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Case Report

Multifocal malignant peripheral nerve sheath tumor in patients with neurofibromatosis type I: Report of two cases and review of literature

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ABSTRACT

Background: Malignant peripheral nerve sheath tumors (MPNSTs) are one of the rarest soft-tissue sarcomas with a prevalence of 0.001% in the general population. It is closely associated with a unique neurocutaneous stigmata under the spectrum of the dermatological manifestations of neurofibromatosis type 1 (NF1). Almost 81% of MPNST arises from a precursor neuroma, and multifocality of these lesions is extremely rare, making up to 0.001% of cases. Moreover, spinal cases are extremely uncommon with only four cases reported internationally. Here, we present the fifth and sixth spinal MPNST cases with a brief review of literature.

Case Description: We describe two unusual cases of multifocal MPNST in relation to NF1 occurring in the spinal cord. Both patients presented with local pain and myelopathic symptoms. The two patients underwent wide surgical resection, followed by neoadjuvant radiotherapy and reported immediate postoperative improvement of the presented complaint; however, one patient suffered from rapid recurrence and metastasis.

Conclusion: Due to the scarcity of spinal cases related to MPNST, no clear guidelines regarding the management of these cases are set in the literature. Histopathological diagnosis remains as the most pivotal diagnostic tool as they can mimic other peripheral nerve sheath lesions, such as neuromas and schwannomas, in imaging. Cases that were managed by early surgical intervention in addition to neoadjuvant radiotherapy reported the best outcome. However, cases of MPNST in concomitance with NF1 were found to be resistant to both chemo and radiotherapy and have high recurrence rate.

Keywords: Malignant peripheral nerve sheath tumor, Neurofibromatosis, Neuro-oncology, Neurosarcoma, Peripheral nerve tumor

INTRODUCTION

Neurofibromatosis is a neurocutaneous syndrome that causes the individual to develop a wide spectrum of pathologies, including multiple painless nodules, referred to as neurofibromas, as a result of mutation – both as inherited autosomal dominant trait or sporadic mutation – in the tumor-suppressor gene. There are two types of this syndrome: Type 1 and 2. Neurofibromatosis type 1 (NF1), also known as Recklinghausen syndrome, is the most prevalent of the two with an incidence rate of 1:2,500–3,000.[4] In NF1, the mutation is located on the 17th chromosome that encodes for the neurofibromin proteins with a 100% penetrance, resulting in complete loss of

function. It is known that the rare occurrence of malignant peripheral nerve sheath tumors (MPNSTs) in the background of NF1 is associated with a lifetime risk of developing MPNST in up to 13% of NF1 patients.[2] In this study, we describe two case reports of unusual multifocal MPNST occurring in the background of NF1 with a brief literature review.

CASE DESCRIPTION

Case 1

A 50-year-old male who was medically and surgically free with cutaneous stigmata of neurofibromatosis type I since birth. The patient presented with 3 months' history of backache and left femoral nerve distribution neuropathic pain and claudication with intact sensory/motor/sphincter performance. On examination, he was found to have cutaneous stigmata of NF1, congenital left 6th cranial nerve palsy, and left posterior thigh mass; but otherwise, he was neurologically intact with no long tract signs. A radiological assessment with magnetic resonance imaging (MRI) brain scan showed diffusely increased leptomeningeal enhancement and multiple numerous enhancing nodules in the scalp. An MRI of the cervical spine displayed a hyperintense well-circumscribed mass in the right carotid space in the neck extending from C1 to T1 levels. It measures 4.8 × 4.9 cm in the anterior-posterior and transverse planes, respectively [Figure 1a]. It is predominantly T2 hyperintense with peripheral T2 hypointense with thick, irregular rim showing enhancement. An MRI of the lumbar spine revealed an additional large T2 hyperintense with a well-circumscribed mass centered in the left neural foramen of the L2 vertebra (L2/L3), extending to L1/L2 foramen with a large intraspinal extradural component and an extraspinal component extending into the left paravertebral muscles with a tumor bulk measuring 6.2 × 2.9 × 5.9 cm in the anterior-posterior, transverse, and craniocaudal planes, respectively [Figure 1b]. The patient underwent a computed tomography (CT)-guided biopsy of the lumbar lesion, which confirmed the presence of a malignant peripheral nerve sheath tumor (grade II). After discussing with the neuro-oncology tumor board, the patient agreed to undergo a surgical resection. The patient underwent a two-stage surgery, starting with the anterior cervical approach with an uneventful gross total resection of the cervical lesion removing 22 lymph nodes. The patient was kept intubated, and the following day, a procedure was performed with a posterior thoracolumbar approach with L2 corpectomy and fixation from T10 to L4 and a subtotal resection of the tumor, leaving a small residual on the nerve roots. Postoperatively, the patient had an intact neurological performance, noting an improvement in his pain levels. Re-assessment of the cervical and lumbar lesion re-confirmed the diagnosis of MPNST grade II with negative lymph nodes in the neck. The tumor board recommended a referral to a radiation oncology for an adjuvant external beam radiation therapy (EBRT). The patient is currently still undergoing EBRT and following up with neurosurgery. Radiological follow-up after radiation showed regression in the spinal residual, maintaining the same intact neurological performance.

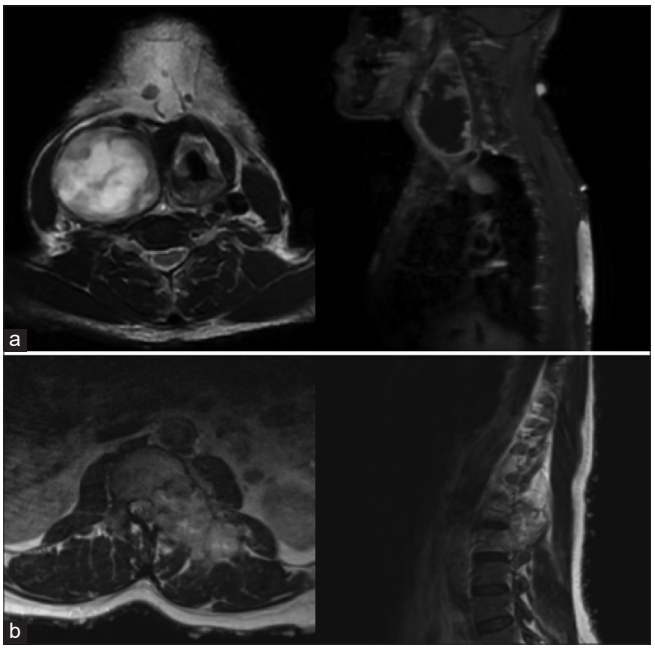

Figure 1: (a) Preoperative axial and sagittal cut of magnetic resonance imaging (MRI) (T2) cervical spine showing a well-defined heterogeneous mass in the right carotid space in the neck extending from C1 to T1 levels. (b) Preoperative axial and sagittal cut of MRI (T2) lumbar spine showing another a large intraspinal extradural mass with similar intensity in the lumbar spine at the level of L1–L3. There is scalloping and sclerosis as well as abnormal enhancement of the L2 vertebral body secondary to tumor involvement.

Case 2

Patient information

A 27-year-old female who was recorded to have NF1 syndrome 6 years ago, who underwent two previous surgeries for the removal of peripheral neural tumor grade II in the left arm and the right retropharyngeal space, and is currently being followed for spinal neuroma, presented with an ongoing right lower limb weakness for 7 months now. An examination of her appearance revealed a healthy-looking female with multiple cafe au lait spots. Examination of the left lower limb revealed power of -4/5 all over and hyporeflexia. The rest of the neurological examination was unremarkable. Her abdomen was soft and lax with a palpable solid mass in the right upper quadrant extending to the right flank area with minimal tenderness. An MRI brain scan showed a stable hyperintensity focus on T2 within the

left occipital lobe, which was stable since November 2016 and a bilateral globus pallidus hamartoma that is larger in the right side [Figure 2a]. An initial contrasted MRI of the spine revealed a homogeneously enhancing right paraspinal extraforaminal mass at levels L3–4 that is mostly a neurofibroma. The mass measured 6.6 × 7.6 × 8.7 cm in the anterior-posterior, transverse, and craniocaudal planes, respectively, and extended transforaminal to the abdomen [Figure 2b]. On follow-up, the mass was showing interval progression in its size (8.7 × 8.9 × 9.7 cm in the same planes, respectively). It is caused a widening and remodeling of the right neural foramina with an encasement of the existing nerve roots (L3). It also induced a mass effect on the abdominal structures, mainly pushing the inferior border of the right kidney. There was no change in the signal characteristics and it maintained heterogeneous enhancement. There was no interval development of new spinal lesions. The vertebral alignment, the vertebral height, and the intervertebral disc spaces were preserved. Moreover, there was no abnormal bone marrow signal intensity. The patient was admitted for peripheral nerve tumor sheath resection of the right leg and the retroperitoneal resection of the lumbar MPNST. Intraoperatively, the right tibial nerve showed decreased amplitude throughout the procedures, and the motor response was transient but went back to normal. Postoperatively, the patient complained of pain on the surgical site and reported motor function improvement in the right leg (5/5) with mild restriction in the left lower limb due to pain (2/5). The patient was discharged and sent home with a referral to radiation oncology for neoadjuvant radiotherapy. Four months later, the patient experienced worsening in the hoarseness of her voice. An MRI scan showed recurrence in the right retropharyngeal MPNST measuring 3.3 × 2.1 × 5.1 cm in the anterior-posterior, transverse, and craniocaudal planes, respectively [Figure 2c]. She was admitted for surgical resection using a transcervical submandibular approach and then discharged home after a short, uneventful stay in the general ward. The hoarseness in her voice improved, she tolerated orally with aspiration to thin liquids only. The patient continued with the radiation therapy. Two months later, she was readmitted for recurrent peripheral nerve tumor sheath resection on the right common peroneal nerve. A local examination of the right leg showed a large, hard, tender, and round swelling behind the knee measuring 10 × 10 cm. There were no skin changes, the previous wound healed well, and the power in both lower limbs (+4/5) was limited by pain. The rest of the examination was unremarkable. An MRI of the right leg showed multiple posterior deep compartment lesions representing a recurrence of the nerve sheath tumor. She was admitted again for another surgery of the right leg. Surgery was uneventful, and the patient had a short stay in the high dependency unit for blood pressure monitoring. She was then shifted to the general ward the next day and discharged

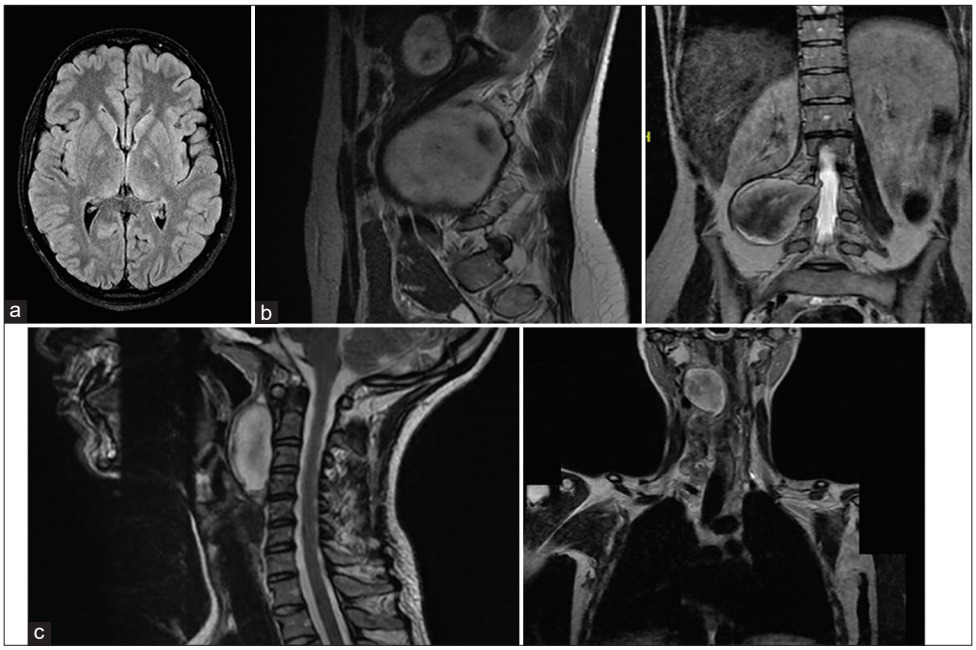

Figure 2: (a) Axial cut of magnetic resonance imaging (MRI) brain (fluid-attenuated inversion recovery) showing bilateral hamartoma in globus pallidus. (b) Preoperative sagittal and coronal cut MRI T2 of lumbar spine showing an ill-defined mass at the level of L3–5. (c) Preoperative sagittal and coronal cut MRI T2 of the cervical spine showing a predominantly hypodense well-defined mass found in the right retropharyngeal space.

Table 1: The reported cases in literature of spinal Malignant peripheral nerve sheath tumor (MPNST).

Reference	Case description	Identifiable risk factors	Location	Histopathology	Type of intervention	Outcome
Cunha KS, *et al.*[2]	23 F	-	Sacrum and spine	High grade	Radiation	Survived for 7 months followed by Lung metastasis then deceased.
Christi A, *et al.*[1]	43 M	-	Thoracic spine	High grade	Resection and radiation	Survived by 18 months then the patient was bedridden with loss of bladder control.
Newell C, *et al.*[7]	35 F	NF1	Cranial nerves and Lumbar spine	High grade	Resection. Mets radiation	Passed away at the age of 36.
V.R Roopesh Kumar, *et al.*[9]	40 M	HIV	Spinal		Resection	Metastasis occurred 3 months later. received palliative radiotherapy for spinal recurrence and cerebral metastasis.

F: Female, M: Male, NF1: Neurofibromatosis type 1, HIV: Human immunodeficiency virus

home with an improvement in power of the right lower limb. On further discussion with the tumor board, the patient was planned for adjuvant radiotherapy and serial follow-up with MRI. Before commencing with radiotherapy, the patient did an MRI for the right lower limb, which showed a large multi-lobulated mass measuring approximately 9.1 × 6.8 × 15.4 cm, encircling the popliteal fossa vascular component and extending to the upper aspect of the leg at the level of the femoral condyles. She was evaluated by the orthopedic oncology team and was recommended for an above-knee amputation, but she was reluctant. Neurosurgery discussed the option of palliative resection of the recurrent tumor after chemotherapy. After receiving four cycles of doxorubicin and ifosfamide, an MRI scan showed a rapid increase in size of the mass with large, necrotic, cystic, and peripherally enhancing components. CT chest-abdomen-pelvis showed interval stability of the right upper thoracic paravertebral soft-tissue lesion extending into the lower neck and bilateral paratracheal lobulated soft-tissue nodules, most likely presenting as neurofibromas. The patient will continue with her chemotherapy with the addition of goserelin injection.

DISCUSSION

MPNSTs, previously known as neurological sarcoma or neurofibrosarcoma, are rare, aggressive, and rapidly progressive soft-tissue carcinoma with an incident of only 0.001% in the general population.[3] They make up 10% of peripheral nerve lesions, although MPNST is not inclusive of tumors originating from the epineurium or the vasculature of the peripheral nerves. They can occur any time between the second and fifth decade of life. About 90% of MPNST cases are primary, of which 50% are associated with NF1 syndrome[3] as 81% arise from a precursor plexiform neurofibroma.[4] MPNST associated with NF syndrome are detected earlier, for instance, during the second decade of life, present as central lesions, and behave more aggressively with high malignancy markers in histopathology.[3,4] The remainder 40% accounted for are sporadic cases arising from *de novo* mutations, which are currently being investigated.[4] Secondary MPNST comprises about 10% of recorded cases and is typically encountered in post radiation patients.[4] Multifocality is extremely rare, making up only 0.001% of the cases, with only six cases reported internationally.[3,5] The etiology behind such unique lesions is poorly understood due to the wide genomic defects related to it and the involvement of multiple pathways. Studies showed that downregulation in the tumor protein p53 (TP53) gene has been prominently associated with MPNST development.[4,5]

Clinical presentation varies depending on the location and size of the MPNST. Most commonly, patients will present with rapidly expanding mass, neuropathic pain, and local neurological defects (weakness or paresthesia). The duration of the onset of symptoms ranges from months to years[3] MPNST frequently involves large nerve roots and bundles in the extremities (i.e., brachial plexus) and pelvis (i.e., sciatic nerve), most commonly affecting the sciatic nerve.[3] Areas of previous irradiation are also frequently affected with a mean latency period of 16 years post radiotherapy.[3] In addition, cranial nerves are rarely involved, and they arise almost exclusively from preexisting schwannoma rather than neurofibroma.[5,10] Spinal cases are extremely uncommon with only four cases reported internationally.[1,7,11] Our cases are the fifth and sixth spinal MPNST [Table 1].

Establishing an accurate diagnosis from imaging is a major challenge. Contrasted MRI is the preferred modality in diagnosing and surgical planning of MPNST. Some case reports even utilized whole body MRI (WB-MRI) to identify any synchronous lesions for grading.[8] Typically, MPNST appears as a well-defined heterogeneous mass that is isointense on T1 and hypointense on T2 heterogeneous with a homogenous enhancement pattern on a contrasted study. The average size of the mass at the time of diagnosis is >5 cm with rapid growth

in the interval imaging.[4] Infiltration into the surrounding tissue is also common. The size of the mass is found to have a positive correlation to the malignancy of the tumor. Despite recent advances in MRI modalities, it is still difficult to differentiate MPNST from its premalignant precursor lesions or sarcomas. In such cases, positron-emission-tomography scan or scintigraphy can assess in distinguishing MPNST by showing a high uptake of nuclear material;[4] however, such extensive measures are rarely used.

As for the diagnostic workup, there are many techniques in retaining a tissue biopsy with no specific guidelines; however, excisional biopsy showed the least amount of false negative as other modalities may only show segments of the precursor benign lesion.[3] Except for MPNST with an association to NF1 syndrome, the diagnosis can only be made in the presence of evident features of Schwann cells differentiation. Histologically, MPNST is composed of interwoven fascicles of spindle cells arranged in a "herringbone" or an "S-shaped" pattern. There are various degrees of tumor cellularity, pleomorphism, and mitotic activity of these spindle cells – all of which affect grading. It should be noted that the majority of MPNSTs are high grade.[4] In case these findings were not evident in histopathology, then a microscopic electron ultrastructural study can be utilized. If diagnosis is still not established, immunohistochemistry can be used to identify expression of S-100 to prove Schwann cell differentiation.[3] There are three histopathological variants that are well-recognized in the literature: epithelioid MPNST, MPNST with perineural differentiation (malignant perineurioma), and MPNST with rhabdomyoblastic differentiation (malignant tritor tumor). Differentiating between these three variants is important in planning the treatment modalities as the rhabdomyoblastic subtype, for instance, is particularly aggressive and requires a combination of complete surgical resection and neoadjuvant chemo/radiation therapy.[3]

Early wide surgical resection remains pivotal in the treatment of MPNST. Cases that were managed with subtotal resection combined with adjuvant radiotherapy resulted in rapid recurrence and metastasis and ended with mortality. Wide excision alone achieved 43% survival rate; on the other hand, combining it with high-dose radiation achieved the best outcome with the lowest recurrence rates for patients. Thus, the latest literature suggests that adjuvant radiation should be given to all MPNST regardless of the stage of the disease to reduce the recurrence rates. It is important to note that some cases that were treated with local radiation later on developed radiation-induced sarcomas; as such, close follow-up is of extreme importance. For peripheral MPNST, amputation is considered the definitive management, but most cases ended in mortality as surgeries were delayed.[3] Advanced or metastatic MPNST cases carry a poor prognosis. Chemotherapy can be utilized to stabilize the disease; however, most cases associated with NF1 tend to be refractory.[4] The combination of doxorubicin and ifosfamide is frequently used as they have a response rate of up to 25%.[6] However, recent data suggest that MPNST responds better to the combination of carboplatin and etoposide for both sporadic and NF1 cases.[12]

MPNST generally carry poor prognosis, with high mortality rates reaching up to 68%[3] due to recurrent relapse, which can occur in 13 months, and with poor response to chemotherapy. MPNST secondary to irradiation are known to carry even worse prognosis independent of histologic type.[4] The 5-year survival with NF1 is 16% and with other groups at 53%.[3] Up to 50% of patients with NF1 present with metastatic disease, usually to the lungs, followed by soft tissue, bone, liver, abdominal cavity, mediastinum, and brain.[3,4] The poor prognostic factors include the following: correlation with NF1 syndrome, large size on presentation (>5 cm), location on trunk, surgical margin status, local recurrence, high-grade histological features, heterogeneous components on imaging, and a malignant tritor tumor variant. Molecular prognostics include p53 expression, Ak strain transforming (AKT), Target of Rapamycin (TOR), and the MNNG HOS transforming gene (MET) pathway activation,[3,4,9] with the size of the tumor on presentation being the most important prognostic factor.[4]

CONCLUSION

MPNST is a rare tumor that is closely related to NF1 syndrome. It presents as a large expansile mass that causes pain and local neurological defects due to its mass effect. Due to the scarcity of spinal cases involving MPNST, there is insufficient clinical experience that can be based on to set guidelines in their management. Moreover, WB-MRI proved to be the most useful modality in both diagnosis and grading. To this day, the gold standard in diagnosis remains to be histopathology. Radical excision with wide safe margins followed by adjuvant radiotherapy has the highest success rates in the reported cases. Further investigation is required to help better understand the behaviors of such obscure lesions and the future means of its management.

Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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