CASE REPORT

Recurrent vulvar melanoma in a patient with neurofibromatosis and gastrointestinal stromal tumour

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SUMMARY

We report a case of a 51-year-old woman with neurofibromatosis who presented in 2012 with postmenopausal bleeding. Excision biopsy of a pigmented lesion of the labia minora was consistent with an ulcerated vulvar BRAF wild type malignant melanoma (MM). Initial excision was followed by radical vulvectomy and adjuvant interferon. Local recurrence in January 2017 was further resected. Positron emission tomography (PET)-CT in May 2017 identified an FDG avid omental deposit; consistent histologically with MM when resected. Postoperative PET-CT in August 2017 demonstrated local recurrence. In the setting of resected stage IV disease and a third local recurrence, the decision was made to instigate immunotherapy. Vulvar melanoma is rare accounting for 0.2% of all melanoma. Presentation is typically a decade later than cutaneous melanoma with a tendency to late metastases and poorer prognosis. Given their rarity the treatment paradigm is less clearly defined and largely extrapolated from that of cutaneous melanomas.

BACKGROUND

Mucosal melanomas are rare compared with their cutaneous counterparts, accounting for 1.3% of all melanoma, according to US data.¹ They exhibit a different biology and pattern of recurrence to cutaneous melanoma. Because of their rarity, little is known about the natural progression of mucosal melanoma. Treatment guidelines are therefore not as clearly defined and generally follow those for cutaneous melanoma for which there is a much larger body of evidence. This case illustrates an unusual pattern of recurrence of vulvar melanoma with an isolated omental metastasis followed by local recurrence in the setting of neurofibromatosis (NF) and coexistent gastrointestinal stromal tumour (GIST). NF has an increased risk of malignancy and is commonly associated with GISTs. To this author's knowledge, this is the first case report of vulvar melanoma and GIST in a patient with NF. It highlights the aggressive nature of vulvar melanoma and points to a deficit in evidence-based recommendations regarding the optimum management and follow-up of such cases. It also illustrates the increased risk of malignancy with NF, highlighting the need for close surveillance in this patient population and suggests a possible unifying driver mutation.

CASE PRESENTATION

A 51-year-old woman presented to a local hospital with a 1-month history of postmenopausal bleeding on a background of NF, bilateral hearing loss, severe scoliosis and previous hysterectomy. Examination demonstrated a 2.2 mm pigmented mass on the left labia minora in addition to multiple neurofibromata. Histology from a simple excisional biopsy was consistent with a vulvar nodular malignant melanoma with Clark's level of 4 and Breslow's depth of 4.8 mm (figures 1–3). Ulceration was present and there was no lymphovascular or perineural invasion. The mitotic count was high at 4/mm². Immunohistochemical stains were positive for S100, Melan-A and HMB-45 (figure 1). A radical left vulvectomy was performed with 2 cm negative margins in all directions and no residual disease on histology. She did not have sentinel lymph node sampling at the time of surgery but ultrasound groin was negative for lymphadenopathy and positron emission tomography (PET)/CT scan was negative for metastatic disease. Final staging was T4bN0M0, International Federation of Gynaecology and Obstetrics (FIGO) stage IIc. She was treated adjuvantly with interferon (IFN) alpha-2A for a total duration of 10 months from September 2012 to July 2013.

Surveillance PET/CT in February 2013 identified an incidental nodal mass at D2/D3. Endoscopic biopsies were non-diagnostic and consequently she proceeded to open laparotomy and biopsy in May 2013. Histology was consistent with GIST. Due to proximity to the ampulla a Whipple's procedure was required for complete resection. Histology was again consistent with a GIST, 30 mm in maximum dimension, with a mitotic count of less than 2/50 high power fields, no mucosal invasion or lymph node involvement. Testing for c-KIT mutation was negative. IFN alpha which had been held preoperatively was poorly tolerated at its reintroduction and was consequently discontinued.

In January 2017, 5 years from her original diagnosis, a 1.5/2 cm polypoid lesion was identified at the anterior lip of the external urethral meatus. Differential on examination included recurrence of melanoma, a new primary malignancy or a neurofibroma which had become necrotic or ischaemic. Biopsy of the external urethral meatus confirmed locally recurrent melanoma and she proceeded to an anterior radical vulvectomy including the lower distal third of the urethra in April 2017. Histology

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Figure 1 First vulval excision showing diffuse strong HMB-45 positivity in the nodules of tumour.

was positive for metastatic melanoma, staining positive for S100, Melan-A and HMB-45, negative for CD117 (figures 4–5). There was no mutation seen in BRAF or NRAS. PET-CT perioperatively was negative for metastatic disease.

Follow-up PET/CT postoperatively in May 2017 showed a new fludeoxyglucose (FDG) avid peritoneal nodule in the left hypochondrium (figures 6–7). Imaging was reviewed at multi-disciplinary meeting and the consensus was that of metastatic disease likely secondary to previous GIST rather than malignant melanoma. Laparoscopic surgery was performed to remove the peritoneal lesion; surprisingly histology was consistent with metastatic melanoma staining positive for S100, HMB-45 positive and again negative for BRAF and NRAS mutations.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of pigmented vulvar lesions includes malignancy, infections and benign conditions. Examples of malignant conditions include basal cell carcinoma, squamous cell carcinoma, vulvar intraepithelial neoplasia, Kaposi's sarcoma, dysplastic nevi and melanoma. Benign lesions may be caused by seborrhoeic keratosis, dermatofibromata, neurofibromata, acanthosis nigricans, pemphigoid, pemphigus, skin tags and a vast array of other conditions. Infections such as genital warts, molluscum contagiosum, candidiasis, herpes simplex and zoster, bacterial vaginosis, syphilis and scabies may also manifest as pigmented vulvar lesions.

TREATMENT

In line with international guidelines, this patient underwent local resection of the metastatic peritoneal melanoma deposit with curative intent.

Figure 2 First vulval excision showing nodules of metastatic melanoma. H&E.

Figure 3 First vulval excision showing metastatic melanoma. H&E.

OUTCOME AND FOLLOW-UP

The patient recovered well postsurgery. Subsequently, on surveillance examination, imaging and biopsy in October 2017, she was found to have further local recurrence. At this juncture in the setting of previously resected stage IV melanoma and a third confirmed local recurrence which was not resected, systemic therapy in the form of pembrolizumab was commenced. Three cycles of pembrolizumab were administered without significant toxicity and first restaging imaging in January 2018 showed no evidence of metastatic disease with resolution of previous FDG avidity at site of local recurrence.

DISCUSSION

NF type 1 is an autosomal dominant condition caused by germline mutation in the NF-1 tumour suppressor gene with a high rate (50%) of new mutations.² Mutations generally result in decreased levels of neurofibromin protein, which leads to increased cascade signalling of the RAS/MAPK pathway. This results in prolonged activation of the RAS/MAPK signalling pathway and ultimately a loss of growth control and increased cellular proliferation.³ The PI3K/AKT/mTOR pathway is also stimulated which protects cells from apoptosis. Hence, the NF population has a higher incidence of malignancy. A Swedish cancer registry study reported a fourfold increase in malignant conditions in the NF-1 population.⁴ The most commonly associated malignancies are peripheral nerve sheath tumours, gliomas, breast cancer, GIST, malignant fibrous histiocytomas, pheochromocytomas and rhabdomyosarcomas.⁵ Though melanoma can be associated with mutation in the NF-1 gene, the risk of melanoma in patients with NF-1 is only minimally increased compared with the general population.²

Figure 4 Re-excision of vulva showing melanoma in situ. H&E stain.

Figure 5 Re-excision of vulva showing melanoma in situ. HMB-45 immunostain.

Approximately 7% of patients with NF develop GIST in their lifetime.⁴ NF-1-associated GISTs demonstrate a higher prevalence in the small intestine as in our case.⁶ NF-1-associated GISTs are phenotypically and genotypically distinct from sporadic GISTs. They tend to have a low mitotic rate, stain positive for CD117 and are not associated with KIT and PDGRA mutations.^{6,7} In addition, 17% of patients with GIST develop additional cancers.⁸ There have been two previous case reports of synchronous melanoma and GIST, one of which was a mucosal melanoma.^{9,10} To the authors knowledge, there have been no previous case reports of vulvar melanoma and GIST in a patient with NF.

Vulvar melanoma is rare and accounts for 7%–10% of vulvar malignancies. In the USA, it is estimated to have an annual incidence rate of 1 per 1 000 000 women.¹¹ Mucosal melanomas present one decade later on average than cutaneous melanoma and usually at a more advanced stage; consequently, they are associated with a higher mortality rate than cutaneous melanoma. Vulvar melanoma can be associated with late metastases and 5-year survival rates are in the order of 25%–50%.¹¹ The mean time of survival from first metastasis is 9.1 months.¹² There are no established protocols for staging and treatment of mucosal melanomas due to their scarcity.¹¹ Tumour thickness is the strongest prognostic factor, and therefore, used most frequently for staging.¹³ Lymph node status and ulceration are also important prognostic factors. In most cases, standard staging and resection principles for cutaneous melanoma are applied to the mucosal melanoma patient population.

Figure 6 Peritoneal nodule on CT Scan.

Figure 7 Peritoneal nodule on PET/CT scan. PET, positron emission tomography.

Mucosal melanomas also have distinct molecular features which distinguish them from cutaneous melanomas. BRAF mutation, common in cutaneous melanoma, is rare in mucosal melanoma and gain of function mutations in c-KIT may be present up to 39% according to Curtin *et al.*¹⁴ There have been several reports of c-KIT directed therapies in the treatment of mucosal melanoma which show some promise^{15–17}; although the specific KIT mutation present may be critical for appropriate patient selection. c-KIT mutations are also commonly found in GISTs with 80%–90% found to stain immunohistochemically for c-KIT (CD117). Of these, over half contain activating mutations in the c-KIT receptor tyrosine kinase.¹⁸ The GIST tumour in our case was found to be diffusely positive for CD117 but there was no mutation detected in KIT as would be expected with an NF-associated tumour. Somatic NF-1 mutations may be critical drivers in multiple cancers and are associated with 12%–30% of sporadic melanoma.¹² Recent studies have begun to better characterise the mutational profile of mucosal melanoma using next generation sequencing with the intention of identifying therapeutically targetable mutations. Cosgarea *et al* analysed samples from 75 patients with mucosal melanoma at a number of anatomical sites; 25 of these originated in the genital area.¹⁹ NF-1 was the most common driver mutation identified in 18.3% of those tested; in two in three of these patients, a clearly inactivating mutation was present resulting in a nonsense or frameshift mutation which would be important for constitutive MAPK activation. RAS alterations were identified in 16.9% of samples but, BRAF and KIT mutations were identified in <10% of samples. Similarly, in a population of anorectal melanomas, Yang *et al* found that 3/15 samples harboured NF-1 mutations.²⁰ In most cases, this was a single driver mutation and NF-1 mutation was mutually exclusive with KIT, RAS, BRAF mutations. As in Cosgarea's study, the majority were loss of function mutations and were associated with RAS activation as well as mitogen activated protein kinase kinase (MEK) dependence in the melanoma cell lines. This raises the possibility of MEK inhibition as a potential treatment strategy. NF-1 mutations are also important in the acquisition of drug resistance, for example, BRAF and EGFR inhibitors.¹² NF-1 mutations have been found in melanomas that lack both BRAF and NRAS mutations, with 25%–30% of such melanomas found to harbour deleterious NF-1 gene mutations. Melanomas with NF-1 mutations typically occur on chronically sun-exposed skin however, which is not the case with mucosal melanoma.² In fact, there are some data to suggest that sunshine may be a protective factor in the development of vulvar melanoma.²¹

Lymphatic drainage of the vulva is usually first to the superficial inguinal nodes followed by the cribriform fascia to the deep inguinal or femoral nodes. There are three distinct patterns of metastatic dissemination of melanoma—to regional lymph nodes, direct distant metastatic spread and by satellite or in-transit metastases. In vulvar melanomas, the most common sites of metastases are the inguinal lymphatic nodes. Other reported sites of metastases are the lungs, vagina, liver and brain.¹ The pattern of spread to an isolated omental site in the absence of disease elsewhere is unusual.

Primary treatment of vulvar melanoma is surgical excision with adequate tumour-free margins. Historically, the surgery consisted of a radical vulvectomy with bilateral inguinal lymphadenectomy. Most authors conclude that radical surgery however does not improve survival.²² Prophylactic lymph node dissection is no longer recommended based on several retrospective studies that failed to show any benefit in clinical outcome.⁴ Expert consensus now recommends wide local excision with macroscopic tumour-free margins of 2 cm. Sentinel lymph node sampling is routinely done in vulvar melanomas that are greater than 1 mm thick or ulcerated.²³ In de Hullu *et al*'s study, sentinel lymph node procedures increased the risk of locoregional recurrence, especially in thick tumours, therefore, the authors recommended sentinel lymph node biopsy only in tumours of depth 1–4 mm.¹³ National Comprehensive Cancer Network (NCCN) guidelines recommend discussion of sentinel lymph node biopsy in stage 2 disease, however, there is a lack of proven survival advantage. Therefore, the authors recommend that during discussion, consideration be given to what will be done differently if the sentinel node status is known. In our case, as adjuvant therapy was planned regardless of sentinel node status given the Breslow depth of 4.8 mm, and both groin ultrasound and PET imaging were negative for nodal disease, it was decided to proceed without sentinel lymph node biopsy. The role of completion lymph node dissection (CLND) in the event of a positive sentinel node is also controversial. It has been found to improve recurrence-free survival but has shown no benefit in overall survival (OS) or melanoma-specific survival. There are two trials currently ongoing to investigate the therapeutic value of CLND.

Our patient received high-dose IFN 2A in the adjuvant setting following initial resection. For patients with completely resected high-risk disease, recommendations thus far for mucosal melanoma are as for cutaneous melanoma. High-risk IFN 2A has been shown in a number of trials to increase relapse-free survival in cutaneous melanoma and though individual trials have had varying results, meta-analysis showed improved OS.²⁴ Pegylated IFN improved recurrence-free survival compared with observation but with no increase in OS.²⁵ Biochemotherapy as adjuvant therapy for fully resected stage III cutaneous melanoma was investigated in the Southwest Oncology Group (SWOG) S0008 phase 3 randomised trial which compared cisplatin, vinblastine, dacarbazine, interleukin-2 (IL-2) and IFN with high-dose IFN alfa-2b monotherapy.²⁶ At 7.2 years, recurrence-free survival was 4.0 vs 1.9 months favouring the biochemotherapy arm, with no significant difference in OS, however, mucosal melanomas were excluded from this trial. There has been one randomised phase II trial specifically looking at adjuvant treatment of resected mucosal melanoma.²⁷ Lian *et al* randomised 189 patients with resected stage II/III mucosal melanoma to observation, high-dose IFN or high-dose temozolomide/cisplatin. Estimated median OS was 21.2, 40.4 and 48.7, respectively, indicating that in the mucosal melanoma

subgroup, temozolomide/cisplatin might be a preferential regimen to high-dose IFN.

Immunotherapy has revolutionised the management of cutaneous melanoma, with durable effects both in the adjuvant setting for high-risk disease^{28–30} and in the metastatic setting.^{31–33} However, there are limited data on the use of immunotherapy in the setting of mucosal melanoma as this cohort has often been excluded from larger phase III trials. A 2013 study in Memorial Sloan Kettering reviewed 33 cases of advanced mucosal melanoma treated with the CTLA-4 inhibitor ipilimumab and found overall response rates to be low, with a median OS from first dose of ipilimumab of 6.4 months.³⁴ An evaluation of 71 patients with metastatic mucosal melanoma treated with ipilimumab via the expanded access programme in Italy found a similar overall response rate of 6.4 months.³⁵ Anti-PD-1 agents look more promising. A cross-centre analysis of using nivolumab alone and in combination with ipilimumab demonstrated greater efficacy for the combination than with either drug alone, but the progression-free survival was still markedly inferior in the mucosal melanoma group versus the cutaneous melanoma group (5.9 months vs 11.7 months).³⁶ This may be due to reduced mutational burden in the mucosal group. A similar multi-institutional study assessing the efficacy of PD-1 inhibition in acral and mucosal melanomas, most of whom had been pretreated, found an overall response rate of 23% in the mucosal melanoma group with median OS of 12.4 months supporting further exploration of the use of anti-PD-1 agents in clinical practice.³⁷ A recent case series from Memorial Sloan Kettering indicated a positive response to combination radiation therapy and ipilimumab to mucosal melanoma of the lower genital tract, however, this included just four patients.³⁸

In terms of follow-up, the NCCN guidelines for melanoma recommend routine imaging be considered every 3–12 months for stage IIb to stage IV disease. Routine imaging for asymptomatic recurrence or metastatic disease is not recommended after 3–5 years. Given that our patient was 5 years from original diagnosis at the time of recurrence, and in light of the fact that mucosal melanomas tend to recur later, it may be justified to extend the period of routine imaging in this subgroup of patients.

Patient's perspective

I have always had neurofibromatosis but have no family history of it.

I noticed abnormal bleeding and went to my GP who referred me on to my local hospital. I was then referred to the University Hospital and they have picked everything up since. I had never heard of vulvar melanoma before my diagnosis. I never really had any symptoms after the bleeding. I go back to the dermatology department and get regular skin examinations and everything has been picked up that way or through scans with the oncology department.

Overall I have tolerated the treatments well. I bounced back after every surgery with no real difficulty. I feel very lucky. The immunotherapy has been fine so far. I had a rash on my nose the first week afterwards, but nothing else. I'm hoping that I can avoid an operation. I have not been back to work yet. Because I haven't had many symptoms, I am a little worried about going back, but I'm hoping to start working again soon.

Written by patient and sister.

Learning points

- Vulvar melanomas are clinically, biologically and molecularly distinct from cutaneous melanomas, with later presentation, more advanced stage and increased mortality.
- Given the rapidity of recurrence in this case, consideration should be given to 3 monthly positron emission tomography-CT scanning once metastases have been diagnosed, even if fully resected.
- In particular, in the evolving era of immunotherapy trials, preplanned subgroup analyses should be performed to assess responsiveness of mucosal melanomas where possible as they have so far responded inferiorly when compared with their cutaneous counterparts.
- Ongoing genomic studies will help to better clarify distinct molecular features of mucosal melanomas and identify therapeutically targetable driver mutations.
- Neurofibromatosis is associated with an increased risk of malignancy, therefore, frequent clinical assessment and examination is of paramount importance.

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