A 6-month-old male infant refuses to move his left leg

Evie Huang, Unikora Yang, Mona P. Gera*

Department of General Pediatrics, Children’s Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, California, USA

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*Correspondence:
Dr. Mona P. Gera,
E-mail: mpatel@chla.usc.edu

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ABSTRACT

Chronic granulomatous disease (CGD) is a rare, genetically heterogeneous condition that occur from mutations in NADPH oxidase, resulting in recurrent infections from catalase-positive organisms and granuloma formation. It is most commonly diagnosed within the first two years of life. We present a case of a six-month-old infant who presented with left tibial pain with initial concerns for child abuse and was found to have CGD. A skeletal survey revealed multiple lytic lesions, diffuse osteopenia, and opacities in the lungs. MRI revealed a tibial subperiosteal abscess and, after incision and drainage, cultures grew Serratia marcescens, an unusual catalase-positive organism. Targeted testing for immunodeficiency revealed 0% NADPH oxidase activity on nitro blue tetrazolium (NBT), confirming the diagnosis.

Keywords: Chronic granulomatous disease, Catalase-positive organisms, DHR test, NADPH oxidase, NBT test

INTRODUCTION

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency in which phagocytes lack or have functional inactivation of the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.1 The most frequent first manifestations of CGD are infections of the lung, skin, lymph nodes, and liver by catalase-positive organisms such as Staphylococcus aureus, Escherichia coli, Serratia marcescens, Burkholderia cepacia, Klebsiella and Listeria species. Fungal organisms including Aspergillus and Candida species are common causes of infections.2 CGD is a rare disorder but must be considered in patients who present with atypical or uncommon infections.

CASE REPORT

A six-month-old fully vaccinated term male infant presented to the emergency room for refusal to move his left leg. He was meeting his developmental milestones but had poor weight gain. One week prior to presentation, his mother noticed that the he was not using his left leg, but continued to move his right leg. He had more pain with movement of his left leg with stretching and diaper changes. His left knee became more swollen compared to the right knee and he was tender to palpation distal to his left knee. He did not have fevers, warmth, erythema, trauma, or skin breakdown.

The patient’s social history revealed he had recently been removed from his mother’s custody for neglect and was currently in custody of the paternal aunt. Five days prior to presentation, the patient was left in the full care of his mother as the paternal aunt was overwhelmed by the patient’s frequent crying.

On examination, the patient was in moderate distress and intermittently consolable. His left leg was held in a fixed, flexed, and externally rotated position. His left knee was swollen and warmer than his right knee, but not erythematos. The patient was in distress during
palpation around his left knee and with extension of his left leg. He was kicking vigorously with his right leg but was unable to move his left leg.

Laboratory tests revealed the following: white blood cell count, 23.0×10^9/L (×10^9/L); hemoglobin, 11.3 g/dL (113 g/L); platelet count, 631×10^3/μL (631×10^9/L); aspartate aminotransferase, 490 U/L (8.33 μkat/L); and alanine aminotransferase, 260 U/L (4.42 μkat/L). His erythrocyte sedimentation rate was markedly elevated at 130 mm/hour and C-reactive protein was elevated at 3.8 mg/L. Ultrasound of his hip and knee showed soft tissue edema overlying the left hip joint. There was no sonographic evidence of left hip or left suprapatellar joint effusion. X-ray of his left knee demonstrated generalized osteopenia with periosteal reaction at the proximal left fibula shaft and lateral left proximal tibial diaphysis. A skeletal survey revealed multiple lytic lesions in his bilateral humeri, a right tibia pathologic fracture or lytic lesion, diffuse osteopenia of his bones, and opacities in his lung fields.

There was concern for septic joint of the left knee, so a blood culture was obtained prior to starting ceftriaxone and vancomycin. MRI of his left hip and leg showed marked soft tissue edema, adenopathy, and phleghmonous regions at the proximal calf where a tibial subperiosteal abscess 4×13×24 mm in size was visualized. There was also a minor suprapatellar bursa joint fluid at the knee seen on imaging. Orthopedic surgery evaluated the patient and he was taken for incision and drainage of his left knee and left tibia. Wound culture from the left tibia grew Serratia marcescens.

The patient did not have tachypnea or hypoxemia, but the skeletal survey incidentally revealed pulmonary opacities. A high-resolution non-contrast chest computerized tomography (CT) was obtained for focused evaluation of the lungs. The CT showed bilateral hilar lymphadenopathy with multiple nodules and areas of consolidation throughout the lungs, particularly in the right middle lobe and right upper lobe. Bronchoalveolar lavage cultures were negative for bacteria, fungi, and mycobacteria.

**DISCUSSION**

CGD results from defects in the NADPH oxidase complex required in innate immunity to produce the superoxide anion necessary for normal killing of catalase-positive organisms such as *Serratia marcescens*. Catalase breaks down hydrogen peroxide produced via the host’s immune system enabling accumulation of hydrogen peroxide to fight off the infection.

The most common cause of CGD is due to an X-linked mutation in the CYBB gene that encodes gp91phox, one of the five subunits of NADPH oxidase. A mutation in this gene accounts for approximately two-thirds of cases. An autosomal recessive pattern of inheritance in genes coding for other phox subunits accounts for one-third of cases.

Infants with CGD are typically healthy at birth but will often present in infancy with severe infections involving the lung, skin, gastrointestinal tract, bones, lymph nodes, and occasionally, the brain. The most common sites for abscesses are perianal or perirectal and hepatic, which are most often caused by *S. aureus*. Recurrent aphthous ulceration is also a common finding.

Aspergillus pneumonia is a frequent cause of pneumonia in children with CGD but in this case report, the patient’s pulmonary findings were most likely granulomatas. Patients with CGD are prone to form granulomatas, which can affect any hollow viscus. It is hypothesized that CGD cells fail to degrade apoptotic cells normally, causing persistent inflammation, leading to granulomatas. In addition to multiple foci of infections, an early warning sign is failure to thrive. In a case series of CGD patients in the United Kingdom, 75% were below the mean for height and weight at the time of diagnosis. The patient in this case presented with decreased growth velocity, multifocal osteomyelitis and abscess formation with growth of Serratia, and extensive pulmonary granulomatas suggestive of CGD.

The fastest method of diagnosis is by the nitro blue tetrazolium (NBT) test which measures the qualitative activity of NADPH oxidase activity. Phagocytes with normal NADPH oxidase use superoxide to reduce the yellow NBT into a dark blue or black substance, formazan. Normal phagocyte activity results in at least 95% positive cells in this assay. Phagocytes lacking NADPH oxidase or with dysfunctional NADPH oxidase, are unable to reduce NBT and the assay remains yellow in color. This test is limited by operator subjectivity. The dihydrorhodamine (DHR) test is a quantitative analysis of NADPH oxidase activity. DHR is taken up by NADPH oxidase positive phagocytes.

Flow cytometry is applied to distinguish between the subpopulations of phagocytes and it can detect the different forms of CGD. The patient’s NBT test returned with 0% activity, making the diagnosis of CGD. The patient’s mother completed the DHR test which suggested the patient’s CGD is X-linked. Genetic testing can further be used as confirmatory testing and may be beneficial for counseling on future bone marrow transplantation or gene therapy treatment.

Patients with CGD should be immediately initiated on lifelong, daily antimicrobial prophylaxis: trimethoprim-sulfamethoxazole for bacterial prophylaxis and itraconazole or voriconazole for antifungal prophylaxis. Some institutions in the United States also initiate immunomodulatory cytokine therapy with interferon-gamma. The mechanism of IFN-gamma is unclear and may be associated with upregulation of superoxide. Steroids may also be used to treat inflammatory disease.
or as an adjuvant. Early diagnosis of infections and aggressive prophylaxis have been associated with decreased mortality and morbidity. 

Before antimicrobial prophylaxis, CGD was initially termed “fatal granulomatous disease of childhood” as patients rarely survived past their first decade. Recent experience from centers specializing in the care of patients with CGD suggests that the current mortality has fallen to under 3% with the average patient surviving to 40 years old. Survival length depends on the form of CGD. Multiple studies found patients with X-linked CGD had lower rates of survival than autosomal recessive CGD. One study found that the median age of death for X-linked CGD is 23 years of age, whereas the median age of death for autosomal recessive CGD is 32 years of age.

The patient in this case was started on itraconazole prophylaxis and trimethoprim-sulfamethoxazole prophylaxis, which was later stopped because of skin rash reaction. He was started on ceftinir, which is an appropriate alternative for antibacterial prophylaxis for patients with sulfonamide allergies. For the active multifocal osteomyelitis secondary to Serratia, he was treated with six weeks of inpatient antibiotics. He was initially on ceftriaxone, but due to persistently elevated transaminases, he was transitioned to ertapenem. As an outpatient, he continued with two weeks of ciprofloxacin.

The frequency of outpatient follow up in CGD patients varies based on age of onset and severity. Inflammatory markers, ESR and CRP, should be trended and elevations should prompt imaging. Live bacterial vaccines should be avoided, but live viral, inactivated or subunit vaccines continue to be recommended.

CONCLUSION

Hematopoietic cell transplantation is the only curative therapy for CGD. It can be used in patients with recurrent, serious infections despite prophylaxis and treatment, and severe inflammatory disease. The risk of infection and mortality is great in these patients. Gene therapy is an interesting and promising treatment option that is currently underway. However, trials have been limited and success rates are currently low.

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