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Case Report

Challenges in staging and surveillance of patients with neurofibromatosis and cutaneous malignant melanoma

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ABSTRACT

Malignant melanoma is a skin neoplasm with a rising trend of incidence. Positron Emission Tomography in combination with Computed Tomography (PET-CT) imaging is an essential diagnostic tool for both staging and surveillance of melanoma patients; especially in metastatic disease, where prognosis is poor. We report a case of a patient with known Neurofibromatosis type 1 (NF-1) who presented to the Skin Cancer Multidisciplinary meeting with 11 mm Breslow thickness malignant melanoma of the left forearm. His extensive dermal neurofibromatoses proved a diagnostic challenge to the team. There have been published studies linking NF-1 with malignant melanoma. However the incidence and significance of this has yet to be established. We also discuss the use of PET-CT imaging and skin surveillance in the monitoring and staging of this patient.

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Case report

A 76-year old man with known Neurofibromatosis Type 1 (NF-1) presented to our plastic surgery outpatient department with an ulcerated lesion on his left forearm via 2-week wait referral system. The lesion was suspected to be either a squamous cell carcinoma or malignant melanoma due to its pedunculated, nodular appearance with a central ulceration. However the presence of extensive dermal neurofibromas of varying sizes identified throughout patient's body, particularly in areas on the left arm and axilla, complicated the diagnosis and plan of management.

The patient had undergone an excision biopsy that showed a diagnosis of a 33×26 mm extensively ulcerated nodular malignant melanoma with a Breslow thickness of 11 mm. Further histologic analysis showed that the tumor cells have a frequent mitoses amounting to $61/mm^2$ but with no lymphovascular invasion and negative BRAF V600 mutation. The patient was discussed at the skin cancer multidisciplinary meeting and as recommended a further 2 cm wide local excision of the lesion was performed, which returned with clear histological margins. Sentinel lymph node biopsy was deemed inappropriate in this case, in view of the patient's multiple neurofibromas in the left axilla.

His first staging PET-CT scan [Figure 1] proved a diagnostic challenge to the musculoskeletal radiologists as it demonstrated extensive hypermetabolic subcutaneous deposits throughout body and spinal canal that was difficult to differentiate between neurofibromatosis and disseminated malignancy. The patient then underwent an ultrasound of left arm and neck, which demonstrated well defined, mixed hyperechoic lesions typical of neurofibromatosis with no evidence of metastatic disease. Recognizing that the use of interval PET-CT scans was unhelpful, the skin MDT recommended that clinical follow-up as per NICE guidelines with regular self-examination was more practical in monitoring for disease progression.

The patient is currently being followed-up at 3 monthly intervals at the plastic surgery outpatient clinic using a combination of clinical examination, ultrasound of suspicious lesions and excision of changing or symptomatic lumps that may include pre-existing dermal neurofibromatosis. To date, no recurrence or metastatic disease is evident.

Discussion

Malignant melanoma is a malignancy of the melanocytes and the third most common skin cancer in the UK. It accounts for more cancer deaths than all other skin cancers combined. The incidence of melanoma continues to rise worldwide. Risk factors include pale skin and intense sun exposure. An increasing number of younger people are being diagnosed annually with melanoma in the UK, with studies showing melanoma being the second most prevalent cancer in adults aged between 25 and 49 years.[1]

NF1 is an autosomal dominant neurocristopathological disorder that possesses an increased risk of developing neural crest derived neoplasms. There is a belief that NF1 and cutaneous melanoma may be closely associated, as melanocytes are embryological derivatives of the neural crest. NF1 patients have also been found to have an increased number of melanocytes in their *cafe-au-lait* spots and normal skin, suggesting a proliferative process of melanocytes. It is hypothesized that these melanocytes are predisposed to malignant transformation due to mutations of the NF1 gene.[2,3] Since there are established links between the NF1 gene mutation and other neural crest-derived tumors such as malignant peripheral nerve sheath tumors, phaeochromocytoma and giant congenital melanocytic nevi,[4] its association with malignant melanoma is deemed possible.

Most of the literature describing the association between NF1 and cutaneous melanoma consist of case studies showing inconsistent results.[5–11] Approximately 0.1–5.4% of these patients with NF1 have been reported to have cutaneous melanoma.[3] Hope and Mulvihill reviewed 395 and 223 patients with NF1, respectively, in Danish and Michigan cohort and Crowe et al. studies;[12] none of which had cutaneous melanoma. In a study of 900 patients with NF1, only one patient was diagnosed with melanoma,[8] where as another found only 4 patients in a review of 791 patients.[5] Perhaps a more significant study from Brasfield and Das Gupta[13] demonstrated 6 cases of cutaneous melanoma in a group of 110 patients with NF1. Nevertheless, none of these studies were able to demonstrate a statistically significant correlation between cutaneous melanoma and NF1.

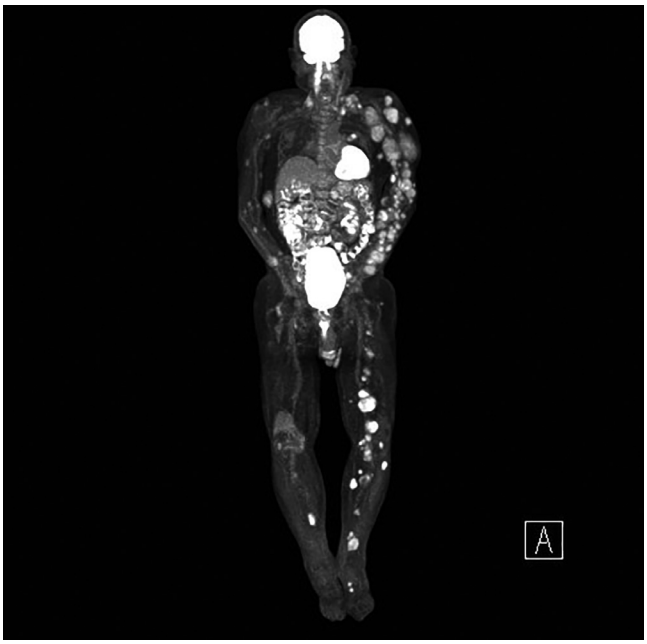

Figure 1. Extensive hypermetabolic deposits noted particularly on the left side at first PET-CT staging scan.

A number of cases of cutaneous melanoma developed in *café'-au-lait* spots or in skin overlying a neurofibroma have been reported.[9,11] In our case study, our patient was diagnosed with an 11 mm Breslow thickness melanoma. One possible explanation for this may be due to a delay in early detection of the disease amongst the various skin lesions and hyperpigmentations seen in NF1.

Patients with melanomas greater than 4 mm in Breslow thickness have 50% or more risk of locoregional and distant metastasis.[14] Commonly used imaging modalities for staging and surveillance in melanoma patients include ultrasonography, computed tomography (CT), positron emission tomography (PET), and a combination of PET and CT (PET-CT). CT imaging is the gold standard for staging and surveillance of patients with high risk or metastatic melanoma. The British Association of Dermatologists (BAD) guidelines do not recommend routine investigations and imaging for patients staged as I and II on the American Joint Committee on Cancer (AJCC) system due to the high incidence of false positive findings. CT is deemed as the standard modality for excluding distant metastases for both stage III and IV disease, and for planning regional lymph node dissection or chemotherapy in stage III patients. Sentinel lymph node biopsy (SNLB) is useful in detecting subclinical regional nodal disease and may be recommended in stage IB disease and above.

PET-CT is a combined imaging modality that can reliably detect the differences in metabolism and function of malignant lesions that complement anatomical imaging techniques. It has rapidly gained acceptance as the modality of choice for identifying disease recurrence, staging nodal and metastatic spread, and monitoring a patients' response to treatment. PET-CT has been proven to be very useful in detecting deep soft-tissue, lymph node and visceral metastases. A meta-analysis has shown that PET-CT had the highest sensitivity in staging and surveillance of distant metastasis when compared to CT or PET alone.[15] However, a higher number of false positive results led to the loss of precision. Therefore, PET-CT is more suitable for the detection of distant metastases in intermediate to high-risk patients when distant metastases are clinically present. In addition to that, ultrasonography was showed to be the superior imaging of choice for assessing lymph nodes, especially in patients at low risk of lymph node metastasis where SLNB can be avoided.

In our case study, our patient presented with a stage pT4b tumor and disease stage IIC at minimum, which led to the skin MDT's decision for performing an initial PET-CT scan. However the

multiple neurofibromatoses, particularly in the left axilla showed up as areas with increased metabolic activity and uptake on his scan. The high number of false positives made the differentiation between benign disease to metastatic tissue extremely difficult in the staging and disease surveillance of this patient. The risk of morbidity secondary to extensive pre-emptive resection of all lesions detected was carefully considered and it was agreed that close monitoring and skin surveillance, with interval ultrasound scanning and excision of suspicious lesions where indicated, was deemed to be more appropriate.

This case highlights the incidence of primary cutaneous melanoma in a patient with NF1 and also emphasizes the importance of the multidisciplinary approach in managing its complex clinical presentation and the potential challenges in diagnosis, staging and surveillance of the disease. It is suggested although PET-CT is advantageous in following-up patients with melanoma; it may be less useful in patients with NF1. As there is some evidence suggesting ultrasonography as the best diagnostic test in investigating symptomatic, targeted lesions, this may be a more useful alternative in detecting lymph node metastases and disease progression.

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Disclosures/Conflict of interest

None declared.

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