



Cytologic diagnostic approach of pleuropulmonary blastoma: a case report

Auliya Suluk Brilliant Sumpono^{1,2*}, Alva Sinung Anindita¹, Junaedy Yunus³, Didik Setyo Heriyanto^{1,2}

¹Department of Anatomical Pathology, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, ²Dr. Sardjito General Hospital, Yogyakarta, ³Department of Anatomy, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

ABSTRACT

Submitted: 2021-09-19
Accepted : 2021-10-24

Pleuropulmonary blastoma (PPB) is a very rare pediatric lung tumor that arises in the pulmonary parenchyma, mediastinum, and pleura. The tumor has rapid disease progression and therefore the prognosis is remarkably poor. We reported a 4-year-old girl who complained of high fever and shortness of breath for the past 8 weeks. The patient was referred from the previous hospital with a pulmonary mass. CT scan of the chest with contrast showed a solid cystic mass with necrotic areas in the 1st, 2nd, and 3rd segments of the left lung with sized 4.8 x 8.1 x 6.6 cm³. As the tumor mass was inoperable, an ultrasound-guided fine-needle aspiration biopsy (FNAB) was conducted to diagnose the pulmonary lesion. We concluded that the lung tumor was a PPB based on FNAB cytology and immunocytochemistry staining. The histopathology feature of PPB appeared similar to fetal lung tissue. Cytologic features obtained from fine-needle aspiration cytology smears and cell blocks followed by immunocytochemistry assay could provide a proper and accurate diagnosis in an inoperable surgical pathology case.

ABSTRAK

Pleuropulmonary blastoma (PPB) merupakan jenis tumor paru yang sangat langka pada anak yang berkembang pada parenkim paru, mediastinum, dan pleura. Tumor jenis ini berkembang dengan cepat sehingga prognosinya sangat buruk. Kami melaporkan pasien anak perempuan berusia 4 tahun yang datang dengan keluhan demam tinggi dan sesak napas selama 8 minggu terakhir. Pasien dirujuk dari rumah sakit sebelumnya dengan adanya suatu massa pada paru. Hasil CT scan dada dengan kontras menunjukkan adanya suatu massa kistik padat dengan area nekrotik pada segmen 1, 2, 3 paru kiri dengan ukuran 4,8 x 8,1 x 6,6 cm³. Karena massa tumor tidak dapat dioperasi, maka biopsi aspirasi jarum halus (AJH) dengan panduan ultrasonografi dilakukan untuk penegakan diagnosis lesi paru. Dari hasil pemeriksaan sitologi AJH yang dilanjutkan dengan pemeriksaan imunositokimia, kami berkesimpulan bahwa tumor paru tersebut adalah PPB. Gambaran histopatologi PPB memiliki kemiripan dengan histologi jaringan paru janin. Gambaran sitologi yang diperoleh dari apusan sitologi AJH dan blok sel yang diikuti dengan pemeriksaan imunositokimia dapat membantu penegakan diagnosis yang tepat dan akurat pada kasus patologi bedah yang tidak dapat dioperasi.

Keywords:
pleuropulmonary blastoma;
pediatric tumor;
cytology;
pulmonary parenchyma;
mediastinum

INTRODUCTION

Pleuropulmonary blastoma (PPB) is an infrequent type of pediatric tumor originating in the lungs and usually presenting in early childhood with the majority of cases diagnosed in children less than 6 years of age.¹ There are only about 300 reported cases of PPB worldwide.² Confirming the diagnosis of PPB is important not only for the patient but also for close family members since the incidence of hereditary PPB and other malignancy in patients with PPB and their young close relatives are about 25%.^{3,4} PPB is commonly associated with cystic malformations of the lung and is classified into three different subtypes, extending from type I (entirely cystic), type II (mixed cystic and solid), and type III (entirely solid), based on the histopathological features.⁵ Multimodal therapy has increased the survival rates and approximately >90% of pediatric patients with type I, >70% with type II, and >50% with type III PPB can be fully recovered.^{5,6} PPB has been well described in histological studies but only a few literatures describe its cytological features. We described a case report of PPB in a 4-year-old girl in addition to cytological, immunocytochemical, and radiological findings.

CASE

A 4-year-old girl suffered from high-grade fever and dyspnea for the past 8 weeks before hospital admission. The patient was initially diagnosed with an upper respiratory tract infection and treated with antipyretic and antibiotic drugs for 2 weeks at the previous hospital, but the complaints did not improve with the therapy. The patient was referred to our hospital with a

pulmonary mass as the diagnosis. When came to our hospital the patient, she was suffering from a fever and shortness of breath. Results of a physical examination showed signs of tachypnea (38 breaths per min), tachycardia (140 beats per min), microcephaly, hypertelorism, bilateral exophthalmos, bilateral proptosis, conjunctival anemia, maxillary hypoplasia, mandibular prognathism, decreased vesicular breath sound on the left lung, and hepatomegaly. Laboratory examination revealed anemia, leukocytosis, neutrophilia, and lymphopenia. CT scan of the chest revealed a solid cystic mass with necrotic areas in the 1st, 2nd, and 3rd segments of the left lung (FIGURE 1). The initial diagnosis of this patient was a left pulmonary mass with suspected Pfeiffer syndrome.

Based on clinical decision-making by the clinician, radiologist, and pathologist, the tumor mass was inoperable and therefore an ultrasound-guided fine-needle aspiration biopsy (FNAB) was planned for further investigation. The patient was treated with paracetamol if she had a fever during the diagnosis process. Microscopic cytology and cell block analyses showed that the tumor cells were polymorphic, medium to large in size, and some cells had scanty cytoplasm, displacing the nuclei eccentrically, whereas it was relatively abundant in other cells. The nuclei were round, oval, or spindle-shaped with irregular membranes and distinct nucleoli (FIGURE 2). Immunocytochemistry assay showed positive expression of vimentin and negative expressions of cytokeratin and synaptophysin (FIGURE 3). The results of cytological examination followed by immunocytochemistry led us to the conclusion that the lung tumor was a pleuropulmonary blastoma.



FIGURE 1. Axial section of CT scan of the chest. A solid cystic mass with an amorphous shape, irregular margin, and areas of necrosis was found in the left superior pulmonary lobe (*), sized 5.32 x 6.18 x 6.96 cm³.

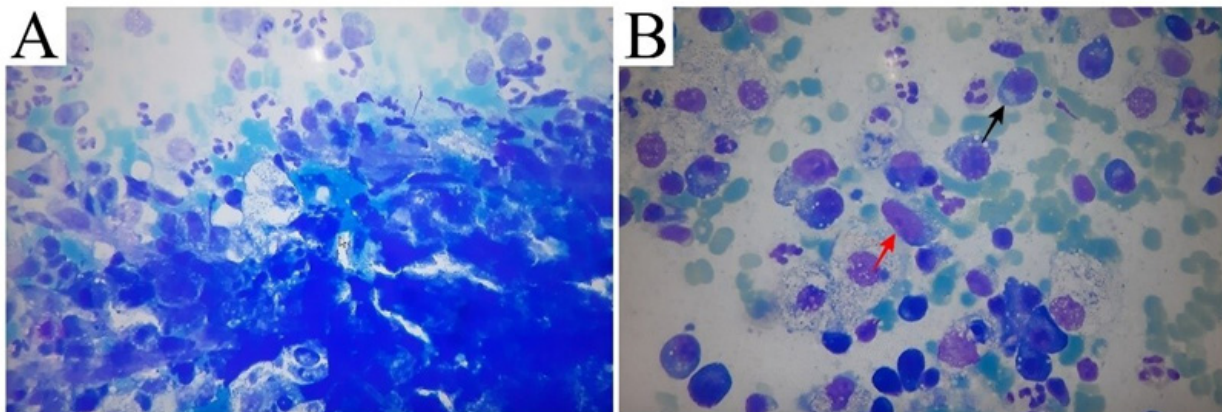


FIGURE 2. Cytologic examination of the pulmonary tissue. (A) Low-power photograph (100x) of cytological smear shows a dimorphic population of tumor cells. (B) High-power photograph (400x) of cytological smear shows a spindle-shaped cell with a high nuclear to cytoplasmic ratio, irregular membrane, distinct nucleolus (red arrow), and another type of round to oval cell with a high nuclear to cytoplasmic ratio, hyperchromatic nucleus, and distinct nucleolus (black arrow).

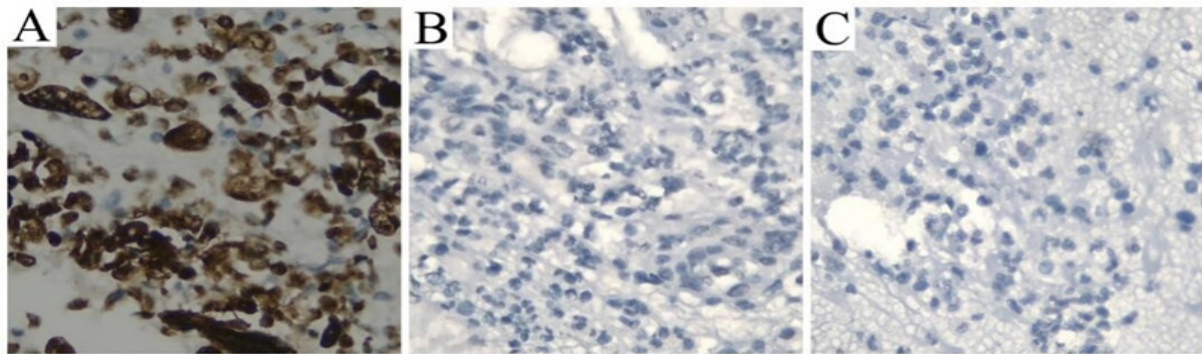


FIGURE 3. Immunocytochemistry staining of the pulmonary mass from cell blocks. High-power photographs (400x) of immunocytochemistry show diffusely positive cytoplasmic staining for vimentin (A), negative cytoplasmic stainings for cytokeratin (B), and synaptophysin (C).

After all examinations were performed and had been consulted to the Division of Medical Genetics, the patient was diagnosed with pleuropulmonary blastoma with Pfeiffer syndrome. The patient received chemotherapy with vincristine 0.8 mg, ifosfamide 500 mg, cyclophosphamide 400 mg combined with mesna 240 mg, and etoposide 80 mg in 6 cycles for 6 months. During chemotherapy, the patient also received leukokine drug after each chemotherapy cycle and paracetamol if the patient had a fever. Follow-up after 6 months of therapy showed improved patient condition and tumor size reduction by 37.5% based on CT scan evaluation (partial response according to RECIST 1.1 criteria).

DISCUSSION

There are three morphological stages in the formation of PPB, i.e., type I or purely multicystic, type II or mixed solid and cystic, and type III or purely solid stage.⁷ Previous report of 50 cases of PPB shows a correlation between the morphological type of PPB and the median age at diagnosis, i.e., type I with a median age of 10 months, type II with a median age of 34 months, and type III with a median age of 44 months. In

addition, the age at diagnosis correlates with the prognosis of PPB.⁸ Type I PPB has a better prognosis, while type II and III PPB have a poor prognosis due to the frequent relapses and distant metastases, especially to the brain and bones. Due to its poor prognosis, PPB is aggressively treated with multimodal therapy, including surgery, chemotherapy, and/or radiotherapy. The combination of those therapies depends on the type and aggressiveness of the disease.⁹ Clinically, PPB patients may present with chest or upper abdominal pain, dry cough, fever, dyspnea, tachypnea, fatigue, respiratory distress with or without an associated pneumothorax, hemoptysis, anorexia, malaise, or neurological symptoms resulting from brain metastases.¹⁰

PPB is often difficult to diagnose due to non-specific imaging findings. It may appear as a cystic lung mass and therefore it should be considered in the differential diagnosis of other benign cystic lung lesions on imaging findings. Early recognition and differentiation of PPB from congenital pulmonary airway malformations and other benign cysts are notably important due to increased survival rates at early diagnosis. On CT scan imaging, type I PPB emerges as a single or multicystic pulmonary lesion (ranging from 2 to 9 cm in diameter)

that causes a mass effect on surrounding structures, sometimes with mediastinal deviation toward the contralateral side. Type II PPB appears with both solid areas and air- or fluid-filled cavities.¹¹ Bleeding or infection in the intracavitary lesions may permeate the cysts and present as more solid areas. An enormous lesion can concur with pleural effusion and mediastinal shift to the contralateral side. Type III PPB appears as solid lesions with low attenuation on CT scan and heterogeneous enhancement pattern with contrast medium administration, with or without pleural effusion, atelectasis, and mediastinal deviation to the contralateral side. Necrotic areas often present without enhancement in contrast-enhanced CT scans. Whereas, the tumor masses are typically large and heterogeneous on MRI imaging.¹² In our case, the patient was categorized as type II PPB based on CT scan results that showed a solid cystic mass and the time when first diagnosed in which type II PPB generally occurs in children over 2 years old (4 years old in our case). Based on previous studies, the long-term survival in this patient is less than 50% and the prognosis is poor. The recommended treatment for this type of PPB is aggressive surgery and chemotherapy.¹³ Our patient had received chemotherapy in 6 cycles for 6 months and showed an improvement. The clinicians are discussing the next steps of therapy for this patient.

The histopathological pattern of PPB involves biphasic cell proliferation. One element comprises primitive cells with single round hyperchromatic nuclei, sometimes with clear nucleoli and sparse cytoplasm, causing high nuclear to cytoplasmic (N/C) ratios. Another major malignant component of PPB is mesenchymal spindle cells. Epithelial cells are not often found in this type of tumor, but the cells could present as entrapped benign epithelium or mesothelium. Focal mesenchymal

differentiation is frequently identified as chondrosarcomatous, liposarcomatous, and particularly rhabdomyosarcomatous components. Cytomorphological findings of PPB from FNAB may conclude its histopathological elements.¹⁴ In our case report, there are two major cell types, including the primitive blastemal cells and mesenchymal spindle cells, reflected in the fine needle aspiration smears. The blastemal cells appear as both solitary cells and cohesive aggregates with round to oval cells, high N/C ratio, hyperchromatic nuclei, and distinct nucleoli. The mesenchymal spindle cells appear mostly as individual scattered malignant cells. However, our specimens do not demonstrate any specific mesenchymal differentiation. In another previous case report, some additional components could be found in the aspiration smears, including the chondroid matrix, pleomorphic giant cells, and myxoid matrix.^{15,16} Other tumors in the small round cell category should be considered as differential diagnoses in cytology samples.¹⁷ The primitive neuroectodermal tumor originating within thoracic soft tissue is one of them. The small primitive malignant cells from both cases may be identical in the aspiration smears. Rosette-like structures may be related to primitive neuroectodermal tumors, which may also display a fibrillar background.¹⁴ In our case, we did not find any rosette-like structure. Moreover, we exclude primitive neuroectodermal tumors in the differential diagnosis by synaptophysin immunocytochemistry that shows negative cytoplasmic expression. Other primitive embryonal malignant neoplasms in the lung also need to be considered in the differential diagnosis, including pulmonary blastoma. According to the WHO 2015 classification of lung tumors, pulmonary blastoma is separated from fetal adenocarcinoma (epithelium

only) and pleuropulmonary blastoma (mesenchymal only).¹⁸ Pulmonary blastoma displays a biphasic histological pattern with both mesenchymal and epithelial components.¹⁹ Immunocytochemistry on cell blocks from FNAB is notably helpful to exclude the differential diagnosis of pulmonary blastoma, in which cytokeratin and vimentin immunocytochemistry show positive cytoplasmic expression in tumor cells of pulmonary blastoma. In our case, only diffusely positive expression of vimentin is detected in tumor cells indicating a mesenchymal phenotype.

PPB is reported to be associated with the DICER1 mutations in 66% of the cases.⁵ The patient has the possibility to develop malignancies in other organs when DICER1 mutations are detected during screening. In our case, the patient might have Pfeiffer syndrome which is a rare autosomal dominantly inherited disorder caused by mutations in the fibroblast growth factor receptor genes FGFR1 or FGFR2.²⁰ Unfortunately there are no previous studies showing a relationship between these two diseases since they have different mutations. Further investigation needs to be done on the genetic background of our patient.

CONCLUSION

We reported a case of pleuropulmonary blastoma in a 4-year-old girl based on cytopathological findings due to an inoperable tumor mass. Diagnosis of PPB using the cytology approach is very challenging, thus additional information from further immunocytochemical assay, radiological findings, and clinical examination is greatly helpful for diagnostic procedures.

ACKNOWLEDGEMENTS

We are grateful to Mrs. Agustin Supriyanti for providing technical assistance.

REFERENCES

1. Bisogno G, Sarnacki S, Stachowicz-Stencel T, Minard Colin V, Ferrari A, Godzinski J, *et al.* Pleuropulmonary blastoma in children and adolescents: The EXPeRT/PARTNER diagnostic and therapeutic recommendations. *Pediatr Blood Cancer* 2021; 68 Suppl 4:e29045. <https://doi.org/10.1002/pbc.29045>
2. Priest JR, Magnuson J, Williams GM, Abromowitch M, Byrd R, Sprinz P, *et al.* Cerebral metastasis and other central nervous system complications of pleuropulmonary blastoma. *Pediatr Blood Cancer* 2007; 49(3):266-73. <https://doi.org/10.1002/pbc.20937>
3. Boman F, Hill DA, Williams GM, Chauvenet A, Fournet JC, Soglio DBD, *et al.* Familial association of pleuropulmonary blastoma with cystic nephroma and other renal tumors: a report from the International Pleuropulmonary Blastoma Registry. *J Pediatr* 2006; 149(6):850-4. <https://doi.org/10.1016/j.jpeds.2006.08.068>
4. Pai S, Eng HL, Lee SY, Hsaio CC, Huang WT, Huang SC, *et al.* Correction: Pleuropulmonary blastoma, not rhabdomyosarcoma in a congenital lung cyst. *Pediatr Blood Cancer* 2007; 48(3):370-1. <https://doi.org/10.1002/pbc.20965>
5. Messinger YH, Stewart DR, Priest JR, Williams GM, Harris AK, Schultz KAP, *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. <https://doi.org/10.1002/cncr.29032>
6. González IA, Mallinger P, Watson D, Harris AK, Messinger YH, Schultz KAP, *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.
<https://doi.org/10.1038/s41379-021-00735-8>
7. Dehner LP, Messinger YH, Schultz KAP, Williams GM, Wikenheiser-Brokamp K, Hill DA. Pleuropulmonary blastoma: evolution of an entity as an entry into a familial tumor predisposition syndrome. *Pediatr Dev Pathol* 18(6):504-11.
<https://doi.org/10.2350/15-10-1732-OA.1>
 8. Priest JR, McDermott MB, Bhatia S, Watterson J, Manivel JC, Dehner LP. Pleuropulmonary blastoma: a clinicopathologic study of 50 cases. *Cancer* 1997; 80(1):147-61.
 9. Christosova IR, Avramova BE, Drebov RS, Shivachev HI, Kamenova MA, Bobev DG, et al. Diagnosis and treatment of pleuropulmonary blastoma-single center experience. *Pediatr Pulmonol* 2015; 50(7):698-703.
<https://doi.org/10.1002/ppul.23047>
 10. Ferrara D, Esposito F, Rossi E, Shangolabad PG, D'Onofrio V, Bifano D, et al. Type II pleuropulmonary blastoma in a 3-years-old female with dyspnea: a case report and review of literature. *Radiol Case Rep* 2021; 16(9):2736-41.
<https://doi.org/10.1016/j.radcr.2021.06.022>
 11. Orazi C, Inserra A, Schingo PMS, De Sio L, Cutrera R, Boldrini R, et al. Pleuropulmonary blastoma, a distinctive neoplasm of childhood: report of three cases. *Pediatr Radiol* 2007; 37(4):337-44.
<https://doi.org/10.1007/s00247-006-0402-0>
 12. Geiger J, Walter K, Uhl M, Bley TA, Jüttner E, Brink I, et al. Imaging findings in a 3-year-old girl with type III pleuropulmonary blastoma. *In Vivo* 2007; 21(6):1119-22.
 13. Khan AA, El-Borai AK, Alnoaiji M. Pleuropulmonary blastoma: a case report and review of the literature. *Case Rep Pathol* 2014; 2014:509086.
<https://doi.org/10.1155/2014/509086>
 14. Nicol KK, Geisinger KR. The cytomorphology of pleuropulmonary blastoma. *Arch Pathol Lab Med* 2000; 124(3):416-8.
<https://doi.org/10.5858/2000-124-0416-TCOPB>
 15. Gelven PL, Hopkins MA, Green CA, Harley RA, Wilson MM. Fine-needle aspiration cytology of pleuropulmonary blastoma: case report and review of the literature. *Diagn Cytopathol* 1997; 16(4):336-40.
[https://doi.org/10.1002/\(sici\)1097-0339\(199704\)16:4<336::aid-dc6>3.0.co;2-b](https://doi.org/10.1002/(sici)1097-0339(199704)16:4<336::aid-dc6>3.0.co;2-b)
 16. Drut R, Pollono D. Pleuropulmonary blastoma: diagnosis by fine-needle aspiration cytology: a case report. *Diagn Cytopathol* 1998; 19(4):303-5.
[https://doi.org/10.1002/\(sici\)1097-0339\(199810\)19:4<303::aid-dc16>3.0.co;2-r](https://doi.org/10.1002/(sici)1097-0339(199810)19:4<303::aid-dc16>3.0.co;2-r)
 17. Monaco SE, Teot LA, editors. *Pediatric Cytopathology*. Berlin, Heidelberg: Springer Berlin Heidelberg; 2017.
 18. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol* 2015; 10(9):1243-60.
<https://doi.org/10.1097/JTO.0000000000000630>
 19. Smyth RJ, Fabre A, Dodd JD, Bartosik W, Gallagher CG, McKone EF. Pulmonary blastoma: a case report and review of the literature. *BMC Res Notes* 2014; 7:294.
<https://doi.org/10.1186/1756-0500-7-294>
 20. Vogels A, Fryns JP. Pfeiffer syndrome. *Orphanet J Rare Dis* 2006; 1:19.
<https://doi.org/10.1186/1750-1172-1-19>