Persistent Pneumonia in an Infant

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An eight month old boy presented with a subacute febrile illness and radiological evidence of multifocal cavitatory consolidations in the lungs. He continued to worsen despite multiple oral and intravenous antibiotics. Preterminally, he developed respiratory distress, hepatosplenomegaly, bicytopenia, and hepatic dysfunction. Investigation for cause of persistent pneumonia resulted in a diagnosis of chronic granulomatous disease on the basis of Dihydrorhodamine assay and genetic analysis. Postmortem blood culture grew *Burkholderia cenocepacia*. Autopsy revealed necrotizing granulomatous inflammation with massive necrosis and abscesses in bilateral lungs. No organism could be identified by traditional stains on autopsy. Conventional PCR targeting 16S ribosomal DNA yielded *Nocardia pseudobrasiliensis*. In conclusion, an unusual course of pneumonia warrants invasive investigations for isolation of underlying organism, which not only provides guidance to choice of antimicrobials but also provides clue to an underlying disease.

Keywords: *Autopsy, Burkholderia cenocepacia, Chronic granulomatous disease, Nocardia pseudobrasiliensis.*

CLINICAL PROTOCOL

History and examination: An 8 month old boy presented with history of fever and insidious onset cough for 1 month. He was asymptomatic till the age of 7 months when he developed fever lasting for a week, for which he received oral antibiotics. After an afebrile period of 1 week, he started having intermittent episodes of fever upto 101ºF. Child had loose stools transiently for 3 days. Subsequently, he developed cough which worsened gradually. He had received 1 week of oral amoxicillin-clavulanic acid and 2 weeks of intravenous ceftriaxone and amikacin without any response, before being referred to our centre.

He was second born to a nonconsanguineously married couple, immunized for age, as per National immunization schedule, with a normal development. During this admission, he weighed 7.5 kg with length and head circumference of 79 cm and 45 cm, respectively. Vitals were stable and systemic examination was unremarkable.

Course and management: Based on clinical and radiological investigations, the patient was treated along the lines of pneumonia, with presenteral meropenem and vancomycin for 3 weeks, as the child had already received first and second-line antibiotics earlier. In spite of persisting fever, patient was discharged on parental request, only to be readmitted after 5 days with worsening respiratory distress. During the second admission, he was found to have hepatosplenomegaly and investigations showed severe anemia, thrombo-cytopenia, coagulopathy with very low fibrinogen and high d-Dimer, high serum ferritin and transaminitis with conjugated hyperbilirubinemia (**Table I**). In view of persistent pneumonia, immuno-deficiency was considered and investigations were sent accordingly (**Table II**). His condition deteriorated fast and despite antibiotics, antifungals and supportive therapy, the child died. Preterminally he developed hypotension, hypo-glycemia and left pneumothorax. A family history of chronic granulomatous disease (CGD) in a paternal second-degree female cousin was elicited just prior to demise.

Unit's final diagnosis: *Burkholderia cenocepacia* sepsis with pneumonia (bacterial or fungal) with left hydroureteronephrosis (infective or obstructive due to granulomatous inflammation) and secondary hemo-phagocytic lymphohistiocytosis (HLH), with underlying autosomal recessive (AR) CGD (p67 deficiency).

DISCUSSION

Important points of discussion in the index child are whether CGD could have been considered in the first admission, reason for a relatively early fatality and explanation for the other findings such as left hydroureteronephrosis and preterminal events.

The index child presented with fever and insidious onset, progressive cough for 1 month. Investigations revealed leucocytosis, thrombocytosis, sterile blood and urine cultures, nonprogressive left hydronephrosis and radiological evidence of consolidation in both lungs. Consolidation is suggestive of an infectious pathology, and common bacteria responsible for community-acquired

Table I Hematological and Biochemical Laboratory Parameters

Day of hospitalization	*Day 5*	*Day 27*	*Day 32*	*Day 42*
Hemoglobin (g/dL)	6.3	6.6	7.1	4.7
Total leukocyte count (/µL)	21530	37,000	14,960	14,000
Platelets (/µL)	5,64,000	4,25,000	2,28,000	90,000
Differential count (%)	$P_{46}L_{47}M_{5}E_{0.2}$	$P_{36}L_{60}M_{2.9}E_{0.2}$	$P_{57}L_{35}M_{6.1}E_{0.7}$	$P_{57}L_{35}M_{6.1}E_{0.7}$
PT/APTT (s)	15/29.5			37/70.5
Fibrinogen (g/L)	–	–	–	0.48
d-Dimer (ng/ml)	–	–	–	1194
CRP (mg/dL)	125.4	231	–	107
Procalcitonin (ng/mL)	0.749	–		
Sodium/Potassium (mEq/L)	132/4.5	129/4.4	129/4.6	138/2.6
BU/Creatinine (mg/dL)	15/0.08	14/0.1	12/0.08	56/0.3
AST/ALT/SAP (U/L)	83/40	66/24/209	154/58	821/319/171
Bilirubin (mg/dL)[a]	0.33	0.66	0.68/0.20	3.3/2.4
Total protein/albumin (g/dL)	6.3/3.1	6.8/3.0	5.6/2.8	3.7/1.5
Triglycerides (mg/dL)	–	–	307	
Ferritin (ng/mL)	–	–	376	4000

PT-prothrombin time; APTT-activated partial thromboplastin time; BU-blood urea; AST-aspartate amino transferase; ALT-alanine aminotransferase; SAP-serum alkaline phosphatase. [a]second value, when given, is conjugated bilrubin.

Table II Other Investigations in the Index child

Urine microscopy	No cells (30/9, 6/10, 31/10)
Blood culture	Sterile (30/9, 06/10, 26/10, 30/10);
	Burkholderia cenocepacia (06/11, postmortem culture)
Urine culture	Sterile (30/9, 6/10, 31/10)
Fluorodeoxyglucose positron emission tomography	FDG avid consolidations in the bilateral lungs
(FDG-PET)- CT scan (16.10.19)	FDG avid mediastinal lymph nodes
	Left hydroureteronephrosis
USG abdomen (1.10.19, 5.10.19)	Left hydronephrosis with anteroposterior diameter 0.9-1.2 cm with few internal echoes and dilated left upper ureter
USG abdomen (02.11.19)	Liver 8 cm with no space occupying lesion;
	Gall bladder edematous wall;
	Spleen 7 cm with multiple tiny hypoechoic foci;
	Left kidney mild fullness of pelvis
Mantoux test	Not reactive
Gastric lavage for acid fast bacilli	Both smears and cultures: Negative (30/10, 01/11, 02/11)
Parents' chest *X*-ray	Normal
Echocardiography	No evidence of infective endocarditis
HIV serology	Not reactive
Serum IgG (04.11.2019)	841 mg/dL (reference range 300-1000 mg/dL)
Serum IgA (04.11.2019)	56 mg/dL (reference range 20-70 mg/dL)
Nitroblue tetrazolium (NBT) test (04.11.2019)	No reduction seen
Dihydrorhodamine 123 assay (DHR) (05.11.2019)	Δ Mean fluorescence intensity (MFI) 471.58, Stimulation index (SI) 2.75 (Δ MFI 70286, SI 272.4 in control)
b558 expression on gated neutrophils (05.11.2019)	Normal
Targeted next generation sequencing (NGS)	Homozygous mutation c.835_836delAC, p.Thr279fs in *Neutrophilic cytosolic factor*-2 (*NCF*2) gene encoding for p67 component of phagocyte oxidase
Plasma soluble CD25 (pg/mL)(05.11.2019)	49 670 (Normal 400-2600)

pneumonia (CAP) at this age, are *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Moraxella catarrhalis* and *Hemophilus influenzae* [1]. Usually, CAP responds to antibiotics like amoxycillin-clavulanic acid and ceftriaxone, unless complicated with empyema or lung abscess. Since the child had an indolent course with onset of respiratory distress two months after onset of fever and did not respond to usual antibiotics, CAP is unlikely and causes of persistent pneumonia need to be considered [2]. Though *Mycobacterium tuberculosis* is an important cause of persistent pneumonia, early cavitation is extremely rare in infants [3]. This suggests possibility of infections due to unusual organisms such as opportunistic bacteria or fungi. Clinical manifestations and radiology both lack specificity for underlying organism and yield of blood culture is low at 10-30% [2]. In the absence of fine needle aspiration cytology (FNAC) from lung lesions or bronchoalveolar lavage, while alive, it is difficult to pinpoint etiologic organism for persistent pneumonia.

Recurrent/persistent infections in one lobe of lung can occur due to congenital malformations (sequestration, bronchogenic cysts, cystic adenomatoid malformation) and external or internal compression of airway by lymph nodes, foreign body, or tumours. However, these were unlikely in the index case, because he had multifocal consolidations in both lungs. Recurrent/persistent infec-tions in bilateral lung fields occur in a setting of congenital heart disease, aspirations, impaired mucociliary clearance (ciliary dyskinesia, cystic fibrosis) and immunodeficiency. While humoral immunodeficiencies are usually associated with infections due to community acquired bacteria, which respond to usual antibiotics, pneumonia in cystic fibrosis, combined immunodeficiency and phagocytic defects may be due to opportunistic pathogens [4,5]. HIV infection was ruled out in the index case.

Normal lymphocyte count rules out severe combined immunodeficiency. As the index child had evidence of phagocytic defect documented by no reduction in NBT test and negligible stimulation index on DHR assay, CGD is likely. Further investigations showed normal b558 expression ruling out the possibility of X-linked CGD and AR-CGD due to p22 deficiency. Diagnosis was further confirmed by genetic analysis which showed a homozygous mutation (c.835_836delAC; p.Thr279fs) in *NCF*2 gene which encodes for p67 component of phagocytic oxidase. Thus the index child was convincingly proven to have AR-CGD caused by p67 deficiency.

The index child succumbed to the disease during infancy. While X-linked CGD is associated with more severe disease, severity is variable in AR-CGD due to variable phagocyte oxidase activity [6, 7]. Severe disease in the index child can be explained by near absent activity of phagocyte oxidase with SI of 2.75.

Most infections in CGD are caused by catalase positive organisms including fungi such as *Aspergillus* and bacteria such as *Staphylococci*, *Burkholderia*, *Serratia* and *Nocardia*. Enterobacteriaceae and *Candida* are other important pathogens [5,6]. After introduction of cotrimoxazole and itraconazole prophylaxis, infections with *Aspergillus*, *Burkholderia* species and *Nocardia* have been on rise [6]. Nearly 80% patients with CGD have at least one episode of pneumonia, with *Aspergillus*, *Staphylococci*, *Burkholderia*, and *Nocardia* being responsible for two-thirds of the organisms [6]. In contrast to bilateral lung involvement in the index case, *Aspergillus* pneumonia in CGD typically involves one lobe with contiguous spread to pleura, ribs and vertebrae [8].

B. cenocepacia found in post-mortem blood culture, in the index case, is a signature organism in both cystic fibrosis and CGD [4,6]. However, there are marked differences between the infection pattern in cystic fibrosis and CGD. In cystic fibrosis, this organism causes colonization of the tracheobronchial tree [9] and can rarely cause invasive cepacia syndrome. These patients are not able to clear the colonized organisms and hence, spectrum of *Burkholderia* species is narrow. Isolation from sputum helps in diagnosis.

In contrast, this organism causes bronchopneumonia with central cavitation in patients with CGD [9]. Tissue from lungs is required for isolation of organism. Antibiotics can eradicate this organism but reinfection with same or

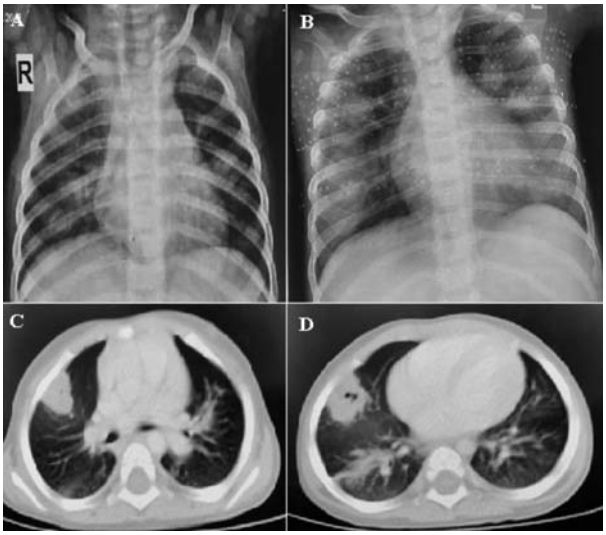

Fig. 1 A. Chest *X*-ray showing bilateral air space consolidations (right > left); B. Chest *X*-ray one month later showing progression of consolidations; C and D. PET-CT images showing pleura based cavitating nodules.

different *Burkholderia* species is common. Invasive disease with secondary bacteremia has been described with high mortality. The clinico-radiologic profile in the index child is consistent with *B. cenocepacia* infection.

Left-sided hydroureteronephrosis, seen in this case, could be due to granulomatous inflammation, a known cause of obstruction of urinary tract in infants with CGD [5]. Anemia and thrombocytosis, early in the course were likely to be multifactorial, related to both iron deficiency anemia and chronic inflammation [5]. Preterminally, this child developed hepatosplenomegaly, bicytopenia, coagulopathy with very low fibrinogen and high d-Dimer, high serum ferritin and transaminitis with conjugated hyperbilirubinemia. All these features could be explained by secondary HLH [10], which is further supported by the high plasma soluble CD25 levels. Left-sided pneumo-thorax could be due to rupture of cavitating consolidation or as a complication of ventilation.

Gastroenterologist: The diagnosis of CGD is confirmed, though the organism causing consolidation may be debated upon.

Pulmonologist 1: Was Mucor considered in view of cavitatory consolidations?

Clinical discussant: Though Mucor is an important differential in patients with cavitatory consolidations, it is not a typical organism in CGD.

Pediatrician 1: Why Galactomannan elevation is not common in CGD?

Clinical discussant: In CGD, *Aspergillus* is locally invasive and hematogenous spread is rare, thus making galactomannan and β-D glucan elevations uncommon in patients with *Aspergillus* pneumonia in CGD [8].

Microbiologist 1: Galactomannan in bronchoalveolar lavage fluid may be more sensitive than serum galactomannan in CGD.

PATHOLOGY PROTOCOL

A partial autopsy was performed. All serous cavities were normal.

Both lungs together weighed 220.5 g. Pleural surface was dull and outer surface of both lungs showed multiple nodules of varying sizes with predilection towards lower lobes. Multiple lymph nodes measuring 0.5-1 cm were present in pretracheal and paratracheal regions. Tracheobronchial mucosa was congested. Cut surface of lungs showed similar nodules (**Fig. 2A**). Central area of large nodules showed necrosis with abscess formation. Some nodules showed evidence of rupture of abscess wall. Microscopy showed large irregular geographic areas of necrosis limited by interlobar septae (**Fig. 2B**). Necrosis was palisaded by dense inflammatory infiltrate rich in epithelioid histiocytes (**Fig. 2C**), with well-formed epithelioid cell granulomas, and numerous giant cells were also noted in some places. Numerous micro-abscesses surrounded by similar inflammatory infiltrate were observed (**Fig. 2D**). No fungal profiles were identified on PAS and Groccot stains. Gram stain and Ziehl-Neelsen stain did not reveal any organisms. Adjoining alveolar spaces were densely infiltrated by neutrophils and macrophages. There was evidence of diffuse acute alveolar damage in the form of homogenous, eosinophilic hyaline membrane along the alveolar ducts and alveoli at some places (**Fig. 2E**). Other areas showed proliferative phase of diffuse alveolar damage. There was extensive fibrinous pleuritis. Lung tissue was subjected to conventional PCR targeting 16S ribosomal DNA region followed by Sanger sequencing. Nucleotide sequence obtained was matched with gene bank, which revealed presence of *Nocardia pseudobrasiliensis*. PCR for *M. tuberculosis* and non-tubercular mycobacteria was negative.

Liver and spleen weighing 490 g and 186 g, respectively, had an unremarkable capsule with mottling on the cut surface of liver and prominent white pulp and few greyish white lesions in cut surface of spleen. Peripancreatic and perisplenic lymph nodes were enlarged. Microscopic examination of liver showed preserved architecture, centrizonal hepatocyte necrosis, dense infiltration of sinusoids by histiocytes and micro-abscesses with central necrosis surrounded by palisading histiocytes (**Fig. 2F**). Microscopic examination of spleen showed similar abscesses. No organism could be identified by Gram stain, Ziehl–Neelsen stain, PAS and Groccot stains.

Both kidneys weighed 121 g with unremarkable capsule. Left ureter was grossly dilated throughout its length (**Fig. 2G**). Cut surface of left kidney showed minimally dilated pelvis, the latter showing attenuated transitional lining microscopically. No abscess or granuloma was seen in kidneys. Tubular necrosis was seen in greyish-white lesions of left kidney. Sections from vesicoureteric junction and urinary bladder showed invagination of surface mucosa into lamina propria. Lamina propria showed mild mixed inflammatory infiltrate of histiocytes. No well-formed granulomas were seen.

Small intestine showed prominent Peyer's patches. Focal loss of intestinal folds was seen in large intestine. Microscopically, granulomas were seen in lamina propria palisaded by lymphomononuclear cells. Characteristic pigmented histiocytes were seen in some of these granulomas (**Fig. 2H**). There was no evidence of cryptitis or crypt abscesses. Peyer's patches showed similar granuloma without necrosis.

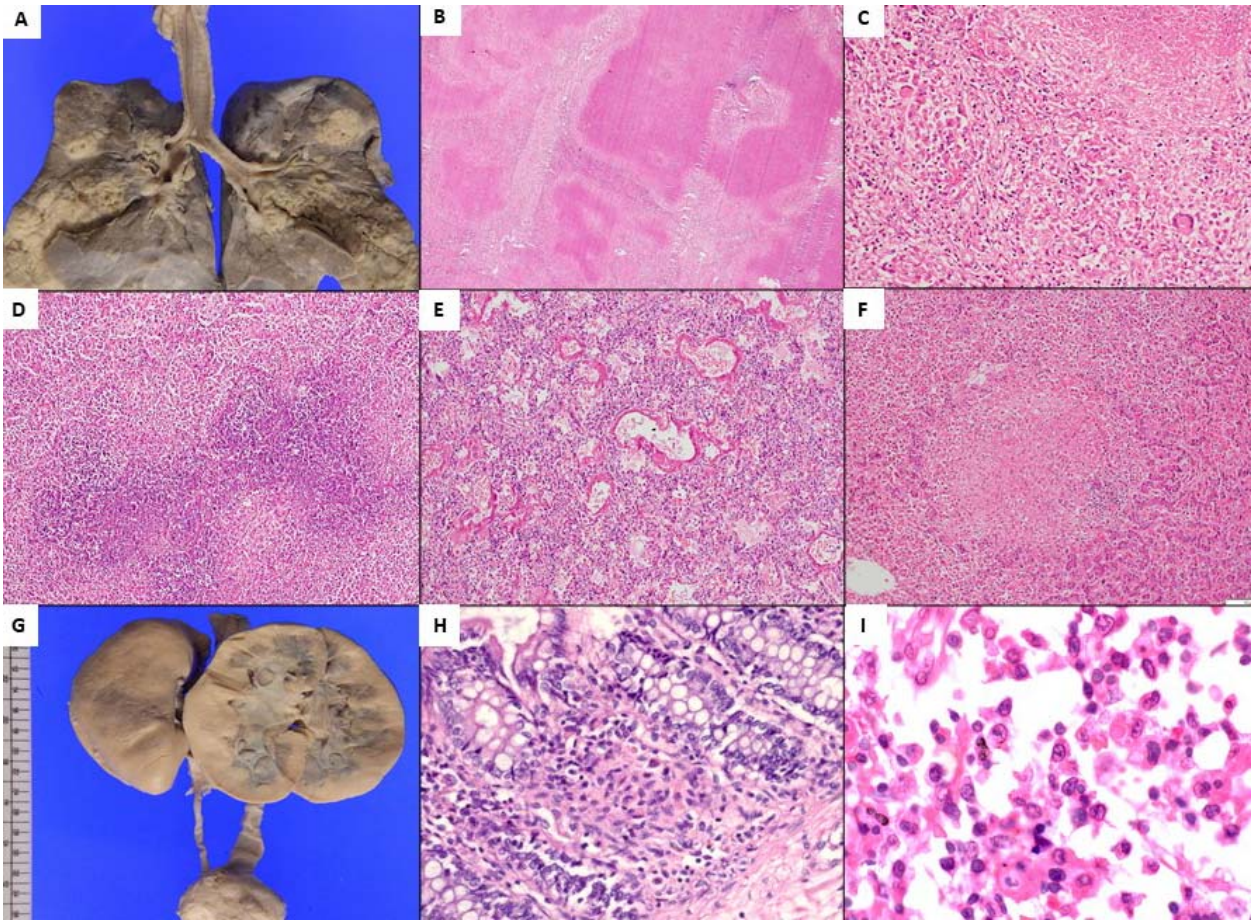

Fig. 2 A. Cut surface of both lungs shows greyish white nodules of variable size with central necrosis in larger nodules (Gross photograph); B. Large geographic type necrosis of lung parenchyma limited by interlobular septae (20X, H&E); C. Necrosis is palisaded by epithelioid cell granuloma with giant cell formation (200X, H&E); D. Abscess formation with dense neutrophils rich inflammation in adjoining alveolar spaces (200X, H&E); E. Glassy eosinophilic membrane noted along alveolar wall indicating diffuse alveolar damage (200X, H&E); F. Microscopy of liver showing necrosis with palisading epithelioid histiocytes (200X, H&E); G. Left ureter is dilated from vesico-ureteric junction to renal pelvis. Cut surface of left kidney shows mildly dilated pelvicalyceal system (Gross photograph); H. Microgranulomas with pigmented histiocytes are seen in the lamina propria of large intestine (200X, H&E); I. Bone marrow shows increase in number of histiocytes with significant hemophagocytosis (100X, H&E).

The sinus spaces of lymph nodes were markedly distended and infiltrated by benign histiocytes. Well-defined granulomas without central necrosis and occasional multinucleated giant cells were seen.

Bone marrow was hypercellular with increased histiocytes, and hemophagocytosis of neutrophils, lymphocytes and RBC in histiocytes (**Fig. 2I**). Focal hemophagocytosis was observed in liver, spleen and lymph nodes.

Other organs such as heart, thymus, testis, adrenal and skeletal muscles were grossly and microscopically normal.

Final autopsy diagnosis was necrotizing granulomatous inflammation with massive necrosis and abscesses *(N. pseudobrasiliensis*), diffuse alveolar damage in the lungs with necrotizing granulomatous inflammation and microabscesses in liver and spleen with granulomatous colitis with left sided hydro-ureteronephrosis, granulomatous cystitis and granulomatous lymphadenitis. The overall pathologic features are consistent with a diagnosis of CGD with features of shock and HLH

OPEN FORUM

Microbiologist 1: *Nocardia pseudobrasiliensis* is usually multidrug resistant and only cotrimoxazole may work in this infection [11,12].

Pathologist 1: What is the role of FDG-PET in such a child?

Clinical discussant: FDG-PET is done in a child with prolonged fever with no obvious cause on routine investigations. The index child had evidence of bilateral consolidation during first admission. CT scan of chest may have served the purpose of delineating the consolidations better and to decide on invasive investigations for microbiologic diagnosis.

Pediatrician 2: Could the choice of antibiotics have been different?

Clinical discussant: Empiric therapy for infections in a patient with CGD includes staphylococcal cover (cloxacillin or vancomycin) and cover for gram negative bacteria (carbapenam or fluoroquinolone) [13]. Antifungal cover may be added if the patient is sick. Change in regimen may be required once an organism is isolated from clinical specimens [13].

Pharmacologist 1: Ceftriaxone and cotrimoxazole could have been good choice in this child.

Gynecologist 1: What counselling was done for the family?

Clinical discussant: Parents have been counseled about the disease, need to investigate elder sibling and risk of recurrence of 25% in any pregnancy. They have been counseled regarding need of chorionic villous sampling at 9-10 weeks of gestation for prenatal diagnosis.

DISCUSSION

Microbiological identification of organism requires invasive investigations in a child with persistent pneumonia as clinical and radiological profiles lack etiologic specificity and yield of blood culture is extremely low [2]. An early FNAC from lung lesions may have altered the outcome in the index child. Identification of organism is not only important for appropriate antimicrobials but also gives clue regarding underlying disease.

CGD is a prototype phagocytic defect due to reduced phagocyte oxidase activity. Genetic defects can cause deficiency of any of the four components namely gp91, p22, p47 and p67 of phagocyte oxidase [13]. Reduced activity of phagocyte oxidase results in defective phagocytosis and consequent infection with catalase positive bacteria and fungi. Pneumonia, lymphadenitis, subcutaneus or visceral abscesses, and osteomyelitis are frequent infections. Bacteremia and fungimea are less frequent. Initial infection with unusual organisms such as *Burkholderia*, *Nocardia*, *Serratia* and *Aspergillus* should raise the suspicion [14]. Recurrent deep staphylo-coccal infections should also warrant investigation.

Besides infections, hyperinflammation can result in failure to thrive, hepatosplenomegaly, lymphadenopathy, anemia, thrombocytosis, and raised inflammatory parameters [5]. Organ specific inflammation can present as colitis, granulomatous cystitis, gastric outlet obstruction, and hydronephrosis [5]. Diagnosis is clinched by demonstration of reduced phagocyte oxidase activity by NBT or DHR assays [5]. Expression of b558 helps in demonstrating gp91 and p22 components of phagocyte oxidase. While X-linked CGD due to gp91 deficiency is the commonest type in the West [6], the same is not true in other countries [7]. Owing to frequent consanguinity, AR-CGD contributes to 50-60% of all CGD patients in Asia. Severity of disease depends on residual activity of phagocyte oxidase [7]. Cotrimoxazole and itraconazole prophylaxis with or without interferon-ã have resulted in significantly better outcomes [13]. Failure of the prophylaxis warrants hematopoietic stem cell transplantation.

Both *Burkholderia* and *Nocardia* are signature opportunistic organisms in CGD. Pulmonary involvement due to *Nocardia* can present with focal or multifocal consolidations with central cavitation and pleural effusions [11,12]. Most *Nocardia* species are susceptible to sulphonamides, linezolid, amikacin, imipenam, minocycline, and moxifloxacin with *Nocardia pseudobrasiliensis* being more resistant [11]. Prolonged combination therapy with 2-3 drugs is preferred for invasive disease. Steroids have been used in combination with appropriate antibiotics in CGD patients with *Nocardia* infections [15].

In conclusion, we need to be more invasive for microbiologic diagnosis when the clinical course does not suggest CAP. Isolation of organism not only provides guidance to choice of antimicrobials but also provides clue to underlying disease.

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REFERENCES

1. Skolnik N, Tien P. Community-acquired pneumonia in infants and children. Fam Pract News. 2011;41:22.
2. Yousif TI, Elnazir B. Approach to a child with recurrent pneumonia. Sudan J Paediatr. 2015;15:71-7.
3. Roya-Pabon CL, Perez-Velez CM. Tuberculosis exposure, infection and disease in children: A systematic diagnostic approach. Pneumonia. 2016;8:23.
4. Davies JC, Alton EWFW, Bush A. Cystic fibrosis. BMJ. 2007;335:1255-9.
5. Song E, Jaishankar G, Saleh H, Jithpratuck W, Sahni R, Krishnaswamy G. Chronic granulomatous disease: A review of the infectious and inflammatory complications. Clin Mol Allergy. 2011;9:10.
6. Winkelstein JA, Marino MC, Johnston RB, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore). 2000;79:155-69.
7. Köker MY, Camcýoðlu Y, van Leeuwen K, et al. Clinical,

functional, and genetic characterization of chronic granulomatous disease in 89 Turkish patients. J Allergy Clin Immunol. 2013;132:1156-63.e5.
8. King J, Henriet S, Warris A. Aspergillosis in chronic granulomatous disease. J Fungi. 2016;2:15.
9. Greenberg DE, Goldberg JB, Stock F, Murray PR, Holland SM, LiPuma JJ. Recurrent burkholderia infection in patients with chronic granulomatous disease: 11-year Experience at a large referral center. Clin Infect Dis. 2009;48:1577-9.
10. Henter J-I, Horne A, Aricó M, et al. HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124-31.
11. Wilson JW. Nocardiosis: updates and clinical overview. Mayo Clin Proc.2012;87:403-7.
12. Minero MV, Marín M, Cercenado E, Rabadán PM, Bouza E, Muñoz P. Nocardiosis at the turn of the century: Medicine (Baltimore). 2009;88:250-61.
13. Thomsen IP, Smith MA, Holland SM, Creech CB. A comprehensive approach to the management of children and adults with Chronic Granulomatous Disease. J Allergy Clin Immunol Pract. 2016;4:1082-8.
14. Marciano BE, Spalding C, Fitzgerald A, et al. Common severe infections in Chronic Granulomatous Disease. Clin Infect Dis Off Publ Infect Dis Soc Am. 2015;60:1176-83.
15. Freeman AF, Marciano BE, Anderson VL, Uzel G, Costas C, Holland SM. Corticosteroids in the treatment of severe Nocardia pneumonia in chronic granulomatous disease. Pediatr Infect Dis J. 2011;30:806-8.