



NOTE

Internal Medicine

Pulmonary hypertension due to unclassified interstitial lung disease in a Pembroke Welsh corgi

Tomoya MORITA¹), Kensuke NAKAMURA^{2)*}, Tatsuyuki OSUGA¹),
Atsushi KOBAYASHI³), Osamu ICHII⁴), Akira YABUKI⁵) and Mitsuyoshi TAKIGUCHI¹)

¹Laboratory of Veterinary Internal Medicine, Department of Veterinary Clinical Sciences, Graduate School of Veterinary Medicine, Hokkaido University, N18 W9, Sapporo, Hokkaido 060-0818, Japan

²Organization for promotion of Tenure Track, University of Miyazaki, 1-1 Gakuenkibanadai-nishi, Miyazaki 889-2192, Japan

³Laboratory of Comparative Pathology, Department of Veterinary Clinical Sciences, Graduate School of Veterinary Medicine, Hokkaido University, N18 W9, Sapporo, Hokkaido 060-0818, Japan

⁴Laboratory of Anatomy, Department of Biomedical Sciences, Graduate School of Veterinary Medicine, Hokkaido University, N18 W9, Sapporo, Hokkaido 060-0818, Japan

⁵Laboratory of Veterinary Clinical Pathology, Joint Faculty of Veterinary Medicine, Kagoshima University, 1-21-24 Korimoto, Kagoshima 890-0065, Japan

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ABSTRACT. A 12 year-old intact male Pembroke Welsh corgi weighing 10.8 kg was presented for evaluation of a 3-month history of dyspnea, and a 1-week history of exercise intolerance and anorexia. Severe hypoxemia (PaO₂ 56 mmHg), diffuse lung alveolar infiltration, and severe pulmonary hypertension (PH) (tricuspid regurgitation pressure gradient was 81 mmHg) were identified. A tentative diagnosis of severe PH due to lung disease or pulmonary thromboembolism was made and treated intensively. After 5 days of hospitalization, the dog died despite oxygen supplementation and anticoagulant therapy. This dog was diagnosed as unclassified interstitial lung disease based on histopathological findings.

KEY WORDS: canine, echocardiography, respiratory disease

Pulmonary hypertension (PH) is caused by several diseases and conditions, such as lung disease and/or hypoxia, left-sided heart disease, and pulmonary thromboembolism (PTE) [16]. PH due to lung disease and/or hypoxia is the second most common in dogs [18, 29]. While many lung diseases have been reported to induce PH, interstitial lung disease (ILD) except for interstitial pulmonary fibrosis (IPF) in West Highland Terriers, are uncommon in dogs [4, 7, 14, 15]. The authors report a case of severe PH due to unclassified ILD in Pembroke Welsh corgi.

A 12 year-old intact male Pembroke Welsh corgi weighing 10.8 kg was presented for evaluation of a 3-month history of dyspnea, and a 1-week history of exercise intolerance and anorexia. Three months prior to referral, the dog was treated by oral furosemide, benazepril, prednisone, and theophylline were administered by the referring veterinarian. This resulted in transient relief of dyspnea.

On presentation to our institution, physical examination revealed tachypnea (66 breaths/min), dehydration, and mucous membranes were slightly pale and dry. There were no abnormalities on heart and lung auscultation. Heart rate was 156 bpm, and capillary refill time was within the normal limit. Pulse oximetry (Life Scope A, Nihon Kohden Corp., Tokyo, Japan) demonstrated a SpO₂ on room air of 77%. Systolic and diastolic blood pressure measurement with an oscillometric blood pressure measurement unit (PetMAP graphic, Ramsey Medical Inc., Tampa, FL, U.S.A.) identified systemic hypertension (170/88 mmHg). Blood pressure was not measured repeatedly.

The complete blood count was within the normal range. Significant findings from the serum biochemical profile included severe azotemia (blood urea nitrogen, 120.8 mg/dl [reference range, 9.2–29.2 mg/dl]; creatinine, 4.8 mg/dl [reference range, 0.4–1.4 mg/dl]), hyperphosphatemia (14.2 mg/dl [reference range, 1.9–5.0 mg/dl]), hypercalcemia (13.9 mg/dl [reference range, 9.3–12.1 mg/dl]), mild hyperkalemia (5.1 mEq/l [reference range, 3.8–5.0 mEq/l]), a slight increase in alanine aminotransferase (158 IU/l [reference range, 17–78 IU/l]), and a slight increase in aspartate alkaline phosphatase (612 IU/l [reference range, 47–254 IU/l]). C-reactive protein (0 mg/dl [reference range, <1.0 mg/dl]) was within the normal range. Arterial blood gas

*Correspondence to: Nakamura, K.: kenvet@cc.miyazaki-u.ac.jp

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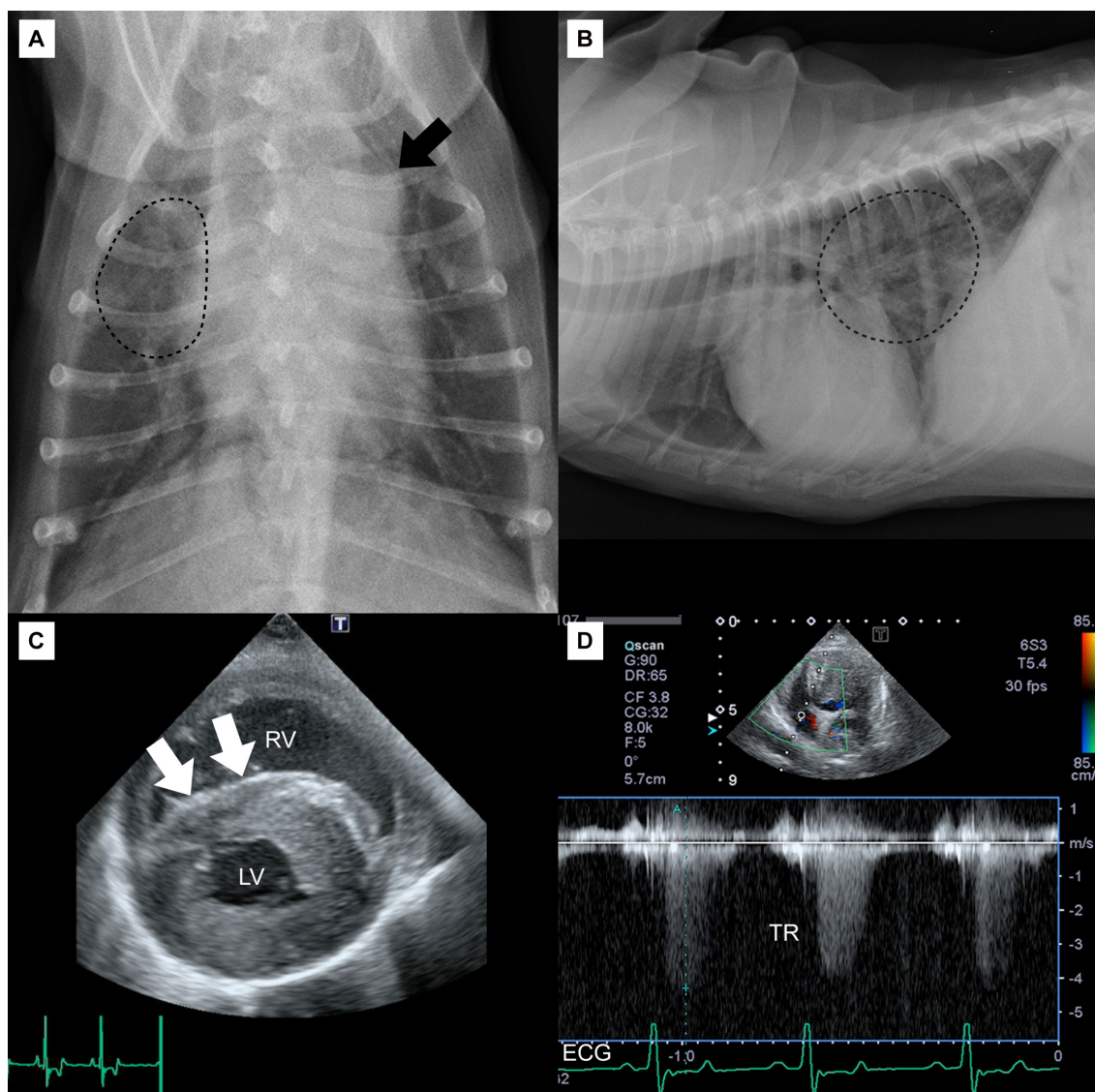


Fig. 1. A-Dorsoventral thoracic radiograph showing unstructured interstitial and alveolar lung patterns in all lung lobes, especially right middle lobe (black dashed line), and main pulmonary artery enlargement (black arrow). B-Right lateral thoracic radiograph showing unstructured interstitial lung patterns in all lung lobes, especially caudal lobe (black dashed line). C-Transthoracic echocardiography recorded from the right parasternal short axis view at the level of the papillary muscles. Left ventricular free wall and septum were thickened, and interventricular septum was mildly flattened at end-diastole (white arrows). D-Continuous-wave Doppler image of tricuspid regurgitation in the apical 4-chamber view.

analysis revealed hypoxemia (PaO_2 , 56 mmHg [reference range, 80–110 mmHg]), hypercapnia (PaCO_2 , 51 mmHg [reference range, 40–45 mmHg]), high alveolar-arterial oxygen gradient (65 mmHg [reference range, <15 mmHg]), low HCO_3^- (11.9 mM [reference range, 19–24 mM]), low base excess (–13.9 mM [reference range, –5–5 mM]), and high anion gap (23.1 mM [reference range, 12–20 mM]) on room air, and mild metabolic acidosis (pH, 7.32 [reference range, 7.35–7.45]). Urinalysis demonstrated isosthenuria (urine specific gravity, 1.013 [reference range, 1.015–1.030]) and proteinuria (urine protein creatinine ratio, 2.5 [reference range, ≤ 0.2]). On standard 6-lead electrocardiogram, sinus rhythm and heart rate were 106 bpm.

Two-view thoracic radiographs revealed enlargement of the main pulmonary artery in the dorso-ventral (DV) view, and unstructured interstitial and alveolar lung patterns in all lung lobes in the DV and right lateral view (Fig. 1A and 1B). Two-view abdominal radiographs showed right kidney enlargement and renal mineralization in both kidneys.

Transthoracic echocardiography demonstrated increased left ventricular (LV) wall thickness (Fig. 1C) and main pulmonary artery dilation (main pulmonary artery to aorta ratio, 1.19 [reference range, <0.98 [29]]). The mild interventricular septal flattening at end-diastolic was observed from the right parasternal short axis view (Fig. 1C). The velocity of tricuspid regurgitation (maximum velocity, 4.4 m/sec; pressure gradient, 81 mmHg) and pulmonary regurgitation (maximum velocity, 3.5 m/sec; pressure gradient 53 mmHg) was high (Fig. 1D), and the right atrial pressure was estimated as 10 mmHg because right atrial dilation was present without right-sided congestive heart failure [12]. The systolic and mean pulmonary arterial pressure were estimated 91

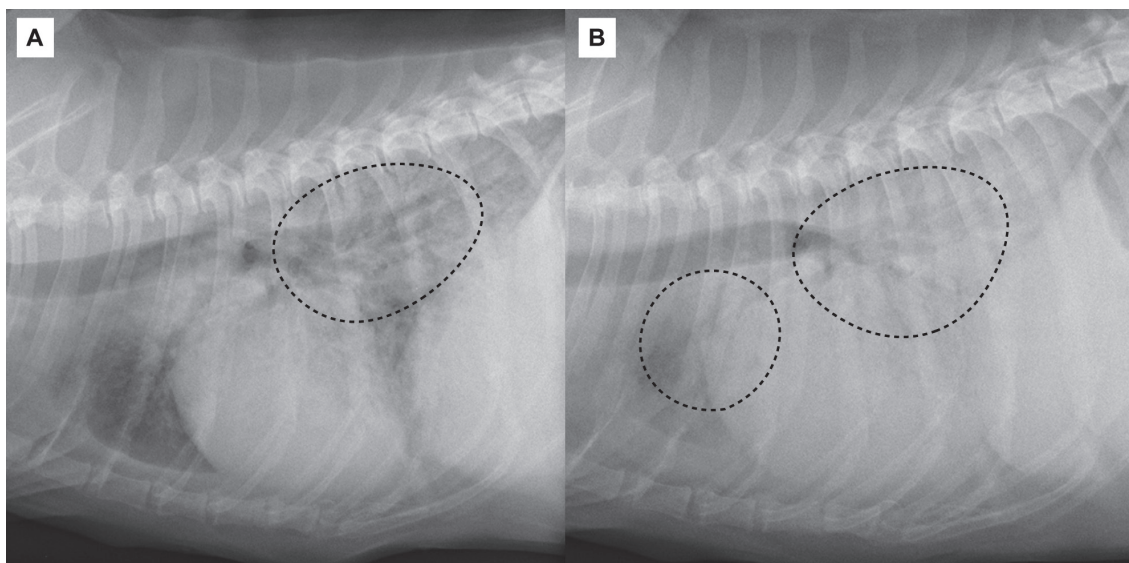


Fig. 2. A-Right lateral thoracic radiograph on day 4 of hospitalization showing a severe alveolar pattern in the caudal lobe (black dashed line).
B-Right lateral thoracic radiograph on day 5 of hospitalization showing a more severe alveolar pattern in all lung lobes (black dashed line).

and 63 mmHg. These findings were consistent with severe PH. Mild mitral regurgitation without left atrium enlargement (left atrium to aorta ratio, 1.38 [reference range, 0.86–1.57 [28]]) was identified. Left ventricular diameter in diastole was 22.3 mm, and normalized left ventricular diameter in diastole was 1.11 [reference range, 1.35–1.73 [8]]. The transmitral flow pattern was an impaired relaxation pattern (E velocity, 0.60 m/sec; A velocity, 0.89 m/sec; E/A, 0.67). The echocardiographic indices of the right ventricular (RV) function were impaired (RV Tei index derived from dual-pulsed wave Doppler, 1.36 [reference range, 0.23–0.31 [21]]; RV longitudinal strain derived from speckle tracking echocardiography, -11.5% [reference range, -16.4% – -21.6% [22]]). Abdominal ultrasound revealed increased echogenicity in the renal cortex, and irregular cortical margin of both kidneys. A tentative diagnosis was PH due to diffuse parenchymal lung disease, which is also described as interstitial lung disease (ILD) or pulmonary thromboembolism and chronic kidney disease with proteinuria.

The dog was treated in the intensive care unit, and oxygen therapy was initiated. To replace the volume deficit, lactated Ringer's solution was intravenously administered at an infusion rate of 3 ml/kg/hr. Low molecular heparin (150 IU/kg SC q 8 hr, Fragmin, Kissei Pharmaceutical Corp., Tokyo, Japan) was administered to prevent intravenous blood clotting. Respiratory status and azotemia mildly improved during hospitalization. However, on day 4 of hospitalization, the dog exhibited dyspnea and C-reactive protein was elevated (5.0 mg/dl). Thoracic radiographs revealed a severe alveolar pattern in the caudal lobes (Fig. 2A). The next day (on day 5 of hospitalization), a severe alveolar pattern in all lung lobes was evident on thoracic radiographs (Fig. 2B), and the dog became apneic with cyanotic mucous membranes and entered full cardiac arrest, for which cardiopulmonary resuscitation was initiated. Cardiopulmonary resuscitation was unsuccessful, and the body was submitted for necropsy examination. The plasma D-dimer concentration on day 1 (0.80 $\mu\text{g/ml}$ [reference range, $<1.0 \mu\text{g/ml}$]) was within the normal range, and antinuclear antibody test on day 1 was negative.

On necropsy, the lungs were solid with multiple dark red mottled or white foci diffusely located in all lung lobes. Pulmonary thrombus was not detected in any lung lobes. The LV and septum were markedly thickened, and LV cavity was decreased. The RV free wall was mildly thickened. The mitral and tricuspid valve leaflets were mildly thickened. The right kidney was moderately enlarged, and there were multiple white foci in the outer layer of the medulla in both kidneys.

Histological examination of the lung was performed on the right middle lobe and left caudal lobe, and demonstrated diffuse interstitial pneumonia, characterized by a moderately thickened alveolar wall with infiltrations of lymphocytes and macrophages, and fibrosis (Fig. 3A). There was diffuse hyperplasia of type II pneumocytes with microvesicular cytoplasmic change (Fig. 3B). Lymphocytes, plasma cells, macrophages, and multinucleated giant cells infiltrated moderately to severely into the alveolar space, and there were also occasional foamy macrophages. There was no honeycombing, obliteration alveolar architecture, eosinophilic infiltration, or eosinophilic proteinaceous material in the alveolar space. No bacteria or fungi were observed in the lung. Multiple dark red mottled foci were consistent with hemorrhages, and white foci were consistent with inflammatory cell clumps. Pulmonary arteriolar wall was thickened, and intravascular space were narrowed. There was no plexiform lesion. The LV wall and septum were markedly thickened, but cardiomyocyte disarray was not evident.

Histological examination of the kidney revealed severe chronic tubulointerstitial nephritis characterized by infiltration of lymphocytes, plasma cells, and macrophages, as well as interstitial fibrosis. Furthermore, we noted moderate membranoproliferative glomerulonephritis characterized by the diffuse thickening of the glomerular basement membrane, and increase of mesangial cells and their matrixes. The present case showed weak granular IgG-positive reactions along subendothelial

regions of the thickened glomerular basement membrane by immunofluorescent microscopic observation, but clear immune complex deposition was not detected with transmission electron microscopy. Thus, we were not able to determine whether the membranoproliferative glomerulonephritis in the present case was an immune complex-mediated disease or not. The reason for this result may be that the immune complex was masked by therapy or degraded by postmortem changes.

Based on these findings, the present case was diagnosed as unclassified ILD.

The present case had severe PH concurrent with severe hypoxia and lung lesions. PH is caused by several diseases and conditions, such as lung disease or hypoxia, left-sided heart disease, congenital cardiovascular shunts, pulmonary thromboembolism, heartworm disease, and idiopathic causes [16]. The present case had only mild mitral regurgitation without left heart enlargement and did not have congenital cardiovascular shunts, but had thickened LV wall. Thickened LV wall can be caused by hypertrophic cardiomyopathy, dehydration (pseudohypertrophy), or systemic hypertension. Hypertrophic cardiomyopathy was ruled out by histological examination. The present case was treated with furosemide, and dehydration was suspected by physical examination and echocardiography (LV underfilling based on small left ventricular diameter in diastole). However, LV wall was certainly thickened on histological examination. Therefore, the thickening of the LV wall may be due to hypertension rather than dehydration. However, in the present case, since repeatedly blood pressure measurement and fundic examination were not performed, systemic hypertension could not be confirmed.

Although systemic hypertension can cause chronic LV diastolic dysfunction and PH due to elevated LV filling pressure [23], the normal left atrial size and unelevated transmitral E velocity indicated low probability of LV diastolic dysfunction in the present case. In addition, pulmonary thromboembolism was ruled out by the D-dimer concentration and histological examination. Heartworm disease was also ruled out by histological examination. Therefore, the present case was diagnosed as PH due to lung disease or hypoxia. In dogs, lung disease or hypoxia have been reported to be the second most common cause of PH, with an incidence rate of approximately 13 to 50% in dogs with PH [18, 29]. Many respiratory diseases, including pneumonia, tracheobronchial disease, tumors, and IPF have been reported to induce PH [4, 7, 14, 15]. Although the present case exhibited severe pneumonia, infectious pneumonia was ruled out because the present animal was well vaccinated and histological examination detected no bacteria or fungi. Therefore, the present case was diagnosed as PH due to ILD.

ILD can be caused by inhaled chemical fumes, mineral fibers, dusts, or allergens, drugs, as well as connective tissue disease, and idiopathic, involving the interstitium in human and dogs [1, 27, 32]. In the present case, there were few possibilities of inhalation of these materials or exposure to toxins and drugs. In dogs, only systemic lupus erythematosus has been reported as the connective tissue disease causing ILD [5, 9]. The present dog had glomerulonephritis, but there was no other finding supporting the diagnosis of systemic lupus erythematosus. Microscopic polyangiitis and Goodpasture's syndrome that can cause severe inflammation and hemorrhage in both kidneys and lungs were also not suspected in the present case because of the lack of characteristic hemorrhagic lesions [11].

Several types of ILD, including IPF, bronchiolitis obliterans with organizing pneumonia (cryptogenic organizing pneumonia), eosinophilic pneumonia, endogenous lipid pneumonia, and pulmonary alveolar proteinosis, have been previously reported in dogs [6, 14, 24–26, 30]. In this case, the histopathological findings were inconsistent with those previously reported for ILD. Therefore, the present case was diagnosed as unclassified ILD. Indeed, in dogs, a definitive classification of ILD is currently difficult because little is known about comprehensive clinical data in dogs with ILD, except for IPF, which is one of the most common ILD [7, 14, 20]. Further studies are needed to clarify the histological criteria of ILD in dogs.

The incidence rate of PH due to ILD has not been clarified in dogs. The prevalence of PH was 14% in human patients from a heterogeneous group with ILD [2]. Furthermore, the presence of PH was associated with greater mortality in patients with ILD [2, 19]. The standard treatment for human patients with PH due to lung disease or hypoxia is long-term oxygen therapy, and PH-

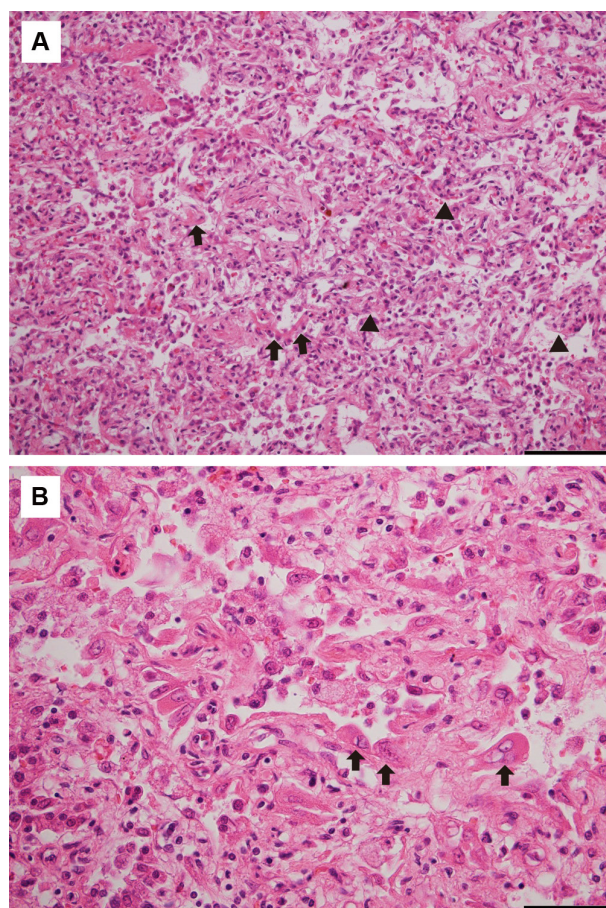


Fig. 3. A-Microscopic image of the middle lobe (200 ×) showing that the alveolar wall was moderately thickened with infiltration of lymphocytes and macrophages (arrowheads), and fibrosis (arrows). H&E staining, bar=100 μm, B-Microscopic image of the middle lobe (400 ×) showing diffuse hyperplasia of type II pneumocytes with microvesicular cytoplasmic changes (arrows). H&E staining, bar=50 μm.

specific therapy (e.g. sildenafil) has not been recommended [10]. However, there are some reports on the effects of sildenafil on survival and exercise capacity in human patients with severe PH due to lung disease or hypoxia [13, 31]. Furthermore, the previous reports demonstrated the efficacy of sildenafil in dogs with PH. Kellum *et al.* reported that sildenafil treatment resulted in clinical improvement in 22 dogs with PH due to several causes, including respiratory disease (n=11) [18]. Bach *et al.* [3] and Kellihaan *et al.* [17] reported the efficacy of sildenafil on amelioration of the clinical signs and the velocity of tricuspid regurgitation in 13 and 10 dogs (included 5 and 7 dogs with respiratory disease), respectively. Although the present case was not treated with PH-specific therapy, it may be an effective treatment.

In conclusion, this report describes the comprehensive clinical data, including physiological data, diagnostic imaging findings, and histological findings, of PH due to unclassified ILD in a dog. Further studies are needed to reveal the incidence rate and to establish optimal therapy of PH due to ILD.

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