

## Multiple primary malignancies and prolonged survival in a patient with widespread metastatic cutaneous melanoma

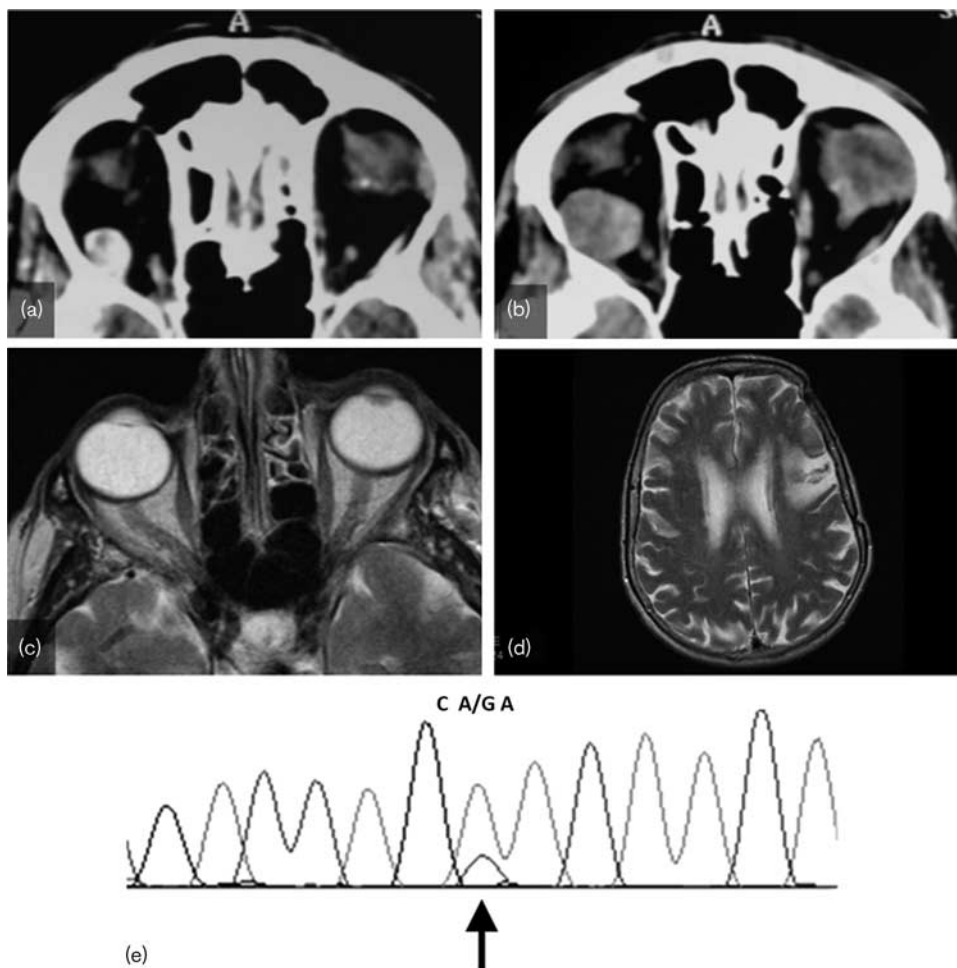
Anna M. Rose<sup>a,b</sup>, Utsav K. Radia<sup>b</sup>, Rong Luo<sup>b</sup>, Helen Kalirai<sup>d</sup>, Channa N. Jayasena<sup>b</sup>, Philip Luthert<sup>a</sup>, Sarah E. Coupland<sup>d</sup> and Geoffrey E. Rose<sup>a,c</sup>, <sup>a</sup>UCL Institute of Ophthalmology, University College, <sup>b</sup>Department of Medicine, Imperial College, <sup>c</sup>Orbital Service, Moorfields Eye Hospital, London and <sup>d</sup>Department of Molecular and Clinical Cancer Medicine, Institute of Translational Medicine, University of Liverpool, Liverpool, UK

Correspondence to Geoffrey E. Rose, DSc, FRCOphth, Orbital Service, Moorfields Eye Hospital, NHS Trust, City Road, London EC1V 2PD, UK  
Tel: +44 207 566 2034; fax: +44 207 566 2073;  
e-mail: geoff.rose@moorfields.nhs.uk

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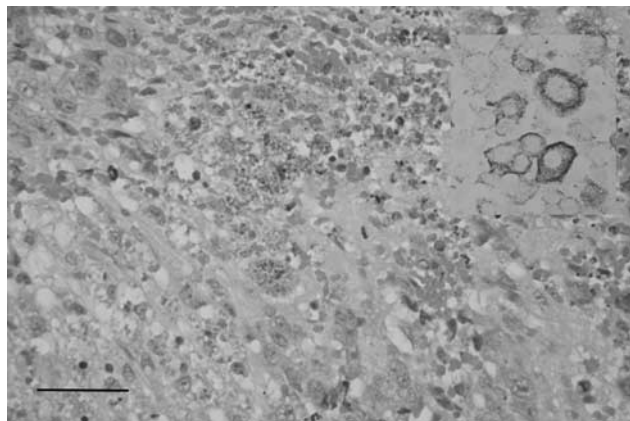
We report a possibly unique patient who developed four different primary malignancies, in the absence of any detectable germline genetic abnormality or a family history of malignancy. The patient has also survived for more than 15 years after local treatments (without immunotherapy) of cutaneous melanoma metastatic to her orbit, brain, skeleton and peritoneum. A 68-year-old White British woman was referred to the Orbital Service at Moorfields Eye Hospital with a 4-month history of right proptosis and true binocular diplopia, this being 41 months after having a 0.8-mm superficial spreading malignant melanoma of her left ankle treated with wide local resection. She underwent resection of a left frontal

Fig. 1



Imaging of orbital and intracranial disease in a patient with disseminated cutaneous malignant melanoma. (a, b) Orbital computed tomography at presentation showed a well-defined soft-tissue mass supero-temporally in the right retrobulbar fat. (c) MRI showed no recurrence of orbital disease 14 years after excision of the orbital mass and radiotherapy. (d) MRI showing gliosis at the site of previous surgical excision and radiotherapy for left frontal metastases, but without disease recurrence at 15 years after treatment of the intracranial disease. (e) Sequencing of DNA extracted from the patient's metastatic melanoma excised from her orbit, this showing a heterozygous point mutation (c.A182G; p.Q61R) (arrowed) in exon 3 of *NRAS*.

Fig. 2



Light micrograph of resected orbital tumour showing a population of pleomorphic cells with large nuclei and prominent nucleoli (scale bar = 40  $\mu$ m). Pigmentation is present, consistent with metastatic cutaneous melanoma. The inset panel shows immunoreactivity for HMB45.

lobe metastasis a year before orbital presentation. Computed tomographic scan showed a well-defined Supero-temporal soft-tissue mass in the right retrobulbar fat (Fig. 1a and b). The patient underwent anterior orbitotomy through an upper eyelid skin-crease incision, with macroscopic excision of the mass, and histological examination showed infiltrative melanoma compatible with metastasis from her previous skin malignancy (Fig. 2). She underwent external beam radiotherapy (30 Gy in five fractions over 2 weeks) to the right retrobulbar tissues.

Three months after the orbitotomy (44 months after the primary skin tumour), the patient was found to have a right femoral bony metastasis, which responded well to local radiotherapy and insertion of an intramedullary femoral nail. At 57 months after the primary skin lesion, the patient underwent resection of multiple retroperitoneal deposits of metastatic melanoma. There has been no further recurrence of metastatic cutaneous melanoma at 17 years following removal of the primary tumour (14 years after orbital presentation) (Fig. 1c and d).

The patient also had a melanoma of soft parts resected from her left thigh musculature at the age of 35 years. At age 48, she underwent left lumpectomy, radiotherapy and axillary nodal clearance for breast adenocarcinoma. The patient more recently has developed – at age 80 – squamous cell carcinoma of her scalp, this being treated with wide local excision; the tumour was remote from any area of previous periocular radiotherapy.

There is no family history of malignancy, even on interrogation of an extended family pedigree.

This study received ethics approval from Moorfields Eye Hospital Biobank ethics board (15/SW/0104). Written, informed consent was obtained from the family for participation in research and from the patient to publish her clinical history, imaging and genetic results.

DNA was extracted from the orbital tumour by standard methods and analysed for point mutations in common driver genes for cutaneous melanoma (*BRAF*, *NRAS*, *KRAS*) and ocular melanoma (*GNAQ*, *GNA11*); primer sequences and PCR conditions are available upon request. Sequencing of *NRAS* exon 3 showed a heterozygous point mutation (c.A182G; p.Q61R) (Fig. 1e). Sequencing of orbital tumour DNA was also performed for genes related to melanoma prognosis (*SF3B1* and *EIF1AX*), with no somatic mutations being found. MLPA analysis for copy number variation indicated disomy of chromosome 3, with gain of chromosome 6p.

Genomic DNA extracted from peripheral blood under standard conditions was analysed by next-generation sequencing [Hereditary Cancer Syndromes, Comprehensive Diagnostics (ID 93.00); MGZ, Munich, Germany] – this being a multigene diagnostic panel testing for mutations in 94 genes that have been associated with familial-cancer or multiple-cancer syndromes. No germline mutations were shown for this patient.

Our patient is enigmatic on two counts: first, she has survived a perhaps unparalleled period of more than 15 years with cutaneous melanoma metastatic to the orbit, bone, peritoneum and brain. Second, she has had four different primary malignancies, these being cutaneous melanoma, melanoma of soft parts, breast adenocarcinoma and cutaneous squamous cell carcinoma.

Metastatic malignant melanoma has a poor prognosis, with the 5-year survival (with or without residual disease) for stage IV cutaneous melanoma being 15–20%, and about 10% survival by 10 years [1]. Tumour metastases to the brain are associated with significant neurological deficit and a very poor survival – less than 8% having a 2-year survival [2] and, without treatment, cerebral metastatic melanoma has a dismal prognosis, with a median survival of 3 months [3]. The use of BRAF inhibitors possibly improves the outcome for metastatic melanoma treated with local radiotherapy [4–9], although these retrospective clinical studies are susceptible to selection bias [10].

Remarkably, our patient remains well at 15 years after local resection and radiotherapy (without immunotherapy) for cutaneous melanoma metastatic deep in her left frontal lobe, as well as metastatic deposits in the orbit, femur and retroperitoneum. There are sporadic case reports of patients with long survival following surgical excision of intracerebral metastases, but these are very rare. For example, a case reported in 1950 reports survival

of at least 3 years 9 months following the removal of melanoma deposit in the left frontal lobe [11]. Two further cases of prolonged survival were reported in 1968, with one patient living for 14 years and a second patient surviving 10 years, both following surgical excision of solitary intracranial metastases [12]. More recently, a case reported disease-free survival of 16 years following surgical resection, stereotactic radiation and chemotherapy for multiple intracranial melanoma lesions [13]. It is clear, then, that on rare occasions, surgical metastasectomy – with or without adjuvant therapy – can be associated with surprisingly good outcomes. In this case, the patient underwent metastasectomy at three sites (retroperitoneal, intracerebral and orbital). A large analysis of over 4000 patients with metastatic cutaneous melanoma suggested that metastasectomy is beneficial; it was shown that – compared with patients who did not undergo the procedure – patients who underwent metastasis resection had an improved median survival (12 vs. 5 months) as well as higher percentage of 5-year overall survival (16 vs. 7%) [14]. It is clear, though, that the case reported here is an outlier to these survival rates and thus metastasectomy cannot be the sole factor that has played a role in her long survival.

It is interesting to speculate whether the identified tumour mutation (*NRAS* p.Q61R) played a role in the long survival in our patient. *NRAS* mutations occur in 13–25% of cutaneous melanoma [15,16], the p.Q61R change accounting for ~35% of *NRAS*-mutated tumours [17]. Advanced cutaneous melanoma containing *NRAS* mutations have a worse prognosis, with shorter median survival and more aggressive disease [18,19]. This suggests that our patient's long survival is not attributable to her tumour driver mutation in *NRAS*. Furthermore, our patient did not have a mutation in *SF3B1* or *EIF1AX*, two mutations associated with a better prognosis in uveal melanoma – although only rarely reported in cutaneous melanoma [20,21]. It is, therefore, plausible that our patient's tumour has a currently unidentified protective mutation and next-generation sequencing of the tumour DNA might be valuable here.

MLPA analysis showed normal disomy 3, but gain of chromosome 6p in our patient's orbital tumour. Aberrations of chromosome 6 are the most common cytogenetic change in melanomas, with 6p gain in up to 85% of uveal melanomas, and more than 90% of sinonasal and cutaneous melanomas [22]. Gain of chromosome 6p (with chromosome 3 disomy) occurs in approximately one-third of uveal melanomas and is associated with better survival [23,24]. However, gain of chromosome 6p would normally confer a poorer prognosis in cutaneous melanoma and several other tumours such as colorectal and bladder carcinoma, and sarcoma [22,25]. The median survival for patients with melanoma metastatic to the orbit is 24 months after orbital diagnosis, but some patients can have a very long survival (of up to 33 years)

[26]. However, tumours of cutaneous origin were reported to have the worst survival of all melanoma metastatic to the orbit and thus, again, our patient's extremely long survival appears to be unusual [26].

The second enigmatic feature of our patient is her multiple primary malignancies, including the particularly rare malignant melanoma of soft parts. With her also developing nonfamilial breast cancer before the age of 50 years, cutaneous melanoma and squamous cell carcinoma, there was a high clinical suspicion that she would carry a germline mutation predisposing to malignancy; notably, however, there was no history suggesting a familial-cancer predisposition syndrome.

The patient's germline DNA did not show any mutations in 94 known cancer genes, which raises two possible scenarios: first, our patient might just have been 'unlucky' and – without any predisposing germline mutation – has developed random somatic mutations giving rise to four separate malignancies. The second possibility is that she harbours an unidentified germline mutation in a very rare oncogene that is not included in the comprehensive diagnostic panel; whole-exome sequencing of her germline DNA might reveal a novel oncogenic or tumour-suppressor gene.

In summary, this patient is a unique case of cutaneous melanoma with multiple metastases, who has survived for a remarkable 14 years after orbital and intracranial disease – despite being treated before the introduction of immunotherapy. Furthermore, she has had four separate primary malignancies – without apparent familial or germline predisposition to cancer.

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### Conflicts of interest

There are no conflicts of interest.

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## Clinical, dermoscopic, and confocal features of nevi and melanomas in a multiple primary melanoma patient with the *MITF* p.E318K homozygous mutation

Sara Bassoli<sup>a,\*</sup>, Cristina Pellegrini<sup>d,\*</sup>, Caterina Longo<sup>a,c</sup>, Lucia Di Nardo<sup>d</sup>, Francesca Farnetani<sup>a</sup>, Anna M. Cesinano<sup>b</sup>, Giovanni Pellacani<sup>a</sup> and Maria Concetta Fargnoli<sup>d</sup>, <sup>a</sup>Dermatology and Venereology Department, <sup>b</sup>Pathology Department, University of Modena and Reggio Emilia, Modena, <sup>c</sup>IRCCS Arcispedale Santa Maria Nuova, Reggio Emilia and <sup>d</sup>Department of Dermatology, University of L'Aquila, L'Aquila, Italy

Correspondence to Maria Concetta Fargnoli, MD, Department of Dermatology, University of L'Aquila, Via Vetoio, Coppito, 67100 L'Aquila, Italy  
Tel: +39 086 236 8519; fax: +39 086 243 3433;  
e-mail: mariaconcetta.fargnoli@univaq.it

\*Sara Bassoli and Cristina Pellegrini contributed equally to the writing of this article.

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The development of multiple primary melanomas (MPM) is suggestive of hereditary melanoma predisposition and has been associated with mutations in the high-penetrance susceptibility genes cyclin-dependent kinase inhibitor 2A (*CDKN2A*), cyclin-dependent kinase 4 (*CDK4*), and protection of telomeres 1 (*POT1*) and with variants in the intermediate-risk genes melanocortin-1 receptor (*MC1R*) and Microphthalmia-associated transcription factor (*MITF*) [1].

*MITF* is a transcription factor acting as a master gene of melanocyte homeostasis. The rare germline *MITF* p.E318K variant has been associated with melanoma and/or renal cell carcinoma [2–7]. p.E318K interferes with *MITF* SUMOylation, resulting in enhanced *MITF* transcriptional activity, thus supporting an oncogenic role for *MITF* [2], and reduces the program of senescence, potentially favoring melanoma progression *in vivo* [8].

The p.E318K variant has always been reported in heterozygosity in melanoma [2–7]. We report the first case of a homozygous *MITF* p.E318K mutation occurring in melanoma in a MPM patient, describing the dermoscopic and confocal features of his melanomas and melanocytic nevi.

A man was referred to our clinic because of a personal history of three melanomas, all located on the back, and of a high number of melanocytic nevi ( $n = 283$ ) (Fig. 1a). He had skin type II, light brown hair, and green eyes. Two melanomas were synchronous at age 48: melanoma 1 was associated with a congenital nevus and measured 1.0 mm in Breslow thickness; melanoma 2 was an in-situ melanoma, excised during the wide margin excision of melanoma 1; and melanoma 3 was an in-situ melanoma, diagnosed at age 50. His family history was negative for melanoma or other visceral malignancies.

Dermoscopic images of melanomas 1 and 3 and of several melanocytic nevi were available. Melanoma 1 was characterized by a peripheral atypical network, areas of a negative pigment network, and different degrees of pinkish and gray pigmentation (Fig. 1b). A regular

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