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Original Article

Primary Spinal Extradural Extraosseous Primitive Neuroectodermal Tumor/Ewing's Sarcoma: A Critical Analysis and Review

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Abstract

Primary spinal extradural Ewing's sarcoma/primitive neuroectodermal tumor (PNET) is rare malignant tumor of childhood and early adulthood. The World Health Organization classifies PNET as an undifferentiated round cell tumor arising from primitive neuroepithelial cell. It can be central or peripheral PNET depending on site of presentation. Usually, the presenting symptoms are chronic back pain and myelopathy. Overall prognosis and survival are dismal in spite of total surgical resection and adjuvant therapy. Because of the rarity and malignant behavior, definite management of spinal PNET has never been described. After review of medical record at Acharaya Vinoba Bhave Rural Hospital, Sawangi, India, we identified four patients of spinal PNET and were included in our study. Age at diagnosis ranging from 15 to 26 years old with mean age of 20 years old. All four cases were epidural in location, two of which were of Askin type tumor with spinal cord compression. Rural population with low literacy and financial constraints were the key reasons of late presentations at our hospital. Counseling and proper education regarding the disease are a must for early case detection and early treatment of those living in rural areas and suffers from financial constraints. Due to rarity of the disease and its poor prognosis, a well-organized multicentric controlled trial is required to formulate a standard guidelines in the management of this disease.

Keywords: *Central primitive neuroectodermal tumor, Ewing's sarcoma, immunohistochemistry, peripheral primitive neuroectodermal tumor, World Health Organization*

Introduction

Primary spinal extradural Ewing's sarcoma (ES)/primitive neuroectodermal tumor (PNET) is rare malignant tumor of childhood and early adulthood. The World Health Organization (WHO), classifies PNET as an undifferentiated round cell tumor arising from primitive neuroepithelial cell. It can be central or peripheral PNET depending on site of presentation.[1] Usually, these tumors presented with chronic back pain and myelopathy. These tumors can undergo complete removal if detected early. They have clear histopathological picture with distinct immunohistochemistry (IHC) differentiating central PNET from peripheral PNET. Overall prognosis and survival are dismal in spite of total surgical resection along with adjuvant therapy. Because of their rarity and malignant behavior, definite guidelines for the management of PNET are not described. Spinal Epidural PNET/peripheral primitive neuroectodermal tumor (pPNET) have incidence of <1% of primary spinal tumor and not more than 25 cases are reported in literature so far.[2,3] Here, we are illustrating four cases of primary spinal extradural PNET with two of which are thoracopulmonary type PNET (Askin Tumor) with their presentation, management, and comprehensive review of literature at our rural hospital located in central India.

Subjects and Methods

Case series

Case 1

A 20-year-old male, with no known comorbid illness, was admitted with a history of back pain on and off in dorsal region for 2 years. Weakness was gradually progressive from 3 months and was rapidly progressed from the past 1 month. The patient was bedridden since 2 days. He also had urinary retention for which he was catheterized at other hospital and referred to our center for further management.

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On examination, he was conscious, alert, oriented and paraplegic with Nurick grade 5 (completely bed-ridden). Neurological examination revealed power of 5 in both upper limbs and 0 in bilateral lower limbs (Medical Research Council [MRC] grading). He had sensory loss below T8 dermatome, deep tendon reflex were normal in upper limb and exaggerated in lower limb along with bilateral extensor planters. Physical examination revealed 4 cm × 3 cm swelling over dorsal region. Magnetic resonance imaging (MRI) revealed T1-isointense and T2–hypo-iso intense lesion, heterogeneously enhancing space occupying lesion in extradural compartment at T8-T10 with dumbbell shaped extension into neural foramen with left posterior mediastinum and paraspinous muscle and bony involvement s/o aggressive lesion nerve sheath tumor Askins tumor [Figure 1a]. He underwent T8–T9 laminectomy with gross total excision of tumor [Figure 1b]. Postoperatively, he developed hemothorax, which was treated appropriately with chest tube drainage. Histopathological examination (HPE) of tumor showed sheets and lobules of small round cells with scant cytoplasm suggestive of PNET/Askin's tumor. Tumor was positive for CD 99. He received 6 cycles of chemotherapy and adjuvant radiotherapy. At the follow-up after 6 months, he was able to walk with support and had no bladder dysfunction. However, at last follow-up at 1 year, he again started deteriorating with decrease of power in lower limbs. He was advised repeat imaging but he deferred due to financial constraints and lost follow-up.

Case 2

Another similar case of 19-year-old male who presented with back pain for 2 years gradually progressive, ascending weakness in lower limb for the past 4 months. History of fever on and off for 3 months. He was bed ridden for 1 month and developed pressure sores. He also had urinary retention since 1 month for which he was catheterized at other hospital and treated symptomatically and later referred to our tertiary care center (rural hospital) for further management.

On examination, he was conscious, paraplegic with Nurick grade 5. He had sensory loss below T9 dermatome.

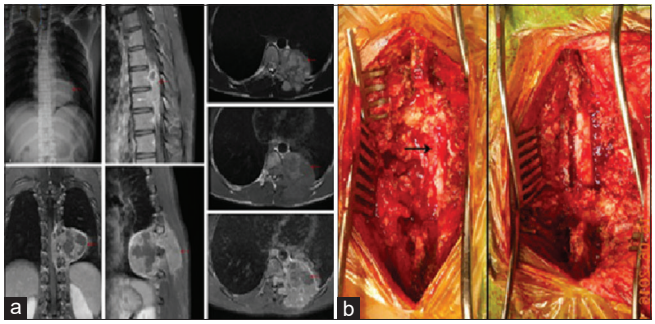

Figure 1: (a) X-ray and magnetic resonance imaging Thoracic spine showing T2 hypointense and T1 contrast-heterogeneously enhancing lesion extradurally compressing dural sac with extension into thoracic cavity. (b) Intraoperative picture showing lesion extradural in location encasing thecal sac. Postoperative complete removal of lesion. (Black arrow showing lesion)

Physical examination revealed large pressure sore over gluteal region. MRI thoracolumbar spine revealed T1-hyper, T2-iso to hypo intense lesion, T9-T11 large dumbbell shaped space occupying lesion heterogeneously enhancing with severe cord compression. He underwent T8–T11 laminectomy with gross total excision of tumor. HPE of tumor was suggestive of PNET and was positive for CD 99. He did not received chemo or radiotherapy in view of comorbidities and financial constraints. At the follow-up after 3 months he was bed ridden with only minimal power improvement in lower limb (MRC grade 1/5, Nurick grade 5). Hence, further adjuvant therapy has deferred and subsequently lost follow-up.

Case 3

A 15-year-old male child presented with gradual right-sided weakness upper limb > lower limb over period of 2 months. He also complained of neck pain. There was no autonomic nervous system involvement. Clinically, he had increased tone in right upper and lower limbs. Power in the right upper limb was 3/5 (MRC grade) with grip weakness. Similarly, the right lower limb has power of 4/5 while left side had 5/5 power (MRC grade). Mild sensory involvement was present. He was evaluated for compressive myelopathy of cervical origin and MRI cervical spine with contrast was planned. His MRI suggestive of T1 iso-T2 hyperintense lesion with T1 brilliantly contrast enhancing lesion along C3-4-5 level extradural in location on right side. It was measuring 6 cm × 3 cm × 2.5 cm, severely compressing cord and small part of lesion was going across neural foramen at C4 level. The patient underwent C3-4-5 hemi laminectomy and near total excision of lesion was performed. It was highly vascular and extradural portion compressing thecal sac could be taken out. His HPE suggestive of PNET/ES which was positive for CD99. Postsurgery he received six cycles of chemotherapy and fractionated radiotherapy. After 2 ½ years of follow-up, he had no recurrence of lesion and was ambulant with Nurick grade 1.

Case 4

A 26-year-old female presented with complaints of mid back pain radiating to right side since 2 months with gradual weakness in both lower limbs since 1 month. It has increased over period of time and was able to walk with support. She did not have bladder and bowel complaints. On examination tone in both lower limb was increased with power 3/5 (MRC grade). Sensory involvement was present in graded manner below xiphisternum for pain/touch and temperature. Her MRI was suggestive of T1 hyper-T2-hypointense lesion in D2-D4 area, which was intensely contrast enhancing with poor plane with surrounding muscle on right side. It was measuring 5.5 cm × 3.5 cm × 2 cm [Figure 2a and b]. The patient underwent D2-D4 laminectomy with gross total resection of lesion. It was exclusively extradural lesion with poor

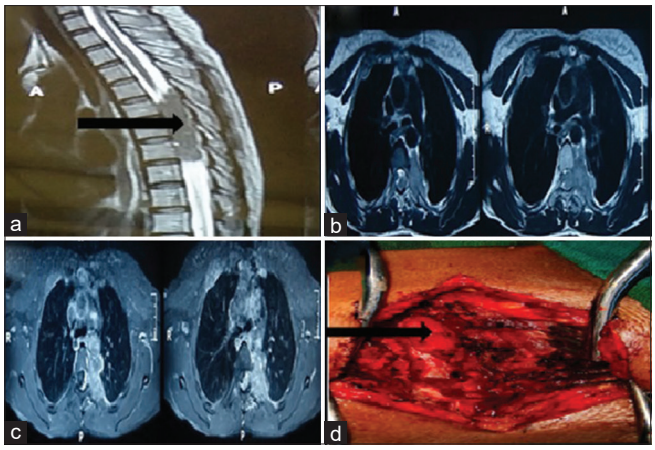

Figure 2: (a) Magnetic resonance imaging thoracic spine s/o T2 sagittal image showing well-defined lesion hypointense, extradural in location compressing thecal sac. (b) T2 axial images showing well-defined extradural lesion hypointense , compressing thecal sac on right side and involving bone and muscle. (c) T1 axial contrast images s/o heterogeneously enhancing extradural lesion on right side compressing thecal sac involving bone and muscle and extending into thoracic cavity. (d) Intraoperative lesion encasing thecal sac with compression and extradural in location. Right > left. (Black arrow showing compressive lesion)

plane with muscle and impinging on bone [Figure 2c and d]. Following which patient improved completely to 5/5 power in both lower limbs and independent for activities. Her HPE suggestive of PNET and IHC was confirmed about CD99 positivity and KI 67-15-20% positivity. She was advised adjuvant therapy but because of financial conditions, she refused and lost to follow-up after 3 months.

Discussion

PNET of spinal origin with epidural in location are extremely rare. They are aggressive and progressive tumors with malignant potential, eventually has poor prognosis. These tumor belong to ES family. James Ewings in 1921 described them as diffuse endothelioma. Later Oberling in 1928 coined term ES. In 1973, Hart and Earle first pointed out and embossed the term primary PNET. However, in 1969 Smith *et al*. have reported first ever spinal PNET but that time diagnostic criteria was not clear and transparent. According to Hart and Earle, term PNET means tumor arising from central neuraxis with more than 90%–95% undifferentiated cells and considered to be arise from single progenitor cell. In 1993 WHO considered PNET in same group as round cell tumor group (medulloblastoma/pinealoblastoma). Gradually with subsequent advancement in histopathology and commencement of IHC, tumor of embryonal origin with abundant neuropil and true rosettes considered in separate group. Similarly, with the help of IHC these PNET kept in different group than round cell tumor in recent WHO classification for central nervous system (CNS) tumors.

PNET can be central or peripheral (spinal) in location. Spinal PNET can be primary where central PNET is absent or it can be secondary because of cerebrospinal fluid (CSF) seedling from cPNET spinal lesion. Similarly, PNET with dorsal spine location and extension in thoracic cavity (ribs) are termed as Askin tumor. These are aggressive lesion characterized with rapid growth and shorter duration of presentation. Recurrence occurs in almost all patients. Overall, extraosseous ES, PNET, Askin tumor belong to same family of ES with similar molecular typing.

Epidemiology

Spinal PNET are rare with scanty literature about incidence. They are <1% of total CNS tumors.[3] However, because of recent technical advances and awareness the diagnosis has improved. Spinal PNET shows male predominance with almost 2:1 (male: female) ratio but Central PNET has female predominance. Average age of presentation is between 20 and 30 years of age. In our series male predominates with average age of presentation at 20 years.

Clinical presentation and location

The most common presenting complaint is chronic back pain or neck pain followed by myelopathy (weakness in lower and upper limbs). Back pain and paresthesia seems to be due to irritation and compression of spinal cord and nerve roots.[4] Autonomic involvement (bladder) is late and present in two of our cases. Mean duration of onset and presentation was 2 months to 1 year in our series. The most common location of tumor was thoracic > lumbar > cervical region. Spinal PNET are mostly intradural (intramedullary) in location. Extradural location is rare and until now, <20 cases are reported in literature so far. We have four cases all are epidural in location. Two of which were of Askin type tumor with epidural compression. Rural population with low literacy and financial constraints did not allow early detection, hence patients presented in late stages at our rural hospital.

Radiological findings

MRI of PNET is usually nonspecific. Most of the lesion show well circumscribed, T1W image-iso to hyperintense. T2 Iso to hypo suggestive of high cellularity. Intense contrast enhancement present, which can be homogenous in most cases but can be heterogeneous in few cases. In our series, we have similar findings. According to Duan *et al*.,[5] MRI showing intradural extramedullary or extradural lesion large, usually well circumscribed which extends out from intervertebral foramen and invades paraspinal soft tissue (muscle/ligament) and surrounding bones. Metastasis and lymphoma or myeloma usually has very similar MRI picture but age group can differentiate from both. Neurofibroma could be very near differential diagnosis as it can travel through neural foramen and has intense contrast enhancement, but rarely has poor plane with muscle or surrounding bones. fluorodeoxyglucose positron emission tomography (FDG PET) is useful in locating recurrence and tumor progression. Spinal PNET can be metastatic from primary lesion at presentation or they may

metastasize out of the spine. Computerized tomogram (CT) scan Thorax is more useful for Askin's tumor showing large soft tissue mass based on single chest wall with or without pleural involvement or effusion and rib damage.

Histopathological diagnosis and genetics

PNET histologically on light microscopy appears predominantly as poorly differentiated small blue round or spindle shaped cells. These cells are densely packed in sheets or nests with hyperchromatic nuclei and have scanty cytoplasm with few mitotic figures. Homer Wright rosette are often present. Frequently this tumor shows vascular endothelial proliferation. Electron microscopy shows scanty cytoplasmic organelles, compact cytoplasmic glial differentiation and presence of growth cones (suggestive of ganglionic differentiation).

Immunohistochemistry confirms diagnosis

Routinely, it divides cPNET fron P PNET/ES. Positive for neuronal and glial marker such as neuron-specific enolase, synaptophysin, class III beta tubulin, GFAP, S100, CD 99. PNET differentiate from other small round cell tumor, lymphoma, ES, rhabdomyosarcoma and small cell carcinoma using neural differentiation. pPNET shows strong expression of glycoprotein CD99 which differentiate it from cPNET. pPNET strongly expresses glycoprotein CD99, encoded by the microneme protein 2 (*MIC2*) gene and shows reciprocal translocation between chromosomes 11 and 22 showing the specific chimeric gene of *EWS–FLI1*. In contrast, all central PNETs are negative for *MIC2* and *EWS–FLI1*. This distinction is critical because of differences in specific chemotherapeutic regimen, radiation dose, and its extent. The membrane protein HNK1 and CAV 1 have been implicated in ES and PNET as well.[6] *In situ* hybridization of mRNA expression is also helpful in identifying Spinal PNET. The presence of an (11;22) (q24; q12) translocation is necessary for definitive diagnosis. The FLI-1 protein, the gene product of FLI-1, t (11:22), is positive in 85% of all EWS/PNET cases.[7]

Management

Currently, spinal PNET is treated as other CNS PNETs and extraspinal PNETs. Surgery remains the mainstay of the treatment.[8] There is no standardization till now in management of Spinal PNET.

Surgery is mainstay of treatment for long-term survival. Surgery can be in the form of biopsy/near complete resection/complete resection depending upon adherence and accessibility of lesion.

By surgery we can:

1. Decrease pressure from neural tissue by decompression
2. Histopathological diagnosis can be made
3. In advance stages, tumor debulking can be done so that adjuvant therapy can be helpful.

Laminectomy with preservation of facet joint and laminoplasty in children is generally advocated. In our series, we did laminectomy and excision of lesion. In three cases, we were able to do total resection but in one we did near total resection. All lesions were extradural in location. These lesion are usually very vascular with difficult to resect completely and even embolisation is not useful.[9]

Adjuvant therapy

Adjuvant therapy has significant role in overall survival. Most of the centres they do offer radiation therapy to entire neuraxis.[10] Mostly fractionated radiotherapy is to be given with dose 30–60 Gy. Recently hyperfractionated radiotherapy is reported but lacking long-term results. Chemotherapy can also be used but have multiple side effects (e.g., bone marrow suppression). In our series, only one patient received chemotherapy and his survival increased. Other patient did not make it because of financial constraints. Most commonly used chemotherapy drugs vincristine/cyclophosphamide/cisplatin/ifosfamide showed some promise but long-term survival is still questionable. Randomized controlled trials still lacking regarding prolonging overall survival of patient with pPNET with adjuvant therapy.[11]

Follow-up and prognosis

Follow-up in rural and poor population is not satisfactory, hence proper counseling and education regarding disease is must. It is either through social worker or through regular camps in interior of villages. People should make aware of government schemes and financial assistance.

Favorable predictors of survival are (1) localized disease at presentation, (2) time to local therapy <4 months, and (3) primary origin in bone, and objective response to chemotherapy.[12]

Over all prognosis is poor and median survival in majority of case series and reports were 1–2 years.[13] Some patient have CSF spread throughout neuraxis but some patient has spread extraneurally in bone, liver, lung, and lymph node. Hence, follow-up MRI and FDG PET scanning is required.[14]

Conclusion

Spinal PNET are very aggressive tumors with limited survival options. Because of awareness and technical advancement lesion can be detected in early stage. In adolescents extradural, spinal lesion should be considered as PNET and gross total resection should be the policy. There is no standardize treatment for spinal PNET, but we reemphasize that, gross total resection should be the aim of surgery. These lesions whenever possible after surgery should be given adjuvant therapy for better long-term survival. Early detection and early treatment has a role in overall survival. Counseling and proper education regarding disease is must for further cases detection and

early treatment in poor and rural area. For standardization of treatment multicentric Controlled trial is need of the hour.

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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Nil.

Conflicts of interest

There are no conflicts of interest.

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