Sarcoma in neurofibromatosis 2

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Sarcoma in neurofibromatosis 2; case report and review of the literature

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Abstract:	Neurofibromatosis type 2 (NF2) is associated with the development of several types of benign nervous system tumours, while malignancies are rare. We report a 22-year-old man who presented with retroperitoneal and spinal high-grade sarcomas with epithelial features. Samples showed a mixed epithelioid and spindled cell content with little associated matrix and inconclusive immunochemistry. Genetic analysis of a schwannoma and matched blood samples demonstrated a constitutional de novo substitution at the splice donor site of intron 8 of the NF2 gene and aa acquired large deletion of the entire NF2 gene as a second hit, with some loss of SMARCB1. The sarcoma also showed evidence of loss of SMARCB1 and NF2 with loss of INI1 staining. Unfortunately the mass was unresectable and the patient died 6 months after diagnosis. This malignancy was most consistent with SMARCB1-deficient epithelioid malignant peripheral nerve sheath tumour, although a significant differential was proximal-type epithelial sarcoma. Each differential has previously been reported only once with NF2. This demonstrates an extremely rare potential complication of the condition.
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CASE REPORT

Sarcoma in neurofibromatosis 2; case report and review of the literature

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Abstract

Neurofibromatosis type 2 (NF2) is associated with the development of several types of benign nervous system tumours, while malignancies are rare. We report a 22-year-old man who presented with retroperitoneal and spinal high-grade sarcomas with epithelial features. Samples showed a mixed epithelioid and spindled cell content with little associated matrix and inconclusive immunochemistry. Genetic analysis of a schwannoma and matched blood samples demonstrated a constitutional *de novo* substitution at the splice donor site of intron 8 of the NF2 gene and an acquired large deletion of the entire NF2 gene as a second hit, with some loss of *SMARCB1*. The sarcoma also showed evidence of loss of *SMARCB1* and NF2 with loss of INI1 staining. Unfortunately the mass was unresectable and the patient died 6 months after diagnosis. This malignancy was most consistent with SMARCB1-deficient epithelioid malignant peripheral nerve sheath tumour, although a significant differential was proximal-type epithelial sarcoma. Each differential has previously been reported only once with NF2. This demonstrates an extremely rare potential complication of the condition.

Keywords

Neurofibromatosis type 2, epithelioid malignant peripheral nerve sheath tumour, proximal-type epithelial sarcoma, SMARCB1

Introduction

Neurofibromatosis type 2 (NF2) is an autosomal dominant syndrome predisposing growth of nervous system tumours (Evans et al Orphanet 2009). With an incidence of one in 25000-33,000 (Evans et al Am J Med Genet 2010), the condition is caused by the heterozygous inactivation of the neurofibromin 2 (NF2) gene on chromosome 22q 11.2, which leads to loss of the moesin/ezrin/radixin family protein Merlin. NF2 is associated with its hallmark bilateral vestibular schwannomas and benign tumours of the cranium, spine and peripheral nerves, posterior subcapsular opacification and other eye abnormalities. The development of malignant tumours in NF2 is relatively rare in contrast to its counterpart neurofibromatosis 1 (NF1) [1,2].

We present a young patient with NF2 who had an abdominal high grade sarcoma with epithelioid features. The proximal location and deep tissue origin of the tumour was remarkable, as well as its unique immunocytochemistry, representing transformation towards malignancy. This highly unusual potential complication of NF2 presented a wide differential diagnosis including proximal type epithelioid sarcoma and malignant peripheral nerve sheath tumour (MPNST).

Case Report

A 22 year-old male presented with a six month history of severe back pain, weight loss and anorexia, microcytic anaemia, foot drop and mononeuropathy in his right leg. The patient had a life-long history of NF2 associated vestibulocochlear tumours. He was originally diagnosed aged 5 years old as a result of visual loss from a retinal hamartoma. The patient had surgical intervention at the age of 7 for an intraventricular meningioma and at 14 for a left sided vestibular schwannoma, when a cochlear implant was inserted. He remained relatively healthy up to the age of 20, using his cochlear implant alongside his good hearing ear.

On examination a hard mass was palpated in the patient's left hypochondrium. Unusually, the patient had not undergone a spinal magnetic resonance imaging (MRI) for 6 years, as his parents had not wished to compromise his cochlear implant. An urgent computed tomography (CT) scan showed a 23x10x10cm retroperitoneal abdominal mass, displacing the pancreas, spleen and bowel loops. The mass was cystic with multiple foci of calcification. NF2 is not usually associated with retroperitoneal tumours, suggesting the mass might be a metastatic deposit. Accordingly, the parents consented to an MRI scan to investigate possible primary tumours. MRI revealed multiple nerve root tumours including a 2.4cmx1.5cm lesion on the left nerve root at L2/L3, a 2x2.6cm lesion on the right exiting nerve root of L5/S1 and a schwannomata on the apical section of T11. Positron emission tomography (PET) showed low fludeoxyglucose uptake throughout the periphery of the retroperitoneal mass, which increased between early and delayed scans, and high activity in the lower half of the mass. This diverse metabolic activity strongly indicated malignancy, while central areas of photopenia suggested focal necrosis. The T11 lesion showed increased metabolic activity on PET-CT scan.

A CT-guided core needle biopsy of the retroperitoneal mass showed an extensively necrotic high grade malignant tumour (figure 1) composed of malignant epithelioid and spindled cells with little associated matrix (figure 2) and no signs of specific differentiation. Apoptosis and atypical mitoses were numerous. Immunohistochemistry showed the tumour cells to express vimentin, but not other markers including pan-cytokeratins, epithelial membrane antigen, desmin, human melanoma black 45 (HMB45), glial fibrillary acidic protein, thyroid transcription factor 1 (TTF-1), CDX2, PAX-8, actin and S100 antigen. There was loss of INI1 staining by tumour cell nuclei but not associated non-neoplastic cells (Figure 3). Altogether, the biopsy resembled a high-grade sarcoma with epithelioid features lacking any specific differentiation/histogenetic morphology.

On MRI, the L3 vertebra showed a fracture, with diffuse and abnormal signal characteristics suggesting involvement by a malignant tumour – suspicious for a metastatic deposit. Biopsy of L3 revealed active bone remodelling and marrow replacement by malignant tumour of similar appearance to that seen in the retroperitoneal biopsy.

Lung metastases were also found on the lower lobes.

Genetic analysis discovered a *de novo* germline guanine to adenine substitution at the splice donor site of intron 8 of the NF2 gene (c.810+1G>A). Additionally a cutaneous schwannoma showed a large deletion of the entire NF2 gene as a second hit (data not shown). DNA extracted from the lesion showed Loss of Heterozygosity (LOH) at 16% for an intragenic polymorphism (Intron 10) but not for flanking markers including D22S268, as such this could be regarded as inconclusive. There was nonetheless some evidence of loss of *SMARCB1* from LOH analysis.

The delay in diagnosis of the malignancy may be explained by the misinterpretation of his recent symptoms as the side effects of the trial drug Sorafenib. In light of the severity of the disease, the patient opted for Doxorubicin as palliative chemotherapy. Sadly he died just 6 months after diagnosis.

Discussion

Initial H&E examination of the needle biopsy of the retroperitoneal mass raised a wide differential diagnosis, including epithelioid malignant peripheral nerve sheath tumour (EMPNST), epithelioid sarcoma, melanoma and poorly differentiated carcinoma. The inconclusive cytochemical results for the case study make diagnosis difficult

Malignant peripheral nerve sheath tumours (MPNST) are rare soft tissue sarcomas that are common complications of NF1 and occasionally radiotherapy [3]. MPNSTs are extremely unusual in NF2 and have only been reported once in the absence of previous radiation treatment [4,5]. Although our case had undergone frequent cranial CT scans there was no evidence for increased exposure in the lumbar region. Most MPNSTs present with a significant spindle cell content, although less than 5% of MPNSTs have a mixed epithelioid spindle composition, in a variant known as epithelioid malignant peripheral nerve sheath tumour (EMPNST) [5,6]. This more aggressive deep tissue neoplasm commonly metastasises to lung and is the most likely form to arise from a malignant transformation of a benign neurofibroma [6]. Both tumour subtypes involve major nerves and are frequently found in the trunk, though rarely the vertebrae [7,4].

EMPNSTs have varied cytological characteristics, but largely resemble the histology of the case study mass. EMPNST generally segregate into large, poorly defined nodules against a myxoid matrix background [7]. In contrast to the spindle cell fascicular composition of typical MPNST, EMPNSTs form sheets and cords of epithelioid and spindle cells, separated by scanty fibrillar collagen. The tumour cells are typically large and melanoma-like with prominent nuclei and eosinophilic cytoplasm [6]. Necrosis is often extensive and mitotic rate is characteristically high. Commonly, EMPNST expresses S-100 protein and is negative for melanoma-associated antigen and cytokeratins [8,9]. In this case the retroperitoneal mass appears to be an EMPNST, with loss of expression of S-100.

The aggressive, proximal-type subset of epithelioid sarcomas has a similar histology to the case study lesions. Proximal type epithelioid sarcomas are rare, usually located in deep pelvic

and perineal tissue, although the retroperitoneal site has been reported [9] [10,6]. The tumours have irregular nodules with a varying spindled and epithelioid cellular appearance, including large and vesicular nuclei with prominent nucleoli, displaced eccentrically in the cell by intracytoplasmic globules [10]. Epithelioid sarcomas show central necrosis with a granuloma-like pattern [11,9]. However, epithelioid sarcoma is distinctly uncommon in NF2; previously described only once [12]. Furthermore, only 9 cases of epithelioid sarcoma of the spine region have been reported, with over half reporting lung metastases [13,14]. Additionally, the retroperitoneal tumour was negative for key biomarkers of epithelioid sarcoma, including cytokeratins (CK), CD34 and epithelial membrane antigen, although the characteristic loss of INI1 (SMARCB1) was present in our case.

The mass described has features that resemble both epithelioid sarcoma and EMPNST. However, due to the history of NF2, the tumour is likely to have an origin in the nerve sheath and thus represent a highly progressive, undifferentiated EMPNST. The similarity between the spinal and retroperitoneal lesions indicates that they derive from the same malignancy - most likely is that the retroperitoneal mass is a metastasis of the spinal tumour, expressing few cellular markers due to anaplasia through tumour progression. Of the differential diagnoses under consideration, the immunohistochemical profile is most consistent with a SMARCB1-deficient epithelioid malignant peripheral nerve sheath tumour. Malignant transformation of this nature is very unusual in NF2.

Compliance with Ethical Standards

Ethical standards

Informed consent was obtained from all involved participants in this study

Conflicts of interest

The authors declare that they have no conflict of interest

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Figure 1 (objective magnification x2): Histological section of the retroperitoneal mass biopsy showing necrotic (upper end) and viable tumour tissue.

Figure 2 (a & b) objective magnification x10 and x40 respectively:

A - Epithelioid tumour cells forming disorganised sheets and vague nests with prominent associated vasculature.

B - Tumour cells undergo apoptosis and atypical mitosis.

Figure 3: Plexiform schwannoma showing S100 staining