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Case Report

Cervicomedullary primitive neuroectodermal tumor of the spine: Case report

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Abstract

Background: Intramedullary primitive neuroectodermal tumors (PNETs) are tumors found rarely in the cervical region, with only five such cases described in the literature. The available literature contains only one report regarding cervicomedullary junction PNET.

Case Description: The authors present a case report of a 45-year-old male patient who had undergone urgent hospitalization owing to progressive tetraparesis and subtle impairment of respiratory function. He underwent magnetic resonance imaging, which showed an extensive enhancing cervical intramedullary tumor extending from C5 to the bulbar region. Since he developed severe impairment of respiratory function, he required tracheostomy. He then underwent microsurgery 2 days after his admission, and a partial tumor resection was performed. The pathological diagnosis of PNET of the cervicomedullary junction (CMJ) was made. He had slight worsening of strength after surgery with subsequent deterioration over the next 3 weeks. The tumor displayed aggressive growth; thus, radiotherapy was indicated. Unfortunately, he developed severe febrile neutropenia and died after 2 weeks of radiotherapy. Given the rarity of the condition, we wish to review the epidemiology, pathophysiology, and treatment options of his population.

Conclusion: Intramedullary PNETs of the cervical spine and CMJ are exceedingly rare in adults; treatment of such patients remains a challenge, despite the modern neurosurgical armamentarium that is available.

Key Words: Cervicomedullary, intramedullary, neuroectodermal tumor, pathology, primitive, treatment

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INTRODUCTION

Primary tumors of the spinal cord represent only approximately 2%–4% of all primary tumors of the central nervous system (CNS); these spinal cord tumors can be divided into three anatomical categories: intramedullary, intradural extramedullary, and extradural.[4,6,8] Of those, purely intramedullary spinal cord tumors represent approximately 8%–10% of all primary tumors of the spinal cord[18] and most tumors that occur in adults are one of the following three pathologies: ependymoma, astrocytoma, or hemangioblastoma.[15] Less frequent types of primary tumors such as primitive neuroectodermal tumors (PNETs) have an even lower overall incidence in adults, which is estimated at ~0.62 per million in the US population[20] and are even less frequently located in the spinal cord proper, with ~107 such cases described in the literature.[9,13]

Spinal PNETs are further subclassified as a central subtype developing within the spinal cord and a peripheral subtype mainly occurring in the cauda equina.[13] The lumbar region is affected twice as often as are the thoracic and cervical spine.[19] There have also been reports of 18 cases of extradural PNETs that occurred in the cervical region.[13] There are five cases of exclusively cervical intramedullary spinal PNETs [Table 1] and 25 primary intradural intramedullary PNETs in the current literature.[7,10,12,16,20,22] However, there is only one report of PNET afflicting the cervicomedullary junction. In this paper, we report a case of intraspinal PNET of the cervical spine and cervicomedullary region and review important aspects of this pathology.

MATERIALS AND METHODS

Through January 2018, a database search was performed through PubMed, ScienceDirect, EMBASE, and SciELO in order to identify eligible articles for the review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were strictly followed throughout this review.

Search strategy

Studies were deemed eligible for inclusion if they report cervical intramedullary spinal PNET. The keywords used were "spinal cord neoplasms," and "primitive neuroectodermal tumors." The exclusion criteria included involvement of the thoracic, lumbar, or sacral levels.

Table 1: Exclusively cervical intramedullary spinal PNETs

Case no	Author(s)	Age (year)/sex	Tumor level	Radiographic appearance (MRI)	Pathological staining patterns	Treatment course	Survival
1	Jain *et al*. (2006)[10]	54/F	C2-C5	The cord was enlarged and an exophytic component of the mass extended left into the subarachnoid space T1-iso- to hypointense T2-hyperintense Contrast enhancing	MIC2, MYCC, MYCN, Trk-c, B-catenin (−) Synapthophysin (+)	S + RT	Patient was still living at the timing the source article was written
2	Kampman *et al*. (2006)[12]	3/M	C2-C6	Perifocal edema Contrast enhancing	Focal synapthophysin GFAP (+) CD99 (−)	S	7 days
3	Ellis *et al*. (2011)[7]	27/M	C5-C7	T1-hypointense T2-hyperintense Contrast enhancing	GFAP (+) Synapthophysin (+) CD99 (−)	S + CT	Patient was still living at the time the source article was written
4	Mulholland *et al*. (2011)[16]	27/M	Medulla-C4	No description	GFAP (+) Synapthophysin (+) CD99 (+)	S+CT	3 months
5	Sharma *et al*. (2016)[20]	11/M	C3-C6	T1/T2-hypointense Contrast enhancing	CD99 (+)*	Partial resection	The patient succumbed to sepsis, secondary to chest infection
Index case	Nery *et al*. (2018)	45/M	Bulbar region-C5	T1-hypointense T2-hyperintense Contrast enhancing	AE1/AE3, Fli-1, S-100, and vimentin (+) CAM 5-2, CD-34, EMA, GFAP, HMB15, and Melan A (−)	Partial resection +R	5 weeks

PNET=Primitive neuroectodermal tumor, MRI=Magnetic resonance imaging, F=Female, M=Male, R=Radiotherapy, S=Surgery. *The diagnosis of pPNET was made, although full battery of immunohistochemical and other tests were not performed, RT=Radiotherapy, CT=Chemotherapy

RESULTS

A summary of the flow of studies through the review is presented in Figure 1.

CASE DESCRIPTION

In 2013, a 45-year-old male patient experienced progressive tetraparesis over about 1 week, which led him to seek medical attention. Based on the currently available British medical research council (MRC) grading system, neurosurgical evaluation revealed grade IV tetraparesis and global hyperreflexia with pyramidal liberation. Therefore, urgent brain and cervical spine magnetic resonance imaging (MRI) was requested, but he did not undergo said exam on the same day.

Four days after his first medical visit, he represented with subtle respiratory impairment, for which he was urgently admitted to our hospital for evaluation. An MRI was expeditiously obtained and showed an intramedullary lesion extending from the C5 level to the bulbar region with heterogeneous appearance and hypointense signal on T1-weigthed imaging, and without cystic or calcified components [Figure 2]. T2-weighted images showed a heterogeneous hyperintense intramedullary lesion, featuring signs of invasion of the bulbar region; administration of MRI contrast agent showed significant enhancement of the lesion [Figure 3]. Use of STIR sequences did not show an adipomatous component of the lesion [Figure 3]. Neuroaxial MRI did not show any additional lesions. He did have to undergo tracheostomy placement on the day of admission and underwent partial resection of the cervical lesion on the next day. Microsurgical resection was limited since intraoperative monitoring showed discrete evoked motor potential worsening during the case. After surgery, the patient displayed a discrete loss of motor function with global grade III tetraparesis but the remainder of the postop course was uneventful. The worsening of motor function of the patient has occurred due to surgical manipulation and by tumor aggressiveness. Histopathological analysis showed a high number of small blue cells in loose arrangement, scarce cytoplasm, round hyperchromatic nuclei, and perivascular pseudorosette formation [Figure 4].

Immunohistochemical analysis revealed positive staining for the following markers: AE1/AE3, Fli-1, S-100, and vimentin. Besides this, CAM 5-2, CD-34, EMA, GFAP,

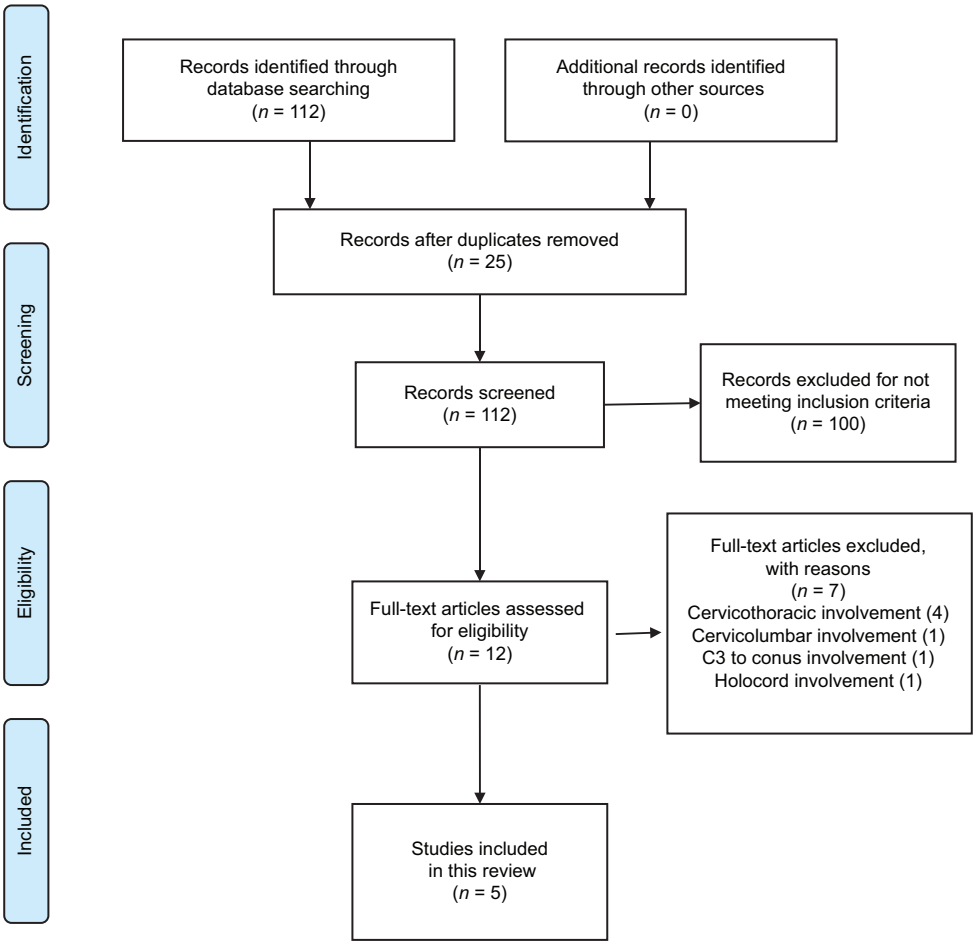

Figure 1: Flowchart showing the identification and selection process of studies included in this review

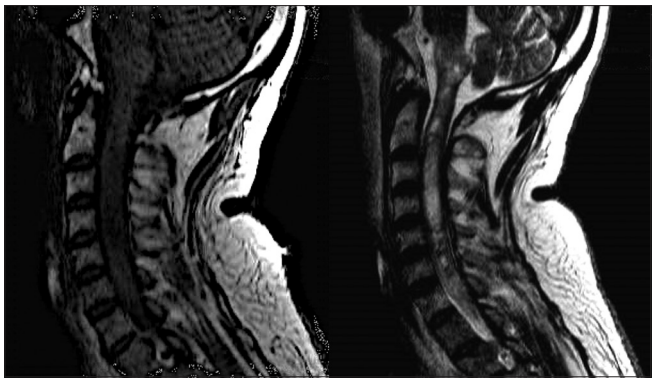

Figure 2: Magnetic resonance imaging scan showed an intramedullary lesion extending from the C5 level to the bulbar region, with hypointense and hyperintense signal in T1- and T2-weighted images, respectively

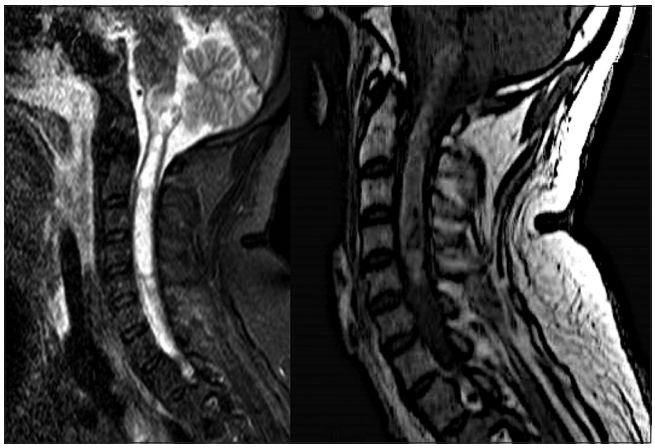

Figure 3: Magnetic resonance imaging scan showed an intramedullary lesion extending from the C5 level to the bulbar region, showing the absence of an adipomatous component in the tumoral lesion and exquisite enhancement with the STIR sequence and after gadolinium administration, respectively

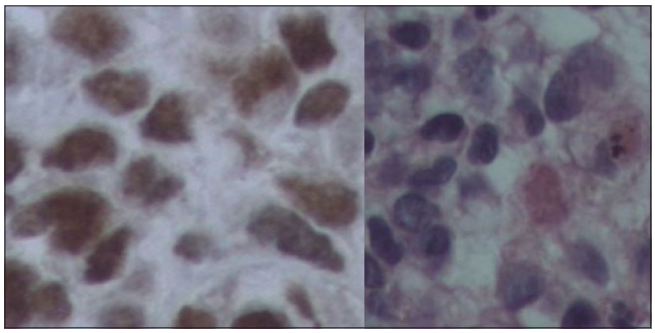

Figure 4: Histopathological analysis showed a high amount of small cells with loose arrangement, scarce cytoplasm, round hyperchromatic nuclei, and perivascular pseudorosette deposition

HMB15, and Melan A stains were negative. Ten percent of the analyzed cells were positive for Ki-67, and the pathological characteristics were thought to be the most compatible with PNET.

Unfortunately, 3 weeks after establishing the diagnosis, he presented with severe worsening of motor and respiratory function, and with significant progression of the lesion on imaging, and he was subsequently referred for radiotherapy as adjuvant therapy. Due to clinical worsening, radiation of the neuroaxis was given only with 1,620 centigray. After 2 weeks of radiotherapy, he developed severe febrile neutropenia, and despite aggressive treatment, he died during the hospitalization.

DISCUSSION

Primary spinal cord tumors (PSCT) comprise 2%–4% of all primary nervous system tumors and are ~15 times less frequent than comparable primary intracranial tumors.[4,9] Based on their anatomical compartment, PSCTs are divided into three main categories: extradural, intradural extramedullary, and intradural intramedullary tumors. Extradural tumors mainly consist of secondary metastases; in contrast, intradural extramedullary tumors mainly consist of meningiomas (50%) and peripheral nerve sheath tumors (50%).[4,21] Intramedullary spinal cord tumors represent only 8%–10% of all primary spinal cord tumors, with the majority represented by gliomas, of which 60%–70% are ependymomas and 30%–40% are astrocytomas.[18]

Intramedullary tumors present with variable clinical manifestations such as pain and mixed sensorimotor or syringomyelic disturbances; furthermore, intramedullary tumors are often accompanied by dissociation of pain/temperature and proprioception. Purely intramedullary primary tumors are rare; PSCTs more commonly involve the thoracic and lumbar spine.

Here, we present a rare, purely intramedullary PNET in a unique location and this constitutes the second report of such a PNET involving the cervical spine and bulbar region.

Hart and Earle were responsible for creating the term "primary neuroectodermal tumors" in 1973 to describe predominantly undifferentiated brain tumors containing 90%–95% undifferentiated cells and not meeting diagnostic criteria for other tumor entities.[1] Ten years later, Rorke, Becker, and Hinton independently argued that all tumors of the CNS predominantly composed of primitive neuroepithelial cells should be called PNETs.

PNETs were first defined as a new tumor entity in the World Health Organization Classification from 2007, which defines a PNET as an embryonic tumor composed of undifferentiated or poorly differentiated neuroepithelial cells that have the ability to exhibit a divergent differentiation along neuronal, ependymal, muscular, or melanocytic lines.[1,3]

Spinal PNETs occur most often in children[18] but may occasionally also appear in adulthood.[16] Whether there is a difference that is prevalence between sexes has not

yet been fully established and is inconsistent across in different reports.[2,5,10] The average age of presentation for patients with intraspinal PNETs was reported to be 24.1 years (but varying from 3 months to 69 years); this mean age is considered to be much higher than that for intracranial PNETs.[11] The duration of the disease is often short, typically <4 months and sometimes only a few days.

PNETs can occur at any level of the spine, more commonly in the thoracic and lumbar spine.[19] PNETs can also be divided into central PNET (cPNET), which develop from CNS, most commonly the cerebellum, and peripheral PNET (pPNET) arising from the neural crest. Both are aggressive tumors and have similar survival rates. However, they differ in their clinical presentation and pattern of propagation.[14] cPNET and pPNET also have different immunohistochemical profiles [Table 2], clinical evolution, and treatment protocols. cPNET is disseminated through the cerebrospinal fluid and rarely metastasizes outside the CNS; pPNET can spread to distant sites. However, intraspinal PNET is locally aggressive, and local recurrences are common.[14,17] One feature that distinguishes primary intraspinal PNET from primary intracranial PNET with spinal metastasis are cranial symptoms that are not a feature of intraspinal PNET.[9]

The immunohistopathological features of PNET include the following:

- Small round or spindle cells with a low level of differentiation;
- Densely packed architecture or in the form of leaves or nests;
- Cells that are generally positive for neuronal markers such as neuron-specific enolase; they may also be positive for intermediate precursor filaments such as nestin, vimentin, or microfilaments; depending on cell differentiation, they may also be positive for synaptophysin or GFAP; it is also common for them to also be positive for S-100;
- In the case of undifferentiated cells, they cannot present positive results for any analysis.[14,18] Similarly, *in situ* hybridization analysis of mRNA expression for specific genes can be used to diagnose PNET subtypes and to plan a treatment protocol.[15]

The diagnosis of a primary PNET of the spinal cord can be corroborated by MRI results, and exclusion of cranial involvement is necessary. PNET of the spinal cord is characterized by a rapid progression of the symptoms. When spinal cord biopsy results suggest the diagnosis of a primary PNET of the spinal cord, it is prudent to perform complete neuroaxial imaging, CSF cytology, and a whole-body PET scan. Due to their rarity, the diagnoses are generally not anticipated in the preoperative period.[9,13]

Table 2: Immunohistochemical profile and genetic backgrounds of pPNET and cPNET

	pPNET	cPNET
MIC2 glycoprotein (CD99)	+	–
(11; 22) (q24; q12) translocation	+	–

pPNET=Peripheral primitive neuroectodermal tumor, cPNET=Central primitive neuroectodermal tumor

Complete surgical resection is considered the best treatment, which is usually followed by radiotherapy and chemotherapy. However, primary PNETs of the spinal cord are prone to metastasize throughout the subarachnoid space, so their prognosis is poor, and the tendency for metastases and relapses are common. Reported survival varied from several days to 36 months or alive at 15 months after diagnosis, with a median survival of more than a year.[12] Intraspinal primary PNETs are considered rare, and their optimal management is still unknown. Therefore, all cases contribute to the understanding of treatment and prognosis of PNET. As the prognosis for patients with intraspinal PNETs is poor, treatment should consist of a gross total resection if possible, radiation therapy of the neuroaxis with an increased dose in the primary site of the tumor, and multiagent chemotherapy.[18] Successful results have been reported using combinations of the chemotherapies cyclophosphamide or ifosfamide, as well as cisplatin or carboplatin and vincristine-peplomycin. The chemotherapy protocol for cPNET should be different from that for pPNET, as the latter is more closely related to Ewing's sarcoma.

CONCLUSION

In conclusion, intramedullary PNETs are rare, particularly in the cervical spine and bulbar region. There remains a lack of information regarding the molecular pathology of such distinct PNETs and there are no established targeted treatment protocols available at present. Preoperative MRI study of the affected region and of the neuroaxis, as well as multiprofessional teamwork is paramount for treating PNETs. The rare occurrence of such lesions makes the presurgical diagnosis difficult, and despite possible complete resection of such lesions, treatment will probably have a poor outcome due to the location of the lesion, even when adjuvant radiotherapy and chemotherapy are administered. However, with increasing molecular data emerging allowing for targeted oncological therapy, we hope that with increasing knowledge about this distinct PNET type further treatment will emerge.

Authors' contributions

BN, LCTP, RAFC, RMQ, LGA, EQ, LHC, ISTP, CHM, and FBF contributed to conception and design as well as the acquisition, analysis, and interpretation of data. RMQ, LGA, ISTP, and CHM contributed to

acquisition and interpretation of imaging data. BN, LCTP, RAFC, RMQ, LGA, EQ, LHC, ISTP, CHM, and FBF documented the patient's status and contributed to analysis and interpretation of data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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