Primitive neuroectodermal tumor of the orbit: A case report.

Dr. Ashka Shah[1*], Dr. Ruju Unadkat[2], Dr. Swati Ravani[3], Dr Kruti Shroff[4]

[1,4] Third year resident, [2]Second year resident, [3]Associate Professor and Head, Oculoplasty Clinic, M & J Western Regional Institute of Ophthalmology, B. J. Medical College & Civil Hospital, Ahmedabad, Gujarat.

Abstract:

Primitive neuroectodermal tumor (PNET) is a small round cell malignant tumor of neuroectodermal origin.It is seen in young adults, rarely involves the orbit and affects males and females equally. Most of the PNETs occur in the central nervous system (CNS). PNETs recognized outside of CNS are diagnosed as peripheral PNET (pPNET). pPNET shows characteristic small round cell tumor with rosette or pseudo-rosette, positive immunohistochemistry (IHC) and in some cases ultrastructural findings of neurosecretory granules. It expresses MIC-2 gene (CD99) and is said to be least aggressive after complete tumor resection. We report a case of a twelve-year old male child presenting with unilateral eccentric proptosis diagnosed as primary peripheral primitive neuroectodermal tumor (pPNET) on histopathology and immunohistochemistry. We describe its distinguishing features with emphasis on multimodal and aggressive treatment approach which ensures appropriate management of these cases.

Keywords: - CD 99, Ewings sarcoma, orbit, Primitive Neuroectodermal tumor.

Introduction:

Primitive neuroectodermal tumor (PNET) is a small round cell malignant tumor of neuroectodermal origin. It is seen in young adults and adolescents, rarely involves the orbit and affects males and females equally. Most of the PNETs occur in the central nervous system (CNS)and the ones occurring elsewhere are called peripheral PNET (pPNET). pPNET shows characteristic small round cell tumor with rosette or pseudo-rosette, positive immunohistochemistry (IHC) and in some cases there are ultrastructural findings of neurosecretory granules. It expresses MIC-2 gene (CD99) and is said to be least aggressive after complete tumor resection.

Ewing's sarcoma is a sarcoma of bone, classically described under small round cell tumors. There is considerable clinical and histologic overlap between this tumor and the PNET. Ewing's sarcoma arises within the bone, but can also occur within the soft tissue (extra-osseous Ewing's sarcoma) and PNET arises within soft tissues. Ewings Sarcoma mainly affects the pelvis and the femur region and predominates in the second decade of life.The term, "PNET" includes tumors of the thoracopulmonary region (Askin's

* **Corresponding Author:**
Dr. Ashka Shah
Email: ashkashah12@gmail.com

QR Code:

tumor), extraskeletal Ewing's sarcoma, peripheral neuroblastoma, and peripheral neuroepithelioma.[1]

PNETs of the orbit are rare and generally not included as common differentials for orbital tumors.We report a case of a twelve-year old male child presenting with unilateral eccentric proptosis with mass involving extraconal and intraconal compartment, diagnosed as primary peripheral primitive neuroectodermal tumor (pPNET) on histopathology and immunohistochemistry.Ours is the third case of orbital PNET in literature to show positiveMIC-2 fraction of immunohistochemistry.[2,3] We describe its distinguishing features with emphasis on multimodal and aggressive treatment approach which ensures appropriate management of these cases.

Case report:

A twelve-year-old male child presented to our outpatient department with protrusion of the right eye associated with redness and watering since 15 days. [Image 1] There was no history of trauma, foreign body, chronic cough, fever, weight loss or any other systemic symptoms.

On examination, a solid, irregular, nontender, firm, fixed, non-pulsating globular mass was palpated in the supero-temporal quadrant of the right orbit. Ocular movements in right eye were restricted in lateral superior and medial gaze. Magnetic Resonance Imaging(MRI) and Commuted Tomography (CT) scans of the orbit and brain showed presence of well defined, osteolytic soft tissue lesion in superolateral aspect of right orbit with erosion of greater wing of sphenoid and zygomatic bone resulting in proptosis. [Image 2]

Basic blood investigations including cell counts, renal function tests, chest x-ray were within normal limits. Screening tests for HIV and HBsAG were negative. Right eye orbitotomy was done under general anaesthesia and en bloc excisional biopsy of the tumour was done and sent for histopathological examination. On gross examination, 1.8*1.5 cm sized greyish brown mass was found. It was embedded in paraffin and sections were stained with hematoxylin-eosin. Microscopic examination of the tumour revealed scattered cells with round ovoid nuclei many of which showed hyperchromasia & vacuolated cytoplasm. Tumour cells admixed with few eosinophilic areas of necrosis were seen with findings suggestive of malignant round cell tumour. [Image 3]

Sections were studied by IHC for vimentin:positive ,CD99(MIC 2):positive, FLI-1:positive, Tdt:positive, CD20(PanB):negative.[Image 4] On the basis of these findings, a diagnosis of malignant round cell tumor ;primary pPNET of the orbit was made. Patient was symptomatically better after surgery. Patient was referred to an oncologist for complete systemic evaluation. CT Scan of brain, paranasal sinuses,neck thorax, abdomen & pelvis was suggestive of residual lesion in right orbit, few nodes in bilateral level 2&5, axilla, preparatracheal region mesentery, upper mid lower paraaortic region. Patient is currently undergoing chemotherapy (18 cycles of ifosfamide and etoposide) for residual lesion and extraorbital involvement as advised by the oncologist.

Image 1: Gross image showing proptosis.

Image 2: MRI Skull -t showing mass in both intraconal and extraconal compartment.

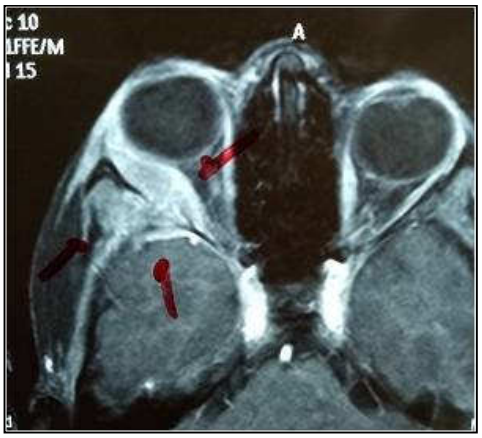


Image 3: Round cell tumor H&E (10X)

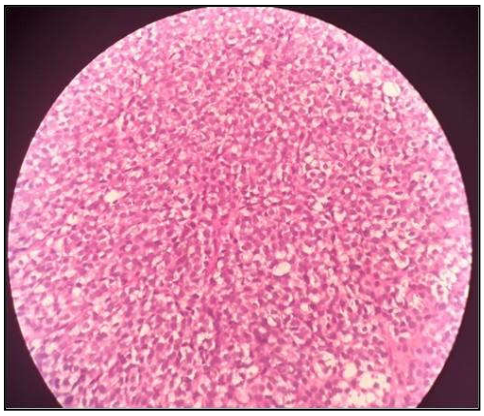
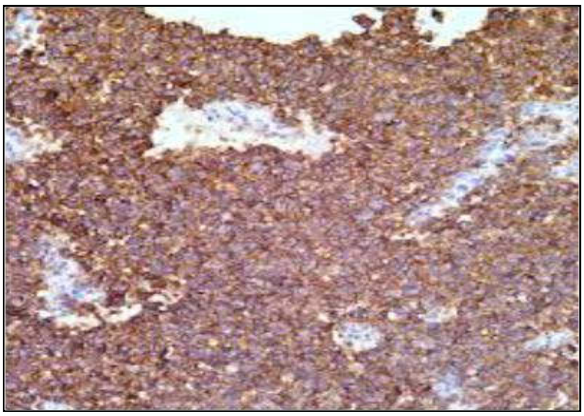


Image 4: CD99 positive marker Immunohistochemistry (10X)



Discussion:

Primitive neuroectodermal tumors are believed to have a neural histogenesis based on evidence of neuroectodermal differentiation.The differential diagnosis of pPNET of the orbit includes other small blue round cell tumors which include rhabdomyosarcoma (Actin+, Vimentin+, Desmin +, S-100-ve), Ewing's sarcoma (PGP9.5+, MIC-2+), lymphoma (LCA+, CD45+/CD20+/ CD3+), neuroblastoma (PGP9.5+, MIC-2 –ve) and metastatic retinoblastoma to orbit (NSE+, GFAP+).[4] Immunohistochemistry helps in differentiating this entity from other tumors. Lack of staining with desmin and myoglobin excludes the possibility of rhabdomyosarcoma. CD45 helps to differentiate it from lymphoma and Factor VIII to rule out vascular tumors.

Microscopically, primary peripheral PNET is cellular tumor with characteristic small round cells with hyperchromatic nuclei, and a high nuclear–cytoplasmic ratio. Ultrastructural studies by electron microscopy show cytoplasmic filaments and neurosecretory granules. This may aid in the diagnosis of neuroectodermal tumor and to differentiate it from extraosseous Ewing's sarcoma.[4,5,6] There are varying degrees of neuronal differentiation,

beginning with NSE expressivity, followed by Homer–Wright rosette formation, phenotypic ganglion cell differentiation, and finally by neurofilament protein expression. Presence of Homer-Wright rosettes is associated with these tumors but it is not diagnostic of these tumors.[7] Pseudo-rosette formation and strong membrane positivity for the MIC-2 gene product in IHC is the hallmark for diagnosis of pPNET. In some cases they are NSE, synaptophysin and S-100-positive.[7]

Alyahya et al. had reported an orbital, intraconal pPNET in a five-year-old child with microphthalmia since birth. Their case report was the first orbital case of pPNET to express the MIC-2 gene.[2] The MIC-2 gene is a pseudo-autosomal gene located on the short arms of both X and Y chromosomes. The proteins programmed by MIC-2 gene are neuraminidase and protease sensitive. Since the MIC-2 gene products are most strongly expressed on cell membranes of Ewing's sarcoma and pPNET, expression of the gene products allows for the differentiation of these tumors from other round cells tumors of childhood and adolescence.[8]

Out of nine previous reported cases of isolated orbital PNET,[4,9,10] age group varied from less than one year to 13 years with two cases reported in adults (52 years and 28 years). There was a predilection for lateral orbit in five cases, inferior orbit in three cases and superior orbit in one case. Bony involvement was present in three cases. Our case showed involvement of the superior orbit with involvement of sphenoid and zygomatic bone.

Management varied as three cases were treated with external beam radiotherapy and two cases with bone involvement were managed by both external beam radiotherapy and chemotherapy. The remaining four patients were not given additional chemotherapy or radiotherapy. Our case was managed with primary resection which was followed by 18 cycles of chemotherapy (ifosfamide and etoposide) for residual lesion under guidance of oncologist. Radiotherapy was not advised in our patient. Patient is currently on his 4th cycle of chemotherapy and shows no signs of recurrence or new lesion at 3 month follow up. However a longer follow up and observation is required to determine the prognosis of this patient.

Conclusion:

The present case report highlights that differential diagnosis of hypercellular small round cell tumor of the orbit should be recognized and pPNET must be considered as possible diagnosis by the ocular pathologists. This rare tumor can be confirmed by IHC. Management should be comprehensive with a dedicated team of ophthalmologist, oncologist and radiotherapist aggressively managing the condition.These patients should be followed up for life to rule out recurrence, metastasis and treatment-related malignancies.

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