# Response to Imatinib in a Patient with Double-mutant *KIT* Metastatic Penile Melanoma

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Primary penile melanoma (PM) is a rare malignant mucosal tumour with poor prognosis. The mainstay of initial treatment is surgery, but excision with adequate margins often requires penile amputation, which may result in major impairment in the patient's quality of life without improving survival (1). Unresectable and metastatic cases of PM are difficult to treat because of poor efficacy of new treatments, which have recently transformed the prognosis of advanced cutaneous melanomas (CMs). Checkpoint inhibitors have not been specifically evaluated in PMs, but the response rate of patients with metastatic mucosal melanoma (MM) treated with anti-CTLA-4 or anti-PD-1 antibodies remains low (2). The oncogenic drivers of PMs are widely unknown because of the rarity of this tumour. In MMs from other mucous sites, the main drivers commonly found in CMs (i.e. *BRAF* and *NRAS*) have low mutation rates (3). In contrast, *KIT* mutations are more frequent in MMs (13%) than in CMs (3). Responses to KIT inhibitors, such as imatinib, have been reported in *KIT*-mutated MMs (4). Although these responses were more often partial and of short duration, complete and long-term responses have also been reported (4, 5). To the best of our knowledge, no patient with KIT-mutant metastatic PM and response to KIT inhibitors has been reported to date.

## CASE REPORT

A 69-year-old man consulted for a PM. He had a 10-year history of hyperpigmentation of the penis, with a nodular development over 8 months. Physical examination revealed a 4×3 cm pigmented macula of the glans and adjacent foreskin (**Fig. 1**a) with a 12×8 mm, thick, nodule at the balano-preputial junction, without lymphadenopathy. Histopathological examination of the nodule showed a malignant, *BRAF* wild-type melanoma. Whole-body 18F-Fluorodeoxyglucose positron emission computed tomography evaluation was otherwise negative. The patient declined radical, mutilating surgery and was therefore first treated with the anti-PD-1 antibody pembrolizumab. After 8 months, the penile nodule increased in size and palpable inguinal lymph nodes appeared, without detectable distant metastases. Bilateral radical lymph node dissection was positive for melanoma in 2 nodes on the right side and 1 node on the left side. After receiving 3 doses of the anti-CTLA-4 antibody ipilimumab, the patient developed a grade-2 colitis requiring systemic corticosteroids, and a solitary brain metastasis, which was treated with stereotactic radiotherapy. Pembrolizumab was then rechallenged, until lung and pleural metastases were visualized on F-FDG PET/CT and confirmed by histopathological examination 6 months later, along with growing penile metastatic nodules (Fig. 1b). Next generation sequencing molecular analysis of 1 nodule identified double pathogenic *KIT* mutations, in exon 11 (c.1727T>C, L576P) and exon 18 (c.2540C>T, T847M). The patient was given imatinib, 400 mg twice per day, with good tolerance. The penile nodules disappeared rapidly and the brain MRI and whole-body F-FDG PET/CT, performed after 3 months of therapy, did not show any residual metastasis, while the CT scan still visualized a small pleural nodule, consistent with a complete metabolic, nearly morphologically complete, remission. After a progression-free period of 6 months, lung and pleural metastases recurred. The patient received 7 cycles of dacarbazine, leading to a partial response, followed by progression. The anti-PD-1 antibody nivolumab was then administered, once again with a partial response. The patient's lactate dehydrogenase level was normal. The patient was alive in good general condition with only a minor residual disease 2 years after first distant (brain) metastases and 18 months after the initiation of imatinib for rapid progression.

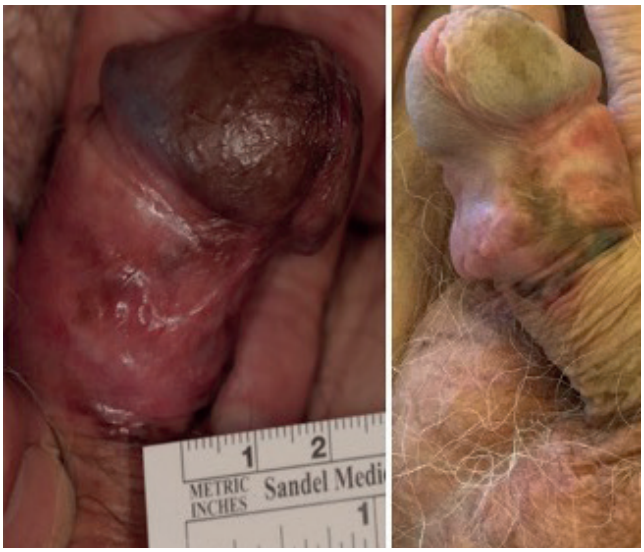


**Fig. 1. Penile melanoma (a) at initial examination, (b) at initiation of imatinib treatment.**

## DISCUSSION

To our knowledge, this is the first reported case of a *KIT*-mutated PM treated successfully with a KIT inhibitor. Also rare, the *KIT* L576P mutation is the most common oncogenic *KIT* variant in melanomas (5). The



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*KIT* T847M mutation has been reported in one case of conjunctival melanoma (6) and is considered pathogenic (https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=165056644).

An exhaustive literature review (references available on request) identified one *KIT* mutation (Q575_P577del in exon 11) (7) among 21 cases of PMs tested for *KIT*. In these cases, no details of treatment or outcome were given. Most responses in *KIT*-mutated melanomas and other *KIT*-mutated tumours as gastrointestinal stromal tumours (GISTs) have been observed in patients with exon 11 variants (5). In contrast, patients with exon 18 *KIT*-mutated tumours generally had no response. The dramatic response observed in the current patient with both exon 11 and 18 mutations is therefore of interest.

Unexpected responses to chemotherapies or previously ineffective treatments have been reported after responses to various emerging therapies, suggesting that an initial response may modify the molecular profiles and sensitivity of tumour cells (8). We therefore hypothesize that the current patient benefitted from the KIT therapy beyond the initial response.

Although the frequency of *KIT* mutations in PMs remains unknown (1/21=4.8%, 95% confidence interval 0–14%) and seems lower than that of vulvo-vaginal melanoma (35%) and head and neck melanoma (25%) (3), our observation suggests that a molecular analysis including *KIT* should be performed before any decision is made to use aggressive surgical treatment or systemic therapy in patients with PM.

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*The authors have no conflicts of interest to declare.*

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