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CASE REPORT

Congenital malformation of the pulmonary airway type IV and pleuropulmonary blastoma type I, benign, malignant or pathological expression of the same entity? Clinical case

Malformación congénita de la vía aérea pulmonar tipo IV y blastoma pleuropulmonar tipo I, ¿benigno, maligno o expresión patológica de una misma entidad? Caso clínico

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Abstract

Introduction: *Congenital pulmonary airway malformation (MCAP) IV is considered a benign unilateral and multicystic lesion with a distal acinar origin and is histopathologically indistinguishable from malignant cystic pleuropulmonary blastoma (BPP) I, with an association and potential progression between the two.* **Case description:** *28-week-old fetus with a fetal lung mass and at 7 months with a left pneumothorax, computed tomography scan with parenchymal cystic lesions; thoracotomy shows a 10 cm cystic-bullous lesion, peripherally adhered to the lower lobe and pathology with a cystic lesion of a septate cavity with abundant cuboidal epithelium with loose myxoid stroma, it is difficult to differentiate between MCAP IV and BPP I, due to being positive for the DICER1 mutation and high risk for degeneration into BPP I, a lobectomy is performed and 3 years later with a favorable evolution.* **Discussion:** *An embryonic theory has been associated, where BPP I would have its origin in an unresected MCAP IV. To distinguish between both entities we support the diagnosis of potential progression to BPP in the presence of the prenatal diagnosis, symptoms (pneumothorax), complex cyst and the DICER1 mutation.*

Keywords: *Congenital malformation of the pulmonary airway type IV. Pleuropulmonary blastoma type I. DICER1 mutation.*

Resumen

Introducción: *La malformación congénita de la vía aérea pulmonar (MCAP) IV es considerada una lesión benigna unilateral y multiquística con un origen acinar distal y que resulta histopatológicamente indistinguible del blastoma pleuropulmonar (BPP) I quístico maligno, existiendo una asociación y potencial progresión entre ambas.* **Descripción del caso:** *Feto de 28 semanas de gestación con masa pulmonar fetal y a los siete meses con neumotórax izquierdo, tomografía con lesiones quísticas parenquimatosas; en toracotomía se observa una lesión quístico-bullosa de 10 cm periférica, adherida a lóbulo inferior y en patología con lesión quística de cavidad septada con epitelio cuboidal abundante con estroma laxo mixoide. Complicado diferenciar entre MCAP IV y BPP I, por positivo para mutación DICER1 y alto riesgo para degeneración en*

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BPP I se realiza lobectomía, a tres años con evolución favorable. **Discusión:** *Se ha asociado una teoría embrionaria donde el BPP I tendría su origen en una MCAP IV no resecada. Para distinguir entre ambas entidades apoyamos el diagnóstico de potencial progresión a BPP en la presencia del diagnóstico prenatal, síntomas (neumotórax), quiste complejo y la mutación DICER1.*

Palabras clave: *Malformación congénita de la vía aérea pulmonar tipo IV. Blastoma pleuropulmonar tipo I. Mutación DICER1.*

Introduction

Congenital pulmonary airway malformation (CPAM) type IV is a peripheral cystic lesion described as a defect in distal alveolar development. These cysts are lined by alveolar-type epithelium, which may be flat or cuboidal, and have no connection with bronchiolar structures. Histologically, CPAM type IV is indistinguishable from type I cystic pleuropulmonary blastoma (PPB), and controversy remains regarding a potential association and progression from CPAM type IV to malignancy. The absence of rhabdomyoblasts in CPAM type IV appears to be insufficient to distinguish it from type I PPB, the most common primary malignant lung tumor in childhood.[1,2]

Case presentation

A male fetus at 28 weeks of gestation was found to have a mixed cystic-solid fetal lung mass on prenatal ultrasonography, without evidence of mediastinal shift or hydrops. At 7 months of age, the patient developed a left pneumothorax and underwent pleural drainage, with incomplete resolution and persistence of symptomatic pneumothorax. Computed tomography (CT) showed a loculated pneumothorax and adjacent parenchymal cystic lesions suggestive of congenital cystic adenomatoid malformation (Fig. 1). Thoracotomy was performed and revealed a peripheral cystic-bullous lesion measuring 10 cm in diameter, adherent to the visceral surface of the lower lobe, without a bronchopleural fistula and receiving vascular supply from the subclavian vessels. The lesion was resected as a congenital peripheral pulmonary cyst. Pathological examination showed a giant multiseptated cyst lined microscopically by abundant cuboidal epithelium, without ciliated columnar or mucus-producing epithelium. The septa contained small elongated cells within a loose myxoid stroma. Based on these findings, differentiating between cystic CPAM (formerly congenital cystic adenomatoid malformation) type IV and cystic type I PPB was difficult because the histological criteria may overlap between the 2 entities. Therefore, 1 month later, a lower lobectomy with lymph node resection was performed. Histopathological examination of the left lower pulmonary lobe and lymph nodes showed a granulomatous reaction and was negative for neoplastic cells. Genetic testing was positive for a DICER1 mutation, indicating a high risk of progression to cystic type I PPB. At 3 years of follow-up, the patient had a favorable clinical course without recurrence (Fig. 2).

Discussion

According to the Stocker classification, CPAM is categorized into 5 types. Types I and II, the most common forms, are cystic; type 0 presents as alveolar dysgenesis; and type III consists of branching bronchioles and appears as a solid lesion. A defect in epithelial-mesenchymal signaling is considered the underlying mechanism in all types. Type IV is a peripheral cystic lesion with a thin wall lined by pneumocytes. CPAM type IV has been confused with type I PPB, and some authors have even questioned its existence.[2] There are 3 pathological subtypes of PPB: type I, purely cystic; type II, mixed cystic-solid; and type III, purely solid. The 5-year survival rates for type I, II, and III PPB are 91%, 71%, and 53%, respectively.[3] Type I PPB is the most common primary malignant lung tumor in children. The primary treatment for PPB is complete surgical resection. The role of chemotherapy remains controversial in type I PPB, whereas it forms part of the treatment of types II and III.[4] Prenatal presentation of PPB is extremely rare, with only a few cases reported in the international literature.[5] PPB is frequently diagnosed on histopathological examination of a pulmonary resection specimen obtained because of suspected symptomatic CPAM, as occurred in our patient.

The presence of desmin-positive rhabdomyoblasts rules out CPAM type IV. In contrast, the stroma of type I PPB contains rhabdomyoblasts, primitive fetal cells, and myofibroblasts. However, desmin is not entirely specific for rhabdomyoblasts, and although primitive stromal cells are readily identified in type II and III PPB, they cannot always be recognized in type I PPB,

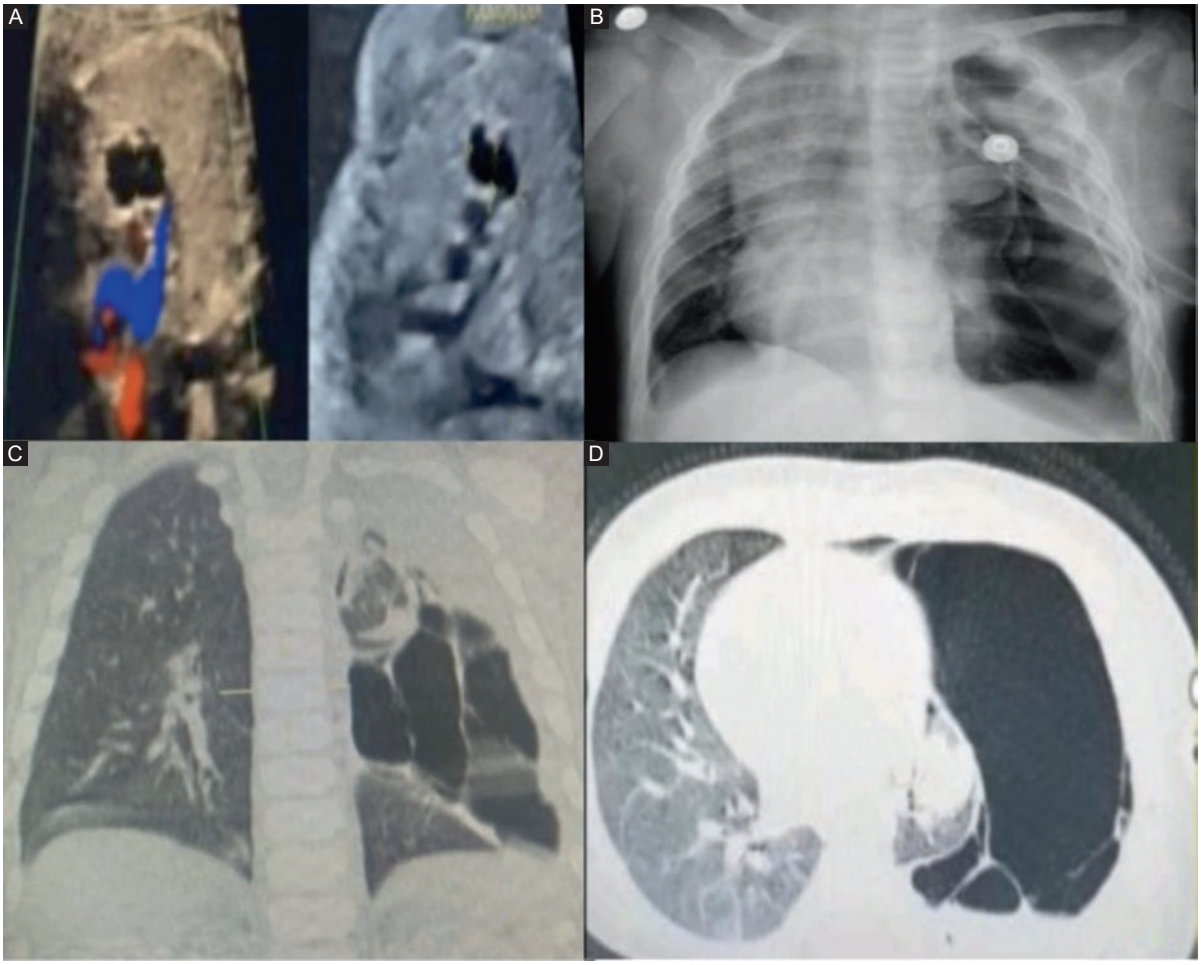


Figure 1. A: prenatal ultrasonography showing a mixed cystic-solid fetal lung mass at 28 weeks of gestation. **B:** persistent symptomatic left pneumothorax despite pleural drainage at 7 months of age. **C:** coronal chest CT showing multiple cystic lesions and the appearance of a loculated pneumothorax. **D:** axial chest CT showing mediastinal shift and lung collapse due to multiple high-pressure cystic lesions.

as occurred in our case. Genetic testing for DICER1 mutations is therefore required in all cases. Mutation analysis of DICER1 has been proposed to better differentiate type I PPB from CPAM type IV.[2,6]

We believe that CPAM type IV is a distinct entity and that all peripheral cystic lesions should be carefully evaluated, primarily for the presence of rhabdomyoblasts within the stroma. In addition, mutation analysis involving members of the DICER1 family and *RAS* genes should be performed. This approach supports the hypothesis proposed in previous reports that stromal cells within CPAM type IV may acquire a DICER1 mutation and progress to type I PPB.[2] DICER1, located on chromosome 14q32.13, is a member of the ribonuclease III family and participates in the generation of microRNAs that modulate posttranscriptional gene expression.[7] Individuals with pathogenic DICER1 variants have an increased risk of certain malignancies, including PPB, cystic nephroma, ovarian Sertoli-Leydig cell tumors, genitourinary sarcomas, neuroendocrine tumors, and several other sarcomas. Approximately 70% of patients with PPB harbor DICER1 mutations that can be identified using standard clinical genetic testing, as occurred in our patient.[8] A diagnosis of PPB should prompt evaluation for familial DICER1 syndromes because of the predisposition to malignancies in other organs. Given the current association between DICER1 and PPB, low-dose chest CT is recommended in the evaluation of all fetal lung masses at birth. Children with a confirmed germline DICER1 mutation should undergo chest CT at 9 months of age to detect type I PPB, allowing resection before potential progression to type II or III

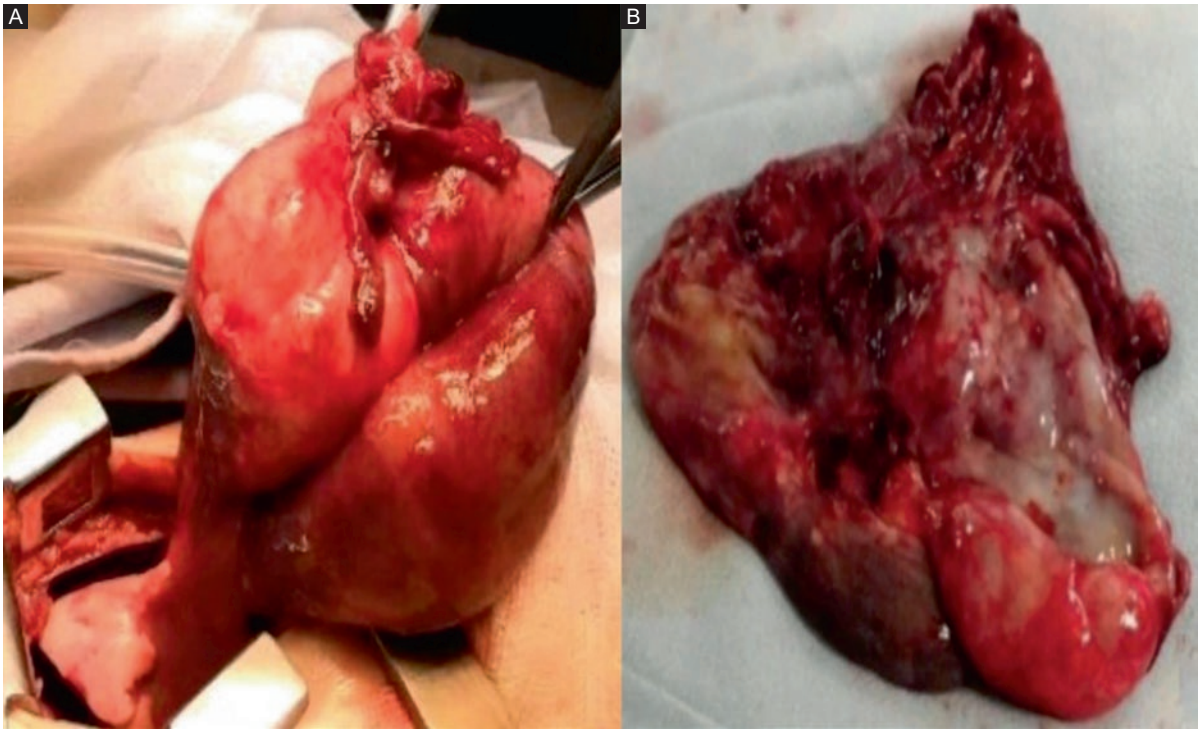


Figure 2. A: giant multiseptated cystic lesion adherent to the visceral pleura of the left lower lobe. **B:** multiseptated peripheral cyst after resection, containing serohemorrhagic fluid and lined internally by mucosal epithelium, corresponding to the gross appearance of congenital pulmonary airway malformation type IV.

PPB. If chest CT findings are normal, a follow-up examination is recommended at 2.5 years of age.[9]

To identify clinical and radiological features that distinguish these 2 entities, a study found that the presence of antenatal lesions was the factor most strongly associated with CPAM (OR, 89.4; 95% CI, 33.8-236.6; $p < 0.0001$; positive predictive value [PPV], 93%). Other associated findings included aberrant blood supply from systemic vessels suggestive of pulmonary sequestration (OR, 61.7; 95% CI, 3.7-1031.8; $p < 0.0001$; PPV, 100%), the presence of simple cysts on CT (OR, 14.8; 95% CI, 7.0-31.3; $p < 0.0001$; PPV, 75%), and absence of symptoms (OR, 8.0; 95% CI, 4.3-14.9; $p < 0.0001$; PPV, 75%). Features most suggestive of PPB included bilateral or multifocal lesions and the presence of pathogenic DICER1 variants.

An algorithm incorporating features suggestive of each disease achieved a correct diagnosis in 96.7% of cases. In another study, factors associated with malignant lesions included tumors without systemic vascular supply, bilateral tumors (OR, 42.03; $p < 0.0041$), a past medical history of pneumothorax (OR, 7.34; $p < 0.0835$), and radiological suspicion of malignancy on CT (OR, 42.15; $p < 0.0001$).[10]

According to these criteria, our patient had several risk factors for malignancy: a mixed fetal lung mass not associated with suspected pulmonary sequestration, postnatal presentation with pneumothorax, and CT evidence of a persistent complex cyst with mediastinal shift, which supported surgical resection. Only during surgery was the presence of a giant peripheral pulmonary cyst recognized, subsequently confirmed histopathologically as CPAM type IV. Given the pathological difficulty in distinguishing the 2 entities and their shared distal alveolar embryological origin, a multidisciplinary decision was made to extend surgical treatment by resecting the residual pulmonary lobe from which the CPAM type IV arose. The presence of a DICER1 mutation further supported this radical surgical approach because of the high risk of association with and progression from CPAM type IV to type I PPB.

Conclusions

There appears to be a strong association and potential progression from benign CPAM type IV to malignant type I PPB. Surgical resection based on clinical and radiological risk factors, together with

rigorous pathological assessment of the primitive stroma of both lesions and evaluation of the risk of malignancy associated with DICER1 mutations within this stroma, may not only help distinguish these 2 entities but also enable timely treatment aimed at preventing progression from CPAM type IV to type I PPB.

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Conflicts of interest

The authors declared no conflicts of interest whatsoever.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data. Given the nature of the study, individual informed consent was not required. Relevant ethical recommendations were followed.

Declaration on the use of artificial intelligence. The authors declare that no type of generative artificial intelligence was used in the writing or creation of content for this manuscript.

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