ONKO RESEARCH
ISSN Electronic version

CASE REPORT

A case report of pleuropulmonary blastoma: a challenging diagnostic and therapeutic path in pediatrics

Reporte de un caso de Blastoma pleuropulmonar: un desafiante camino diagnóstico y terapéutico en pediatría.

Gloria Paredes[1], Omar Reyes[1], José Somocurcio[2], Alex Rivera del Carpio[3]

[1] Pediatric Oncology Unit, Hospital Nacional Edgardo Rebagliati, EsSalud, Lima, Peru.
[2] Pathology department, Hospital Nacional Edgardo Rebagliati, EsSalud, Lima, Peru.
[3] Department of Thoracic Surgery, Hospital Nacional Edgardo Rebagliati, EsSalud, Lima, Peru.

OPEN ACCES

Cite as:
Paredes G, Reyes O, Somocurcio JR, Rivera A . pleuropulmonary blastoma: report of 1 case in a pediatric patient under 5 years of age with recurring respiratory difficulty in the Hospital Nacional Edgardo Rebagliati Martins,Lima -Peru. Onkoresearch. 2023;2(1).

Received:
10-01-2023

Approved:
01-08-2023

Author's contributions:
GP, OR, JS and AR participated in the conception of the article, discussion of evidence, writing and approval of the final version.

Financing:
None.

Conflicts of interest:
The authors declare that they have no conflict of interest.

Correspondence:
Gloria Paredes Guerra
E-mail: gloriaparedes2000@yahoo.com

ABSTRACT

A 3-year-old female with a history of bullectomy at the age of 1-year-old, presented a course of progressive respiratory difficulty, dry cough and fever. Extension studies showed a solid tumor that covered almost the entire right hemithorax, displacing the mediastinum. An upper right lobectomy and lumpectomy were performed but a residual mass remained after surgery. Pleuropulmonary blastoma (PPB) type II-III with DICER 1 germinal mutation was diagnosed. She received the IVADo regimen, reducing the tumor size; however, the remaining residual tumor was inoperable. Consequently, she proceeded with a maintenance phase using the Vinorelbine/Cyclophosphamide regimen, being both regimens part of the non-standardized RMS-2005 protocol. A biopsy of the residual mass reported non evidence of cancer. After a 2-year follow-up, she remains cancer-free. This is a very rare disease lacking a standardized treatment protocol until now. It is associated with a genetic basis in 40% of it cases, linked to DICER1 mutation, and typically manifests within the first five years of life. The multidisciplinary management is key in this disease that can improve improves survival.

Keywords
Pulmonary Blastoma; Cáncer; Tumor (source: MeSH-NLM).

RESUMEN

Niña de 3 años con antecedente de bulectomía al año de edad, cursó con dificultad respiratoria progresiva, tos seca y fiebre. Los estudios de extensión mostraron una tumoración sólida que cubría casi todo el hemitórax derecho, desplazando el mediastino. Se realizó una lobectomía superior derecha y lumpectomía, dejando una masa residual. Se hace el diagnóstico de blastoma pleuropulmonar (PPB) tipo II-III con mutación germinal DICER 1. Recibe tratamiento con régimen IVADo, el cuál reduce el tumor, pero deja una masa residual inoperable. Se procede a continuar con esquema de mantenimiento de Vinorelbina/Ciclofosfamida, siendo ambos esquemas parte del protocolo RMS-2005. Una posterior biopsia de la masa residual reportó no evidencia de cáncer. Luego de 2 años de seguimiento, la paciente se mantiene sin evidencia de cáncer. Esta es una enfermedad muy rara donde existe una falta de tratamientos estandarizados a la fecha. Está asociado a una predisposición genética en el

40% de casos, asociado a la mutación DICER1 y típicamente se manifiesta en los primeros cinco años de la vida. El manejo multidisciplinario es clave en esta enfermedad que puede mejorar la sobrevida.

Palabras clave
Blastoma Pulmonar; Cancer; Tumor (fuente: DeCS-BIREME).

INTRODUCTION

Pediatric intrathoracic neoplasms are rare. Most cases are usually due to the involvement of mediastinal structures, such as lymphomas, thymomas, or metastases from other tumors [1]. However, primary pulmonary neoplasms are even rarer and estimated to be 0.2% of all childhood malignancies [2,3].

A large recent study that evaluated the incidence of pulmonary neoplasms in children, found that the carcinoid tumor was the most common histology (29.6%), followed by pulmonary blastoma (PB) (22.3%), being the PB the most common pulmonary malignancy in children younger than 6 years-old [3].

PB is divided into 3 types: Type I is purely cystic, Type II is cystic and solid, and Type III is clearly solid [4]. The reported 5-year survival rate is 70.5%, which is lower than that for carcinoid tumors (97%) [3].

We present a 3-year-old patient with PB type II-III, who presented a challenging diagnostic scenario. The patient underwent a multidisciplinary approach, involving surgery and chemotherapy, resulting in disease remission after 2 -years of follow-up.

CASE REPORT

A 3-year-old female patient from Arequipa, Peru, has a history of presenting a bulla at 1 year and 8 months of age. She underwent a right-sided bullectomy. Eight months later, she developed a new mass in the mediastinum, which was operated, and the pathology report indicated a thymoma. At the age of 3 years, the patient experienced progressive respiratory difficulty, dry cough, fever, and hyporexia. As a result, she was taken to Ilo Hospital in Moquegua, where initial chest X-rays revealed a significant opacity covering the upper two thirds of the right hemithorax (Figure 1).

The initial diagnosis of recurrent bullae versus bronchogenic cyst was proposed. The patient underwent surgery two weeks after the onset of symptoms and underwent an incomplete tumor resection. The pathology report indicated cystic thymic hyperplasia.

She was discharged from the hospital and remained asymptomatic for 3 months. However, she subsequently experienced fever, hyporexia, and dry cough once again. A reassessment of the pathology was conducted, confirming the diagnosis of pleuropulmonary blastoma type II-III. Subsequently, she was referred to the Pediatric Oncology Unit at the Hospital Nacional Edgardo Rebagliati Martins. A chest computerized tomography (CT) scan was performed, revealing a solid tumor covering nearly the entire right hemithorax and displacing the mediastinum (Figure 2).

An upper right lobectomy and lumpectomy were performed. The pathology report revealed a high-grade

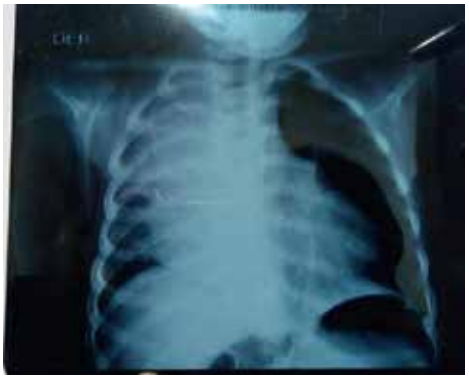


Figure 1. The thorax radiography shows a significant opacity covering the upper two thirds of the right hemithorax.

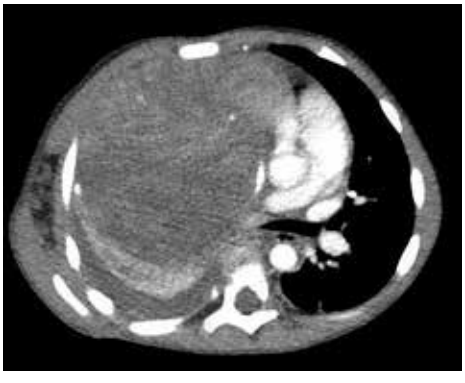
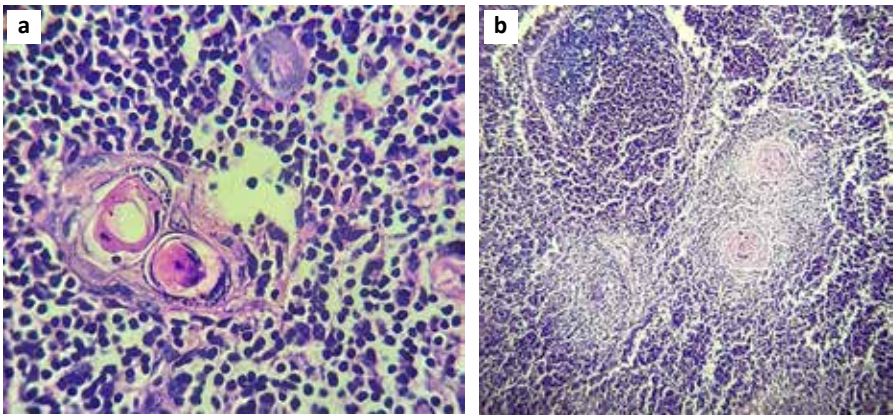


Figure 2. Chest CT scan revealed a solid tumor displacing the mediastinum.



Figures 3. a. Hematoxylin and eosin staining (40X) shows evidence of a heterogeneous solid tumor with a blastemal component. **b.** Hematoxylin and eosin staining shows a spindle cell component with mitotic activity.

primitive mesenchymal malignancy with focal areas of tumor necrosis with vascular thrombosis. (Figures 3a y 3b). The atypical cells exhibited positive staining for CD99, Desmin, CD56, and Vimentin, while being negative for S100 and Actin. The Ki-67 index was 70%. These findings were consistent with pleuropulmonary blastoma type II-III.

The post-surgery chest CT scan reported tumor persistence and described an extensive heterogeneous mass that involves the right hemithorax with extension towards the mediastinum, displacing large vessels, and heart silhouette towards the contralateral side.

Subsequently, the patient underwent to the RMS 2005 protocol, completing 9 cycles of the IVADo regimen (Table 1).

A control chest CT scan after a five-round cycle of chemotherapy revealed a 70% reduction of the mass. The mass measured approximately 28 x 26 x 38 mm and was in contact with the parietal pleura.

After completing the 9th cycle, a positron emission tomography (PET-CT) scan was conducted, revealing a solid mediastinal lesion with poorly defined edges measuring approximately 25 x 17 mm. The lesion exhibited heterogeneous contrast enhancement, and an additional satellite nodular lesion near to the paracardiac region measuring aroun8x5mm with a SUV max of 1.7.

An echocardiography revealed infiltrates in the right atrial and pericardium with irregular morphology. Due to this finding, the condition was considered inoperable at this time, and the decision to proceed with chemotherapy for up to 12 cycles as a consolidation treatment strategy was made. A follow-up chest CT scan after 12 cycles of chemotherapy showed a persistent mass with a 50% reduction in size compared to the previous CT scan. In parallel, a molecular genetic study was done and revealed a pathogenic variant of the DICER1 germinal gene.

Next, she continued with a maintenance chemotherapy according to the RMS-2005 protocol with Vinorelbine and Cyclophosphamide. A last PET CT was performed and reported a discrete change in glycolytic activity compared with the previous study (SUV Max 1.7 vs 1.1) suggesting persistence of the disease (Figure 4).

Table 1. The IVADo regimen.

***CYCLE 1 -4**	
Vincristine 1.5 mg/m^2/day iv bolus	D 1,8,15 (cycle 1-2)
Dactinomycin 1.5 mg/m^2 iv bolus	D1
Doxorubicin 30 mg/m^2 iv if 4 hours	D1-2
Mesna 1 gr/m^2 iv pre ifosfamide	D1
Ifosfamide 3 gr/m^2 ev iand mesna 3 gr/m^2 iv in 3 hours	D1-2
Mesna 3 gr/m^2 iv by 16 hours	D1 d2 (12 h)
***CYCLE 5-9**	
Vincristine 1.5 mg/m^2 iv bolus	D1
Dactinomicin 1.5 mg/m^2 iv bolus	D1
Mesna 1 gr/m^2 iv 1hour pre ifosfamide	D1
Ifosfamide 3 hr/m^2 iv and mesna 3 gr/m^2 iv by 3 hours	D1-2
Mesna 3 gr/m^2 iv if by 21 hours	D1-d2 (12h)

*Repeat every three weeks

Source: Bisogno G, Ferrari A, Bergeron C, Scagnellato A, Prete A, at al. The IVADo regimen--a pilot study with ifosfamide, vincristine, actinomycin D, and doxorubicin in children with metastatic soft tissue sarcoma: a pilot study of behalf of the European pediatric Soft tissue sarcoma Study Group. Cancer. 2005 Apr 15;103(8):1719-24. doi: 10.1002/cncr.20928. PMID: 15754335.

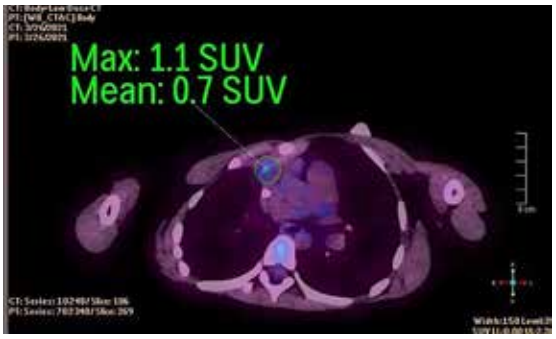


Figure 4. PET-CT scan revealing a decreased glycolytic activity after maintenance therapy.

A decision was made to perform a residual tumor excision of the anterior mediastinum due to the presence of the residual mass. The pathology report revealed a hypotrophic thymic gland with fatty infiltration fibrosis, isolated lymph nodes with nonspecific chronic adenitis, and no evidence of neoplastic disease.

The patient is currently undergoing outpatient follow-up, and both clinical assessments and tomographic images show evidence of disease remission as of the time of this article's publishing.

Ethical considerations

Informed consent and assent were obtained from the patient's parents. The confidentiality of the data obtained from the medical records was maintained.

DISCUSSION

PB is an exceptionally rare disease, with 40% of cases having a genetic basis associated with the DICER1 gene. It typically manifests within the first 5 years of life and constitutes 72% of pediatric lung malignant neoplasms [5,6]. This tumor is characterized by its dysembryogenic nature, with its precursor potentially being the cystic adenomatoid malformation [7].

DICER1 gene is located in the nucleus of chromosome 14, and encodes an enzyme that processes microRNA molecules. Besides its association with PB, it is linked to other neoplasms including those of the kidneys, ovaries, brain, eyes, gastrointestinal tract, nasal passages, and thyroid [5].

In PB, it is observed that type I (clearly cystic) tumors can recur as type II or III disease. These tumors typically arise in patients with preexisting, non-operated pulmonary cysts, often being identified at an average age of approximately 30 months [8]. On the other hand, the usual onset of type II and type III cases falls within the range of 24 to 60 months [9], and they frequently metastasize to the brain [10]. Type III PB tends to occupy an entire hemithorax, presenting as a well-defined mass. The majority of blastomas originate in the subpleural area, frequently in the right lung, with more than half occurring in the lower lobes [7]. Diagnosis with a measurement exceeding 5 cm or involving pleural or mediastinal regions significantly raises the likelihood of metastasis [11].

Although at this time there is not an standardized treatment for PB, it is highly recommended a multidisciplinary approach, predominantly involving surgery, aiming to resect as much mass as feasible, and then a second look procedure may be considered if needed [12,13]. Chemotherapy and, in some instances, radiation therapy, can also contribute to the treatment strategy [9,14].

For type II and type III PB, it is often recommended to encompass rhabdomyosarcoma regimens combined with early or late surgery. Among these regimens, anthracycline-containing protocols have shown superior results, with IVADo (Ifosfamide, Vincristine, Actinomycin and Doxorubicin) exhibiting the most notable reduction in disease progression [15]. In certain cases, a neoadjuvant chemotherapy approach followed by surgery and subsequent adjuvant treatment is also recommended. Hence, the implementation of a multidisciplinary management approach right from the outset, coupled with the accessibility to first-line drugs designed for this type of neoplasm, markedly enhances survival in children with the variant DICER1 gene associated with PB.

All patients with PB should undergo screening for the DICER1 gene mutation because it is also associated with several other benign and malignant tumors, including thyroid, ovarian, and cystic neoplasms [16]. An immediate and correct identification of this gene will enable a more effective lifelong follow-up that will prolong survival in these patients.

Collaborative and prospective efforts should be done to standardize a unique protocol in order to improve survival on these patients. Remarkably, this is the first case with remission and long-term survival in the Pediatric Oncology Unit of the Hospital Nacional Edgardo Rebagliati Martins in Lima, Peru.

REFERENCES

1. Orman G, Masand P, Hicks J, Huisman TAGM, Guillerman RP. Pediatric thoracic mass lesions: Beyond the common. Eur J Radiol Open. 2020;7:100240. doi: 10.1016/j.ejro.2020.100240.

2. Sengupta S, Chatterjee U, Bandyopadhyay R, Bhowmick K, Banerjee S. Primary pulmonary neoplasms in children: A report of five cases. Indian J Med Paediatr Oncol. 2011;32(4):223-6. doi: 10.4103/0971-5851.95146.
3. Shao W, Liu J, Li B, Guo X, Sun J, Li H, et al. Primary lung cancer in children and adolescents: Analysis of a surveillance, epidemiology, and end results database. Front Oncol. 2023;13:1053248. doi: 10.3389/fonc.2023.1053248.
4. Madaan PK, Sidhu HS, Girdhar S, Mann KK. Pleuropulmonary blastoma: A report of three cases and review of literature. Radiol Case Rep. 2021;16(10):2862-8. doi: 10.1016/j.radcr.2021.06.046
5. Hill DA, Jarzembowski JA, Priest JR, Williams G, Schoettler P, Dehner LP. Type I pleuropulmonary blastoma: pathology and biology study of 51 cases from the international pleuropulmonary blastoma registry. Am J Surg Pathol. 2008;32(2):282-95. doi: 10.1097/PAS.0b013e3181484165.
6. Dishop MK, Kuruvilla S. Primary and metastatic lung tumors in the pediatric population: a review and 25-year experience at a large children's hospital. Arch Pathol Lab Med. 2008;132(7):1079-103. doi: 10.5858/2008-132-1079-PAMLTI.
7. María Elena Ucar G, Osvaldo Ibáñez B, Celia Ferrari R, Daniel Pollono F. Tumores pulmonares en pediatría. Rev Chil Enferm Respir. 2012;28(3):199-211. doi: 10.4067/S0717-73482012000300005.
8. Priest JR, Hill DA, Williams GM, Moertel CL, Messinger Y, Finkelstein MJ, et al. Type I pleuropulmonary blastoma: a report from the International Pleuropulmonary Blastoma Registry. J Clin Oncol. 2006;24(27):4492-8. doi: 10.1200/JCO.2005.05.3595.
9. 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.
10. Tan Kendrick A. Cerebral metastasis proven 1 year after an embolic cerebral infarct from pleuropulmonary blastoma. Pediatr Radiol. 2004;34(3):283. doi: 10.1007/s00247-003-1105-4.
11. Priest JR, Williams GM, Hill DA, Dehner LP, Jaffé A. Pulmonary cysts in early childhood and the risk of malignancy. Pediatr Pulmonol. 2009;44(1):14-30. doi: 10.1002/ppul.20917.
12. Indolfi P, Bisogno G, Casale F, Cecchetto G, De Salvo G, Ferrari A, et al. Prognostic factors in pleuro-pulmonary blastoma. Pediatr Blood Cancer. 2007;48(3):318-23. doi: 10.1002/pbc.20842.
13. Knight S, Knight T, Khan A, Murphy AJ. Current Management of Pleuropulmonary Blastoma: A Surgical Perspective. Child (Basel, Switzerland). 2019;6(8):86. doi: 10.3390/children6080086.
14. Sparber-Sauer M, Seitz G, Kirsch S, Vokuhl C, Leuschner I, Dantonello TM, et al. The impact of local control in the treatment of type II/III pleuropulmonary blastoma. Experience of the Cooperative Weichteilsarkom Studiengruppe (CWS). J Surg Oncol. 2017;115(2):164-72. doi: 10.1002/jso.24416.
15. Bisogno G, Brennan B, Orbach D, Stachowicz-Stencel T, Cecchetto G, Indolfi P, et al. Treatment and prognostic factors in pleuropulmonary blastoma: An EXPeRT report. Eur J Cancer. 2014;50(1):178-84. doi: 10.1016/j.ejca.2013.08.015.
16. Caroleo AM, De Ioris MA, Boccuto L, Alessi I, Del Baldo G, Cacchione A, et al. DICER1 Syndrome and Cancer Predisposition: From a Rare Pediatric Tumor to Lifetime Risk. Front Oncol. 2021;10:614541. doi: 10.3389/fonc.2020.614541.