CASE REPORT

Perianal melanoma with a BRAF gene mutation in a young Portuguese Roma native

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SUMMARY

A case of a young man diagnosed with perianal nodular melanoma with a gene mutation, accompanied by regional and pulmonary metastases on initial presentation, and later on with hepatic and bone involvement, is presented. The patient underwent wide local excision but was unresponsive to dacarbazine. Targeted therapy with vemurafenib had shown clinical improvement for a 5-month duration until he showed signs of disease progression. Just after the shift of adjuvant therapy to ipilimumab, he was diagnosed with multiple cerebral metastases that eventually led to his demise 6 months after initiation of vemurafenib, having had a 12-month survival period from the time of initial melanoma diagnosis.

BACKGROUND

Perianal localisation of melanoma and BRAF (V-raf murine sarcoma viral oncogene homolog B1) mutation in sun-protected areas are both rare occurrences. The role of this gene mutation in melanomagenesis is not yet fully understood,¹ whereas there are still no clearly identifiable risk factors for melanomas on shielded sites. The localisation and mutation are both contributory to poor prognosis, with the latter being associated with either a propensity for early lymphatic spread or a rapid evolution at its metastatic stage unless treated with a signal-transduction inhibitor. This report aims to add to the scant existing literature on cases of anorectal malignant melanoma (AMM).

CASE PRESENTATION

The patient, a 25-year-old Portuguese Romani (*cigano*) man with Fitzpatrick skin phototype IV, had a 10-year history of an asymptomatic hyperpigmented perianal nodule. Baseline characteristics as well as evolution of the lesion were not familiar to him due to its inaccessible location. He had a few episodes of self-limited, localised bleeding 2 years before the consult, without other associated gastrointestinal symptoms. Medical history was unremarkable, except for morbid obesity with a body mass index of 45 kg/m². Family medical history was positive for pulmonary and colon cancer.

Signs of inflammation with purulent exudates surrounding the lesion started at 5 months prior to consult, in January 2014, at which time the patient presented with an ulcerated nodule, measuring 2.5×1.5×1 cm³ at 11 o'clock in supine position, 2 cm from the anus. He also had multiple palpable bilateral inguinofemoral adenomegalies.

INVESTIGATIONS

The patient underwent an emergency wide local excision (WLE) of the perianal nodule on admission. Histopathology revealed nodular malignant melanoma with ulceration, Breslow thickness of 15 mm and Clark level V. BRAF V600 mutation was detected by real-time PCR method, utilising Cobas 4800, Roche. Initial metastatic work up, including an integrated positron emission tomography and CT scan, showed multiple bilateral inguinofemoral adenomegalies with necrotic components, more extensive on the left, the largest of which had a diameter of 5 cm. There were also small adenomegalies on the left latero-aortic and iliac regions, and a solid 5 mm nodular pleural mass on the pulmonary lingula.

DIFFERENTIAL DIAGNOSIS

AMMs typically present with symptoms of bleeding, pain and palpable mass, 30% of which are amelanotic.² Hence, they can be initially mistaken for haemorrhoids, fissures or abscess.³

TREATMENT

After the initial diagnosis, our patient subsequently underwent cytoreduction of the left inguinal lymph node and was given three cycles of dacarbazine (1000 mg/m²), from April to June 2014. However, his repeat CT scan with contrast (August 2014) showed multiple metastatic osteolytic bone lesions in the sternum, right humeral head, multiple vertebral bodies and in both wings of the sacrum and iliac bones. There were also miniature pulmonary nodules, as well as ill-defined hepatic nodules. The adenopathies in the lumboaortic, external iliac and inguinal chains were maintained. In the same month, bone gammagraphy (99mTc-HMDP) showed discrete focal hyperfixation of the radiotracer on the right fronto-parietal calvarium and left paramedian, as well as right temporal areas. There was also discrete irregularity from D11 to L2, and the left acetabulum.

The patient's systemic therapy was then shifted to vemurafenib at a well-tolerated twice a day-dose of 960 mg in July 2014. The level of lactate dehydrogenase (LDH) decreased 2.5 times 4 weeks after initiation of targeted therapy.

OUTCOME AND FOLLOW-UP

Despite showing favourable clinical response and decreasing LDH levels for 5 months, the patient's repeat CT scan in November 2014 showed progression of lesions in the liver, spleen, lymph nodes and bones. He was able to receive a single dose of

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ipilimumab at a dose of 3 mg/kg in December 2014, just before he was diagnosed with multiple cerebral metastases; he finally succumbed to death in January 2015.

DISCUSSION

Melanoma of the anal margin is a rare occurrence, representing 0.6–1.6% of all melanomas.² It is generally grouped with AMM and is regarded as an atypical site for melanoma; although strictly speaking, it is defined as the perianal skin encompassing a radius of 5 cm.² Other reported atypical sites for primary malignant melanoma are the lower genitourinary tract, particularly in females;⁴ cerebral cortex; nasal cavity; tongue; breast; and tonsillar fossa.⁵

In contrast to sun-exposed cutaneous malignant melanoma (CMM), the role of UV radiation as the major risk factor for the development of melanoma on these non-sun-exposed sites is not clear. For one, there is neither observed geographic latitudinal gradient for the latter, nor any significant racial associations unlike in cutaneous melanomas.⁶ Moreover, while the incidence of CMM increases, the rate for melanoma on the shielded sites tends to decrease or remain constant.⁶

On the other hand, BRAF, a serine/threonine protein kinase activating the mitogen-activated protein kinase (MAPK) signalling pathway that controls cell proliferation, differentiation and apoptosis, is one of the most common gene mutations occurring in CMM.⁷ It is present in around 82% of melanocytic nevi,⁸ and has a reported prevalence of 33–47% in primary melanomas and 41–55% in metastatic melanomas.⁹ It is unlikely to be a susceptibility gene for melanoma, as studies on familial melanoma did not show evidence of germ-line BRAF mutations.¹⁰

Patients with BRAF oncogene mutations generally present with younger age at diagnosis, both for primary (median age of 52 years vs 61 years) and metastatic melanoma (median age of 56 years vs 63 years).⁹ The following factors have also been significantly associated with BRAF in primary CMM: single or occult primary melanoma; truncal location; superficial spreading and nodular melanoma subtypes; and presence of mitoses.⁹ Most of these are compatible with our patient's characteristics: young adult with single, primary nodular melanoma. The perianal site, however, is an uncommon location for this type of mutation. In the literature, BRAF mutation has been reported in a case of melanoma arising from perianal fistula, also in a young male patient;⁸ the authors have also referenced other case reports with this mutation involving anal mucosal melanomas, as well as in thyroid, colorectal, pancreatic and ovarian cancers. It is hypothesised that, in these areas, persistent or chronic inflammation leads to oxidative damage caused by free radicals, and eventually to BRAF mutation.⁸

Surgical management of AMMs can either be through WLE or abdominoperineal resection (APR). Neither has an advantage over the other in controlling locoregional recurrences.¹¹ APR is recommended if the surgical margins are invaded, in the case of local recurrence or if the tumour is inaccessible.¹² Although recently, WLE with conservation of the anal sphincters has been preferred for a better quality of life after surgery.¹¹ The main objective of surgery is to achieve a negative resection margin for local control, either through the use of intraoperative frozen sections or reoperative excision of margins.¹³ However, at a certain depth and size of tumour (>3 mm thick and >30 mm diameter), curative surgery cannot be achieved, in which case conservative local excision and adjuvant therapy can result in a better prognosis.¹¹ Our patient's primary tumour was 15 mm thick and 25 mm wide. Complete resection was achieved, but without safety margins. Given his advanced stage, the surgeons

opted for conservative management with cytoreduction of one of the left inguinal nodes.

In terms of adjuvant treatment, two approaches have shown better response rates in randomised trials when compared with chemotherapy: one is by immunotherapy through checkpoint inhibition, and the other by targeting the MAPK pathway. The first approach—checkpoint inhibition—can be achieved either through anti-programme cell death-1 (anti-PD-1) antibodies (which include pembrolizumab and nivolumab), or anti-CTLA-4 antibody (ipilimumab). Favourable results were seen in patients with and without BRAF mutations.^{14–16} The second approach—targeting the MAPK pathway—is indicated for unresectable or metastatic BRAF-mutated melanoma. This pertains to the inhibition of BRAF (using vemurafenib or dabrafenib) or MEK (mitogen-activated ERK-extracellular signal-regulated kinase-activating kinase) (trametinib and cobimetinib). These inhibitors, singly or in combination, have already shown significant improvement in response rates, albeit still far from attaining cure.^{17–21} The optimal choice of regimen remains to be fully elucidated, with various combinations and different sequences of individual treatment currently being investigated in ongoing clinical trials.¹⁵

Ideally, the patient could have also been tested for cKIT driver mutation that is increased in AMMs;¹³ this could have given the patient another treatment option using a tyrosine kinase inhibitor (imatinib).²²

Our patient showed clinical improvement and significantly decreasing LDH levels during the 5-month-course of vemurafenib therapy, after which his disease took a rapid downhill course, and he eventually succumbed to death 6 months after initiation of targeted therapy, with a 12-month survival period from the time of initial melanoma diagnosis.

The reported mean survival time for all patients with AMM has been reported as 15 months;²³ others report 19–26.4 months.¹¹ There was no reported age or survival difference between races; neither was there 5-year projected survival advantage identified for location (anal canal, rectum, anus).²³ The 5-year survival rate varies according to the presence of metastases, with a reported rate of 10–26% at best.³

Learning points

- ▶ Perianal melanoma, together with anorectal malignant melanomas (AMMs) in general, is a rare occurrence. Nevertheless, it can be an important differential diagnosis when presented with patients with haemorrhoids, anal fissures or abscess, and, especially, a significant number of AMMs can be amelanotic.
- ▶ Unlike in cutaneous malignant melanomas, UV radiation does not have a direct correlation with the development of AMMs. To date, its risk factors are still not clearly elucidated.
- ▶ BRAF (V-raf murine sarcoma viral oncogene homologue B1) mutation involving non-sun-exposed areas is another uncommon event. In these cases, chronic inflammation leading to oxidative damage is hypothesised as a possible explanation.
- ▶ BRAF mutation is overall a poor prognostic factor for patients with metastatic melanoma; however, it also signifies increased responsiveness to signal-transduction inhibitors.

Unfortunately, 37% of patients have already had distant or regional metastasis at the time of diagnosis.¹¹ Lymphatic spread is common and tends to involve mesenteric and inguinal lymph nodes; the brain is the most common metastasis site, followed by liver and lung.¹¹ The latter two were already affected in our patient, in addition to the extensive adenopathies, early in the course of disease.

In terms of the prognostic significance of BRAF mutation, its lack of correlation with Breslow thickness could mean that it has no role in genetic instability during early stages of primary tumour growth.¹⁰ For the past many years, the poor prognosis associated with BRAF gene mutation has been attributed to melanoma's rapid evolution after the diagnosis of distant metastases—unless treated with a BRAF-inhibitor.⁹ However, more recent findings suggest the role of BRAF as a strong oncogenic driver, bearing a strong propensity for early lymph node involvement and perhaps brain metastasis, in addition to its associated early age at diagnosis.²⁴

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REFERENCES

- Venesio T, Chiorino G, Balsamo A, et al. In melanocytic lesions the fraction of BRAF V600E alleles is associated with sun exposure but unrelated to ERK phosphorylation. *Mod Pathol* 2008;21:716–26.
- Leonard D, Beddy D, Dozois EJ. Neoplasms of anal canal and perianal skin. *Clin Colon Rectal Surg* 2011;24:54–63.
- Fripp VT, Esquivel J, Cerruto CA. Perianal melanoma disguised as hemorrhoids: case report and discussion. *J Natl Med Assoc* 2005;97:726–31.
- Zamurovic M, Soldo V, Cutura N, et al. Amelanotic malignant melanoma of the perineum: a case report. *Eur J Gynaecol Oncol* 2013;34:269–70.
- Das P, Kumar N, Ahuja A, et al. Primary malignant melanoma at unusual sites: an institutional experience with review of literature. *Melanoma Res* 2010;20:233–9.
- Micu E, Juzeniene A, Moan J. Comparison of the time and latitude trends of melanoma incidence in anorectal region and perianal skin with those of cutaneous malignant melanoma in Norway. *J Eur Acad Dermatol Venereol* 2011;25:1444–9.
- Ascierto PA, Kirkwood JM, Grob JJ, et al. The role of BRAF V600 mutation in melanoma. *J Transl Med* 2012;10:85.
- Martinez-Cadenas C, Bosch N, Peñas L, et al. Malignant melanoma arising from a perianal fistula and harbouring a BRAF gene mutation: a case report. *BMC Cancer* 2011;11:343.
- Long GV, Menzies AM, Nagrial AM, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. *J Clin Oncol* 2011;29:1239–46.
- Shinozaki M, Fujimoto A, Morton DL, et al. Incidence of BRAF oncogene mutation and clinical relevance for primary cutaneous melanomas. *Clin Cancer Res* 2004;10:1753–7.
- Nam S, Kim CW, Baek SJ, et al. The clinical features and optimal treatment of anorectal malignant melanoma. *Ann Surg Treat Res* 2014;87:113–17.
- Lerondeau B, Granel-Brocard F, Cuny JF, et al. Mélanome de la marge anale. *Annales de dermatologie et de vénéréologie* 2013;140:444–7.
- Carcoforo P, Rajji MT, Palini GM, et al. Primary anorectal melanoma: an update. *J Cancer* 2012;3:449–53.
- Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in Advanced Melanoma. *N Engl J Med* 2015;372:2521–32.
- Scott LJ. Nivolumab: A Review in Advanced Melanoma. *Drugs* 2015;75:1413–24.
- Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711–23.
- Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med* 2012;366:707–14.
- Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 2012;380:358–65.
- Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med* 2012;367:107–14.
- Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med* 2015;372:30–9.
- Larkin J, Ascierto PA, Dréno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med* 2014;371:1867–76.
- Hodi FS, Corless CL, Giobbie-Hurder A, et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. *J Clin Oncol* 2013;31:3182–90.
- Cagir B, Whiteford MH, Topham A, et al. Changing epidemiology of anorectal melanoma. *Dis Colon Rectum* 1999;42:1203–8.
- Pracht M, Mogha A, Lespagnol A, et al. Prognostic and predictive values of oncogenic BRAF, NRAS, c-KIT and MITF in cutaneous and mucous melanoma. *J Eur Acad Dermatol Venereol* 2015;29:1530–8.

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