Mucosal melanomas account for 0.5–2.0% of all melanomas and anorectal melanomas account for less than 25% of all mucosal melanomas [1–8]. Anorectal melanoma is a rare, lethal neoplasm and frequently arises from melanocytes of the anal squamous zone distal to the dentate line [9–12]. They typically present in the fifth or sixth decade of life and predominantly in women. Patients have initial local symptoms like rectal bleeding and a changed defecation pattern [1,3–6,12,13]. These symptoms can interfere with benign conditions such as hemorrhoids and polyps. Here, we reviewed the morphological and clinical features of 14 anorectal melanomas.

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METHODS

The clinical and pathological records of 14 patients who were diagnosed with anorectal malignant melanoma between 1997 and 2004 were reviewed. The clinical features of the patients at the time of admission and follow-up information were obtained from hospital records or directly from the patients’ families. Patients were evaluated with regard to age, sex, histopathological findings, treatment modality and survival. We defined survival as the time that elapsed between initial diagnosis and death attributable to carcinoma. Histopathological findings were obtained from surgically resected specimens from files in the Department of Pathology. Histological sections of formalin-fixed, paraffin-embedded material stained with hematoxylin and eosin were reviewed to assess tumor size, cell type, pigmentation and lymph node or distant metastasis. Tumor cells were classified as epithelioid, lymphoma-like, spindle cell, or...
pleomorphic. Pigmentation was graded as present or absent. The treatment modality was based both on the clinical stage that was assessed by digital rectal examination and surgeons’ preference.

**RESULTS**

The clinical features at initial diagnosis and follow-up for all 14 cases are given in the Table. The mean age was 58 years (range, 27–75 years). Eight patients were female and six were male. The most common presentation was rectal bleeding (7 cases), followed by pain (5 cases), changes in bowel habits (2 cases), and anal mass (8 cases). The size of melanoma ranged from 3 cm to 8 cm (mean = 4.4 cm). All patients were diagnosed preoperatively with malignant melanoma by colonoscopic biopsy.

Eleven patients were treated with abdominoperineal resection (APR) and three with local excision (LE). There was lymph node metastasis in 11 patients and distant metastasis in all patients; liver and brain were the most affected sites. Seven patients received adjunctive therapy including radiotherapy and chemotherapy. All patients died of the disease during follow-up. Mean survival was 8.7 months (range, 3–29 months).

Histopathologically, two cell types were observed: epithelioid and spindle cell. Pathological evaluation revealed epithelioid and spindle cell type tumor in seven and two patients, respectively, whereas, in the remaining seven patients, tumor was composed of both cell types. Lymphoma-like or pleomorphic type was not encountered. Epithelioid-type tumor cells usually formed granular cytoplasm, and enlarged, irregular and often angulated nuclei. Nuclear membranes were irregularly thickened with vesicular chromatin. Nucleoli were large and often eosinophilic (Figure A). Spindle tumor cells generally did not display vesicular chromatin patterns or prominent nucleoli. They had enlarged, elongated, somewhat angulated nuclei with diffuse hyperchromasia (Figure B). Pigmentation was apparent in all tumors. The malignant cell population showed strong and diffuse immunohistochemical staining for S-100 protein in all cases (Figure C). The majority of cases stained with HMB-45, although there was greater variability in the strength and distribution (Figure D).

**DISCUSSION**

Melanocytes migrate as neuroectodermal derivatives in the ectodermally-derived mucosa, and can be found in the mucous membranes of the upper aerodigestive (mouth, nose, and paranasal sinuses), gastrointestinal (anorectum, esophagus, stomach and gallbladder), and urogenital (vagina, penis and urethra) tracts [1,10,14–17]. Some of these cells show an age-related increase, with a large number of them being found at

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)/ sex</th>
<th>Symptom</th>
<th>Size (cm)</th>
<th>Cell type</th>
<th>Pigment</th>
<th>LN metastasis</th>
<th>Distant metastasis</th>
<th>Treatment</th>
<th>Follow-up outcome</th>
<th>Survey (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70/F B, P</td>
<td>3×3×2</td>
<td>E</td>
<td>+</td>
<td>Brain</td>
<td>APR</td>
<td>DOD</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>55/M M, P</td>
<td>5×5×2.5</td>
<td>E</td>
<td>+</td>
<td>Brain</td>
<td>APR</td>
<td>DOD</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>66/F M</td>
<td>4×4×1</td>
<td>E+S</td>
<td>+</td>
<td>Liver</td>
<td>APR+RT</td>
<td>DOD</td>
<td>10</td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>60/F C</td>
<td>5×5×3</td>
<td>E+S</td>
<td>+</td>
<td>Brain, lung</td>
<td>–</td>
<td>DOD</td>
<td>5</td>
<td></td>
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</tr>
<tr>
<td>5</td>
<td>43/M B, P</td>
<td>5×5×2.5</td>
<td>E</td>
<td>+</td>
<td>Brain, liver</td>
<td>APR+CT+RT</td>
<td>DOD</td>
<td>6</td>
<td></td>
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<tr>
<td>6</td>
<td>55/F B, M</td>
<td>3×2×2</td>
<td>S</td>
<td>+</td>
<td>Liver</td>
<td>LE+CT</td>
<td>DOD</td>
<td>29</td>
<td></td>
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</tr>
<tr>
<td>7</td>
<td>66/F M</td>
<td>3×3×2.5</td>
<td>E+S</td>
<td>+</td>
<td>Liver, lung</td>
<td>APR+CT+RT</td>
<td>DOD</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>63/M B</td>
<td>7×6×3</td>
<td>E</td>
<td>+</td>
<td>Brain</td>
<td>APR</td>
<td>DOD</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>52/M M, P</td>
<td>6×6×5</td>
<td>E</td>
<td>+</td>
<td>Brain, liver</td>
<td>APR+CT+RT</td>
<td>DOD</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>27/M B</td>
<td>8×5.5×3.5</td>
<td>E+S</td>
<td>+</td>
<td>Brain, lung</td>
<td>APR+CT+RT</td>
<td>DOD</td>
<td>4</td>
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<tr>
<td>11</td>
<td>67/F M</td>
<td>3×2×2</td>
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<td>Liver</td>
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<td>13</td>
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</tr>
<tr>
<td>12</td>
<td>75/M M</td>
<td>3×3×2</td>
<td>E</td>
<td>+</td>
<td>Brain</td>
<td>LE</td>
<td>DOD</td>
<td>12</td>
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<tr>
<td>13</td>
<td>73/F B, P</td>
<td>5×4×3</td>
<td>E</td>
<td>+</td>
<td>Liver</td>
<td>APR</td>
<td>DOD</td>
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</tr>
<tr>
<td>14</td>
<td>61/F B, C, M</td>
<td>3×3×2</td>
<td>E+S</td>
<td>+</td>
<td>Brain, lung</td>
<td>APR+CT</td>
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<td>3</td>
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</tbody>
</table>

LN=lymph node; B=bleeding; P=Pain; E=Epithelioid; APR=abdominoperineal resection; DOD=died of disease; M=mass; S=spindle; RT=radiotherapy; C=change in bowel habits; CT=chemotherapy; LE=local excision.
or beyond the seventh decade of life in both sexes [12,18]. These cells give rise to malignant melanomas of the mucous membranes. Although both cutaneous and extracutaneous melanomas arise from transformed melanocytes, they differ substantially in clinico-pathological and molecular aspects. This probably reflects the lack of association with sun damage, family history, familial predisposition, genes, and precursor nevi in extracutaneous melanomas [1,12,19,20]. Contrary to cutaneous melanomas that usually disseminate to regional lymph nodes, extracutaneous melanomas disseminate hematogenously to the liver, skin, lung and brain [12]. This frequent vascular invasion is associated with tumor necrosis, aggressive behavior and poor prognosis [12]. Das et al reported that most patients (48/72; 66%) presented with distant metastases. Nineteen patients (19/24) had positive lymph node disease, and the mean disease-free survival in these patients was 10.3 months. Disease-free survival in the node-negative patients was 26.5 months [21].

Patients present with rectal bleeding, painful defecation, change in bowel habits and pigmented or non-pigmented polypoid masses that prolapse through the anal verge, with the same presentation as hemorrhoids [9,12]. The tumor is frequently mistaken for benign conditions such as hemorrhoids or rectal polyps [22,23]. Magnetic resonance imaging and endoscopic ultrasonography have been shown to be useful in making an earlier and more accurate diagnosis [22,23]. On computed tomography scans, anal melanoma appears as a bulky, intraluminal fungating mass in the distal rectum, which focally expands and obscures the lumen without causing obstruction, with perirectal infiltration and frequently enlarged lymph nodes [22,23].

The ideal treatment for anorectal melanoma remains controversial, with 90% of patients dying
irrespective of the surgical approach or adjuvant radiotherapy and chemotherapy [12]. The role of adjuvant radiotherapy, immunotherapy and chemotherapy in this disease has not been established. Adjuvant therapies have been used after surgical resection in some studies, with no strong evidence of improvement in outcome [4,24]. Surgical treatment of this specific tumor has a wide spectrum that varies from conservative treatment such as LE, to radical operations such as APR. [4–8,19,25]. In a review that included 17 large case series, Yap et al compared the survival of patients who underwent APR or LE. The analysis revealed no statistically significant difference between two treatment modalities, even at all stages of the disease [26]. Moozar et al reported a better survival rate in patients who underwent wide excision when compared with LE in a study of 14 patients [27]. In our study, 11 patients underwent APR and three were treated by LE, but there was no difference with respect to survival in both groups.

These non-cutaneous malignant melanomas are rare tumors with aggressive behavior and dismal outcome [1,11]. The prognosis of patients is poor: the 5-year survival rate is estimated at between 6% and 22% [3,28,29]. The median survival of patients with anorectal melanomas in the United States is 10 months for those with distant metastasis, 13 months for those with regional spread, and 34 months for those with localized disease [28]. Twenty to sixty-two percent of patients with anorectal melanomas have metastatic disease at the time of initial diagnosis as a result of the rich lymphatic system of the anorectal region [12,30]. The tumor can disseminate after a latent period of 2–20 years to several sites such as lymph nodes, bone, lungs, liver, spleen, gastrointestinal tract, kidneys, adrenal glands and subcutaneous tissue [1,11].

The most important prognostic indicators in anorectal melanoma include age, sex, size, anatomic site, stage of disease, duration of symptoms, nodal involvement and molecular markers like proliferating cell nuclear antigen and Ki67 [6]. The Clark level and Breslow indexes that are used for evaluation of cutaneous malignant melanomas are not applicable to extracutaneous malignant melanomas [12]. However, tumor thickness seems to be a strong predictive factor for the risk of local recurrences, as reported by Ballo et al in 2002 [31]. In this respect, anorectal melanoma seems to be similar to cutaneous melanoma, for which tumor thickness is used to plan therapeutic procedures.

Invasion into the submucosa gives the tumor cells access to lymphovascular channels, which help in their dissemination [6]. Owing to the rarity of the tumor and its histological variability, misdiagnosis is common; particularly in amelanotic cases with unusual morphological features that can be mistaken for lymphoma, carcinoma, and/or sarcoma [13]. Histologically, the tumor can mimic adenocarcinoma, small cell carcinoma and sarcoma, and the lesion often mimics hemorrhoids [29].

In conclusion, anorectal melanoma is a rare and challenging disease. It affects mostly older patients and has a female predominance. It differs from cutaneous melanoma with regard to risk. The preoperative staging has an important role in influencing treatment decisions, however, according to our experience, the type of surgery does not alter the natural history of this disease. Quality of life needs to be considered when making treatment decisions.

References