Megan Kilvert, MD,* Ashley Roberts, MD, MEd,† Kyla J. Hildebrand, MD, MScCH‡

*Department of Pediatrics, †Department of Infectious Diseases, and ‡Department of Clinical Allergy and Immunology, BC Children’s Hospital, Vancouver, British Columbia, Canada

PRESENTATION

An 8-month-old unimmunized fraternal-twin boy, born at term, presents to the hospital with fever, cough, rhinorrhea, and right-sided neck swelling with drainage. On history, the fever and neck swelling began 7 weeks earlier, at which time he presented to a rural hospital where ultrasonography confirmed a cervical lymph node abscess. The abscess spontaneously drained and was positive for Staphylococcus aureus. He was treated with intravenous (IV) cefotaxime for 6 days, followed by 14 days of oral cefuroxime. The fever resolved completely after 4 days of treatment, but the neck lesion continued to drain during the next 7 weeks. One week before his presentation to our hospital, he had recurrence of daily fever (to 104°F [40°C]) associated with neck drainage, cough, and rhinorrhea. Further history reveals an otherwise healthy infant boy with normal energy, appetite, and appropriate development. There is no history of weight loss, night sweats, or risk factors for tuberculosis.

The boy is febrile (to 103.1°F [39.5°C]), with otherwise normal vital signs. Growth plots on the 25th percentile for weight and length. The site of previous lymphadenitis is nontender, with distorted subcutaneous tissue. There is no other lymphadenopathy. Results of abdominal and respiratory examinations are normal.

Initial laboratory evaluation reveals a white blood cell count of 38,000/µL (38×10^9/L) (neutrophils, 25,000/µL [25×10^9/L]; and lymphocytes, 7,740/µL [7.74×10^9/L]). The C-reactive protein level is 84.0 mg/L (800.0 nmol/L).

Broad-spectrum IV antibiotic drug therapy is initiated with vancomycin and cefotaxime, and he is admitted to the hospital for further evaluation. Ultrasonography and computed tomographic scans of the neck find no fluid collection. Results of chest radiographs, bacterial and fungal cultures of blood and urine samples, and respiratory virology panels are negative. Fever persists for the next 12 days despite broadening IV antibiotic drug therapy to include anaerobic and atypical mycobacterium coverage with metronidazole and azithromycin, respectively. Infectious disease and immunology services are notified, the differential diagnosis is broadened, and a single test confirms the diagnosis.

The Case Discussion and Suggested Readings appear with the online version of this article at http://pedsinreview.aappublications.org/content/38/3/141.
**DISCUSSION**

Results of the dihydrorhodamine 123 (DHR) assay were abnormal, consistent with the diagnosis of chronic granulomatous disease (CGD). Ancillary investigations, including abdominal ultrasonography, revealed splenic microabscesses that were thought to be the cause of his fever, although they were not amenable to drainage based on their size and location. Results of a bone scan and a computed tomographic scan of the chest were normal. Antibiotic treatment with IV cloxacillin, directed at *S. aureus*, was started. In consultation with the infectious diseases and immunology teams, he was treated with trimethoprim-sulfamethoxazole (TMP-SMX) and ciprofloxacin. He defervesced and was discharged from the hospital on treatment doses of ciprofloxacin and TMP-SMX for 4 weeks, followed by prophylactic doses of TMP-SMX to prevent *Pneumocystis jirovecii* pneumonia and itraconazole to prevent fungal infections.

Our patient had no family history of immunodeficiency. His mother’s DHR assay demonstrated 50% activity, confirming X-linked inheritance. She had no history of infections. The patient’s fraternal twin was tested and unaffected. His maternal grandmother had normal DHR assay findings, suggesting a de novo mutation in the mother. Evaluation for hematopoietic stem cell transplant was initiated.

**The Condition**

Chronic granulomatous disease is a primary immunodeficiency caused by a disorder of the nicotinamide adenine dinucleotide phosphate oxidase system. It was first described in the 1950s and initially termed fatal granulomatous disease of childhood. It results in phagocyte functional defects and subsequent infections with bacterial and fungal pathogens. The host is particularly susceptible to infection from catalase-positive organisms because phagocytes lack the ability to destroy these organisms. The main pathogen implicated is *S. aureus*, although other organisms frequently causing infection include *Serratia marcescens*, *Burkholderia cepacia*, *Nocardia*, and *Aspergillus* species.

Chronic granulomatous disease is a rare disorder affecting approximately 1 in 250,000 individuals. It is inherited by one of four gene defects: one X-linked and three autosomal recessive in inheritance. The clinical presentation is variable; however, infections and granulomatous lesions are usually the first manifestations of disease. Common sites of infection include the lymph nodes, lungs, skin, bones, and liver. The age at presentation and severity of infections are variable.

The diagnosis of CGD can be made using either the nitroblue tetrazolium (NBT) test or the DHR assay. Presently, the DHR assay is considered the preferred diagnostic test for CGD. The NBT test is the older of the two tests and is limited by its subjectivity and reliance on an experienced technician to assess a color change from yellow to blue under microscopy on oxidation of neutrophils. As a result, the NBT test has a high false-negative rate. The DHR assay is a quantitative assay that uses flow cytometry to measure the fluorescence produced from the oxidative activity of neutrophils on activation. The DHR is a more sensitive test and allows a clinician to determine the inheritance pattern (X-linked versus autosomal recessive) and detect carrier status for CGD. This is particularly helpful for clinicians in practice settings where genetic testing may be difficult to organize or fund, possibly resulting in delay in treatment.

**Management**

Hematopoietic stem cell transplant is the only known cure for CGD. Supportive management includes prophylaxis of infections with oral TMP-SMX and itraconazole. Fevers require prompt evaluation, and cultures should be obtained immediately. Patients with CGD with fever without an obvious focus should undergo imaging studies to assess for abscesses in deep-seated locations, such as the lungs, liver, and bones. Often, empirical treatment with broad-spectrum parenteral antibiotic drugs is required.

**Lessons for the Clinician**

- The diagnosis of a primary immunodeficiency must be considered in the setting of unexplained, persistent fever and/or recurrent, invasive, or unusual infections that do not respond to usual therapy, even if the family history is negative for immunodeficiency.
- Once the diagnosis of chronic granulomatous disease (CGD) has been made, it is important to expand the search for sites of disseminated infection to ensure that appropriate antimicrobial drug therapy is initiated. In addition, prophylactic antimicrobial and antifungal drug treatments should be initiated to prevent opportunistic infections.

**Suggested Readings**


Case 3: Persistent Fever in an 8-month-old Boy
Megan Kilvert, Ashley Roberts and Kyla J. Hildebrand
Pediatrics in Review 2017;38;141
DOI: 10.1542/pir.2015-0145

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pedsinreview.aappublications.org/content/38/3/141