Case Report

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Severe Pulmonary Arterial Hypertension Secondary to Interstitial Lung Disease in a 2.5 Year Old-Child with Trisomy 21: A Case Report

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Citation Pourmirzaiee MA. Severe Pulmonary Arterial Hypertension Secondary to Interstitial Lung Disease in a 2.5 Year Old-Child with Trisomy 21: A Case Report. Case Reports in Clinical Practice. 2025; 10(6): 265-269. DOI:10.18502/crcp.v10i6.21612

Running Title Down Syndrome Associated Lung Disease

Article info:
Received: October 29, 2025
Revised: November 24, 2025
Accepted: December 18, 2025

Keywords:
Down syndrome; Pulmonary arterial hypertension; Interstitial lung disease

ABSTRACT

Respiratory complications are the leading cause of mortality in Down syndrome, yet "Down syndrome-associated lung disease" (DSLD) remains frequently under-recognized. DSLD represents a distinct phenotype characterized by the convergence of alveolar simplification, vascular dysgenesis, and immune dysregulation. I present a 2.5-year-old boy from those who visit the clinic with trisomy 21 and congenital hypothyroidism who presented with failure to thrive, progressive tachypnea, and signs of right heart failure. Physical examination revealed diffuse fine crackles and a loud P2. Echocardiography confirmed severe, suprasystemic pulmonary arterial hypertension (PAH) disproportionate to his minor cardiac septal defects. High-resolution computed tomography (HRCT) demonstrated the hallmark findings of DSLD: diffuse subpleural cysts and interlobular septal thickening. Polysomnography confirmed concurrent moderate obstructive sleep apnea. This case illustrates the aggressive nature of DSLD, where structural alveolar hypoplasia (subpleural cysts) correlates with intrinsic vascular fragility and severe PAH. The patient's stabilization required a multimodal strategy targeting three pathogenic axes: hemodynamic off-loading (sildenafil), airway obstruction (CPAP/surgery), and parenchymal inflammation (corticosteroids). Clinicians must recognize subpleural cysts as a "red flag" for this complex pan-pulmonary disorder to initiate early, targeted intervention.

Introduction

Down syndrome (Trisomy 21), first characterized by Down in 1866 and identified as a chromosomal abnormality by Lejeune and colleagues in 1959, is the most common genetic cause of intellectual disability [1-3]. While medical advancements have significantly improved life expectancy, respiratory complications remain a primary driver of morbidity and mortality in this population [4, 5]. The spectrum of pulmonary disease in individuals with Down syndrome is exceptionally broad, stemming from a confluence of anatomical, immunological, and developmental anomalies [6, 7]. These include a high incidence of obstructive sleep apnea (OSA) due to characteristic craniofacial features and hypotonia, immune dysregulation predisposing

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to recurrent infections, and parenchymal lung disease [8-10].

Among the gravest complications is pulmonary arterial hypertension (PAH), a condition with a higher prevalence and a more aggressive clinical course in Down syndrome compared to the general pediatric population [11,12]. The pathophysiology of PAH in these patients is distinctly multifactorial. Beyond the significant hemodynamic burden from often-coexistent congenital heart defects (CHD), there is compelling evidence for an intrinsic pulmonary vasculopathy. This is underpinned by developmental anomalies such as pulmonary hypoplasia, which results in a reduced total number of alveoli and a diminished pulmonary vascular bed [9]. This structural abnormality is compounded by inherent endothelial dysfunction, leading to abnormal vascular remodeling and a heightened response to vasoconstrictive stimuli [12]. Extrinsic factors, most notably the chronic intermittent hypoxia from untreated OSA, act as potent amplifiers, driving persistent hypoxic vasoconstriction and accelerating the progression of vascular disease [8].

Concurrently, a subset of children with Down syndrome develops a form of interstitial lung disease (ILD), now increasingly recognized and sometimes termed Down syndrome-associated lung disease (DSLD). This condition is often characterized by abnormal lung architecture, including alveolar simplification (hypoplasia), lymphatic dilation, and the development of subpleural and parenchymal cystic lesions [13-15]. These parenchymal changes contribute independently to gas exchange abnormalities and chronic hypoxia, further compounding the risk and severity of coexistent PAH.

While PAH and ILD are well-documented as individual morbidities, the simultaneous presentation of severe ILD and severe, life-threatening PAH in early childhood represents a critical clinical challenge.

Herein, we report the case of a 2.5-year-old boy with Trisomy 21 who presented with this dual pathology of severe ILD and severe PAH leading to right heart failure.

Case presentation

A 2.5-year-old male with a known diagnosis of trisomy 21 (Down syndrome) was brought to the clinic with a history of failure to thrive, persistent low energy, and increased work of breathing, particularly noticeable during feeding and activity. The patient was a product of a twin birth (healthy female co-twin). Pertinent past medical history included congenital hypothyroidism managed with levothyroxine, small atrial and ventricular septal defects (ASD, VSD), and global developmental delay. He had a history of recurrent upper respiratory infections and two hospitalizations for lower respiratory tract infections in infancy. Parents reported progressive tachypnea and diaphoresis during feeds, alongside poor weight gain despite high-calorie supplementation.

Physical examination revealed a child small for his age with weight (9.1 kg) and height (78 cm) both below the 3rd percentile. Vital signs demonstrated tachycardia (HR 142 bpm), tachypnea (RR 52/min), and hypotension (BP 88/54 mmHg). Oxygen saturation (SpO_2) was 92% on room air at rest, desaturating to 87% with mild activity. Notable dysmorphic features included a flat facial profile, upslanting palpebral fissures, and hypotonia. Respiratory examination showed subcostal and intercostal retractions with diffuse fine crackles bilaterally and reduced air entry.

Cardiovascular assessment revealed a loud pulmonic component of the second heart sound (P2) and a grade 2/6 systolic murmur at the left upper sternal border. Mild pitting edema of the ankles and a palpable liver edge 2 cm below the right costal margin were noted, suggestive of right heart failure. Chest radiography displayed diffuse increased interstitial markings with perihilar and basal infiltrates and honeycombing, without focal consolidation (Figure 1).

High-Resolution Computed Tomography (HRCT) of the chest confirmed findings suggestive of Interstitial Lung Disease (ILD), specifically showing interlobular septal thickening, thick-walled small cysts predominantly in the subpleural regions, and architectural distortion with traction bronchiectasis (Figure 2).

Echocardiography demonstrated severe pulmonary hypertension with an estimated Right Ventricular Systolic Pressure (RVSP) of 90-95 mmHg (systemic pressure). Additional findings included a dilated pulmonary artery, a flattened interventricular septum in systole, and a tricuspid regurgitation jet velocity of 4.6 m/s. Laboratory evaluation revealed an elevated B-type Natriuretic Peptide (BNP) of 450 pg/mL, consistent with right ventricular strain. Arterial blood gas analysis showed mild hypoxemia (pO2 65 mmHg) and normocapnia (pCO2 45 mmHg). An infectious workup for respiratory viruses was negative.

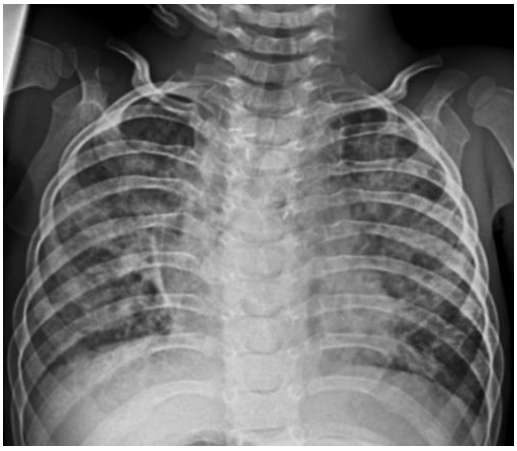

Fig. 1. Chest radiography of patient

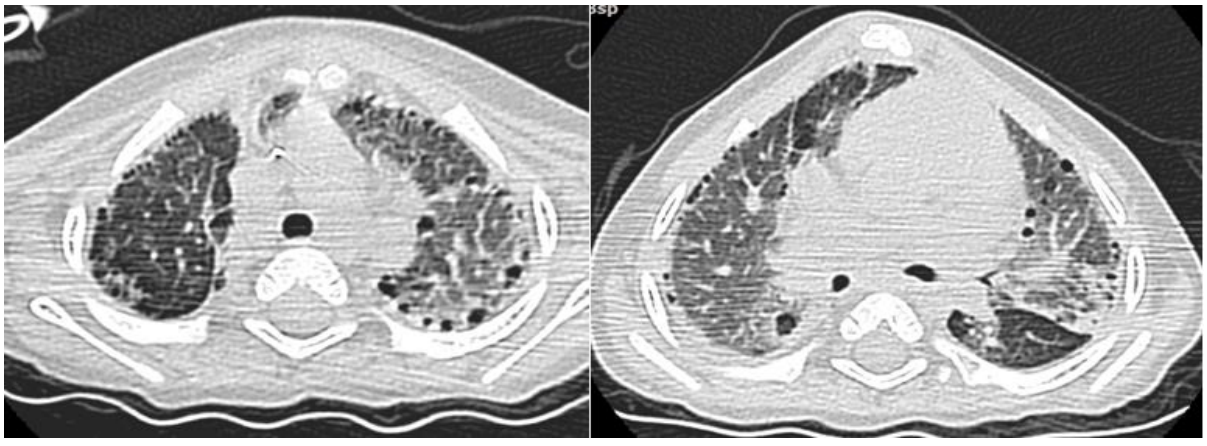

Fig. 2. High-Resolution Computed Tomography (HRCT) of the chest

Polysomnography confirmed moderate Obstructive Sleep Apnea (OSA) with an obstructive apnea-hypopnea index (OAHI) of 8.2 events/hr and a nadir SpO2 of 80%.A multidisciplinary management plan was established addressing the multifactorial nature of the patient's hypoxia.

1. Pulmonary Hypertension: Targeted therapy was initiated with oral sildenafil (0.5 mg/kg/dose TID). Diuretic therapy with low-dose furosemide (1 mg/kg/day) was added to manage right ventricular failure. Continuous supplemental oxygen was prescribed to maintain SpO2 >92% at rest and >90% during sleep to mitigate hypoxic vasoconstriction.

2. Interstitial Lung Disease: Given the severity of the ILD and its contribution to the PH, an immunomodulation trial with oral prednisolone (1 mg/kg/day) was initiated for 4–6 weeks.

3. Supportive Care: Nutrition was optimized via nasogastric (NG) tube placement for nocturnal supplemental feeds to improve caloric intake and reduce the respiratory work of feeding. An urgent ENT consultation was scheduled for adenotonsillectomy to address the OSA component.

Following the initiation of the multidisciplinary management plan, the patient's clinical status demonstrated marked stabilization. He showed improved tolerance to feeds and a reduction in the work of breathing. Oxygen saturation levels were successfully maintained within the target range (>92%) on continuous low-flow nasal cannula. The patient was subsequently discharged home on the prescribed regimen comprising sildenafil, oral corticosteroids, furosemide, and supplemental oxygen, alongside nutritional support via nasogastric tube. Long-term follow-up data are currently unavailable; however, a coordinated care plan involving cardiology, pulmonology, and ENT services was established to monitor the response to immunomodulation and pulmonary vasodilator therapy.

Discussion

The simultaneous presentation of severe Pulmonary Arterial Hypertension (PAH) and Interstitial Lung

Disease (ILD) in this 2.5-year-old patient illustrates the aggressive nature of "Down Syndrome-associated lung disease" (DSLD). This case challenges the historical view that pulmonary hypertension in Trisomy 21 is solely a consequence of congenital heart defects (CHD). Instead, it supports emerging evidence that DSLD is a distinct, pan-pulmonary developmental disorder characterized by three converging mechanisms: alveolar simplification, vascular dysgenesis, and immune-mediated injury [6].

A defining feature of this case was the presence of subpleural cysts on HRCT. While historically under-recognized, recent literature identifies these cysts as a hallmark of DSLD. A retrospective review of 134 chest CTs found subpleural cysts in 17% of children with Down Syndrome, noting they are morphologically distinct from typical emphysematous changes [16].

Histopathologically, these cysts represent "alveolar simplification"—a developmental arrest resulting in enlarged, hypoplastic airspaces and a reduced alveolar surface area [6, 16]. This structural immaturity renders the lung parenchyma less capable of supporting normal gas exchange and vascular development.

The severity of PAH in this patient (suprasystemic RV pressure), despite only minor septal defects, points to an intrinsic pulmonary vascular phenotype. Saji emphasizes that Pulmonary Vascular Disease (PVD) in Down Syndrome often progresses rapidly and can occur independently of significant intracardiac shunting [11]. This is consistent with findings that children with Down Syndrome are prone to developing PAH earlier and more severely than their non-syndromic peers, a process often accelerated by chronic hypoxemia [17]. Molecular studies highlight that overexpression of anti-angiogenic genes on Chromosome 21 (such as *RCAN1* and *DSCR1*) inhibits endothelial cell proliferation, leading to a hypoplastic vascular bed [6].

This intrinsic vascular vulnerability is further compounded by vascular fragility. Alimi et al. reported that children with Down syndrome have a significantly higher incidence of idiopathic pulmonary hemosiderosis (IPH) compared to the general population [18]. While overt hemorrhage was not documented in our patient, the "ground-glass" opacities seen on imaging and the rapid progression of right heart failure may reflect a spectrum of capillary fragility and low-grade vasculitis.

The significant clinical improvement following corticosteroid therapy in this case aligns with the hypothesis of an underlying inflammatory or autoimmune driver. Individuals with Trisomy 21 exhibit a baseline "cytokine storm" profile due to the location of four Interferon (IFN) receptor genes on Chromosome 21 [6]. Immunosuppressive therapy, including corticosteroids, has been identified as a cornerstone of management for pulmonary vascular fragility and hemosiderosis in this population [18].

Finally, the contribution of upper airway obstruction cannot be overstated. Structural abnormalities such as laryngomalacia, subglottic stenosis, and macroglossia are highly prevalent in children with Down Syndrome [7]. The resulting Obstructive Sleep Apnea (OSA) acts as a persistent "second hit" to the already compromised pulmonary vasculature, necessitating aggressive airway management alongside pharmacological interventions.

Conclusion

This case supports the classification of Down syndrome-associated lung disease as a specific clinical entity. The presence of subpleural cysts on imaging should serve as a "red flag" for underlying alveolar and vascular hypoplasia. Successful management requires a paradigm shift from purely hemodynamic support to a multimodal approach that addresses vascular resistance, parenchymal inflammation, and airway patency.

Ethical Considerations

Ethical approval

Ethical approval code: IR.ARI.MUI.REC.1404.262.

Funding

No funding was obtained for this study.

Conflict of Interests

The authors have no conflict of interest to declare.

Consent

Written informed consent was obtained from the patient's parents to publish this case report and any accompanying images.

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