Anal Mucosal Melanoma with KIT-Activating Mutation and Response to Imatinib Therapy – Case Report and Review of the Literature

Imke Satzger  Uta Küttler  Bernward Völker  Florian Schenck  Alexander Kapp  Ralf Gutzmer
Skin Cancer Center Hannover, Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany

In December 2007, a 79-year-old female patient complained of anal bleeding. In coloscopy a pigmented nodular lesion was discovered in the posterior wall of the lower rectum. A biopsy of the tumor mass revealed proliferation of atypical epithelioid cells with pleomorphic features. Immunohistochemistry showed strong positivity for HMB45 and Melan A, whereas cytokeratins 1, 7, 5 and 14 and S-100 expression were negative, consistent with the diagnosis of anal mucosal melanoma. In addition, c-KIT staining demonstrated positive results in 75% of tumor cells. DNA sequence analysis revealed a KIT-activating mutation of L576P in exon 11. CT scans of the chest and abdomen revealed no evidence of metastasis, and complete removal of the tumor was achieved by wide local excision. In September 2008, the patient suffered from an extensive local recurrence with a visible part of the tumor mass at the posterior rectum. CT scans of the chest and abdomen demonstrated 12 pulmonary metastases and pathological lymph nodes in the inguinal region on both sides. S-100 protein (2.56 µg/l, upper normal limit 0.2 µg/l) and lactate dehydrogenase (592 U/l, upper normal limit 235 U/l) in serum were highly elevated. The recurrence could not be resected completely; a diverting colostomy had to be implanted for palliative therapy. The patient suffered from weakness, weight loss and loss of appetite; the tumor mass at the posterior rectum caused a painful foreign-body sensation. From October 2008, the patient was started on oral imatinib 400 mg daily as palliative therapy. Already 2 weeks later, her performance status was markedly improved. The visible part of the rectal tumor mass decreased and the patient was no longer impeded by the foreign-body sensation. From October 2008, the patient was started on oral imatinib 400 mg daily as palliative therapy. Already 2 weeks later, her performance status was markedly improved. The visible part of the rectal tumor mass decreased and the patient was no longer impeded by the foreign-body sensation. From October 2008, the patient was started on oral imatinib 400 mg daily as palliative therapy. Already 2 weeks later, her performance status was markedly improved. The visible part of the rectal tumor mass decreased and the patient was no longer impeded by the foreign-body sensation. From October 2008, the patient was started on oral imatinib 400 mg daily as palliative therapy. Already 2 weeks later, her performance status was markedly improved. The visible part of the rectal tumor mass decreased and the patient was no longer impeded by the foreign-body sensation. From October 2008, the patient was started on oral imatinib 400 mg daily as palliative therapy. Already 2 weeks later, her performance status was markedly improved. The visible part of the rectal tumor mass decreased and the patient was no longer impeded by the foreign-body sensation. From October 2008, the patient was started on oral imatinib 400 mg daily as palliative therapy. Already 2 weeks later, her performance status was markedly improved. The visible part of the rectal tumor mass decreased and the patient was no longer impeded by the foreign-body sensation. From October 2008, the patient was started on oral imatinib 400 mg daily as palliative therapy.
up to 1.8 cm before treatment (fig. 4a) decreased to 1.2 cm (maximal diameter, fig. 4b). The inguinal lymph node metastases were slightly enlarged (before treatment 42 and 44 mm, respectively; after treatment 44 and 48 mm, respectively). However, the radiologist considered both inguinal lymph nodes to be possibly enlarged as a reaction to therapy (table 1).

Unfortunately, the patient developed concurrent problems unrelated to melanoma and imatinib therapy. First, she suffered from a loss of vision due to aggravation of a preexisting glaucoma. Second, she became more and more depressive due to her familial situation.

Thus, she decided to discontinue imatinib therapy although it was highly recommended for melanoma treatment. Finally, she died in March 2009 only 10 weeks after the end of imatinib therapy.

**Review and Discussion**

Thus far in unselected patients suffering from metastatic melanoma, the use of targeted therapies which target specific mechanisms involved in the oncogenic process have been more or less frustrating [1].

One of the reasons for these findings might be that melanoma is not one disease but heterogeneous. In recent years, certain subgroups of melanoma patients characterized by certain targets have been described that may predict susceptibility to targeted therapies. However, it is currently unclear if patients will clinically benefit from targeted therapies that are guided by the absence or presence of susceptibility parameters.

One subgroup comprises melanomas that harbor \(BRAF\) mutations. In small numbers of patients, specific \(BRAF\) inhibitors (PLX4032 and RAF265) induced tumor regressions in up to 70% of patients with \(BRAF\) V600E mutated metastatic melanomas [2, 3]. Further studies are ongoing to prove this treatment approach in a higher number of patients with \(BRAF\) V600E mutated melanomas.

Melanomas with aberrations of the \(KIT\) gene might represent another subgroup which benefit from a therapy targeting the gene product c-KIT. Expression of c-KIT can be demonstrated in most mela-
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Nomomas by immunohistochemistry. However, studies of c-KIT blockers such as imatinib in unselected melanoma patients have been unsuccessful [4, 5]. Recently, an increased frequency of KIT aberrations was described in mucosal melanomas and acral melanomas but not in melanomas of areas from intermittent sun exposure [6, 7]. These KIT aberrations comprise mutations or copy number increase of the KIT gene. KIT mutations occur in melanomas with no or little UV exposure (mucosal melanomas and acral melanomas) in up to 20%, in cutaneous melanomas in 2.6% [8] or 2% of patients [9]. KIT gene amplifications in the absence of a KIT mutation occur in 18% of mucosal melanomas and 25% of acral melanomas but not in melanomas from sites of intermittent sun exposure [6]. In contrast, c-KIT protein expression can be detected in the majority of mucosal melanomas (up to 91% [7]), but also in a high percentage of cutaneous melanomas, i.e. up to 84% [10]. If KIT mutation or amplification rather than c-KIT expression is relevant for susceptibility to targeted therapies based on c-KIT blockade [11–14], this might be the reason why phase II trials with the c-KIT blocker imatinib in unselected patients with metastatic cutaneous melanoma have been disappointing [4, 5].

Our case presented here and a growing number of case reports and interim data from ongoing phase II studies provide promising results that patients with KIT-mutated metastatic melanomas are amenable to single-agent therapy with one of the c-KIT inhibitors imatinib [13, 14], dasatinib [15, 16], sunitinib [17] or sorafenib [18]. In addition to this case, to our knowledge 13 further cases have been reported thus far who suffered from KIT-mutated metastatic melanoma and were success-

Fig. 2. Visible part of the tumor mass at the anus before treatment (a), decreasing after 7 days (b), 14 days (c) and 28 days (d) of imatinib therapy.

Fig. 3. The serum tumor marker S-100 fell during the treatment with imatinib from 2.56 µg/l before therapy (day 0) to 0.68 µg/l after 35 days (normal <0.2 µg/l).
fully treated with kinase inhibitors targeting c-KIT (table 2). Twelve patients suffered similarly to our patient from metastatic melanoma with KIT mutations in exon 11 or exon 13 affecting the juxta-membranous region of the c-KIT protein, presumably resulting in an activation of c-KIT (table 2). One patient showed only a KIT amplification (table 2). Only 1/13 patients with KIT mutations had progressive disease during c-KIT-inhibiting therapy.

The patient with KIT amplification had a stable disease. Given the fatal outcome of metastatic melanoma without therapy, this strongly suggests a prognostic and therapeutic relevance of KIT mutations in melanoma, whereas the evidence for patients with KIT amplification without mutation is less clear.

It is interesting to note that all 5 patients described in detail in the literature and our patient responded rapidly to therapy with c-KIT inhibitors [13, 14, 16, 18]. Within the first 4 weeks of therapy, tumor masses and serum tumor markers decreased significantly in all patients. However, in our patient the tumor did not resolve completely. Lutzky et al. [14] reported a dose-dependent response to imatinib therapy in their patient, which raises the question if the imatinib dose of 400 mg p.o. daily, given to our patient due to the side effects of therapy, was too low. Future

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**Table 2. Treatment of patients with KIT-mutated metastatic melanomas with tyrosine kinase inhibitors**

<table>
<thead>
<tr>
<th>Type of melanoma</th>
<th>Patients</th>
<th>KIT mutation</th>
<th>Therapeutic agent</th>
<th>Dose mg/day</th>
<th>Response to therapy</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Mucosal melanoma</td>
<td>1</td>
<td>K642E, exon 13</td>
<td>imatinib</td>
<td>400–600</td>
<td>complete response</td>
<td>14</td>
</tr>
<tr>
<td>Mucosal melanoma</td>
<td>1</td>
<td>7-codon duplication, exon 11</td>
<td>imatinib</td>
<td>400</td>
<td>major response</td>
<td>13</td>
</tr>
<tr>
<td>Acral and mucosal melanoma</td>
<td>5</td>
<td>exon 11 mutation (3 patients), exon 11 amplification (1 patient), exon 13 mutation (1 patient)</td>
<td>imatinib</td>
<td>300–800</td>
<td>3 patients partial response, 2 patients stable disease</td>
<td>12</td>
</tr>
<tr>
<td>Mucosal melanoma</td>
<td>1</td>
<td>V560A, exon 11</td>
<td>sorafenib</td>
<td>800</td>
<td>complete response (5 months)</td>
<td>18</td>
</tr>
<tr>
<td>Mucosal melanoma</td>
<td>2</td>
<td>L576P, exon 11</td>
<td>dasatinib</td>
<td>140</td>
<td>both patients partial response (&gt;50%)</td>
<td>16</td>
</tr>
<tr>
<td>Advanced melanoma</td>
<td>2</td>
<td>(1) exon 13 (2) deletion exon 11</td>
<td>dasatinib</td>
<td>140–200</td>
<td>(1) partial response (2) no response</td>
<td>15</td>
</tr>
<tr>
<td>Mucosal melanoma</td>
<td>1</td>
<td>V559A, exon 11</td>
<td>sunitinib</td>
<td>37.5</td>
<td>partial response (70%)</td>
<td>17</td>
</tr>
<tr>
<td>Mucosal melanoma</td>
<td>1</td>
<td>L576P, exon 11</td>
<td>imatinib</td>
<td>400</td>
<td>stable disease</td>
<td>this report</td>
</tr>
</tbody>
</table>

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**Fig. 4.** Pulmonary metastases of anal mucosal melanoma at diagnosis of metastatic disease with a maximal diameter of 18 mm (a) and 12 weeks later with smaller diameter (maximum 12 mm; b).
studies are necessary to determine effective treatment parameters.

In summary, current data strongly indicate that melanomas with activating KIT mutations and possibly also with KIT gene amplifications respond to therapy with tyrosine kinase inhibitors blocking c-KIT. Thus, subgroups of patients with metastatic melanoma prone to KIT mutations, such as primary mucosal and acrolentiginous melanomas, should be analyzed for their KIT status. In case of an activating mutation or gene amplification, a therapeutic attempt with c–KIT blocker is reasonable. Clinical studies in such patients are warranted to better define the subgroup responsive to targeted therapy with c-KIT inhibitors.

References


