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Oral primitive neuroectodermal tumor associated with mandibular lymphadenopathy in three-year-old female Indonesian children: A rare case report

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Abstract
Introduction: Primitive neuroectodermal tumors (PNETs) are rare and aggressive malignancies derived from primitive neural crest cells in the CNS, with peripheral variants known as peripheral PNETs (pPNETs) found in soft tissues. Diagnosing PNETs is challenging due to their rarity and resemblance to other neoplastic conditions like Ewing's sarcoma and rhabdomyosarcoma.
Case Presentation: A 3-year-old female child presented with a growing bump on her lips, causing obstruction of the mouth and both of the nostrils hence impairing daily living. Examination revealed an irregular mass with signs of tissue necrosis and bleeding. A blood test and head CT scan indicated a benign mass, potentially a hemangioma, with submandibular lymphadenopathy and leukocytosis. The patient underwent a debridement procedure and a subsequent operation to excise part of the mass for histopathological analysis. The results revealed a primitive neuroectodermal tumor, specifically a melanotic neuroectodermal tumor of infancy (MNTI).
Discussion: Peripheral PNETs are more commonly seen in older individuals with abdominal/pelvic and thoracic-pulmonary lesions being the most frequent. Our case of a 3-year- old Indonesian child with a distinct oral cavity PNET is considered rare among the age and race groups.
Conclusion: The case of a three-year-old Indonesian female child with peripheral PNET in the submandibular region is an uncommon presentation in terms of age, tumor location, race, and ethnicity. Clinicians should be aware of such rare possibilities and follow thorough histopathology and immunohistochemistry tests to establish an accurate diagnosis.

Keywords: Primitive neuroectodermal tumor, PNET, oral cavity

Introduction
A primitive neuroectodermal tumor (PNET) is a rare and aggressive malignancy that arises from primitive neural crest cells in the central nervous system (CNS) [1]. However, the identification of these tumors in the soft tissues of the trunk and axial skeleton demonstrated the existence of variants of peripheral primitive neuroectodermal neoplasms (pPNETs) that were probably derived from undifferentiated mesenchyme [2-4]. pPNET is considered a well-differentiated version of the small cell tumor family, while Ewing's sarcoma and Askin's thoracic tumor are considered poorly differentiated variants of small round cell tumors (tumors in the Ewing's sarcoma family) [4]. Identifying and accurately diagnosing PNETs can be challenging due to their rarity and overlapping features with other neoplastic conditions. The diagnosis of this lesion is often confused by its histopathological similarity to Ewing's sarcoma and rhabdomyosarcoma, resulting in insufficient literature to establish definitive treatment strategies for their management [2, 5]. Therefore, it is extremely important to document and discuss their diagnostic morphological, histological presentation, and treatment protocol. The purpose of this article is to highlight one such case of pediatric mandibular PNET referred to our center.

Case
Presentation: A 3-year-old female child was referred to our center with a noticeable bump on her lips. The patient complained of a mass obstructing her mouth and nose. The patient reported that the mass had first appeared when she was 1.5 years old, but over the past month, it had grown in size and started causing obstruction of the mouth and both of the nostrils. The patient also complained of difficulty eating and breathing (Due to the obstructing mass).

Table 1: Initial Blood Work Result

Test Parameter	Values
Hemoglobin	9.2 g/dL
Hematocrit	28%
Leukocyte Count	15.4 x 103/µL
Thrombocyte Count	421 x 103/µL
Erythrocyte Count	3.40 x 103/µL
PT	13.5 s
APTT	25.2 s
INR	1.000 s
Random Plasma Glucose	94 mg/dL
Blood Types	O+
Serum Ureum	15 mg/dL
Natrium Serum	133 mmol/L
Potassium Serum	4.1 mmol/L
Chloride Serum	106 mmol/L
HbsAg	Non-Reactive

Upon examination, an irregular mass was observed originating from within the oral cavity in the submandibular area (Fig 1A). The lesion appeared irregular and had a curtsied shape, with signs of tissue necrosis and active bleeding at the apex of the mass. Considering the concerning appearance of the lesion, a blood test and head CT scan was ordered. The imaging findings suggested a benign mass, possibly a hemangioma, along with submandibular lymphadenopathy. The blood work revealed a marked leukocytosis. The patient opted for a debridement procedure, which was performed at our center one month before the first partial excision surgery to partially remove the mass. After the debridement procedure, the necrotic and prone-to-bleed tissue was removed (Fig. 1B).

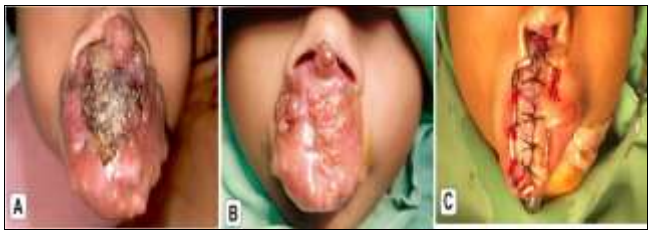

Fig 1: Pictures of initial lesion appearance (A); After debridement and first partial excision surgery (B); After the reclosing of the wound after the second partial excision surgery (C).

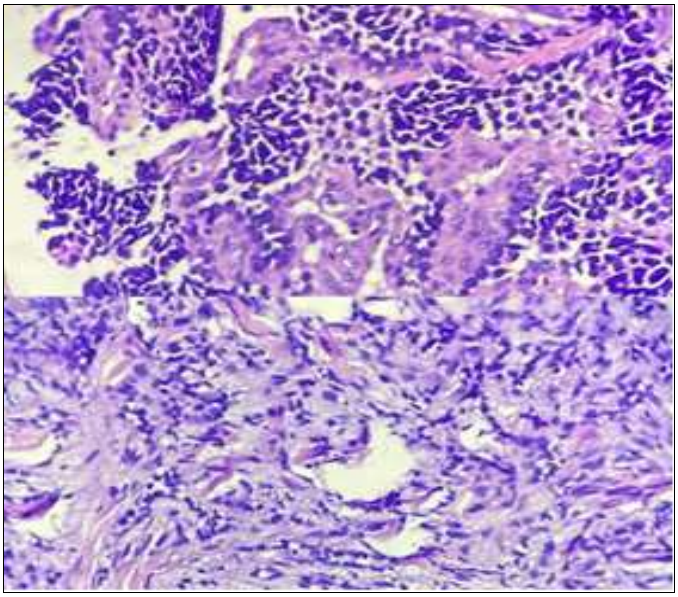

Fig 2: The patient's histopathology result suggests peripheral PNET.

A serial follow-up operation was conducted later with the goal to excise a part of the mass and obtain a histopathology sample for further analysis. The objective of the first (early) partial excision surgery is to remove the remaining or reappearing necrotic tissue and to reduce the size of the mass gradually (to relieve patients' breathing difficulty). However, the wound become dehisced due to suboptimal wound care (due to the patient's age). Hence, the wound was re-sutured. After the mass was partially excised, a tissue sample from the upper lip region was obtained and sent to the pathology anatomy department to be assessed further.

Pathology anatomy analysis of the sent tissue from the second and third surgery reveals microscopic findings of a group of lobulated tumor cells with invasive epithelioid appearance. The cells appeared uniform with a predominant atypic nucleus, hyperchromatic with a rosette appearance (Fig. 2); Suggesting a primitive neuroectodermal tumor.

Discussion

Primitive neuroectodermal tumors (PNETs) can be classified into two main categories based on their location: central and peripheral. Central PNETs primarily originate in the central nervous system (CNS), including the brain and spinal cord.6 These tumors commonly exhibit an intracranial or intraspinal location and are associated with symptoms such as headaches, seizures, and neurological deficits [6]. Histologically, central PNETs demonstrate small round blue cells with high cellularity and a characteristic Homer Wright rosette formation, indicating neuronal differentiation (Fig. 3) [7]. On the other hand, peripheral PNETs arise in soft tissues outside the CNS, such as the trunk, limbs, or peripheral nerves. These tumors may occur in sites like the chest wall, abdomen, pelvis, or extremities [1-4, 8, 9].

Peripheral PNETs share similarities with central PNETs in terms of histology, showing small round blue cells and a high proliferation rate. Peripheral PNETs also showed a Homer-Wright rosette formation similar to PNETs with mitotic figures, necrosis, and endothelial hyperplasia [8, 9].

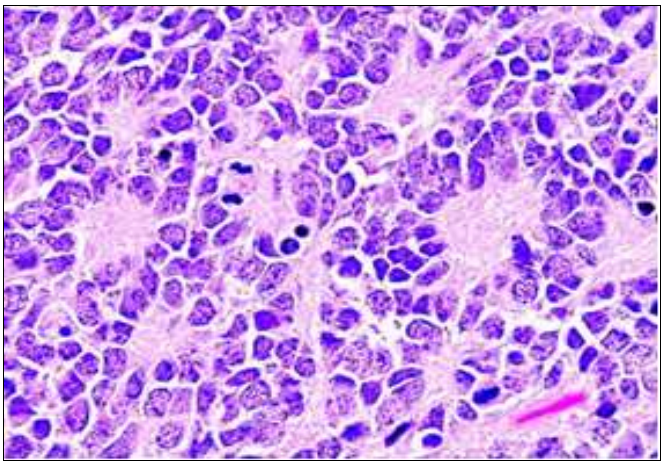

Fig 3: A PNET photomicrograph showing multiple Homer Wright rosettes. Each rosette's halo-like cluster of cells surrounds a central area of fiber-rich neuropil (H&E; 400x magnification).7

The incidence of PNET, in general, is 0.15 per 100,000 children aged 0–4 years and 0.15 per 100,000 children aged 5–9 years. 0.05 per 100,000 and 0.04 per 100,000 children aged 10–14 years. 0.03 per 100,000 adolescents ages 15–19.10 However, the actual incidence of peripheral PNET is still difficult to estimate due to its rarity, the upbringing of certain cases only relies on case reports and review. Hence, in itself is considered a very rare

disease.

Based on a recent literature review on peripheral PNETs, people over the age of 20 are more likely than those under the age of 20 to develop peripheral PNETs. The most common lesions were abdominal/pelvic, followed by thoracic-pulmonary lesions. Areas, where involvement is less common, are the paraspinal and head and neck regions. Extremities were the least reported cases of this lesion. This tumor occurs slightly more often in women than in men [11].

Our 3-year-old Indonesian case is considered rare among the age and race groups. There hasn't been a documented case report among the Indonesian race and ethnicity developing PNETs or pPNETs. This case is considered to be within the youngest group of pPNETs onset, previously documented from India recorded the age of 3 months to 7 years old individuals developing pPNETs.12 Also, the progression of tumors originating from the oral cavity itself is not a common finding in pPNET cases documented [4, 9].

In this particular case, a tissue sample was obtained from the second surgery following the debridement procedure. The sample was sent to the histopathological department. The pathologist concluded that the appearance of invasive, epithelioid, and lobulated, cells with rosette appearance was suggestive of neuroepithelial cells of origin. The diagnosis of PNET was made only based on histopathological characteristics, however, the pathologist suggests a follow- through test for immunohistochemistry to be done.

Establishing a diagnosis of primitive neuroectodermal tumors (PNETs) requires a comprehensive approach that combines clinical evaluation, imaging studies, histopathological examination, and molecular testing. The gold standard test for confirming the diagnosis of PNETs is histopathology, which involves the microscopic examination of tissue samples obtained through biopsy or surgical resection. The histopathological analysis allows for the identification of characteristic features such as small round blue cells, high cellularity, and the presence of Homer Wright rosettes in central PNETs.

Along with histopathology, Immunohistochemistry is often employed to further support the diagnosis by evaluating the expression of specific markers associated with neural differentiation. PNETs usually tested positive with CD99, synaptophysin, Chromogranin A, and cytokeratin.4 The integration of these diagnostic modalities enables accurate identification and classification of PNETs, leading to appropriate treatment planning and management strategies.

Treatment plans for PNETs range from a very vast option. In functional PNETs, surgical intervention is considered the best approach due to the need for symptom control or potential curative effect. Nonfunctional PNETs, conversely, can be managed non-operatively [13]. The options vary from radiotherapy, chemotherapy, and targeted therapy of all which had shown beneficial effects in reducing tumor growth rate and relapse [14-16].

Until now, a standard management guideline for peripheral PNET is still unavailable. With the scarce number of cases with varying lesion predilection, the "one-size-fits-all" approach for tumor management was not preferred. Currently, the optimal therapeutic approach of PNETs is similar to the Ewing sarcoma treatment (due to its similar nature to PNETs) with a multimodal approach of surgery, chemotherapy, and radiotherapy [17, 18]. Before deciding the optimal treatment option for the patients, it's important to assess if the tumor impairing the patient's daily living or not. If the patients are severely impaired, surgical approaches are recommended as the initial treatment and can be continued by chemotherapy (with or without adjuvant radiotherapy) in order to improve daily living and restrain the tumor progression [18].

The surgical approach can vary based on tumor location and size. The ideal management for PNETs surgically is complete tumor resection. Complete tumor resection contributes to a better overall survival number.17 In cases of difficult anatomic location, metastasis, or a very large tumor, partial resection can be done and continued by other modalities such as radiotherapy and chemotherapy.

Radiotherapy can be utilized for PNETs, and it's reported that PNETs respond well to radiation therapy. Use of radiotherapy for local treatment can be utilized, especially when complete local resection of the tumor couldn't be achieved (due to the difficult anatomic location, a very large tumor, or metastatic case of the tumor). The use of adjuvant radiotherapy after the surgical resection as local control for PNETs can decrease the risk of local recurrence and metastasis, especially with patients undergoing a partial tumor resection [17, 18].

The standard chemotherapy regimen used for PNETs (and Ewing sarcoma) consists of vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide (VDC-IE) regimen [17, 18]. The protocol of chemotherapy for PNETs is similar to which used for managing Ewing's: The first neoadjuvant phase and continued by the adjuvant phase. The goal of each phase is to obtain local control prior to preventing tumor metastasis [17]. It's important to personalize the given therapy to each patient, especially the dose, intensity, and cycle number of the regimen based on the patient's risk assessment, and adherence to the regimen.

The optimal multimodal management (following the sequence of complete surgical resection to remove the primary tumor, chemotherapy to restrain the tumor, and radiotherapy to achieve local control) contributes to better overall survival and progression-free survival number among patients diagnosed with peripheral PNETs.17 However, there are still a small number of reported cases reporting recurrence and ongoing tumor growth after the complete sequence of therapy had been done [17]. It's needed to identify risk factors contributing to disease progression even after the optimal treatment had been done.

Conclusion

A case of peripheral PNET in the submandibular region affecting three years old Indonesian female child is in itself an uncommon presentation of the tumor in respect of the onset age, tumor location, race, and ethnicity. The classical tumor symptoms of a mass raising and progressing from within the oral cavity may suggest an epithelial cell of origin yet it was discovered to be a neuroectodermal tumor. Therefore, clinicians should be aware of rare possibilities and follow a thorough histopathology and immunohistochemistry test as a standard for establishing diagnosis.

Conflict of Interest

Not available

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Not available

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