12 Diagnosis and Management of Malignant Tumours in NF1: Evolution from Atypical Neurofibroma to Malignant Peripheral Nerve Sheath Tumour and Treatment Options

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Contents

12.1 History

In 1840 the surgeon Frederick Hale Thomson esquire delivered a lecture to his medical colleagues, in which he described a 36-year-old coachman with longstanding multiple cutaneous tumours [5]. The patient sought help from Thomson for a rapidly increasing swelling of the right thigh that caused severe throbbing. Despite the best available treatment with iodide of mercury, opiates and lard followed by turpentine and sulphuric acid he succumbed to his illness in agony; in retrospect, his case is consistent with an early description of NF1 associated malignant peripheral nerve sheath tumour (MPNST).

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12.2 Introduction

Neurofibromatosis 1 is an inherited tumour suppressor disease and affected individuals have an increased propensity to develop both benign and malignant tumours [1]. Neurofibromas are peripheral nerve sheath tumours that are emblematic of the disease and form as discrete cutaneous or subcutaneous lesions or plexiform growths that may involve multiple nerve fascicles. Benign neurofibromas are the source of significant morbidity as they may cause pain and itching, disfigurement, neurological deficit and haemorrhage [1]. Cutaneous neurofibromas are invariably benign, but subcutaneous and plexiform growths have malignant potential. There is a 15.8% lifetime risk of developing a malignant peripheral nerve sheath tumour (MPNST) and high grade tumours metastasize widely, frequently presaging a poor prognosis [2, 3]. NF1 associated MPNSTs usually arise in pre-existing plexiform neurofibromas, they can occur at any age but are commonest in people in their late 20s and early 30s and tend to develop earlier than in sporadic disease [3, 4].

12.3 Diagnosis of NF1 Associated MPNST

12.3.1 Risk Factors

A number of factors have been identified that potentially are associated with a higher risk of developing MPNST and indicate the need for meticulous surveillance (Table 12.1) [4].

In a self-reported questionnaire sent to 4801 NF1 individuals, there were 878 respondents [6]. Family history was a significant risk factor for developing MPNST in people with NF1 and 19.4% with a diagnosis of MPNST had an affected family member, compared with 7.5% with no family history of MPNST. The tumour was diagnosed at an earlier age than in NF1 patients without a family history.

MPNSTs have been identified in NF1 patients following radiotherapy; in one retrospective national study in England 18 people with NF1 were irradiated for optic pathway glioma and four MPNSTs were diagnosed in the radiation pathway with a mean duration of 21 years following treatment [7].

About 4.7–11% of individuals with NF1 have a severe clinical phenotype associated with large deletions that involve the whole of the *NF1* gene and flanking regions at 17q11.2 [8]. These patients have a high tumour burden and are reported to have an increased lifetime risk (16–26%) of developing MPNST that may occur earlier

Table 12.1 Risk factors for development of malignant peripheral nerve sheath tumours in NF1

Family history of MPNST
Previous treatment with radiotherapy
NF1 microdeletion
Large internal plexiform neurofibroma burden
NF1 neuropathy
Atypical neurofibroma

than in people without *NF1* microdeletions [9, 10]. Furthermore, the co-deletion of the *SUZ12* gene as part of polycomb repressive complex 2 (PRC2) further exacerbates the risk for MPNST in this group of patients [11, 12]. PRC2 has histone methyltransferase activity and is involved in chromatin silencing, thereby repressing transcription.

Previous studies have suggested that individuals with a large number of internal plexiform neurofibromas are at increased risk for developing MPNST. Mautner and colleagues performed whole body MRI on 13 patients with NF1 associated MPNST and on 26 matched controls without MPNST [13]. They reported that only three out of 11 patients under 30 years without MPNST had internal plexiform neurofibromas, whereas all six patients with MPNST of similar age had internal plexiform neurofibromas.

NF1 is associated with a length dependent sensory motor axonal neuropathy that is diagnosed in adults. Affected individuals have thickened peripheral nerves, early development of cutaneous neurofibromas and multiple spinal nerve root neurofibromas [14]. Although the clinical manifestations are mild and the neuropathy is indolent, it has been reported in patients who have developed malignant change in plexiform neurofibromas. The neuropathy may either pre-date or occur after the diagnosis of MPNST.

Atypical neurofibromas are considered to be neurofibromas with potential for malignant transformation, they may co-exist with MPNST in different sites of the body and may occur before or after the development of an MPNST [15]. Atypical neurofibroma is a histological diagnosis based on a combination of high cellularity, nuclear atypia and less than 3/10 mitoses per high powered field (HPF) [16]. Neurofibromas that exhibit nuclear atypia in isolation are defined as benign tumours; conversely, the presence of necrosis and high mitotic activity is indicative of malignancy [3, 4]. A recent working group proposed the term atypical neurofibroma tous neoplasm of uncertain biological potential (ANNUBP) to describe these lesions because of the overlap between the pathology of atypical neurofibromas and low grade MPNSTs; they proposed a retrospective study of atypical neurofibromas and low grade MPNST to help clarify the potential for malignancy [4]. Chromosomal copy number loss of the CDKN2A/B gene locus has been identified in atypical neurofibromas and malignant peripheral nerve sheath tumours, but is absent in benign neurofibroma, supporting the premise that atypical neurofibromas are pre-malignant lesions [17].

A multi-centre retrospective study of 63 NF1 individuals with 76 atypical neurofibromas reported that the median age of diagnosis of the atypical lesions was 27.1 years [15]. The atypical neurofibromas were detected throughout the body and were predominantly intramuscular and were multiple in 15 patients (24%). The majority of tumours caused symptoms and pain was the most frequent complaint and was mostly accompanied by tumour growth. Distinct nodular lesions predominated and most tumours were positive on ^{18}F fluorodeoxyglucose positron emission tomography computerised tomography (FDG PETCT). Four atypical neurofibromas transformed to high grade MPNST and 17 patients had an MPNST in another region of the body. Two incompletely excised lesions recurred, but resection of atypical neurofibromas without wide margins was curative in 57 tumours.

Table 12.2 Clinical Manifestations of MPNST
(N.B. the symptoms may overlap with symptoms from benign neurofibromas)

Persistent and/or nocturnal pain
Rapid growth
Change in texture from soft to hard
Weakness, tingling, numbness or incoordination
Difficulty swallowing or breathing
Bladder or bowel disturbance
Sexual dysfunction
Haemorrhage

12.4 Clinical Manifestations of MPNST

The majority of malignant tumours arise in pre-existing subcutaneous or plexiform neurofibromas, but occasionally develop de novo [1, 4]. Rarely, MPNSTs may be asymptomatic and diagnosed incidentally, but usually present with one or more symptoms or signs, which frequently overlap with symptoms experienced by people with benign neurofibromas (Table 12.2) [3, 4]. It may be difficult to identify which neurofibroma has undergone malignant change when there are multiple symptomatic neurofibromas in the same region of the body, and patients do not automatically regard the development of a new lump as unusual in the context of NF1. Furthermore, NF1 individuals may have multiple co-existing complications of the disease with symptoms that are difficult to disentangle and cause diagnostic confusion. For instance, back pain attributed to a symptomatic spinal neurofibroma may be difficult to distinguish from symptoms arising from scoliosis.

12.5 Diagnosis of NF1 Associated MPNST

A meticulous clinical history should be elicited from NF1 individuals presenting with symptoms suggestive of MPNST, and should include inquiry about risk factors (see section on risk factors) as well as general and neurological assessment. Visible neurofibromas should be measured and photographed and magnetic resonance imaging (MRI) should be undertaken to determine the site, extent and volume (or three linear measurements) of the tumour.

Whole body MRI (WBMRI) using a short Tau inversion recovery sequence (STIR) has been advocated as a useful monitoring tool for individuals with NF1, to detect internal disease burden and to image large plexiform neurofibromas that involve more than one anatomical site [18]. Lobulation within the tumour, irregular contrast enhancement on T1-weighted images and ill-defined margins have been identified as features on WBMRI that are associated with MPNSTs, but do not have as high a sensitivity as FDG PET CT. Both 1.5 Tesla and 3.0 Tesla magnet strengths have been used but there is currently no consensus as to whether axial or coronal approaches are the optimal imaging planes, or whether 2D is better than 3D acquisition. A small retrospective study was performed on 22 benign neurofibromas and 9 MPNSTs with functional MRI using diffusion weighted imaging or apparent

diffusion coefficient (ADC) mapping, dynamic contrast enhanced MRI [19]. Minimal ADC and average tumour diameter were highlighted as potentially useful markers of malignancy, but further research is necessary.

The dynamic imaging technique FDG PET CT visualises and quantifies glucose metabolism in cells. FDG PET CT plays a role in distinguishing the increased glucose metabolism of malignant tumours compared with benign plexiform neurofibromas. Previously it has been shown that FDG PET CT with delayed imaging has a sensitivity of 0.95 (95% CI 0.76–0.96) and specificity of 0.89 (95% CI 0.88–0.98) [20]. The maximum standard uptake value (SUVmax) with early and delayed imaging is a semi-quantitative imaging technique that reflects the regional metabolic uptake of glucose. Warbey et al. used early imaging at 90 min and delayed imaging at 4 h to demonstrate a significant difference between benign and malignant tumours [21]. They showed a correlation between mean SUVmax and tumour grade, but there was significant overlap and the grade of tumour could not be predicted for an individual patient. There was a significant difference in the mean SUVmax between benign and atypical neurofibromas, reinforcing the premise that atypical neurofibromas are at the lower end of the malignant spectrum (see section on atypical neurofibroma). C-11 Methionine PET reflects cellular proliferation and Bredella et al. advocated using this tracer in combination with FDG PET in order to increase specificity in equivocal cases, but the tracer has not been adopted as a routine imaging modality in symptomatic plexiform neurofibromas [22].

Unfortunately, the use of PET as a diagnostic tool across different institutions has become increasingly difficult. The type of scanner, scanner performance, tracer, imaging protocols and time points vary between institutions, and interpretation of PET across different centres is problematic [4]. There does not appear to be any benefit in undertaking regular surveillance with FDG PET CT in asymptomatic people with NF1 because of the radiation dose, and tumours may undergo malignant transformation in the interval between scans.

Pre-surgical biopsy of potentially high grade MPNSTs in an expert centre is advocated to plan optimal surgical management [4]. Atypical and low grade MPNSTs may be resected without prior biopsy, based on clinical and imaging findings [16]. It is difficult to distinguish atypical neurofibromas from low grade MPNSTs on pathology (see section on atypical neurofibroma), but high grade MPNSTs exhibit a high mitotic rate >10/10 per HPF, increased cellularity, atypical nuclei, necrosis and rhabdomyoblastic change may be identified [16]. Biomarkers may be useful in indicating malignant change, including tumour suppressor genes, Tumour Protein (Tp) 53 and p16/ cyclin dependent kinase inhibitor (CDKN)2A, proliferation markers (ki67), loss of Schwann cell lineage markers (S100 /Sox10) and loss of cluster of differentiation fibroblastic framework (CD)34 [16].

12.6 Management

The aim is to excise atypical neurofibromas or low grade MPNST without causing significant pain or functional impairment, wide margins are not required as there is no evidence that these tumours recur once they have been excised [16]. The goal for

high grade MPNST is complete removal with wide resection, amputation should be reserved for extensive lesions and nerve reconstruction is not recommended for brachial plexus or lumbosacral plexus MPNST, because of the potential for suboptimal tumour removal [3, 16]. Radiotherapy is recommended for large, high grade or inadequately excised lesions, preferably administered pre-operatively, so that a small radiation field can be used to minimise toxicity [3, 16].

Individuals with NF1 appear to have a worse response to chemotherapy than their sporadic counterparts and chemotherapy is usually employed for metastatic disease. Few drugs have proved to be effective and the mainstay of treatment is doxorubicin alone, or in combination with ifosfamide to improve symptom control or to reduce the size of the tumour to achieve surgical resection [3, 4].

A recent clinical trial included 34 patients with NF1 associated high grade MPNST and 14 individuals with sporadic disease who received 2 cycles of neoadjuvant ifosfamide and doxorubicin followed by 2 cycles of ifosfamide and etoposide [23]. Etoposide and doxorubicin are inhibitors of topoisomerase 2 alpha which has been expressed in high grade MPNSTs. Five of 28 evaluable NF1 patients had a partial response (17.9%) compared with four out of nine patients with sporadic disease (44.4%) and 22 NF1 patients had stable disease compared with 4 sporadic MPNSTs. The trial did not have sufficient power to differentiate the objective response of NF1 versus sporadic patients but most patients achieved stable disease.

12.7 Patient Education

The difficulty in diagnosing NF1 associated MPNST cannot be overstated, particularly as the symptoms overlap with problems arising from benign neurofibromas. and physicians in primary care encounter the tumour rarely, if at all. Neurofibromatosis clinics, clinical nurse specialists and NF lay organisations are the ideal forum to educate patients and families and to advise when to seek medical help for symptomatic plexiform neurofibromas. In our national neurofibromatosis service, we provide a card with the contact details for our unit on one side and important symptoms on the other side with the acronym HELP—*H*ard, *E*nlarging rapidly, *L*imb weakness, numbness or incoordination, *P*ain that is persistent or nocturnal. Attention should be focused on adequate psychological support for patients and families affected by, or at risk of this serious complication and patient focused quality of life measures may be helpful in evaluating individual need [24].

12.8 The Future

It is discouraging that the current therapeutic options remain limited for individuals with N1 and MPNST. There is a need for international collaboration to collect cohesive data from patients with these malignant tumours in order to improve our understanding of the natural history [4]. Diagnostic imaging including MRI, diffusion weighted imaging and PET require standardisation across different institutions and

auditing for diagnostic efficacy. Terminology amongst pathologists should be uniform and informative for the treating physician. Central storage of blood and tumour samples should be set up to facilitate the search for biomarkers to predict patients at risk for MPNST, response to therapy and prognosis. Pre-clinical models including DNA-fingerprinted MPNST lines, animal models replicating disease onset and metastasis and to screen novel therapy, and patient derived-xenograft models will contribute to understand the disease. Clinical trials should evaluate novel therapy and explore combination therapy and the use of appropriate outcome measures, including disease specific patient focused quality of life questionnaires are essential.

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