CASE REPORT

Primary anorectal melanoma: report of 4 cases and literature review

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Abstract

Anal melanoma is a rare aggressive disease, representing 0.4% to 1.6% of all melanomas and 1% of tumors of the anal canal. Its diagnosis is complex and in most cases is made in later stages with diffused disease, which contributes to its poor prognosis. Due to its low incidence, most studies are based on case reports and there is no consensus on the best diagnostic and therapeutic course of treatment. As a rule, the cure rate is low and the expected 5-year survival is 20%. As a consequence, therapy should be individualized, evaluated on a case-by-case basis, aiming locoregional control to provide better quality of life for the patient.

Keywords: anus neoplasms, case report, melanoma, rectal neoplasms.

INTRODUCTION

Anorectal melanoma is rare and represents only 1% of malignant neoplasms affecting the anorectal region[1]. Nevertheless, this is the third most frequent site of tumors, after the skin and eyes[2,3], and is the most common area of involvement of the gastrointestinal tract. The first case of anorectal melanoma was described in 1857 by Moore, who reported a patient with metastatic disease[4]. The most prevalent age group is between the sixth and eighth decade[5].

The diagnosis is usually delayed since this tumor is often confused with benign diseases such as thrombosed hemorrhoids and rectal polyps, and many patients present with advanced disease. Approximately 15% to 40% of lesions are amelanocytic[5,6], which further complicates their identification. Immunohistochemistry for detecting S100, Melan-A and HMB-45 is extremely important. Early diagnosis enables an improved prognosis.

Due to its low incidence, primary anorectal melanoma has limited treatment experience with no consensus of course of treatment. Some options are wide local excision, radical abdominoperineal resection, palliative surgery, adjuvant chemotherapy and radiotherapy, and immunotherapy. The prognosis is poor for any of the surgical treatments and the expected 5-year survival is about 20%[7-9]. The benefits of using chemotherapy, radiotherapy and immunotherapy are not yet clear[8,9].

In this case review, we report four cases of patients with anorectal melanoma and conduct a literature review discussing the data in the literature, focusing on diagnosis, treatment and prognosis. The characteristics of patients are summarized in Table 1.

CASE REPORTS

Case 1

A 54-year-old man presents with a 5-month history of masses in the perianal region previously treated as hemorrhoidal disease, who is now experiencing bleeding and ulceration of the lesion. A local resection was performed for a suspected benign polypoid lesion (Figure 1). Pathological examination found the lesion to be invasive melanoma with ulceration encroaching on skeletal muscle, with 7 mm depth and affected margins. Immunohistochemistry was positive for S100 protein, vimentin and HMB-45 antibody, and negative for cytokeratin.

Enlargement of the resection margin was performed along with bilateral inguinal sentinel lymph node biopsy. Anatomopathological exam showed metastasis of melanoma only in the left inguinal lymph node (2.5 x 2.0 cm) and a subsequent left inguinal lymphadenectomy was performed.

After two years, the patient presented worsening health, cachexia, anal incontinence, painful nodules in the perianal region and nodules on the scalp. The condition presented rapid evolution of the disease from stage III to IV, resulting in death of the patient in four months despite chemotherapy.

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Table 1. Characteristics of 4 patients with anorectal melanoma.

Case Report	1	2	3	4
Sex	M	M	F	F
Age (years)	54	81	47	40
Onset of symptoms (months)	5	NF	24	NF
Thickness (mm)	7	NF	5	1.8
Initial staging	III	IV	III	I/II
Surgical treatment	WLE	RAR	WLE	WLE
Sentinel lymph node biopsy	Positive for metastasis	NF	Positive for metastasis	Negative for metastasis
Lymphadenectomy	Yes	NF	Yes	No
Chemotherapy/Radiotherapy	CT	CT and RT	No	No
Survival (months)	33	24	36	60

M: male; F: female; WLE: wide local excision; RAR: radical abdominoperineal resection; CT: chemotherapy; RT: Radiotherapy; NF: Not found.

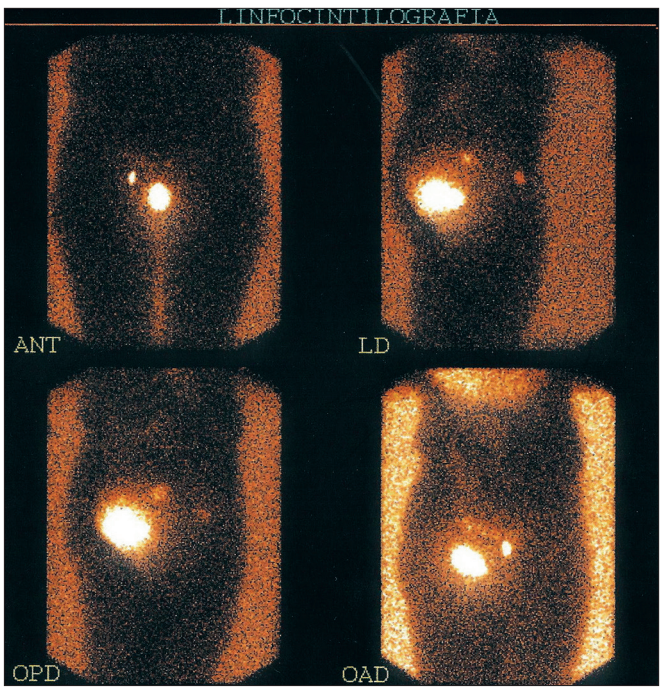

Figure 1. Anal melanoma (polyp lesion).

Case 2

An 81-year-old man was referred to our service due to the diagnosis of advanced anorectal melanoma. The patient had undergone abdominoperineal amputation 18 months prior with adjuvant combined chemotherapy and radiotherapy for 15 days. Although the patient had the referral report with diagnosis, the anatomopathologic results from the hospital of origin were not available. Clinical examination found clinically advanced bilateral inguinal lymphadenopathy, treated with local radiotherapy, observing total clinical regression. The patient had hepatic and pulmonary metastases after one year. He died in hospice care after six months of locoregional control of disease with preserved quality of life.

Case 3

A 47-year-old woman presents with a 2-year history of a perianal nodule with occasional bleeding. The patient underwent an excisional biopsy and subsequent anatomopathological examination concluded that it was an invasive cutaneous melanoma with superficial spreading, vertical growth phase, Clark level IV, Breslow thickness of 5 mm, with free deep surgical margin and affected lateral margins.

Margin enlargement was performed along with sentinel lymph node biopsy, resulting in a diagnosis of metastatic melanoma in the left inguinal node. The patient then underwent left inguinal lymphadenectomy with initial staging of stage III anal melanoma.

Four months later, the patient received six doses of polypeptide vaccine by intranodal injection following clinical protocol. The patient is in regular clinical control, good general condition without complaints. There is no evidence of locoregional recurrence or distant metastasis.

Case 4

A 40-year-old woman presents with perianal pigmented nodules initially treated as thrombosed hemorrhoids. The patient was subjected to surgical excision, whose anatomopathologic analysis concluded that it was melanoma with a Breslow thickness 1.8 mm.

In sentinel lymph node biopsy in the left inguinal region, all four sentinel lymph nodes resected were negative for metastases (Figure 2). The patient is in regular clinical follow-up for five years with no evidence of locoregional recurrence and distant metastases.

DISCUSSION

The skin is the main site of primary melanoma, but other sites can be affected, such as the oral cavity, nasal, central nervous system, eye, esophagus and intestines[5]. The anal region is the third most frequent site of tumors, after the skin and eyes[2,3], and is the most

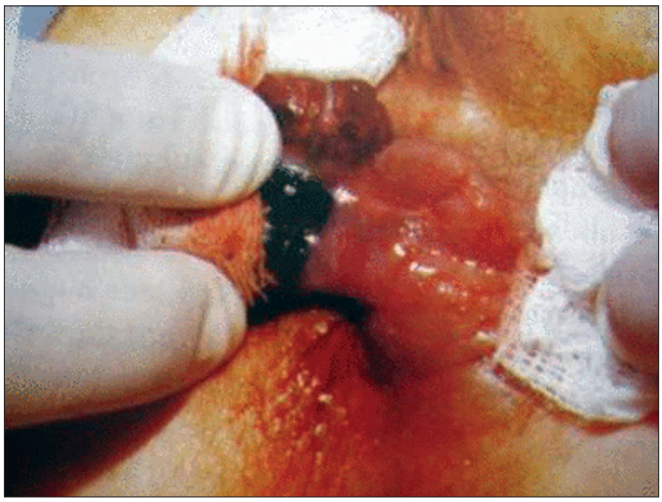

Figure 2. Lymphoscintigraphy showing sentinel lymph nodes.

common area of involvement of the gastrointestinal tract. As being a region not exposed to solar radiation, other factors must be considered in its pathophysiology. To date there has been increasing incidence, but it is unclear whether growth is real or is due to greater awareness of the disease by physicians and pathologists and the improvement of diagnostic techniques such as immunohistochemistry[10].

The most prevalent age group is between the sixth and eighth decades of life, with higher incidence in white patients, which was observed in cases 1 and 2. Although some studies show no difference in prevalence between the sexes, larger series reported female predominance[5,8,11], which was not found in our patient population. There are authors who consider the human immunodeficiency virus (HIV) as a risk factor, especially in young men[8].

Anorectal melanoma is a tumor of neuroectodermal origin, originating from melanocytes of the transition zone above the dentate line, with proximal growth toward the rectum or distally toward the anal canal and anus[10]. Tumors may be located in the rectal region (very rare), anorectal and anal. Most tumors present in the form of nodular or ulcerated tumors[10]. We observed nodular form and anal location in 3 of the 4 patients, with one of those having an ulcerated lesion.

With regard to symptomatology, anorectal melanoma, as well as other anorectal malignancies, may manifest with bleeding, itching, discharge and anal pain, pain during bowel movements, changes in bowel habits, tenesmus, fecal incontinence, narrowed stool in rectangle or tape shape and weight loss. These characteristics hinder and delay the diagnosis because they are often attributed to hemorrhoids, plicomas or fissures, which were observed in our study. The mean duration of reported symptoms varies according to the literature, generally between 3 and 12 months[5,8].

Dissemination may be hematogenous and/or lymphatic, and not related to lesion size[5]. The main metastatic sites via hematogenous routes are the liver, lungs, brain and bones. When lymph node metastases occur, they are located in the inguinal, mesenteric and para-aortic chain, and the spread may also occur locally. In the presence of distant metastases, expected survival is less than 10 months and no patient has survived more than five years after diagnosis[12], which was observed in cases 1 and 2. The rich vascular and lymphatic network of the anal region contributes to the early spread of the tumor[11,12].

The diagnosis is not always easy and in most cases is made in later stages with diffused disease. This is due to several factors, including the high frequency with which this neoplasm is confused with benign diseases and the fact that there is early dissemination. In 15% to 40% of the cases, lesions may be amelanocytic, further contributing to the diagnostic difficulty[5,6,8,13]. At times, fear, shame or ignorance on the part of patients end up delaying the diagnosis.

The pigmentation of these tumors is highly variable and may present from reduced to absent. Only case 4 showed pigmented nodules, which raised the suspicion of hemorrhoidal thrombosis. When melanin is present, the anatomopathologic diagnosis is enough, but in cases of amelanocytic tumors and in biopsies with scant yield, the diagnosis should be made with the help of an immunohistochemical marker panel or by tests of tyrosine hydroxylase and dopa oxidase activity[5,8].

Melanoma cells are positive for vimentin in almost all cases, while fixation in formalin could negatively affect their detection[10]. The S-100 protein is also a very sensitive marker expressed in at least 95% of melanomas[10]. HMB-45 is positive in almost 90% of melanomas and is considered a specific marker of this tumor[10]. These neoplastic cells are negative for cytokeratin, leukocyte common antigen (LCA)[14] and carcinoembryonic antigen (CEA)[10].

Immunohistochemical testing complements the diagnostic investigation of imaging tests such as ultrasound, computed tomography or magnetic resonance, which is especially useful in locoregional staging and site of metastasis that define the prognosis and course of treatment[6].

Due to the low incidence of primary anorectal melanoma, experiences about their treatment are limited and so far there is no consensus. Some options are wide local excision (WLE), radical abdominoperineal resection (RAR), palliative surgery, adjuvant combined chemotherapy and radiotherapy and immunotherapy. These treatments are ineffective, having a low success rate with a vast majority of patients who die due to distant metastases within five years[12].

Surgical treatment is preferred, but there is no consensus regarding the most appropriate procedure[13,15,16]. Cooper and colleagues reviewed 255 cases and found that

no statistically significant difference comparing survival after wide local excision or radical abdominoperineal resection[10]. Kannan and colleagues, in a recent review of over 600 cases, concluded that 5-year mortality is around 15% for local and wide resection and 14% for abdominoperineal excision and the average life expectancy after WLE was 20 months and 21 months after RAR[16]. Several other studies corroborate these findings[8-14,16]. Nevertheless, it must be considered that surgery can contribute to longer disease-free survival and may improve the quality of life. The radical abdominoperineal resection is the most widely used procedure. It has the benefit of reducing the incidence of local recurrence, as it allows tumor resection with wide surgical margins, reduce local symptoms such as bleeding and allow lymphadenectomy of pelvic and mesenteric lymph nodes[7,8]. On the other hand, RAR is not without risk and morbidity is high by the need for permanent colostomy. The argument in favor of WLE is lower morbidity and mortality without the need for colostomy and survival similar to RAR. WLE was chosen for all three patients who underwent surgery by our team. RAR should be reserved for cases where WLE cannot be made, in cases of risk of positive surgical margins or in cases of isolated local recurrence[8,12,16]. Regardless of the technique chosen, resection with free surgical margins is fundamental.

Bilateral prophylactic inguinal lymphadenectomy performed in patients without clinical evidence of lymph node involvement is not indicated, since it does not improve survival and adds considerable to morbidity. Thus, lymphadenectomy should be performed only when there is presence of affected lymph node[8]. Inguinal lymphadenectomy was indicated for our patients through the use of sentinel lymph node biopsy. When the ganglia appeared to be positive for metastases, lymph node dissection was performed.

The use of chemotherapy is controversial and does not seem to affect the survival of patients[7-9]. The major chemotherapeutic agents used in adjuvant or palliative treatment are dacarbazine, 5-fluorouracil, vincristine and cisplatin[5,8]. Some studies suggest benefit in the use of chemotherapy in metastatic disease[12], but further studies are needed for definitive conclusion. Due to the excellent clinical conditions in case 1, the patient underwent chemotherapy that ultimately showed no benefit in survival. In case 2, we opted for palliative care due to age and clinical conditions of the patient.

As for radiotherapy, its efficacy is unclear[9,11,13] because it is a radioresistant tumor[5,11]. The benefits of immunotherapy also need further investigation.

The prognosis of this condition is very poor due to diagnosis at an advanced stage, with 5-year survival around 20%[7-9,14] and average life expectancy around 20 months[5]. In the US, the mean survival of patients with distant metastasis is 10 months, with regional dissemination is 13 months and with localized disease is 34 months[9].

Some factors that influence prognosis are sex, tumor stage, size and depth according to Breslow scale, resection with free margins, duration of symptoms, invasion of lymph nodes, amelanotic melanoma, and perineural invasion[8,12,13].

CONCLUSION

Anal melanoma is a rare disease with aggressive biological behavior, representing 0.4% to 1.6% of all melanomas and 1% of tumors of the anal canal. The diagnosis is complex and in most cases is made in later stages with disseminated disease that contributes to its poor prognosis and low rate of cure. Due to the low incidence of primary anorectal melanoma, experiences about their treatment are limited and so far there is no consensus. Several studies have found no significant difference in survival when WLE or RAR is performed with free margins. Application of chemotherapy, radiotherapy and immunotherapy are controversial. The accurate staging of the tumor, the determination of its depth, the presence of lymph node metastases and the distance should be done prior to performing any surgical intervention. The prognosis is very poor, with 5-year survival around 20% and average life expectancy around 20 months. Treatment should be defined on a case-by-case basis due to diagnosis at an advanced stage, where in most cases a curative treatment is not possible. In the surgical approach chosen, it is essential to obtain free surgical margins.

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