. *Cureus.* 2020;12(5):e8115. doi:10.7759/cureus.8115
25. Li Z, Šandera P, Beer M, Weber M. A rare case of recurrent primary anorectal melanoma emphasizing the importance of postoperative follow-ups. *BMC Surg.* 2020;20(1):68. doi:10.1186/s12893-020-00727-6

CONFLICTS OF INTEREST

The authors have each completed and submitted an ICMJE form for disclosure of potential conflicts of interest. The authors declare that they have no competing interests, financial or otherwise, related to the current work. This research was partially funded by the European Union's Horizon Europe framework program project name: European Partnership for the Assessment of Risks from Chemicals (PARC).

FUNDING

This research was partially funded by the European Union's Horizon Europe framework program project name: European Partnership for the Assessment of Risks from Chemicals (PARC).

ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval and informed consent were not required for this study.

DATA AVAILABILITY

The data supporting this research is available from the authors on reasonable request.

AUTHORS' CONTRIBUTIONS

AV, RI and MM conceived the work idea and formed the layout of the manuscript. MM, BG and OG wrote the final draft of the manuscript. MZ, IB, CC and LA contributed in the patient data collection and carried out literature search. MT and OG contributed to the final manuscript format adjustments and content editing. All authors read and approved the final manuscript.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.