

## Rare disease heralded by pulmonary manifestations: Avoiding pitfalls of an “asthma” label

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### ABSTRACT

Pulmonary manifestations are seldom recognized as symptoms of storage disorders. The report describes the diagnostic journey in a 30-month-old male infant, born of a third-degree consanguineous marriage referred to our institute as severe persistent asthma. History revealed that the child had progressively worsening breathlessness and persistent dry cough not associated with fever but accompanied by weight loss. On physical examination, there was growth failure, respiratory distress, clubbing, hepatosplenomegaly, and occasional rhonchi. Blood gas revealed hypoxemia which improved with oxygen administration. Plain X-rays and high-resolution computed tomography of the chest showed perihilar alveolar infiltrates and patchy consolidation. The clinicoradiological features did not support a diagnosis of asthma but favored interstitial lung disease (ILD). Bronchoalveolar lavage was performed as a first-tier investigation. It showed periodic acid–Schiff-negative foamy macrophages. The clues of consanguinity, visceromegaly, ILD, and foamy macrophages in the bronchoalveolar fluid prompted consideration of lysosomal storage disorders as the likely etiology. Gaucher disease and Niemann–Pick disease A/B were ruled out by enzyme estimation. Niemann–Pick disease type C was suspected and confirmed by detecting a homozygous mutation in the *NPC2* gene. This case serves to caution physicians against labeling breathlessness in every toddler as asthma. It emphasizes the importance of searching for tell-tale signs such as clubbing and extrapulmonary clues which point to a systemic disease such as lysosomal storage disorders as a primary etiology of chronic respiratory symptoms.

**KEY WORDS:** Asthma, bronchoalveolar lavage, cough, interstitial lung diseases, Niemann–Pick disease

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### Case Details

A 30-month-old male infant of Asian Indian origin was the first issue of a third-degree consanguineous marriage. He presented with progressively increasing breathlessness (without periodic exacerbations) for the past 18 months, chronic dry cough for 12 months, and weight loss for 3 months. There was no history of cyanosis, hemoptysis, feeding difficulties, fever, or tuberculous contact. No recognized allergens were identified as a cause for the symptoms. The child had achieved normal milestones in all domains by 10 months of age. Thereafter, only gross motor milestones lagged. He could stand with support at 10 months,

but standing without support was achieved at 18 months, while walking independently was achieved at 24 months.

The child was being treated as asthma in a town in Central Maharashtra. There were documented multiple outpatient visits for nebulization with salbutamol and budesonide over the past 10 months. He was also prescribed daily treatment with metered dose inhalers (budesonide and salbutamol in adequate doses) with a spacer and baby mask. Although the compliance and inhalation technique was good, there was no relief of symptoms.

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**Question 1:** How does one define “chronic” cough? Apart from asthma, which disorders manifest with chronic cough in toddlers?

**Answer:** In <15 years of age group, chronic cough is defined as any cough that lasts for more than 4 weeks.<sup>[1]</sup> Common causes of chronic cough in toddlers are enumerated in Table 1.<sup>[1,2]</sup>

**Case Details (Continued)**

On examination, the heart rate was 124 beats/min, respiratory rate was 54 breaths/min, and blood pressure was 94/60 mmHg. Respiratory distress was evident by subcostal and intercostal retractions. The weight (8.5 kg) and length (85.5 cm) were less than the 3<sup>rd</sup> centile. His head circumference (47 cm) was between the 3<sup>rd</sup> and 15<sup>th</sup> centile (WHO growth charts). He had Grade II clubbing. Cyanosis and lymphadenopathy were absent. On respiratory system examination, there was no chest deformity, shift of mediastinum, or abnormal vocal resonance. The auscultation findings revealed bilateral equal and normal breath sounds with occasional rhonchi. This was disproportionately milder than expected from clinical history and physical signs of respiratory distress. There was firm hepatosplenomegaly (liver 3.5 cm below the subcostal margin, span 7.5 cm; spleen 3.5 cm below the subcostal margin). Cardiac and neurological examinations were normal. The arterial oxygen saturation by pulse oximetry on room air was 90%, which increased to 98% on supplementation with oxygen by face mask at 4 L/min.

**Question 2:** Can asthma be clinically ruled out in the present case?

**Answer:** There were several significant clues in our patient that precluded a diagnosis of asthma and pointed to an alternative diagnosis: (1) poor response to bronchodilator therapy for asthma, (2) respiratory system abnormalities of clubbing and relatively insignificant auscultatory signs of airway obstruction (rhonchi and/or crepitations) not commensurate with overwhelming signs of respiratory distress, and (3) firm hepatosplenomegaly.<sup>[3,4]</sup>

**Case Details (Continued)**

The preliminary investigations are summarized in Table 2 and Figures 1 and 2. The sweat chloride test for cystic fibrosis could not be performed as the parents perceived the cost to be prohibitive (INR 3800 from a local laboratory).

**Question 3:** On the basis of clinicoradiological features, what is the most likely diagnosis? What are the options for further diagnostic evaluation?

**Answer:** Our patient had a chronic respiratory disease without acute febrile or infectious exacerbations resulting in failure to thrive, respiratory distress, clubbing, paucity of abnormal respiratory auscultatory findings, and hypoxemia (improving with oxygenation). This was associated with radiological abnormalities of alveolar infiltrations along with patchy consolidation on chest radiograph

**Table 1: Differential diagnosis of chronic cough in a toddler<sup>[1,2]</sup>**

Pulmonary diseases	Extra-pulmonary diseases
Asthma	Aspirations
Bronchiectasis *	Neuromuscular disorders (Cerebral palsy, Guillain-Barre syndrome, spinal muscular atrophy, muscular dystrophy)
Cystic fibrosis *	Esophageal structural anomalies (eg. tracheoesophageal fistula H-type)
Chronic infections/post-infectious* (e.g.tuberculosis, pertussis)	Gastroesophageal reflux disease
Congenital anomalies of the airways (e.g. tracheobronchomalacia)	Congenital heart disease
Drug adverse effects (e.g.ACE inhibitors)	Cyanotic *
Environmental pulmonary toxicants (e.g.tobacco smoke, outdoor air pollution caused due to traffic, indoor air pollution due to traditional/stove cooking)	Acyanotic
Interstitial lung diseases *	Immunodeficiency disorders *
Chronic undiagnosed foreign body *	Primary
Pulmonary hypertension *	Secondary
Allergic rhinitis	

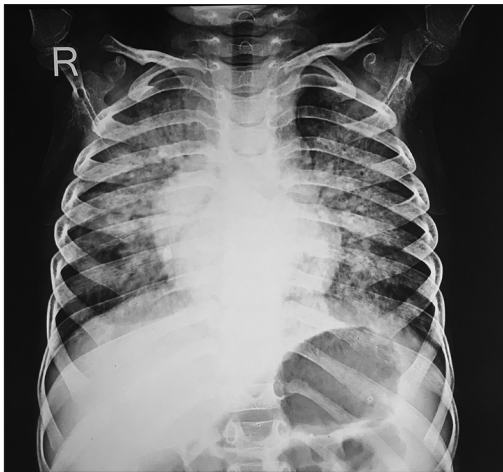
\*Disorders manifesting with clubbing

**Table 2: Preliminary investigations in our patient**

Investigations	Result
Hemoglobin	1.97 mmol/L
Leucocyte count and differential count	12 x 10 <sup>9</sup> cells/L (78% neutrophils, 22% lymphocytes)
Platelet count	200 x 10 <sup>9</sup> cells/L
Erythrocyte sedimentation rate	Normal
Serum electrolytes, AST, ALT, serum albumin, BUN, serum creatinine	Normal
Prothrombin time	Normal
2D Echocardiography & Colour Doppler	Normal
Mantoux test, gastric lavage for acid fast bacilli; serology for HIV, hepatitis B and hepatitis C	Negative
Arterial blood gas	pH- 7.42, PaCO2-39, PaO2-66, HCO3-23.2, SpO2-96
On room air	
On oxygen with face mask at 4 L/min	pH- 7.43, PaCO2-35, PaO2-96, HCO3-24, SpO2-99

and high-resolution computed tomography (HRCT) of the chest. This clinicoradiological constellation prompted us to consider interstitial lung disease (ILD) as the most likely diagnosis.<sup>[5,6]</sup>

ILD is a heterogeneous group of rare diseases that involve the pulmonary parenchyma and the distal airspaces, thus interfering with the normal gas exchange.<sup>[5]</sup> Diagnostic criteria for childhood ILD are any three of the following in the absence of a known primary disease: (i) respiratory symptoms (cough, difficult breathing, or exercise intolerance), (ii) respiratory signs (tachypnea, retractions, crackles, digital clubbing, failure to thrive, or respiratory failure), (iii) hypoxemia, and (iv) diffuse chest infiltrates on chest X-ray



**Figure 1:** Chest radiograph (frontal view) at 30 months of age (on presentation to our institution) showing perihilar alveolar infiltrates with sparing of the lung peripheries

or computed tomography scan.<sup>[5,7]</sup> Our patient fulfilled all the above criteria.

The etiology of ILD can be primary as in idiopathic pulmonary hemosiderosis<sup>[6]</sup> or secondary to systemic diseases such as malignancies, autoimmune disorders, pulmonary vasculitis, granulomatous diseases, storage disorders, and eosinophilic lung diseases.<sup>[5,7]</sup> Causes of ILD typically manifesting in the first 2 years of life include developmental disorders and growth abnormalities of the lung (e.g., acinar dysplasia, alveolar–capillary dysplasia with pulmonary vein misalignment, congenital alveolar dysplasia, pulmonary hypoplasia, bronchopulmonary dysplasia, and structural alveolar abnormalities due to congenital heart disease or chromosomal abnormalities), inborn errors of surfactant metabolism (due to mutations in *SPFTB*, *SPFTC*, *ABCA3*, or *NKX2.1* genes), familial alveolar proteinosis (granulocyte/macrophage colony-stimulating factor [GM-CSF] receptor defects), pulmonary interstitial glycogenesis, and neuroendocrine cell hyperplasia of infancy.<sup>[5,7]</sup> In the presence of hepatosplenomegaly, the differential diagnosis of ILD in a toddler would be infectious diseases such as HIV and CMV,<sup>[5,8]</sup> Langerhans cell histiocytosis,<sup>[5,8]</sup> lysinuric protein intolerance,<sup>[9]</sup> granulomatous disease such as sarcoidosis,<sup>[5,10]</sup> and lysosomal storage disorders (Gaucher disease and Niemann–Pick disease).<sup>[5,11]</sup>

Typical radiological features of ILD include pulmonary infiltrates which can be interstitial, alveolar, or mixed.<sup>[6]</sup> Nature of infiltrates could be reticular, nodular, or reticulonodular or honeycombed.<sup>[6]</sup> However, chest X-rays have low diagnostic specificity for evaluating a suspected ILD and the imaging modality of choice is HRCT of the chest.<sup>[6]</sup> HRCT helps to characterize the nature, extent, and distribution of the diseased lung and has the added advantage of guiding the best target area for the lung biopsy, which is the gold standard for the diagnosis of ILD.<sup>[5,7]</sup> The various patterns described on HRCT which can point toward ILD include ground glass opacification, interlobular septal thickening, intralobular lines, geographic distribution of pulmonary hyperlucency, consolidation, cysts, and nodules.<sup>[5,6]</sup> In situations where a lung biopsy is not easily



**Figure 2:** High-resolution computerized tomography of the chest, transverse cut showing perihilar patchy alveolar consolidation (without involvement of periphery of lungs)

feasible, the etiology of ILD may be ascertained by HRCT and bronchoalveolar lavage (BAL) analysis.<sup>[12,13]</sup>

### Case Details (Continued)

A BAL fluid analysis and simultaneous lung biopsy were planned. However, as the child developed severe hypoxemia during bronchoscopy, only the BAL fluid could be procured and lung biopsy had to be abandoned.

BAL fluid physical analysis revealed milky fluid with some mucous plugs. Notable microscopic findings were a fair number of periodic acid–Schiff (PAS)-negative foamy macrophages and absence of bacteria (Gram and Ziehl–Neelsen stains), malignant or atypical cells. The fluid culture did not grow bacteria, fungi, or mycobacteria, eliminating an infective etiology. Since foamy macrophages in BAL occur in certain ILD,<sup>[14]</sup> our suspicion of an underlying ILD was heightened.

**Question 4:** What is the role of BAL fluid analysis in ILD?

**Answer:** BAL is a minimally invasive procedure for obtaining a sample of the alveolar cells.<sup>[14]</sup> The relative distribution of the cell population within the BAL can provide valuable insights into the underlying lung pathology. Occasionally, BAL histology reveals pathognomonic abnormalities<sup>[14]</sup> such as foamy macrophages detected in our case. Foamy macrophages in the BAL are seen in ILD secondary to lipoid pneumonia, surfactant protein C deficiency, pulmonary alveolar proteinosis (anti-GM-CSF antibody-mediated), Niemann–Pick disease, aspiration pneumonia, hypersensitivity pneumonitis, and amiodarone lung toxicity.<sup>[5,13–16]</sup> Foamy macrophages in pulmonary alveolar proteinosis are PAS positive,<sup>[13]</sup> a feature absent in our case.

### Case Details (Continued)

In view of consanguinity, coupled with multiorgan (liver, spleen, and lung) involvement, clinicoradiological suspicion of an ILD and foamy cells on BAL which were PAS-negative; a storage

disorder such as lysosomal storage disorders was considered as the most likely etiology in our patient.

**Question 5:** What are lysosomal storage disorders? Which lysosomal storage disorders are associated with pulmonary manifestations in the toddler age group?

**Answer:** Lysosomal storage disorders are a diverse group of inborn errors of metabolism, involving storage of substrates within the lysosome (a subcellular organelle which is the recycling unit of the cell).<sup>[11]</sup> These multisystem disorders result from mutations of single genes leading to deficiency of any one of the fifty lysosomal proteins (including the enzymes acid hydrolases and transporters) involved in complex macromolecule degradation or cellular trafficking pathways of cholesterol, cholesterol esters, glycogen, sphingolipids, and polypeptides.<sup>[11]</sup> Depending on the nature and storage site of the specific substrate, the spectrum of manifestations is wide<sup>[11]</sup> and includes hepatosplenomegaly, neurological manifestations (neuroregression, delayed development, peripheral neuropathy, ataxia, dystonia, macrocephaly), skeletal disease (joint stiffness or laxity, recurrent fractures), ophthalmic manifestations (cherry red spot, optic atrophy, corneal clouding), facial dysmorphism, and cardiac involvement (cardiomyopathy, valvular heart disease).<sup>[11]</sup>

Pulmonary manifestation in lysosomal storage disorders occurs in Gaucher disease (beta-glucocerebrosidase enzyme deficiency due to *GBA1* gene mutations),<sup>[5,7,17]</sup> Niemann–Pick disease type A/B (acid sphingomyelinase enzyme deficiency due to *SMPD1* gene mutations),<sup>[5,7,17]</sup> and Niemann–Pick disease type C (disorder of cholesterol transport resulting from mutations in the *NPC1* or *NPC2* genes; the respective gene products are involved in trafficking of cholesterol out of the lysosome).<sup>[18]</sup> Gülhan *et al.*<sup>[16]</sup> have recently analyzed pulmonary involvement in Niemann–Pick disease and Gaucher disease. In their case series of 113 cases, only 23 patients (20.3%) had pulmonary involvement.<sup>[16]</sup> Their diagnoses were made before 2 years of age in six out of ten toddlers with Niemann–Pick disease and in three out of seven toddlers with Gaucher disease. Of these 17 toddlers, only 7 (41%) had respiratory symptoms preceding diagnosis.<sup>[16]</sup> Pulmonary involvement reported in these toddlers were recurrent respiratory infections, ILD, aspiration pneumonia, bronchitis, respiratory failure, pulmonary hypertension, and hepatopulmonary syndrome.<sup>[16]</sup> In this study by Gülhan *et al.*, three of the ten children with Niemann–Pick disease were primarily investigated for a lung parenchymal disease and underwent lung biopsy, which disclosed diagnosis of Niemann–Pick disease.<sup>[16]</sup> The other seven children had an established diagnosis of Niemann–Pick disease and developed pulmonary manifestations subsequently. Four out of these ten children underwent BAL and lipid-laden macrophages were detected in all. Two children with Niemann–Pick type C disease underwent bone marrow aspiration for demonstration of sea-blue histiocytes.<sup>[16]</sup> Six children suspected to have Gaucher disease had pulmonary symptoms at presentation. Bone marrow study was performed in all seven cases for demonstration of Gaucher cells and two of these underwent BAL.<sup>[16]</sup>

Gaucher disease and Niemann–Pick disease are differentiated by demonstrating characteristic storage cells in the bone

marrow.<sup>[19,20]</sup> Gaucher cells are large cells having an eccentric nucleus and cytoplasm with striations (described as “crumpled silk” appearance) whereas lipid-laden foamy cells (cells with vacuolated cytoplasm) are seen in Niemann–Pick disease.<sup>[19,20]</sup> Although foamy macrophages on BAL fluid can be seen in Niemann–Pick disease as well as in some inborn errors of surfactant metabolism, the presence of foamy macrophages in the bone marrow is not a feature of the latter.<sup>[21]</sup>

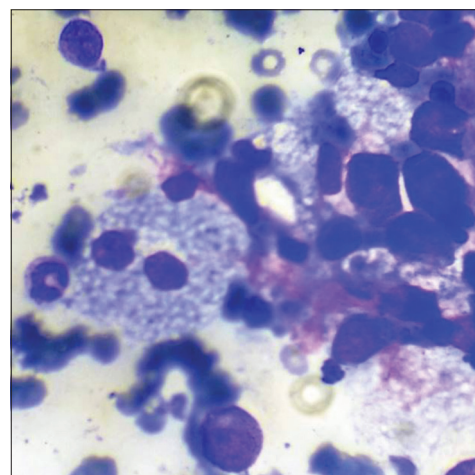
Confirmatory diagnosis of lysosomal storage disorders requires demonstration of the corresponding enzyme deficiency in peripheral blood leukocytes or skin fibroblasts and/or genotyping.<sup>[11]</sup> Niemann–Pick disease type C is suspected when foam cells are detected on bone marrow examination, but the leucocyte sphingomyelinase activity is normal.<sup>[18]</sup> Diagnostic confirmation for Niemann–Pick disease type C requires highly specialized tests such as filipin staining of cultured skin fibroblasts or genotyping.<sup>[18]</sup>

### Case Details (Continued)

The bone marrow biopsy examination in our patient revealed foamy histiocytes [Figure 3]. The beta-glucocerebrosidase and acid sphingomyelinase activities in leukocytes were normal, ruling out Gaucher disease and Niemann–Pick disease type A/B, respectively. Thus, with strong evidence for Niemann–Pick disease type C, the patient’s DNA was sequenced by bi-directional Sanger sequencing of *NPC1* and *NPC2* genes. Detection of a pathogenic homozygous mutation (IVS1 + 2[T>C] [c. 82 + 2 T>C]) in intron 1 of *NPC2* gene confirmed the extremely rare diagnosis of Niemann–Pick disease type C2 in our patient.

**Question 6:** What are the clinical implications of the correct diagnosis of this rare LSD for the child and his family?

**Answer:** The implications to the family following the timely diagnosis of the rare genetic condition in our case are summarized in Table 3.<sup>[15,22]</sup>



**Figure 3:** Bone marrow aspirate, Giemsa stain (×1000), showing a macrophage with foamy cytoplasm suggestive of Niemann–Pick disease



**Table 3: Management options for our patient's family with Niemann-Pick type C<sup>[18,22]</sup>**

Management	Modality
For the child	Supportive <ul style="list-style-type: none"> <li>Regular chest physiotherapy</li> <li>Aggressive and prompt treatment of pulmonary infections</li> <li>Special vaccines against respiratory pathogens: <i>Hemophilus influenzae</i> type B conjugate vaccine (single dose), influenza vaccine and pneumococcal conjugate vaccine followed by pneumococcal polysaccharide vaccine eight weeks later</li> <li>Bronchodilator therapy (budesonide and salbutamol)</li> </ul>
	Specific <ul style="list-style-type: none"> <li>Oral substrate reduction therapy: Miglustat (N-butyl-deoxyojirimycin) for stabilizing the neurological features of the disease</li> <li>Disadvantages: Expensive, not available in India</li> <li>Surveillance: Three monthly follow-up for monitoring History (including assessment of milestones) and examination to detect development of neurological signs such as abnormal saccadic eye movement (usually the first neurological manifestation)</li> <li>Growth</li> <li>Immunization</li> <li>Pulmonary infections, pulmonary functions tests</li> <li>Swallowing and feeding problems</li> <li>Sleep disturbances</li> </ul>
Exploratory/Investigational	<ul style="list-style-type: none"> <li>Hematopoietic stem cell or bone marrow transplant (parents declined) for amelioration of visceral manifestations</li> <li>Disadvantages: Cost, expertise, donor availability and complications of transplant</li> <li>Low cholesterol diet</li> <li>Curcumin (active component of turmeric)</li> <li>Investigational drugs: Allopregnanolone, Cyclodextrin, Rab 9 overexpression agents, imatinib</li> </ul>
	Genetic counseling <ul style="list-style-type: none"> <li>Autosomal recessive inheritance with 25% risk of recurrence in future offspring</li> <li>Carrier detection by testing for the pathogenic variant found in the proband</li> <li>Prenatal diagnosis by chorion villous biopsy or amniotic fluid sampling by targeted testing for the IVS1+2(T &gt;C) (c. 82+2 T &gt;C) mutation in the fetus</li> </ul>
For the parents	Prognosis and course of the disease <ul style="list-style-type: none"> <li>In those with isolated severe pulmonary forms (visceral presentation), early death reported due to pulmonary insufficiency</li> <li>Progressive neurological course in almost all affected by Niemann-Pick disease type C</li> <li>Severe disorder with attenuated life span (death by 10-25 years, commonly due to aspiration) in a majority</li> </ul>

## Conclusions

In a child with chronic respiratory illness (cough and wheeze), correlation of history (symptoms) with physical examination, correct interpretation of key physical signs (clubbing), and vigilance toward lack of clinical response to bronchodilators would avoid pitfalls of labeling such children as having asthma. Our case also serves to emphasize that in such a child, presence of pulmonary infiltrates on chest X-ray and hepatosplenomegaly is highly evocative of an infiltrative disorder and, when accompanied by consanguinity, should alert the physician to a possibility of an underlying inborn error of metabolism like lysosomal storage disorders (Gaucher disease or Niemann-Pick disease). Although Niemann-Pick disease type C is an extremely rare cause of ILD in toddlers, a timely diagnosis has prognostic and genetic implications and serves to lessen the financial and psychological burden to the family. It also serves to empower the family to make appropriate reproductive decisions when the disease involved is life-threatening with no easily available or economically viable therapeutic options.

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## Conflict of interest

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