Unusual cause of cyanosis in young infant

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Devadharshini, 52 day old infant first born of 3rd degree consanguineous marriage admitted with complaints of difficulty in breathing and fever for past 3 days
History of presenting illness

Full term cesarean section BW - 2.8 kg normal transition to extraterine life admitted with
Difficulty in breathing – 3 days
Fever for past 3 days – high grade intermittent subsided with medication
h/o refusal of feeds – 1 day
No history s/o congestive heart failure, cyanosis
No h/o running nose, cough
No h/o vomiting, loose stools

Birth and neonatal h/o-uneventful except
Past h/o-surgery at 21 days of life for pyloric stenosis-pyloromyotomy done at ICH
Examination

Baby verbal
Nasal flaring
Grunting
Pallor
Failure to thrive
Febrile
Peripheral cyanosis
No dependent edema

RS – BAE, ICR/SCR, Crackles
CVS- s1s2
Soft systolic murmur

P/A – Liver 4cm
Spleen 4 cm
Liver span 8cm

VITALS
HR – 164/m
RR – 72/m
+++/++
SpO2 around 80% in all 4 limbs with O2
65 - 70% without O2
Laboratory Investigation

- CBC – Hb – 6.6gm
  TC – 12300
  DC – P63 L29 M8
  PLT – 42000
  PCV – 20%
- CXR – cardiomegaly hepatomegaly congestion b/l pleural fluid
- RFT – N
- Sr. elec – N
- Liver enzymes – N
- NEC – NG
- Urine C/S – NG
- USG abd & craniun - N
Provisional diagnosis

congenital cyanotic heart disease with increased pulmonary blood flow
with clinical sepsis
COURSE IN HOSPITAL

Child was on oxygen, iv fluids, antifailure treatment, iv antibiotics, blood transfusion to improve oxygenation.

Distress settled
Thrombocytopenia improved
Direct breast feeds
Saturation improved to 85 – 90% with o2
Echo – done – within normal limits
Cause for cyanosis???
ABG - PaO2 - Low r/o methemoglobinemia

Once clinical condition and saturation improved
Rpt CXR - b/l lung haziness
Echo repeated - N
Hyperoxia test - pass
This led to possibility of pulmonary cause for cyanosis
CT Scan – features suggestive of interstitial lung disease – ground glass opacity- reticulonodular pattern
ILD in children is defined as the presence of respiratory symptoms and/or diffuse infiltrates on chest radiographs, abnormal pulmonary function tests with evidence of restrictive ventilatory defect and/or impaired gas exchange, and persistence of any of these findings for >3 months.
Interstitial lung disease (ILD) in children (chILD) is very different in many aspects to the adult disease. First, chILD is rare, estimated at 0.36 per 100,000, compared with 60–80 per 100,000 for ILD in adults.

In ICH - 2007-2012.
- Total cases - 42
- Total death - 6
- Newborn - Nil
Fig. 1. – Age distribution (in yrs) of the patients with interstitial lung diseases included in the European Respiratory Society Task Force study.
Diagnosis

- Common symptoms at presentation included cough, dyspnea, tachypnea and chest wall retraction, exercise limitation and frequent respiratory infections.
- Tachypnea - 80% of patients
  the earliest and most common respiratory symptom
- Cough - 75% of the patients
- Unexplained fever - 30%
- Failure to thrive 37%
Clinical findings

Inspiratory crackles

tachypnea and
retraction.

- In a child with a normal birth history, these are strongly suggestive of ILD.
- advanced stage - clubbing (13%)
  cyanosis during exercise or at rest
Forms of ILD most prevalent in infancy

- Diffuse developmental disorders\[^{12}\]
  - Acinar dysplasia
  - Congenital alveolar dysplasia
  - Alveolar capillary dysplasia with pulmonary vein misalignment (This is associated with a poor prognosis.)

- Growth abnormalities
  - Pulmonary hypoplasia
  - Chronic neonatal lung diseases (prematurity-related BPD and acquired chronic lung diseases in term infants)
  - Structural pulmonary changes with chromosomal abnormalities (eg, trisomy 21)
  - Abnormalities associated with congenital heart disease in otherwise healthy children
- Specific conditions with unknown etiology
  - PIG
  - NEHI
- SDMs and related disorders
  - SFTP B genetic mutations (PAP as dominant histologic pattern; see below)
  - SFTP C genetic mutations
  - ABCA3 genetic mutations
  - Granulocyte-macrophage colony stimulating factor (GM-CSF) receptor mutations
Genetic and/or familial disorders

- SDMs and related disorders
- Familial hypocalciuric hypercalcemia
- Lysinuric protein intolerance
- Farber lipogranulomatosis
- Hermansky-Pudlak syndrome
- Storage disorders – Niemann pick, Gaucher’s
Imaging

Plain radiographs are usually performed in a child suspected of ILD at first presentation but information is often limited.
The most common HRCT feature of ILD is widespread ground-glass attenuation.

Intralobular lines, irregular interlobular septal thickening and honeycombing are less common findings.

Large subpleural air cysts in the upper lobes adjacent to areas of ground-glass opacities have been also reported in young children with ILD.

HRCT is useful for ILD diagnosis and selection of lung area to be biopsied.

It is proposed that it also may contribute to monitor disease activity and/or severity.
### Table 2: Specificity and Sensitivity of HRCT in ILD

<table>
<thead>
<tr>
<th>HRCT</th>
<th>ILD present</th>
<th>ILD absent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>True positive</td>
<td>False positive</td>
</tr>
<tr>
<td>44 patients (88%)</td>
<td></td>
<td>2 patients (4%)</td>
</tr>
<tr>
<td>False negative</td>
<td></td>
<td>True negative</td>
</tr>
<tr>
<td>2 patients (4%)</td>
<td></td>
<td>6 patients (12%)</td>
</tr>
</tbody>
</table>

- Sensitivity 95%
- Specificity 75%
- Positive predictive value 95%
- Negative predictive value 75%
Role of BAL

- BAL can have several indications.
- In cases of infections, BAL can provide specimens for cytological examination, microbial cultures, and molecular analysis.
- BAL - pulmonary alveolar proteinosis, milky appearing fluid, abundant extracellular and intra-macrophage proteinaceous PAS positive material.
- Hemosiderin laden macrophages - alveolar hemorrhage.
- Langerhans cell histiocytosis - presence of CD1a positive cells (in 5% of BAL cells).
- Storage disorders.
Normal BAL

- Alveolar macrophages - 90%
- Lymphocytes - 6-8%
- Neutrophils - 3-4%
Lung biopsy

Techniques of choice are open lung biopsy and video assisted thoracoscopy biopsy
Diffuse parenchymal lung disease in children

- DLPD of known association (e.g. drug, aspiration, connective tissue disorders, infection, environment)
  - Hypersensitivity pneumonia
    - Patterns of interstitial pneumonia (NSIP, DIP, LIP, UIP, DAD, CP)
    - Hypersensitivity pneumonia
  - Chronic pneumonia of infancy

Idiopathic interstitial pneumonias
- NSIP cellular/fibrotic
  - LAM
  - LCG
  - Alveolar proteinosis
  - Sarcoidosis
  - Eosinophilic pneumonia
  - Idiopathic/infantile pulmonary haemosiderosis
  - Persistent tachypnoea of infancy
  - Pulmonary interstitial glycogenolysis

- Other forms of interstitial pneumonia
  - DIP (IEMs)
  - LIP (IDS)
  - Lipoid pneumonia (IEMs)
  - ? NSIP/UIP (Familial CFA)
  - Disease specific (?HPS)
  - Alveolar proteinosis (surfactant B deficiency)
  - Other surfactant deficiencies (e.g. surfactant C)
Treatment

- Among the anti-inflammatory agents used in pediatric ILD, steroids are the preferred choice, administered orally and/or intravenously.
- This has been well illustrated by the results of the ERS Task Force on pediatric ILD.
- Oral prednisolone is most commonly administered at a dose of 1-2 mg/kg/day for 6 – 8 wks.
- Children with significant disease are best treated with pulsed methylprednisolone at least initially. This is usually given at a dose of 10-30 mg/kg/day for 3 days consecutively at monthly intervals.
• An alternative to steroids is hydroxychloroquine with a recommended dose of 6-10 mg/kg/day

• Some patients combination of steroids and hydroxychloroquine is also used

• Immunosuppressant's and antifibrotic agents (pirfenidone)
Further investigations

ESR 9 and 18
CRP Neg
Sr. Ca – 9 mgs
Ca Cr ratio < 0.2
Barium swallow – N
BAL – 80% neutrophils
  15% macrophages
  4% lymphocyte
TORCH - Neg

Bone marrow – no storage cells seen
Ophthal opinion – N
Sweat chloride – Neg
HIV – Neg
Lung biopsy – mother not willing
High index of suspicion is needed to diagnose ILD
Activity

Activity may be limited by the patient's degree of dyspnea.

Oxygen saturation during exercise should be measured. A prescribed, monitored, exercise program may be beneficial to prevent deconditioning in older children.
ILD associated with systemic diseases

- Connective tissue diseases (2-4%) (juvenile rheumatoid arthritis [JRA], dermatomyositis/polymyositis, systemic sclerosis, systemic lupus erythematosus [SLE], ankylosing spondylitis, Sjögren syndrome, Behçet syndrome, mixed connective tissue disease)
- Autoimmune diseases (antiglomerular basement membrane antibody disease)
- Pulmonary vasculitis (polyarteritis nodosa, Wegener granulomatosis, Churg-Strauss syndrome)
- Liver disease (chronic active hepatitis, primary biliary cirrhosis)
- Bowel disease (2%) (e.g., ulcerative colitis, Crohn disease)
- Amyloidosis
- Neurocutaneous disorders (tuberous sclerosis, neurofibromatosis, ataxia-telangiectasia)
- Bronchiolitis obliterans
Lipid disorders with lung involvement represent another indication of BAL. This includes congenital lipid-storage diseases (Gaucher's disease and Niemann-Pick disease) or chronic lipid pneumonia due to chronic aspiration [47, 48]. However, in cases of aspiration syndromes, the presence of lipid laden AM may be sensitive but not specific [49]. In other pathological situations, BAL can usefully serve to direct further investigations. Accumulation of BAL T-lymphocytes with prevalence of CD4+ cells is suggestive of sarcoidosis, whilst prevalence of CD8+ cells is suggestive of hypersensitivity pneumonitis [50]. Also, an increase in BAL eosinophils suggests pulmonary infiltrates associated with eosinophilia syndromes [51]. Finally, BAL may help identifying lung involvement in children with nonprimary lung disorders, for example collagen vascular diseases, inflammatory bowel diseases, or liver disease.
Disorders with unknown causes

- Undetermined (19-27%)
- Pulmonary hemorrhage syndromes
- DIP (4-8%)
- Lymphocytic interstitial pneumonitis
- UIP (2-4%)
- Lymphangiomatosis (4%)
- Nonadenoviral bronchiolitis obliterans (4%)
- Sarcoidosis (2%)

- Pulmonary alveolar proteinosis (PAP [2%]) (see below)
- Eosinophilic syndromes (2%)
- Idiopathic bronchiolitis obliterans organizing pneumonia (BOOP), also called cryptogenic organizing pneumonia (COP)
- Bronchocentric granulomatosis
- Nonspecific interstitial pneumonia
- Acute interstitial pneumonitis
<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
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<th>Patients aged &lt;2 yrs</th>
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<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
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<tr>
<td>Parental consanguinity</td>
<td>13</td>
<td>7</td>
<td>5</td>
<td>9</td>
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<tr>
<td>Affected siblings</td>
<td>18</td>
<td>10</td>
<td>8</td>
<td>7</td>
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<tr>
<td>Symptoms</td>
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<tr>
<td>Cough</td>
<td>145</td>
<td>78</td>
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<td>73</td>
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<tr>
<td>Tachypnoea/dyspnoea</td>
<td>140</td>
<td>76</td>
<td>49</td>
<td>84</td>
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<tr>
<td>Failure to thrive</td>
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<td>37</td>
<td>36</td>
<td>62</td>
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<tr>
<td>Fever</td>
<td>37</td>
<td>20</td>
<td>17</td>
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<td>Physical findings</td>
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</tr>
<tr>
<td>Cyanosis</td>
<td>51</td>
<td>28</td>
<td>31</td>
<td>54</td>
</tr>
<tr>
<td>Clubbing</td>
<td>24</td>
<td>13</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Crackles</td>
<td>81</td>
<td>44</td>
<td>33</td>
<td>57</td>
</tr>
</tbody>
</table>
Disorders with known causes

- **Infection (8-10%)**
  - Viral infection (eg, adenoviral bronchiolitis obliterans [5%], cytomegalovirus [CMV] infection, infection with Epstein-Barr virus [EBV])
  - Bacterial infection (eg, pertussis or infection due to *Legionella*, *Mycoplasma*, *Chlamydia*, or *Mycobacterium* species)
  - Fungal infection (eg, infection due to *Histoplasma*, *Aspergillus*, or *Pneumocystis* species)
  - Parasitic infection (eg, *visceral larva migrans*)

- **Environmental conditions (13%)**
  - Exposure to organic dusts (*hypersensitivity pneumonitis* [7-12%])
  - Exposure to inorganic particulates (eg, silica, asbestos, talc, zinc)
  - Exposure to chemical fumes (eg, sulfuric acid, hydrochloric acid, methyl isocyanate)
These disorders are characterized by inflammatory and fibrotic changes that affect alveolar walls. Typical features of ILD include the presence of diffuse infiltrates on chest radiograph, and abnormal pulmonary function tests with evidence of a restrictive ventilatory defect (in older children) and/or impaired gas exchange [3].

The frequent clinical findings are inspiratory crackles (44%), tachypnea and retraction. In a child with a normal birth history, these are strongly suggestive of ILD. Other findings associated with an advanced stage of lung disease include finger clubbing (13%) and cyanosis during exercise or at rest (28%)
Among the anti-inflammatory agents used in pediatric ILD, steroids are the preferred choice, administered orally and/or intravenously. This has been well illustrated by the results of the ERS Task Force on pediatric ILD [9]. Oral prednisolone is most commonly administered at a dose of 1-2 mg/kg/day [1]. Children with significant disease are best treated with pulsed methylprednisolone at least initially [61,204]. This is usually given at a dose of 10-30 mg/kg/day for 3 days consecutively at monthly intervals. The minimum number of cycles recommended is 3 but treatment may need to be continued for a longer period of 6 months or more depending on response.
An alternative to steroids is hydroxychloroquine with a recommended dose of 6-10 mg/kg/day. Individual case reports have described a response to hydroxychloroquine even in the presence of steroid resistance [1,205,206]. Some groups have proposed to base the decision as to which agent to use on the lung biopsy findings, with a preference for steroids in case of large amount of desquamation and inflammation and for hydroxychloroquine if increased amounts of collagen representing pre-fibrotic change are found. However, as documented in the ERS Task Force on pediatric ILD, the preferred choice between steroids or hydroxychloroquine in children is highly dependent on the expertise of the center in charge of the patient, and does not seem to be oriented by the histopathological pattern [9]. In case of severe disease, steroids and hydroxychloroquine may be associated.