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## Original Article

# Anorectal melanoma – histopathological and immunohistochemical features and treatment☆

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## ARTICLE INFO

## ABSTRACT

Anorectal melanomas should be characterized by location (anal, rectal and anorectal), color, size, shape and mobility and microscopically, by melanocyte subtypes, grade of melanin pigmentation, junctional changes in the squamous epithelium, atypical mitotic index, cellular atypia, inflammatory infiltrate, vascular and perineural invasion, sentinel lymph node, and anorectal parietal penetration. Anorectal melanomas must be staged by American Joint Committee on Cancer (AJCC) and/or TNM Classification of Malignant Tumours (TNM) criteria. As melanocytes can present with several shapes, sometimes the differential diagnosis with other tumors in this region may be difficult. Because of this, immunohistochemistry is mandatory to attain a precise diagnosis. This study is a report of 14 patients with anorectal melanoma, in whom histological examinations were remade and immunohistochemistry was performed with several markers for melanocytes and for other tumor cells of the anorectal region, properly establishing the diagnosis. The most rational surgery is the extended local resection, when the disease is restricted to the area or the abdominoperineal resection to advanced lesions. Regardless of the technique used, the results are always poor. The authors deny any efficacy of current radio and/or chemotherapy as part of treatment of anorectal melanoma. Target-therapy for metastatic disease has been considered a good strategy, but the results are still inconclusive.

## Melanoma anorretal – diagnósticos histopatológico e imunohistoquímico e tratamento

R E S U M O

*Palavras-chave:*
Melanoma anorretal
Câncer anorretal
Histopatologia
Imunohistoquímica
Tratamento cirúrgico

Os melanomas anorretais (ARM) devem ser caracterizados pela localização (anal, retal e anorretal), coloração, dimensão, forma e mobilidade. Microscopicamente, por tipos de melanócitos, graduação da pigmentação melânica, alterações juncionais sob o epitélio escamoso, índice mitótico atípico, atipias celulares e citoplasmáticas, infiltrado inflamatório, invasões vascular e perineural, linfonodo sentinela e penetração parietal. Devem ser estadiados pelos critérios American Joint Committee on Cancer (AJCC) e/ou TNM Classification of Malignant Tumours (TNM). Como as células do ARM são variáveis, isto torna difícil o diagnóstico diferencial com outros tumores da região anorretal. Assim, faz-se necessária a realização de IHC. Apresentamos uma série de 14 pacientes, nos quais foram refeitos exames histológicos e realizados IHCs com vários marcadores, firmando corretamente o diagnóstico. Os trabalhos mostram que a cirurgia mais racional é a excisão local alargada (ELA) em casos de doença localizada e ressecção abdominoperineal do reto (APR) para lesões avançadas. Independente da técnica, a sobrevida de cinco anos é inferior a 35%; a sobrevida média não ultrapassa 26 meses; o tempo livre de doença é inferior a 10 meses; e a sobrevida global não ultrapassa é de 32 meses. Não há correlação entre melhora dos resultados com qualquer tratamento adjuvante. As terapias-alvo para doença metastática começam a apresentar resultados animadores, ainda inconclusivos.

## Introduction

The anorectal melanoma (ARM) is a tumor that originates in melanocytes – cells that produce melanin – and which develops in the anal canal. The first description of ARM in the literature dates from 1897, by Moore.[1] ARMs are rare. The most common sites of incidence of melanomas are the skin (91.2%), followed by eyes (5.2%) and the anorectal region (less than 1%).[2] ARMs occur more often between the sixth and eighth decades of life[3] and are more frequent in women.[4] The etiology of ARMs is associated to exposure of the skin to ultraviolet rays, which explains its rarity in the anorectal region, usually not exposed.[5]

The symptoms are common to other tumors of the anorectal region: elimination of mucus and blood through the anal canal, anal pain, feeling of rectal fullness or incomplete evacuation, externalization of tumor and changes in bowel habits. The proctologic examination allows detection of the tumor, but it may be misdiagnosed as other diseases of the anal canal: thrombosed hemorrhoids or other tumor lesions, especially if the lesion is not pigmented. Examination of the inguinal regions should be performed to search for metastatic nodes. A biopsy is mandatory to attain proper diagnosis.[5]

Histological (hematoxylin–eosin) examination characterizes the lesion regarding cell type, degree of melanin pigmentation and mitotic index. Melanocytes can be found in four different forms: epithelioid, lymphoma-like, spindle-cell and pleomorphic, which complicates the differential diagnosis of some diseases such as Paget, Bowen, lymphomas, undifferentiated carcinomas, sarcomas and gastrointestinal stromal tumor (GIST). Thus, especially in amelanic ARMs (but also in melanocytic ones), immunohistochemistry should be performed – the study of protein expressions of melanocytes.[6]

The possible surgical procedures are: local excision, which may be extended, and abdominoperineal resection with or without inguinal lymphadenectomy. Several authors advocate extended local excision as the preferred procedure, as the prognosis is poor and similar, regardless of the surgical approach (whether economic or radical).[3,7,8] However, in advanced cases, or as rescue surgery after extended excision and recurrence, abdominoperineal resection can be performed.[9]

Adjunctive treatments show that low efficacy and melanomas are radio-resistant. Thus, radiation therapy is indicated only in special cases, as a palliative measure. Several chemotherapeutic agents have been tried without any substantiated conclusions about their benefit.[10] The possibility of studying specific mutations in ARMs has shown that melanomas are heterogeneous regarding their tumor biology.[11] Target molecules can be identified in some subgroups, allowing more specific treatment with better response. One of these subgroups includes patients with mutations in the BRAFV600E gene. BRAF inhibitors induce tumor regression in up to 70% of patients with metastatic disease.[12]

Another subgroup includes patients with melanomas with KIT gene aberrations, who can benefit from c-KIT blockers: imatinib, dasatinib, sunitinib and sorafenib. There are several ongoing phase II case reports, with promising results.[13]

This study reports 14 cases of melanoma diagnosed and treated at the Coloproctology Unit of Santa Casa de Belo Horizonte, during a 30-year period (1982–2012). The objectives are to report cases and demonstrate that immunohistochemistry is the gold-standard diagnostic method (Fig. 1).

**Fig. 1 – Illustrations of the 14 patients with ARMs: four surgical specimens of abdominoperineal resection (patients A, B, C and D), five patients submitted to local resection (patients E\*, F, G, I, L), one with protective stoma (patient E\*), one to extended local resection (patient H), one to relief colostomy (patient K), two to hemorrhoidectomy with the incidental finding of melanoma (patients M and N), and one who did not undergo surgery (patient J).**

## Methods

This is a historical series, given the rarity of the lesion, where the organization and method of the main investigator were essential for the completion of the work. It was only possible to carry it out because the necessary material was stored and cataloged, allowing new tests to be performed.

Review of medical records and histopathological and immunohistochemistry studies were performed in slides and paraffin blocks of tumors. Age, gender, ASA classification

**Table 1 – Main IHC markers used in the diagnosis of ARM and several other anorectal diseases, making the differential diagnosis between them.**

|  | ARM | Paget | Bowen | Lymphoma | UCA | GIST | LMS |
|---|---|---|---|---|---|---|---|
| *ARM markers* | | | | | | | |
| S-100 protein | S | | | | | | |
| HBM-45 | S | | | | | | |
| Melan-A/MART-1 | S | | | | | | |
| Vimetime | S | | | | | S | |
| C117 (c-kit) | S/N | | | | | S/N | S |
| PDGFRA | S | | | | | S | |
| *TU markers no ARM* | | | | | | | |
| CEA | | S | | | | | |
| CK high MW (34BE12, AE1) | | | S | | | | |
| CK low MW (35BE12, AE2, AE3) | | S | | | | | |
| CD34 (QBEN-10) | | | | | | S | |
| CD45 (PTPRC) | | | | S | | | |
| CD68 | | | | | | | |
| Chromogranin A (CHGA) | | | | | S | | |
| Synaptophysin (SYP) | | | | | S | | |
| Desmin (DES) | | | | | | S | S |
| Caldesmon (CALD-1) | | | | | | | S |
| DOG-1 | | | | | | S | |

GIST, Gastrointestinal Stromal Tumor; UCA, undifferentiated carcinoma; TU, Tumor.

of patients, type of surgery, TNM classification and survival/mortality data were collected from the sample.

The patients were submitted to the four basic types of surgery: local resection, extended local resection, colostomy derivation (alone or associated with local resection) or abdominoperineal resection of the rectum (APR).

Histopathological analysis was performed with H&E staining (hematoxylin–eosin) in 5-mm slides. Cell type (epithelioid, spindle cell, lymphoma-like and pleomorphic); degree of melanin pigmentation (severe, moderate and focal, or absent); junctional activity under the squamous epithelium; melanocytic involvement of the anorectal junction; presence of abundant and eosinophilic cytoplasm; type of nuclei (round and vesicular); prominent eosinophilic nucleoli; presence of inflammatory infiltrate; perineural and vascular invasion; parietal invasion and mitotic index per microscopic field were characterized. New slides were made from the paraffin blocks of eight patients. In the remaining patients, the slides were reviewed (four) or only considered (two). All analyses were performed by the same pathologist.

Immunohistochemistry (IHC) was performed in 12 patients. In four cases IHC was performed only for ARM markers. In eight cases IHC was performed for ARM markers and other non-ARM anorectal tumors. The immunohistochemical study was not possible in only two patients. All examinations were performed by the same pathologist. Immunohistochemistry allows confirmation of melanoma and the differential diagnosis with other anorectal tumors. Table 1 shows the major markers studied.

All the materials used (clinical records, histopathology and immunohistochemistry reports, slides-12 patients and paraffin-9 patients); the free and informed consent forms signed by the four patients still alive and approval by the Research Ethics Committee of Santa Casa de Belo Horizonte approving the project are in the possession of the main investigator.

## Results

Table 2 shows the sample descriptive data: age, gender, ASA classification of patients, type of surgery, TNM classification and survival/mortality. Age ranged from 44 to 81, with a mean age of 64.7 years. There were nine (64.3%) females and only two melanodermic patients (14.2%). The time of anorectal symptoms varied between three and 12 months (85.7%) with a mean of 7.7 months. Only eight patients (57.1%) perceived the presence of an anal tumor, but 92.2% complained of bleeding in stools and/or clothing. Most patients complained of symptoms during evacuation (92.9%): anal pain (57.1%), sensation of incomplete evacuation (14.2%), tumor prolapse during evacuation (21.4%). Fecal incontinence occurred in four (28.6%). Six (42.8%) had clinical symptoms of anemia and five patients (35.7%) had overall poor health status.

### Comorbidities

According to the ASA – American Society of Anesthesiology – classification, six patients were ASA I, three were ASA II and five were ASA III. The comorbidities were hypertension in eight patients, diabetes mellitus in three, congestive heart failure in two, chronic obstructive pulmonary disease in one, lower-limb varicose disease in two, anemia in four and two patients were cachectic.

Eight patients had good overall health status, three had regular and three patients had poor health status, one of them with synchronous breast cancer.

| Number | Age | Gender | ASA | Surgery | TNM | Survival/mortality |
|--------|-----|--------|-----|---------|-----|--------------------|
| **Table 2 – Sample characteristics – patients numbered from 1 to 14.** | | | | | | |
| 1 | 66 | M | III | APR | T3N1M0 | Death <1 month |
| 2 | 66 | F | I | APR | T3M0N0 | Death 36 months |
| 3 | 71 | F | II | APR | T3N1M1 | Death 8 months |
| 4 | 62 | M | I | APR | T3N1M1 | Death 14 months |
| 5 | 56 | M | I | LR | T3N1M1 | Death 5 months |
| 6 | 46 | M | II | LR | T3N0M0 | Death 12 months |
| 7 | 44 | F | I | ELR | T1N0M0 | DFS 7 years |
| 8 | 52 | F | I | ELR | T1N1M1 | Death 7 months |
| 9 | 66 | M | III | ELR | T1N0M0 | DFS 2 years |
| 10 | 81 | F | III | NO | T3N1M1 | Death 1 months |
| 11 | 72 | F | III | S | T4N0M0 | Death 8 months |
| 12 | 71 | F | III | ELR | T1N0M0 | DFS 14 years |
| 13 | 62 | F | I | HEM | T1N0M0 | DFS 17 years |
| 14 | 72 | F | II | HEM | T1N0M0 | DFS 12 years |

M, male; F, female; ASA, American Society of Anesthesiology, classification; APR, abdominoperineal resection; LR, local resection; ELR, extended local resection; NO, not operated; S, palliative stoma; HEM, hemorrhoidectomy; TNM, tumor staging system; DFS, disease-free survival.

### Proctologic examination and colonoscopy

The tumor was visible on inspection in eight (57.1%) patients. In 11 patients the tumor was palpable and the pectineal line was affected by the tumor in 13 (92.9%) cases. In 10 patients the tumor was anorectal, in three cases it was located in hemorrhoidal papilla and in one case the tumor was entirely rectal. The mean size was 3.7 cm. Nine tumors were dark, one was light in color (amelanic) and two had dark and light mixed areas. In nine patients (64.3%) the tumor was fixed and in five mobile, of which one was pediculated and two found in hemorrhoidal disease. In these two patients the diagnosis was made after histological analysis of the hemorrhoidectomy specimen. The tumors were ulcerated in one case, vegetating in 10 cases and flat in one case, in addition to the two located in hemorrhoids.

### Staging

With the exception of the two patients whose diagnosis was attained in hemorrhoidectomy specimens, all others underwent staging according to the tests available at the time of diagnosis. Imaging studies were most often performed.

### ARM staging characteristics

1. Tumor location: in 10 cases (71.4%) the tumor was anorectal; in three cases (21.4%) it was located in hemorrhoidal papilla, of which two were casual findings during hemorrhoidectomy, and in one case (7.1%) the tumor was rectal.
2. Anorectal wall thickening: present in five patients (35.7%), absent in seven (50.0%) and HD in two cases (14.2%).
3. Lymph nodes: para-iliac lymph nodes were observed in six patients (42.9%); inguinal chain lymph node in five patients (35.7%); paravertebral chain lymph nodes in four patients (28.6%), concomitantly. Invasion of the vagina and bladder was observed in one patient (7.1%).
4. Metastases: liver metastases were diagnosed in five patients (35.7%); lung metastases in four (28.6%), no bone metastases; subcutaneous metastases spread throughout the body in two (14.2%). At the second visit, due to disease recurrence, pelvic-perineal recurrences, bone metastases and overall metastases occurred.

### Surgeries performed, chemotherapy and radiotherapy, staging (TNM) of tumors, survival, disease-free interval and mortality

1. Surgeries performed: four patients underwent APR (28.6%), three underwent ELR with curative intent (21.4%), three underwent LR without curative intent (21.4%), two did not have the tumors resected (14.2%), and two underwent surgery for HD with HP examination showing ARM postoperatively (14.2%). Two were reoperated due to recurrent disease (14.2%). One was operated after the first surgery and underwent left lobe hepatectomy for single metastasis in the left lobe of the liver (7.1%).
2. Staging (TNM classification): S (stage)-I (To-T2, No/Nx, Mo), three patients; S-II (T3-T5, No/Nx, Mo), two patients; S-III (To-T5, N1, Mo), one patient; and S-IV (To-T5, No/Nx, M1), six patients.
3. Chemotherapy/radiotherapy: only one patient received CT and none received RT.
4. Survival, disease-free interval and mortality: of the 14 patients, nine died (64.3%) and five remain alive and disease-free (35.7%). For the nine patients who died, survival ranged from one to 36 months, with a mean survival of 8.4 months. Disease-free survival ranged from 2 to 17 years in the 5 patients who are still alive (Table 2).

### Histopathological analysis

1. Cell subgroups: pleomorphic cells were identified in two cases; all the remaining 12 patients (85.7%) had epithelioid cells concomitantly with spindle cells and "lymphoma-like" cells were not observed in any cases.
2. Melanin hyperpigmentation: 10 patients (71.4%) showed diffuse and intense melanin hyperpigmentation; one patient had no pigmentation; and three patients had pigmented and non-pigmented areas.

**Table 3 – IHC test results of 14 cases of ARM.**

| | Immunohistochemistry analysis (IHC) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Antigens associated to the melanoma | | | | Partial antigens | | Antigens not associated to the melanoma–associated to other anorectal tumors | | | | | | | | |
| | S-100 | HMB-45 | MART-1 | Vimetina (V9) | c-kit | CEA | AE-1 | AE-2 | ACT | DES | h-CAL | SYN | QBEN-10 | CD10 NEP | CD45 PTPRC |
| 1 | PD | PD | PD | PD | PF | N | N | N | N | N | N | N | N | – | N |
| 2 | PD | PD | PD | P/N | N | N | – | – | – | – | – | – | – | – | – |
| 3 | PD | PD | PD | – | –N | N | N | N | – | – | – | – | – | – | – |
| 4 | PD | PF | PD | PD | N | N | N | N | N | N | N | N | N | – | – |
| 5 | PD | PD | PD | PD | N | N | N | N | – | – | – | – | – | – | – |
| 6 | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| 7 | PD | PD | PD | PD | N | N | N | N | – | – | – | – | – | – | – |
| 8 | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| 9 | PD | PD | PD | – | N | N | N | N | – | – | – | – | – | N | – |
| 10 | PD | PD | PD | – | PF | N | N | N | – | – | – | – | – | N | – |
| 11 | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| 12 | PD | PD | PD | PD | PF | N | N | N | – | – | – | N | – | – | N |
| 13 | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| 14 | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |

PD, Positive/Diffuse; PF, Positive/Focal; N, Negative; –, not performed.

3. Junctional activity under the squamous epithelium: it was not found in one case and it was not reported in five cases; in the remaining eight patients, junctional activity under the squamous epithelium was described (57.1%).
4. Elevated and Atypical Mitotic Index: except for one patient, all the other 13 patients had elevated and atypical mitotic index described (92.9%).
5. Perineural and Vascular Invasion: it was not found in three patients, not reported in three patients and it was found in eight patients, being only perineural in one patient, vascular in two patients and perineural and vascular in the other five patients.
6. Parietal Invasion: could not be studied in five patients (three unresectable tumors and two inoperable ones). In the remaining nine patients: tumor invasion beyond the musculature in four patients; mucosal invasion only in two patients, up to the lamina propria in two and up to the submucosa even in one case.
7. Chain lymph nodes: studied in four cases in which radical surgery was performed. Fourteen ganglia were found in two, all without metastases, and two had 18 ganglia, three with malignancy and 14 ganglia, 12 with metastases.
8. Other lymph nodes: ganglia found by imaging tests could not be studied.

*Immunohistochemical findings*

Immunohistochemical (IHC) analyses were not performed in five of the 14 patients: in the first three because they were very old patients and IHC was not available, and in the last two due to the scarcity of material (hemorrhoidectomy). IHC analysis was performed in all other nine patients with S-100 protein and melanoma-associated antigens (HMB45 and Melan-A or MART-1). Vimentin (V9) was tested in six patients. The c-kit, CEA and cytokeratins (AE-1 and AE-2) were tested in the nine patients studied with S-100 protein and melanoma-associated antigens. Actin, desmin, caldesmon-h and CD34 or QBEN-10 were tested in two patients; synaptophysin in three patients, CD10 or NEP was tested in two patients, and CD45 or PTPRC was tested in two patients (Table 3).

The tumor cells stained by markers and counterstained with Giemsa, showed strong positivity for Vimentin – V9 (100%) and for melanoma-associated antigens – S-100 protein (100%), HMB45 (100%) and MART-1 or Melan-A (100%). The c-kit showed focal positivity in three cases (33%), and CD-68 and Iron were positive in one case in which they were tested. They showed negativity for high molecular weight cytokeratins (AE1 and 34BE12); they were negative for low molecular weight cytokeratin (35BE12 and AE2); negativity for CEA, smooth muscle actin, Desmin, h-caldesmon, synaptophysin, CD34 (QBEN-10), CD-10 (NEP) and CD45 (PTPRC) in cases in which they were tested (Table 3 and Fig. 2).

## Discussion

Anorectal melanomas (ARMs) are rare tumors. In a review of cancer cases in nine states, until 1993, Weinstock[4] found an incidence of 1.7 ARM cases per million inhabitants. In other studies, the incidence ranged from 1 to 2% per million inhabitants.[14,15]

In this study we cannot assess the real impact of ARMs. Of the series of 14 cases, six were treated by the main investigator, within a universe of 40,000 anorectal examinations (0.15% incidence) and among 973 cases of colorectal cancers (0.6% of them).

The highest incidence of ARM is between the sixth and eighth decades of life.[3] In a review of 126 cases of ARMs treated from 1973 to 2001, Podnosy et al. reported a higher prevalence in women (61%), with a mean age of 69.2 years.[16] Weinstock[4] reported that the incidence was higher in women (between 54 and 76%) and higher in whites than in blacks. In this study we also found a mean age of 64.7 years and a higher prevalence
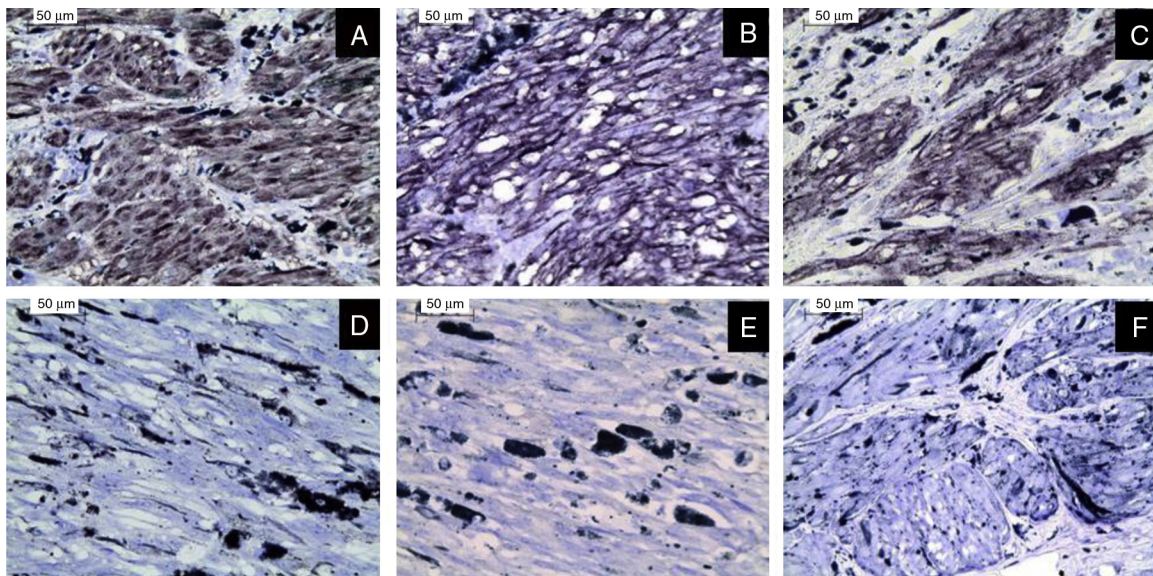
Fig. 2 – IHC of the ARM of patient I (9) (counterstaining with Giemsa). (A) S-100 protein: positive result (enucleate cytoplasmic staining, with evident brownish color), (B) Melan-A: positive result (brownish cytoplasmic staining), (C) HMB-45 positive result (brownish cytoplasmic staining with granular pattern, corresponding to melanosomes), (D) CK-AE1/AE3: negative result (the melanin pigment, originally brownish, acquires a greenish hue); (E) CD10: negative result (no brownish staining), (F) c-kit: negative result (absence of brownish staining).

among women (nine). Of the fourteen patients, twelve were white.

Slingluff, Collmer and Seigler, in a review of 24 ARM cases, identified rectal bleeding as the most common symptom, followed by anal pain, visible or palpable mass, pruritus ani, tenesmus, prolapse and change in bowel habits.[17] The symptoms of patients in this series coincide with this report, in addition to overall poor health status in five patients (35.7%).

Proctologic examination in this series showed that the tumor was visible (57.1%) or palpable (92.9%) in almost all cases. The mean size was 3.7 cm and in 12 patients the tumor was dark in color. These data show that the diagnosis is easily suspected, although almost always delayed. In 13 patients the pectineal line was affected, which is consistent with the literature.[18] Tumor staging showed stage I in 21.4% of patients (two incidentalomas found during hemorrhoidectomy) and stage IV (42.9%) in most symptomatic patients. Lymph node metastasis was found in six patients and distant metastases in five (liver, lung and disseminated subcutaneous). These findings are variable in the literature,[3,18] but corroborate the fact that the disease is severe at the diagnosis.

Chute et al.[6] evaluated 17 cases of primary ARM with special reference to histopathology and IHC. The morphological characteristics evaluated microscopically included cell morphology, melanin pigmentation, junctional change and mitotic rate. Morphological subtypes of ARM were: epithelioid (12 cases), spindle-cell (seven cases), lymphoma-like (10 cases) and pleomorphic (six cases). Melanin pigmentation was present in nine cases; junctional change was present in six cases and mitotic rate was three or more per high-frequency microscopy field in eight cases.

These findings coincide with those of this series: as cell subgroups, in 12 patients (85.7%) the ARMs had epithelioid cells concomitantly with spindle cells; 10 patients (71.4%) had diffuse and intense melanin hyperpigmentation; junctional activity under the squamous epithelium was present in eight patients (57.1%) and the high and atypical mitotic index occurred in 13 of the 14 patients (92.9%). However, there is no correlation between the morphological characteristics described and prediction of survival.

As the differential diagnosis between amelanic ARM with epithelioid cells and other anorectal diseases (Paget's disease, lymphoma, undifferentiated carcinoma and GIST) can be difficult when considering only the histopathological criteria, IHC has become a very important resource to establish the correct differential diagnosis. Thus, after this test became available (after 1985), almost all studies mention performing IHC for the diagnosis of ARM and differential diagnosis with other diseases. Almost all test the ARM panel of markers (S-100 protein, Vimentin, Melan-A, HMB-45) and include specific markers such as cytokeratins (Paget's disease), CD45 (lymphoma), chromogranin and synaptophysin (undifferentiated carcinoma), CD34 (GIST) and Desmin and caldesmon (sarcoma).[19]

In this series there was a strong positivity for Vimentin (100%), S-100 protein (100%), HMB45 (100%) and MART-1 or Melan-A (100%), consistent with the literature.[19] c-Kit showed focal positivity in 33% and CD-68 and iron showed focal positivity in the only case in which they were tested. As for the markers tested for differential diagnosis, they were all negative (cytokeratins, CEA, smooth muscle actin, Desmin, h-caldesmon, synaptophysin, CD34, CD10 and CD45).

None of these markers were predictive of survival.[6] However, Ben-Izhak et al. described two markers – Ki67 and PCNA

(Proliferating Cell Nuclear Antigen), which were associated with advantage in survival – patients with high Ki67 and low PCNA scores. These data have not been validated by subsequent studies.[20]

As for surgery, there is a consensus that the disease is severe, with poor results and there is no difference in survival of patients undergoing local excision or extended surgery, such as abdominoperineal resection of the rectum. Considering the risks of major surgery and the inconvenience of a definitive stoma, with significant impact on quality of life, the choice of most authors is the extended local excision, reserving APR for advanced cases or rescue in case of recurrence after local resection.[9,21–23]

Four of the 14 patients in this series underwent APR due to invasive ARMs, as ELR was not feasible. Three patients underwent ELR with curative intent (21.4%), as they had localized ARMs. Three patients underwent ELR without curative intent (21.4%), as APR was not possible due to patient overall status. Two patients did not have their tumors resected (14.2%), as they were not fit to undergo the surgical procedure and were considered inoperable. And two patients underwent surgery for hemorrhoidal disease, with the histopathological analysis disclosing the presence of ARM postoperatively (14.2%).

Of the 14 patients studied, nine died and five remain alive and disease-free. The mean survival time was 8.4 months. In the literature, the overall survival varies among authors, but there is consensus that it depends on the surgical technique used (extended local resection or APR).[9,22–23]

Only one case series mentions the incidental finding of ARM in an eventual anal surgery. In eight of the 50 patients with ARM, in the report of Thibault et al., ARM was found incidentally during anal surgery (16.0%), and five of them were reoperated, two with APR and three with ELR, with no tumor trace in the surgical specimen at the microscopy.

The findings of these authors are similar to findings in this series of 14 ARMs: two were ARM cases incidentally found during hemorrhoidectomy (14.2%). However, none of them required reoperation, and both are alive – one 17 years after surgery and the other 12 years after surgery. Therefore, it can be concluded that these small tumors were cured with local resection only.

Radiotherapy and chemotherapy are considered ineffective for treatment of ARM. Some authors who have used RXT reported that they did not observe any advantage.[3,24] In this study, only one patient received chemotherapy and none received RXT. The use of targeted therapies against metastatic melanoma was considered frustrating by Satzger et al.[11] However, knowledge of the different processes of oncogenesis of melanomas can lead to more precise therapies. One of the subgroups of ARM, with mutations in the BRAF gene, respond to the action of BRAF inhibitors (PLX4032 and RAF265), leading to regression of disease in up to 70% of patients with metastatic melanoma with BRAF V600E mutation.[25]

Another subgroup of ARM, with KIT gene mutation, is sensitive to c-KIT (imatinib) blocker action.[25] Other blockers of c-KIT have been studied in ARMs, however, in a very small number of patients, which prevents drawing an immediate conclusion.

## Conclusion

ARMs are tumors with high malignant potential, and their rarity makes it difficult to establish diagnostic and therapeutic procedures with statistically significant results. Histopathology does not always confirm the diagnosis and IHC is essential for attaining a definitive diagnosis.

The most rational surgical approach is the ELR in cases of localized ARMs and APR for advanced cases of the disease. Regardless of the surgical technique used, the overall survival is very low.

There is no outcome improvement with CXR and CT. The use of targeted therapies is starting to show encouraging results for some subtypes (with mutations in BRAF and/or KIT genes).

## Conflicts of interest

The authors declare no conflicts of interest.

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