AN INCIDENTAL FINDING OF INTERSTITIAL LUNG DISEASE

Maya Hills
PGY-III
LSU Pediatric Residency
Objectives

• Review the diagnostic criteria of childhood interstitial lung disease.
• Discuss the extensive classification system of chILD syndrome.
• Establish knowledge of diagnostic workup and management of childhood interstitial lung disease.
• Expound on the need for further research of chILD syndrome.
Case Presentation

Chief Complaint: Abnormal CT findings

4 year old male with chronic ITP with hepatosplenomegaly x 3 months.

Workup included bone marrow biopsy and CT abdomen to evaluate organomegaly and noted to have abnormal lung findings.
Review of Systems

- No recent fevers.
- Nasal congestion and rhinorrhea x 2-3 days.
- Persistent productive cough since birth.
- No rashes.
- Easy bruising.
- Normal activity/energy level.
Past Medical History

- Chronic ITP
- Frequent Infections
  - URI/Sinusitis
  - Recurrent Otitis Media
  - History of Herpes Zoster (shingles) infection
- History of poor weight gain in infancy
- Poor response to immunizations (Hepatitis B, Pneumococcal)
Additional History

Birth History: Born at full-term via repeat Cesarean section, no prenatal or postnatal complications, no NICU stay

Past Surgical History: PE tube placement

Family History: Noncontributory, no reported history of immunodeficiencies, autoimmune diseases, or respiratory illnesses.
Additional History

Medications: Ferrous Sulfate

Allergies: Augmentin

Immunizations: Up to date. Repeated Hepatitis B series, received Pneumovax on day of admission.

Social History: Lives with parents and 9 year old brother. No recent travel. No known TB or environmental agent exposures.
Physical Examination

T 98.5 P 118 R 20 BP 100/63 Wt 17.6 kg (30%ile) Ht 103 cm (5%ile)
General: well-appearing, NAD
HEENT: NC/AT, TM normal, oropharynx nonerythematous, tonsils 2+ without exudates, no oral lesions
CVS: RRR, normal S1/S2, no murmurs, pulses 2+ and equal
Resp: good and equal WOB, scant fine crackles heard in bilateral bases R>L
Abdomen: soft, nontender, full, active bowel sounds, palpable liver edge 3-4 cm below costal margin, splenomegaly with spleen edge palpated at umbilicus
Lymph: mobile 1-2 cm nontender right posterior nontender lymph node, no cervical, axillary, or inguinal lymphadenopathy
Skin: small bruises to left shin, no rashes or lesions
Laboratory Findings

<table>
<thead>
<tr>
<th>IgG 355</th>
<th>IgA &lt;7.8</th>
<th>IgM 34.5</th>
<th>IgE &lt;3.6</th>
</tr>
</thead>
</table>

Subpopulations:
- CD19 114
- CD20 104
- CD4 1230
- CD8 940
- NK 240

- S39 B6 L33 M13 E3 AL6
- MCV 70.3
- ESR 5
- CRP <0.3
- LDH 256
- CMV negative
- EBV negative
- ANA panel negative
- Viral Panel negative
Assessment

4 year old M with chronic ITP and frequent infections with bilateral pulmonary nodules suggestive of interstitial lung disease, hepatosplenomegaly, and hypogammaglobulinemia consistent with common variable immunodeficiency.
CHILDHOOD INTERSTITIAL LUNG DISEASE (chILD SYNDROME)
Childhood Interstitial Lung Disease

- Group of rare heterogeneous diseases that cause disruption of pulmonary interstitium and impaired gas exchange
- Also referred to as diffuse lung disease
- High morbidity and mortality
- Diagnosis of exclusion

Childhood Interstitial Lung Disease

- Estimated prevalence of 3.6 cases per 1 million
- Most cases are diagnosed in infancy in the first year of life
- Slightly more common in males than females

Pathophysiology

- Multi-Hit Hypotheses
  - Predisposition of altered repair of lung epithelium
  - Improper alveolar repair and apoptosis mechanisms
  - Diffuse fibroblast proliferation causing worsening lung function
  - Extensive angiogenesis contributes to altered repair of damaged tissue
  - Alveolar thickening and decreased gas exchange

Dylag, Ivana et al. “Poor Weight Gain, Cough, Shortness of Breath, and Chest Pain in an 11-year-old Boy” Pediatrics in Review
Clinical Presentation - History

- Precipitating Factors
  - Exposure to mold/birds
  - Severe lower respiratory infection
  - Prematurity
  - Feeding difficulties
  - Hemoptysis
  - Rash/Joint Complaints

- Family history
  - Other infants with severe respiratory disorders
  - Systemic disorders
chILD Diagnostic Criteria

1. Respiratory Symptoms
   - Chronic Cough
   - Difficulty breathing
   - Exercise intolerance

2. Respiratory Signs
   - Tachypnea
   - Retractions
   - Adventitious Sounds
   - Digital Clubbing

3. Impaired Gas Exchange

4. Diffuse abnormalities on chest radiography/CT scan
Clinical Presentation

- Unexplained respiratory failure
- Severe respiratory disease course out of proportion to cause
- Continuous symptoms
- Cyanosis
- Prominent S2 on cardiac examination

![Bar chart showing frequency of various symptoms including hypoxia, tachypnea, retractions, gastroesophageal reflux, pulmonary hypertension, failure to thrive, crackles, cough, normal auscultation, and wheeze. The chart indicates the presence or absence of each symptom in a given number of cases.](chart.png)
A Class of Its Own

- Vastly different from adult ILD
- Lung injury occurs during the process of lung growth and differentiation.
- Limited knowledge of disease process
  - Varied presentation
  - Lack of controlled clinical trials
A Class of Its Own

chILD Diagnoses
Lung Growth Disorders
  PIG
  NEHI

Adult Diagnoses

Both
  LIP
  BOOP
  Genetic

(UIP
AIP
IPF)
chILD Classification

1. Disorders Diagnosed in Infancy <2 years of age

2. Disorders Diagnosed Beyond Infancy (2-18 years of age)

3. Histopathologic Diagnoses

Deutsch, Gail et al. “Diffuse Lung Disease in Young Children: Application of a Novel Classification Scheme” American Journal of Respiratory Critical Care Medicine
chILD Classification

Diagnosed In Infancy <2 years

Abnormal Lung Growth/Development
Unspecified Etiology
Surfactant Dysfunction
<2Y: Abnormal Lung Growth/Development

- Diffuse Developmental Disorders
- Alveolar Capillary Dysplasia with misalignment of the pulmonary veins (ACD-MPV)
  - Typically with cardiac, GI, and renal malformations
  - Mutation of FOXF1 gene on chromosome 16
- Acinar dysplasia
- Congenital Alveolar Dysplasia
<2Y: Abnormal Lung Growth/Development

- Lung Growth Disorders
  - Bronchopulmonary dysplasia
  - Chronic lung disease
  - Early postnatal injury
  - Chromosomal abnormalities
  - Congenital Heart Disease
  - Pulmonary hypoplasia
<2Y: Undefined Etiology

- Pulmonary Interstitial Glycogenosis (P.I.G.)
  - Only occur only in young infants
  - Only diagnosed with biopsy
- Neuroendocrine cell hyperplasia of infancy (NEHI)
  - Presents in the first months to first year of life
  - Symptoms tend to improve with time
<2Y: Genetic Surfactant Disorders

- Autosomal Recessive
  - SFTPB
  - ABCA3
- Autosomal Dominant
  - SFTPC
  - NKX2.1
  - Associated with hypothyroidism
chILD Classification

Diagnosed at 2-18 years

- Immuno-competent
- Systemic Disorders
- Masquerading Disorders
- Immuno-compromised
2-18Y- Immunocompetent

- Infectious/Postinfectious Syndromes
- Aspiration Syndromes
- Bronchiolitis Obliterans
- Hypersensitivity Pneumonitis
2-18Y- Systemic

- Cystic Fibrosis
- Connective Tissue Disorders
- Sarcoidosis
- Malignancy
- Storage Diseases
2-18Y- Masqueraders

- Vasculopathies
- Lymphatic Disorders
- Congestive changes related to cardiac dysfunction
2-18Y- Immunocompromised

- Malignancy
- Opportunistic Infections
- Transplantation/Rejection Syndromes
- Immunodeficiencies
Primary Immunodeficiencies and Pulmonary Complications

- May present as upper airway disease or lower respiratory tract disease
- Lower respiratory tract infections are more specific for primary immunodeficiency
- Noninfectious causes: interstitial lung diseases, bronchiectasis, and benign lymphoproliferation of the bronchioles

CVID

- Most frequently occurring symptomatic primary immunodeficiency
- Pathophysiology
  - Immune dysfunction of B and T lymphocytes and dendritic cells
  - Inability of B cells to differentiate into plasma cells capable of secreting all immunoglobulin types
- Diagnosis
  - Low levels of IgG, IgA, and/or IgM
  - Presence of B cells
  - Poor or absent response to immunizations
- Typically diagnosed later in life
CVID and ILD

- Up to 73% develop pulmonary complications
  - Recurrent respiratory tract infections
  - Interstitial Lung Disease
  - Chronic bronchitis
  - Bronchiectasis
  - Obstructive/Restrictive Lung Disease
  - Unusual atypical or opportunistic infections
- Worse pulmonary prognosis compared to other primary immunodeficiencies

Workup for Suspected chILD

- Exclude common causes of chronic respiratory symptoms
- Chest Radiography
- Thin-Cut High resolution CT Scan
- Pulmonary Function Testing
- Tissue analysis via bronchoalveolar lavage or biopsy

CT Scan Findings

- Findings may reduce need for biopsy
- Features of chILD
  - Septal thickening
  - Ground glass opacification
  - Geographic hyperlucency
  - Lung cysts/nodules

Pulmonary Function Testing

- Generally restrictive lung physiology
- Some with obstructive physiology
  - Bronchiolitis obliterans
  - Hypersensitivity pneumonitis
Histopathologic Patterns of chILD

- Histopathologic classification can be useful to link to certain causes of interstitial lung disease
  - Lymphocytic interstitial pneumonia → autoimmune diseases, immunodeficiencies
  - Pulmonary Alveolar proteinosis --> genetic disorders of surfactant dysfunction, autoimmune diseases
  - Organizing pneumonia → bronchiolitis obliterans
- Several cases have no recognized cause and not associated with systemic disease

Workup for Suspected chILD

- Echocardiogram to evaluate for pulmonary hypertension
- Genetic evaluation

**Newborn**

<table>
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<tr>
<th>RDS/PPHN</th>
<th>Other anomalies?</th>
<th>No</th>
<th>ABCA3 SFTPB</th>
<th>negative</th>
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<td></td>
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<td>Yes</td>
<td>FOXF1</td>
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<tr>
<th>hypothyroid</th>
<th>abnormal tone or movements?</th>
<th>Yes</th>
<th>NKX2-1</th>
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<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>SFTPC ABCA3</td>
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**Childhood**

chILD Syndrome

<table>
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<tr>
<th>Surfactant Dysfunction or Unknown?</th>
<th>Yes</th>
<th>SFTPC ABCA3</th>
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Management

- Corticosteroids
- Hydroxychloroquine
- Other immunosuppressive agents such as cyclophosphamide, cyclosporine, methotrexate
- Supportive management
- Lung transplantation for severe or rapidly progressive disease
Long Term Outcomes

- 5 year mortality rate approximately 60%
- Poor prognostic indicators
  - Pulmonary hypertension
  - Failure to Thrive
  - Severe fibrosis

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<tr>
<th>Score</th>
<th>Symptoms</th>
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<tr>
<td>1</td>
<td>Asymptomatic</td>
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<tr>
<td>2</td>
<td>Symptomatic, normal room air oxygen saturation</td>
</tr>
<tr>
<td>3</td>
<td>Symptomatic, abnormal oxygen saturation with sleep or exercise</td>
</tr>
<tr>
<td>4</td>
<td>Symptomatic, abnormal resting room air oxygen saturation</td>
</tr>
<tr>
<td>5</td>
<td>Symptomatic with pulmonary hypertension</td>
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Future of chILD Research

- Modifications to broad classification system of chILD syndrome
- Further studies to ascertain true prevalence of chILD as well as long term morbidity/mortality
- Standardized management of chILD syndrome
Back to Our Patient

- Patient admitted for extensive workup
- Infectious Disease, Allergy/Immunology, Pulmonology services consulted
- Underwent bronchoscopy, which was negative
- Infectious Workup negative
  - HIV, Legionella, PCP, Aspergillus, AFB, Viral, Bacterial, Fungal Cultures
- Started on monthly IVIG infusions for CVID
Back to Our Patient

- Readmitted for open lung biopsy
- Pathology findings significant for lymphocytic interstitial pneumonia
- Further workup is pending
References


Young, Lisa. “Approach to the Infant and Child with Interstitial Lung Disease” UpToDate, 2014.

Young, Lisa. “Classification of Interstitial Lung Disease in Infants and Children.” UpToDate, 2015.