Case Report

ANAL MELANOMA – A CLINICALLY UNSUSPECTED DIAGNOSIS: A REPORT OF TWO CASES

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Received: October 26, 2012
Revision received: November 20, 2012
Accepted: November 27, 2012

Summary

Anorectal malignant melanoma is an infrequent and lethal tumor. We describe two cases of this rare entity: a 72-year-old female with several months complaint of painful rectal bleeding and prolapsed tumor masses through the anus initially described as hemorrhoids. On histology amelanotic melanoma was diagnosed. The patient refused additional treatment, suffered liver metastasis ten months after diagnosis and succumbed to her disease 11 months after presentation. An 82-year-old female complained of blood in stool and fatigue with 12 months duration. She underwent colonoscopy and under suspicion of carcinoma, biopsy was taken. Less than 1 year after the diagnosis the disease progressed and lung metastases were found. Immunohistochemical phenotype of the both lesions is identical: S-100 protein, HMB-45, Melan-A, Vimentin, CD117 positivity in tumor cells and negative expression of Cytokeratin AE1/AE3. Our cases exemplify the diagnostic challenge clinicians face when dealing with anorectal malignant melanoma. It is often underrecognised, being in the differential far behind more commonly encountered hemorrhoids and carcinoma. Pathologists are at ease when diagnosing melanoma with confidence when a short antibody list is used, like HMB-45/Melan-A and Cytokeratin.
Key words: anorectal malignant melanoma, histology, immunohistochemistry

Introduction

Malignant melanoma of the anorectum is a rare tumor that has a highly aggressive course and poor prognosis. It accounts for less than 1% of all melanomas and up to 4% of all malignancies of the anal canal [1, 2]. In Bulgaria for a 5-year-period (2006 - 2010) 474 new cases of anal canal malignant entities were diagnosed, only 9 of them were melanomas [3]. The location of the lesion can be either in the anal canal or the rectum, and usually arises from the dentate line. Only 2% of cutaneous melanoma metastasize to the gastrointestinal tract, and of these, metastases to the rectum are 2% whereas metastatic disease to the anus is exceedingly rare [4]. Females are more likely to be affected than males and most patients present in the sixth decade of their lives [5, 6]. Anorectal malignant melanoma is

challenging to diagnose in the clinical setting due to lack of specific symptoms, as well as its anatomic location. The most common presenting complaints are bleeding, anal pain, anal mass, pruritus, tenesmus, and change in bowel habits. Diagnosis is frequently delayed, as these lesions can be misdiagnosed for hemorrhoids or skin tags [7]. Furthermore, approximately 30% of anorectal melanomas are amelanotic and can endoscopically resemble benign polypoid lesions [8]. Unfortunately, often the tumor has widely metastasized at the time of initial diagnosis, making cure next to impossible.

Case 1

A 72-year-old female was referred to the surgery department with several months complaint of painful rectal bleeding and prolapsed tumor masses through the anus. At endoscopy, internal and external hemorrhoids were described; surgery ensued with excision of the mass. The received biopsy material, on gross examination revealed a single piece of whitish tissue measuring 20 x 15 mm. Histology disclosed ulcerated epithelium overlying a tumor with nested and diffuse growth pattern, composed of atypical large, polygonal and epithelioid cells with central nuclei without discernible nucleoli; high mitotic rate – up to 25 mitotic figures per 10 HPF (Figure 1 A, B). No pigment was noted in the cells. The founding was highly suspicious for malignant melanoma, immunohistochemical (IHC) investigation was performed to reveal S-100 protein, HMB-45, Melan-A, Vimentin positivity in tumor cells while negative for Cytokeratin AE1/AE3 (Dako) (Figure 2). Interestingly, neoplastic cells stained positively for CD117 (c-kit). Amelanotic melanoma was diagnosed. The patient refused additional treatment, suffered liver metastasis ten months after diagnosis and succumbed to her disease 11 months after presentation.

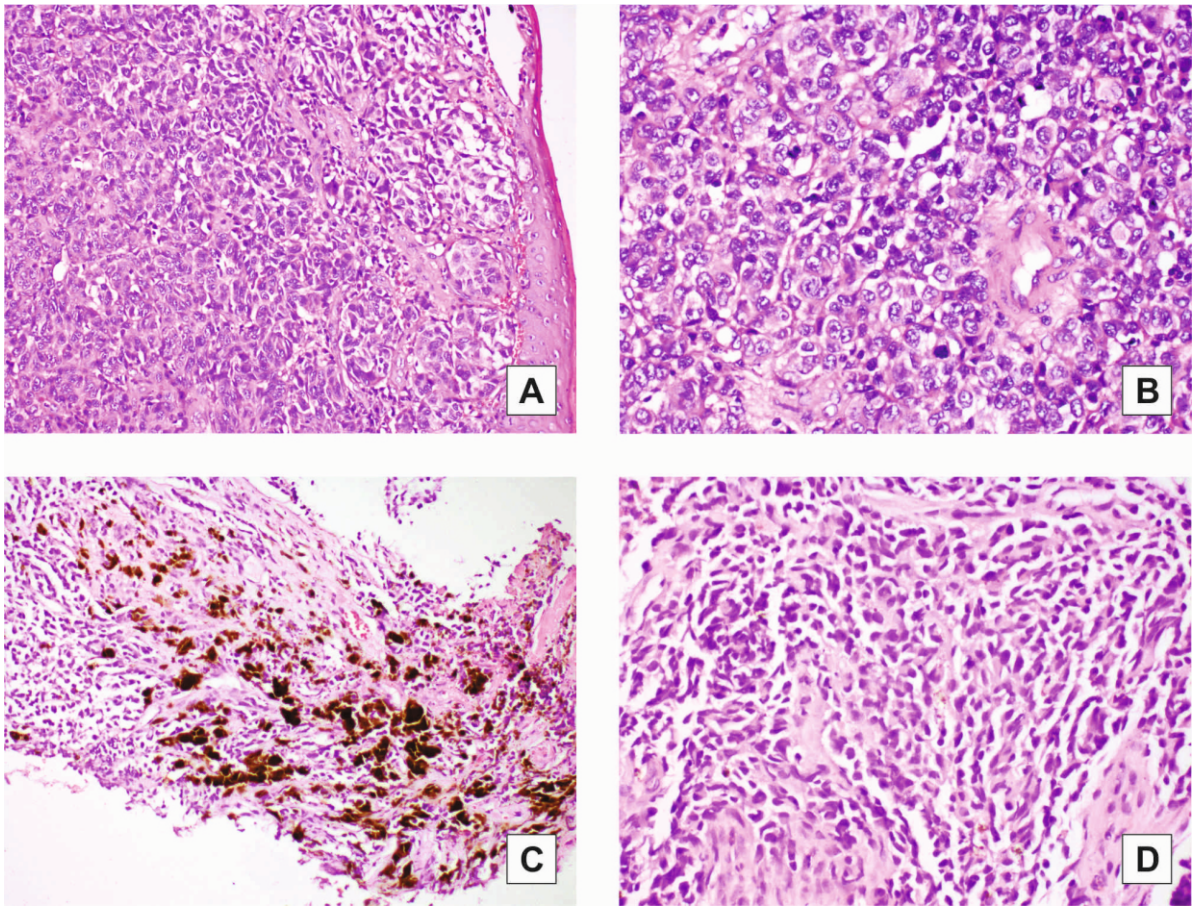

Figure 1. H&E: A – case 1, objective x10; B – case 1, objective x40; C – case 2, objective x10; D – case 2, objective x40

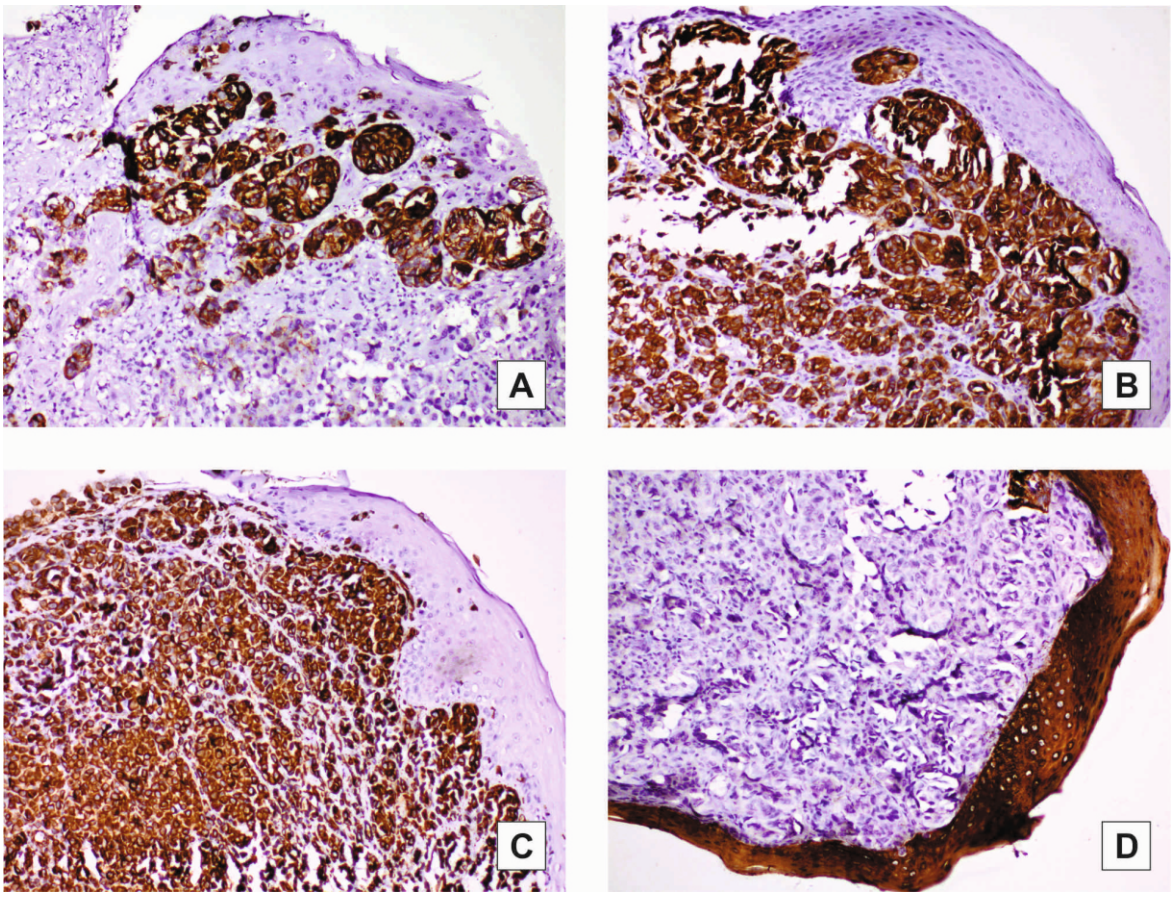

Figure 2. IHC (case 1, objective x10): A – HMB-45; B – Melan-A; C – Vimentin; D – Cytokeratin AE1/AE3

Case 2

An 82-year-old female complained of blood in stool and fatigue with 12 months duration. She underwent colonoscopy to reveal an ulcerated, uneven, bleeding tumor lesion located 4-5 cm above the anus. Under suspicion of carcinoma, biopsy was taken. H&E slides showed pieces of solid tumor, composed of monotypic spindle-shaped cells arranged in short fascicles (Figure 1C, D). Large necrotic areas and brown pigment were noted. Rarely, mitotic figures were found - up to 3 mitotic figures per 10 HPF. Malignant melanoma was verified by identical IHC phenotype: S-100 protein, HMB-45, Melan-A, Vimentin, CD117 positivity in tumor cells and negative expression of Cytokeratin AE1/AE3 (Dako) (Figure 3). Local excision of the tumor was performed in other hospital. The patient was followed-up 12 months, at this point patient is alive with progressive disease – lung metastases were found and immunotherapy was offered.

Discussion

Anorectal malignant melanoma is an extremely rare and lethal tumor. The first case was reported by Moore in 1857 [9]. Melanomas are malignancies that can affect any anatomic region where melanocytes exist (e.g. the epidermis, eyes, mucous membranes, leptomeninges). The most common form of melanoma involves the epidermis and constitutes 91.2% of melanoma cases, whereas ocular and mucosal forms account for 5.3% and 1.3% of cases, respectively [1]. For mucosal melanomas, the distribution of head and neck, anal/rectal, female genital and urinary tract sites was 55.4%, 23.8%, 18.0%, and 2.8%, respectively [1]. Risk factors remain unknown, but unlike cutaneous melanomas, anorectal ones are not influenced by sunlight exposure. There is some data that suggest a role of immunity in the development of anorectal melanoma because of higher incidence in patients with HPV and also HIV [10]. Recent genetic analyses demonstrate molecular differences between cutaneous and mucosal melanomas. Mutations in exon 15 of B-

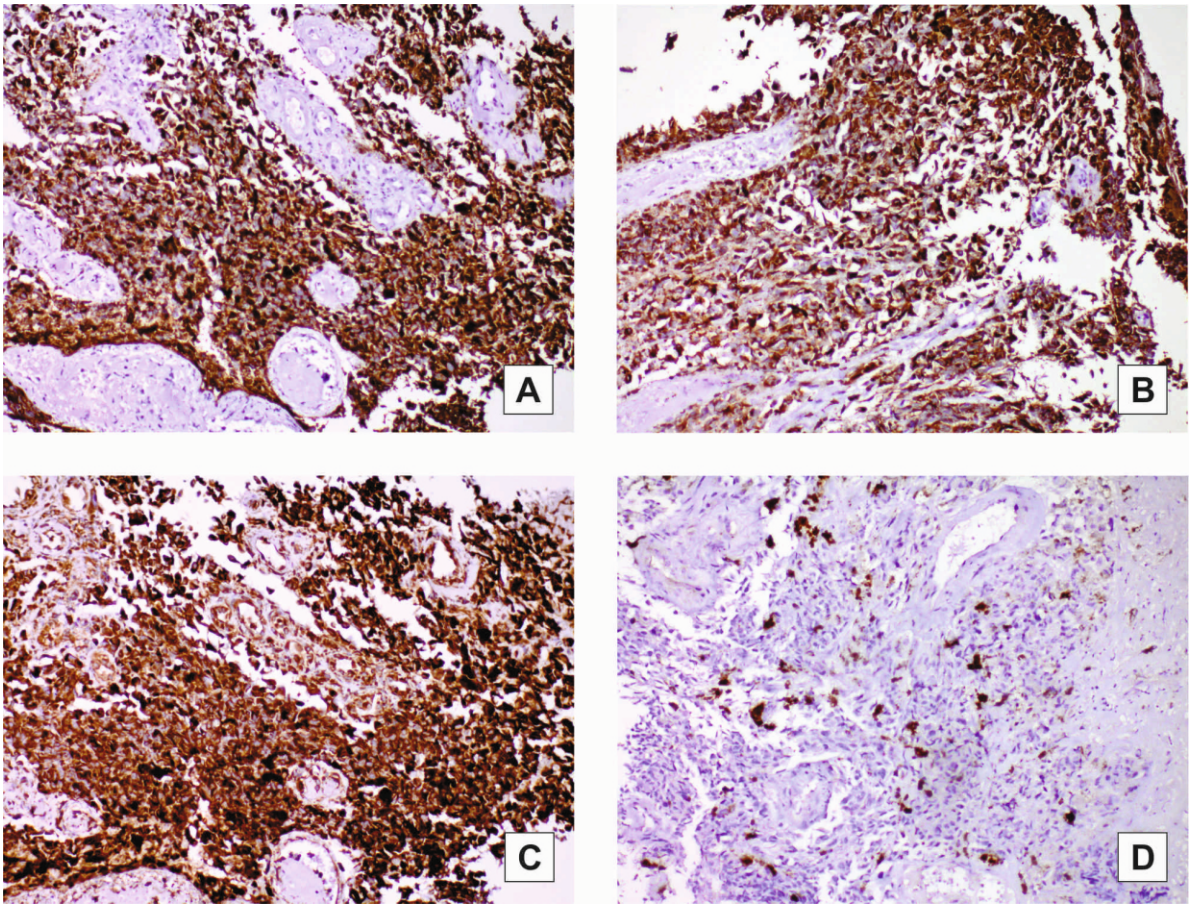

Figure 3. IHC (case 2, objective x10): A – HMB-45; B – Melan-A; C – Vimentin; D - Cytokeratin AE1/AE3

raf are found in up to 69% of primary cutaneous melanomas, but no mutations have been found in any of the 13 mucosal melanomas examined [11]. Given the clinical, biologic, and molecular differences, mucosal and cutaneous melanomas may be distinct disease entities.

Patients tend to present late and clinicians may have a lower suspicion due to anorectal melanoma rare incidence. The most common presenting complaints are bleeding per rectum or diarrhoea with tenesmus. Thus, malignant melanomas masquerade as thrombosed haemorrhoids. The growth may ulcerate giving rise to severe pain on defecation. If metastatic disease is present, symptoms may include weight loss, anemia, fatigue, groin masses, pelvic masses, or even bowel obstruction. Physicians should obtain biopsies from any suspicious lesions that do not respond to usual treatments. Anorectal melanoma may be discovered at the time of screening endoscopy for unrelated symptoms. Rarely, melanoma can be identified during the routine pathology examination of a hemorrhoidectomy specimen [12]. In the study of Che et al. misdiagnoses occurred in 57.14% from the observed 56 cases [6]. Misdiagnoses included hemorrhoids, adenomas or polypus, cancer, carcinoid, fibroma etc.

Macroscopically, the majority of anorectal melanomas are polypoid, pigmented and arise near the dentate line. They may also present as nodular prolapsed masses [8]. Anorectal malignant melanoma shows considerable morphologic variability. Histologic subtypes include epithelioid; spindle cell; lymphoma-like; and pleomorphic types. Melanin pigment within the malignant cells is the clue for pathologic diagnosis. The appearance of junctional changes, that is, the presence of atypical intraepithelial cells or pleomorphic spindle cells adjacent to the focus of malignant tumor are useful adjuncts in arriving at the correct diagnosis. Atypical junctional changes can extended laterally from the overt invasive neoplasm for distances up to 1 cm but may be difficult to identify in the ulcerated lesions [8]. The main differential diagnoses include colorectal squamous carcinoma and extramammary Paget disease. Without melanin

or junctional changes, routine immunohistochemistry is helpful. A single study of Chute et al. reported positivity for S-100, HMB-45, Melan-A in 100, 94, and 93% of lesions examined; Vimentin and c-kit in 93 and 75%; Pankeratin was absent in all case [13]. Frequent expression of c-kit, particularly in cases with spindle cell morphology may lead to confusion with gastrointestinal stromal tumors.

There are many histologic markers that may have association with prognosis. Tumors with necrosis, perineural invasion, spindle cell histology and larger diameter were associated with poor outcome [14]. The only significant prognostic factor associated with long-term survival was tumor perineural invasion. In contrast to cutaneous melanoma, factors such as lymphovascular invasion, ulceration, and nodal status were not associated with outcome in patients with anorectal melanoma. Tumor histologic type was associated with recurrence, but not with survival. Tumors with pure epithelioid histology were less likely to recur compared with tumors showing pure spindle cell or mixed histology [14].

There are two methods of staging in anorectal melanoma. The American Joint Commission on Cancer has developed a staging method based on presence of tumor in lymph nodes and depth of primary tumor [1]. Another staging system is based only on disease spread. It describes local disease only as stage 1, regional lymph node disease as stage 2, and metastatic disease as stage 3.

Because of the delays in diagnosis and the aggressive nature of the disease patients with anorectal melanoma frequently present with advanced disease. The abundant lymphatics of the anorectum and the rich vascular network in this area probably facilitate the high rate of inguinal and iliac lymph node metastastes and hematogenous spread to liver, lung, bone, brain, and other organs. The treatment of anal melanoma, unfortunately, is only a modest success. Surgery remains the cornerstone of treatment. Chemoradiation and immune therapy have a limited role. The spectrum of different surgical approaches varies from a relatively simple wide local excision (WLE) with minimal morbidity to a more extensive resection such as an abdominoperineal resection (APR), which is associated with high morbidity rate and functional compromise. A retrospective study of patients failed to show an advantage of APR over WLE with respect to overall survival, although there was a trend for better local control with APR [6, 15]. Primary wide local excision followed by adjuvant radiotherapy to the pelvis and inguinal lymph nodes is the preferred choice in cases with totally resectable tumors [16]. APR can be performed as a rescue therapy when WLE is impossible, the margins of the local excision are positive, or in the event of recurrence.

Despite attempted curative surgery, the median survival for anorectal melanoma is only about 20 months and most patients die within 5 years regardless of the type of intervention used [5, 6, 14 - 17]. At the time of diagnosis, up to one-third (16-33%) of the patients have disseminated disease [17]. For these patients, palliative treatment with chemotherapy might be a treatment option. However, this therapy still has to be further evaluated and currently no standard systemic therapeutic regimen exists for metastatic anorectal melanoma. Future study of the molecular mechanisms of anorectal melanoma oncogenesis and tumor progression is needed to develop innovative treatment paradigms that may ultimately impact outcome.

Conclusion

In summary, our cases exemplify the diagnostic challenge clinicians face when dealing with anorectal malignant melanoma. It is often underrecognised, being in the differential far behind more commonly encountered hemorrhoids and carcinoma. Pathologists are at ease when diagnosing melanoma with confidence when a short antibody list is used, like HMB-45/Melan-A and Cytokeratin.

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