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Case Report

# The Pneumonia That Would Not Go Away

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**Abstract**

A seven-year-old previously healthy Hispanic male presented with persistent fevers and a nonproductive cough. After an initial course of outpatient antibiotics, the patient was admitted to the hospital for further management of a right upper lobe consolidation. Initial bronchoscopy revealed a high lipid laden macrophage index. The patient improved after prolonged intravenous antibiotics and was discharged home on further oral antibiotics. Subsequently the fevers recurred and the patient was re-admitted for worsening of his right upper lobe consolidation. A repeat bronchoscopy was positive for rare Burkholderia cepacia group. Given the new finding, further work-up revealed an underlying diagnosis of Chronic Granulomatous Disease.

## ABBREVIATIONS

CT: Computed Tomography; BAL: Bronchoalveolar Lavage; LLMI: Lipid-Laden Macrophage Index; NBT: Nitroblue Tetrazolium; DHR: Dihydrorhodamine; CGD: Chronic Granulomatous Disease.

## CASE PRESENTATION

A 7 year old previously healthy Hispanic male presented to an emergency department with 1 week of a non-productive cough and intermittent fevers measured at home to 103.5°F for one day. Family reported being prescribed a 5 day course of azithromycin in the emergency department and then discharged home. After taking 3 days of the medication the patient returned to the same emergency department for persistent cough and fever. He was then admitted to the pediatric unit at the hospital after a chest x-ray was obtained and consistent with right upper lobe pneumonia (Figure 1); he was then started on ceftriaxone intravenously (IV). After multiple days on ceftriaxone and later vancomycin he continued to be febrile. A chest computed tomography (CT) was obtained which found a dense consolidation in the right upper lobe (RUL) without effusion or empyema (Figure 2), and several calcified perihilar lymph nodes. Further infectious work up showed Aspergillus IgM negative/IgG positive, PPD negative, Coccidiomycosis antibody negative, and Mycoplasma pneumoniae IgM negative. He continued to have fevers to 102.8°F after 2 weeks of hospitalization so he was transferred to a children's hospital for further evaluation and management.

Upon arrival patient's vital signs were as follows: temperature 39°C, heart rate 110 beats/min, respiratory rate 20 breaths/min, blood pressure 115/65mmHg and oxygen saturation 100% on room air, weight 28.8kg (79%), height 127cm (52%). Physical exam revealed a pleasant boy in no apparent distress. His tympanic membranes were clear with no lesions on oropharynx. Respiratory exam was without increased work of breathing, and only mildly decreased breath sounds in the right upper fields. The rest of his exam was unremarkable. There was no other significant past medical history. Family history was remarkable for asthma, and was negative for immune deficiencies or recurrent infections. The patient was in second grade, without developmental or learning concerns. He lived with his mom, maternal grandparents, and 2 maternal uncles. Patient also had a healthy younger half-brother from one of his mother's relationships.

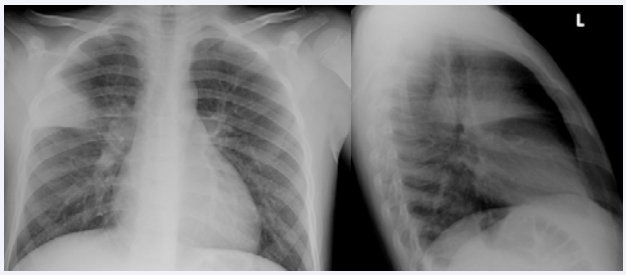


**Figure 1** PA and lateral x-rays revealing right upper lobe consolidation.

Laboratory studies showed a normal white blood cell count, mildly low hemoglobin 10g/dL, ESR 97mm/hr (normal 0-10mm/hr), and CRP 6.9mg/dL (normal 0-0.9mg/dL). Patient was continued on ceftriaxone and vancomycin, although the latter was discontinued after a few days due to a rising creatinine and concern for possible nephrotoxicity. Patient remained persistently febrile and was started on an

empiric course of fluconazole for possible Coccidiomycosis but this was discontinued on the third day of therapy when Coccidiodal antibodies by complement fixation were negative. QuantiFERON-TB Gold was also negative. Pulmonology was consulted and performed a bronchoscopy with bronchoalveolar lavage (BAL). Bronchoscopy was significant for diffuse areas of pale mucosa and edema, and an area of bronchiole constriction in the right upper lobe. BAL was negative for bacterial culture, fungal culture, Aspergillus antigen, and mycobacteria. Pathology analysis of the BAL was significant for presence of lipid-laden macrophages, with a lipid-laden macrophage index (LLMI) of >240 (Figure 3). Given that in our institution a LLMI > 86 is concerning for aspiration pneumonia the patient was started on IV ampicillin/sulbactam and ceftriaxone was discontinued. Repeat high-resolution chest CT with thin slices was performed which demonstrated a possible lesion in the right upper lobe posterior segmental bronchus but it was unclear if the lesion was within or adjacent to the bronchus (Figure 4). About 36 hours after initiation of ampicillin/sulbactam, the child became consistently afebrile for the first time since admission. Patient was evaluated by the dysphagia team and no signs of aspiration were observed. He completed 7 days of ampicillin/sulbactam IV and was discharged home on oral amoxicillin/clavulanic acid for an additional 14 days. A pulmonology follow up was arranged with plans for repeat bronchoscopy as an outpatient.

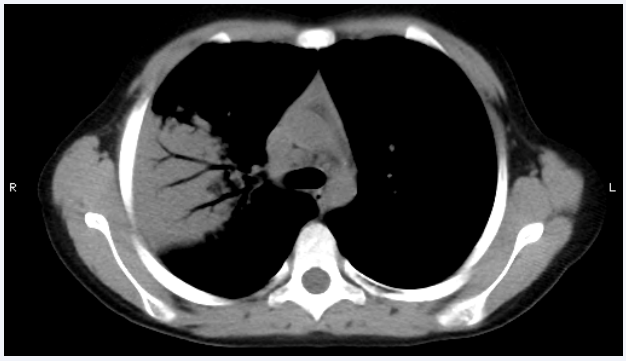


**Figure 2** Chest CT scan demonstrating consolidation involving the posterior segment of the right upper lobe.

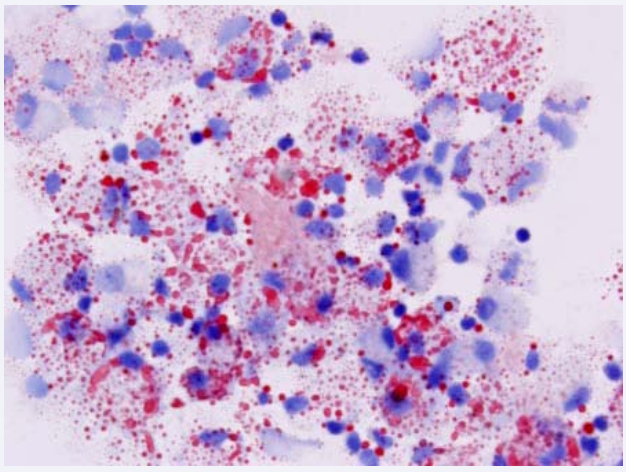

**Figure 3** Analysis of BAL with oil-red-o stain demonstrating lipids.

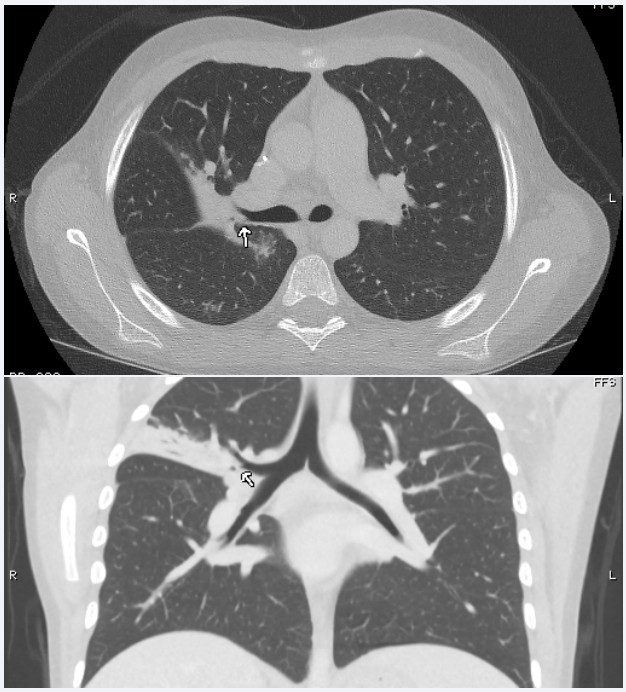


**Figure 4** Chest CT scan demonstrating consolidation involving the posterior segment of the right upper lobe. Arrow demonstrates subtle soft tissue density within or adjacent to the right upper lobe posterior segmental bronchus.

Sixteen days after discharge from the hospital, the patient presented to the children's hospital emergency department with fevers x 3 days. Temperatures ranged between 100.4-102 °F with no other significant symptoms except for a mild cough. He had been taking the prescribed amoxicillin/clavulanic acid. His vital signs on readmission were as follows: temperature 38.8°C, heart rate 98 beats/min, respiratory rate 21 breaths/min, blood pressure 103/55mmHg and oxygen saturation 100% on room air, weight 28.7kg (77%). Physical exam again was remarkable for a pleasant boy in no apparent distress without any increased work of breathing, and mild decreased breath sounds in the right upper fields. Laboratory studies again showed a normal white blood count, mildly decreased hemoglobin 9.5g.dL, ESR 75mm/hr, and CRP 6.9mg/dL. A chest x-ray was done which showed worsening of the right upper lobe opacity. He was started back on IV ampicillin/sulbactam. Respiratory viral panel by PCR was negative for Influenza A/B virus, RSV, Rhinovirus, Metapneumovirus, Adenovirus, and Parainfluenza virus. Mycoplasma pneumoniae PCR was also found to be negative. Due to continued fevers with no significant improvement a repeat bronchoscopy was performed. Bronchoscopy showed that the airway mucosa of the right upper lobe was pale in color, edematous, with some clear-to-white mucous adherence to the walls. BAL was again negative for fungal culture, Aspergillus antigen, and acid fast bacillus stain, but was found to be positive for rare Burkholderia cepacia group. BAL pathology was again significant for a LLMI of 88. Due to isolation of B. Cepacia, he was evaluated for cystic fibrosis and chronic granulomatous disease (CGD). A sweat chloride test was obtained and the results were negative. A nitroblue tetrazolium reduction (NBT) test showed only 1% of cells with oxidative activity and a dihydrorhodamine

test (DHR) showed 46% of cells with normal oxidative activity. In light of this new diagnosis, ampicillin/sulbactam was changed to meropenem to treat B. Cepacia and he was started on itraconazole and sulfamethoxazole-trimethoprim for prophylaxis.

The patient initially remained febrile on meropenem, but defervesced after the addition of vancomycin. He was discharged home on meropenem and vancomycin, administered by family members via a peripherally-inserted central catheter. He will complete an additional eight weeks of IV antibiotic therapy at home. At the time of discharge and soon thereafter, the child remains afebrile and without further hospitalizations. He is also being evaluated for a possible bone marrow transplant per Immunology's recommendations. Insurance approval is pending for further genetic testing of the patient for prognostic reasons, as well testing of his half-brother for diagnostic purposes.

## DISCUSSION

This patient illustrates an unusual presentation of a rare disorder, and his clinical course provided many opportunities for further exploration. The initial bronchoscopy in our patient revealed a high lipid-laden macrophage index. LLMI has traditionally been used as a marker for aspiration of lipid-containing gastric contents into the lower respiratory tract [1,2]. A sampling of 100 alveolar macrophages are rated from 0-4 based on their lipid content, with the final LLMI ranging from 0-400, and with normal cutoff values varying widely from 67-200, but with 100 being a generally-accepted cutoff for normal [2,3]. Recent investigation however has found LLMI to be more useful as a marker of respiratory tract inflammation as opposed to a specific marker of aspiration. Multiple studies have found no significant correlation between acid and reflux events, as measured by 24-hour intraesophageal pH monitoring and pH multichannel intraluminal impedance testing, and elevation in LLMI [4,5]. LLMI may instead be more specific for chronic respiratory inflammation, given that elevated LLMI has been found in cystic fibrosis, graft-versus-host disease, chemotherapy and cancer, organic substance inhalation, and bronchial obstruction [1,6]. One proposed underlying mechanism is a state of chronic inflammation leading to recruitment of immune cells, resulting in increased deposition of lipid-containing cellular components and membranes leading to the elevated LLMI [3,7]. It thus remains a possibility that for our patient, without any apparent clinical signs of aspiration, but with possible bronchiole obstruction seen on high-resolution CT and bronchoscopy, that the elevated LLMI was a result of a previously-undiagnosed bronchiole constriction or chronic respiratory inflammation as opposed to aspiration pneumonia.

The repeat bronchoscopy was found to be positive for rare Burkholderia cepacia group, leading to further work-up for a possible immunodeficiency. Burkholderia Cepacia (B. Cepacia) is an aerobic, non-lactose-fermenting, catalase-producing gram-negative bacillus that is primarily an opportunistic pathogen. The B. Cepacia complex comprises of at least 10 species including B. cepacia, B. multivorans, and B. cenocepacia [8]. The organism was first discovered in 1950 by William Burkholder in rotten onion bulbs which he initially named Pseudomonas cepacia [9]. In 1992, P. cepacia and several other related species were transferred to the new genus, Burkholderia. B. cepacia is found ubiquitously in plant root, soil, and moist environments. They can develop with minimal nutrition, in harsh environments and can be resistant to common disinfectants.

The most widely known patient population to be infected with B. cepacia complex is patients with cystic fibrosis. B. cepacia complex has been associated with pulmonary infections in patients with cystic fibrosis usually late in the course of their disease. However, infection with B. cepacia can result in several clinical scenarios: no change in the rate of pulmonary decline, chronic infection with a more rapid decline, or rapid deterioration resulting in death also known as "cepacia syndrome" [10]. It is now known that B. cepacia can be transmitted from person to person which has resulted in separation of cystic fibrosis patients infected with B. cepacia from those not infected [11].

There are several other populations affected by B. cepacia. B. cepacia causes several types of infections in chronic granulomatous disease patients, most commonly pneumonia, but also lymphadenitis and abscesses [12]. Infections such as bacteremia/sepsis, catheter related infections, and UTIs have also been reported in premature infants requiring prolonged hospitalization and children with hemoglobinopathies, malignant neoplasms, and other immunodeficiencies [13]. There are also several reports of outbreaks due to contamination of mouthwash, chlorhexidine solutions, nasal sprays, ultrasound gels, and other hospital equipment [14-17]. Pseudoinfections have been reported when hospital equipment such as blood gas analyzers and bronchoscopes were contaminated [9,18].

Treatment of B.cepacia can be difficult as many strains of the organism are resistant to many antimicrobial agents. The most commonly used antimicrobials are trimethroprim/sulfamethoxazole, ceftazidime, meropenem, quinolones and pipercillin. Combination therapy is sometimes used however there is not clear evidence that it is more effective than monotherapy [13].

The discovery of B cepacia from the second BAL culture initiated further diagnostic workup which ultimately revealed that our patient had Chronic Granulomatous Disease. CGD is a rare primary immunodeficiency that arises from the defective function of phagocytes. The incidence of this disease is approximately 1 per 200,000 live births in the U.S. [19]. In contrast to other disorders of this component of the immune system, both neutrophils and monocytes have normal chemotactic, phagocytic, and degranulating abilities. The dysfunction of phagocytes in CGD stems from the inability to produce reactive oxygen metabolites via the NADPH oxidase enzyme or the so-called oxidative burst. This deficiency leads to an inability to combat catalase-positive organisms and manifests itself in the creation of phagocytic vacuoles that lack these reactive oxygen species. The organisms that are phagocytosed are unable to be properly digested, leading to granuloma formations, which gives the disease its name.

The majority of infections in North American in patients with CGD are due to four bacterial organisms (Staphylococcus aureus, Serratia marcescens, Burkholderia cepacia complex, and Nocardia species), as well as species of the fungus Aspergillus [20]. Patients with CGD usually present with pneumonia, lymphadenitis, osteomyelitis, and skin infections. Other manifestations of the

disease include chronic infection, poor growth, gingivitis, and perirectal abscesses. Furthermore, because of the possibility of granulomatous colitis, CGD patients are at an increased risk for inflammatory bowel disease [21]. The diagnosis is made by history, noting the presence of recurrent infections (especially pneumonias and pyogenic skin lesions) as well as a positive family history for early deaths from infection or other members of the family who are plagued with recurrent infections. The diagnosis can be confirmed by nitroblue tetrazolium reduction (NBT) or dihydrorhodamine oxidation (DHR) [22].

In the past NBT was considered to be the test of choice, however this assay is very laborious and subjective, making it difficult to standardize among different laboratories. It is based on the reduction of nitroblue tetrazolium to formazan during the oxidative burst. Formazan is a blue insoluble substance that precipitates marking the cytoplasm of cells that have an oxidative burst from those that do not; thus, patients with CGD do not have cells that have blue cytoplasms.. The DHR assay is now considered the test of choice as it is better able to detect subtle differences in patients who have different forms of CGD as well as carriers of the disease [23]. DHR utilizes flow cytometry to identify cells that lack or have a decreased oxidative burst. The cells are treated with a fluorescent dye called dihydrorhodamine, which changes its spectrum of fluorescence when it is reduced during the oxidative burst. This allows the use of flow cytometry to quantify the quantity and distribution of cells that demonstrate activity, allowing for identification of disease carriers as well as those that have the disease. Nonetheless this test can still miss some cases as some cases may require subtle interpretations.

CGD is usually thought of as an X-linked disorder; this is because approximately 65% of patients inherit the disorder in this fashion. The inheritance pattern of CGD can be understood by looking at the molecular component of the NADPH oxidase complex. There are 4 components of this complex (and their associated genes) that are currently identified as the cause for this disorder such that the lack of function of any of these components will lead to a failure to produce the oxidative burst that is required for killing catalase-positive organisms. These four components are $gp91^{phox}$, $p47^{phox}$, $p67^{phox}$, and $p22^{phox}$ [24]. The most common defect is in $gp91^{phox}$ which is encoded by the CYBB gene in the X-chromosome, leading to the X-linked inheritance pattern that is usually encountered in patients with CGD. On the other hand, the other components of the NADPH complex ($p47^{phox}$, $p67^{phox}$, and $p22^{phox}$) are coded for by autosomes, leading to an autosomal recessive pattern of inheritance in the other forms of CGD.

The majority of patients (~76%) are diagnosed before the age of five, about 10% are not diagnosed until the second decade, and about 4% during their third decade. The autosomal recessive forms of the disease are associated with presentations later in life [19]. Like many other disorders, the severity of this disease is along a wide spectrum of phenotypes. Interestingly, severity of disease is not necessarily related to which gene is dysfunctional in a particular patient. Studies that have looked at the degree of production of reactive oxygen species in patients with CGD have shown that those patients who have higher residual production of reactive oxygen species have improved survival [25].

With the advancements that have been made in anti-infective medications, especially the azoles such as itraconazole, voriconazole, and posaconozale, the life expectancy of patients with CGD has improved. About 90% of patients with CGD will be able to live to adulthood [22]. Much of the data on survival precedes the advent of some of these medications therefore it is difficult to predict what the survival would be for a patient such as the one described in this case report, however there are numerous patients that survive well beyond the sixth decade. The data also appears to demonstrate increased survival for patients with the autosomal recessive form of the disease [19].

Antibiotic use has not only improved survival in CGD but it is also the mainstay of therapy for the disease. Prophylactic use of trimethoprim/sulfamethoxazole can reduce the incidence of skin infection, and the use of itraconazole can also help reduce fungal infections. Some institutions recommend the use of interferon-gamma as well as part of the treatment for the disease. An alternative option is bone marrow transplantation, which offers the possibility of achieving full remission of CGD but with the associated potential complications which may arise (e.g., graft versus host disease).

Finally, the implications for the family are numerous, including long term medications, careful monitoring for signs of infections, genetic testing of parents and siblings, and the possible risk for future pregnancies.

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