CASE REPORT

A Child with Recurrent Pneumonia: Approach to Diagnosis and Management

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ABSTRACT

In children, recurrent pneumonia is defined as the occurrence of more than one episode of pneumonia within a single year, or greater than three episodes within any duration; with radiographically documented clearing between episodes. Although childhood pneumonia is one of the most common clinical problems in children, when a child presents with recurrent pneumonia, there are additional diagnostic considerations because most cases are associated with an underlying illness. A meticulous clinical approach and judicious choice of laboratory investigations tailored to the differential diagnoses can clinch the diagnosis and guide management. We describe the case of a 10-year-old girl, presenting with a history of recurrent pneumonia, and the clinical approach toward an unusual diagnosis.

Keywords: Chronic granulomatous disease, Clinical approach, Recurrent pneumonia.

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CASE DESCRIPTION

An 11-year-old girl presented with history of recurrent episodes of fever, cough, and rapid breathing since the age of 5 years. Each episode had a similar pattern with moderate grade fever, wet cough, fast breathing, and requirement of oral antibiotics for resolution. The frequency and severity of these episodes increased over time. There was no history of coughing up blood or pain in the chest. There was associated breathlessness, initially during the episodes, but later in between episodes as well. It progressed in recent years, such that at the time of presentation, the child was breathless even on minimal exertion. In addition, there was a history of recurrent episodes of pus collection at the base of the thumbs, which required incision and drainage on a few occasions. These episodes were managed with antibiotics but did not correlate temporally with the episodes of respiratory symptoms. The family reported that the child’s growth had faltered in recent years, and she was not gaining any weight for the past 2 years. There was no history of passage of greasy or bulky stools, persistent purulent nasal discharge, recurrent episodes of middle ear discharge, episodes of syncope or chest pain, swelling of the feet, inhalation of a foreign body, aspiration during eating or drinking, and history of blood transfusion or injections administered in an unsafe manner. There was also no history of retention of primary dentition, recurrent bone fractures, close contact with tuberculosis, and recurrent or severe diarrheal episodes in the past.

The child was born to a fourth-degree consanguineously married couple (parents were third cousins). The maternal obstetric history included six spontaneous abortions—all of which occurred in the first trimester. There was no family history of a similar or significant illness in any family member, on the paternal or maternal side.

The child had a normal neuro-development profile and had been vaccinated as per the National Immunization Schedule (till the age of 5 years).

At presentation, heart rate was 130/minute, respiratory rate 38/minute, blood pressure 103/61 mm Hg, temperature 99°F, and oxygen saturation 86% in room air. There were signs of respiratory distress manifested by tachypnoea, intercostal, and subcostal retractions. She was promptly administered supplemental oxygen through nasal prongs, with which saturation improved but did not normalize. Therefore, continuous positive airway pressure (CPAP) was initiated. Broad-spectrum antibiotics were started viz. Ceftazidime and Cloxacillin.

Anthropometric measurements revealed weight of 23 kg (corresponding to −1.96 z score), height of 129 cm (corresponding to −1.85 z score) and BMI of 13.8 (corresponding to −1.39 z score). There was mild pallor, grade 3 pandigital clubbing, oral mucositis, but no icterus, lymphadenopathy, elevated jugular venous pressure, or nutritional deficiency signs. Examination of the thumbs was unremarkable.

Chest examination revealed a hyperinflated barrel-shaped chest, centrally positioned trachea, appropriately located apex beat, diminished breath sounds in the left mammary area, and diffuse coarse crackles and occasional expiratory wheeze. Cardiovascular examination was normal, and there was no clinical evidence of pulmonary arterial hypertension. Abdominal and neurological examinations were normal.
A syndromic diagnosis of recurrent pneumonia with bronchiectasis was considered, secondary to primary immune deficiency, postinfectious state (tubercular, postviral), or cystic fibrosis. Investigations were planned to confirm these differential diagnoses.

At admission, complete blood count report showed haemoglobin 9.2 g/dl, total leukocyte count 28,600/mm³ (84% polymorphs, 8% lymphocytes, 7% monocytes, 1% eosinophils), platelet count 300,000/mm³, and the following red cell indices: mean corpuscular volume (MCV) 71.4 femtolitres, mean corpuscular haemoglobin (MCH) 22.2 picograms, mean corpuscular haemoglobin (MCHC) 31.3 g/dl and red cell distribution width (RDW) 19.3%. Peripheral blood smear showed microcytic hypochromic anaemia with aniso-poikilocytosis. Metabolic profile reports showed serum sodium 134 meq/l, potassium 4.9 meq/l, chloride 103 meq/l, urea 17 mg/dl, and creatinine 0.3 mg/dl confirming normal renal function. Serum protein was 6.4 g/dl, with albumin 1.9 g/dl and globulin 4.5 g/dl, that is, reversal of A-G ratio. C-reactive protein (CRP) was elevated to 223 g/dl. Reversal of A-G ratio and elevated CRP prompted us to consider an underlying chronic inflammatory condition. Tables 1 and 2 summarize these investigations and their trend during the hospital admission.

The child presented with a chest x-ray (CXR) done elsewhere five days before admission. It showed bilateral lung hyperinflation with increased peri-hilar vascular markings with silhouetting of left cardiac border by an irregular homogenous radiopacity in the left lung parenchyma with clear bilateral costophrenic angles (Fig. 1).

Blood culture at admission was sterile. Sputum culture done at admission showed growth of commensal organisms. Investigations for the underlying cause of recurrent pneumonia revealed reactive HIV serology, and sweat chloride level 21 meq/l (within the normal range). Serum immunoglobulins IgG, IgM, and IgA were all elevated to 1610 mg/dl, 421 mg/dl, and 540 mg/dl, respectively, suggesting intact B lymphocyte function. Screening Blood Nitro Blue Reduction Test for chronic granulomatous disease (CGD) was suggestive of CGD, hence confirmatory Dihydro Rhodamine assay was done which showed reduced stimulation index of patient’s neutrophils compared to control neutrophils; consistent with chronic granulomatous disease (CGD). Molecular test to confirm CGD could not be done.

The child did not improve with supportive therapy and antimicrobials. Subsequent CRX showed worsened consolidation, bronchiectasis, and soft tissue shadows within suggestive of finger in gloves appearance. Sputum culture done after 7 days of admission showed Stenotrophomonas maltophilia, for which appropriate antibiotics were administered.

Non-Contrast enhanced Computed Tomography (NCCT) of the chest showed bilateral hyperinflated lungs with emphysematous changes. There were multiple nodules in both lungs with consolidation, showing breakdown in the anterior segment of the left upper lobe with emphysematous changes and air-filled cyst in bilateral lungs (Fig. 2).

Sputum samples were processed multiple times for detecting tuberculosis by staining and culture. Acid fast bacilli (AFB) were detected in a single sputum however culture collected after 42 days did not yield any growth. Standard four-drug Antitubercular therapy (ATT) was added to her treatment.

Investigations for Allergic Broncho Pulmonary Aspergillus (ABPA) workup showed total IgE 1142 IU/mL, Aspergillus specific IgE 1.95 KUA/L, and Aspergillus specific IgG 209 IU/mL. Sputum fungal smear and culture yielded yeast on three occasions. Serum galactomannan sent twice did not suggest invasive aspergillosis as was anticipated in a child with CGD. Oral prednisolone @1.5 mg/kg and broad-spectrum antifungal IV amphotericin were added.

On day 17 of hospitalization, her sensorium deteriorated suddenly. Clinical examination revealed Glasgow Coma Scale (GCS) score of 8/15, increased tone in all limbs, brisk deep tendon reflexes, and extensor planter reflex. Respiratory efforts were poor and there was bradycardia. She was intubated, and mechanically ventilated. Intracranial hemorrhage (and associated raised intracranial pressure), or neurologic tuberculosis was considered the most likely causes. Therefore, immediately after stabilizing her, CECT head was done. It showed mildly prominent supratentorial ventricular system (Fig. 3).

The child developed hypovolemic shock (BP <5th centile, tachycardia and poor peripheral and central pulses). As it did not respond to fluid bolus administration, it was managed with inotropes (maximum support of Adrenaline 0.3 mcg/kg/min and noradrenaline 0.3 mcg/kg/min) with which shock was controlled. Pediatric neurology consultation suggested a possibility of ischemic vasculitis secondary to tubercular meningitis. Hence contrast-enhanced brain magnetic resonance imaging (CEMRI) was done which showed mild noncommunicating hydrocephalus with shift of the frontal horn of the right lateral ventricle to the left side (Fig. 4). There was a small area of diffusion restriction along left pons, cerebellum, cerebellar vermis, and left frontal lobe suggesting vasculitic infarcts. Enhancing basal exudates were present (Fig. 4).

The child was stabilized with antitubercular medication with steroids, measures to control raised ICP, and mechanical ventilation. However, the parents declined to continue further treatment and insisted on leaving against medical advice.

**Discussion**

In children, “recurrent pneumonia” is defined as the occurrence of two episodes of pneumonia within 1 year, or three episodes.
Table 2: Metabolic profile

<table>
<thead>
<tr>
<th>Date</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 4</th>
<th>Day 10</th>
<th>Day 15</th>
<th>Day 21</th>
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<tr>
<td>Na (mEq/L)</td>
<td>134</td>
<td>132</td>
<td>134</td>
<td>138</td>
<td>133</td>
<td>136</td>
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<td>K (mEq/L)</td>
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<td>4.6</td>
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<td>3.4</td>
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<tr>
<td>Cl (mEq/L)</td>
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<td>101</td>
<td>104</td>
<td>104</td>
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<td>96</td>
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<td>Urea (mg/dl)</td>
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<td>20</td>
<td>20</td>
<td>19</td>
<td>17</td>
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<tr>
<td>Creatinine (mg/dl)</td>
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<td>0.22</td>
<td>0.31</td>
<td>0.33</td>
<td>0.40</td>
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<td>Protein (g/dl)</td>
<td>6.4</td>
<td>6.4</td>
<td>6.5</td>
<td>6.7</td>
<td>6.5</td>
<td>6.5</td>
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<tr>
<td>Albumin (g/dl)</td>
<td>1.9</td>
<td>1.8</td>
<td>2.0</td>
<td>1.7</td>
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<tr>
<td>Total bilirubin (mg/dl)</td>
<td>0.41</td>
<td>1.69</td>
<td>0.42</td>
<td>1.12</td>
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<td>Direct bilirubin (mg/dl)</td>
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<td>0.13</td>
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<td>31</td>
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<tr>
<td>ALT</td>
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<td>102</td>
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<tr>
<td>ALP</td>
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<td>102</td>
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<td>26</td>
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<td>Calcium (mg/dl)</td>
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<td>8.1</td>
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<tr>
<td>Phosphate (mg/dl)</td>
<td>4.9</td>
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<td>4.8</td>
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<tr>
<td>CRP (mg/dl)</td>
<td>223</td>
<td>202</td>
<td>266</td>
<td>231.86</td>
<td>243.88</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1: Sequential chest x-ray images showing multiple areas of patchy consolidation, showing poor response to antimicrobial agents in including specific antibacterial antibiotics, antituberculosis therapy, and empiric antifungal therapy.

Fig. 2: Axial NCCT chest (lung window) showing multiple nodules in bilateral lungs with large patch of consolidation on left side (arrow).
its pattern must be obtained. It is important to determine if the cough was initially dry and later became wet-sounding. Nocturnal or early morning dry cough with associated wheeze may point toward bronchial asthma, which could be complicated by a secondary problem, giving the impression of pneumonia. Cough temporally related to feeding or swallowing may suggest swallowing dysfunction, or fistulous communication between the airway and gastrointestinal tracts. In contrast, cough occurring several minutes after feeding may suggest gastroesophageal reflux disease, especially if it is associated with characteristic posturing. History of growth faltering is observed in many systemic conditions associated with recurrent pneumonia. The passage of bulky, greasy stools suggests cystic fibrosis (CF). Past or present history of recurrent skin infections or ear infections or recurrent diarrhoea could be clues to an underlying immunological abnormality. History of similar complaints amongst the family members must also be obtained to identify heritable disorders.

Clinical Examination

History
A thorough history beginning with the age at which the child developed the first chest infection (early onset points toward a congenital anomaly or hereditary disorder), is the first step. Information regarding the nature of cough, duration, and occurring within any time frame; with radiological clearance in between. Recurrent pneumonia usually results from deficiencies in the local pulmonary or systemic host defences, or from underlying disorders that modify the lung defences. These can be broadly classified into the following categories: (1) congenital malformations of the upper or lower respiratory tract and cardiovascular system; (2) recurrent aspirations; (3) defects in the clearance of airway secretions; and (4) disorders of systemic and local immunity.

Clinical Approach

History
A thorough history beginning with the age at which the child developed the first chest infection (early onset points toward a congenital anomaly or hereditary disorder), is the first step. Information regarding the nature of cough, duration, and occurring within any time frame; with radiological clearance in between. Recurrent pneumonia usually results from deficiencies in the local pulmonary or systemic host defences, or from underlying disorders that modify the lung defences. These can be broadly classified into the following categories: (1) congenital malformations of the upper or lower respiratory tract and cardiovascular system; (2) recurrent aspirations; (3) defects in the clearance of airway secretions; and (4) disorders of systemic and local immunity.
and neurological system can also provide clues to the underlying cause of recurrent pneumonia.

**Approach to a Child with Recurrent Pneumonia**

When a paediatrician encounters a child suspected to have recurrent pneumonia, there are five basic questions that need to be addressed, viz. (1) Do the individual episodes qualify for the diagnosis of pneumonia? (2) If yes, do the episodes fulfill the criteria for recurrent pneumonia? (3) Are the episodes localized to a specific site in either lung, or is it diffuse (i.e., involving multiple areas of both lungs)? (4) What are the extrapulmonary manifestations in the child? and (5) What are the differential diagnoses, and the focused investigations that can clinch the diagnosis? This step-wise approach is implemented as follows:

Do the episodes quality for the diagnosis of pneumonia? In children, community-acquired pneumonia (CAP) is defined clinically by the presence of cough or difficulty breathing and tachypnoea (defined using age-specific cut-off values). In fact, the presence of hallmark symptoms commonly seen in adults (such as productive cough, fever, etc) are not necessarily present in children. Even radiological findings of consolidation are not regarded essential for the diagnosis in children. In the index child, several of the episodes fulfilled the criteria, hence it is reasonable to presume that these were “pneumonia” episodes. However, similar history is also possible in upper airway infections and viral episodes triggering asthma exacerbations.

Do the episodes fulfill the criteria for recurrent pneumonia? As mentioned previously, recurrent pneumonia is defined by the occurrence of two episodes of pneumonia within 1 year, or three episodes occurring within any time frame; with radiological clearance in between. In contrast, the term “persistent pneumonia” is used when there is persistence of symptoms and radiographic abnormalities for more than 1 month. In this child, the history was suggestive of recurrence of episodes of illness with apparent response to antibiotics and a period of relative normalcy in between. Therefore, even though radiological clearance was not documented, a diagnosis of recurrent, rather than persistent pneumonia was made. However, there is often a fine line between the two conditions, and sometimes it is not possible to clearly distinguish between them.

Are the episodes localized to a specific site in either lung; or is it diffuse (i.e., involving multiple areas of both lungs)? Recurrent pneumonia can be broadly categorized into uni-lobar or multilobar patterns, although this classification is not standardized. Hence this point helps to establish whether a single area or lobe is involved repeatedly. Pneumonia involving a single lobe of the lung suggests localized pathology. This could be due to intra or extraluminal airway obstruction, or structural malformation of the bronchus. In children, an important cause of intraluminal obstruction is a foreign body. It can also happen with fistulous communications between the airway and gastrointestinal system, and some aspiration syndromes. In contrast, more widely distributed lesions generally indicate nonlocalized pathology or systemic disorders. However, it should be noted that diffuse pathology can sometimes start with involvement of a single lobe.

In localized disease, the first step in the diagnostic workup is the flexible bronchoscopy, although if there is a strong past history of inhaled foreign body then rigid bronchoscopy can be both therapeutic and diagnostic. If bronchoscopy is negative then computed tomography (CT) scan of the chest could be done, which better identified cause of extraluminal obstruction. An aortogram can be helpful to confirm the diagnosis of sequestered lobe.

Multilobar pneumonia can be either associated with normal or impaired immunity; the latter could be either acquired or congenital. Postinfective bronchiectasis is well known to follow pertussis, measles, and pulmonary tuberculosis. In developed countries, aspiration is considered to be the commonest cause of recurrent pneumonia; this could be due to gastroesophageal reflux disease (GERD) or oropharyngeal incoordination. Cystic fibrosis is the commonest cause of chronic supplicative lung disease in Caucasian children; the diagnosis is by sweat test with confirmation by genetics studies, to identify cystic fibrosis transmembrane regulator (CFTR) mutations. Primary ciliary dyskinesia (PCD) has to be considered in children presenting with sinusitis, otitis media, or chronic rhinitis. Rarely, patients also exhibit dextrocardia, congenital heart disease, and infertility. Ciliary ultrastructural evaluation can be completed after doing nasal and bronchial brushings and studying them under electron microscopy. Nasal nitric oxide is also helpful as a screening tool for primary ciliary dyskinesia (PCD).

If immunodeficiency state is suspected, then immunological work up is carried out. This includes complete blood count (CBC) with immunoglobulin profile and IgG subsets. Hyper gamma globulinemia is an important predictor of HIV infection. If it is not abnormal, then antibodies response to tetanus, Haemophilus influenzae type B and pneumococcal vaccine antigen can identify functional immunodeficiency status. Neutrophil disorders include chronic granulomatous disease, the Job syndrome (hyper-IgE), myeloperoxidase deficiency, Chediak-Higashi syndrome, and others. In general, these patients have recurrent or persistent cutaneous infections or abscesses in addition to respiratory tract complaints. Children with defects in quantity or quality of phagocytosis present with recurrent infections due to defective killing of bacteria such as *S. aureus*, *Serratia*, or *Burkholderia* as well as the fungi *Candida* and *Aspergillus*. Tests to be considered include nitro blue tetrazolium test (NBT), and Dihydrro Rhodamine Assay (DHR) for chronic granulomatous disease. GERD can be confirmed by oesophageal pH study, while videofluoroscopy can be used to confirm swallowing dyscoordination.

In the index case, neither the past medical documents nor previous chest x-ray records were available to establish localization of the previous episodes. Since the chest x-ray in the present admission showed bilateral diffuse involvement of the lung parenchyma, a generalized disease was considered more likely. On account of the recurrent nail fold infections and respiratory symptoms, a possibility of CGD was considered.

What are the pulmonary and extrapulmonary manifestations in the child? Pediatricians give special attention to the history and physical examination findings to identify features providing clues to the pathology of the condition and also the differential diagnosis. A few clues in representative conditions are summarized in Table 3.

What are the differential diagnoses, and the focused investigations that can clinch the diagnosis? It is emphasized that there is no “minimum set” of investigations to be performed in every child with recurrent pneumonia. Rather, a meticulous clinical approach as outlined above should lead to a limited set of differential diagnoses. Laboratory investigations are then tailored to identify the cause, complications, and consequences of the underlying condition. The index child provided ample opportunity to put this principle to use. Figure 5 summarizes the algorithm for investigating a child with recurrent pneumonia.
Child with Recurrent Pneumonia

**Table 3:** Extrapulmonary symptoms and signs in conditions associated with recurrent pneumonia

<table>
<thead>
<tr>
<th>History</th>
<th>Extrapulmonary examination findings</th>
<th>Probable diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained neonatal respiratory distress, Recurrent middle ear discharge, Persistent or recurrent nasal discharge</td>
<td>Persistent mucopurulent nasal discharge, serous discharge from middle ear, presence of grommets, situs inversus, dextrocardia, male infertility</td>
<td>Primary ciliary dyskinesia</td>
</tr>
<tr>
<td>Recurrent episodes of sinopulmonary infection</td>
<td>Coarse facial features, absence of tonsils and lymph nodes, oculocutaneous albinism, ocular telangiectasia, eczema, features of thrombocytopenia</td>
<td>Primary immunodeficiency disorders– T cell defects B cell defects Phagocyte disorders Combined immune deficiency disorders</td>
</tr>
<tr>
<td>Recurrent skin abscesses, deep seated abscesses, recurrent diarrhoea, oral or cutaneous candidiasis Persistent infections after receiving live vaccines</td>
<td>Displaced location of apex beat, cardiac murmur(s), palpable heart sounds</td>
<td>Congenital heart disease with left-to-right shunts</td>
</tr>
<tr>
<td>Feeding difficulties in infancy, forehead sweating while feeding, suck-rest-such cycles, palpitations,</td>
<td></td>
<td></td>
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</table>

**Summary**

- A 11-year-old developmentally normal girl born to fourth degree consanguineously married couple presented with recurrent episodes of fever, cough, rapid breathing, and progressively increasing breathlessness since 5 years of age and failure to gain weight for the past 2 years. There was history of recurrent episodes of pus collection in bilateral thumbs.
- She had oral mucositis, pandigital grade 3 clubbing, pallor, hyp erinflated chest, tachypnoea with hypoxemia, intercostal retractions, and diffuse coarse crackles with occasional expiratory wheeze on auscultation.
Child with Recurrent Pneumonia

- A syndromic diagnosis of recurrent pneumonia with bronchiectasis complicated by allergic bronchopulmonary aspergillosis (ABPA) was considered, secondary to primary immune deficiency, postinfectious state (tubercular, postviral), or cystic fibrosis.
- A step-wise clinical approach confirmed the diagnosis of underlying chronic granulomatous disease with bronchiectasis, with disseminated tuberculosis involving the lungs and central nervous systems, complicated by ABPA.

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References