Peripheral Primitive Neuroectodermal Tumor (pPNET) in the Pharynx Metastasizing to the Lungs

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Abstract

Primitive Neuroectodermal tumor (PNET) is an aggressive rare subtype of Ewing's sarcoma with small blue round cells presenting predominantly among adolescents and young adults. Head and neck PNET reports are limited in previous literature. We present a case of a 29-year-old male diagnosed with a massive PNET in the pharynx which rapidly expanded locally and metastasized to the lungs. He received one cycle of chemotherapy before he deteriorated rapidly leading to his death four months after the onset of symptoms. We describe the clinical, radiological and pathological accompaniments of pharyngeal PNET. Clinical and radiological diagnosis is confirmed using histological and immunohistochemical studies. Early diagnosis and multimodal treatment may improve the outcome in some patients.

Keywords: Primitive Neuroectodermal tumor; PNET; metastasis; Oropharynx; Nasopharynx; Oncology.

Introduction

Primitive Neuroectodermal tumor (PNET) is an aggressive rare type of tumor comprising small undifferentiated neuroectodermal cells that belong to the family of Ewing Sarcoma.[1] The term was originally used to describe central nervous malignancies of neural, ependymal, and glial origin. However, it was later expanded to include peripherally located tumors with similar histological features, now classified under peripheral PNET.[2] This tumor commonly arises in adolescents and young adults <35 years old with a slight male predominance.[1] The most commonly reported origin sites are the chest wall ("Askin tumor"), pelvis and extremities.[2,3] Cases of PNET arising in the head and neck, particularly in the pharynx, are rare in previous literature. We herein present the first known case of a pharyngeal PNET in a young adult with aggressive local and regional metastasis to the lungs.

Case Report

A 29-year-old male, previously healthy, presented to the emergency department with a sore throat, dyspnea and fever for one week. His symptoms worsened two days before the presentation with bloody sputum and right-sided otalgia. Throat examination revealed a hypertrophied bleeding mass protruding from the right side of the tonsillar fossae, occupying the whole oropharynx, and significantly compromising the oropharyngeal airway. CT scan of the neck revealed a large intensely enhancing naso/oropharyngeal soft tissue lesion. The patient declined the recommendation for an emergency tracheostomy and chose to leave the hospital against

medical advice. Four weeks later, he was re-admitted with progressive respiratory distress and noisy breathing. Emergency tracheostomy was performed, and the patient was admitted to the intensive care unit. MRI of the neck showed a large complex multiloculated mass with a mixed cystic and solid component. The epicenter of the lesion was in the nasopharynx measuring 5.4 x 6.2 x 9.9 cm, extending to the oropharynx, left parapharyngeal space, epiglottis, base of the skull, encasing and displacing the carotid arteries [Figure 1]. The complex mass showed a heterogenous enhancement of the solid component and a peripheral enhancement of the cystic component. In addition, a 2.2 x 1.6 cm lesion with similar enhancement of the cystic component at the left lung apex, a second rounded solid nodule measuring 1.0 x 0.9 cm in the right middle lobe [Figure 2] and a smaller nodule in the lateral segment of the middle lobe were seen. Magnetic resonance angiogram (MRA) showed no significant stenosis in the common carotid, internal carotid and vertebral arteries.

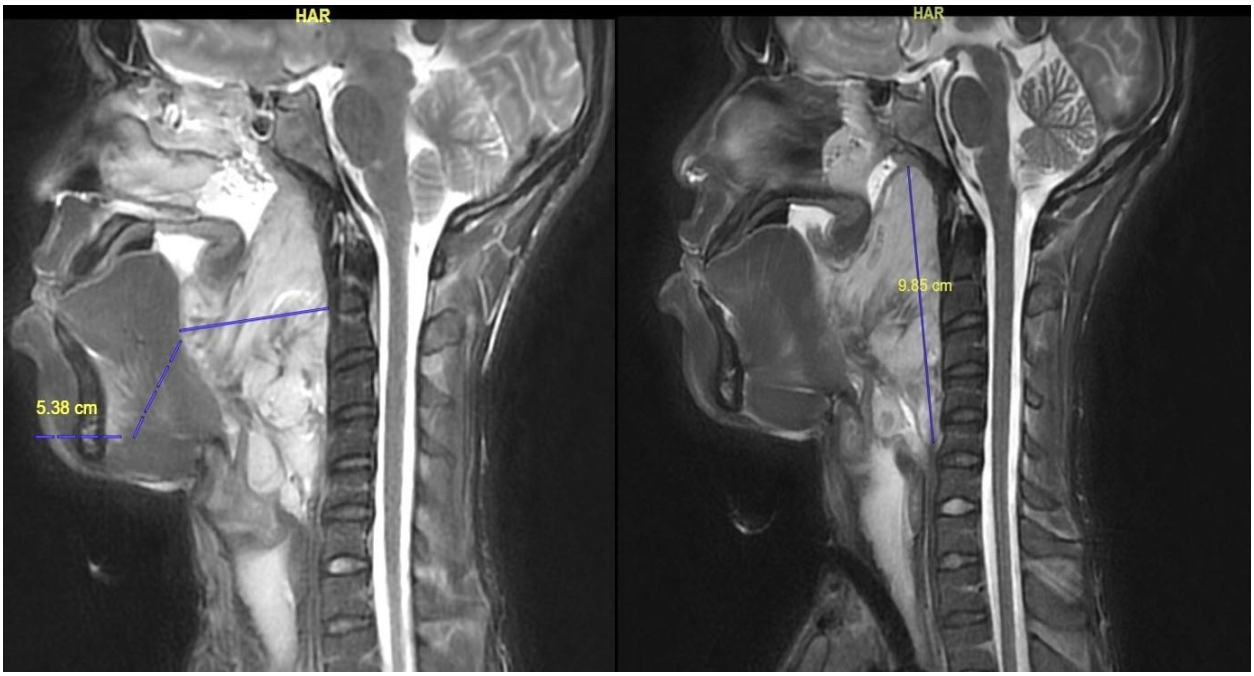

Figure 1: T2-weighted sagittal neck MRI scan showing a massively infiltrating mass in the naso/oropharynx measuring 5.4 x 6.2 x 9.9 cm.

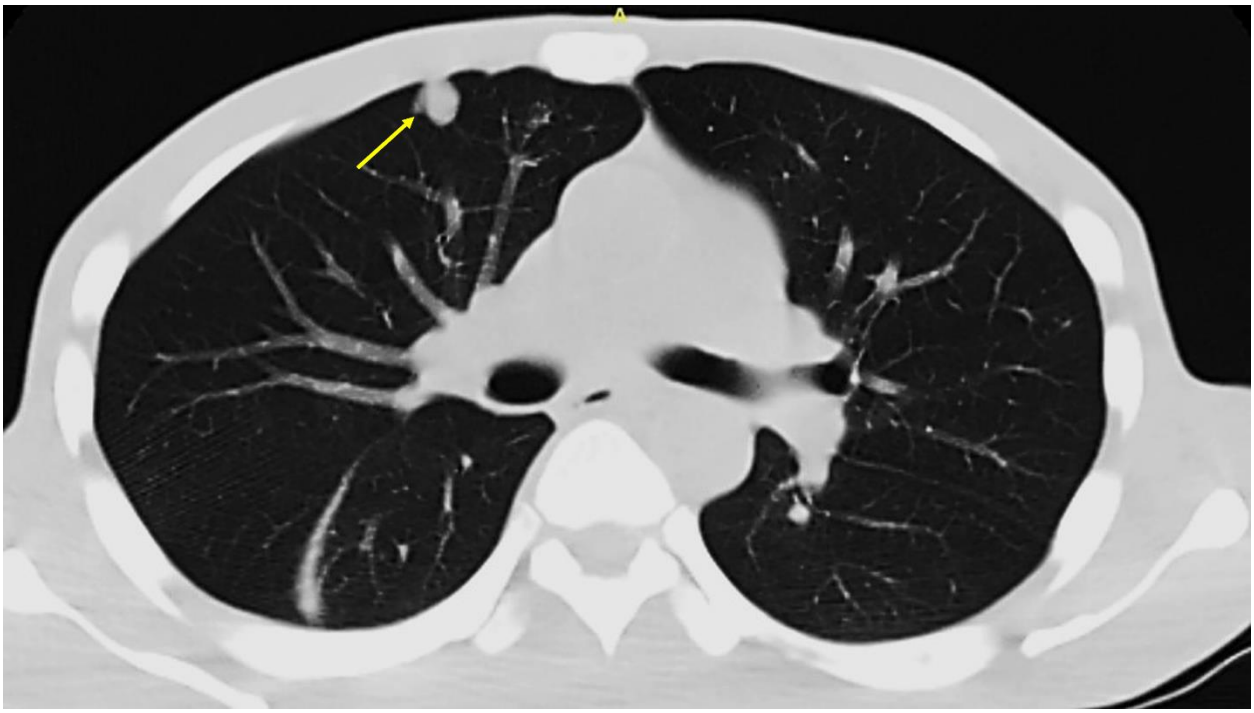

Figure 2: Chest CT scan showing a rounded nodule in the right middle lobe with markedly increased vascular markings.

Nasopharyngeal biopsy via the nasal route was performed. Histopathology revealed solid sheets of highly malignant rounded blue cells with large hyperchromatic nuclei, pleomorphism, and frequent atypical mitotic figures [Figure 3]. Hypervascularity, areas of hemorrhage, and focal tumor necrosed area were also observed. Immunohistochemical staining results are shown in Table 1. The final diagnosis was metastatic nasopharyngeal PNET cT4NxM1. The patient was planned for inductive chemotherapy followed by concurrent palliative chemo-radiotherapy. Given the location, extension and encapsulation of the carotid artery, the tumor was deemed inoperable. He received one cycle of the recommended chemotherapy regimen VAC-IE (Vincristine-Adriamycin-Cyclophosphamide alternating with Ifosfamide-Etoposide). His condition deteriorated rapidly with multiple episodes of acute massive bleeding. He died four months after the onset of symptoms from hemorrhagic shock.

Table 1: Immunohistochemical staining results.

Immunohistochemical stain	Result
CK AE1/AE3	Negative
EMA	Negative
S100	Positive
LCA	Negative
CK5/6	Negative
CD99	Positive
CD20	Negative
CD31	Negative

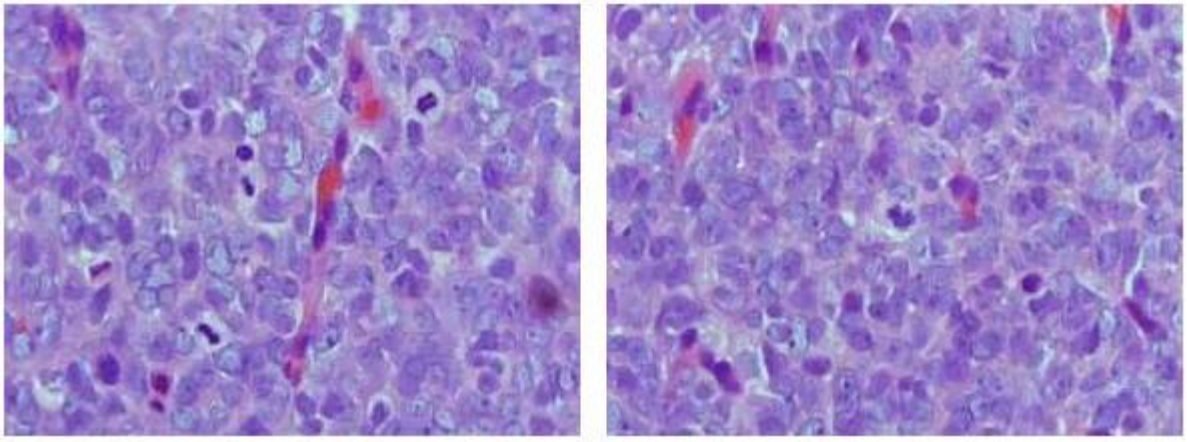

Figure 3: Section from biopsy reveals solid sheets of highly malignant rounded cells with large hyperchromatic nuclei, pleomorphism and frequent atypical mitotic figures.

Discussion

PNET is a rare tumor characterized by the presence of a 21;22 rearrangement involving the EWS promoter gene at 22q12, or a balanced chromosomal translocation t11;22 (q24;q12).[4,5] The most common originating site is the chest wall followed by the pelvis.[2,3] Few case reports described PNET arising as a primary tumor in the head and neck region including maxillary sinus, neck, nasopharynx,[6] cervical spine[7] and larynx.[2] To our knowledge, this is the first case report in English literature describing PNET occupying the naso-oropharynx.

PNET is mostly seen in adolescent and young adult males and is commonly metastasized by the time of diagnosis.[1,5] Occasionally, PNET may manifest with systemic findings including anemia, leukocytosis, fever and elevated inflammatory markers.[7] A combination of clinical, pathological, and radiological findings may aid in PNET diagnosis. Imaging studies such as CT scan and MRI provide important information regarding the size and extension of the tumor but are usually insufficient for diagnosis.[4,5] CT scan often reveals heterogeneous masses that involve the surrounding structures, while T2-weighted MRI shows nonhomogeneous hyperintense masses with ill-defined margins.[5] Histology reveals sheets of densely cellular uniform small- to medium-sized blue round cells with or without Homer-Wright rosettes. The cells are characterized by large nuclei with fine to coarse chromatin and small nucleoli.[5] Immunoreactivity to vimentin, CD99, S100 and neuron-specific enolase (NSE) plus negative immunoreactivity to leukocyte common antigen (LCA), Desmin, and chromogranin may be useful to differentiate PNET from other types of small round cell tumors such as olfactory neuroblastoma, rhabdomyosarcoma and synovial sarcoma.[3,5,7] Increased level of inflammatory mediators including Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio were linked to advanced stages of PNET in previous studies.[8] In our case, Immunohistochemical stain results showed a positive CD99, positive S-100, and negative LCA.

Patients usually present with a recurring locally aggressive tumor that metastasizes early to local lymph nodes, lungs, liver and bone.[7] Multimodal treatment is the gold standard for PNETs, with a treatment strategy similar to Ewing sarcoma given the rarity of the syndrome that limits the development of tumor-directed guidelines.[2,3] Previous studies also reported favorable outcomes with VAC-IE regimen.[2] Given reports of PNET dependence on the chemotactic abilities of angiogenic factors, including VEGF, to stimulate angiogenesis in the tumor area, anti-angiogenic regimen are actively being studies in this setting. A Phase II trial in 2014 reported the use of thalidomide in a 5-drug regimen in recurrent/progressive cancer. One patient achieved complete response, partial response, and stable disease, each respectively, while 5 patients had progression of disease.[9] Another case report in 2017 reported a complete remission of PNET in a 17-year-old adolescence after treatment with Thalidomide.[10] Programmed death-ligand 1 (PD-L1) is a protein expressed on the membrane of certain tumors that regulates the activity of inflammatory cells through binding to its receptor, PD-1. PD-1

has been recently deemed a target for immune-checkpoint inhibitors (ICI), most notably Pembrolizumab and Nivolumab.[11] A study in 2016 proved high expression of PD-L1 in PNET tissue which correlated significantly with survival.[11] These findings encourage investigating the use of ICI in PNET in future studies. Surgical resection with wide margins within three months of diagnosis followed by local irradiation correlated with improved survival in some studies.[2] In our case, pharyngeal location, extent of the tumor, and the encapsulation of the carotid artery limited the option of surgical resection. Previous studies reported a five-year disease-free overall survival (all stages) of 45-55%, while the median survival for those with metastatic disease was two years.[4]

Conclusion

PNETs of the head and neck are locally aggressive rare tumors requiring a thorough and exhaustive workup for early detection and management. Clinicians should maintain a high index of suspicion for young adults presenting with a rapidly expanding mass with obstructive symptoms. Early multimodal treatment may improve outcomes in these patients.

Informed Consent

The authors certify that they obtained an informed consent from the patient.

Conflict of Interest

None declared

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Conflict of interest

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Author Contributions

MBH, YG and LK contributed to conception of the study, acquisition of data, drafting the manuscript and figures.

Ethics Statement

Appropriate written consent was taken from the patient and a copy of the consent is available. The paper is a case report of a single patient and did not require IRB approval.

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