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Fulminant Sepsis Due to *Granulibacter bethesdensis* in a 4-Year-Old Boy With X-Linked Chronic Granulomatous Disease

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Abstract

Granulibacter bethesdensis is a Gram-negative bacillus described as a pathogen exclusively in patients with chronic granulomatous disease, a phagocytic disorder that impairs the ability to clear catalase-producing organisms. *Granulibacter* usually causes chronic and recurrent lymphadenopathies. We report the fatal case of a 4-year-old boy with chronic granulomatous disease, who presented with sepsis after a few days of abdominal pain and diarrhea.

Keywords

Granulibacter bethesdensis; chronic granulomatous disease

Chronic granulomatous disease (CGD) is a primary immunodeficiency that can be caused by mutations in the proteins that form the nicotinamide adenine dinucleotide phosphate oxidase enzyme complex which result in a phagocyte dysfunction. Affected individuals are at high risk of infections with catalase-producing organisms, that is, *Staphylococcus aureus*, *Burkholderia cepacia*, *Nocardia* and *Aspergillus*.¹ Certain organisms, like *Granulibacter bethesdensis*, have been described as human pathogens exclusively in host with CGD. There is limited information regarding the clinical presentation of *G. bethesdensis*, with most reports describing a chronic and recurrent lymphadenitis. We report the case of a child with CGD, who had a fulminant and fatal infection with this bacterium.

CASE REPORT

A 4-year-old boy with CGD presented to the emergency department with 4 days of diarrhea and fever. Five days before presentation, his mother noted weight loss, whitish plaques on

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the oral mucosa and a fever to 39.6°C. The following day he developed profuse watery diarrhea with intermittent blood as well as diffuse abdominal pain and decreased activity.

He had a history of nonadherence to prophylactic trimethoprim-sulfamethoxazole and voriconazole and intermittent loss to care. His medical history was significant for multiple episodes of pneumonia starting at 7 weeks of life. At 5 months of age, he was admitted for evaluation after 2 weeks of fever. He had a right-sided cervical adenopathy. The bacterial culture from the lymph node was negative, and pathology was reported as nonspecific sinus hyperplasia. He had an elevated sedimentation rate and *Aspergillus* galactomannan antigen. The neutrophil oxidative burst showed no detectable increase in stimulated granulocyte dihydrorhodamine fluorescence, suggestive of CGD, and he was started on trimethoprim/sulfamethoxazole and voriconazole. His mother was found to have 2 neutrophil populations, compatible with a carrier state of X-linked CGD. At 11 months of age, he developed annular plaques on his face, lips and tongue. Biopsy of these lesions showed a granulomatous infiltrate with negative stains for bacteria, viral and fungal infections. These annular lesions persisted for several years. His inflammatory markers remain elevated for almost 2 years and he had intermittent fevers. He took no other medication aside from prophylactic antimicrobials and was fully vaccinated. Family history was significant for an older brother who presented at 4 weeks of age with pneumonia and *Serratia marcescens* sepsis; a very high serum ferritin was noted and hemophagocytosis was demonstrated in his bone marrow. He expired on the second hospital day. Autopsy demonstrated dense histiocytic infiltrations, and cultures grew *Candida lusitanae* and *Serratia marcescens*. Gene tests for known causes of familial hemophagocytic lymphohistiocytosis were negative.

Vital signs on arrival were remarkable for hypothermia (35.3°C), tachycardia (122 bpm), tachypnea (50 bpm) and normal blood pressure (104/70 mm Hg). He was lethargic with mottled skin and cold extremities, and an intraosseous access was required for fluid resuscitation. Initial laboratory results showed a severe metabolic acidosis (venous pH 7.058), acute kidney injury (creatinine 1.4 mg/dL), leukopenia (white blood cell count 3.5 k/ μ L with 66% neutrophils and 13% bands), severe anemia (hemoglobin 7.5 g/dL), thrombocytopenia (platelets 12,000/ μ L) and a normal glucose. The chest x-ray showed a pulmonary infiltrate in the right upper lobe, and he received 1 dose of ceftriaxone before transfer to the pediatric intensive care unit.

Once in the ICU, his temperature decreased further to 34.5°C, his respiration had a Kussmaul breathing pattern and he developed hypotension (90/52 mm Hg). He was unresponsive, peripheral pulses were diminished. He had hematemesis and was bleeding from the nares and oropharynx. His abdomen was soft on examination, and he had no clinical or radiographic signs of obstruction. He was intubated for respiratory failure shortly after arrival to the unit. He was empirically started on broad-spectrum antimicrobials with meropenem, vancomycin and amphotericin B. His course was complicated by disseminated intravascular coagulopathy (prothrombin time 38 seconds with an international normalized ratio (INR) 3.6, activated partial thromboplastin time >200 seconds and fibrinogen <70 mg/dL), worsening metabolic acidosis (pH 6.71, bicarbonate 8 mEq/L), acute hepatitis (aspartate transaminase 669 U/L, alanine transaminase 89 U/L, alkaline phosphatase 107 U/L, total protein 3.8 g/dL, albumin 1.5 g/dL, total bilirubin 1.2 mg/dL, direct bilirubin 1.2

mg/dL) and hypoglycemia (glucose <20 mg/dL). As part of a critical resuscitation effort, he was placed on vasopressors and given multiple units of fresh frozen plasma, packed red blood cells and platelets. Despite these efforts, his hemoglobin decreased to 4.7 g/dL in 4 hours. His abdomen became tender and then rigid. An upper gastrointestinal endoscopy showed no evidence of acute bleeding, and an abdominal ultrasound showed small amount of free fluid and thickened bowel walls. He underwent an emergency decompressive laparotomy and was found to have a severe gastrointestinal bleed. During the surgical procedure, he had a cardiac arrest and expired. The family declined an autopsy. Four days later, all 6 blood culture bottles turned positive for short, nonmotile Gram-negative bacilli. Conventional microbiologic methods and matrix-assisted laser desorption/ionization time of flight mass-spectrometry did not identify the organism, but 16s rRNA analysis (500 pb) showed 100% match with *G. bethesdensis* (GenBank ID NR_043197). Sputum or peritoneal cultures were not sent for analysis.

DISCUSSION

G. bethesdensis is a Gram-negative bacillus that belongs to the family of the Acetobacteraceae. These bacteria can be found worldwide, and some of them can cause infections in immunocompromised individuals. *G. bethesdensis* was identified for the first time in the excised lymph node of a 39-year-old patient with CGD who had several months of extensive necrotizing lymphadenitis despite multiple courses of antibiotics.² *G. bethesdensis* has since been described as having in-vitro resistance to multiple antibiotics, including quinolones, colistin and beta-lactams.³ This bacterium is also able to resist and even multiply in oxygen-dependent and oxygen-independent systems inside the lysosomes of human macrophages despite their acidic environment.⁴

Although it has been reported that 25% of healthy donors and 45% of patients with CGD have a serologic response to *G. bethesdensis*,⁵ it is unclear if this bacterium can cause disease in healthy individuals or persist in a latent form. The primary mechanism of elimination of this organism is through reactive oxygen species production by polymorphonuclear neutrophils.⁶ This represents a challenge for patients with CGD, where mutations in the proteins of the nicotinamide adenine dinucleotide phosphate oxidase enzyme complex result in an inability to generate reactive oxygen species (ROS). The pathogenicity of *G. bethesdensis* in CGD was demonstrated in a mouse model, where CGD mice developed pyogranulomatous abscesses after intraperitoneal inoculation of *G. bethesdensis*, compared with wild-type mice that only developed lymphoid hyperplasia.²

Seven cases of chronic necrotizing lymphadenitis have been reported in 2 different case series, all of them in patients with CGD.^{7,8} The first case was a 39-year-old man with fever and necrotizing axillary and cervical lymphadenitis, treated with doxycycline and meropenem. He had 3 recurrences in 2 years and was finally treated with ceftriaxone and doxycycline for 1 year. The second case was a 36-year-old man with intrathoracic, retroperitoneal, iliac and inguinal lymph nodes and multiple splenic lesions. He received ceftriaxone for 6 weeks followed by trimethoprim/sulfamethoxazole and gamma-interferon. He had recurrence of splenic lesions after 2 years, and, after failing to improve on antibiotics, he required a splenectomy a year later. The third case was a 13-year-old boy with

intrathoracic lymphadenitis, treated with tobramycin and ceftriaxone for 2 and 4 months, respectively, and doxycycline for a year. Two years later, he presented with subcarinal lymphadenitis and finally resolved after treatment with cefdinir for 8 months. The fourth case was a 17-year-old boy who presented with cervical and mediastinal lymphadenitis that worsened during treatment with levofloxacin, but responded to doxycycline. The fifth case was a 37-year-old man with mediastinal and supraclavicular lymphadenitis and liver and spleen lesions. He was initially treated with levofloxacin and linezolid, but the disease worsened during treatment. He responded to a combination of ceftriaxone for 4 months followed by doxycycline and trimethoprim/sulfamethoxazole for almost 6 months.⁷ The sixth case was a 19-year-old man with a tonsillar exudate, who required tonsillectomy and 5 weeks of ceftriaxone, followed by 8 weeks of cefdinir, doxycycline and rifampin. Finally, the seventh case was a 36-year-old man, who presented after 1 year of fever, malaise and fever. He had supraclavicular, axillary, mediastinal, celiac, periaortic, retroperitoneal and mesenteric lymphadenitis, with hepatosplenomegaly. He was treated with ceftriaxone and doxycycline for 15 months with significant improvement but not complete resolution of lymphadenopathy.⁸ These 7 patients had fever and increased inflammatory markers for prolonged periods of time. Interestingly, recurrences of infection were a frequent occurrence even after 2 and 3 years, raising the concern that this bacterium can cause a latent infection.

In this report, we present the case of a 4-year-old boy with severe sepsis. *G. bethesdensis* was cultured in 6 of 6 blood culture bottles. Our patient died of disseminated intravascular coagulopathy and multiorgan failure a few hours after arrival to the hospital. Only 2 other fatal cases have been reported to be associated with this bacterium. The first one was a 10-year-old boy with CGD from Spain who was admitted for fever, diarrhea, vomiting and abdominal pain. He received multiple courses of antibiotics for approximately 2 months. An extensive microbiologic work-up yielded only negative results, except for 2 blood cultures, from which a slow growing Gram-negative coccobacillus was isolated. The bacteria was identified as *G. bethesdensis* by 16s rRNA analysis with a 99.7% match (GenBank ID EF_408914). His clinical course deteriorated over several weeks until he developed multiple organ failure and died.³ The second fatal case was a 16-year-old boy from Portugal, who presented fever, cough and altered mental status. He was found to have bilateral pneumonia and multiple intraparenchymal brain abscesses. The cerebrospinal fluid studies were unremarkable. He was treated with meropenem, ciprofloxacin, amikacin, doxycycline, teicoplanin and voriconazole, eventually recovering. One month later, he was readmitted with fever and focal neurologic examination. Cerebrospinal fluid studies were consistent with meningitis, and *G. bethesdensis* was identified by 16s rRNA analysis with a 99.7% match. The patient died as a consequence of obstructive hydrocephalus and multiorgan failure.⁸ It was postulated that this slight genetic difference may represent some regional variability, with a consequent different clinical presentation and a more invasive organism.^{7,8} Although the 16s rRNA analysis identified the bacteria from our patient in New York as *G. bethesdensis* (GenBank ID NR_043197), the specimen was not longer available to confirm this result by reanalyzing it using 1500 bp.

Only a small proportion of patients with CGD may develop clinical symptoms, but it is important to recognize that the spectrum of severity of disease related to *G. bethesdensis*

seems to be extremely broad, ranging from asymptomatic or subclinical infections, to chronic and recurrent necrotizing lymphadenopathies, to severe sepsis and death.

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