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ORIGINAL ARTICLE

Rapidly Fatal "Congenital Lung Dysplasia": A Case Report and Review of the Literature

Massimiliano Don,[1] Maria Orsaria,[2] Eva Da Dalt,[1] Carmela Tringali,[1] and Bruno Sacher[1]

[1]*"Sant'Antonio" General Hospital, Pediatric Care Unit, San Daniele del Friuli, Udine, Italy;*
[2]*Department of Medical and Biological Sciences, Pathology Unit, University of Udine, Udine, Italy*

Acinar dysplasia congenital alveolar dysplasia and alveolar capillary dysplasia with misalignment of pulmonary veins belong to the diffuse developmental disorders (congenital lung dysplasia), very rare fatal disorders of infancy that occur early in lung development. A case of quickly fatal congenital lung dysplasia in a full-term infant is presented and underlines the necessity to suspect this disease in a newborn suffering from severe and refractory respiratory distress.

Keywords: acinar dysplasia, alveolar capillary dysplasia with misalignment of pulmonary veins, congenital alveolar dysplasia, congenital lung dysplasia, interstitial lung disease

INTRODUCTION

"Congenital lung dysplasia" groups three rare pediatric lung diseases, belonging to the primary diffuse developmental disorders: acinar dysplasia (AD), congenital alveolar dysplasia (CAD) and alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV) [1]. When the impaired alveolarization severely involves both lungs, this invariably leads to the patient's death, after progressive refractory respiratory distress. We present a case of rapidly fatal "congenital lung dysplasia" and discuss it by an updated overview of this spectrum of diseases.

CASE REPORT

Clinical course

A full-term male infant, without fetal abnormalities on ultrasound at 20 weeks' gestation and with normal fetal heartbeat monitoring, was born to a 29-year-old Caucasian primiparous woman with an uneventful pregnancy. Maternal serological workup was negative. The delivery was carried out without problems.

At birth, the baby cried and breathed spontaneously. Apgar scores were 10 and 9 at 1 and 5 min, respectively. Cyanosis and hypotonia rose up at 2 min of life, so tactile

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Address correspondence to Dr Massimiliano Don MD, PhD, Pediatric Care Unit, "Sant'Antonio" General Hospital, Viale Trento Trieste 33, 33038 San Daniele del Friuli, Udine, Italy. E-mail: max.don@libero.it

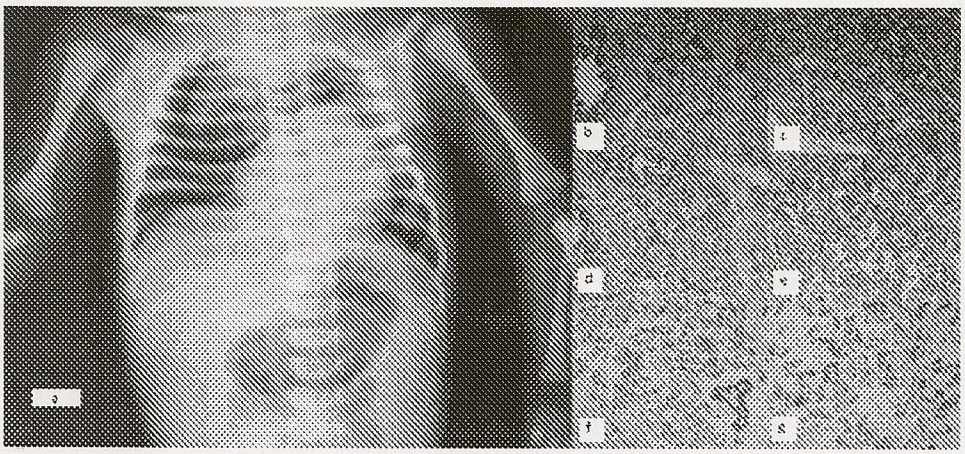

Figure 1. (a) Chest X-ray at 70 min of life (anteroposterior view): "Rim of pneumothorax appears at the medium and upper right field. Thin pneumothorax rim is evident along the left edge. A thin pneumomediastinum rim is present around the left side of the heart. Thymus is shifted to the right superior hemithorax". (b–c) Lungs, postmortem examination: small airways lined by degenerated, low columnar to cuboidal epithelium are present; these structures may represent more distal airway divisions. No alveolar ducts or distinct well-formed alveoli are evident (hematoxylin-eosin 10× and 20×); (d–e) fibrous and edematous interlobular septa with vascular congestion (AFOG 10× and 20×); (f–g) small airways lined by degenerated, low columnar to cuboidal epithelium (CK AE1-AE3 10× and 20×).

stimulation, oropharyngeal suction and ventilation with self-inflating bag were carried out for approximately 2 min. At 5 min of life, the infant appeared tonic and reactive (HR > 100 min^{-1}), with valid crying and peripheral cyanosis. The infant was placed in an incubator with free-flowing oxygen supplementation for 25 min; after that, due to a progressive fall of oxygen saturation to 60%, he was connected to a continuous positive airway pressure circuit (FiO2 80%). At 60 min, he was intubated for persistent cyanosis and SaO2 under 60% and ventilated by self-inflating bag with pure O2 at 100%. Cyanosis worsened with SaO2 in constant decline and mild bilateral pneumothorax and pneumomediastinum (due to neonatal resuscitation attempts) (Figure 1a). The child went into cardiac arrest and died 100 min after delivery.

Post-mortem Examination

The infant weighed 2850 g and his measurements were within normal limits. On autopsy, the heart was macroscopically normal; both foramen ovale and ductus arteriosus were patent. Lungs resulted airless, reddish in color, firm and parenchymatous in consistency; the lung-floating test was positive. The other organs and systems all appeared normal.

Histological Findings

Histologically (Figures 1b–1g), all lung sections demonstrated tiny lobules with unexpanded to poorly expanded pulmonary parenchyma, with macroscopically visible fibrous and edematous interlobular septa. Developmental architecture was arrested in between the canalicular and saccular stages. No alveolar ducts or distinct well-formed alveoli were evident. There was marked vascular congestion that highlight abnormal capillarization related to the growth arrest. No convincing artery-vein pairing or misplacement of veins was identified.

Gross and histologic findings were consistent with the diagnosis of "congenital lung dysplasia".

DISCUSSION

"Congenital lung dysplasia" is a terminology that may be used to group three rare, lethal, neonatal developmental lung diseases (AD, CAD and ACD/MPV), in which incidence and prevalence are not yet known.

After MacMahon in 1948 [2] first described an entity called "congenital alveolar dysplasia," a term that actually reflects a spectrum of lung developmental disorders characterized by a defective development of pulmonary alveoli, very few cases have been reported. A literature search up to October 2012 concerning the pediatric age (0–18 years), was performed using MEDLINE (www.ncbi.nlm.nih.gov). Including the term "congenital alveolar dysplasia" 75 articles were only evidenced (15 reviews and 30 mainly considered ACD/MPV). Moreover, also the portal for rare diseases and orphan drugs, Orphanet, takes into account ACD/MPV but not CAD or AD [3]. In 2007, these three diseases, which were not included in a specific European classification in 2004 [4], were considered in the Children's Interstitial Lung Diseases (chILD) Classification [1], which collected rare and newly described pediatric lung diseases (Table 1). Of the 187 finally enrolled chILD cases, only 2 were CAD cases and none AD [1], highlighting the rarity of these diseases.

CAD, AD and ACD/MPV, are three diseases classified under the group of diffuse developmental disorder of chILD (Table 1). CAD and AD are fatal conditions with incomplete alveolarization due to a growth arrest at the saccular and canalicular stage

Table 1. Children's Interstitial Lung Disease (chILD) Network Classification of Diffuse Lung Disease in Children, focalized on the disorders of neonates and infants (modified from Deutsch GH et al. [1] and Dishop MK [5]).

DISORDERS MORE PREVALENT IN INFANCY
• *Diffuse developmental disorders*
Acinar dysplasia
Congenital alveolar dysplasia (CAD)
Congenital alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV)
• *Growth abnormalities reflecting deficient alveolarization*
Pulmonary hypoplasia
Chronic neonatal lung disease of the prematurity
Related to chromosomal diseases
Relate to congenital heart diseases
• *Specific conditions of uncertain etiology*
Neuroendocrine cell hyperplasia of infancy (NEHI)
Pulmonary interstitial glycogenosis (PIG)
• *Surfactant dysfunction disorders*
Surfactant protein B (*SFTPB*) mutations
Surfactant protein C (*SFTPC*) mutations
ABCA3 mutations
Surfactant dysfunction disorders without known genetic etiology
Pulmonary alveolar proteinosis
Chronic pneumonitis of infancy
Desquamative interstitial pneumonia
Nonspecific interstitial pneumonia
DISORDERS RELATED TO SYSTEMIC DISEASE PROCESSES
DISORDERS OF THE IMMUNOCOMPETENT HOST
DISORDERS OF THE IMMUNOCOMPROMISED HOST
DISORDERS MASQUERADING AS INTERSTITIAL LUNG DISEASE

of development, respectively [2, 5]. These diseases may vary in extension and degree: if the changes are segmental they are compatible with life, [6] whereas if they are diffuse death is the outcome [2, 5]. In practice, in the diffuse forms there are not enough alveoli to sustain life nor an adequate lung elasticity to ensure normal expansion and contraction, so the newborn presents with progressive refractory respiratory distress leading to death within the first 48 h of life [2].

From a clinical point of view, the differential diagnosis comprised a complex congenital cardiopulmonary disease in view of the poor representation of the great vessels on the chest-X-ray (Figure 1a) and an interstitial fetal pneumonia, not confirmed by a pathologist.

The histological aspects (alveolar maldevelopment, with thickened alveolar walls and excess of interstitial tissue rich in dilated capillaries well apposited with the epithelium) oriented the diagnosis towards CAD or AD. In consideration of CAD, the lungs were of normal size, compared to the smaller of AD. On the other hand, AD takes a very rapid clinical course, leading to death within 2 hr; CAD typically has a more prolonged clinical course (weeks to months). This case, albeit, could represent a borderline condition between the two entities and lead us to think that these could represent different steps of the same disease [7], so it is possible to group both under the general term of "congenital lung dysplasia."

ACD/MPV is the third defined diffuse developmental disorder of the lung that may be confused with CAD and AD. Some authors reported that they are separate entities [5], while others assert they are variants of the same disease [7]. Features diagnostic of ACD/MPV, including arteriole-vein pairing with absent pulmonary veins in interlobular septa, were not present in this case, as other congenital extrapulmonary anomalies that are usually associated with ACD/MPV [8].

CONCLUSIONS

chILD are rare and potentially life-threatening diffuse lung diseases. As suggested by MacMahon [2], "congenital lung dysplasia" may be an appropriate designation of this type of morphologic anomaly of the neonatal lungs. In literature, there are very few reports of similarly affected siblings [9]; however, the molecular defects, genetic basis and mode of inheritance for this spectrum of disease have not been adequately studied because of the very limited published cases. It is likely that most cases are sporadic. We think the present report underlines the necessity to increase the suspect of chILD in newborns suffering from severe and refractory respiratory distress and cyanosis. In an appropriate clinical setting, lung biopsy remains the gold standard for the diagnosis.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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