

CHRONIC GRANULOMATOUS DISEASE: A CASE REPORT

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Abstract: Chronic granulomatous disease is one form of the phagocyte function disorder. Unlike most patients with chronic granulomatous disease who develop signs and symptoms of chronic and recurrent pyogenic infections during the first 2 years of life, patients with mild forms of the disease may not present until the teenage years or even adulthood. Thus, the diagnosis in these mild-form patients is often delayed. This paper describes a patient with the mild form of chronic granulomatous disease. A 7-year-old boy was admitted to our ward with intermittent high fever and a left neck mass present for about 1 week. He had a history of persistent infection in the bilateral lower face lasting for about 1 year during his fourth year of life. Family history was unremarkable except that the patient's elder sister had a history of persistent oral mucosal wound infection for about 1 year during the fifth year of life. On physical examination, there were scars over the patient's bilateral lower face. Bacterial culture of pus drained from the neck mass revealed *Burkholderia cepacia*, a rare species in patients without immunodeficiency. A series of antibiotics, including oxacillin, clindamycin, and piperacillin, was given, and two incision operations for drainage and debridement were performed. The neck mass resolved completely about 1.5 months later. This history indicated that the patient might have chronic granulomatous disease. A definite absence of superoxide activity in the patient's granulocytes detected by chemiluminescence and nitroblue tetrazolium dye test confirmed this diagnosis.

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When a patient presents with recurrent infection of the skin, mucosa, lymph nodes, and lung caused by catalase-positive microorganisms, as well as poor wound healing with abscesses and granuloma formation, chronic granulomatous disease (CGD) should be suspected. CGD is the most common of the inherited disorders of phagocytic function and is characterized by susceptibility to recurrent severe infection associated with dysfunctional nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. The intracellular killing function of the patient's phagocytic cells is defective but other phagocytic cell, B-cell, and T-cell functions are normal. The lung, skin, lymph nodes, liver, spleen, and bone are the most commonly affected organs and often present with abscess or granuloma.

Case Report

A 7-year-old boy was admitted to our ward because of intermittent fever and a neck mass for about 7 days. Before admission, he had been sent to several medical clinics and received medication but the symptoms had persisted. On physical examination, a neck mass about 2.5 x 2 cm with prominent tenderness was found over the left submandibular region, and some scars were obvious over the bilateral lower face. His body temperature was around 38°C to 39°C. History revealed recurrent wound infection of the bilateral lower face throughout his fourth year of life. The hemogram revealed normal white cell counts (9,590/ μ L) and differential counts (neutrophil/lymphocyte/monocyte ratio, 75/11/13). The

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C-reactive protein concentration was initially raised (8.86 mg/dL). There was no particular birth, trauma, or family history. After admission, intravenous oxacillin was prescribed under the diagnosis of neck lymphadenitis, but intermittent high fever and the tender neck mass persisted. On day 12, the antibiotic regimen was shifted to clindamycin and gentamicin, but the symptoms worsened. Computerized tomographic (CT) scan revealed a central low-density lesion in the inferior portion of the left parotid space about 3 x 3 cm in size (Fig. 1). On day 14, pus-like fluid without a foul smell was found by sonoguided fine needle aspiration, and Gram stain revealed gram-negative rods. Culture of the pus showed *Burkholderia cepacia*. Due to persistent symptoms and the results of pus culture, piperacillin was administered and an incision was made for drainage by an ENT specialist. One week later, the patient's general condition improved and fever resolved, but poor wound healing was still noted. On day 22, he underwent debridement and delayed primary suture, and little discharge and granulation tissue were noted over the wound area. He was then discharged and received oral antibiotics at our outpatient department. The wound was completely healed 2 weeks after discharge.

Underlying CGD was strongly suspected because of the unusual microorganism cultured from pus and poor wound healing with granulation tissue. The patient's elder sister also had a history of persistent oral mucosal wound infection with poor response to antibiotic treatment for about 1 year during her fifth year of life, so we also screened the patient's father, mother, and elder sister. For nitroblue tetrazolium (NBT; Sigma Chemical Co, St. Louis, MO, USA) dye test, the neutrophils of the patient and the control group (patient's father, mother, and sister and one control case) were suspended at a concentration of 2×10^6 /mL in Hanks balanced salt solution (HBSS; GIBCO, Grand Island, NY, USA) and were stimulated using 1 μ g/mL phorbol myristyl acetate (PMA; Sigma). All samples were incubated with NBT at 37°C for 15 minutes and then spread on slides using a cytospin

machine. The slides were examined under a microscope. The soluble, yellow NBT dye is reduced in the presence of superoxide to the blue, insoluble product formazan [1]. The test revealed no blue color change in the patient's neutrophils after stimulation with PMA (Fig. 2). Granulocytes were prepared for chemiluminescence assay from venous blood collected in heparin and were suspended in gel-HBSS to a final concentration of 2.5×10^4 cells/mL. PMA and gel-HBSS were added to each scintillation vial (4.5 mL), including one control sample and one sample each from the patient, father, mother, and sister, which were placed in a fluorometer for at least 20 minutes before assay to record the background chemiluminescence. The granulocyte suspension was added to the vials and counted sequentially for 1 hour [2]. Absence of superoxide generation by neutrophils activated by PMA on the chemiluminescence assay confirmed the diagnosis of CGD (Fig. 3).

The NBT test revealed a well-stained blue color on neutrophils for his mother, a poor-stained blue color for his father, and absence of blue stain for his sister. Similar results were found on the chemiluminescence assay (Fig. 3).

Discussion

CGD is the most common of the inherited disorders of phagocyte function. It is inherited as either an X-linked or an autosomal recessive disorder. There are four different genetic forms based on different biochemical abnormalities and patterns of inheritance. The human neutrophil NADPH oxidase complex consists of two cytochrome B membrane subunits, an α -subunit (22 kD) and a β -subunit (91 kD), and two cytosolic cofactors (67 and 47 kD), which are required for the

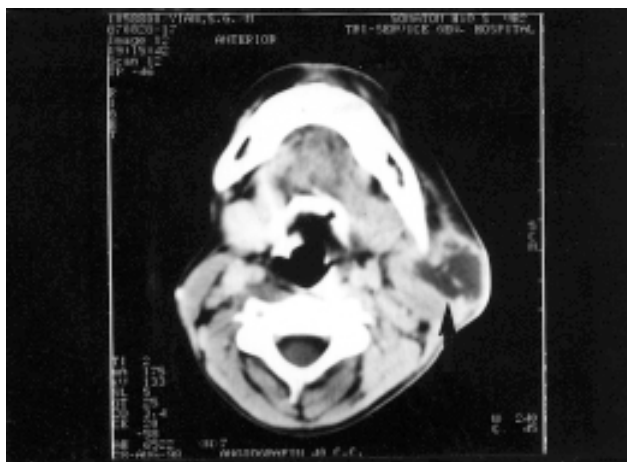


Fig. 1. On computerized tomographic scan, a central low-density lesion in the inferior portion of the left parotid space (arrow), about 3 x 3 cm in size, is evident.

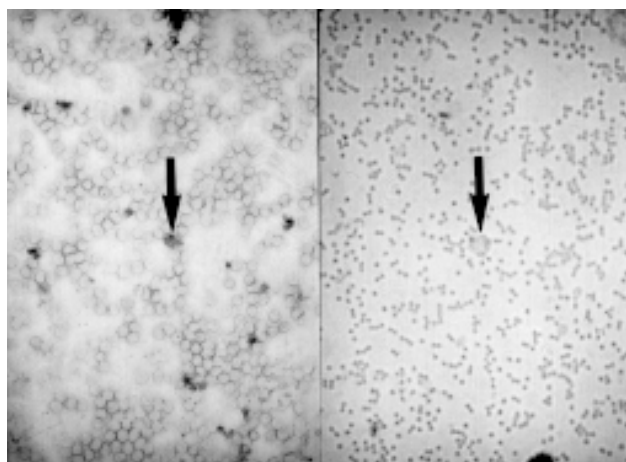


Fig. 2. Nitroblue tetrazolium slide test reveals blue-stained neutrophils in the positive control (left) and no blue color change in the patient's neutrophils (right) after stimulation by phorbol myristyl acetate.

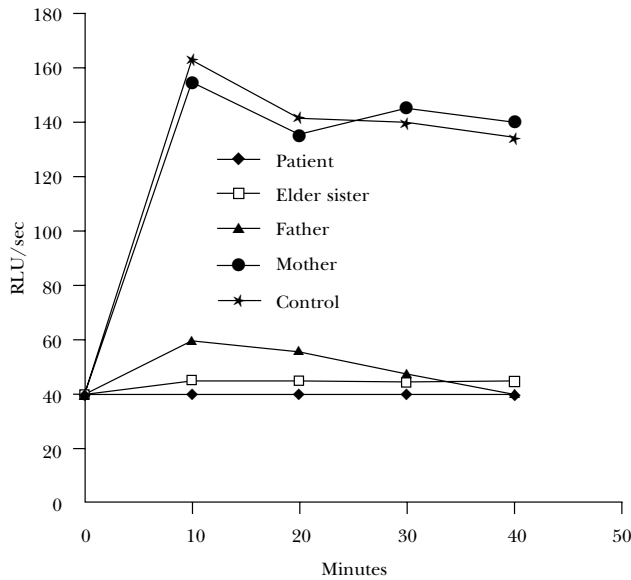


Fig. 3. Chemiluminescence assay shows no superoxide generation in the patient's neutrophils activated by phorbol myristyl acetate.

respiratory burst. Mutations in the gene for the 91-kD subunit of cytochrome B account for all cases of X-linked CGD and about 60% of all CGD patients. The remaining CGD patients have autosomal recessive disorders with defects in the 22-kD subunit or the 67-kD and 47-kD cofactors [3–5]. The defective respiratory burst that follows within seconds after phagocytes are activated make phagocytes of CGD patients ineffective against catalase-positive microbes.

In the family of our patient, the inheritance pattern may have been autosomal dominant because the disease occurred in the father, the patient, and the patient's elder sister, but not in the mother. There was a milder form of CGD in the family, seen in the milder clinical symptoms and late onset. However, we cannot confirm the exact inheritance pattern unless we perform further genetic analysis.

Most patients with CGD have at least one unusual incident of susceptibility to serious infections before their second birthday. Milder forms of the disease have been described with onset occurring in the teenage years or even in adulthood. Patients usually manifest a typical response to infection with fever, and an appropriate localized inflammatory response results in granulomatous lesions characterized by collections of phagocytes and giant cells often containing pigmented lipid material. The regions primarily involved in CGD are those that receive constant challenge from bacteria, such as the skin, lung, and perianal tissue, as in other types of phagocytic disorder [6]. Abscess formation is the hallmark of CGD and may occur in any organ of the body, particularly in the liver, spleen, lung, and bones

[7]. Most infections are caused by a relatively limited spectrum of catalase-positive microbes, the most common of which are *Staphylococcus aureus*, *Serratia marcescens*, and *Escherichia coli*, and *Pseudomonas* and *Aspergillus* species [6, 8].

Subcutaneous abscesses, recurrent skin furunculosis, eczematoid dermatitis, and impetigo around orifices may be presenting manifestations involving the integumentary system. Pulmonary disorders occur in nearly all children with CGD and include recurrent pneumonia, hilar lymphadenopathy, empyema, and lung abscess. Chest radiography may show reticulonodular densities, which represent areas of granuloma. Lymphadenopathy occurs in almost all cases and requires incision and drainage. Granuloma formation may lead to obstruction of the esophageal outlet, pylorus, or urethra, a fairly common manifestation of CGD.

The NBT slide test is sensitive and specific for the diagnosis of CGD [1, 9]. Neutrophils from CGD patients generate little or no superoxide, and the NBT test in these patients is negative; that is, neutrophils from CGD patients do not contain formazan because NBT remains soluble and colorless in the absence of superoxide. A chemiluminescence assay is a sensitive but less specific indicator of superoxide generation. The assay is a useful screening test for CGD because neutrophils from CGD generate essentially no chemiluminescence [10].

The primary aim of therapy for patients with CGD is prevention and cure of infected lesions. Long-term trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis appears to increase the duration of infection-free periods and is now standard therapy [11]. Infectious lesions should be managed aggressively by isolating the causative microbe, instituting appropriate intravenous antibiotics, and using short-term (average 1 week) granulocyte transfusions selectively to achieve control of persistent infections, especially those with gram-negative bacteria [12]. A large multicenter study revealed that γ -interferon administered subcutaneously at a dose of 0.05 mg/m² three times per week reduced the number of new infections and improved the response to existing infections [13]. Bone marrow transplantation has been accomplished in patients with CGD. Patients with CGD are ideal candidates for gene therapy because the biochemical defect is known and the involved genes have been cloned [14].

B. cepacia, a catalase-producing gram-negative saprophyte, is an uncommon pathogen in human disease, except in immunocompromised patients. *B. cepacia* is an important and virulent pathogen in patients with CGD and may be difficult to culture. Since *B. cepacia* are often highly resistant to a wide range of

antibiotics and may be difficult to identify early, the initial empiric antimicrobial regimen for invasive infection in patients with CGD should include ceftazidime, high-dose TMP-SMZ, or a similar agent with predictably broad antimicrobial activity [15].

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