CASE REPORT

Atypical presentation of chronic granulomatous disease with *Burkholderia cepacia*Mac Vining,¹ Nirupma Sharma,² Margaret Guill³¹Georgia Regents University, Augusta, Georgia, USA²Department of Pediatrics, Georgia Regents University, Augusta, Georgia, USA³Department of Pediatric Pulmonology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USACorrespondence to
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SUMMARY

Chronic granulomatous disease (CGD) is a rare inherited disorder of neutrophil oxidative burst. In patients with CGD, phagocyte destruction of catalase-producing organisms is impaired, resulting in recurrent and potentially fatal infections. *Burkholderia cepacia*, a catalase-producing organism, is known to infect patients with dysfunctional immune systems. We report a case of a 3-year-old boy with this rare infection that unravelled the diagnosis of CGD.

BACKGROUND

Chronic granulomatous disease (CGD) is a rare inherited disorder of neutrophil oxidative burst. In patients with CGD, phagocyte destruction of catalase-producing organisms is impaired, resulting in recurrent and potentially fatal infections. Recently discovered *Burkholderia cepacia*, a catalase-producing organism, is described but rarely reported to infect patients with dysfunctional immune systems such as CGD. We report a case of newly diagnosed CGD in a 3-year-old boy with repeated episodes of pneumonia.

The patient was referred to our hospital after unsuccessful treatment of three frequent episodes of pneumonia by his paediatrician. After an initial visit with both paediatric pulmonology and haematology, he was admitted to the Children's Medical Center for further workup of an underlying illness. After extensive workup, *B. cepacia complex* was isolated as the cause of his lung infection and successfully treated. Subsequently, a diagnosis of CGD was confirmed on laboratory testing. A multidisciplinary approach to this diagnosis and treatment was used involving general paediatrics, infectious disease, pulmonology, haematology, paediatric cardiology and immunology subspecialists. We present this case and recognise that further investigation into the relationship and awareness between CGD and *Burkholderia*, a relatively new pathogen, is necessary.

CASE PRESENTATION

A 3-year-old Caucasian boy presented to a paediatric pulmonologist for repeated versus persistent chest infections and the paediatric haematologist due to chronic anaemia. Per history he had experienced recurrent otitis media, sinusitis and pneumonias since birth. On admission, his mother reported a new onset of 3 days of high fever, cough and irritability besides recurrent pneumonias. Exposure history revealed that his grandmother had recently inadvertently exposed him to active tuberculosis (TB); however, the patient had a negative purified

protein derivative (PPD) prior to admission. His examination was consistent with bilateral otitis media with effusion, a I/VI short systolic ejection murmur, dullness over the right lung fields, liver edge 4 cm below the costal margin, a palpable spleen tip, clubbing in the fingertips and crusty vesicular lesions on the lower lip. Initial laboratories revealed anaemia with microcytosis, C reactive protein 24.3 mg/L and lactate dehydrogenase 499 U/L. Antibody titres for *Bartonella*, diphtheria/tetanus, *Blastomyces*, *Mycoplasma*, *Histoplasma*, cytomegalovirus and Epstein-Barr virus were all negative. He also had a sweat chloride test, which was normal. He had no previous sputum bacterial isolates.

He began empiric treatment with ceftriaxone intravenous for pneumonia and acyclovir intravenous for herpes simplex. A second PPD was placed and he was started on empiric four drug anti-TB treatment, consisting of rifampin, isoniazid, pyrazinamide and ethambutol. An echocardiogram showed a structurally normal heart with no evidence of endocarditis. An abdominal ultrasound showed normal liver and biliary architecture. A bone marrow biopsy was performed showing microcytic anaemia consistent with iron deficiency. There was no evidence of neoplasm, granuloma or microorganisms in the bone marrow. Chest radiograph demonstrated a small left pleural effusion and focal airspace disease bilaterally. He then underwent a contrasted CT of the chest which showed multifocal airspace disease involving all lobes of the lungs, and paratracheal and parahilar lymphadenopathy concerning for an infectious versus inflammatory versus malignant process (figure 1). A needle biopsy of the lung was

Figure 1 Contrasted thoracic CT scan demonstrating bilateral necrotising pneumonias in our patient.

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Figure 2 Caseating granuloma from lung biopsy (H&E stain).

performed showing an inflammatory reaction associated with non-caseating granulomas but no malignancy (figures 2 and 3). Biopsy cultures were sent and grew *B. cepacia*. His antibiotic therapy was changed accordingly to sulfamethoxazole-trimethoprim and ciprofloxacin. Per recommendation of paediatric infectious disease and allergy-immunology, a neutrophil oxidative burst was conducted and was absent, suggesting CGD. A dihydrorhodamine (DHR) assay was then performed on the patient and his mother which confirmed the diagnosis of CGD.

DIFFERENTIAL DIAGNOSIS

This case was initially a diagnostic dilemma with multiple confounding factors creating a conundrum. We entertained:

1. Congenital lung pathology predisposing to recurrent/persistent infection;
2. TB: patient exposed to active TB;
3. Underlying malignancy in the setting of severe anaemia and radiographic lung findings;
4. Immune defects leading to recurrent infections.

With a multispecialty approach we were able to tease through this conundrum and rapidly approach the correct diagnosis of CGD as detailed above.

OUTCOME AND FOLLOW-UP

After his acute symptoms resolved, he was discharged home on 6 weeks oral antibiotic therapy. After completion of the 6-week course of antibiotic therapy, he was instructed to start daily

Figure 3 Granuloma from lung biopsy (H&E stain).

low-dose maintenance therapy with sulfamethoxazole-trimethoprim. He was scheduled with an appointment with the allergy-immunology department as an outpatient to discuss long-term care, including future interferon- γ therapy versus bone marrow transplant.

DISCUSSION

CGD is a rare genetically inherited disorder characterised by recurrent life-threatening bacterial and fungal infections. In the USA 1 in 200 000 people are affected with CGD.¹ Most infectious processes in these patients are caused by catalase-positive organisms such as *Staphylococcus aureus*, *Proteus*, rarely *Pseudomonas* and *Aspergillus*.² Patients with CGD typically cannot mount an appropriate response to infections caused by catalase-positive organisms due to their inability to produce reactive oxygen compounds. Frequent sites of infection are lung, skin, lymph nodes and liver. Another hallmark of this disease, as the name suggests, is granuloma formation, and these are especially difficult to treat in the gastrointestinal and genitourinary tracts. The characteristic clinical presentation of CGD is recurrent infections of the epithelial surfaces which contact the environment; that is, skin, lungs and gastrointestinal tract. The median age at diagnosis is 2–3 years of age.^{3–4} The most common presenting symptoms are lymphadenitis, skin abscesses, pneumonia and hepatomegaly.^{5–6} Of all clinical complications in one cohort study, pneumonia was the most common (79%), followed by lymphadenitis (53%), subcutaneous abscess (42%), liver abscess (27%) and sepsis (18%).⁷ Anaemia is commonly found in patients with CGD. It is understood from medical literature that individuals with X linked CGD have a more severe clinical phenotype and increased mortality than those with autosomal mutations.⁷

The oldest and quickest test for CGD is the nitroblue tetrazolium (NBT) test. In this test, superoxide produced by normal phagocytes in vitro will convert yellow dye to dark blue in at least 95% of the test matter. A negative reaction is indicative of respiratory burst dysfunction; however, this test is limited by observer subjectivity and a high rate of false-negative results.⁸ A more refined version of this test, using flow cytometry, was developed in the 1980s and is known as the DHR assay. DHR is normally cleaved to the strongly fluorescent molecule rhodamine by phagocytes and can be quantitatively measured under flow cytometry. Inability to cleave the compound indicates respiratory burst dysfunction in phagocytes.⁸ The DHR assay has now replaced NBT as the preferred screening tool for CGD. This testing modality is limited in that similar medical conditions that affect neutrophil respiratory burst (eg, myeloperoxidase deficiency) may cause a negative DHR.⁹ Confirmatory testing is administered via immunoblot analysis, however this method cannot distinguish between the X linked and autosomal recessive mutations. A positive immunoblot test should prompt genetic sequencing and counselling for the family. A database of genetic mutations for CGD has been established and is available for reference.¹⁰

Primary medical treatment of patients with newly diagnosed CGD usually involves acute management of the presenting illness. Aggressive treatment with intravenous antibiotics and antifungals is often necessary. Initial empiric therapy must cover the most common catalase-producing pathogens. Recently, ciprofloxacin has been chosen as first-line therapy, due to its appropriate spectrum of coverage and lipophilic properties.¹¹

B. cepacia complex is a group of non-lactose fermenting Gram-negative bacilli formerly classified as *Pseudomonas cepacia*. The complex was originally isolated from soft rot in plants such

as garlic and onions and gained recognition as an organism responsible for occasionally causing severe resistant lung infections in patients with cystic fibrosis (CF).¹² This organism is considered non-pathogenic for healthy persons; however, in patients with dysfunctional immune systems it frequently may cause life-threatening respiratory tract infections.^{13 14} Although recent literature has defined *Burkholderia* as a separate genus from *Pseudomonas* and described its impact on patients with CF, relatively little is understood about these bacteria in patients with CGD although more studies have recently elucidated the prevalence, virulence and pathophysiology of this infection in patients with CGD.^{15 16} Our patient grew *Burkholderia* from his lung biopsy specimen, suggesting it to be the cause of his pneumonitis. *Pseudomonas* infections are a known but rare cause of infections in patients with CGD. *B. cepacia*, being a catalase-positive organism, is described albeit rare and extremely virulent in patients with CGD.

Learning points

- ▶ Patients with chronic granulomatous disease (CGD) may have an atypical or delayed presentation, and this diagnosis should be considered in patients with recurrent infections of the soft tissue and respiratory epithelial tract.
- ▶ Although patients with CGD are usually most vulnerable to catalase-producing organisms such as *Staphylococcus aureus*, *Klebsiella* and *Aspergillus* species, newly emerging organisms such as *Burkholderia cepacia* complex are also epidemiologically significant in patients with dysfunctional immune systems.
- ▶ A multidisciplinary approach involving general paediatricians, pulmonologists, immunologists and infectious disease specialists can lend valuable guidance in diagnosis and long-term care of these patients.

Contributors MV personally took part in the care of the patient depicted and selected the case for manuscript. NS advised throughout the course of the patient and edited the manuscript. MG acted as a subject matter expert and also edited the manuscript prior to submission.

Competing interests None.

Patient consent Obtained.

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