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Case Report

Cranial nerve and intramedullary spinal malignant peripheral nerve sheath tumor associated with neurofibromatosis-1

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ABSTRACT

Background: Malignant peripheral nerve sheath tumors (MPNSTs) are uncommon but aggressive neoplasms associated with radiation exposure and neurofibromatosis Type I (NF1). Their incidence is low compared to other nervous system cancers, and intramedullary spinal lesions are exceedingly rare. Only a few case reports have described intramedullary spinal cord MPNST.

Case Description: We describe the clinical findings, management, and outcome of a young patient with NF1 who developed aggressive cranial nerve and spinal MPNST tumors. This 35-year-old patient had familial NF1 and a history of optic glioma treated with radiation therapy (RT). She developed a trigeminal MPNST that was resected and treated with RT. Four years later, she developed bilateral lower extremity deficits related to an intramedullary cervical spine tumor, treated surgically, and found to be a second MPNST.

Conclusion: To the best of our knowledge, this is the first report of cranial nerve and intramedullary spinal MPNSTs manifesting in a single patient, and only the third report of a confined intramedullary spinal MPNST. This unusual case is discussed in the context of a contemporary literature review.

Keywords: Intramedullary, Malignant peripheral nerve sheath tumor, Neoplasm, Spinal cord, Trigeminal nerve

INTRODUCTION

Malignant peripheral nerve sheath tumors (MPNSTs) are soft-tissue sarcomas believed to arise from Schwann cells of the peripheral nerve sheath.[15] Lifetime incidence in the general population is 0.001%, but is increased to 4.6–13% in patients with neurofibromatosis 1 (NF1).[6,7,21] Previous radiation therapy (RT) has also been identified as a risk factor, and tumors associated with NF1 or prior radiation have poorer prognosis compared to sporadic lesions.[18] MPNSTs arise in the trunk, extremities, head, and neck, with a known propensity to metastasize.[2] To date, only two case reports have documented a spinal cord intramedullary MPNST, one arising *de novo*,[17] and another associated with childhood irradiation for chronic tonsillitis.[20]

Here, we report a case of spinal cord intramedullary MPNST in a patient with a history of NF1 and a prior trigeminal MPNST.

CLINICAL PRESENTATION

The patient was a 35-year-old female with familial NF1. At 3 years of age, she developed visual loss associated with an optic glioma that was treated with RT. She developed progressive left whole facial numbness and corneal irritation at the age of 30. No other cranial nerve abnormalities were noted at the time. This led to the finding of a large left trigeminal MPNST [Figure 1a]. The trigeminal tumor was subtotally resected through a retrosigmoid, microsurgical approach, and the patient was treated subsequently with RT.

Histopathological analysis revealed a hypercellular neoplasm replacing normal peripheral nerve structure, with dominating densely cellular fascicular regions. Tumor cells showed focal positivity for S100 protein, CD57, and p53, but not EMA. The Ki-67 immunolabeling was high, up to 50% in select high-power fields. Overall, this was consistent with trigeminal MPNST.

Further imaging of the entire neuraxis was unremarkable at that time. She recovered to functional independence with no new neurological deficits and no restoration of her facial sensation. Surveillance magnetic resonance imaging (MRI) was performed every 6 months and failed to show recurrence. The patient was referred for genetic consultation after her first surgery.

Five years following the cranial surgery, she developed rapidly progressive bilateral lower extremity sensorimotor deficits leading to functional incapacitation over weeks. Her physical examination demonstrated diffuse weakness in the lower extremities, more pronounced proximally and on the left. There were diffuse hyperreflexia, a positive Babinski's sign, and a T4 sensory level. Rectal tone remained intact, and the upper extremities appeared unaffected. MRI of the cervical spine revealed a contrast-enhancing intramedullary mass extending from C7 to T1 levels, with broader edematous changes in the spinal cord between C3 and T4 [Figures 1b-d]. No other spinal lesions were identified, and cranial imaging was stable. The patient was initiated on dexamethasone therapy at this time.

Surgical resection was planned with intraoperative somatosensory and motor evoked potential monitoring. Following C3–T2 bilateral laminectomies, a midline durotomy was performed and intraoperative ultrasound was used to localize the lesion at the level of C7. A midline myelotomy was performed revealing an infiltrative intramedullary mass with poorly defined borders. Tumor debulking was followed by an expansile duroplasty and C3–T2 posterior spinal instrumentation.

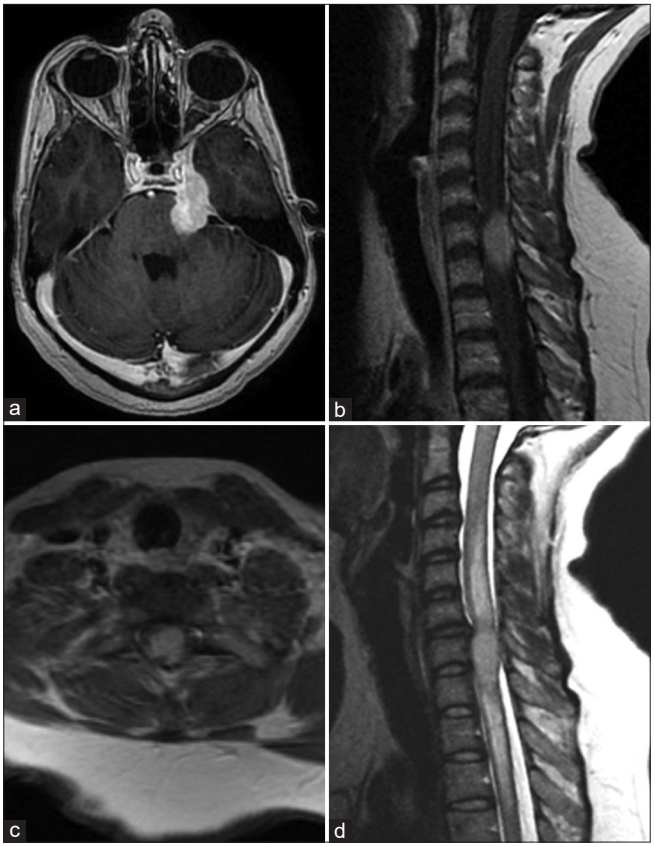

Figure 1: Magnetic resonance imaging of the trigeminal nerve and spinal intramedullary malignant peripheral nerve sheath tumors. Axial T1 with gadolinium cranial imaging demonstrating the left trigeminal nerve mass (a). Sagittal (b) and axial (c) T1 with gadolinium spinal imaging demonstrating the intramedullary mass. Sagittal T2-weighted imaging showing the same intramedullary mass with surrounding cord edema extending caudally and rostrally (d).

On pathological assessment, the biopsy consisted of a spindle cell neoplasm, forming interlacing cellular bundles of spindle cells (herringbone pattern) without distinct cellular borders [hematoxylin and eosin; Figure 2]. There was nuclear atypia with occasional large hyperchromatic nuclei and frequent mitotic figures. Focal necrosis was seen. Tumor cells were patchy positive for S100 protein, focally positive for SOX10 and p53. The Ki-67 immunolabeling was patchy, ranging from 10% to 40%. INI-1 showed partial loss of expression, and myogenin was not expressed. GFAP was positive in the intervening paucicellular areas, suggesting that the tumor had infiltrated neuroglial tissue. Diagnosis confirmed spinal intramedullary MPNST.

The patient remained neurologically unchanged and bedridden following surgery. Over the next year, she developed leptomeningeal deposits, presumed to be metastases, at the levels of the cerebral cortex and cauda equina which were treated with palliative local field RT. The

patient was discharged to hospice and passed away at the age of 36.

DISCUSSION

This report represents the third case of a spinal intramedullary MPNST in the literature to date and is the first case in a patient with NF1 and previous trigeminal MPNST [Table 1]. Spinal intramedullary tumors are often ependymomas and less commonly infiltrative astrocytomas,[8] with rare cases of schwannomas having been reported.[14] Given the paucity of literature, more understanding is needed, and advances in treatment essential to improve the dismal prognosis.

Paolini *et al.* reported the first case of an intramedullary MPNST at the C4–C5 level;[20] this patient was a 50-year-old man without NF1, who presented with tetraparesis and previous childhood RT for chronic tonsillitis. Another report by Marton *et al.* described an intramedullary MPNST at the C2–C3 level in a 56-year-old man with no history of NF1 or spinal radiation.[17] Notably, our patient had childhood radiation treatment for optic glioma and subsequently developed a trigeminal MPNST in adulthood, 27 years following RT. While trigeminal MPNSTs are uncommon,[21] the development of an MPNST following radiation treatment for an optic glioma has been previously documented in the context of NF1[7] – in a case reported by Evans *et al.*, right temporal and left submandibular MPNSTs developed in the same patient, 24 years and 27 years, respectively, following radiation treatment,[7] which is comparable to the timeline in the current case.

MPNSTs localized to the spinal canal are typically intradural and extramedullary in location, and most data are limited to case reports or series due to the rarity of the disease.[3,4,23-25]

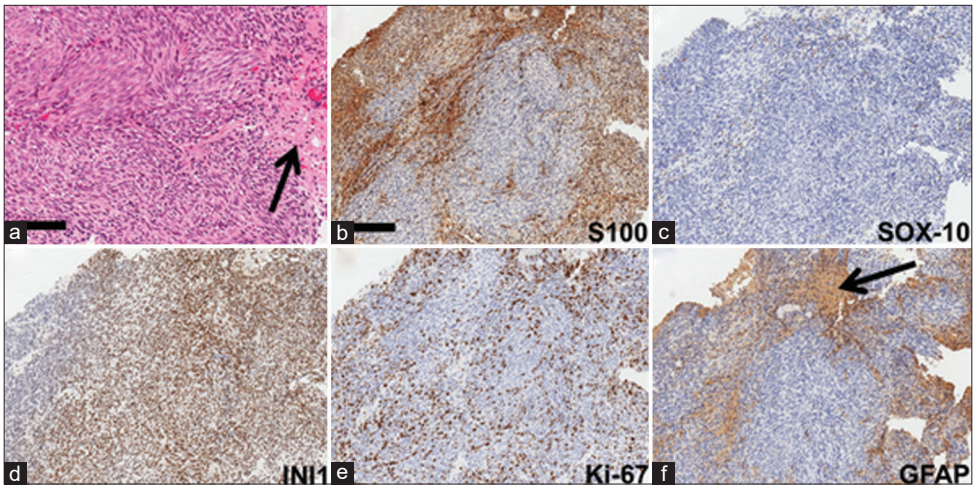

Figure 2: Histopathological imaging of the spinal intramedullary mass. H and E stained slides demonstrate a spindle cell neoplasm with interlacing cellular bundles (herringbone pattern) without obvious cellular borders and moderate pleomorphism (a). There is patchy staining with S100 protein (b). SOX10 (nuclear) stain is primarily lost (only sparse labeling) (c). INI1 is primarily retained, but there was focal lost throughout (d). The Ki-67 proliferation index is elevated (e). There are scattered fragments of CNS (spinal cord) parenchyma seen throughout (arrows), highlighted with GFAP (f). Scale bars (A: 200 μm) (b-f: 100 μm).

Table 1: Published cases of intramedullary malignant peripheral nerve sheath tumors.

Author	Age, sex	Previous radiation	NF1 mutation	Tumor location	Presenting symptom	Management	Adjuvant therapy	Outcome
Paolini *et al.*, 2006[20]	50 M	Yes	No	C4–C5	Severe tetraparesis	Subtotal resection	None	Death – 9 months postoperative, pneumonia complications
Marton *et al.*, 2011[17]	56 M	No	No	C2–C3	Sensory disturbance to the left leg and right arm	Gross total resection	Chemotherapy	No tumor recurrence or complications
Current case	35 F	Yes	Yes	C7	Gait disturbance and paraparesis	Surgical debulking and biopsy	Palliative radiotherapy	Death – discharged to hospice with life expectancy of 3 months

In some reports, the spinal lesions arose *de novo* from the associated nerve roots, and in others, they were presumed to have metastasized from peripheral tissues. In a recent literature review of primary spinal intradural MPNST, recurrence and metastasis rates were high (54% and 45%, respectively), despite aggressive surgical resection and adjuvant RT.[3] The mean age at diagnosis was 32 years (range 3–70 years), and systemic and leptomeningeal metastases were common.[3] The common sites of metastasis for MPNST include lung, liver, lymph nodes, and bones,[2] although intracranial metastases to the medulla oblongata[9] and the corpus callosum[22] have been described. Spinal cord invasion from an extramedullary lesion is relatively common in advanced disease,[3,25] although no lesions in the previous reports were identified to be completely confined to the cord or having arisen from the cord.[3,4,23-25]

MPNSTs have a propensity to develop in association with NF1[7] or as a consequence of prior RT.[18] The median age at diagnosis of MPNST in NF1 patients is 26 years, compared to 62 years in sporadic cases.[21] Standard therapy for MPNST lesions includes surgical resection followed by adjuvant RT, especially in lesions larger than 5 cm in size or with residual tumor. Chemotherapy regimens are similar to those of soft-tissue sarcomas and generally consist of an anthracycline plus ifosfamide,[10] although they may be less effective in NF1 patients.[11]

Given the limited adjuvant treatment options, efforts have been made in targeting pathways regulated by the NF1 protein or other associated mutations. Such targets include tyrosine kinase receptor,[19] epidermal growth factor receptors,[1] platelet-derived growth factor receptor,[5] and Ras/Raf signaling,[16] among others. Inhibition of mTOR signaling has previously been identified as a transiently effective therapy for delaying tumor growth.[13] Ras/Raf/MEK/ERK signaling has been reported to be essential in the pathogenesis of MPNST, and preclinical data support that MEK inhibition may have an anti-tumor effect.[12] As such, there has been enthusiasm in evaluating the efficacy of combination therapies to target different pathways. For example, there is an ongoing Phase II clinical trial evaluating combination therapy with both a MEK and mTOR inhibitor (NCT03433183).

Lesions that arise in the context of NF1 are more likely to metastasize earlier than sporadic cases, although the rate of metastatic disease at presentation is similar among the two groups (10.4%).[18] Furthermore, 5-year survival in cases of MPNST is 21–35% with NF1 cooccurrence and 42–50% in sporadic cases.[7] The prognosis for patients with radiation-induced MPNSTs is also poor, with lower overall survival due to distant metastases and earlier disease progression.[18] In one study, the 5-year overall survival rate for radiation-induced MPNSTs was 23.5%, compared to 58.5% for sporadic tumors.[18] Older adults have poorer prognosis than younger adults or children with regards to progression-free and overall survival rates.[18]

CONCLUSION

We have presented the case of a woman with a history of NF1 and remote trigeminal MPNST who presented with an intramedullary spinal cord MPNST. Interestingly, her trigeminal MPNST predated the spinal cord MPNST by 4 years, questioning whether the spinal lesion was metastatic or arose *de novo*. In addition, this lesion developed outside of the field of previous RT. To the best of our knowledge, this is the third reported case of intramedullary spinal cord MPNST, and the first case in a patient with NF1 and previous trigeminal MPNST. Close clinical follow-up and imaging of the entire neuraxis should be performed when clinically indicated in this challenging patient population.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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