Pathological Findings in Congenital Diaphragmatic Hernia on necropsy studies: A Single-Center Case Series

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Abstract

Introduction: Congenital diaphragmatic hernia (CDH) is known with high mortality rates and significant pulmonary morbidities. The objective of this study was to describe the histopathological findings of necropsy and clinical manifestations in CDH patients to find the clinicopathological correlations. Methods: We reviewed the postmortem findings with associated clinical characteristics retrospectively in 8 CDH cases from 2017 to2022 July. Results: Of the eight cases, one was bilateral congenital eventration diagnosed by autopsy. Severe pulmonary hypertension with a right to left shunting of large patent ductus arteriosus (PDA) obtained from echocardiogram were most common. And the average time of survive was 46 (8-624) h. According to the autopsy reports, the major pathological lung changes were diffuse alveolar damages (congestion and hemorrhage) and hyaline membrane formation. Notably, although the lung volume was significantly reduced, pulmonary structural dysplasia was not observed at all, presented normal lung development (50%); bilateral (25%) or ipsilateral (25%). Lobulated deformities were accompanied in three (37.5%) cases. All patients exhibited large PDA and a patent foramen ovale with increased right ventricle (RV) volume, and the myocardial fibers were slightly congested and swollen. Pulmonary vessels showed mild to moderate arterial media thickening. Lung hypoplasia and diffuse lung damages reduced gas exchange, meanwhile the PDA and PH caused RV failure, contributed a clinical picture of organ dysfunction, which lead to death. Conclusions: Pulmonary structures have certain heterogeneity in CDH. The arteries' pathological changes are not consistent with clinical diagnosis. And the adverse outcome may should be due to the cardiopulmonary vicious cycle.

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Conclusions: Pulmonary structures have certain heterogeneity in CDH. The arteries' pathological changes are not consistent with clinical diagnosis. And the adverse outcome may should be due to the cardiopulmonary vicious cycle.

Keyword: Congenital Diaphragmatic Hernia; Postmortem Examination; Pulmonary Hypoplasia; Pulmonary Hypertension.

1.INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a serious life-threatening malformation, with an incidence of per 2.3 in 10,000 births[1], characterized by abdominal visceral herniation into the chest. Infants with CDH are born with a variable degrees of lung hypoplasia and abnormal pulmonary vasculature, leading to ventilatory insufficiency and pulmonary hypertension (PH)[2]. During the last decades, survival of CDH patients has improved significantly due to the advances in neonatal intensive care and minimally invasive surgery technologies, however there are still 30-50% patients dying of fatal physiological changes[3]. The optimal managements of severe CDH remain challenging. Undoubtedly, severity of pulmonary hypoplasia, pulmonary hypertension, and cardiac dysfunction are major determinants of CDH outcome[4, 5].

CDH can differ in size and location, the most common type are posterolateral defects (Bochdalek hernia), presented in 70%-75% of cases; Anterior defects (Morgagni hernia) present in 23%-28%; and central hernias (2%-3%) are less frequent. Congenital eventration, characterized by incomplete formation of the diaphragm musculature, occurs in different parts of the diaphragm, and does not include communication between the peritoneal and thoracic cavities[6,7]. While diaphragm eventration is certainly a less common phenotype of CDH which often misdiagnosed. Bochdalek hernias occur mostly on the left side, however defects on the right side and bilateral indicate a higher mortality[8]. The pathogenesis of CDH is multifactorial and its epidemiology is poorly understood[9]. Cardiopulmonary pathophysiological processes in CDH patients are still ambiguous; in addition, the permissions of autopsy have continued to decrease in recent decades, and human tissue samples for translational and molecular studies of CDH are rarely available[10]. Postmortem investigation helps to identify the cause of death, as well as to explore the pathogenesis of the disease based

on human. Therefore, in this literature, we performed few comprehensive autopsies of infants with CDH under the permission of parents in our center, observed their pathological changes and clinical characteristics, moreover, it is helpful to establish a biobank to promote the translational study of CDH.

2.MATERIALS AND METHODS

Ethical approval (SHERLLM2022036) was obtained from the Health Research Ethics Board of Children 's Hospital, Capital Institute of Pediatrics. Infants with CDH who were admitted to the intensive care unit between 2017 and 2022 July and died on initial admission at the Department of Neonatal Surgery were included. With the informed consent of the parents, a comprehensive autopsy was assessed by pediatric pathologists in the Department of Pathology of our hospital. All bodies were placed at 4 °C until the autopsy was performed and maximum time from death to autopsy was 2 days postmortem. Paraffin blocks were retrieved from main organs and tissues of the body, stained with hematoxylin and eosin (HE) in 5μm thick sections, were also stained with antibodies against TTF-1 and alpha-smooth muscle actin (HHF35) to better characterize pulmonary epithelial cells and artery muscularization. The relevant clinical diagnosis and treatment data derived from medical records were obtained.

The clinical data of CDH cases were retrospectively collected, including gender, gestational age (GA) at diagnosis, GA in birth, birth weight (BW), mode of delivery, side of hernia, liver herniation, defect size (A, B, C, D) as used by the Congenital Diaphragmatic Hernia Study Group (CDHSG) grade, and length of stay; disease-related information included pulmonary hypertension (PH) (first cardiac ultrasound examination after birth), cardiac anomalies; therapeutic interventions of PH, and repair surgery.

3.RESULTS

The results of clinical data and autopsy reports with CDH are presented in Table 1 and Table 2. Of the 8 patients (males=4, females=4), there were 2(20%) cases of left diaphragmatic hernia, 5(62.5%) cases of right and 1(12.5%) case misdiagnosed as left diaphragmatic hernia, confirmed as bilateral congenital eventration at autopsy; 3 cases (37.5%) of postoperative death and 5(62.5%) were failed to reach preoperative steady state and died. The median GA at birth was 37.5 (range, 29-39, IQR 34.75-38.75) weeks and median GA in diagnosis was 22 (range, 22- 28, IQR 22-24.75) weeks; There were 7(87.5%) cesarean sections and 1(12.5%) spontaneous delivery; the average birth weight was 3006.25g ± 1017.85g; the average time of survive was 127.63h ± 205.62h (range, 8-624) h; defect size by CDHSG were divided into D (57.1%)and C(42.9%), all of which had herniation of the liver significantly. The degree of pulmonary hypertension was all recognized as severe with a right-to-left shunt; Cardiac anomalies such as large patent ductus arteriosus (PDA) and patent foramen ovale (PFO) were diagnosed by echocardiography. After birth, 7 patients (85.7%) received high-frequency ventilator-assisted ventilation (HFOV), with a median initial mean airway pressure (MAP) of 14 (range, 14-22) cmH_2O and up to 18 (range, 16-22) cmH_2O finally. One received ECMO. Inotropic therapy was used to stabilize blood pressure and maintain systemic pressure. All patients were treated with vasoactive drugs including inhaled nitric oxide (iNO) and Sildenafil.

Complications included left ventricular (LV) dysplasia (1/8), pulmonary hemorrhage (3/8), pneumothorax (3/8), scoliosis (1/8), and oliguria (2/8). Due to persistent pulmonary hypertension of newborn (PPHN) at last, patients died for severe refractory hypoxemia, cardiopulmonary failure, uncorrectable decompensated mixed acidosis, and multiple organ failure.

Table 1. Demographics and characteristics of CDH Patients

Parameter	Outcome
GA in diagnosis	22 weeks (range22-28, IQR 22,24.75)
GA at birth	37.5 weeks (range 29-39, IQR 34.75,38.75)
Birthweight (mean ± SD)	3006.25g ± 1017.85g
Mode of Delivery	
Caesarian Section	7/8(87.5%)

Parameter	Outcome
Spontaneous Vaginal Delivery	1/8(12.5%)
Gender	
Male	4/8(50%)
Female	4/8(50%)
Length of stay	127.63h ± 205.62h (range 8-624)
Side of hernia	
Left	2/8(25%)
Right	5/8(62.5%)
Bilateral Eventration	1/8(12.5%)
Liver Herniation	
Yes	8(100%)
Defect Size, n (%)	
C	3/7(42.9%)
D	4/7(57.1%)
Cardiac anomalies	8(100%)
Abnormal LV function	1/8(12.5%)
Pulmonary Hemorrhage	3/8(37.5%)
Pneumothorax	3/8(37.5%)
Oliguria	2/8(25%)
Pulmonary Hypertension	
Severe	8(100%)
Repair Surgery	
Yes	3/8(37.5%)
No	5/8(62.5%)
Ventilator settings	
HFOV	7/8(87.5%)
Initial MAP	14cmH_2O (range 14,22)
Final MAP	18cmH_2O (range 16,22)
ECMO utilization	1/8(12.5%)

(Data were presented as No. (%), the measurement data were described as the mean ± standard deviation, the count data as medians and quartiles.

Abbreviations: GA, gestational age; IQR, interquartile range; SD, standard deviation; PH, pulmonary hypertension; HFOV, high-frequency oscillator ventilation;ECMO, extracorporeal membrane oxygenation.)

All cases had evidence of pulmonary hemorrhage and hyaline membrane formation with varying degrees, as well as alveolar septa, interstitial telangiectasia congestion. Abnormalities of lobation of the lung and pulmonary dysplasia were observed in three cases; Cardiac findings included PDA, PFO, increased right ventricular volume, and mild congestion and swelling of myocardial fibers microscopically; the liver herniated into the thoracic cavity was found significant impression with normal hepatic lobular structure with hepatocyte swelling and degeneration, and significant congestion microscopically; diffuse congestion and bleeding in other organs were observed. The diaphragmatic muscle tissue on the defect side was significantly reduced, hyperplastic fibrous connective tissue was more common, and the contralateral side was normal. The autopsy results showed a consistence with the clinical cause of death.

Macroscopically, the lung volume of the ipsilateral side was significantly smaller than the contralateral side (Fig 1 A), the average proportional weight of ipsilateral vs. total lung weight (%) was 25.06%+-6.99%, the average LBWR was 0.0030+-0.0023. The surface of the lung tissues was dark red and smooth. And the floating test in water was positive. 3 (37.5%) of them had lobulated deformity of the ipsilateral lung while bilobate, trilobate and quadrilobate lungs were found; We found 4 patients with right CDH had poor air

content in both lungs. And 1 patient with left large defect had severe right curvature of the spine, involving the T5- L5 interval, showing that the left thoracic cavity was significantly enlarged compared with the right thoracic cavity. Microscopically, diffuse pulmonary hemorrhage and hemosiderin laden macrophages were observed in bilateral lung; hyaline membrane was formed in 7 cases; diffuse acute and chronic inflammatory cell infiltration was observed in alveolar space, alveolar septum was significantly widened, and capillaries were dilated and congested; exfoliated mucosal epithelial cells, inflammatory exudates and hyaline membrane were observed in small airways, which completely blocked the lumen (Fig 1 B-E); interstitial vessels were significantly dilated and congested with significant edema, pulmonary dysplasia was only found on the ipsilateral sides in 2 cases, bilaterally poor development was observed in 2 cases (bilateral congenital eventration and right CDH)(Fig 1 D-E), acinar hypoplasia was found in the pseudoglandular and canalicular stages of lung development with reduced alveoli and small lumen. 4 patients (50%) had fair lung development (1 on the left side and 3 on the right side) (Fig 1 B-C). Muscular arteries showed media thickening, sometimes with complete occlusion of the lumen (Fig 2).

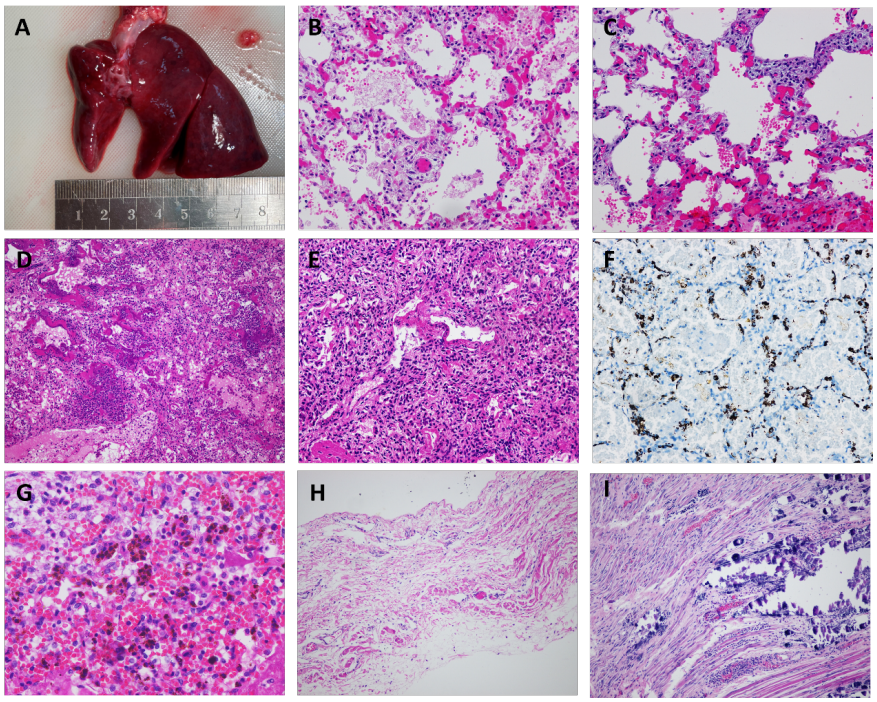

Fig 1. Characteristic histopathological findings observed in postmortem examination.

A, pulmonary dysplasia in gross; B (the contralateral lung), C (the ipsilateral lung) Relatively normal lung development bilaterally was showed in left CDH , hyaline membrane formation in the alveolar space, diffuse pulmonary hemorrhage, widened alveolar septa were found ((hematoxylin and eosin (HE), × 200); D (the contralateral lung), E (the ipsilateral lung) underdeveloped lung structure at canalicular period in both lungs showed in right CDH with decreased number of alveoli, and diffuse alveolar edema and hemorrhage with hyaline membranes, marked inflammatory cell infiltration were found (HE, × 100); F, lung structure development was fair, alveolar hyaline membrane was found(TTF-1, × 200); G, pulmonary hemorrhage, hemosiderin cells found in the lung (HE, × 200); H, aplasia of the musculature within the leaflet of the ipsilateral diaphragm (HE, × 100); I, ipsilateral diaphragm calcification necrosis, inflammatory cell infiltration in right CDH (HE, × 200)

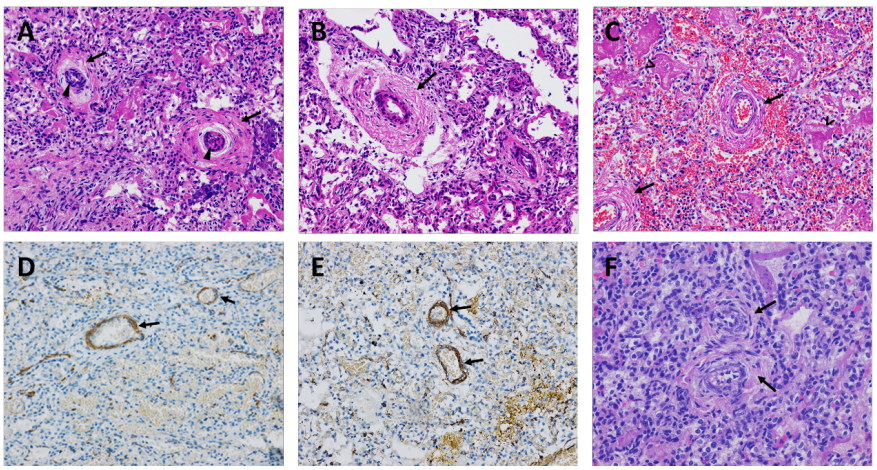

Fig 2. Histopathological findings observed in pulmonary muscular arteries showed variable degrees of arterial media and intima remodeling. (A) Intima (triangles) and media (arrowheads) thickening, hyaline membranes were observed within alveolar septa (hematoxylin and eosin [HE], × 100)). (B) media layer (arrowheads) thickening (HE, ×100). (C) media layer (arrowheads) thickening and diffuse hyaline membrane formation(arrows) in the alveolar space were observed (HE, ×100). (DE) minor thickening of muscular pulmonary arteries(HHF 35, x100) (F) media (arrowheads) thickening (HE x200).

As for cardiac pathological changes, the volume of heart was larger, no significant abnormalities were observed in the exiting or entering great vessels of the heart. All the cases had large PDA and PFO, with a mean diameter of DA 4.6 mm. The average wall thickness of RV was 2.6 mm. Microscopic examination showed turbid swelling of muscle fibers and lytic degeneration of some muscle fibers. There were no significant inflammatory cell infiltration and myocardial cell necrosis. No epicardial changes were observed.

From the hepatic findings, 7 cases showed herniation, liver abnormalities were observed in the unoperated group, significant impression was observed in the herniated part of the liver tissue, and the liver texture was slightly solid. Marked congestion was noted. Microscopic observation showed that normal structure of hepatic lobule was present, and hepatocytes were obviously swollen and degenerated. The sinusoids were markedly dilated and congested with bleeding in some areas. Marked extramedullary hematopoiesis was seen. Focal inflammatory cell infiltration was observed in the portal area, with significant dilatation and congestion of small vessels.

The structure of the diaphragm was absent in the ipsilateral side, while muscle fiber tissues in contralateral side were normal. Striated muscle tissue was still observed in the periphery of defect side. Diaphragm separated by delicate fibrovascular connective tissue either devoid of muscle or with only a few skeletal muscle fibers present in congenital eventration (Fig 1 H). Focal chronic inflammatory cell infiltration was found in operated cases and one of them had significant dilated congestion and calcification necrosis (Fig 1 I).

Two patients had accessory splenic malformation, one had thymic dysplasia and the others showed no significant abnormalities.

Table 2. Histological findings in patients who died from CDH

	Case1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Ipsilateral LW (g)	7.4	2.7	7.2	7.6	6.7	3.4	6.6	38
Contralateral LW (g)	25.7	4.9	26.8	23.8	18.7	17.3	27.6	70.3

	Case1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Proportional weight of ipsi-lateral vs. total lung weight (%)	22.36%	35.53%	21.18%	24.20%	26.38%	16.43%	19.30%	35.10%
LBWR	0.0025	0.0026	0.0022	0.0021	0.0029	0.0011	0.0018	0.0086
Alveolar Hemorrhage	Diffuse	Partial	Partial	Diffuse	Diffuse	Diffuse	Diffuse	Diffuse
Hyaline Membranes	Absent	Diffuse	Diffuse	Diffuse	Partial	Partial	Rare	Rare
Severe Lung Hypoplasia	Absent	Ipsilateral	Bilateral	Bilateral	Absent	Ipsilateral	Absent	Absent
Lung Lobula-tion Anomality	Left	Absent	Absent	Right	Absent	Right	Absent	Absent
Diameter Of DA (mm)	7	4	5	3	5	3	3	7
Thickness Of RV (cm)	4	2	3	4	2	2	2	2
Diameter of RA (cm)	2.4	1.9	2.2	2.4	1.5	2.1	2.4	2.4
Thickness Of LV (cm)	0.5	0.2	0.5	0.5	0.3	0.5	0.5	0.5
Other Abnormalities	Thymic Dysplasia	Scoliosis	Absent	Absent	Accessory Splenic Malformation	Accessory Splenic Malformation	Absent	Absent

(Abbreviations: LW, Lung Weight; LBWR, Lung to Body weight ratio; DA, Ductus Arteriosus; RV, right ventricle; TV, tricuspid valve; PA, Pulmonary valve; LV, Left ventricle)

4.DISCUSSION

4.1. The severity of pulmonary hypoplasia in CDH is inconsistent.

Pulmonary hypoplasia is diagnosed by decreased lung growth and immature in CDH. It is based on measurement of lung-to-body weight ratio(LBWR) <0.012 (>28 weeks)[2], and the pathological characteristics are reduced lung parenchyma and terminal branches of bronchioles, acinar hypoplasia [2]. Gas exchange is impaired severely due to the reduction of alveolar cavity area and thickening of alveolar walls and mesenchyme[11]. Changes in cell phenotype, cell proliferation, and abnormalities in intercellular signaling pathways have been identified as potential pathogenic causes in various animal models of CDH[12]. In this study, LBWR was lower than 0.012, meanwhile a part of postmortem examination identified lung development of CDH stagnating at an earlier developmental stage and presented in the pseudo-glandular or canalicular period, which is consistent with the clinical GA in diagnosis.

The important finding was that histological manifestations of the lung were not consistent. The lung devel-

opment was observed with a relatively normal performance in ipsilateral lungs or bilateral. Current research considers the occurrence of CDH to be a dual-hit hypothesis[13]. This theory holds that the aberrant lung developments exist before the diaphragmatic defect occurs, and the compression secondary to abdominal viscera herniations into the thorax results inhibition of growth and maturation further. Though this study has not fully verified this hypothesis. The hit only occurred in the compression secondary to abdominal viscera herniations, so pulmonary histological development was close to the normal structure. The pathogenesis of CDH is complex in person, and the inconsistency reflects that CDH is a severe disease with strong heterogeneity and evaluating lung development of infants may provide clearer guidance on the management of ventilator settings. Given the low sample size present in this study, we lack statistical significance of predictors for lung hypoplasia.

It was worth noting that in 7 of the 8 cases received HFOV early after birth, which was thought to produce less pulmonary barotrauma[14]. And because of the continuous instability of the physiological state, the ventilator support parameters were adjusted, and the mean MAP increased from 14 to 18 cmH_2O. Based on the autopsy reports, severe pulmonary hemorrhage and hemosiderin deposition in the bilateral lungs and thickening hyaline membrane formation were found, and atelectasis was caused by the small number of alveoli and immature structure. Hyperinflation of the hypoplastic lungs in the ventilation mode of HFOV aggravated the inflammatory response and leads to lung damage. In current neonatal practice, mild ventilation and permissive hypercapnia have become the consensus of ventilator management strategies for neonates with CDH. However, the appropriate adjustment of ventilator parameters cannot be performed with minimal but adequate settings for severe CDH.

4.2 Persistent PH and cardiac dysfunction during fetal-to-neonatal transition in CDH

While the influence factors of PH have been described[15], it remains challenging to pinpoint exactly the factors and at which time point are detrimental in leading to adverse outcome. Elevated right heart pressure, circulatory shunt, hypoventilation, and decreased systemic function, the sequence of physiological process in patients with CDH is complex and varies with the disease severity and progression, which is crucial for guiding treatment to achieve preoperative stabilization and postoperative recovery. In our study, all had been proved severe PH with complete or partial right-to-left shunting across ductus arteriosus, and the ductus arteriosus median size was approximately 4.6 mm at full autopsy, RV volume was enlarged, and the thickness of wall was increased. During fetal cardiopulmonary circulation, pulmonary vascular resistance (PVR) is high and pulmonary blood flow (PBF) is low because the fetal lung is not inflated. Thus, most of right ventricular output is shunted from the ductus arteriosus into the systemic circulation. Left ventricular (LV) preload is derived from the right-to-left shunting of umbilical venous blood flow through the foramen ovale[16]. When umbilical cord clamping, as the low-resistance placental vascular bed is removed, loss of umbilical cord venous return reduces LV preload by 30%-50%, and cardiac output decreases when there is an immediate increase in systemic vascular resistance[17]. Pulmonary ventilation and vasodilation reduce PVR and increase PBF, triggering a transition from fetal to neonatal circulation. Patients with CDH have lower lung compliance and delayed lung ventilation due to lung hypoplasia, which plus a low cardiac index leading to PH[18]. In the process of treatment, lung injury aggravated as well as the degree of respiratory failure, and as hypoxemia and acidosis further stimulate pulmonary vasospasm, PVR persists increased; while the “vicious circle” continued to worsen, the clinical condition deteriorated rapidly. Ultimately, the unstable hemodynamics and rapidity of deterioration of ventilation contribute to the mismatch between oxygen supply and demand. In infants with CDH, PVR is often higher than systemic levels, resulting in extrapulmonary right-to-left shunt and severe hypoxemia. In autopsy cases, the continuous fetal circulation could not be improved with severe PH, thereafter, resulting in more severe right heart failure.

From one of our series, we found the severity of PH and cardiac dysfunction could be unpredictable and disproportionate to respiratory status, whose oxygen saturation remained a high level, however, the patient had severe PDA and died from oliguria. It was also unraveled by Patel [4,19] et al, holding the view that cardiac dysfunction may be a more important determinant of disease severity than PH. Prolonged left-to-right shunting does not further aggravate pulmonary vasculopathy but is a cause of RV failure[20], and the

greater part of the literature ignores the role of PDA and RV failure in CDH. The timing of drug or surgical ligation of the ductus arteriosus is less discussed in CDH, which might indicate the future directions for advancement.

4.3 The pathological manifestations and clinical relationship of CDH-related PH are still unclear.

The CDH-related PH is characterized by an interplay of aberrant structural pulmonary development and postnatal pathologic pulmonary vascular remodeling caused by hypoxic pulmonary vasoconstriction[21]. As acknowledged that histological changes in pulmonary arterioles found in animal models and human are the processive proliferation of muscular vascular medial and adventitial layers, decreased vascular branching and vascular reactivity, as well as reduced lumen diameter[22], however, we found the observed thickening of the media was in a milder degree than our expectations and the number of muscular arteries observed microscopically wasn't decreased. Enlargement and congestion of capillaries in the alveolar septum and lung interstitial showed the severity of pulmonary congestion. Among these cases, pulmonary arteries remained the earliest pathobiological feature of vascular remodeling but presented a severe clinical classification. And the effects of pulmonary vasodilators seemed limited. From our experience, we thought the cardio loading conditions might have an important impact on the outcomes of the treatment for PH. The imbalanced of systemic circulation and pulmonary circulation aggravated the clinical course and the hypoxia pulmonary vasoconstriction impacted less. Based on our small observational study, the view needs further in-depth research.

5.CONCLUSION

In conclusion, the pathological changes of CDH can lead to better introspection by the clinical team. In this study, histopathological findings highlighted that ipsilateral pulmonary structure may be normal despite the reduced volume; it was also noteworthy the pulmonary hyaline membrane formation and diffuse hemorrhage indicated unignorable lung damages.

Modern therapy of the respiratory management still should be improved based on lung protection strategies to avoid barotrauma and atelectasis. A vicious circle of lung hypoplasia combined with severe PH and RV failure contributory to refractory hypoxemia are major fatal factors among our series. The management of severe CDH should focus on the timely correction for vicious circle of persistent PH, which is based on the physiological PH in perinatal transition and synergy with giant PDAs; Medications targeted pulmonary vascular lesions strives to transfer to more personalized ways from the single drug-use pattern. Aim to improve oxygenation and minimize cardiopulmonary symptoms, pulmonary vasodilators, gentle ventilation, fluid resuscitation, and hemodynamic homeostasis need mutual coordination. In addition, collecting CDH tissue to establish a biological sample bank, and further translational research can propose new possibilities for clinical treatment.

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CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interests.

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