An Infant Presenting with Interstitial Lung Disease Diagnosed Later as Hunter Syndrome: A Case Report

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Patient: Male, 1-year-old
Final Diagnosis: Mucopolysaccharidosis type II
Symptoms: Respiratory distress
Medication: —
Clinical Procedure: Bronchoalveolar lavage • CT scan • whole exome sequencing
Specialty: Pediatrics and Neonatology

Objective: Unusual clinical course
Background: Hunter syndrome is a multisystem metabolic inherited disease belonging to the large group of mucopolysaccharidoses (MPSs). Hunter syndrome is also known as MPS type II. Its association with respiratory symptoms has been well documented in the literature; however, it is uncommon that these patients initially present with diffuse lung disease and respiratory failure. Diffuse lung disease has a wide range of differential diagnoses that can overlap in some clinical and radiological aspects, making physicians struggle to quickly reach a final diagnosis.

Case Report: We report a case of a full-term male infant who presented postnatally with progressive respiratory distress, hypoxemia, and radiologically-demonstrated ground-glass opacity and pneumothorax requiring mechanical ventilation and an extensive workup including CT scan of the chest, a flexible and rigid bronchoscopic examination of the airway with bronchoalveolar lavage, and whole-exome sequencing, which eventually resulted in a diagnosis of Hunter syndrome. After enzyme therapy was initiated, the patient showed marked improvement in clinical status and biological and imaging data and was weaned off oxygen a few months later.

Conclusions: The diagnostic approach for patients with diffuse lung disease is challenging and requires centers with expertise to reach a final diagnosis, especially in the presence of an unusual clinical presentation. The choice of the diagnostic approach can be influenced by factors such as the patient’s critical condition, clinical presentation, imaging data, genetic analysis, and family decision.

Keywords: Lung Diseases, Interstitial • Mucopolysaccharidosis II • Respiratory Distress Syndrome, Newborn

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Background

Interstitial lung disease (ILD) in infants younger than 2 years of age is a heterogenic group of diseases with different etiologies that are distinct from those in older children and adults, with greater overlap of etiologies [1,2]. Children’s interstitial lung disease (chILD) syndrome has been defined as an infant with diffuse lung disease (DLD) and with the exclusion of other common disease-causing diffuse lung diseases (eg, cystic fibrosis, primary ciliary dyskinesia, and primary immunodeficiency). Additionally, the diagnosis of chILD requires at least 3 out of 4 of the following criteria: respiratory symptoms, respiratory signs, hypoxemia, and/or diffuse abnormalities on radiological imaging [1]. The most common etiologies have been reported to be neuron endocrine hyperplasia of infancy (NEHI), followed by ATP-binding cassette subfamily A member 3 (ABCA3) transporter deficiency and surfactant protein C deficiency [3]. Mucopolysaccharidosis II, which is also known as Hunter syndrome, is an X-linked lysosomal storage disease that has multisystem involvement, including central nervous system, respiratory, and musculoskeletal involvements [4]. Respiratory track involvement in Hunter syndrome is prominent and manifests as progressive upper airway obstruction [5]; however, as an initial manifestation of Hunter syndrome, respiratory symptoms are rare. Herein, we report a case of an infant who was referred to our center with initial diagnoses of respiratory distress and ILD, which prompted an evaluation that resulted in a diagnosis of Hunter syndrome.

Case Report

We present a case of a full-term baby boy who was delivered via cesarian section due to a previous caesarian section of a mother who was gravida 8 para 7 with an uneventful pregnancy. His Apgar score was 7 at 1 min and 9 at 5 min. At 6 h of age, he developed tachypnea, grunting, and visible reccessions with desaturation and was initially diagnosed with transient tachypnea of newborn vs congenital pneumonia. He was started on antibiotics and required noninvasive ventilation; however, he continued to exhibit respiratory symptoms despite the initial management. Therefore, he was intubated, and 1 dose of surfactant was given. At the age of 4 days, his CT showed small right pneumothorax and small pneumomediastinum with multilocular air-filled cystic lesions and a ground-glass appearance of the lungs (GGO) (Figure 1). He was extubated at the age of 12 days after showing improvement and was discharged home on oxygen at 1 L/M. He was also found to have mild hydronephrosis via renal ultrasound. He was recommended to be referred to us for further evaluation. He presented to us at the age of 3 months; he was on 1 L oxygen and was clinically tachypneic (RR 45-50) with diffuse crepitation bilaterally and pectus excavatum, after which he was admitted to the hospital for further investigation. His initial X-ray showed diffuse GGO (Figure 2).

His family history was negative for any similar conditions or any genetic diseases. At the age of 3 months, his CT (Figure 3) showed patchy ground-glass increased density that was predominantly observed in both upper lobes, the right middle lobe, and the lingula. Patchy hyperlucencies were predominantly observed in the apical segments of both lower lobes and to a lesser extent in both basal segments. Mild fibrotic bands were observed in both lower lobes, with tiny peripheral subpleural pulmonary cysts also being observed.

![Figure 1. Thoracic CT scan showing small pneumothorax (arrow) with small pneumomediastinum (arrowhead).](image)

![Figure 2. Chest X-ray showing diffuse ground-glass opacity with perihilar bronchial wall thickening.](image)
His diagnostic pathway continued with a flexible bronchoscope, and a bronchoalveolar lavage (BAL) using a 2.8-mm flexible bronchoscope was performed, along with a rigid bronchoscope, showing normal airway anatomy. Bronchoalveolar lavage (BAL) fluid was obtained from the right middle lobe, right upper lobe, and left lower lobe. The smears showed pulmonary macrophages and benign endobronchial cells on a background of few inflammatory cells. Rare hemosiderin-laden macrophages were also observed. Additionally, no neoplastic cells were observed and results were negative for any microbial growth. Special stains for fungi were negative, and the periodic acid-Schiff (PAS) stain was negative. The next step included a lung biopsy vs whole-exome sequencing (WES). After discussing options with the family, it was decided to perform WES, as it is less invasive and can reveal the underlying cause of the disease. Two months later, the WES was positive for a hemizygous pathogenic variant in the iduronate-2-sulfatase (IDS) gene causing mucopolysaccharidosis type II (Hunter syndrome).

The patient did not show the common signs and symptoms that raise the suspicion of Hunter syndrome and was referred to genetics and metabolism specialists, and he was started on enzyme replacement therapy with idursulfase. At the age of 10 months, his coarse facial features started to become more apparent (Figure 4). After receiving 6 doses of enzyme replacement therapy, he showed respiratory improvement regarding his oxygen requirement, from 1 liter/minute to room air, RR from 50/s to 30/s, and upper airway obstruction symptoms with decreased intensity of snoring during sleep. A chest X-ray (Figure 5) showed improvement in GGO.

Discussion

Respiratory problems are frequently encountered in patients with Hunter syndrome and contribute to the premature
mortality observed in individuals with the disease. Key respiratory manifestations in mucopolysaccharidosis type II are due to upper airway obstruction, lower airway obstruction, and restrictive lung disease; however, it is rare that these patients initially present with DLD and respiratory failure in early life, thus leading to a workup that ends with a diagnosis of Hunter syndrome. The diagnostic tests for Hunter syndrome consist of an assessment of IDS levels confirmed by molecular genetic testing [6]. Enzyme replacement therapy (ERT) uses a recombinant version of the deficient enzyme and is administered intravenously [4]. ERT has been showed to reduce the frequency of respiratory symptoms in patients with MPS II [4]. The prognosis of Hunter syndrome varies according to the severity of the phenotype. Severe phenotype is associated with high mortality rates due to pulmonary and cardiac complications [6]. Our review of the literature found only a few case reports on patients with Hunter disease presented in infancy with respiratory symptoms. In a small but important study, Dodsworth and Burton reported an increased incidence of respiratory distress in neonates with Hunter syndrome (32%) compared with the overall incidence of respiratory distress from any cause (4-5%) [7]. Smets and Van Daele reported a case of a neonate who was initially diagnosed with pulmonary interstitial glycogenosis and was then later found to have Hunter syndrome [8]. The diagnostic pathway of patients presenting with chILD can vary from center to center, as this disease comprises a group of disorders that vary in pathophysiology, thus making it difficult for the treating team to choose a diagnostic tool to use. Lung biopsy is typically helpful in reaching the final diagnosis, especially if other diagnostic modalities have failed to do so, as each of the diseases under the umbrella of chILD has a unique histopathological appearance. However, lung biopsy should be performed by experts and specimens should be handled and processed as per published protocols, which makes centers with limited resources struggle to follow the diagnostic pathway and reach a diagnosis using lung biopsy [1]. WES is considered a less invasive investigation to help in reaching the final diagnoses of such patients.

Conclusions

Respiratory failure and DLD in early infancy in patients with Hunter syndrome are unusual. Early diagnosis and treatment can improve the clinical condition. The diagnosis of patients presenting with chILD is often challenging and requires extensive workups. The choice of the best modalities to reach the diagnosis quickly is difficult and is often based on a case-by-case approach due to the wide differential diagnosis and variety of disease severity. The presence of an unusual clinical presentation such as in this case can complicate the diagnostic process even more.

Declaration of Figures’ Authenticity

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References: