

Primitive Neuroectodermal Tumor of Lung in Adult with Hemorrhagic Brain Metastasis: An Extremely Rare Case Scenario

Abstract

Primitive neuroectodermal tumors (PNETs) are highly malignant neoplasms of embryonal origin manifesting in children and adolescents, rarely seen in adults. Carcinoma lung with hemorrhagic metastasis to the brain is very common, but primary lung PNET with hemorrhagic brain metastasis is extremely uncommon. We hereby report a 29-year-old female diagnosed as PNET lung was treated with vincristine, adriamycin, and cyclophosphamide alternating with ifosfamide plus etoposide followed by radiotherapy (RT). After 9 months, she developed hemorrhagic brain metastasis from PNET lung confirmed from tissue immunohistology postcraniotomy. Received palliative whole brain RT followed by oral pazopanib resulting in significant improvement in performance status. A thorough review of literature reveals that our case may be the second case of primary lung PNET with hemorrhagic brain metastasis and also the first to be exhibited oral pazopanib resulting in a significant therapeutic effect to be reported in world literature till date.

Keywords: Hemorrhagic brain metastasis, lung, pazopanib, primitive neuroectodermal tumor, whole brain radiotherapy

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Introduction

Primitive neuroectodermal tumors (PNETs) are highly malignant embryonal neoplasms of bone and soft tissues accounting for 4%–17% of all pediatric soft tissue tumors.^[1] Adult affection is extremely rare with a very dismal prognosis. Metastasis at presentation is quite common, with central PNETs metastasizing to cranium and leptomeninges while peripheral PNETs (pPNETs) disseminating to lungs, bone,^[2] liver, and lymph nodes.^[3] Brain is the least common site accounting for a mere 3.4%.^[3] Primary pulmonary PNET is known to metastasize to pancreas, adrenal gland and ovaries^[4] while it metastasizing to brain is exceedingly rare.

Case Report

A 29-year-old female presented with a cough and right-sided chest pain of 1-month duration. Chest roentgenogram revealed a nonhomogenous mass right lower zone. Computed tomography scan of chest [Figure 1] showed an 11.3 cm × 11 cm × 10 cm soft tissue mass lesion in right perihilar region with the loss of fat planes with esophagus, aorta, and diaphragm without chest wall or pleural

involvement. Biopsy showed atypical round to oval cells with scanty cytoplasm intermixed with respiratory epithelium [Figure 2]. Immunohistochemistry (IHC) was positive for neuron-specific enolase (NSE) [Figure 3], synaptophysin, chromogranin, CD 99, and vimentin. Smooth muscle actin (SMA), epithelial membrane antigen (EMA), cytokeratin (CK), leukocyte common antigen (LCA), CD 20, CD 45, thyroid transcription factor (TTF-1) and desmin were negative, confirming the diagnosis of PNET lung.

Magnetic resonance imaging (MRI) brain and positron emission tomography scan showed localized disease. Surgery was not considered as the lung mass invaded vital structures. Received chemotherapy vincristine, adriamycin, and cyclophosphamide alternating with ifosfamide plus etoposide (VAC/IE) resulting in partial response (PR) to therapy. Conformal radiotherapy (RT) was given to postchemotherapy residual volume to a dose of 60 (Gray) Gy in 30 fractions. Post-RT patient experienced significant symptomatic relief with improved performance status though with a static disease.

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How to cite this article: Purkayastha A, Sharma N, Kapur A, Sahai K. Primitive neuroectodermal tumor of lung in adult with hemorrhagic brain metastasis: An extremely rare case scenario. *Indian J Med Paediatr Oncol* 2017;38:84-7.

Access this article online

Website: www.ijmpo.org

DOI: 10.4103/0971-5851.203491

Quick Response Code:



The patient was on follow up for 9 months when she presented with a headache, vomiting, seizures and left-sided hemiparesis. There was no history of head injury. MRI brain [Figure 4] showed an 8.6 cm × 7.5 cm solitary lesion with areas of altered signal intensity at right periventricular and periatrinal parietal lobe with significant perilesional edema suggestive of hemorrhagic metastatic deposit. She underwent right fronto-temporo-parietal craniotomy with excision of tumor and evacuation of hematoma. The postoperative histopathological report revealed high grade poorly differentiated malignant tumor. IHC was positive for synaptophysin [Figure 5a], chromogranin [Figure 5b], vimentin [Figure 5c], and CD 99 [Figure 5d] with Ki67 of 90% while negative for CK, TTF-1, and melan-A which suggested metastasis from primary PNET lung. We treated her with whole brain RT (WBRT) to a dose of 30 Gy in 10 fractions followed by oral pazopanib 800 mg once a day as a palliative

intent. The patient is under follow up for over 1 year with a Karnofsky performance status of 70%.

Discussion

Thoracic PNETs are the most aggressive form of pPNETs arising from chest wall or underlying lung pleura invading bone, lung or mediastinum in children and young adults. They are extremely aggressive with a dismal prognosis as patients may present with an upfront metastatic disease to contralateral lung, bone,^[2] bone marrow, lymph nodes, liver,^[5] pancreas, adrenals, and ovaries.^[4] Primary lung PNET can often be misdiagnosed with a metastatic lung lesion, mucinous adenocarcinoma or squamous cell lung carcinoma.

Since PNETs and other small round cell tumors share the same histological picture, IHC plays a vital role in their differentiation. CD 99, vimentin and S100 are nonspecific^[6]

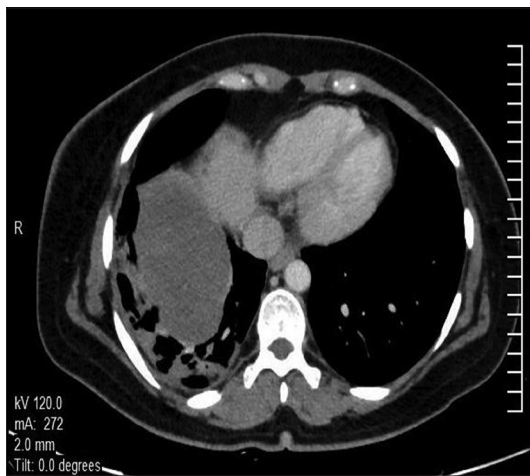


Figure 1: Computed tomography scan (axial section) of thorax showing a large heterogeneously enhancing soft tissue mass lesion in the right perihilar region involving right lower lobe extending into the mediastinum with loss of fat planes with esophagus, aorta, and right crus of the diaphragm. There is no chest wall or pleural involvement

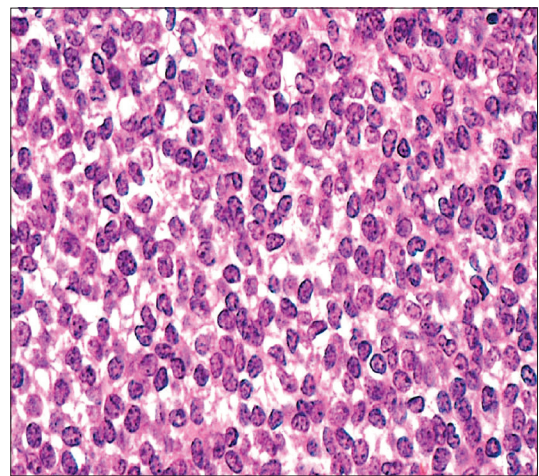


Figure 2: Biopsy from lung lesion showing small round cells with scanty cytoplasm with condensed chromatin and inconspicuous nucleoli (H and E, ×200)

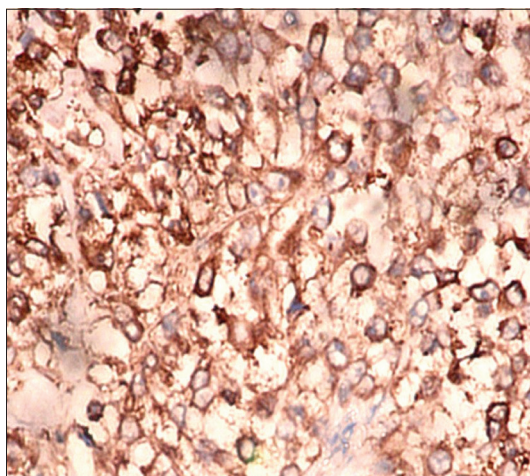


Figure 3: Immunohistochemistry picture from lung lesion showing tumor cells positive for neuron specific enolase (×200)

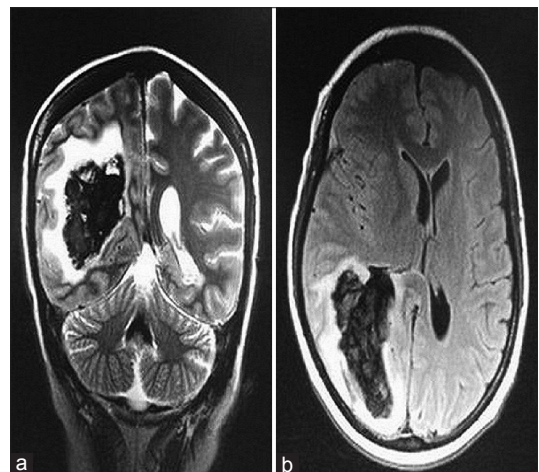


Figure 4: Magnetic resonance imaging brain (a = coronal section and b = axial section) showing a solitary lesion with areas of altered signal intensity at right periventricular and periatrinal parietal lobe with significant perilesional edema suggestive of hemorrhagic metastatic deposit

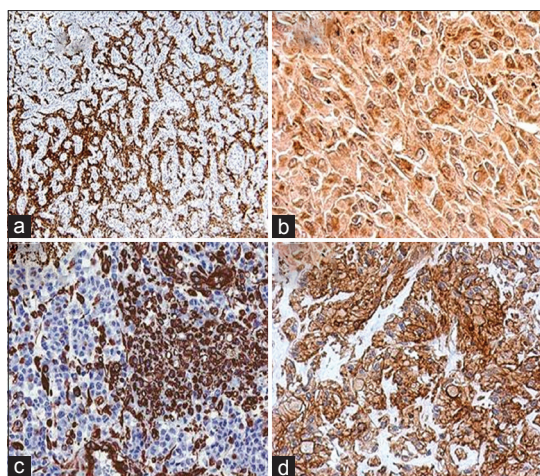


Figure 5: Immunohistochemistry picture from brain metastasis showing tumor cells positive for (a) synaptophysin (×100), (b) chromogranin (×200), (c) vimentin (×100), (d) CD 99 (×200)

while NSE, synaptophysin and chromogranin confirm the diagnosis of PNET. TTF-1 is found in pulmonary adenocarcinomas and thyroid malignancies, CK for carcinoma, desmin for rhabdomyosarcoma, SMA and EMA for soft tissue sarcoma while LCA, BCI-2, CD 20, CD 45 are for acute lymphoblastic lymphoma and leukemia. However, to confirm the diagnosis, amplification of Ewing sarcoma breakpoint region-1 by situ hybridization techniques is required.

According to Javery *et al.*^[2] and previous other series on extraskelatal Ewing sarcoma (EES), lung is the most common site of metastasis followed by bone comprising 80% and 40% cases, respectively. Huh *et al.*^[3] reported lymph nodes as the most frequent metastatic site (75.9%) followed by bone, lung, peritoneum, pleura while least being brain (3.4%). The most prevalent primary sites were extremities, abdomen, pelvis, thorax, paravertebral space followed by head and neck. However, no primary lung PNET was described. Mandava *et al.*^[7] reported a solitary case of primary pulmonary parenchymal PNET with upfront hemorrhagic brain metastasis.

Current treatment recommendations for lung PNET and pPNETs/Ewing's are same with VAC/IE.^[8] RT concurrent with chemotherapy is preferred for the limited stage while sequential RT is beneficial for extensive lesions. We have treated two more cases of adult primary lung PNET although with a radiological PR but a significant symptomatic response. Both patients are on follow-up for more than a year now without any evidence of disease progression or metastasis.

For the management of brain metastasis from PNET lung, at present there is no earmarked treatment protocol. Upfront surgery was employed to provide immediate relief of mass effect. WBRT to a dose of 30 Gy was exhibited as it is the standard of care in patients with brain metastasis which has shown superiority in preventing neurologic morbidity

and mortality. Pazopanib is an oral multikinase inhibitor of angiogenesis indicated mainly for progressive or chemotherapy refractory soft tissue sarcomas.^[9] Although pazopanib is not the standard therapeutic option in Ewing sarcoma, it has demonstrated its efficacy in refractory and EES metastatic cases.^[10]

Since Ewing's tumors and pPNETs share similar genetic characteristics with reciprocal translocations of chromosomes 11 and 22 at EWSR1, differing only in degree of neural differentiation with the former being more differentiated than latter, we, therefore, exhibited pazopanib to our patient with a palliative intent as she had progressed after standard chemotherapeutic regimen. The effectiveness of pazopanib by Children's Oncology Group (COG) NCT01956669 phase-2 study and another multi-kinase inhibitor regorafenib by NCT02048371 and NCT02389244 phase-2 studies for refractory Ewing sarcoma are underway, and the results are awaited.^[10]

Newer prognostic markers should be developed to identify primary PNET lung at risk of developing brain or distant metastases. A better understanding and interpretation of the molecular and biological mechanisms of this entity may help to devise therapeutic strategies to counter the disease process. We recommend craniotomy and excision followed by WBRT for brain metastasis and oral pazopanib to check further dissemination as an incisive treatment guideline, though more prospective data favoring this recommendation is required.

Acknowledgment

We thank the patient and his NOK for allowing us to publish the case report after his death and use the images taken during his stay in the hospital.

We also like to extend our gratitude to Departments of Pathology and Molecular Science, Surgical Oncology, Medical Oncology, Nuclear Medicine and Radiology, Army Hospital (Research and Referral), New Delhi, India.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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