

CASE REPORT

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Case report of pleuropulmonary blastoma: The heterogenous features of a rare primitive neoplasm of the thorax

Lakshmisree Akhila Vemulakonda, Yaritzky Astudillo,
Elayna Maxx Shanker

ABSTRACT

Introduction: Pleuropulmonary blastoma (PPB) is a rare primary neoplasm of the thorax frequently diagnosed in early childhood. Pleuropulmonary blastoma arises from primitive intrathoracic mesenchyme—either pulmonary and pleural, or both. Patients with pleuropulmonary blastoma usually present with respiratory symptoms and are often misdiagnosed as pneumonia in the early clinical course. Pleuropulmonary blastoma can be further classified into types I, II, and III based on histological components. Such histological distinctions have significant implications for the treatment of these lesions as well as prognosis. Currently, the treatment of pleuropulmonary blastoma is surgical resection with or without chemotherapy, based on the histological type.

Case Report: We highlight the histopathological presentation of pleuropulmonary blastoma in a 3-year-old male who presented with nonspecific symptoms. After identifying an intrathoracic mass on imaging, frozen section demonstrated primarily mature cartilaginous tissue without rhabdomyosarcomatous differentiation or anaplasia. Surgical resection specimens, however, contained small areas of proliferating spindle cells with

skeletal muscle features as well as primitive blastema-like cells. Following ancillary testing, the patient was diagnosed with a type II PPB.

Conclusion: This case illustrates the challenges of using frozen sections to diagnose heterogenous neoplasms such as PPB. The histologic features of this patient's tumor identified on frozen section were largely mature and benign-appearing. Only when considering the histology of the surgical specimens in combination with immunohistochemistry and gross morphology, we were able to make an accurate assessment about the type of PPB and corresponding prognosis and treatment plan. Therefore, we urge pathologists to consider PPB for large thoracic masses in pediatric patients.

Keywords: Embryonal rhabdomyosarcoma, Lung cyst, Pediatric pathology, Pleuropulmonary blastoma

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Lakshmisree Akhila Vemulakonda¹, MBBS, Yaritzky Astudillo¹, MD, Elayna Maxx Shanker², BS

Affiliations: ¹Department of Pathology and Microbiology, School of Medicine, New York Medical College, 40 Sunshine Cottage Rd, Valhalla, NY 10595, USA; ²Office of Undergraduate Medical Education, School of Medicine, New York Medical College, 40 Sunshine Cottage Rd, Valhalla, NY 10595, USA.

Corresponding Author: Elayna Maxx Shanker, Westchester Medical Center, 100 Woods Rd, Valhalla, NY 10595, USA; Email: eshanker@student.nymc.edu

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INTRODUCTION

Pleuropulmonary blastoma is a primary neoplasm of the pulmonary parenchyma arising from primitive mesenchymal cells and often associated with cystic lung lesions. They are exceptionally rare and account for nearly 15% of all pediatric pulmonary tumors and less than 1% of all pediatric malignancies. Morphologically,

three major subtypes of pleuropulmonary blastoma are identified based on the proportion of the solid and cystic components [1]. These are type I-largely cystic, type II-mixed cystic/solid, and type III-largely solid [1]. In 2006, type I-r (for regressed type I) was added to the classification system [2]. Pleuropulmonary blastomas are aggressive and it is thought that type I tumors which do not regress eventually evolve to more advanced subtypes with malignant features [1, 2]. In this case report, we describe the clinical presentation of pleuropulmonary blastoma in a 3-year-old male and discuss the microscopic features. The case highlights the heterogeneity of this rare group of tumors and emphasizes certain challenges in tissue diagnosis.

CASE REPORT

We describe a case of a 3-year-old male, with unremarkable medical and family history, who presented to the pediatric emergency department with four days of cough and two days of dyspnea with retractions. For four weeks, the parents had noted increased fatigue but no other issues had been noted. A chest X-ray performed at an outside hospital demonstrated complete opacity of right lung and possible pneumonia. He was treated with antibiotics and was transferred to the emergency department at Westchester Medical Center (WMC) for further evaluation. Repeat imaging at WMC showed a large mass measuring $15.3 \times 14.7 \times 12.2$ cm and occupying the right hemithorax with marked leftward deviation of the cardiomedastinal structures and inferior displacement of the right hemidiaphragm. The right lung appeared completely collapsed centrally toward the hilum, suggesting a pleural process. There were at least three lobulated heterogeneous soft tissue components along the medial aspect of this mass. The largest lesion was noted to be retrocardiac in location, measuring $6.2 \times 2.7 \times 2.7 \times 6.2$ cm. The second largest lesion was paraspinal, measuring $3.3 \times 2.9 \times 3.1$ cm. The third lesion was located at the right pleural base, measuring $1.8 \times 1.9 \times 1.7$ cm. Irregular areas of hyperattenuation identified within the mass represented potential areas of calcification or vessels.

Due to suspicious feature on imaging, right thoracotomy was performed immediately on the patient. The patient did not receive therapy nor have the lesion biopsied prior to the procedure. In surgery, a small piece of pink, firm, friable tissue measuring $2.0 \times 1.0 \times 0.9$ cm was sent for intraoperative consultation. The tissue was representatively submitted for frozen section. Microscopic evaluation of the representative section showed cartilaginous tissue with myxomatous stroma (Figure 1) and was diagnosed as cartilaginous tumor favoring malignancy.

Later, surgical resection was performed and sent for pathological evaluation. Two tissue fragments were examined. Macroscopically, the smallest tissue fragment

was tan white to pink in color, friable, firm and measured $2.7 \times 1.9 \times 1.5$ cm and the large fragment was pink to red in color, soft, fleshy, and measured $5.0 \times 2.6 \times 0.7$ cm. No cystic components could be appreciated. The specimens were processed for histopathological diagnosis using Hematoxylin-Eosin (HE) staining. Routine microscopic examination showed the small tissue fragment exhibiting a proliferation of mature chondrocytes with myxomatous stroma and small foci of proliferating spindle cells and skeletal muscle differentiation including polygonal and elongated rhabdomyoblasts with cross striations (Figure 2). Microscopic examination of the large tissue fragment showed cellular islands of small, primitive blastematosiscellsintermixedwithfibrosarcomatousareas (Figure 3). Rhabdomyosarcomatous and chondromatous differentiations were also identified (Figure 4). There was geographic tumor necrosis. No anaplasia was seen. The lesion was diagnosed as pleuropulmonary blastoma, solid type before outside consultation and ancillary testing.

The histopathological slides were sent out to a pleuropulmonary blastoma registry. They substantiated the diagnosis given at Westchester Medical Center but commented that the sections of this chest wall tumor have unusual aspects compared to a typical pleuropulmonary blastoma. The sections demonstrate prominent cartilaginous components consisting of differentiated nodules of cartilage without overly sarcomatous features. These nodules are separated by stroma in some areas and display somewhat primitive features with the absence of any apparent rhabdomyosarcomatous differentiation or anaplasia. Immunohistochemical stains desmin and myogenin failed to demonstrate any rhabdomyoblastic component. Both vimetin and CD56 highlighted the cellular, primitive appearing mesenchymal areas. p53 showed a low fraction of tumor cells with pale nuclear staining, with less than 25% of tumor cells expressing nuclear staining of p53. Ki-67 revealed that the mesenchymal population, with both nested and diffuse patterns, had 50% or greater positivity. The specimen was sent for molecular analysis and found to have biallelic loss of function and missense RNAase IIIb mutations, each with about 30% allele frequency. This pattern of mutations is typical of DICER1 syndrome tumors. Further assessment suggested a type II pleuropulmonary blastoma due to the weak p53 positivity, which has been previously associated with PPB type. Low (<25%) of p53 expression, as seen in this case, is associated with early PPB lesions and more favorable outcomes, compared to the type III (advanced) PPB [3]. Large areas of benign-appearing cartilage without atypia or other abnormal cell types raised skepticism although there were small areas of necrosis, blastemal, and sarcomatous components identified. Therefore, chest wall hamartoma was included on a long list of differential diagnoses. Ultimately, although the tumor showed features which were well within the spectrum of pleuropulmonary blastoma, classification was complicated by sampling bias with sections which had a dominant mature cartilaginous component.

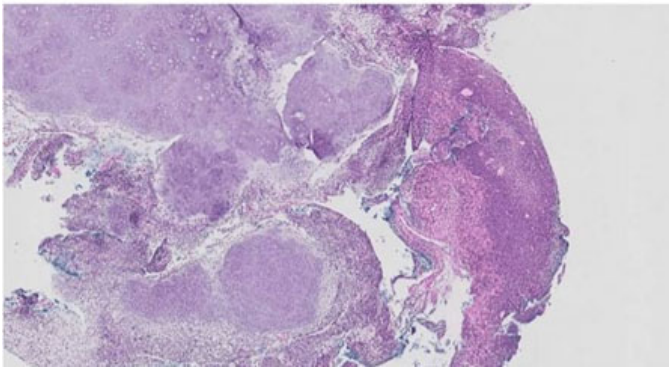


Figure 1: Frozen section, H&E staining at low power showing mature chondrocytes with myxomatous stroma.

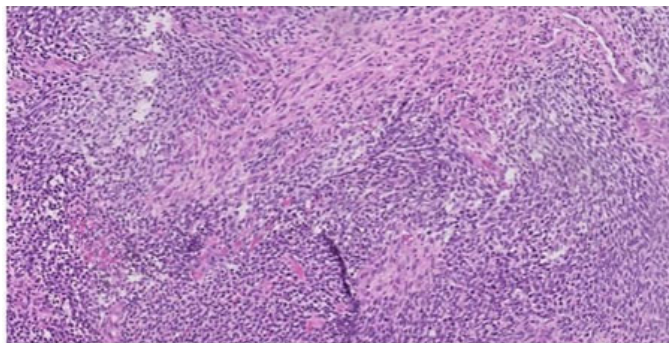


Figure 2: H&E staining, high power showing chondromatous changes and a small focus of blastemal and spindle cell proliferation.

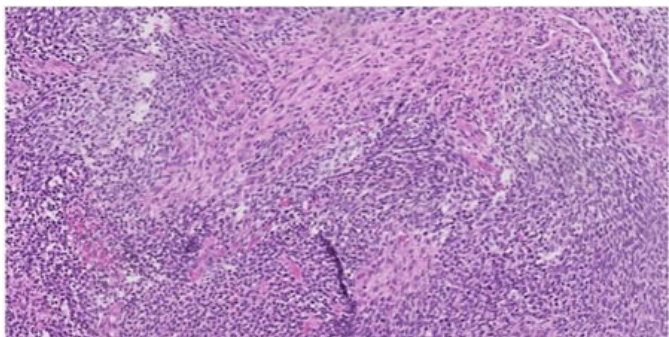


Figure 3: H&E staining, high power showing spindle cell and blastemal cell proliferation.

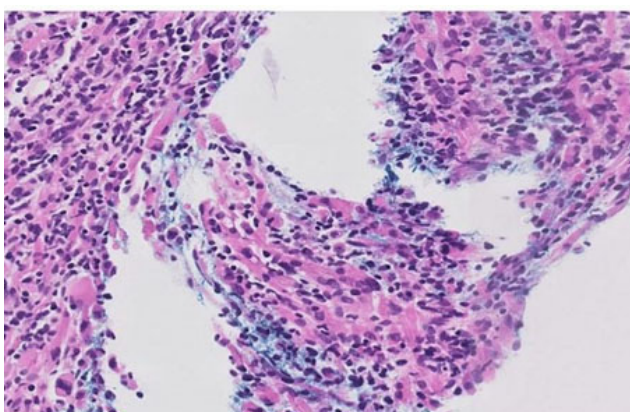


Figure 4: H&E staining, high power showing rhabdomyoblastic differentiation.

The patient promptly began IVADO chemotherapy treatment (ifosfamide, vincristine, actinomycin D, and doxorubicin), as per the PPB registry, approximately one week following his diagnosis. He received 5 cycles of chemotherapy over four months; however, CT showed residual tumor. Right upper lobectomy was completed, following which the patient received 4 additional cycles of chemotherapy. The patient is 11 months post treatment with no lesions detectable on repeat imaging.

DISCUSSION

Pleuropulmonary blastoma is a rare pediatric malignancy of pulmonary, pleural, or combined origin that is classified into three subtypes: Types I, II, and III PPB. Type I pleuropulmonary blastoma is a peripherally located, cystic, thin-walled lesion. The median age at diagnosis is 10 months [2]. Microscopically, the cyst is lined by benign cuboidal or columnar ciliated epithelium. Beneath the lining epithelium, there may be a layer of characteristic primitive round to spindle shaped [2]. Tumor cells may occasionally show rhabdomyoblastic and chondrosarcomatous differentiation within their fibrous septa. Differential diagnosis of type I pleuropulmonary blastoma includes congenital pulmonary airway malformation (a benign cyst without subepithelial malignant cell condensations or immature cartilage) and fetal lung interstitial tumor (characterized by irregular airspaces enclosed by irregularly thickened septa composed of immature mesenchyme and lined by polygonal cells with underlying smooth muscle layer without a cambium layer of blastemal-like cells).

Some of the type I tumors may undergo regression and remain as cystic lesions containing a few spindle-shaped cells and foci of dystrophic calcification in the cyst wall. These are referred to as type-Ir tumors. Type-Ir tumors rarely have subepithelial malignant cell condensation and only 8% progress to later, more aggressive subtypes of PPB [2].

Type II pleuropulmonary blastoma is a mixed solid and cystic tumor characterized by variably thickened nodule-like areas. The median age at diagnosis is 34 months, significantly later than the type I tumors. Microscopically, the cystic areas are similar to that of the type I lesions. However, this subtype more regularly features the thickened or nodule-like areas composed of rhabdomyosarcomatous or blastemal components [2].

The type III pleuropulmonary blastoma is a solid tumor usually presenting as large, well circumscribed masses with or without areas of hemorrhage and necrosis. They may partially fill the hemithorax with or without attachment to the chest wall or mediastinum. The median age at diagnosis is 44 months, the latest presentation of all PPB subtypes. Microscopically, it is a heterogeneous tumor. It is composed of primitive blastemal-like small cells with hyperchromatic nuclei and high nuclear-to-cytoplasmic ratios. There may

be abundant mitoses, spindle and ovoid cells, foci of skeletal muscle differentiation, and nodules of immature or malignant chondroid elements. Large anaplastic cells with atypical nuclear features can also be appreciated [1]. The differential diagnosis of types II and III pleuropulmonary blastoma includes rhabdomyosarcoma, malignant teratoma, monophasic synovial sarcoma, undifferentiated sarcoma, and metastatic Wilms' tumor [4].

Treatment depends on the type of pleuropulmonary blastoma. The recommended treatment for type I pleuropulmonary blastoma is surgical excision and adjuvant chemotherapy. While the specific chemotherapy regimen varies throughout the world, the International Pleuropulmonary Blastoma Registry (IPB) aims to set standards for management. In their trial, treatment of type I tumors with resection and negative margin often follow-up with no chemotherapy. Treatment of types II and III pleuropulmonary blastoma includes reduction of tumor sizes through neoadjuvant chemotherapy followed by surgical excision. The regimen for types II and III often consists of single arm of adjuvant/neoadjuvant ifosfamide, vincristine, actinomycin-D, and doxorubicin (IVADO), for a total of 36 weeks [1].

Prognosis is poor in types II and III pleuropulmonary blastoma due to relapse rate and distant metastases, most often to the brain [1]. Even with recommended treatment, less than 50% of patients with types II and III PPB have a 5-year disease-free survival [5, 6].

Diagnosis may be supported by immunohistochemical staining [5]. Cytokeratin stains epithelial cells lining the cysts. Vimentin stains rhabdomyoblasts, chondrocytes, and other foci of sarcomatous proliferation. Rhabdomyoblasts also stain positive for desmin and muscle specific actin. Primitive blastemal cells stain weakly positive for muscle specific actin and neuron-specific enolase. The immature and mature chondrocyte nuclei stain positive for S100. Tumor cells within PPB may be focally positive for CD117, alpha-1-antitrypsin and weakly positive for CD99. The tumor cells also show positivity to Ki-67, indicating a high proliferative index (>50%).

Recognition of DICER1 mutations may also aid in diagnosis as these mutations are reported in approximately 66% of recorded pleuropulmonary blastoma. DICER1 mutations may occur as part of a constellation of neoplastic diseases including pleuropulmonary blastoma, cystic nephroma, and sarcomas, and comprises a cancer syndrome [7]. As such, genetic testing for germline DICER1 mutations is recommended for close family members. However, DICER1 mutations ultimately have no impact on the clinical features or prognosis of PPB [7]. In contrast, loss of p53, which has also been implicated in the pathogenesis of pleuropulmonary blastoma, may be associated with worse outcomes, as recurrence of disease was higher in a 3-year period following treatment relative to PPB cases with no p53 mutation. Expression of p53 detected by whole genome sequencing was either diffuse

or in distinct cell populations, suggesting that mutations occur subclonal to DICER1 [8–11]. Inactivation of p53 immunohistochemical staining for p53 expression with anti-p53 antibody using an automated stainer can thus guide prognostication and treatment.

CONCLUSION

Diagnosis of pleuropulmonary blastoma is based on clinical features, radiological imaging, and pathological correlation. Making a definitive diagnosis of pleuropulmonary blastoma and corresponding subtype is essential for providing insight into the patient's treatment plan and predicted outcomes. This is because type I PPB has a better prognosis and does not require neoadjuvant chemotherapy, in contrast to later PPB subtypes.

This case report presents a 3-year-old male with newly diagnosed PPB type II who received multimodal therapy with chemotherapy and surgery. The protocol for treatment is per the PPB/DICER1 registry. While this patient's tumor had features consistent with pleuropulmonary blastoma, it also demonstrated significant areas of mature cartilaginous tissue, especially on frozen section. Therefore, chest wall hamartoma was also considered in the differential diagnosis. Classification as a type II PPB ultimately was favored due to focal histologic features in the greater context of gross anatomic morphology, cytology, genetics, and staining.

Like other cases, this one provides key insight into the heterogeneity of pleuropulmonary blastomas. Further, it emphasizes the importance of thoroughly describing and defining all of the histopathological findings, as type classification has implications for prognosis and treatment. Due to the heterogeneous features of this tumor, frozen section diagnosis can be misleading. Pleuropulmonary blastoma included in the differential diagnosis of a large thoracic masses in a pediatric patient should be followed by immunohistochemical staining and p53 for accurate diagnosis and treatment plan.

REFERENCES

1. Arghirescu TS, Cârstea AM, Oprea LA, et al. Type II pleuropulmonary blastoma in a 2-year-old girl: A case report. *Rom J Morphol Embryol* 2019;60(4):1305–10.
2. Khan AA, El-Borai AK, Alnoaiji M. Pleuropulmonary blastoma: A case report and review of the literature. *Case Rep Pathol* 2014;2014:509086.
3. González IA, Mallinger P, Watson D, et al. Expression of p53 is significantly associated with recurrence-free survival and overall survival in pleuropulmonary blastoma (PPB): A report from the International Pleuropulmonary Blastoma/DICER1 Registry. *Mod Pathol* 2021;34(6):1104–15.
4. The International Pleuropulmonary Blastoma/DICER1 Registry. 2021. [Available at: <https://www.ppbregistry.org/>]

5. Knight S, Knight T, Khan A, Murphy AJ. Current management of pleuropulmonary blastoma: A surgical perspective. *Children (Basel)* 2019;6(8):86.
6. Abbo O, Pinnagoda K, Bouchet L, et al. Wilms tumor, pleuropulmonary blastoma, and DICER1: Case report and literature review. *World J Surg Oncol* 2018;16(1):164.
7. Messinger YH, Stewart DR, Priest JR, et al. Pleuropulmonary blastoma: A report on 350 central pathology-confirmed pleuropulmonary blastoma cases by the International Pleuropulmonary Blastoma Registry. *Cancer* 2015;121(2):276–85.
8. Pugh TJ, Yu W, Yang J, et al. Exome sequencing of pleuropulmonary blastoma reveals frequent biallelic loss of TP53 and two hits in DICER1 resulting in retention of 5p-derived miRNA hairpin loop sequences. *Oncogene* 2014;33(45):5295–302.
9. Kusafuka T, Kuroda S, Inoue M, et al. P53 gene mutations in pleuropulmonary blastomas. *Pediatr Hematol Oncol* 2002;19(2):117–28.
10. Vargas SO, Korpershoek E, Kozakewich HPW, de Krijger RR, Fletcher JA, Perez-Atayde AR. Cytogenetic and p53 profiles in congenital cystic adenomatoid malformation: Insights into its relationship with pleuropulmonary blastoma. *Pediatr Dev Pathol* 2006;9(3):190–5.
11. Addanki A, Chaitanya K, Bartakke S, Sethuratnam S. A case report of pleuropulmonary blastoma presenting as tension pneumothorax. *Indian J Med Paediatr Oncol* 2017;38(1):70–2.

Author Contributions

Lakshmisree Akhila Vemulakonda – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Yaritzky Astudillo – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation

of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Elayna Maxx Shanker – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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