Letter to Editor
Small cell malignant melanoma of the anus: a case report with review of the literature

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It has been well recognized that malignant melanoma (MM) can show various structural and cytomorphological features, such as pseudoglandular (adenoid), myxoid, signet-ring cell, rhabdoid, and balloon cell [1-6]. Small cell MM is one of the rarest cytomorphological variants, characterized histopathologically by the proliferation of small round neoplastic melanocytes with scant cytoplasm and a high nuclear/cytoplasmic ratio [7]. The recognition of this variant is important because it may easily be confused or misdiagnosed as other small round cell tumors, such as malignant lymphoma and Merkel cell carcinoma [7].

Anal MM is rare and represents approximately 4% of all anal tumors [8]. Occurrence of small cell MM in the anus is extremely rare, and only four cases have been reported in the English language literature [9-11]. Herein, we describe an additional case of small cell MM of the anus and discuss the differential diagnostic considerations.

A 39-year-old Japanese female presented with anal hemorrhage at the time of defecation. Colonoscopic examination revealed a tumorous lesion with surface erosion, measuring 25 mm in diameter, in the anal verge. Biopsy of the lesion was performed under a clinical diagnosis of mucosal prolapse syndrome.

Histopathological study of the biopsy specimen demonstrated diffuse proliferation of small round cells (Figure 1A). These cells had scant cytoplasm, a high nuclear/cytoplasmic ratio, and round to oval nuclei containing coarse chromatin and conspicuous nucleoli (Figure 1B). Apoptotic bodies were scattered, and mitotic figures were also observed (2/10 high-power fields). No melanin pigment was observed in these neoplastic cells (Figure 1B).

Immunohistochemical studies were performed using an autostainer (Ventana) by the same method as previously reported [12-16]. S-100 protein was expressed in these neoplastic cells (Figure 2A). Melan-A and HMB-45 were also expressed in some of these cells (Figure 2B and 2C). Moreover, c-kit was diffusely expressed in the neoplastic cells (Figure 2D). Cytokeratin, synaptophysin, chromogranin A, CD56, CD3, and CD20 were not expressed.

According to these histopathological and immunohistochemical results, an ultimate diagnosis of small cell MM of the anus was made.

Small cell MM is one of the rarest morphological variant of MM. This type of MM has been documented arising as a complication of congenital nevi and/or as a childhood melanoma, or at a mucosal site (nasal cavity and paranasal sinus) [7, 17]. Hanson et al. reported a case series of small cell MM occurring in adults [7]. In their series, 6 of 11 cases showed a pure small cell morphology, which mimicked malignant lymphoma, and melanin pigment was absent or minimal in these cases [7]. Moreover, S-100 protein was diffusely expressed in all 10 cases, in which immunohistochemistry was performed, and HMB-45 was positive in 8 of 10 cases [7]. Thus, immunohistochemical analyses are essential for its diagnosis.
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Anorectal MM accounts for only 0.31% of all MM cases [18]. Chute et al. analyzed the morphological and immunohistochemical features of 17 cases of anorectal MM [10]. In their series, four histopathological types were recognized: epithelioid, spindle cell, lymphoma-like, and pleomorphic, and the majority of cases (13 cases) showed more than two cell types [10].

Figure 1. Histopathological features of the anal tumor. A: Diffuse proliferation of small round cells. HE, × 100. B: These neoplastic cells have scant cytoplasm, a high nuclear/cytoplasmic ratio, and round to oval nuclei containing coarse chromatin and conspicuous nucleoli. No melanin pigment is observed. HE, × 400.

Figure 2. Immunohistochemical features of the anal tumor. (A) S-100 protein is expressed in the small round cells, × 400. Melan-A (B) and HMB-45 (C) are expressed in some of the neoplastic cells. × 400. (D) c-kit is diffusely expressed. × 400.
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Table 1. Clinicopathological features of anorectal small cell malignant melanoma

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Gender</th>
<th>Chief Complaint</th>
<th>Pigmentation</th>
<th>Immunohistochemistry</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>Female</td>
<td>Perianal pain</td>
<td>None</td>
<td>S-100 protein (+), HMB-45 (+)</td>
<td>[9]</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>Female</td>
<td>Bleeding</td>
<td>None</td>
<td>S-100 protein (+), HMB-45 (+), Melan-A (+)</td>
<td>[10]</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>Female</td>
<td>Bleeding</td>
<td>None</td>
<td>S-100 protein (+), HMB-45 (-), Melan-A (-)</td>
<td>[10]</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>Female</td>
<td>Bleeding</td>
<td>Slight</td>
<td>S-100 protein (+), HMB-45 (+)</td>
<td>[11]</td>
</tr>
<tr>
<td>Present Case</td>
<td>39</td>
<td>Female</td>
<td>Bleeding</td>
<td>None</td>
<td>S-100 protein (+), HMB-45 (+), Melan-A (+)</td>
<td></td>
</tr>
</tbody>
</table>

However, the remaining cases showed only one morphological type, which could be easily confused with non-melanocytic malignancies [10]. Moreover, 8 of 17 cases were amelanotic in their series, which included amelanotic lymphoma-like cases that were thought to correspond to amelanotic small cell MM, as seen in the present case [10]. Table 1 summarizes the clinicopathological features of the previously reported 4 cases of anorectal small cell MM in the English language literature as well as the present one [9-11]. All patients were female, and the average age was 55.8 years (range from 39 to 67). Chief complaint was anal bleeding. Although one case with slight pigmentation was reported [11], most cases were amelanotic.

Immunohistochemical analyses play a very important role in the diagnosis of anorectal MM, especially anorectal small cell MM, because approximately half of the cases are amelanotic [10]. S-100 protein was diffusely expressed in all anorectal MM cases, and HMB-45 (16/17 cases) and Melan-A (14/15 cases) were also expressed in the majority of them [10]. Moreover, S-100 protein was expressed in all 5 cases of anorectal small cell MM, and HMB-45 and Melan-A were also expressed in the majority of these cases (Table 1). However, a case of anorectal small cell MM, which showed positive immunoreactivity for S-100 protein, but lacked expression of HMB-45 and Melan-A, was documented (Table 1) [10].

Anorectal small cell MM must be differentiated from other malignant tumors showing small round cell morphology including malignant lymphoma and small cell neuroendocrine carcinoma. Malignant lymphoma expresses lymphocyte markers, such as CD3 or CD20, and small cell neuroendocrine carcinoma typically express chromogranin A, synaptophysin, or CD56. Although anorectal small cell MM can be associated with decreased expression of melanocytic markers [10], a panel of immunohistochemical markers including S-100 protein, HMB-45, Melan-A, lymphocytic and neuroendocrine markers, and cytokeratin can lead to the correct diagnosis. Further, albeit extremely rare, Merkel cell carcinoma can occur in the anus [19]. This type of carcinoma typically expresses synaptophysin, chromogranin A, and CD56, and dot-like positive immunoreactivity for cytokeratin 20 is characteristic [20]. These immunoprofiles can aid the differential diagnosis.

c-kit is a transmembrane tyrosine kinase receptor that involves the development and proliferation of melanocytes [21]. This protein was expressed in the majority of anorectal MM, including the present case, although two cases of anorectal small cell MM lacked expression of this protein [10]. KIT mutation is observed more frequently in mucosal melanoma than cutaneous melanoma [22, 23], and some cases of mucosal MM including anorectal MM have been reported to show response to tyrosine kinase inhibitors [24].

In conclusion, we describe the fifth documented case of small cell MM of the anus. This rare type of MM may be more frequent in the anorectal area (2/17 cases were pure small cell MM [10]) than cutaneous MM. Thus, mucosal MM including anorectal MM may show frequent small cell morphology. Therefore, MM should be included in the differential diagnostic consideration of small round cell tumors in the anus. Moreover, KIT mutation may be more frequently observed in anorectal MM, similar to other mucosal MM cases. Therefore, further clinicopathological studies are needed for new molecular-targeted therapy, such as c-KIT blocker, for anorectal MM because this tumor shows an aggressive clinical behavior [10].
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Disclosure of conflict of interest

None.

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