

Complete response of stage IV anal mucosal melanoma expressing KIT Val560Asp to the multikinase inhibitor sorafenib

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SUMMARY

Background A 79-year-old man presented to his primary care physician with a 2-month history of pruritus ani and a pigmented nodular lesion was discovered in the posterior rectum. The patient had no other symptoms, or any family history of malignancy.

Investigations Physical examination; excisional biopsy; CT scan of the chest, abdomen and pelvis; lung biopsy; blood tests; tumor immunohistochemistry for KIT, vascular endothelial growth factor platelet-derived growth factor receptor α and β , and mismatch-repair proteins MLH1, MSH2, and MSH6; and *KIT* and *BRAF* tumor genotyping.

Diagnosis Stage IV M1b metastatic anal mucosal melanoma.

Management Wide local excision with mucosal advancement of the rectal wall, external-beam radiation, and sorafenib–temozolomide therapy.

KEYWORDS anal melanoma, KIT, lung metastasis, sorafenib

CME

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe the epidemiology of mucosal melanoma.
- 2 Identify diagnostic characteristics of anal mucosal melanoma.
- 3 Specify genetic mutations common in anal mucosal melanoma.
- 4 Identify the kinase target of therapy in the current case study associated with clinical improvement.

Competing interests

The authors and the Journal Editor L Hutchinson declared no competing interests. The CME questions author CP Vega declared that he has served as an advisor or consultant to Novartis, Inc.

THE CASE

A 79-year-old man presented to his primary care physician with a 2-month history of pruritus ani. The patient had not experienced any constitutional symptoms such as fever, weight loss or loss of appetite, and denied any family history of malignancy. Physical examination showed a pigmented nodular lesion in the posterior rectum. An excisional biopsy performed 2 weeks later revealed the presence of anal mucosal melanoma (AMM; Figure 1) of Breslow thickness 1.7 mm, exhibiting both radial and vertical growth. No evidence of lymphovascular or perineural invasion was observed. Melanoma *in situ* at the distal peripheral margin and invasive melanoma within 0.5 mm of the proximal peripheral margin were present. A CT scan of the chest, abdomen and pelvis showed no evidence of metastatic disease. The patient underwent wide local excision with

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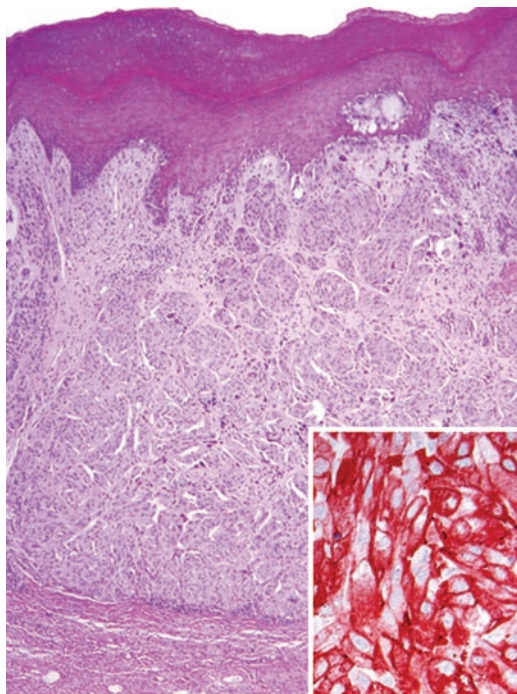


Figure 1 Hematoxylin and eosin and immunohistochemical staining (inset) of the patient's primary tumor. Hematoxylin and eosin staining of a section of the invasive anal mucosal melanoma (20× original magnification) with inset showing KIT immunoreactivity (200× original magnification).

mucosal advancement of the rectal wall, intra-operative lymphatic mapping, and biopsy of the sentinel lymph node of the right inguinal region 4 weeks after the initial biopsy. No evidence of melanoma was found in any of the three lymph nodes biopsied. The final margins of resection were negative. The patient received 30 Gy external-beam radiation to the rectum in five fractions. Subsequently, he was followed-up at regular intervals with no evidence of recurrence. Twenty-one months after the initial presentation, the patient developed a persistent dry cough. A CT scan of the thorax showed multiple lung nodules, with the largest nodules measuring 1.7, 1.1, and 0.5 cm in diameter. A lung biopsy a month later revealed neoplastic cells that immunostained positive for HMB-45, MART-1, and tyrosinase, and negative for CK7, CK20, and TTF-1, confirming the diagnosis of metastatic melanoma. The patient was referred to another institution with a diagnosis of stage IV M1b metastatic AMM. Additional material from the lung biopsy was not available, but immunohistochemical staining for KIT in the primary

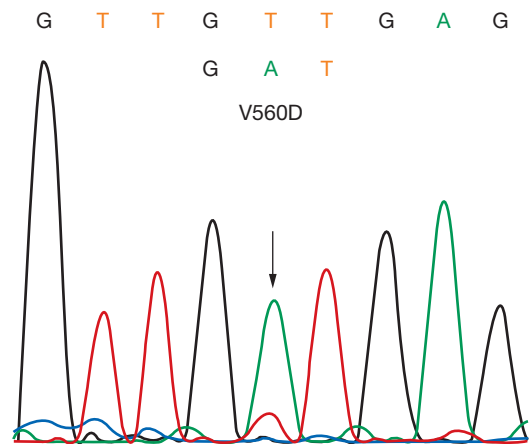


Figure 2 Sequence analysis of *KIT* from the patient's tumor DNA. Sequencing of exon 11 of the *KIT* gene showing a mutation in codon 560 (arrow), which resulted in the substitution of valine by aspartic acid.

tumor revealed diffuse strong cytoplasmic reactivity (Figure 1, inset). The following month, the patient started treatment with sorafenib 400 mg twice daily and temozolomide 75 mg/m² on a 3-week-on/1-week-off schedule. The patient received therapy with sorafenib and temozolomide for 5 months. Within the first 4 weeks of therapy, he developed asymptomatic grade 1 amylase and grade 3 lipase elevations, and grade 2 skin rash, which resolved after decreasing the dose of sorafenib to 200 mg twice daily. Further immunohistochemical testing on the primary tumor revealed weak expression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptor (PDGFR)- β and very weak expression of PDGFR- α . Furthermore, *BRAF* was not mutated, and the intact nuclear expression of the mismatch repair proteins MLH1, MSH2, and MSH6 indicated that the tumor was microsatellite stable. Polymerase chain reaction amplification and sequencing of exon 11 of the *KIT* gene from DNA isolated from the formalin-fixed, paraffin-embedded tumor sample was performed. A base-pair substitution at codon 560 resulting in an amino acid substitution from valine to aspartic acid was demonstrated (Figure 2). Two months later, a CT scan of the chest showed almost complete resolution of the pulmonary nodules, while a repeat CT scan showed no evidence of disease after 4 months of therapy (Figure 3A,B). The complete response was maintained for 5 months, but was followed by progressive disease in the brain and lungs. At

this time, further therapy was limited because of the patient's comorbidities and he subsequently died from his disease.

DISCUSSION OF DIAGNOSIS

AMM is a rare disorder, accounting for less than 1% of cases of melanoma in the US; however, AMM comprises approximately one quarter of cases of mucosal melanoma.¹ Although rare in Western countries, mucosal melanoma is as prevalent worldwide as melanoma arising from sun-exposed skin. The median overall survival of patients with AMM is usually less than 6 months, because of the development of intractable metastatic disease.² AMM represents both a diagnostic and therapeutic challenge given its nonspecific presentation and rarity. Patients with AMM frequently present with an anorectal mass and rectal bleeding. As a consequence, the diagnosis of this disease is not always straightforward, and is often incidental after surgical treatment for presumed benign disorders such as hemorrhoidectomy or lateral internal sphincterotomy. Therefore, and in order to prevent delayed diagnosis, tissue pathological analysis on any atypical anorectal lesion is of critical importance. Immunocytochemical studies are often used in the diagnosis of AMM, which is indicated by overexpression of melanocytic markers such as S-100 protein, HMB-45, microphthalmia-associated transcription factor (Mitf), tyrosinase, and Melan-A (also known as MART-1).³ Since the antibodies used to detect these antigens can react with a broad range of benign and malignant neoplasms, it is standard practice to use a panel of antibodies recognizing melanocytic markers in order to increase the sensitivity of immunohistochemistry testing when diagnosing melanoma.³ It is assumed that the stage of AMM—especially the tumor thickness—is the main prognostic factor that might influence the operative management of this disease.

TREATMENT AND MANAGEMENT

Although locoregional control can occasionally be obtained with surgery in combination with local radiation,⁴ nearly all patients with AMM succumb as a consequence of intractable metastatic disease. Although recent evidence suggests that the molecular pathogenesis of mucosal melanoma is different from that of cutaneous melanoma, most chemotherapy schedules used to treat patients with AMM are based on regimens designed for patients with metastatic

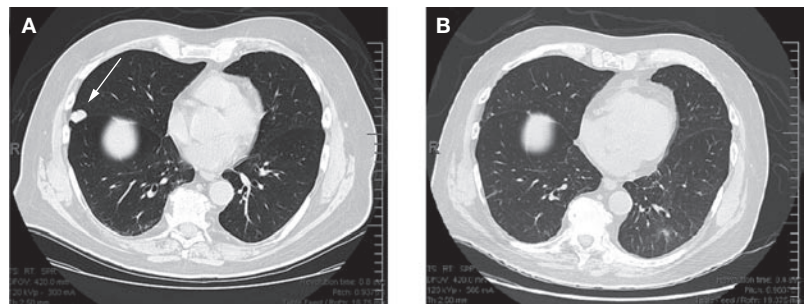


Figure 3 CT scan of the patient's chest before and after sorafenib and temozolomide therapy. **(A)** CT scan prior to therapy showing a 1.7 cm nodule in the right middle lobe adjacent to the minor fissure, which was proven by biopsy to be metastatic mucosal melanoma (arrow). **(B)** CT scan demonstrating complete resolution of the metastatic pulmonary nodules after 4 months of therapy.

cutaneous melanoma. The development of targeted agents that may have efficacy against specific genetic alterations found in mucosal melanoma has opened new avenues for the treatment of patients with this disease.

Typically, patients with metastatic AMM are treated with biochemotherapy involving cisplatin, vinblastine, dacarbazine, interferon- α , and interleukin 2.⁵ In most studies, complete response rates with such approaches range from 5% to 20%, with only 10% of patients surviving beyond 5 years.⁵ A theoretical approach to improve these disappointing outcomes is to tailor therapy to specific targets that drive the pathogenesis of AMM. Although *BRAF* mutations can be found in 59% of melanomas arising on skin without signs of chronic sun-induced damage, these mutations are rare in mucosal melanoma and have only been reported in approximately 3% of cases.⁶ By contrast, mutations and/or copy number increases of the *KIT* gene can be found in 39% of patients with mucosal melanoma, whereas these are infrequent in melanomas occurring on skin without signs of chronic sun-induced damage.⁷ Interestingly, mutations resulting in single amino acid substitutions in exons 11, 13, and 17 of *KIT* are most often demonstrated in melanoma,⁶⁻⁹ in contrast to gastrointestinal stromal tumors (GISTs) where in-frame deletions, primarily in exon 11, are more common than point mutations.¹⁰ Mutations in other exons of *KIT* including 9, 13 and 17,¹¹ and mutations in *PDGFRA* (primarily exons 12, 14, and 18) are also encountered in GISTs.¹² More than half of the point mutations documented in melanoma are also encountered in GISTs. Hence, targeted agents against the *KIT* tyrosine

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Competing interests

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kinase hold promise for the treatment of AMM since these agents are also active against GISTs. Sorafenib is a *bis*-aryl urea analog with potent activity against BRAF kinase.¹³ The regimen employed in this patient was originally developed based on the activity of sorafenib against BRAF, which commonly harbors activating mutations in cutaneous melanoma.^{14–16}

Since *BRAF* mutations are rare in AMM, the inhibitory activity of sorafenib on kinases other than BRAF may be important for its clinical activity. Sorafenib is a potent inhibitor of VEGFR1, VEGFR2, VEGFR3, PDGFR- β , and other receptor tyrosine kinases involved in tumorigenesis, such as KIT.¹³ Complete responses in patients with cutaneous melanoma treated with temozolamide are extremely rare;¹⁷ therefore, it is reasonable to speculate that the inhibition of the KIT kinase by sorafenib may have been a major contributor to the remarkable response observed in this patient. In addition, the activity of other putative targets of sorafenib in this patient was weak, further reinforcing the notion that the clinical response was probably due to sorafenib-induced KIT Val560Asp kinase inhibition. The Val560Asp mutation occurs in the juxtamembrane region, which is encoded by exon 11 of *KIT*, and this mutation is one of the most commonly encountered amino acid substitutions in GISTs.¹⁸ In our experience of treating these tumors, GISTs with this mutation are sensitive to inhibition of the mutant KIT receptor by imatinib mesylate. This particular mutation has not been previously described in melanoma, but a mutation at another codon in exon 11 of *KIT* that results in Leu576Pro seems to be the most common *KIT* mutation in melanoma.^{6–9} Given the differences in the mutational milieus of GIST and melanoma, it is not clear whether melanomas with *KIT* mutations will be as vulnerable to inhibition of the KIT receptor as GISTs.

CONCLUSIONS

AMM is a frequently occurring type of mucosal melanoma with very limited treatment options. The development of metastatic AMM is almost invariably associated with a dismal prognosis. Although the combination of surgical excision and local radiation therapy can occasionally be curative for patients with localized disease, recurrence rates are high and patients frequently

succumb to metastatic disease. This case provides an example of the therapeutic potential of the use of targeted small-molecule kinase inhibitors such as sorafenib against specific mutations (e.g. KIT Val560Asp) in AMM. It will be interesting to investigate the efficacy of this type of strategy in the adjuvant setting after local control of mucosal melanomas with surgery and local radiation.

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