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CASE REPORT

A Rare Case of Primary Spinal Primitive Neuroectodermal Tumor with Long-term Follow-up

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ABSTRACT

Primary primitive neuroectodermal tumors (PNETs) of the spine are rare. There have been 108 reported cases in the literature. These are aggressive malignancies with poor survival rates even after surgery, chemotherapy, and radiation. Since this is a rare disease, there are no standard guidelines for the management of these malignancies. Long-term survival with these tumors is unusual. We report a case of a 47-year-old patient with a primary PNET with 12-year follow-up; this is the longest follow-up recorded in literature.

Keywords: Chemotherapy, Cluster of differentiation 99, Primitive neuroectodermal tumors, Spinal cord.

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CASE REPORT

A 47-year-old male was admitted with complaints of progressive weakness of the lower limbs of 1 month duration without any history of sphincter involvement. The patient had earlier been operated 12 years ago for an intradural extramedullary tumor of the dorsal (D) spine extending from D6 to D10 and had undergone total excision. The biopsy was reported to be a PNET since it showed a cellular tumor composed of sheets of small, round, primitive appearing cells with monomorphic darkly staining round nuclei, small nucleoli, and scant cytoplasm (Fig. 1). Tumor cells showed strong positivity for cluster of differentiation (CD)99 membrane protein (Fig. 2). Synaptophysin was not expressed by the tumor and the Ki-67 proliferation index was 28%. Postoperatively, the patient had received chemotherapy using vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide for six cycles. This was followed by external radiation of 41.4 Gy in 23 fractions to the dorsal spine. He was asymptomatic for 12 years after treatment until his symptoms recurred a month ago.

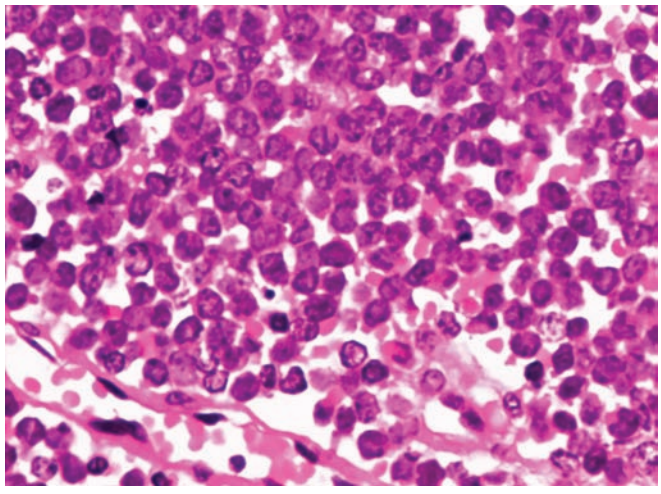

Fig. 1: Histology of the tumor showing sheets of small round tumor cells with prominent darkly staining nuclei, apoptotic bodies, and scant cytoplasm. Hematoxylin and eosin-stained magnification, 100×

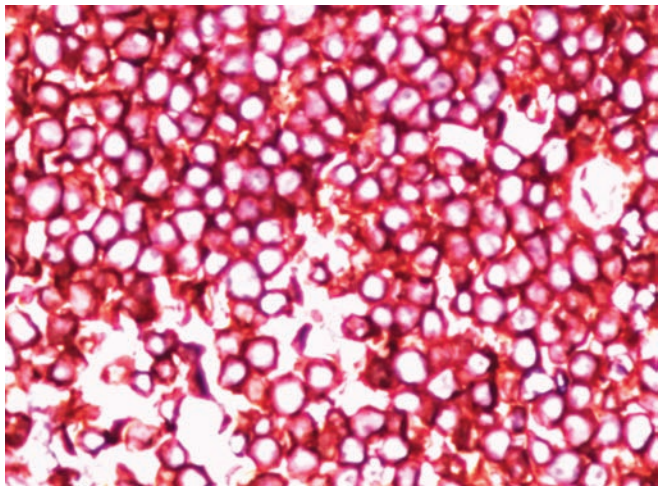

Fig. 2: Cells showing positivity for CD99 membrane protein. Magnification 400×

On examination, he had increased tone in the lower limbs, with the lower limb power being 4/5 on the right and 3/5 on the left with exaggerated deep tendon reflexes in the lower limb and a bilateral positive Babinski's sign. He had decreased sensation for pain and touch below the D6 dermatome. The patient was evaluated with a magnetic resonance imaging (MRI) of the dorsal spine along with a whole-body fluorine 18-labeled fluorodeoxyglucose (FDG) positron emission tomography (PET)

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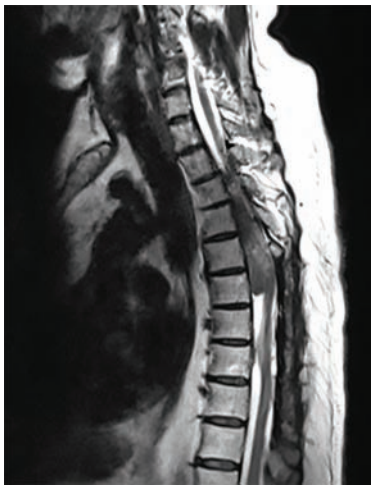

Fig. 3: Sagittal T2-weighted MRI image of the dorsal spine showing heterogeneous intensity of the lesion

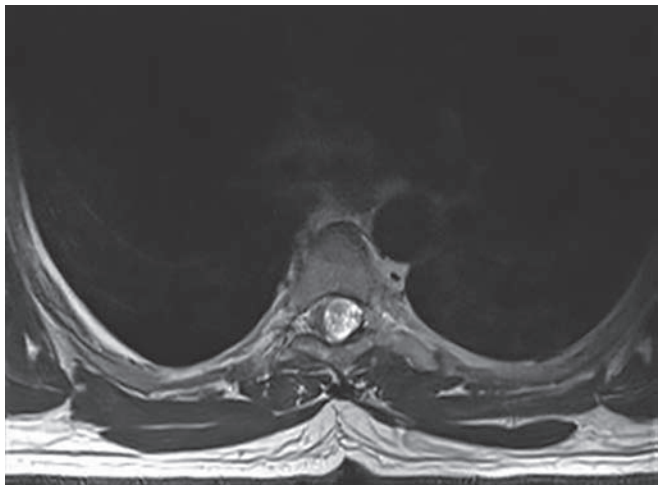

Fig. 4: Axial contrast MRI image of the dorsal spine showing bright contrast enhancement of the intradural extramedullary tumor

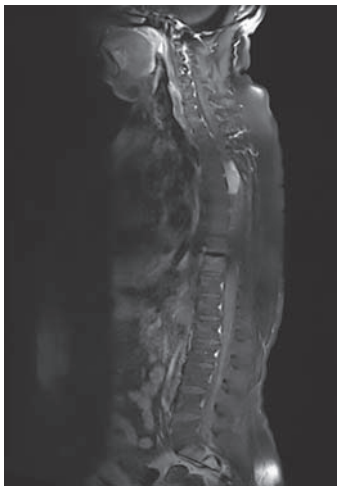

Fig. 5: Sagittal contrast MRI image of the spine showing bright enhancement of the tumor

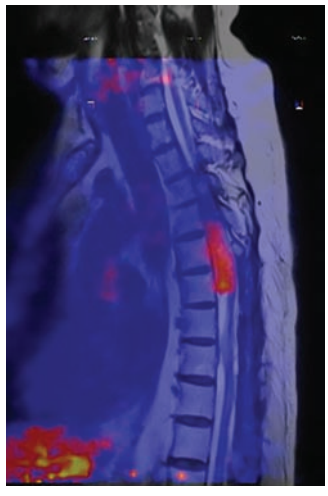

Fig. 6: The PET MRI scan image showing isotope uptake of the tumor

MRI scan. The MRI of the spine revealed an intradural extramedullary recurrence of the tumor at D4 to D6 level. The lesion was heterogeneously hypointense on T1-weighted images and heterogeneously hyperintense on T2-weighted images (Fig. 3) with bright homogeneous contrast enhancement (Figs 4 and 5). The lesion showed FDG uptake on PET MRI images without any spread beyond the local site (Fig. 6).

The patient was taken up for surgery and the dorsal spine explored in the prone position. Intraoperatively, the lesion appeared intradural extramedullary, reddish, soft, and vascular with adhesions to the cord. Gross total excision could be achieved and small bits of tumor tissue adherent to the cord had to be left behind. Postoperatively, the patient had recovered well and regained 4/5 power in both the lower limbs within 2 weeks of the surgery and was able to walk with support. He was administered chemotherapy again with vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide. Having completed five cycles of chemotherapy, he has not shown any worsening of neurological status. The patient's cerebrospinal fluid was positive for malignant cells. He was thus given intrathecal methotrexate also followed by radiation to the spine. He received 27 Gy in 15 fractions for the dorsal spine.

DISCUSSION

Primary PNETs of the spine are an extremely rare group of neoplasms arising from the pluripotent neural crest cells.[1] As per our literature search, 108 cases of primary spinal PNET have been reported worldwide with age ranging from 4 months to 70 years. The PNETs are malignant neoplasms that occur mostly in childhood and early adulthood. Even though these tumors are found both in children and adults, 80% of tumors occur in less than 15 years of age with a male sex predominance of 2:1.[2-6] The nomenclature and criteria for diagnosing PNET were formally introduced by Hart and Earle.[7] These tumors can be

classified as central PNETs (cPNET) or peripheral PNETs (pPNET). The cPNETs need to be differentiated from the pPNETs because of the differences in the biology of tumor growth and their dissemination. The cPNETs very rarely metastasize outside the central nervous system, but disseminate via the CSF pathway in 10 to 30% cases However, pPNETs may metastasize to the brain or extraspinally to the bone, lung, liver, or cervical nodes.[8] Radiation therapy is also given to limited areas of the spine in pPNETs whereas in cPNETs, the entire neuroaxis is irradiated. There is also a difference in the chemotherapy regimens followed based on the classification.[4,9,10]

Contrast MRI is the imaging modality of choice in detecting spinal PNETs; however, there are no pathognomonic features, and findings may vary from case to case. Spinal PNETs are typically hypo- to isointense on T1-weighted MRI and iso- to hyperintense on T2-weighted imaging. There is often minimal contrast enhancement and, less frequently, the appearance of cystic regions. Whole-body FDG PET-CT/MRI is another useful investigation since it can be helpful in detecting metastatic disease and tumor progression. Primary spinal PNETs may metastasize to the brain or extraspinally to the bone, lung, liver, or cervical nodes. Spinal PNETs can be metastatic from extraspinal primary lesions at presentation. Therefore, evaluating the extent of disease by means of FDG PET MRI is important.[11-13] The differential diagnosis includes central PNET, malignant meningioma, neuroblastoma, and lymphoma.[14,15]

The histopathologic diagnosis of this tumor is complex and has led to a variety of treatment approaches. Histologically, PNET cells exhibit a primitive, poorly differentiated morphology with varying degrees of pleomorphism and occasional evidence of neuroectodermal differentiation. Histological analysis alone is not sufficient for diagnosis. The diagnosis of pPNETs requires immunohistochemical analysis.[2,16] Immunohistochemically, tumor cells are positive for CD99 and HBA71 in pPNETs. Immunoreactivity for synaptophysin, NSE, S100, and neurofilament indicate neuroectodermal differentiation.[14]

Upregulation of the *MIC2* gene in pPNETs results in a high degree of expression of the transmembrane glycoprotein CD99, which is rarely expressed in cPNETs. Although this is a useful and important differentiating feature, it is not specific.[2] Cytogenetic studies demonstrate the characteristic translocation t (11; 22) (q24, q12) in more than 90% cases of pPNETs.[2] Most commonly, this involves a rearrangement of the Ewing's sarcoma gene (EWS) located on chromosome 22 with an ets family gene; either a friend leukemia insertion (FLI) 1 located on chromosome 11 (85%) or an ets related gene (ERG) located on chromosome 21 (10%). This is a strong diagnostic tool to differentiate between pPNETs and cPNETs. Using either reverse transcription polymerase chain reaction or fluorescence in situ hybridization, the presence of this translocation may be confirmed.[2,8]

Most reported cases have undergone surgical debulking followed by multipotent chemotherapy, which has been the preferred treatment option. Radiation has been used as an adjuvant for residual disease.[14,16] With radiation, there is also a concern of spinal cord damage to the growing spine in the young age group as more than 80% of the reported cases of PNETs have been below the age of 15 years.

We believe that our patient had a longer disease-free survival probably because he was a middle-aged man, who underwent total excision of the tumor and had a relatively lower Ki-67 labeling index of 28%. On completion of his chemotherapy cycles, he was offered radiotherapy even though there was absence of any residual disease. All these factors contributed to a better outcome. At present, due to their low incidence, there are currently no standard clinical guidelines outlining their management[2] However by employing surgical resection followed by multiagent chemotherapy using vincristine, doxorubicin, cyclophosphamide alternating with etoposide and ifosfamide[14,16] thereafter followed by radiotherapy may help patients have a longer disease free survival.

CONCLUSION

Whole-body imaging using PET MRI or PET CT is necessary to rule out a metastatic disease or a cPNET with a spinal metastasis. In order to confirm a diagnosis of primary spinal PNET, histopathology alone is not sufficient; immunohistochemistry analyses are mandatory. The presence of the t (11; 22) (q24, q12) chromosomal translocation helps in supporting the diagnosis of pPNET. Due to the rarity of disease, no therapeutic protocol exists, but a multimodality treatment option using surgical reduction of tumor volume, chemotherapy, and radiation does give a long-term progression-free survival to patients.

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