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## RESEARCH ARTICLE

### PRIMARY CEREBRAL NEUROBLASTOMA: AN UNUSUAL INTRACRANIAL PNET WITH NEURONAL DIFFERENTIATION.

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#### Abstract

Primary cerebral neuroblastoma, a primitive neuroectodermal tumor (PNET), is one of the rare tumors of infants and children. These are a group of undifferentiated tumors with similar histological features that include dense cellularity and immature cells containing scant cytoplasm with hyperchromatic nucleus. PNET group of tumors includes pineoblastoma, ependymoblastoma, medulloblastoma, medulloepithelioma and primary cerebral neuroblastoma. Primary cerebral neuroblastomas are located mostly in the frontal and parietal lobes with a heterogeneous presentation on imaging including areas showing cyst formation, calcification and hemorrhage. We present a rare case of 10-year-old girl diagnosed with primary cerebral neuroblastoma with neonatal and mesenchymal differentiation, an uncommon feature.

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#### Introduction:-

Primitive neuroectodermal tumors (PNET) are a group of undifferentiated tumors arising in children with similar histological features. These features include dense cellularity, with immature cells containing hyperchromatic nuclei with scanty cytoplasm. The tumors falling under the heading of PNET include, retinoblastoma, pineoblastoma, neuroblastoma, ependymoblastoma, medulloblastoma, and medulloepithelioma (Naqash AA et al., 1997). Central nervous system PNET (CNS PNET) are aggressive neoplasm of brain, most frequently encountered in pediatric population and are WHO grade IV tumors. They are composed of primitive undifferentiated neuroepithelial cells.

Neuroblastoma is the most common extra-cranial solid tumor of childhood with wide variety of tumor location and clinical presentation (8-10% of pediatric cancer) (Caron H et al., 1998). Derived from primordial neural crest cells, they may arise anywhere from a sympathetic nervous system structure, thus having varying clinical signs and symptoms. However, neuroblastomas, with exception of esthesioneuroblastoma, are rarely located in the central nervous system (CNS) (Heideman RL et al., 1997). Primary cerebral neuroblastoma is considered one of the rare CNS PNET. Here we report a case of 10-year child diagnosed as primary cerebral neuroblastoma.

#### Case report:-

A 10-year-old female presented with complaints of headache, vomiting and swelling on left forehead for last 2 months. The patient was apparently asymptomatic two months back when she developed dull headache, gradual onset and relieved on taking medications. Headache was associated with projectile vomiting, 4-6 episodes per day. There was no history of trauma, TB, diabetes or hypertension. There was no such previous family history. On examination, the Glasgow Coma scale was 14/15, E4V4M6. A left frontal bony hard, non-tender swelling was

palpable. The general, systemic and neurological examinations were within normal limit without evidence of any obvious organomegaly.

Serum urea and bilirubin were mildly elevated and rest of the blood investigations were within normal limits. The viral markers were negative. Radiological investigations including contrast-enhanced computerized tomography (CECT) and magnetic resonance imaging (MRI) of Head were done.

CECT revealed a well-defined, intra-cranial, supratentorial, hyper-dense soft tissue mass involving anterior frontal area on left side (Figure 1a), measuring 59x27mm with moderate peripheral edema and calcification. There was evidence of mass effect in the form of compression of ipsilateral frontal horn and body of lateral ventricle with midline shift of 9mm towards the contralateral side. There was also breach in cortex of the overlying frontal bone with hypo-densities within it. Post contrast images showed no significant enhancement. On MRI scan, T1 and T2 weighted axial and coronal images revealed an ill-defined, extra-cranial, heterogeneous mass lesion involving left fronto-parietal region anteriorly (Figure 1b & c). Focal areas also showed few hypointense areas within (cystic areas) with evidence of moderate perifocal edema. Post contrast images showed heterogeneous enhancement. The findings were suggestive of neoplastic etiology, with probability of meningioma (atypical variant).

A left fronto-parietal craniotomy was performed. Intra-operatively, a large intracranial, hyper-vascular, space-occupying lesion (SOL) was seen in the left frontal region, involving the overlying calvarial bone and dura as well as infiltrating into the brain tissue without any clear line of demarcation.

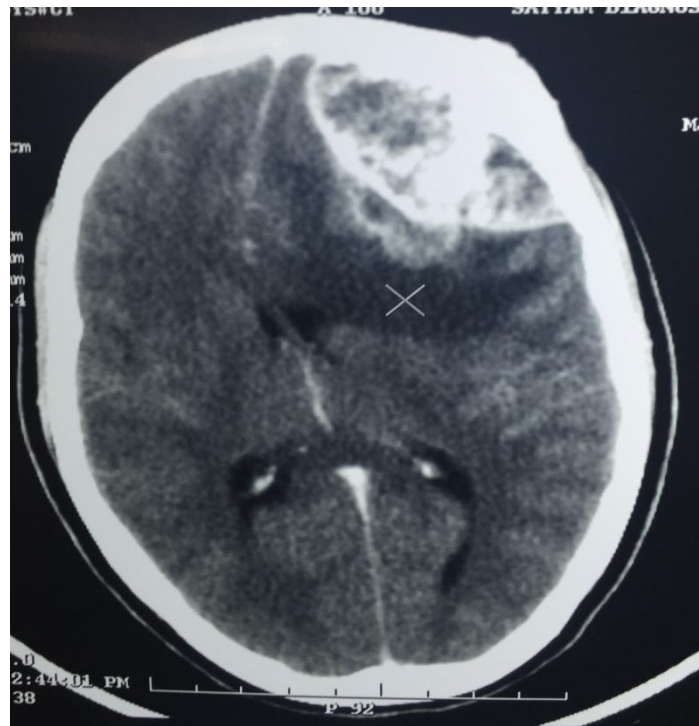
A partial removal of SOL was done, and the tissue was sent for histopathological examination.

Grossly an irregular soft tissue piece was received with areas of hemorrhage, measuring 4x3 centimeter (cm), with attached flat cranial bony piece measuring 8x6 cm. Outer surface of bone showed rounded, globular elevation with thinned out cortex (Figure 2a). Inner surface showed attached adherent variegated tumor tissue with foci of greyish white areas (Figure 2b). Cut surface showed greyish white areas with areas of hemorrhage. Representative sections were taken.

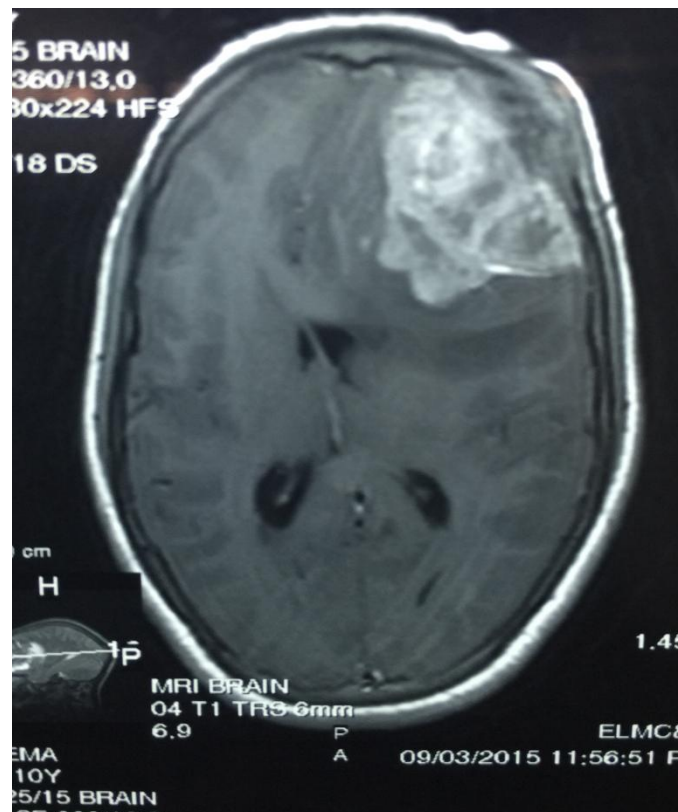
Microscopically, a cellular tumor composed of small sheets of round to oval pleomorphic cells having hyperchromatic nuclei with moderate amphophylic cytoplasm was seen. The cells frequently formed Homer-Wright rosette (Figure 3a), having central tangle of eosinophilic material surrounded by a mantle of similar tumor cells. Large areas of hemorrhage and necrosis were seen with focal calcification. The tumor cells appeared to invade the desmoplastichyalinized stroma (Figure 3b), forming lobules of eosinophilic homogenous material mimicking osteoid like material with calcification suggestive of calcospherites. At several areas, tumor was seen infiltrating the partially decalcified cranial bony trabeculae. Few other areas showed highly pleomorphic bizarre, enlarged cells with pleomorphic, hyperchromatic nuclei and clumped chromatin (anaplastic areas). No definitive glial elements were seen.

A differential diagnosis of cerebral neuroblastoma and poorly differentiated sarcoma was considered. To confirm the diagnosis, IHC panel was ordered. IHC markers revealed positivity for vimentin (Figure 3c), non specific enolase (NSE) (Figure 3d), weak positivity for synaptophysin (Figure 3e) and negativity for cytokeratin.

In view of NSE positivity, presence of Homer Wright rosettes and large areas of hemorrhage and necrosis, a tumor of neural origin was suggested; a diagnosis of supratentorial primitive neuroectodermal tumor probably primary neuroblastoma of the brain was made.

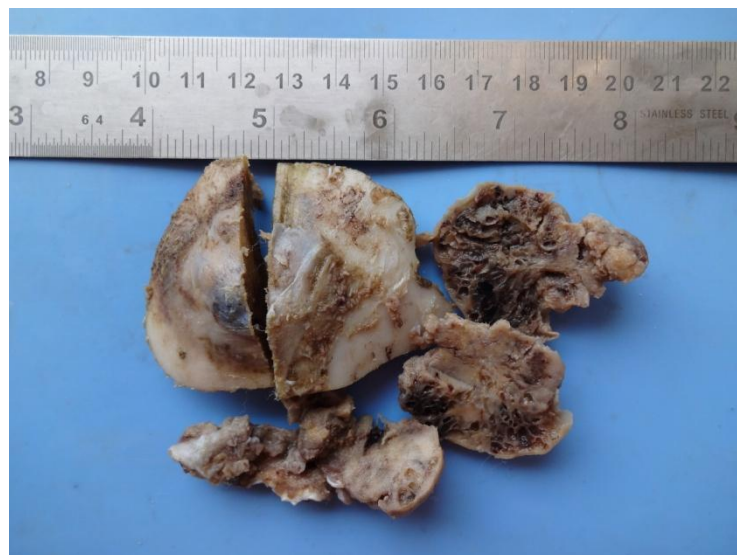


**Figure 1a:-**CECT head revealed a well-defined, intra-cranial, hyper-dense soft tissue mass involving anterior frontal area on left side with perifocal edema and midline shift.



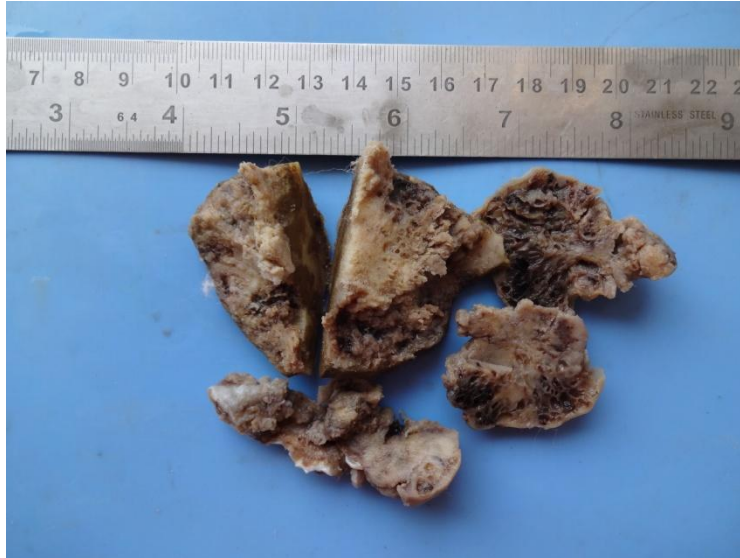


**Figure 1band 1c:-**T2 axial and T1 coronal weighted images revealed an ill-defined, extra-axial, heterogeneous mass lesion involving left fronto-parietal regions anteriorly with surrounding perifocal edema and midline shift.

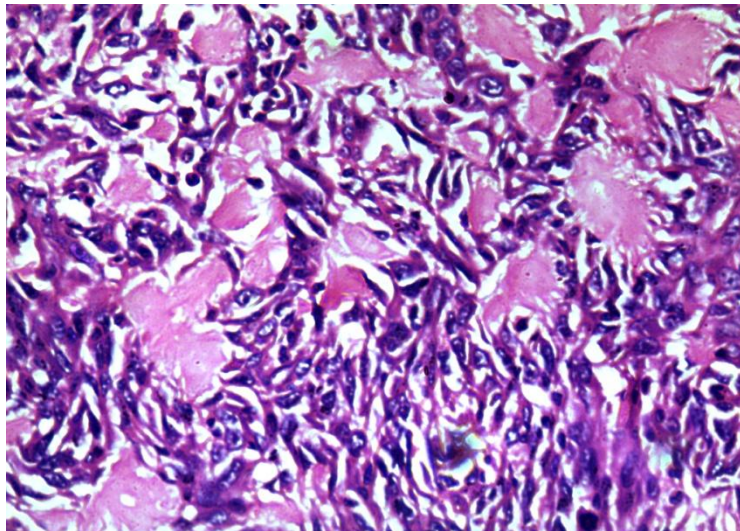


**Figure 2a:-** Gross showing outer surface of the fronto-parietal SOL with overlying thinned out part of cranial bone.

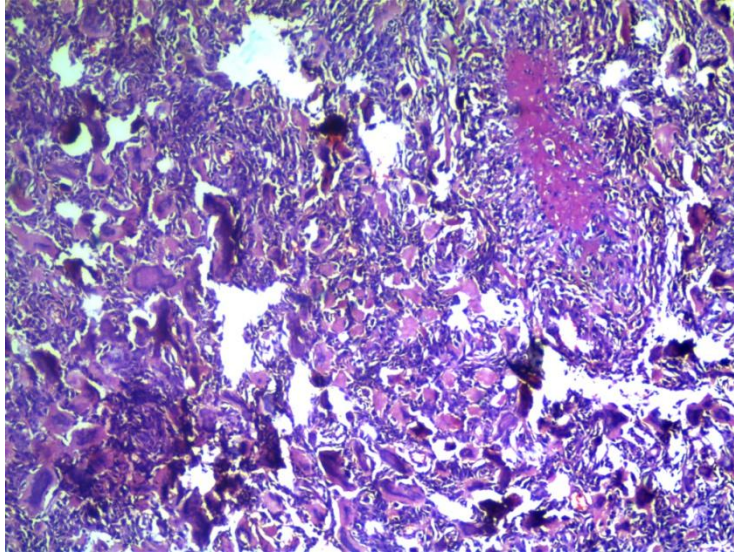




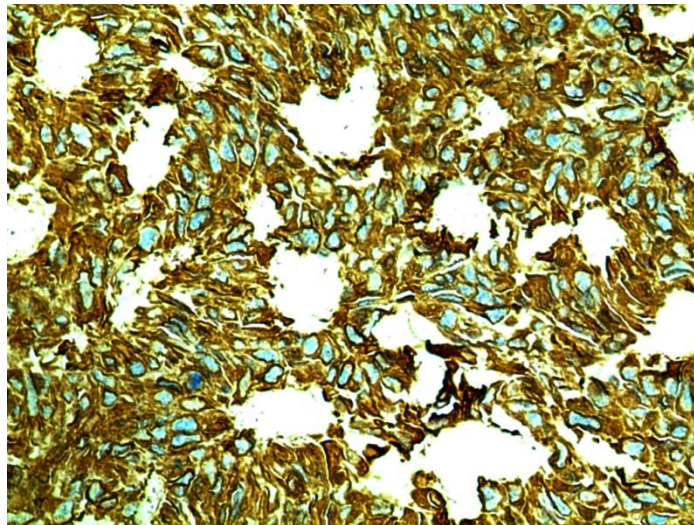
**Figure 2b:-**Gross showing inner surface of the intracranial fronto-parietal SOL.



**Figure 3a:-** Microscopic image showing Homer Wright rosettes (H &E 400x).

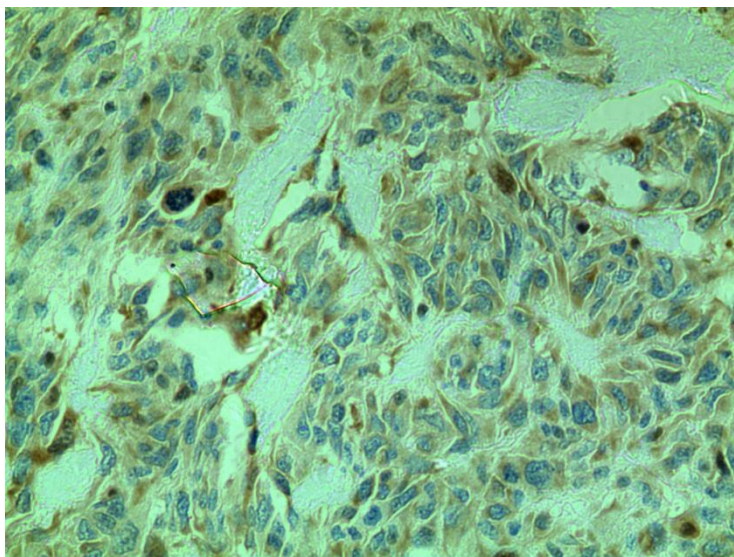


**Figure 3b:-** Microscopic image showing necrosis with Homer Wright rosettes with desmoplastic stroma (H & E 400x).

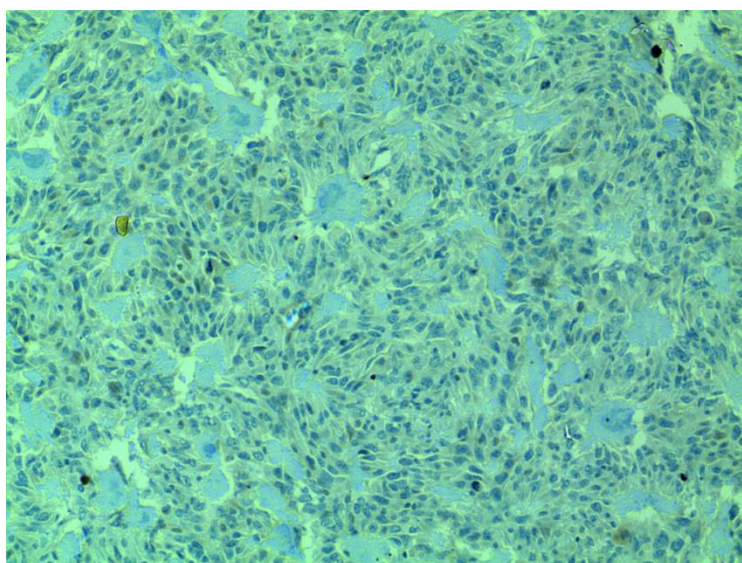


**Figure 3c:-** Microscopic image showing vimentin positivity in tumor cells. (IHC for Vimentin 400x).





**Figure 3d:-** Microscopic image showing positive NSE in tumor cells. (IHC for NSE 400x).



**Figure 3e:-** Microscopic image showing weak positivity for synaptophysin in tumor cells. (IHC for synaptophysin 400x).

### Discussion:-

Primary cerebral neuroblastoma, a rarity, was first described in 1973 by Hart and Earl as supratentorial primitive neuroectodermal tumors. They are extremely variegated in histology and this reflects in their imaging characteristics. CNS-PNET tumors include CNS PNET –not otherwise specified (NOS), CNS neuroblastomas, CNS Ganglioneuroblastomas, Medulloblastomas and Ependymoblastomas. According to WHO, CNS PNET are embryonal tumors composed of undifferentiated or poorly differentiated neuroepithelial cells which have the capacity for, or display divergent differentiation along neuronal, astrocytic, ependymal, muscular or melanocytic lines. Tumors showing neuronal differentiation are termed as CNS neuroblastomas, as well as those showing neuroplastic ganglion cells are termed as CNS ganglioneuroblastoma. Tumors showing features of embryonal neural tube formation are called medulloepitheliomas whereas those with ependymoblastic rosettes are known as ependymoblastomas (Heideman RL et al., 1997; Bennett J et al., 1984). Features to all CNS PNET variants include early onset and aggressive clinical behavior.

Horten and Rubinstein stated that the incidence of primary cerebral neuroblastoma is approximately one case every decade (Becker LE et al., 1983). It was reported that cerebral neuroblastoma constitutes 6% of whole CNS PNET

(Bennett J et al.,1984).The revised WHO classification of pediatric brain tumor used the term PNET with neural cells instead of cerebral neuroblastoma.

Being an uncommon tumor, it is essential to know the histopathological features for differential diagnosis. The production and maturation of neurons from multipotential cells occur in few stages. Stage I or the neurocytogenesis phase exhibits neural development with active cell division but cellular differentiation is not seen at this stage. Stage II shows the origin of neuroblast. The neuroblasts have potential for maturation but are unable to divide in stage III. Thereafter they become neurons (Rubinstein LJ,1972 ; Feigin I et al.,1974)

Thus, neuroblastoma emerges at the second stage of cytogenesis showing a different maturation along one cell line toward neurons (Becker LE et al.,1983; Horten BC et al.,1976; Kosnik EJ et al.,1978; Yagishita S et al.,1978). In some cases, beginning of differentiation toward neurons has been observed (Ahdevaara P et al.,1977). Maturation to adult cell forms is sometimes seen but is more often lacking. Frequently these tumors are so difficult to recognize that some neoplasms, which were originally described as medulloblastoma, ependymoma, undifferentiated primary sarcoma or poorly differentiated oligodendroglioma by some authors, were indeed neuroblastomas (Feigin I et al.,1974; Cushing H, 1930).

Primary CNS neuroblastoma mostly occurs in the first decade with a predilection for parietal and frontal lobes (Becker LE et al.,1983; Berger MS et al.,1983; Dehner LP et al.,1988).In the present case, the tumor was located in fronto-parietal region of a ten-year-old girl.

Clinical presentation is non-specific and cannot be distinguished from other aggressive intracranial masses, invariably showing symptoms of increased intracranial tension, seizures and focal neurological deficit. The mostcommon presenting symptoms and signsare of increased intracranial pressure, since the tumor expands rapidly. In our case the patient had complaints of headache associated with projectile vomiting for last 2 months.

Grossly the tumor is generally well circumscribed withgreyish cut surface and extensive areas of hemorrhage and necrosis (Becker LE et al.,1983; Berger MS et al.,1983; Dehner LP et al.,1988). Secondary attachment with dura is generally formed thus necessitating differentiation from meningioma (Rubinstein LJ, 1981). The gross received in this institute also showed areas of hemorrhage along with attachment to the overlying dura and bone.

Histologically the tumors are highly cellular, showing round to oval cells with hyperchromatic nuclei. Homer-Wright rosette formation is seen in about a quarter to third of cases(Rosai J, 2102) along with areas of hemorrhage and necrosis. These findings were similar to that seen in the present case. Also seen, were areas of osteoid like material along with invasion of tumor cells into the overlying dura and bone.To establish the diagnosis, IHC was required. Silver impregnation studies were not done in this case, but immunohistochemical studies were done which showed positivity for vimentin,a mesenchymal marker, neuron specific enolase, marker of neuronal differentiation, weak positive for synaptophysin, also a neuroendocrine marker, and negative for cytokeratin.

PNET showingvariable microscopic features, such as pleomorphism, glial differentiation,cellular indiffrentiation and fewer noticeable connective tissue areas,show difficulty in confirming adifferential diagnosis using light microscope, but ultra-structural analysis is highly helpful (Ahdevaara P et al.,1977; ,Grisoi F et al..981; Rhodes RH et al., 1978).A unique feature, which sharply distinguishes cerebral neuroblastoma from other neuroepithelial neoplasm, is the unusual capacity of these tumor cells for stromal induction. According to degree and extent of stromal connective tissue, they are classified into 3 subgroups. These include, classic, desmoplastic and transitional types. The classic variant shows limited connective tissue with frequent rosette formation, where as the desmoplastic type shows intense desmoplasticstroma, and the transitional type is intermediate between the two.A prominent homogenous eosinophilic connective tissue component was seen in between highly pleomorphic undifferentiated looking cells in our case, so a differential of poorly differentiated sarcoma was also considered, but in view ofNSE positivity, a diagnosis of neuroblastoma was made.

The present case predominantly mimics a diagnosis of classical neuroblastoma as large areas of rosettes were seen, but peripheral areas showed homogenous eosinophilic connective tissue component with calcification so a differential of poorly differentiated sarcoma was also considered. However in view of NSE positivity, these areas were now considered stromal induction in a neuroblastoma mimicking areas of desmoplasticneuroblastoma.



Also presence of rosettes and IHC panel showing positivity for vimentin and NSE with negativity for cytokeratin favors a diagnosis of neuroblastoma with focal mesenchymal differentiation (unusual PNET “embryonal tumor with abundant neutrophil and true rosette”)

### Conclusion:-

Thus to conclude, primary cerebral neuroblastoma are rare and highly malignant tumor and may present with unusual varied histopathology along with foci of different cellular differentiation thus creating a diagnostic dilemma. It should always be considered as a differential diagnosis in children presenting with signs and symptoms of raised intracranial tension, seizures and focal neurological deficit.

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