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Malignant melanoma of anorectal region: a clinicopathologic study of 61 cases

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ABSTRACT

Anorectal malignant melanomas (AMMs) are aggressive neoplasms, which account for less than 1% of all anorectal tumors. Anorectal malignant melanomas are notorious for their diversity of histologic features and mimic a number of other tumors. Aberrant expression of immunohistochemical stains such as cytokeratins and CD117 (c-kit) further increases the risk of misdiagnosis. Aim of our study was to describe the common as well as unusual architectural and cytologic features that create difficulty in diagnosis. We also discussed the role of immunohistochemical stains in diagnosis of AMMs. We retrieved and reviewed 61 cases of anal melanoma diagnosed in our institution between January 2005 and May 2014. Epithelioid cell type was observed in 57 (93.4%) cases, spindle cells in 35 (57.4%) cases, pleomorphic in 12 (19.7%) cases, and lymphoma-like in 2 (3.3%) cases. Cytoplasmic clearing was observed in 16.4% and nuclear pseudoinclusions in 9.8% cases. Twenty-one point three percent cases were completely amelanotic, and 36.1% showed focal melanin pigment. Average mitotic count was 2 mitoses/high-power fields. Nesting pattern was seen in 24.6%, pseudoalveolar pattern in 11.5%, and peritheliomatous/pseudopapillary pattern in 5% cases. Positive expression of vimentin, S-100, HMB-45, and Melan A was seen in 100%, 100%, 94.4%, and 93.3% cases, respectively. Cytokeratins were positive in 9% and CD117 (c-kit) in 20% of cases in which they were performed. In conclusion, AMMs should be considered in the differential of any malignant tumor of anorectal region without obvious glandular and squamoid differentiation. The knowledge of amelanotic nature, unusual histologic features, and aberrant immunohistochemical expression is helpful in avoiding misdiagnosis.

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1. Introduction

Malignant melanoma (MM) is an aggressive malignant neoplasm, which can arise in a number of anatomic locations. Although the characteristic, morphologic, and immunohistochemical features of these tumors have been well described in literature, the diversity of architectural patterns, cytologic, and nuclear features frequently poses a diagnostic challenge to histopathologists [1].

Anorectal region is the fourth commonest site for MM after skin, uveal tract, and the head and neck region. However, anorectal malignant melanoma (AMM) comprises only approximately 1% of all MMs but 23.8% of mucosal MMs [2]. Anorectal malignant melanomas are rare and constitute less than 1 % of all tumors arising in anorectal region [3]. Anorectal malignant melanomas mainly affect elderly with highest incidence in sixth to eighth decade and show slight female predominance [4,5]. Like carcinomas, they usually present as dark brown to blackish fungating or polypoidal masses, which are associated with nonspecific symptoms such as bleeding per rectum, pain, tenesmus, constipation, etc [6,7]. Microscopically, most of these tumors are arranged in sheets and/or fascicles of epithelioid and/or spindled cells with variable amount of dark brown granular melanin pigment and obvious junctional activity. Although nonspecific, the presence of prominent nucleoli is a useful diagnostic clue [8]. Architectural features less commonly observed in MM are nesting, pseudoalveolar, and perivascular (peritheliomatous/pseudopapillary) patterns [1,8-10]. Apart from the usual epithelioid and spindle morphologic forms, pleomorphic and small cell/lymphoma-like morphologic patterns have been frequently discussed in literature [6,11]. Other features described in the melanoma cells include cytoplasmic clearing, balloon cells, plasmacytoid cells, rhabdoid cells, and Reed-Sternberg–like cells. The nuclei exhibit variable degree of pleomorphism, mitotic activity, and some may show bizarre forms, pseudoinclusions, and multinucleation [8]. Malignant melanoma with unusual histomorphologic features alone especially in absence of melanin pigment can mimic a number of other entities including sarcomas, carcinomas, and even lymphomas [10,12]. In noncutaneous locations (especially anorectum), where these tumors are less common and 20% to 30% are amelanotic, the diversity of features can lead to misdiagnosis [13,14]. A combination of immunohistochemical stains

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for melanocytic differentiation, that is, S-100, HMB-45, Melan A (MART-1), and tyrosinase are very helpful in reaching a correct diagnosis [15]. Aberrant expression of immunohistochemical stains such as cytokeratins, epithelial membrane antigen (EMA), CD117, etc performed to rule out morphologic mimics may further complicate the situation [11,16].

Wide local resection of the primary tumor or abdominoperineal resection (APR) remains the mainstay of treatment [17,18]. Adjuvant therapies such as radiotherapy, chemotherapy, and targeted therapies are also administered in few cases [19-21]. We reviewed 61 cases MM of anorectal region with an emphasis on describing the unusual architectural, cytologic, and nuclear features that create difficulty in diagnosis. We also discussed the role of various immunohistochemical stains for melanocytic differentiation in diagnosis and of nonmelanocytic markers in ruling out other differentials.

2. Materials and methods

We retrieved 61 cases of primary AMM from the surgical pathology database of Section of Histopathology, Aga Khan University Hospital reported between January 2005 and May 2014 through "Integrated Laboratory Management System" software. Because this was a retrospective study and did not involve actual identification of patients, approval from the hospital ethical committee was not sought. Clinical information regarding age, sex, location, presenting complaints, gross appearance, and tumor size was obtained from the pathology reports. Hematoxylin and eosin–stained microscopic glass slides were reviewed by 2 pathologists (Tariq MU and Din NU) and were analyzed for various histologic features including architectural pattern, cellular morphology (epithelioid, spindle, pleomorphic, lymphoma-like, etc), degree of pigmentation (no pigmentation; focal, <5%; moderate, 6%-50%; and diffuse/abundant, >50%), mitotic activity, necrosis, junctional activity, cytoplasmic clearing, nuclear pseudoinclusions, lymphocytic infiltrate, extent of invasion, lymphovascular invasion, perineural invasion, maximum extent of invasion, and lymph node involvement. The various common immunohistochemical stains performed for each were S-100 (1:1000; Dako, Carpinteria, CA), HMB-45 (1:5000; Dako), Melan A (1:1000; Dako), vimentin (Vim 3B4, 1:10; Dako), cytokeratin (clone AE1/AE3, 1:50; Dako), cytokeratin CAM 5.2 (monoclonal, pre-diluted; Becton, Dickinson and Company, Franklin Lakes, NJ), discovered on GIST 1 (DOG-1) (DOG-1, 1:100; Dako), CD117 (c-kit, 1:100; Dako), CD34 (1:100; Dako), placental alkaline phosphatase (PLAP) (1:1000; Dako) EMA (E29, 1:50; Dako), desmin (D33, 1:150; Dako), alpha smooth muscle actin (ASMA) (D33, 1:150; Dako), desmin (D33, 1:150; Dako), leukocyte common antigen (LCA) (1:400; Dako), CD30 (1:400; Dako), CD34 (1:400; Dako), chromogranin A (1:5000; Dako), CD56 (1:50; NovoCastra), neuron-specific enolase (NSE) (1:400; Dako), and synaptophysin (1:400; Biogenex).

Patients were contacted on their telephone numbers provided at the time of specimen submission. Verbal consent was obtained via telephonic conversation, and follow-up information was obtained either from the patients or from the physicians, where possible.

3. Results

A total of 61 cases were retrieved and reviewed by 2 experienced histopathologists. The specimen breakdown was as follows: 14 were APR specimens, 15 excisional biopsies, 27 incisional biopsies, and in 5 cases only blocks received for second opinion. Age of presentation ranged from 22 to 95 years with mean age of 57.38 years ± 14.3 SD. There were 36 males and 25 females; M:F ratio was 1.4:1.

3.1. Site of involvement

Of these 61 cases, 34 (60.7%) involved the anorectal junction, followed by 11 cases each involving the anal canal and rectum exclusively. In 5 cases, exact site was not specified.

3.2. Presenting complaints

Most patients presented with bleeding per rectum (41.4%) and/or anorectal growth/mass (41.4%), which was protruding out from the anus in 9 (22%) cases. Four (9.7%) cases had a clinical diagnosis of hemorrhoids. Other symptoms included constipation, tenesmus, weight loss, anemia, weakness, and urinary obstruction.

3.3. Gross appearance

Among excisional biopsies and APR specimens, 23 (57.5%) cases had fungating gross configuration (Fig. 1), 15 (36.5%) were polypoidal, and 2 (4.8%) were ulcerated.

3.4. Tumor size

Tumor size was assessed in intact excisional biopsies and APR specimens. Tumor size ranged from 3.5 to 8 cm in these 20 tumors with mean ± SD of 5.67 ± 1.2 cm.

3.5. Distant metastases at presentation

Five (8%) cases had distant metastases at the time of presentation. Three cases had liver metastases, whereas 2 had metastases in vertebral column (Table 1).

3.6. Cytomorphologic features

Four morphologic forms appeared either exclusively or in different combinations. The combination of epithelioid and spindle morphology was most frequently observed, seen in 28 (45.9%) cases followed by epithelioid morphology (Fig. 2A) alone in 16 (26.2%) cases. Overall, epithelioid cell type was observed in 57 (93.4%) cases, spindle cells (Fig. 2B) in 35 (57.4%) cases, pleomorphic type (Fig. 2C) in 12 (19.7%) cases, and lymphoma-like (Fig. 2D) in 2 (3.3%) cases. Lymphoma-like morphology was seen in combination with epithelioid morphology only. Large cells with abundant amount of clear cytoplasm (Fig. 2E) were seen in 10 (16.4%) cases. These cells were 5 times the size of neoplastic cells (balloon cells). Six (9.8%) cases, all with pleomorphic morphology, showed nuclear pseudoinclusions. Mitotic activity ranged widely with an average of 2 and maximum of 6 mitoses per high-power field (HPF).

Thirteen (21.3%) cases did not show any melanin pigment; 22 (36.1%) cases showed focal (<5%) melanin pigment; 15 (24.6%) cases showed moderate (6%-50%) melanin pigment; and 11 (18%) cases showed abundant/diffuse (>50%) melanin pigment (Table 2).

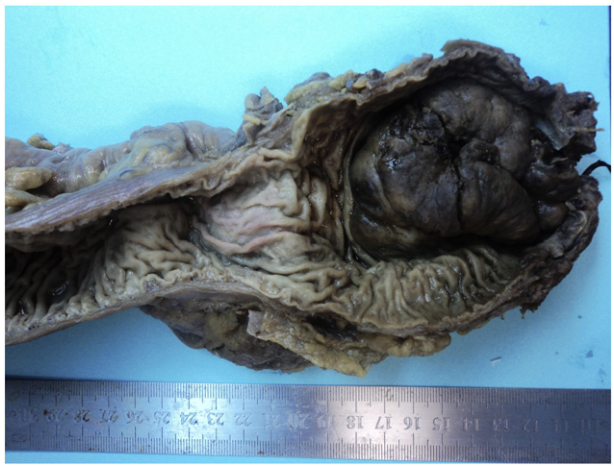

Fig. 1. A large fungating brown tumor involving the anorectal area.

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