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CLINICAL CASE

Prenatal presentation of pleuropulmonary blastoma associated to DICER1 syndrome: differential diagnosis of congenital pulmonary malformation

Blastoma Pleuropulmonar de presentación antenatal asociado a Síndrome DICER1: diagnóstico diferencial de Malformación Pulmonar Congénita

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What do we know about the subject matter of this study?

Pleuropulmonary blastoma (PPB) is the most common malignant primary pulmonary tumor in pediatrics. Its presentation is almost exclusively postnatal; there are few cases of antenatal PPB in the International PPB/DICER1 Registry. None of the reviewed cases described in the literature have studies to evaluate association with DICER1.

What does this study contribute to what is already known?

We present an unusual case of antenatal presentation of PPB, complicating the differential diagnosis with CPM. Considering that the suspicion of malignancy and surgical indication is based on postnatal presentation, the presence of symptoms such as respiratory distress, certain imaging features such as multiple and/or bilateral lesions, and the absence of systemic vessels, it is suggested to consider genetic study in children with an antenatal diagnosis of CPM due to the association with DICER1 syndrome.

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Abstract

Pleuropulmonary blastoma (PPB) is the most common pediatric malignant primary lung tumor. It's associated with the *DICER1* gene pathogenic germline variants. Antenatal presentation is infrequent and poses a challenge in the differential diagnosis of congenital pulmonary airway malformation (CPAM). **Objective:** to report a case of unusual presentation of PPB associated with *DICER1* syndrome and to describe the difficulty in differentiating it from CPAM. **Clinical Case:** Male patient with prenatal diagnosis of hypervascular left lung lesion, with mediastinal shift and progressive growth, initially interpreted as CPAM. He was born at 38 weeks, requiring transitory treatment with positive pressure due to ventilatory impairment. A CT scan with contrast showed a large multilocular cystic mass containing air causing mass effect, requiring open left upper lobectomy. Histology results were compatible with type I PPB, with negative margins, and positive genetic study for *DICER1* syndrome. Seven weeks post-resection, an aerial image was detected in the upper left side of the chest, with progressive growth, requiring a new tumor resection and upper segmentectomy, with biopsy corresponding to recurrence of type I PPB with negative margins. He received adjuvant treatment with chemotherapy, with follow-up for 2 years, remaining asymptomatic, without recurrence, and with negative screening for other neoplasms associated with *DICER1* syndrome. Among the family history, the mother had papillary thyroid cancer and tested positive for the mutation. **Conclusion:** PPB is a rare cancer, difficult to distinguish from CPAM, especially in its antenatal presentation. Nowing its association with DICER1 syndrome and performing a genetic study are key to the early detection of BPP and the search for other tumors associated with the syndrome.

Keywords:
Pulmonary Blastoma;
Cystic Adenomatoid Malformation;
Lung Neoplasms;
Prenatal Diagnosis;
DICER1;
Protein Human

Introduction

Pleuropulmonary blastoma (PPB) is the most common malignant primary pulmonary tumor in pediatrics[1]. The annual incidence rate of primary lung tumors in children is 0.049 per 100,000 inhabitants, of which 16.4% are pleuropulmonary blastoma[2]. It is generally diagnosed before the age of 4 years and the most common presentations are chest X-ray findings, histopathological findings in the resection of a suspected congenital pulmonary malformation (CPM) or symptomatic by chest pain, upper abdominal pain, fever, dyspnea, cough, hemoptysis, anorexia, general condition compromise, or neurological alterations secondary to brain metastases[3]. There are 3 types of PPB: type I is cystic, type II is solid-cystic, and type III is solid[4]. The prognosis is defined according to the classification and the presence of metastases at diagnosis; in the case of type I, patients have a 5-year disease-free survival of 82% and overall survival of 91%, being of better prognosis than type II and III, which present 5-year disease-free survival of 59% and 37% and overall survival of 71% and 53%, respectively[4].

25% of PPB occur in patients with a family history of neoplasms[5] such as rhabdomyosarcoma, synovial sarcoma, PPB, thyroid cancer, ovarian Sertoli-Leydig cell tumors, germ cell tumors, and leukemia[6]. In addition, genetic variants have been associated with this disease, the most important being germline loss-of-function variants of *DICER1*, located on chromosome 14[7,8]. Other mutations associated with this disease include chromosome 8 gain, trisomy 2, unbalanced translocations between chromosome 1 and X, and p53 mutations or deletions[7].

DICER1 syndrome is a genetic disease with autosomal dominant inheritance and predisposition to the generation of tumors, such as PPB, cystic nephromas, ovarian Sertoli-Leydig cell tumors, multinodular goiter, thyroid cancer, rhabdomyosarcoma, and pineoblastoma[9]. The prevalence of pathogenic *DICER1* variants in the general population is 1/10,600[10]. Carrying one of these variants implies a 5.3% risk at 10 years of age of presenting one of the described tumors and the risk at 50 years of age rises to 19.3%[11].

It has been suggested that the mechanism of PPB development in the syndrome would require a biallelic *DICER1* disruption, but in which the second somatically acquired variant is not classically loss-of-function, allowing some *DICER1* activity to ensure survival of PPB cells[8]. In a retrospective study of 350 patients with PPB, 66% presented variants in *DICER1*, where it was also determined that the association of *DICER1* and PPB does not affect the prognosis or severity of the disease[4].

Worldwide, antenatal presentation of PPB is extremely rare, with only eight cases in the International PPB/DICER1 Registry (personal communication) and few case reports in the international literature[12-14]. It is very difficult to distinguish a PPB from a CPM without histological confirmation and this is one of the reasons used to indicate surgical resection of a CPM instead of observation[15].

The objective of this article is to report a very unusual case of PPM associated with *DICER1* syndrome and its management and to describe the difficulty in differentiating this pathology from CPM, which is its main differential diagnosis.

Clinical Case

Male patient with regular prenatal follow-up and normal second-trimester anatomical study. At 31+5 weeks of gestation, an ultrasound showed a left pulmonary lesion of 8.9 cm^3, hypervascularized, and causing mediastinal shift. Follow-up showed an increase in the size of the cystic lesion from 4.1 x 3.3 x 4.6 cm at 34 + 4 weeks to 5.1 x 3.4 x 5.4 cm at 36 + 5 weeks.

The study was complemented with a fetal MRI at 32 weeks (Figure 1A), to evaluate airway involvement. In this image, a left intrapulmonary unilocular cystic lesion was identified, with high signal in T2 sequence and low in T1 sequence, homogeneous, with no diffusion restriction. It was surrounded by a thin hypointense capsule and measured 2.9 x 2.5 x 2.0 cm (7.5 cm^3) in the cephalocaudal, anteroposterior, and transverse axes respectively. At 37 + 2 weeks, a new fetal MRI was performed (Figure 1B) showing a significant increase in size of the lesion up to 58 cm^3 and a cyst volume ratio of 1.6 with mass effect. Due to the characteristics, CPM was suggested as the most probable diagnosis.

Among the family history, the diagnosis of multinodular goiter and operated papillary thyroid cancer of the mother stood out (Figure 2).

He was born at 38 weeks by spontaneous vaginal delivery, Apgar score 8-9, with subsequent respiratory failure, requiring continuous positive airway pressure (CPAP) with positive expiratory pressure (PEP) of 5 mmHg transiently. A chest X-ray at birth (Figure 3A) showed multiple rounded cystic images in the middle third of the left hemithorax, consistent with the diagnostic hypothesis of CPM. Initially, the patient was managed conservatively, but progressed with ventilatory deterioration until on the seventh day of life he presented tachypnea with abolished pulmonary murmur on the left. An X-ray at that time showed enlargement of the lesions, in addition to mediastinal shift and secondary atelectasis (Figure 3B). The patient was intubated and connected to invasive mechanical ventilation. A CT scan with arterial contrast injection of the thorax was performed, which showed an extensive multilocular cystic mass with air content in the left hemithorax with significant mass effect with mediastinal structures deviation to the right, considering CPM as the main diagnosis (Figure 4).

At nine days of life, a left upper lobectomy was performed through a left posterolateral thoracotomy, without incidents. The anatomopathological study described a 5 cm peripheral lung lesion, differentiated from lung tissue, multicystic, with septa lined by low, flattened cuboidal cells, stroma with arterioles and immature mesenchymal cells (Figure 5). The borders were negative with margins greater than 1 cm. With the described findings, a lesion compatible with Pleuropulmonary Blastoma Type 1 was concluded. Given this diagnosis and the mother's history, a genetic study was performed by massive sequencing for *DICER1*, finding the pathogenic variant in exon 8, c.988C > T (p.Gln330*), in heterozygosis.

The patient evolved favorably on invasive mechanical ventilation with low parameters for six days. He was discharged at 22 days of life, in good general condition, and with a physical examination with pulmonary murmur present and symmetrical. The predischarge check-up chest X-ray only described postsurgical changes.

He remained asymptomatic and without complications; but in the radiological check-up at 7 weeks, an aerial image of 4.3 x 4.0 cm was identified in the upper left thorax, which could correspond to a residual lesion after his thoracotomy. Radiological follow-up showed significant growth of the lesion described above, up to 7.35 cm in its major axis. Due to the above and associated with the appearance of polypnea and subcostal retraction, a new chest CT scan with contrast was performed due to the suspicion of recurrence of the pulmonary tumor. This image showed occupation of the left hemithorax by a multiloculated cystic mass of 6.0x3.8x4.0 cm in its cephalocaudal, anteroposterior, and transverse axes respectively (47 cm^3), with thick and irregular walls in its posterior aspect of 6 mm in thickness, with multiple septa that reached a thickness

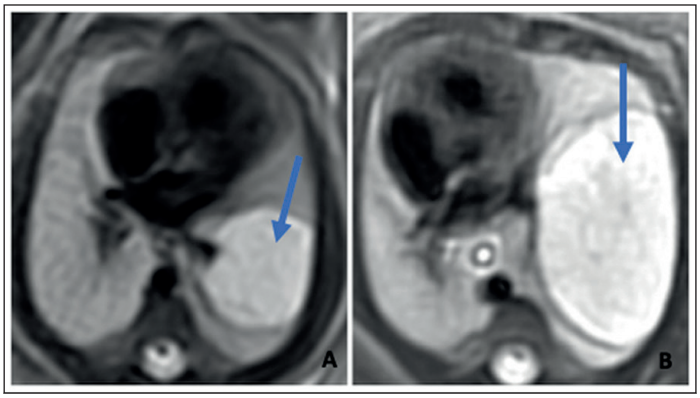

Figure 1. A and B Correspond to different cross-sections of magnetic resonance imaging (MRI) performed during the gestation period. **A.** was performed at 32 weeks gestational age (GA), while **B.** was performed at 37 weeks of GA. In both studies, a lung mass (arrow) can be visualized, at that time described as congenital pulmonary malformation (CPM). An increase in lesion size can be observed between the two studies, with a few weeks of gestation apart.

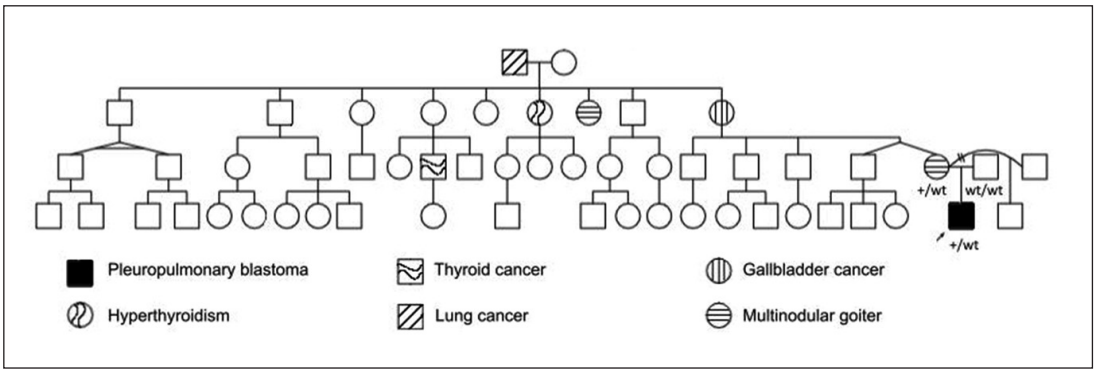

Figure 2. Family genogram of clinical case: +: DICER1 c.988C>T (p.Gln330*). WT: Native allele.

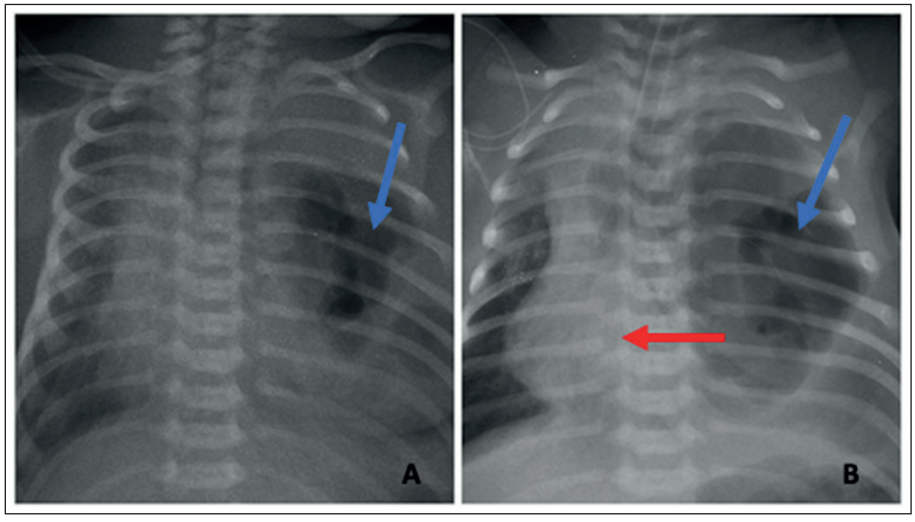

Figure 3. A. Corresponds to anteroposterior (AP) chest X-ray performed at birth without symptoms. **Image B** is an AP chest X-ray performed on the seventh day of life, while the patient presented respiratory failure. On both X-rays, we can see a lung mass indicated by the blue arrow. However, it should be noted that on the seventh day in Figure B, the mass appears to be larger, associated with displacement of the mediastinum, indicated by the red arrow.

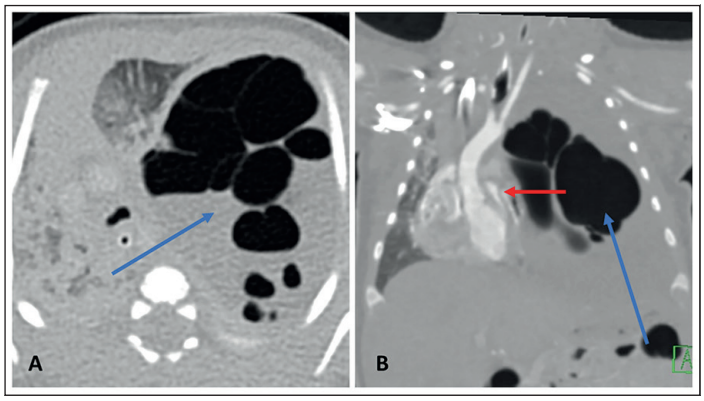

Figure 4. Chest computed tomography (CT) scan at 7 days of age. A corresponds to a cross-section in which the large lung lesion can be seen in the left hemithorax, marked by the blue arrow. **B** shows the same CT scan in coronal section, in which the lung mass (at that time classified as congenital pulmonary malformation (CPM)) is visualized, indicated with a blue arrow, in addition to a displacement of the mediastinum produced by the mass to the right, indicated with a red arrow.

of up to 1 mm and that captured contrast. The lesion determined a mediastinal shift towards the contralateral side. The most probable diagnosis was a local recurrence of PPB.

A new surgery was performed through the previous incision, where cystic lesions with origin in the upper segment of the left lower lobe were detected. A complete resection of the lesions was performed through an upper segmentectomy. In the anatomopathological study, a 5.5 cm PPB with free borders of 0.5 cm was identified. Both surgical specimens were evaluated by the pathologist of the International PPB/DICER1 Registry, confirming these findings. During the postoperative period, the patient evolved positively, remaining on invasive mechanical ventilation for two days. He was discharged four days after surgery.

The International PPB/DICER1 Registry was contacted, and the case was presented at a multidiscipli-

nary rare tumor meeting of the National Pediatric Cancer Program (PINDA), which recommended adjuvant chemotherapy for its management.

The patient received 26 cycles of weekly low-dose vincristine, actinomycin, and cyclophosphamide, with good adherence to treatment. The end-of-treatment CT scan ruled out the presence of new tumor lesions. Screening for other tumors characteristic of *DICER1* syndrome was performed with negative results. The presence of the mutation in the parents was screened for, with the mother testing positive for the mutation and the father negative (Figure 2). Currently, the patient is 2 years 2 months old and is asymptomatic, with no new recurrences, in serial clinical and radiological follow-up.

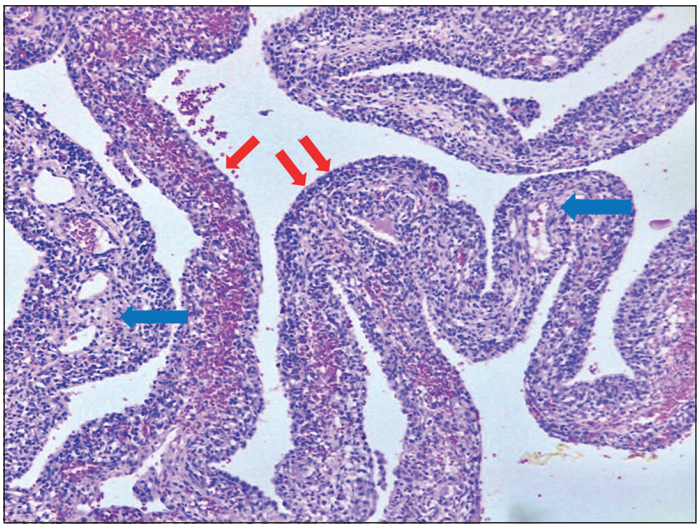

Figure 5. Microphotography with hematoxylin-eosin staining, 10x of the resected mass. It can be seen that the walls of the cysts are composed of immature lax mesenchymal tissue, with the presence of arteries and arterioles (blue arrow), and lined by low and flat cubic epithelial cells (red arrow).

Discussion

Antenatal presentation of PPB is an extremely rare landmark, with few cases reported in the literature of patients with PPB and compatible prenatal imaging[12-14]. These patients, including ours, were initially diagnosed as CPM and later with anatomopathological diagnosis, as type 1 PPB. Prenatal screening in all cases was performed between 21 and 40 weeks of gestation. Of the four cases reported, two patients presented respiratory distress in the first days of life, which led to surgical resection of the tumor, while the other two underwent elective surgery at 4 and 20 months of life[12-14]. These patients had a disease-free survival of between 39 months and 9 years. Among the reported cases, one presented a recurrence two months after the first surgery, which was treated with surgical resection and remains free of disease at nine years of follow-up[12].

The primary treatment of PPB is complete surgical resection. The role of adjuvant chemotherapy is discussed in type I tumors, but not in type II and III in which it is part of the treatment[4,16]. The EXPeRT/Partner group on rare tumors in Europe has created general recommendations to individualize adjuvant therapy in these patients[17]. The management of type III PPB is not standardized, but due to its poor prognosis, there are even cases in which pleural radiotherapy has been used after resection, in addition to adjuvant chemotherapy[18]. The prognosis in recurrent or progressive PPB is even worse, with a 5-year survival of 37%[19].

None of the cases reviewed in the literature, unlike ours, were treated with adjuvant chemotherapy. In this case, the decision was made in common agreement with the PINDA committee for rare tumors and the support of the International PPB/DICER1 Registry, based on the multilobar involvement, the possibility of recurrence, and the presence of demonstrated *DICER1*. The other cases of antenatal diagnosis described in the literature were not studied for germline *DICER1* alterations[12-14]. Patients with *DICER1* syndrome should follow an early detection scheme for potentially associated tumors[9]. Knowing the *DICER1* status in this patient has allowed this screening, early detection of the syndrome in other family members, and genetic counseling.

Differentiating between CPM and PPB remains a challenge for medicine[20]. Currently, the definitive diagnosis of these entities can only be determined through anatomopathological examination[20]. In order to identify clinical and radiological differentiating factors between these two entities, a retrospective study was performed, in which 112 cases of PPB and 103 patients with CPM were evaluated. The presence of antenatal lesions is the factor most strongly associated with CPM (OR 89.4; 95% CI 33.8-236.6; $p < 0.0001$, PPV 93%)[20]. Among the other factors that strongly supported the diagnosis of CPM were systemic vessel irrigation (OR 61.7; CI 3.7-1031.8, $p < 0.0001$, PPV 100%), presence of simple cysts on CT scan (OR 14.8 CI 7.0-31.3, $p < 0.0001$, PPV 75%), and absence of symptoms (OR 8.0; CI 4.3-14.9; $p < 0.0001$, PPV 75%)[20]. Among the characteristics that were most indicative of PPB were bilateral or multisegmental lesions and the presence of pathogenic variants in *DICER1*. From this study, an algorithm was obtained considering the factors indicative of each pathology, which would be a strategy to help distinguish between these entities, achieving a correct diagnosis in 96.7% of the cases[20].

Another retrospective cohort study that also analyzed factors associated with lung tumors, also associa-

tes prenatal dignosis with benign lesions, since none of the 344 cases with prenatal diagnosis turned out to be PPB[21]. Among the factors associated with malignant lesions, the following stand out: tumors not associated with systemic vessels, bilateral tumors (OR 42.03 $p < 0.0041$), history of pneumothorax (OR 7.34 $p < 0.0835$), and suspicion of malignancy in CT scan (OR 42.15 $p < 0.0001$)[21]. According to the above, it is possible to determine that most congenital lung lesions of antenatal diagnosis will correspond to CPM and may therefore be suitable for conservative management[21]. The rarity of this case is that it would constitute an exception to this observation. Another alternative would be to test patients with a diagnosis of CPM for *DICER1* in order to rule out PPM early if non-surgical management is decided upon. This alternative is used in other countries with greater access to genetic testing[22].

Conclusions

In conclusion, PPB is a rare neoplasm, and even more unusual is its antenatal presentation. We describe a new case of antenatal presentation of PPB and its postnatal management, highlighting its association with *DICER1* syndrome. The differential diagnosis with CPM still represents a challenge and requires a high index of suspicion. There are algorithms to differentiate them, being the presence of prenatal imaging as the most important predictor of CPM (over PPB). When the presentation is antenatal, the factors that support the diagnosis of PPB and the surgical indication are the presence of symptoms, imaging findings such as absence of systemic vessels, multiple and/or bilateral lesions, and complex cysts. The genetic study for *DICER1* also helps in this differentiation, in addition to conditioning the patient's follow-up for timely treatment of other associated tumors.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors state that the information has been obtained anonymously from previous data, therefore, Research Ethics Committee, in its discretion, has exempted from obtaining an informed consent, which is recorded in the respective form.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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