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Low grade Schwann cell neoplasms with leptomeningeal dissemination: clinicopathologic and autopsy findings

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Abstract

Leptomeningeal dissemination of low grade Schwann cell neoplasms is an exceptionally rare occurrence, and has not been well documented in the literature. We encountered two cases of leptomeningeal dissemination of low grade Schwann cell neoplasms. Patient 1 was a 63-year-old woman with NF1 and a progressive low grade MPNST developing from a diffuse/plexiform orbital neurofibroma that arose in childhood. The neoplasm demonstrated local and leptomeningeal dissemination intracranially leading to the patient's death. There was partial loss of H3K27 tri-methylation, p16 and collagen IV. Patient 2 was a 60-year-old man without NF1 who presented with cranial nerve symptoms and a disseminated neoplasm with a Schwann cell phenotype. The neoplasm stabilized after irradiation and chemotherapy but the patient died of medical complications. Autopsy findings documented disseminated leptomeningeal disease in the intracranial and spinal compartment. H3K27M tri-methylation was preserved. The clinicopathologic and autopsy findings are studied and presented, and the literature is reviewed.

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Keywords

Neurofibromatosis; MPNST; Schwann Cell; Neurofibroma; NF1; Schwannoma

Introduction

Neurofibromatosis type 1 (NF1) is one of the most common single gene autosomal dominant syndromes, caused by a germline mutation of the *NF1* gene that encodes for neurofibromin, which is a key tumor suppressor protein that regulates RAS signaling. The diagnosis is mainly clinical, with the criteria developed by the National Institutes of Health (NIH) Consensus Conference well accepted for clinical use. Neurofibroma is a benign peripheral nerve sheath tumor and the most common neoplasm developing in the setting of NF1.

Neurofibromas are comprised of neoplastic Schwann cells, as well as other cellular nerve components such as fibroblasts, mast cells, axons and perineurial cells [1]. The classic morphologic features of neurofibroma include wavy neoplastic Schwann cells in a myxoid background, delicate collagen fibers and mast cells. The World Health Organization (WHO) recognizes several clinicopathologic types of neurofibromas, including cutaneous (localized or diffuse), intraneural and plexiform [1]. Malignant transformation (MPNST) occurs in approximately 5% of NF1-associated plexiform neurofibromas. Other sporadic well differentiated Schwann cell neoplasms, including schwannomas, are usually benign but may be locally aggressive, particularly the cellular variant, and can rarely undergo malignant transformation [2]. Leptomeningeal dissemination of low grade Schwann cell neoplasms is an exceptionally rare occurrence, not well documented in the literature. Herein, we report the clinical and autopsy findings of two patients with disseminated low grade Schwann cell neoplasms.

Clinical history

Case 1

A 63-year-old woman with a clinical diagnosis of NF1, status post excision of multiple cutaneous Schwann cell/spindle cell neoplasms, including cutaneous neurofibromas, a hepatic cellular neurofibroma, and a plexiform neurofibroma of the right scalp, face and orbit that was slowly progressive from childhood causing facial disfigurement, presented for re-evaluation of worsening tumor burden. She first underwent surgical resection of the right facial mass in 2006 with pathology revealing diffuse neurofibroma. Additional debulking procedures occurred in 2008 (diffuse neurofibroma), 2009 (atypical neurofibroma), and 2011 (recurrent atypical neurofibroma involving the soft tissues, bone and invading sinonasal tissue as well as cellular neurofibroma involving dura). The tumor remained stable on serial imaging and the patient's pain was well controlled for 16 months. However, in 2013 she was noted to have progressive tumor growth on magnetic resonance imaging (MRI) and her pain returned. Hence, she underwent right anterior fossa craniotomy with orbital exenteration for resection of tumor invading the epidural and intradural space. A diagnosis of low grade MPNST arising in a plexiform neurofibroma was made. Treatment options, including involved field radiation and various chemotherapies, were considered but

deemed of unclear benefit and high risk given the patient's clinical comorbidities. In 2014, her tumor progressed to involve the leptomeninges and her functional status declined with multiple hospitalizations related to altered mental status and pain, which improved with multiple courses of steroid treatment. Cerebrospinal fluid (CSF) analysis showed a protein of 118, glucose of 51, WBC 14 and cytopathology demonstrated increased mononuclear cells, but no malignant cells or monoclonal B cell were detected. Infectious evaluation was negative. Additional tumor sampling of the most active lesion on serial imaging (nodule in right masticator space) showed cellular neurofibroma with extensive reactive changes, but no evidence of MPNST. A computed tomography (CT) with contrast showed a stable 2.2 cm hypodense hepatic lesion with adjacent capsular retraction. Approximately 4 months after the initial diagnosis of leptomeningeal disease, she was readmitted to the hospital with new onset left-sided weakness, bowel and bladder incontinence, and confusion believed to be due to a stroke. An MRI showed new FLAIR signals consistent with ischemia in the right corona radiata as well as increased ventricular size. A CT angiogram of her head and neck showed multiple enhancing lesions and moderate to marked irregular narrowing of the right distal M1/M2 segment. The vascular pathology was thought to account for the left sided weakness. However, mental status improved with a combination of a large volume lumbar puncture and the initiation of dexamethasone for treatment of the leptomeningeal disease. She also had a documented focal seizure activity from the temporal lobe and was started on Lacosamide with further improvement in mental status. MRI prior to discharge showed an interval increase in the regional mass effect involving the anterior right cerebral hemisphere with associated moderate effacement of the right lateral ventricle, 1 cm right to left midline shift, and mild to moderate subfalcine herniation. She was discharged to a rehabilitation facility with palliative care. Her mental status progressively declined over the next two weeks and she subsequently became unresponsive several days prior to her death, 5 months from the diagnosis of leptomeningeal disease. An autopsy was performed.

Case 2

A 60-year-old African American man presented with a two-week history of left facial pain, numbness and intermittent facial droop. There was no relevant past medical history, nor irradiation. MRI studies demonstrated several extra-axial enhancing lesions involving the left cerebellum/tentorium (1.8 cm), right Meckel's cave (1.5 cm), right temporal lobe (0.3 cm), and several lesions in the cervical and thoracic spinal cord. CT scan of the chest, abdomen and pelvis were unremarkable. A biopsy of the left cerebellar lesion showed a cellular spindle cell neoplasm. CSF analysis demonstrated increased protein and negative cytology. A ventriculoperitoneal (VP) shunt was placed for increasing hydrocephalus. The patient developed bilateral pulmonary emboli, but temporarily recovered. Whole brain irradiation and chemotherapy with Irinotecan and Avastin was administered. Subsequent MRI studies demonstrated stable lesions. The patient continued to decline with multiple hospital admissions, respiratory failure and aspiration. The patient died 7 months after presentation. An autopsy was performed.

Neuropathologic Examination

Case 1

Surgical specimen—Multiple biopsies/resections of the orbit and periorbital areas demonstrated changes ranging from neurofibroma to cellular/atypical neurofibroma to low grade MPNST which was more evident in the orbital exenteration (Figure 1). Immunohistochemical stains demonstrated strong S100 protein expression. P53 labeled a subset of cells. There was partial loss of H3K27 tri-methylation, p16 and collagen IV in malignant areas. Autopsy: The fresh brain weight was 1080 g. A portion of dorsal cerebral dura was available for examination and showed right-sided thickening with nodularity over the right frontal lobe. There were two dominant firm, tan-white dural nodules ($7.0 \times 5.5 \times 3.0$ cm; $2.1 \times 1.4 \times 0.7$ cm) over the right frontal cortex, the larger of which markedly compressed the underlying cortex (Figure 2). The leptomeninges demonstrated focal opacities and thickening in the convexities and over the brainstem.

On serial coronal sections the larger frontal dural nodule compressed the underlying right frontal cortex resulting in thinning of the cortical ribbon. The corresponding areas of white matter in the frontal lobe were friable. The right temporal dural lesion overlaid the right orbitofrontal region and was adherent to the right inferior frontal gyrus, insular cortex and superior temporal gyrus, involved the lateral sulcus and compressed the middle cerebral artery. The ventricular system was dilated, most evident in the third ventricle.

H&E sections of the leptomeningeal masses showed a relatively monomorphic population of round to oval cells with minimal cytoplasm, hyperchromatic nuclei, variable cellularity and rare mitotic figures. The cells were focally arranged in fascicles with rare coagulative necrosis, and extensive dissemination in leptomeninges and perivascular spaces of the cerebrum and brainstem. There was tumor involvement in the right orbital surgical bed. The tumor focally invaded the cortex of the right temporal lobe with adjacent white matter rarefaction and swollen axons. Additionally, there were ill-defined areas of subacute white matter injury with rarefaction and reactive astrogliosis in the frontal and parietal lobes. The neocortex showed widespread subpial gliosis and white matter rarefaction. Focal treatment effect, including hyalinization and scarring, was present. Overall, the tumor was viable with evidence of a residual neurofibroma precursor transitioning to areas of MPNST (Figure 1,2). A section of the right middle cerebral artery showed complete encasement by tumor. There was tumor invasion in the adventitia of the walls of the internal carotid and middle cerebral arteries (Figure 2).

The final diagnosis was low grade MPNST with extensive leptomeningeal and perivascular spread involving brain. Additional findings included subacute white matter injury, postsurgical-related changes involving meninges, multiple neurofibromas ($2.5 \times 1.8 \times 1.5$ cm and $0.7 \times 0.6 \times 0.4$ cm) involving liver, cutaneous neurofibromas (0.5 – 2.0 cm in greatest dimension) and café au lait spots (3.1 – 6.6 cm in greatest dimension).

Case 2

Surgical Specimen—Biopsy of the left cerebellar mass showed a cellular spindle cell neoplasm lacking mitotic activity. The neoplasm demonstrated S100 protein, SOX10 and

GFAP co-expression. There was a pericellular collagen IV and reticulin pattern of staining. H3K27 tri-methylation was retained. The Ki-67 labeling index showed patchy increases.

Autopsy Specimen—Examination of the brain after fixation demonstrated a weight of 1225 grams. The gray-white matter interface was well demarcated. Superficial lesions of white-brown appearance were grossly obvious in the left cerebellum and right temporal lobe. Microscopic examination demonstrated a spindle cell neoplasm of moderate cellularity and low mitotic activity resembling that present in the first biopsy. There was extensive dissemination in the cerebrum, cerebellum and spinal cord surface without clear parenchymal invasion (Figure 3). Immunohistochemical stains demonstrated strong S100 protein expression, as well as pericellular collagen IV and reticulin deposition. P16, p53, MART1, HMB45, and MITF were negative. H3K27 tri-methylation was retained. The Ki67 labeling index was low. There were no suspicious lesions outside the CNS, including skin, mucosal surfaces and internal organs. A diagnosis of a well differentiated Schwann cell neoplasm was rendered.

Discussion

MPNSTs are the most frequent malignant neoplasms associated with NF-1. High grade MPNSTs are hypercellular, composed mainly by spindle cells forming herringbone, storiform, or tissue culture-like patterns in a background of fibrous or myxoid stroma. Nuclei are crowded and hyperchromatic, and geographic necrosis and perivascular aggregation of viable tumor cells can be seen. High mitotic counts are frequent ($>4/10\text{HPF}$), but not required for the diagnosis. Low grade MPNST are rare, and the diagnosis is usually applied to areas of malignant transformation within a preexisting neurofibroma in NF1 patients[3].

Malignant transformation is a well recognized feature of neurofibroma, and the risk varies by subtype. Localized cutaneous neurofibromas almost never develop malignant changes, whereas diffuse cutaneous and localized intraneural forms are more likely to do so [4]. The frequency of malignant change is highest for plexiform neurofibroma, and therefore atypical features, particularly in large tumors with worrisome signs (e.g. rapid growth, pain) must be given close clinical attention. Increasing attention has been given to the group of “atypical neurofibroma”, which is a neurofibroma with cellular atypia, but lacking overt malignant change. Increased PET uptake and podoplanin expression has been noted in these areas[5, 6]. Some interpret atypical neurofibroma as premalignant, given the high frequency of *CDKN2A/B* deletions observed [7, 8]. Others have found similar methylation profiles in atypical neurofibroma and low grade MPNST[9]. Of interest as well is that recent genomewide sequencing studies have identified mutations in *SUZ12* or *EED*, components of the polycomb repressive complex 2 (PRC2), in most MPNST[10, 11]. These alterations lead to loss of H3K27 tri-methylation, which can be detected by immunohistochemistry, a useful marker for MPNST[12, 13]. However, loss of H3K27 tri-methylation may be rare to absent in low grade MPNST/atypical neurofibroma in the small number of cases studied[9, 14]. We noticed partial loss of H3K27 tri-methylation in case 1 but retained reactivity in case 2 consistent with these observations.

High grade malignant transformation is relatively easy to recognize, and characterized by hypercellularity, severe cytologic atypia, brisk mitotic activity and necrosis in a subset of cases. However, malignant change in neurofibroma is often low grade (i.e. low grade MPNST), and challenging to diagnose. Antonescu, Scheithauer and Woodruff outlined the triad of hypercellularity (nuclear crowding), nuclear hyperchromasia and nuclear enlargement (3× neurofibroma nuclei) as criteria for malignant change in neurofibroma. Mitotic activity is not required, but supportive when present. The presence of large pleomorphic cells in the setting of moderate cellularity is another variation proposed by the same authors for malignant change in neurofibroma[3].

In case 1, an unusual transformation of diffuse neurofibroma into MPNST was observed in an older patient with multiple recurrences and ultimately invasion of the meninges, brain, optic chiasm and complete encasement of the right middle cerebral artery. The tumor was viable with evidence of residual neurofibroma precursor transitioning to MPNST. MPNST involving the oculofacial region is exquisitely uncommon, and so is malignant transformation of neurofibroma at this site. The largest series of orbital MPNST predating contemporary criteria is that of Jakobiec et al. with 8 patients, two of whom had NF1 with MPNSTs developing in association with neurofibromas[15].

In case 2 there was no clinical or pathologic evidence of NF1. The histologic features were those of a low grade Schwann cell neoplasm. Some of the histologic features and the strong immunoreactivity for S100 protein resembled cellular Schwannoma even at autopsy. However, the pattern of dissemination suggested low grade malignant behavior not immediately obvious from the histology in isolation. Loss of expression of Schwann cell markers is an important feature that separates MPNST from cellular Schwannoma, but this was not evident in this case. It must be noted that a subset of schwannomas in the head and neck region can be infiltrative, unencapsulated, locally aggressive, and may develop intracranial extension[16]. Of interest, our patient 2 presented with cranial nerve symptoms traceable to the left trigeminal nerve. The main lesions identified on MRI were in the left cerebellum and right Meckel's cave, which may be putative primaries in this case. One important entity in the differential diagnosis of this case was desmoplastic/spindle cell melanoma, a known mimicker of Schwann cell neoplasms, particularly at superficial/cutaneous sites with sun exposure. However, these tumors favor Caucasian patients, and detailed clinical and autopsy examination in this case did not reveal any suspicious lesions outside of the central nervous system.

The biologic aggressiveness of low grade MPNST is controversial in the literature[17, 18]. Bernthal et al. published a series of 23 patients in which the disease-specific free survival was 100% regardless of surgical margin[19]. What is unique about our cases is that they demonstrated an exclusive pattern of leptomeningeal spread without involvement of any other organs, a rare occurrence with Schwann cell neoplasms. In our review of the literature, at least 4 cases of MPNST showing this phenomenon have been reported (table 1). All these cases were in patients lacking NF1 history, who had predominant spinal primaries, and who (in 3) demonstrated exclusive intracranial spread [20–23]. In combining these cases with ours, all patients were dead 7–60 months after diagnosis of leptomeningeal disease (median 21 months), supporting the concept that this clinicopathologic presentation is biologically

aggressive. In summary, we present detailed clinicopathologic findings of leptomeningeal spread of two cases of low grade Schwann neoplasms. This phenomenon appears rare, but in the few instances reported the outcome has been uniformly and rapidly fatal. Future studies should provide additional insights into the biological basis for this phenotype that should facilitate optimal management of these patients.

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Figure 1. Imaging and surgical findings of low grade MPNST developing in neurofibroma (case 1)

Axial post-contrast T1 weighted MRI demonstrates progressive increase in size of a neurofibroma in the right orbit/periocular region from 2004 (A), 2009 (B), and 2013 (C). MRI at different levels demonstrate significant burden at the time of malignant transformation with intraorbital (D,E) and intracranial (F) extension. The neurofibroma precursor had a significant diffuse component, enveloping adnexal (H&E $\times 200$)(G). Classic neurofibroma areas (H) as well as increase in cellularity (I) were present (H&Es $\times 400$). Gradual transition to a low grade MPNST was reflected in a decrease in intercellular collagen, nuclear hyperchromasia, enlargement and mitotic activity (arrows)(H&E $\times 600$)(J). S100 expression ($\times 600$)(K) and areas of p16 loss ($\times 400$)(arrows, L) were additional features.

Figure 2. Autopsy findings of low grade MPNST developing in neurofibroma (case 1)

Intracranial leptomeningeal dissemination was present at autopsy, resulting in mass effect on the cerebrum (coronal section) (A) and infiltration of the right middle cerebral vessel wall (H&E ×12.5)(B). Attachment to dura (C) and extension to perivascular Virchow Robin spaces (D) were additional features (H&Ex 40).

Figure 3. Autopsy findings of low grade Schwann cell neoplasm with extensive leptomeningeal extension (case 2)

Extensive leptomeningeal dissemination of a low grade Schwann cell neoplasm was evident in the cerebellum (H&E $\times 40$)(A) and around the spinal cord (H&E 12.5) (B). Histologic features reminiscent of a Schwann cell neoplasm included cellular spindle cell areas (H&E $\times 400$)(C), looser aggregates and a myxoid stroma (H&E $\times 600$)(D) and vascular and stromal hyalinization (H&E $\times 400$)(E). Special stains demonstrated immunolabeling with S100 ($\times 400$) (F), SOX10 ($\times 600$)(G) and collagen IV ($\times 600$)(H). Pericellular reticulin deposition was also observed ($\times 400$)(I).

Table 1

Schwann cell neoplasms with leptomeningeal dissemination in the literature

Reference	Age/Sex	Location	NF1 status	Structures involved	Pathology	Follow-up
Stark et al. 2013 [23]	56/F	S1 nerve root (post-irradiation for lymphoma 15 years prior)	sporadic	Intracranial and spinal leptomeninges, brain parenchyma	MPNST (primary) Metastases not examined	Dead 24 months after diagnosis
Lau et al. 2014 [20]	43/M	Sacral spine (post-irradiation for germ cell tumor)	Sporadic	Kidney, intracranial and spinal leptomeninges	High grade MPNST	Dead 60 months after diagnosis
Mortele et al. 1998 [22]	54/F	Retropertitoneum	Sporadic	Spinal leptomeninges	“malignant schwannoma” (metastases not examined)	Dead 15 months after diagnosis
Li et al. 2014 [21]	33/F	T12/L1 nerve root	Sporadic	Intracranial and spinal leptomeninges	MPNST (low grade?)	Dead 29 months after diagnosis
Present case 1	61/F	Orbit	NF1-associated	Intracranial leptomeninges and dura, Virchow-Robin spaces	Low grade MPNST	Dead with progressive disease 18 months after diagnosis of MPNST
Present case 2	60/M	L CPA? R Meckel cave?	Sporadic	Intracranial and spinal leptomeninges	Low grade Schwann cell neoplasm	Dead 7 months after presentation but with stable disease

NF1=neurofibromatosis type 1, M=male, F=female, MPNST=malignant peripheral nerve sheath tumor