

Articulation infection in patient with chronic granulomatous disease

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To the Editor: A 7-year-old boy underwent surgery at the West China Hospital in Chengdu, China, because of developing a mass in the left distal forearm over 1 month. A biopsy from the surgery resulted in a diagnosis of histiocytosis, with suspected yellow granulomas. The patient also suffered from poor wound healing with purulent secretions. Two months post-operation, the patient was re-admitted to the hospital due to suffer a painful swelling in the left ankle over 10 days. Color Doppler ultrasound examination revealed a left ankle joint synovitis and a left posterior tibialis fasciitis. The patient had a history of recurrent respiratory infections since infancy, for which he had received anti-tuberculosis therapy. However, there was no record of acid-fast bacilli being isolated from the patient. There was also no family history of a similar illness among his siblings or parents. In addition to the respiratory infections, the patient also underwent open drainage of abscesses in the posterior ears and posterior cervical lymph nodes at the age of 5 and the perianus at the age of 6. He was frequently prescribed two- or three-fold antibiotics, such as oxycefazid, vancomycin, and imipenem, because of his recurring multi-site infectious lesions.

Upon re-admission, the patient's vital signs were as follows: the temperature was 38°C, blood pressure was 128/83 mmHg, pulse rate was 132 beats per minute, respiratory rate was 22 per min, blood white blood cell count was 11,200 μ L, platelet count was 287,000 μ L, erythrocyte sedimentation rate was 85 mm/h at the end of the first hour, serum pro-calcitonin level was 0.38 ng/mL, and serum c-reactive protein level was 118 mg/L. The chest computed tomography revealed fibrotic lesions in both lungs and an enlarged liver. X-ray radiography of the left ankle joint showed massive swelling in the left ankle and the left plantar soft tissue. Pathology examination of the distal left radius and left ankle joint synovial membrane revealed granulomatitis with focal necrosis. Notably, no

positive *Mycobacterium tuberculosis* was found in the acid-fast staining and no *M. tuberculosis* DNA fragments were detected from quantitative polymerase chain reaction analysis, which was made to detect *M. tuberculosis*. Diagnostic puncture detected pus, indicating the infection caused due to *Serratia marcescens*. The pus was surgically drained to prevent further infection. Since the patient had a history of multiple infections, congenital immunodeficiency diseases, or malignant histiocytosis was considered. The patient was screened for gene-deficient diseases and related immune system tests were performed. Peripheral blood was extracted after obtaining informed consent from the patient's parents. Upon DNA extraction, protein-coding exome enrichment was performed using 429,826 individually synthesized and quality-controlled probes, which targeted 39 Mb of protein-coding regions (19,396 genes) of the human genome and covered 51 Mb of end-to-end tiled probe space. Finally, high-throughput sequencing was performed, where >99% of the target sequences were sequenced before bioinformatics analysis. The trio whole-exome sequencing test showed *CYBB* chrX: 37653064 c.483 + 1 (IV S5) G > T, as shown in Figure 1. The c.483 + 1 G > T splice site variant in the *CYBB* gene had been previously reported in association with chronic granulomatous disease (CGD).^[1] This pathogenic variant was shown to destroy the canonical splice donor site in intron 5, thereby resulting in a frameshift of codon 112 to codon 133.^[1] Based on the genetic test results, the patient was diagnosed with X-linked CGD (XL-CGD). His current treatment regime includes anti-infective treatment and he is awaiting stem cell transplantation.

CGD is a rare congenital immunodeficiency disorder that affects phagocytes and lymphocytic cells. In patients with CGD, a defective reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase fails to produce superoxide anion, a chemical necessary for the killing of bacterial and fungal microorganisms. This rare condition has an

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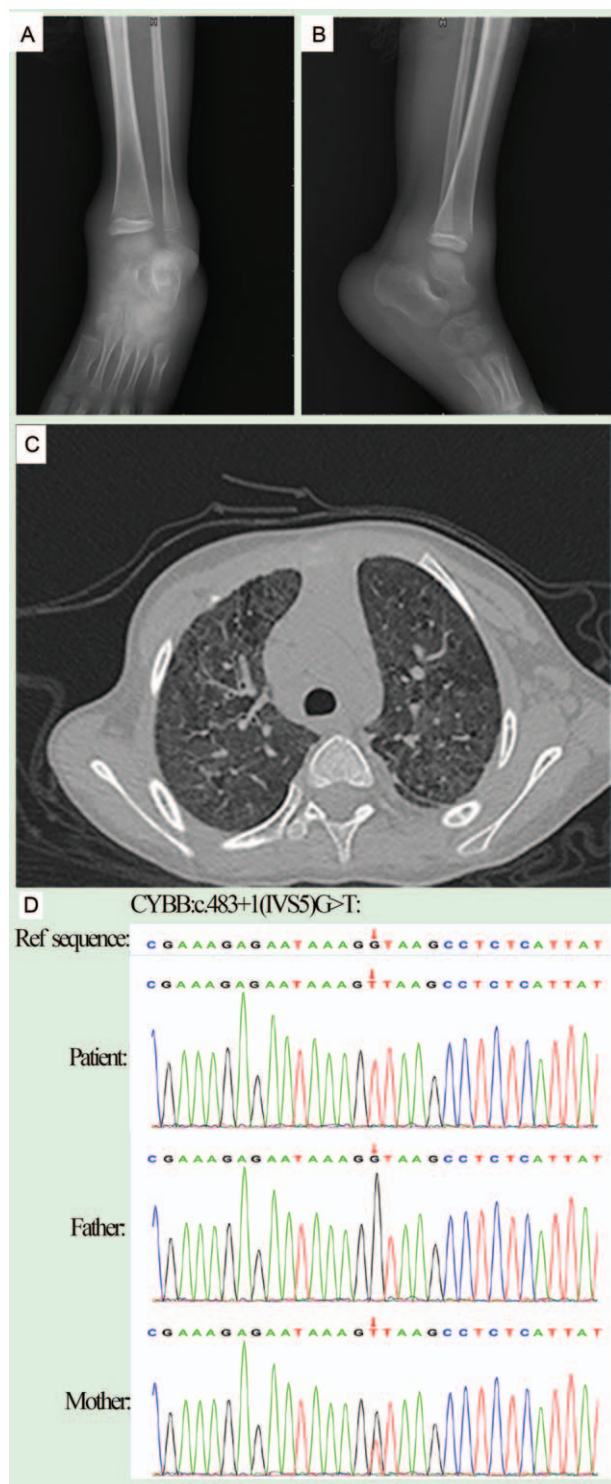


Figure 1: Profile of a 7-year-old patient with CGD. (A) Orthotopic radiography of the left ankle joint indicates left ankle soft tissue swelling. (B) Lateral radiography of the left ankle joint indicates left plantar soft tissue swelling. (C) Chest computed tomography indicates fibrotic lesions in the lungs. (D) Gene sequencing of the patient’s DNA reveals a mutation in the *CYBB* gene: c.483 + 1 (IV S5) G > T. CGD: Chronic granulomatous disease.

is located on the short arm of the X chromosome (Xp21.1-p11.4). The *CYBB* gene encodes gp91^{phox}, which is also called Nox2. Nox2 combines with four other subunits to form NADPH oxidase. CGD is usually diagnosed early in life and is characterized by severe and recurring bacterial/fungal infections in the lungs, skin, soft tissues, liver, and lymph nodes.^[3] There are also reports of CGD affecting the skeletal system. So far, five cases of osteomyelitis arising from CGD have been published, but none of them have reported infectious arthritis. This study rarely reports a diagnosis of XL-CGD using whole exon sequencing, along with a case of infectious arthritis in the left ankle. Infectious arthritis can be categorized as infectious or chronic infectious based on a combination of microorganismal and host factors. For example, age, genetic susceptibility, sex, the presence of co-morbidities, and joint conditions are some of the key host factors. Conversely, purulent bacteria and viruses are mostly responsible for acute infectious arthritis, whereas mycobacteria and fungi cause chronic arthritis.^[4] The patient, in this study, had a genetic mutation that was caused by a G > T mutation in the *CYBB* gene, and his infectious arthritis was bacterial. For children with a history of unexplained repeated infections and joint swelling, the possibility of infectious arthritis should be considered, and the role of genetic mutation needs to be further investigated. Additionally, skeletal system infections can easily be misdiagnosed as a bone tumor; therefore, caution must be taken to perform all necessary examinations. To rule out CGD, the procedure which should be followed is to measure residual NADPH oxidase activity by examining oxygen consumption and superoxide or hydrogen peroxide production.^[5] On the other hand, in CGD patients, etiology can be discovered exclusively through gene sequencing. Knowledge of genetic mutations can help in the diagnosis of carriers and assist in genetic counseling and prenatal screening. Although genetic testing is an expensive procedure, it will be effective in guiding the patient’s and his parents’ future procreation. Therefore, it should be recommended clinically.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient and patient’s guardians have given their consent for their images and other clinical information to be reported in the article. The patient and patient’s guardians understand that their names and initials will not be published and due efforts will be made to conceal the identity of the patient, although anonymity cannot be guaranteed.

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Conflicts of interest

None.

incidence of 1 in 200,000 to 250,000 live births in the United States and 1 in 160,000 to 1,000,000 live births in other countries.^[2] Previous studies have suggested that the most common cause of CGD is a defect in the *CYBB* gene, which

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