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PRIMITIVE BLASTOMA
PERIPHERAL PRIMITIVE NEUROECTODERMAL TUMOR OF THE MANDIBLE

Dentistry

Dr. Dinesh Pilania MDS Senior Resident, Dept of Dentistry Dr. S N Medical College.

Dr. Vikas Deo* MDS Professor & Head Dept of Dentistry Dr. S N Medical College. *Corresponding Author

Dr. C S Chattopadhyay MDS Associate Professor Dept of Dentistry Dr. S N Medical College.

ABSTRACT

Peripheral primitive neuroectodermal tumors (pPNET) are high-grade malignant tumors seen in the early age group {5-25 year}, primarily affecting long bones of extremities afterwards the pelvis, ribs and vertebrae. pPNET in the mandible (head & neck) accounts for only 2% of the reported cases. pPNET agitate difficulty in arriving at a diagnosis due to poor differentiation of small round cells and could be established only by histopathology and immunochemistry. Surgery with chemotherapy is the preferrable treatment of choice in the mandible. In this article, we describe a rare case of PNET of the mandible in 11-year-old boy and review of literature.

KEYWORDS

Primitive blastoma, Peripheral primitive neuroectodermal tumor, Ewing's sarcoma family of tumor.

INTRODUCTION: -

In 1973, ***Hart and Earle***[1] coined the term "primitive neuroectodermal tumor" (PNET), which lime lights the primitive nature of the tumor rather than to its histogenesis. PNET is primarily a disease of childhood[2]; in rare cases, pPNETs of the head and neck region (mandible, cerebellopontine area, and skull base) have been reported.[2] pPNETs and Ewing family of tumors (EFTs) are often mentioned to interchangeably in the literature. Generally, EFTs and pPNETs express different manifestations of the same tumor and have alike genetic alterations. Ewing sarcoma, however, is more usual in bone, while pPNETs are in soft tissues. ESFTs comprise osseous and extra osseous ES, peripheral primitive neuroectodermal tumor (pPNET), and Askin tumors of the thorax. The diagnosis of ES and pPNET is based on a combination of light microscopy, immunohistochemistry, and, if necessary, electron microscopy. Other valuable diagnostic methods include cytogenetic and molecular biologic analysis. Correct diagnosis is critical for the selecting of therapeutic protocols and significantly influences outcome therapy.[3, 4] The combination of both immune phenotypic and genetic analysis with classical morphology has proved useful not only on diagnostic grounds, but also in the context of prognostication.

CASE REPORT: -

An 11 -year-old boy reported with the complaint of swelling on the right side of the face {Fig 1a}. Swelling started 1 month back for which the patient underwent extraction as it was misdiagnosed as an abscess and gradually enlarged to the present size. Extra-orally a diffuse swelling on the right side of the face which extended supero-inferiorly from the ala to tragus, antero-posteriorly from the commisure of mouth to the angle of mandible. Intra-orally, swelling extended from the right canine to the right second molar {Fig 1b}. The swelling was nontender and hard in consistency on palpation without any perforation of the buccal/lingual cortex. No paresthesia of the lower lip was seen. Radiographic findings {CT} showed a sunburst appearance extending from the right mandibular ramus region to the left mandibular canine crossing the midline, provisionally diagnosed as Osteo-sarcoma /Ewing sarcoma {Fig 2a & b}.

On histopathological examination, fibrous, myxomatous connective tissue which was highly cellular & lobulated was noted & lobules were made of round to pleomorphic hyperchromatic cells with rhabdoid morphology & prominent nuclei. The margins of the cell were ill defined & showed anisocytosis. These features were suggestive of an undifferentiated round cell tumor.

IHC investigations were carried out to confirm the clinical diagnosis where the tumor cells expressed neural markers CD56, Synapto physin, Chromogranin A & were immune negative for Desmin Myogenin, Mic -2, LCA, CD 30, CD 20, CD 3, Cytokeratin, EMA, HMB -45, CD-138, S-100 protein & P 63.

The definitive diagnosis in this case was very complex because although it was positive for neural markers CD56, Synaptophysin & Chromogranin A, but surprisingly it was negative for CD99 which is a definitive marker for Ewing sarcoma/ pPNET. Therefore, with the use of immunohistochemical markers the final diagnosis of "Primitive blastoma" of neuro ectodermal origin was made. A surgical procedure was carried out to resect the lesion with magnanimous surgical margins and to reconstruct the resulting defect. The patient underwent wide resection of the right-side mandible after one cycle of primary induction chemotherapy {Fig 3, 4}. The bony defect was reconstructed with a reconstruction plate {Fig 5}. Adjutant chemotherapy comprised 1 cycle of treatment after surgery {Fig 6a, b & c}.

Fig: 1 Intraoral swelling.

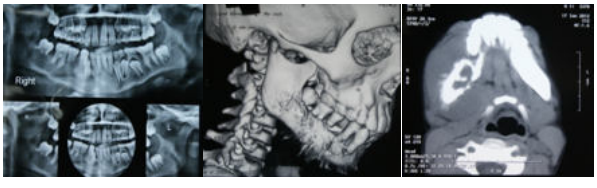

Fig: 2{a, b} Pre-operative: a) OPG **b) CT scans.**

Fig: 3 Incision **Fig: 4 Resected Lesion** **Fig: 5 Reconstruction**

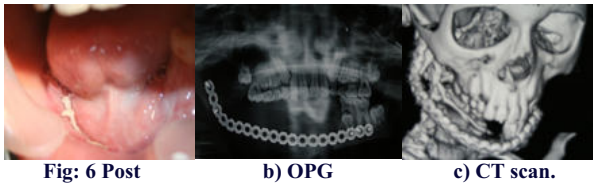

Fig: 6 Post operative: a) Intraoral **b) OPG** **c) CT scan.**

DISCUSSION: -

Primitive neuroectodermal tumors (PNETs) are a group of high-grade

malignant tumors comprised of small round cells of neuroectodermal origin that affect soft tissue and bone. PNETs exhibit great diversity in their clinical manifestations and pathologic similarities with other small round cell tumors. This has made classifying this family of tumors challenging and controversial. ***Batsakis et al*** [5](1996) divided the primitive neuroectodermal tumor (PNET) family of tumors into the following 3 groups based on the tissue of origin:

1. CNS PNETs - derived from the central nervous system.
2. Neuroblastoma - derived from the autonomic nervous system.
3. pPNETs - derived from tissues outside the central and autonomic nervous system.

pPNETs are also classified as part of the Ewing family of tumors (EFTs). Ewing sarcoma, however, is more common in bone, while pPNETs are more common in soft tissues. Immunohistochemical and cytogenetic studies suggest that these tumors all have a common origin.

The following tumors are classified as pPNETs:

1. Ewing sarcoma (osseous and extra osseous)[6]
2. Malignant peripheral primitive neuroectodermal tumors (pPNETs) or peripheral neuro-epithelioma of bone and soft tissues
3. Askin tumor (peripheral neuro-epithelioma of the thoracopulm onary region)
4. Other less common tumors (e.g., neuroectodermal tumor, ectomesenchymoma, peripheral medulloepithelioma)

Stout[7] first described PNETs in 1918, and these tumors were thought to arise directly from nerves. Most pPNETs are apparent in the thoracopulmonary region (Askin tumor), pelvis, abdomen, and extremities. ***Jones and McGill*** [8] reported 11 out of 26 patients with disease in the head and neck. Other published series, however, reveal a paucity of cases in the head and neck region.[9,10,11] Of the published cases involving the head and neck, the sites of presentation are diverse and include the para-nasal sinuses, jugular foramen, oral cavity, nasal cavity, neck, skull, lingual nerve, parotid gland, larynx, retropharyngeal space, maxilla, mandible, masseter, temporal area, pterygomaxillary space, esophagus, and orbit.

Clinical symptoms depend on the site of involvement but invariably include pain and swelling of the surrounding structures due to mass effects. Other reported symptoms and signs are site specific, including individual cranial neuropathies, exophthalmos, epistaxis, nasal obstruction, anosmia, neck mass, and headache.

Differential diagnosis for other small, poorly differentiated, round cell tumors of the head and neck included pPNETs / EFTs, malignant lymphoma, poorly differentiated salivary gland tumors, rhabdomyo sarcoma, neuroblastoma, and undifferentiated nasophary ngeal carcinoma.[8]

Light microscopy, cytogenetic analysis, and the immunohistochemical profile of tumor cells are essential in diagnosing pPNETs. On light microscopy, pPNETs appear as a monotonous collection of small, round, darkly stained cells. However, pPNETs cannot be distinguished from other tumors with small round cells based on histologic studies alone. Other tumors with a similar appearance on light microscopy include rhabdomyosarcoma, neuroblastoma, and non-Hodgkin lymphoma. In these tumors, Homer-Wright rosettes, in which the tumor cells are arranged about a central space filled with fibrillar extension of the cells, can be found. Examination of pPNETs with electron microscopy reveals neurosecretory granules with microtubules and microfilaments. In addition, short dendritic processes lie between cells in pPNETs, in contrast to Ewing sarcoma, in which the dendritic processes are absent.

Cytogenetic analysis of peripheral pPNETs reveal the close relationship among tumors in the EFTs. Approximately 85% of all EFTs includes a translocation that involves the *EWS* gene (22q12) and FLI-1 (11q24).[12] In the other 5-10% of cases, the translocation is found between EWS and ERG (21q22).[13]

The interpretation of the immunohistochemical profile allows the pathologist to distinguish pPNETs and EFTs from other small round cell tumors. Immunohistochemistry can be used to detect antibodies to FLI-1 in the gene fusion product of EWS.[14] The expression of the MIC2 gene produces an antigen, MIC2, which consistently identifies both Ewing sarcoma and pPNETs. In contrast, CNS PNETs and neuroblastomas uniformly lack the expression of the *MIC2*.[15] Furthermore, pPNETs typically coexpress CD99 (the glycoprotein *MIC2*) and vimentin.[16] Other nonspecific markers include S-100, neuron-specific enolase, CD75, and synaptophysin. Tissue biopsy with cytogenetic and immunohistochemical studies are of prime importance in diagnosing pPNETs.

Radiologic studies such as CT scans and MRI are essential in determining the limits of tumor involvement and ruling out metastatic disease. On CT scans, pPNETs appear as heterogeneous masses, often invading surrounding tissues, including bone. MRI reveals a mass isointense to muscle on T1-weighted images, while hyper intense on T2-weighted images.[17] Because of the high incidence of metastasis, a full workup is indicated in a suspected case of pPNET, including chest radiography, CT scanning of the chest, and bone marrow biopsy. Furthermore, the diagnosis of pPNET is based on biopsy findings, more extensive investigations, such as a technetium 99m bone scan or positron emission tomography (PET) scan, may be indicated. Other adjunctive studies include testing for urinary catecholamines and their metabolites, which are positive in patients with neuroblastoma but negative in patients with PNET and EFTs.

The significant prognostic factors of pPNETs include site, tumor volume, and the presence of metastasis. ***Kimber et al***,[18] in a review of 26 patients with pPNET who were treated with chemotherapy, reported that patients with head and neck pPNET had an intermediate prognosis when compared with patients with paraspinal and scapular disease (who fared better) and those with abdominopelvic disease (who fared much worse). Because pPNETs are highly aggressive, patients may have metastatic disease at presentation.

Using RT-PCR technology, several groups have demonstrated micro-metastasis in the bone marrow of up to 30% of patients thought to have localized disease. The most common sites of pPNET metastases include the lung, bone, and bone marrow. In several large series, the rates of metastases range from 20-31%, with abysmal long-term survival rates (< 25%). ***Kushner et al***,[10] in a review of Memorial Sloan-Kettering's experience with pPNET, reported a similarly dismal 25% progression-free survival rate at 2 years in patients with only localized disease. Other series, however, reported better survival rates in patients with localized disease, with 2 large trials showing 2-year and 3-year survival rates of 65% and 56%, respectively.[8,9]

Obtaining a complete resection of the disease with negative margins is paramount in surgically treating primitive neuroectodermal tumors (PNETs) in the head and neck. In some cases, however, the aggressive nature and diffuse spread of these tumors precludes complete surgical excision. Furthermore, complete surgical resection may not be possible when vital structures are involved.

Enneking classification of surgical intervention[19]

1. Intralesional resection	Tumor opened during surgery, or surgical field contaminated, or microscopic or macroscopic residual disease.
2. Marginal resection	Tumor removed en bloc; however, resection through the pseudo capsule of the tumor; microscopic residual disease likely.
3. Wide resection	Tumor and its pseudo capsule were removed en bloc, surrounded by healthy tissue within the tumor-bearing compartment.
4. Radical resection	The whole tumor-bearing compartment removed en bloc.

Chemotherapy and radiation are necessary adjuncts in the treatment of PNETs. Chemotherapy regimens have significantly improved outcomes in patients with pPNETs. The treatment protocol differs based on whether the disease is localized or metastatic. As would be expected, the treatments for pPNETs and EFTs are similar in terms of chemotherapeutic regimens.

Current recommendations advocate complete surgical resection whenever possible, adjuvant versus neoadjuvant chemotherapy, and radiotherapy. Multimodality treatment is advocated to prevent metastatic disease, recurrent disease, and to treat residual tumor after resection. ***Carvajal and Meyers***[20], in a comprehensive review of chemotherapeutic regimens in the treatment of PNETs and Ewing

family of tumors (EFTs), recommend a regimen that includes vincristine, doxorubicin, and cyclophosphamide with ifosfamide and etoposide (IE).

A mitigating factor in the adjuvant use of radiotherapy is the known complication of a second sarcoma that develops subsequent to treatment with radiation. In childhood cancer survivors followed through the SEER cancer registry, the greatest risk of subsequent cancer occurred among those previously diagnosed with EFT and PNETs, nearly a 6-fold increase compared to the general population.[21] The incidence of secondary malignancies increases substantially with radiotherapy treatment doses of more than 60 Gy. ***Kuttesch et al*** [22]reported that 20% of patients who received doses of more than 60 Gy developed secondary malignancies, compared with only 5% in those who received 48-60 Gy. Those treated with less than 48 Gy had no additional risk of second malignancies. While outcomes vary based on disease subsite; patients with metastatic disease uniformly have poor outcomes ranging from 0-25% 5-yr survival rates compared to 40-79% for those with localized disease.[23]

SUMMARY:

pPNETs are a group of aggressive malignancies that commonly involve the thoracopulmonary region (Askin tumor), abdomen, pelvis, and, rarely, in the head and neck. The most significant prognostic factor is the presence or absence of metastasis. Advancement in the diagnostic technology like cytogenetic & immunohistochemistry, as well as improved modalities in the neoadjuvant & adjuvant chemotherapeutic regimens, should improve long-term disease-free survival.

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