Case Series

Primitive Neuroectodermal Tumor at uncommon sites-A Case Series in a tertiary care hospital

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Abstract

Introduction: Primitive neuroectodermal tumors (PNET) are malignant small round cell tumors with a neuroectodermal origin.They belong to Ewing Sarcoma family of tumors (ESFT) which is an aggressive form of malignancy.**Aim:** To study clinical behaviors, anatomical location, histological findings of the tumor and correlation with immunohistochemistry (IHC).**Materials and methods:** This is a prospective study conducted in a tertiary care hospital for 1year. We studied the cases according to their age and sex, the clinical presentations and site of the tumor, the duration of the lesion, its size, the treatment provided and the histopathological findings along with IHC.**Results:** This study comprises six cases of PNET each arising from scalp, nasal cavity, kidney, mandible and two cases from gluteal region with varied presentations.Youngest age group to be affected was 1-year-old and the oldest age group affected was 62-year-old. All the five cases affected were male only a single affected case was a female. The patients have undergone treatment and were referred to oncology department for further management.**Conclusion:**PNET is a small blue round cell tumor and is a diagnostic challenge because of the similar histomorphological features with the large spectrum of small blue round cell tumors. Light microscopy with the help of immunohistochemistry and cytogenetics will aid in precise diagnosis and proper management of the patients.

Keywords: gluteal region, kidney, mandible , nasal cavity, neuroectodermal tumour, scalp.

Introduction

Primitive neuroectodermal tumors (PNET) are malignant small round cell tumors with a neuroecto-dermal origin. They share similar morphological, immunohistochemical features and the same reciprocal translocation t (11; 22) (q24; q12) giving rise to the EWS/FLI-1 fusion gene and so they belong to Ewing Sarcoma family of tumors (ESFT) which is an aggressive form of malignancy[1,2]. They are a rare entity and may arise from the bones or the soft tissue of lower extremities, chest wall, retroperitoneum and in the head and neck region. This study describes six cases of PNET each arising from scalp, nasal cavity, kidney, mandible and two cases from gluteal region with varied presentations.

Materials and methods

This is a prospective study conducted in a tertiary care hospital for 1year from March 2019 to March 2020 comprising of six cases. All patients presented with wide-ranging clinical features in relation to their tumor location. In all cases, complete haemogram and computed tomography(CT scan) or Magnetic Resonance Imaging (MRI) was done. Informed consent was taken. All the surgically excised specimens were sent in the Department of Pathology.Gross examination of the specimens was done. Using light microscopy, histopathological findings were reported. Periodic Acid Schiff (PAS) stain was also performed.The paraffin embedded blocks were then subjected to immunohisto-chemistry by peroxidase-antiperoxidase technique. CD99 [Monoclonal Mouse Antibody; clone:12E7, positive control: oesophagus, membranous staining], vimentin[Monoclonal Mouse Antibody;clone:V9, positive control: tonsil, cytoplasmic staining], Leukocyte Common Antigen (LCA) (CD45) [Monoclonal Mouse Antibody; clone: 2B11+PD7/26, positive control: tonsil, membrane staining], synaptophysin [Monoclonal Mouse Antibody; clone: SY38,positive control:pancreas, membranous staining],human black melanoma (HMB 45) [Monoclonal Mouse Antibody; clone: HMB 45, positive control: melanocytes, cytoplasmic staining], WT1 [Rabbit Polyclonal Antibody; positive control: kidney, nuclear staining],

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cytokeratin 7 (CK7) [Monoclonal Mouse Antibody; clone: OVTL12/30, positive control: lung, cytoplasmic/membranous staining], desmin [Monoclonal Mouse Antibody; clone: D33,positive control: skeletal and cardiac muscle cells, cytoplasmic staining]were the primary antibodies being used.

Results

Case 1 (PNET of the nasal cavity)

A 15-year-old male presented with left nasal obstruction and epistaxis for last 4 months. Nasal examination revealed soft fleshy mass bulging and blocking the left nostril. Right nostril was patent. On further examination, oral cavity and oropharynx showed no abnormality. CT scan showed a soft tissue lesion of size about 82x47 mm in the left nasal cavity extending posteriorly into nasopharynx through choana and the nasal septum is completely displaced towards the right side obstructing the right nasal cavity as well **(Figure 1A).** The tumor mass excision was done. Grossly, the mass was measuring 8x4x2 cm (**Figure 1B).** On light microscopy, section showed sheets of small to medium round cells with fine chromatin and prominent nucleoli (**Figure 1C**). Rosette formation was also seen. The features were indicative of small blue round cell tumor. PAS stained positive. Immuno-histochemical staining for CD99 **(Figure 1D)** and vimentin showed positivity and negative staining for CK7, CD45,CD56,desmin,HMB45, and synaptophysin. The final diagnosis was PNET. The patient was then referred to oncology department for further management.

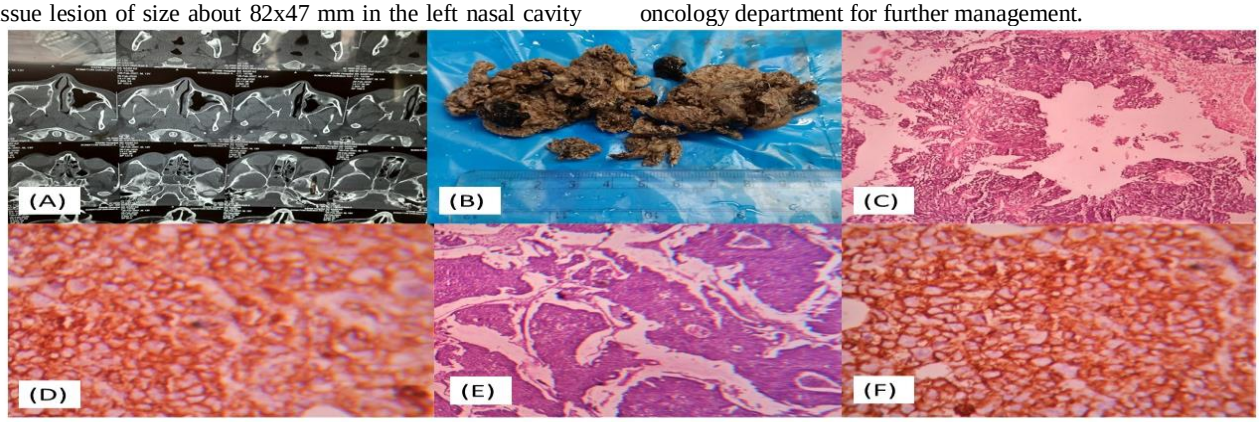

Fig 1:PNET of the nasal cavity (A) CT scan showing soft tissue mass in the left nasal cavity (B) Gross specimen (C) Section shows sheets of small round cells (x100, H&E) (D)IHC staining for CD99 showing positivity (x400). PNET of the mandible (E) Section shows sheets of small round cels separated by fibrous septa (x100, H&E) (F) IHC staining for CD99 showing positivity (x400).

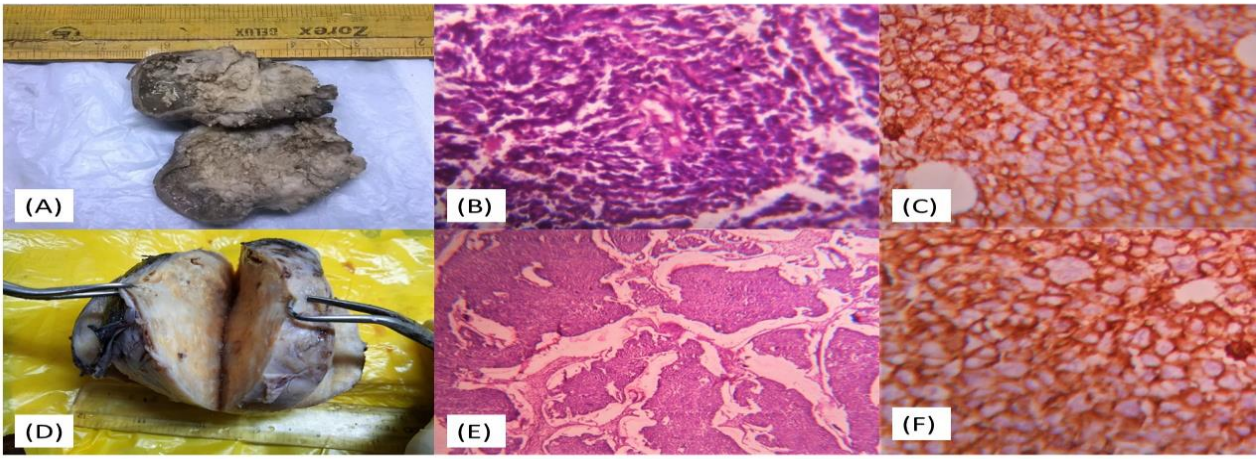

Fig 2:PNET of scalp (A) Gross specimen (B) Section shows small round cells with hyperchromatic nucleus and scanty cytoplasm forming rosettes (x400, H&E). (C) IHC staining for CD99 showing positivity (x400) . PNET of the gluteal region . (D) Gross specimen (E) Section shows nests of small round cells separated by fibrous septa (x100, H&E) (F)IHC staining for CD99 showing positivity (x400).

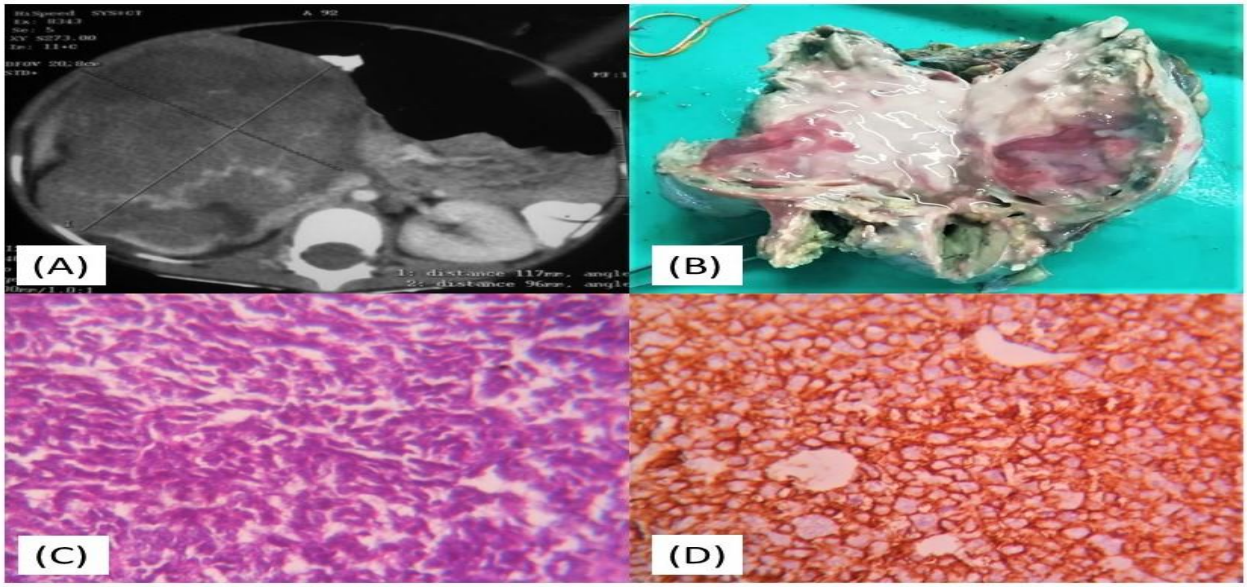

Fig 3: PNET of the kidney (A) CT scan showing heterogenous mass arising from right kidney (B) Gross specimen (C) Section shows small round cells with hyperchromatic nucleus and small nucleoli forming rosettes (x400, H&E) (D) IHC staining for CD99 showing positivity (x400).

Case 2 (PNET of the mandible)

A 25-year-old male presented with an eight-month history of progressively enlarged swelling in the right mandible. On intraoral examination a well-circumscribed non-ulcerated swelling was seen against the vestibular plate of the mandible. The mass was hard in consistency and nontender. CT scan imaging revealed an expansile lytic lesion with wide vestibular plate destruction of the right ramus of the mandible. The tumor mass was completely excised.

Grossly the specimen measured 12x7x3 cm. Sections were taken from the representative areas. Histopatho-logical examination revealed sheets of small round cells with hyperchromatic nuclei and prominent nucleoli separated by fibrous septa (**Figure 1E).** PAS staining showed positivity.CD99 (**Figure 1F)** and vimentin stained positive and CK7, CD45 and synaptophysin stained negative. The diagnosis of PNET was confirmed. Patient was further referred to oncology department.

Case 3 (PNET of scalp)

A 1-year old boy presented with enlarging, non-tender, mobile mass on right anterior scalp for five months. On physical examination a 2-cm firm mobile mass was noted over the right frontoparietal scalp. Skull X-rays showed no osseous abnormalities,with characteris-tically suspicious for a cystic lesion. Keeping both the clinical and X-ray findings, it was suspected as extracranial dermoid cyst. CT scan revealed a local scalp soft tissue tumor with no bony involvement. Surgical resection was performed. Excised specimen was sent to pathology department. Grossly it measured 3x3x0.5 cm **(Figure 2A).** The histopathological examination showed dermal proliferation of hypercellular tumor cells. Individual cells are uniform, small with round hyperchromatic nucleus and scanty cytoplasm (**Figure 2B**). Few rosette-like arrangements were noted. The features were suggestive of small blue round cell tumor. PAS stained positive. The tumor cells were positive for CD99**(Figure 2C)** and vimentin but negative for CK7, CD45, desmin, synaptophysin. PNET of scalp was the final diagnosis. The boy was then referred to the pediatric oncology department for further treatment.

Case 4 (PNET of the gluteal region)

A 62-year old male presented with a huge right gluteal mass for last four months.Local examination revealed a swelling in the above region with no associated tenderness or inflammation. There was no scar/sinus formation. Routine investigations were normal. Ultrasonography (USG) revealed a hypoechoic space occupying lesion (SOL). CT scan showed large lobulated soft tissue mass in right gluteal region with intra-pelvic extension with no bony abnormality. The tumor mass was excised surgically.

Grossly specimen measured 10x9x4 cm (**Figure 2D).** On cut open whitish and homogenous areas were noted. On Histopathological examination the section showed dermal proliferation of hypercellular tumor cells. Individual cells are uniform, small with round hyperchromatic nucleus and scanty cytoplasm (**Figure 2E).** Pseudorosettes were noted. The features were suggestive of small blue round cell tumor. The tumor cells were positive for CD99 (**Figure 2F)** and vimentin and negative for CK7, CD45 and synaptophysin. The diagnosis of PNET was confirmed. The patient was then transferred to oncology department for further treatment.

Case 5 (PNET of the gluteal region)

A 48-year-old female presented with a left gluteal mass for last seven months. On examination, a firm, nontender swelling was palpated. There were no signs of inflammation or ulceration. CT scan imaging revealed a heterogenous soft tissue mass in the left gluteal region without any bony deformity. The tumor mass was completely excised.The specimen measured(8x6x3 cm). Histologically the section

showed nests of small blue round cells with hyperchromatic nuclei and fine chromatin forming rosettes. PAS stained positive. The features were suggestive of small blue round cell tumor. On IHC CD99 and vimentin stained positive and CK7, CD45 and synaptophysin stained negative. The final diagnosis was PNET. Patient was further referred to oncology department.

Case 6 (PNET of the kidney)

A 17 yrs old male presented with a complain of abdominal pain for six months. On examination, a ballotable lump was felt in right lumbar region with severe tenderness. CT scan revealed heterogenous mass lesion arising from the upper pole of right kidney (**Figure 3A).** He underwent right nephrectomy.Grossly the right kidney measured (10x 9x 7) cm (**Figure 3B).** Cut section revealed a brownish, well circumscribed growth measuring(8x8x4) cm at the upper pole of the right kidney. It had a variegated appearance and contained a brownish granular material. On light microscopy sections showed nests, sheets and trabeculae of small to medium sized tumour cells separated by fine fibrous septae. Individual cells bearing scanty pale to clear cytoplasm with a round to oval nucleus having a small nucleoli and finely granular chromatin (**Figure 3C**). PAS staining highlighted the presence of glycogen on the tumour cells. On IHC CD99 (Figure 3D) and vimentin were strongly positive and WT1 was negative. The case was diagnosed as PNET.The patient was then transferred to oncology department for further treatment.

Discussion:

In 1973 Hart and Earle coined the term primitive neuroectodermal tumor to define a rare malignant tumor originating from neuroectoderm [3,4].PNET is further divided into central and peripheral (pPNET), based on their location and source [5]. pPNETs represent only 1% of all sarcomas [6,7]. pPNETs originate outside central nervous system and immunohistochemically stain CD99 positive and also exhibit distinctive chromosome translocation t (11; 22) (q24; q12) giving rise to the EWS/FLI-1 fusion gene [8]. But here, the patients could not afford for the cytogenetics study. pPNETs are extremely aggressive biologically with poor prognosis [7]. pPNETs are most prevalent during adolescence and young adulthood but can affect persons of any age group [9]. The disease has a sudden onset with aggressive course and metastasize to the lungs or bones [10]. The commonest site of involvement is the chest wall followed by thoracopulmonary region, the intraabdominal, intrapelvic and retroperitoneal soft tissues, the head and neck regions and the extremities. The incidence of PNET in sinonasal region is very rare [11,12]. In the sinonasal tract, the differential diagnosis includes olfactory neuroblastoma, undifferentiated carcinoma, sinonasal melanoma, lymphoma, embryonal rhabdo-myosarcoma, small cell neuro-endocrine carcinoma [13-15].Olfactory neuroblastoma is confined generally to cribriform plate they are CD99 positive and NSE negative with absence of rosettes. Undifferentiated carcinoma is CD99 negative and positive for cytokeratin [14]. PNET is the second most common primary malignant tumor in bone after osteosarcoma. 8% of PNET constitutes tumors of head and neck involving skull bones and jaws. Among the jaw bones, mandible is most commonly affected than maxilla [16,17]. The differential diagnosis includes poorly differentiated synovial sarcoma (PDSS), alveolar rhabdomyosarcoma, mesenchymal chondrosarcoma, lymphoma, neuroblastoma, small cell osteosarcoma, small cell carcinoma and small cell variant melanoma [18]. CD45 stains positive in lymphoma. Neuroblas-tomas are CD99 negative and positive for CD56, synaptophysin, neuron specific enolase (NSE). Synovial sarcoma stains positive for CD99, vimentin, bcl-2 and TLE-1 and also shows a specific balanced reciprocal translocation,t(X;18)(p11.2; q11.2) [19]. Mesenchymal chondrosarcoma contains chondroid and small cell osteosarcomas contain osteoid areas along with reticulin meshwork and vascular pattern which is not seen in PNET. Small cell variant of melanoma is strongly positive for human melanoma black 45 (HMB-45) and Melan A [18]. PNET of scalp was first reported by Suster S, et al. [20]. Ewing sarcoma and PNET are round cell sarcoma of childhood that exhibit varying degree of neuroectodermal differentiation. PNET exhibits varying degree of neuroectodermal differentiation, while Ewing sarcoma lacks any evidence of it [21].Histologically PNET is a small blue round cell malignancy with scanty cytoplasm and it may be puzzled with other tumours such as neuroblastoma, rhabdomyosarcoma, and lymphoma. IHC is important in differentiating these tumors. Neuroblastoma is positive for S-100 protein, neuron-specific enolase (NSE), synaptophysin, chromogranin. LCA(CD45) shows positivity for lymphoma. Rhabdo-myosarcoma stains positive for vimentin, myoglobin, myosin and actin.Very rarely these tumors present as soft tissue mass in perivesical, inguinal region or gluteal region without bony involvement. The commonest differentials are benign nerve sheath tumours like neurofibromas, schwannomas, spinal ependymomas, and non-neuroaxis neoplasms like lymphomas.They are differentiated on the basis of radiological finding and histopathology [8]. pPNETs commonly involves retroperitoneum and they evolve from pelvic bones, kidneys, adrenals, pancreas, gluteal region and perirenal spaces [22]. pPNETs in abdomen and pelvis comprise 14% of all peripheral PNETs [23].In 1975 Seemayer TA et al. first described renal PNET as a rare and aggressive malignant tumor [24]. Children and young adults are slightly more affected with a male predilection [25]. And so as in our case a 17-year-old male is affected by renal PNET. The main differential diagnoses are non-Hodgkin lymphoma, synovial sarcoma, small cell carcinoma, and desmoplastic small round cell tumour and Wilms tumor. Wilms tumor stains positive for CD99 and WT1. The characteristic desmoplastic stroma; along with dot like positivity for vimentin, and EMA and WT1 positivity favours desmoplastic small round cell tumor [26]. Lungs, pleura, bones, bone marrow, liver and brain are the most frequent sites of metastases[23]. Chest CT is often done at presentation and during follow-up in patients with pPNET to rule out metastatic lesions.

Conclusion

PNET is a small blue round cell tumor and is a diagnostic challenge because of the similar histomorphological features with the large spectrum of small blue round cell tumors. Light microscopy with the help of immunohistochemistry and cytogenetics will aid inprecise diagnosis and proper management of the patients.

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