

# New Diagnosis of X-Linked Agammaglobulinemia Presenting as Multi-Focal Acute Pseudomonas Osteomyelitis and Septic Arthritis in a 16-Month Old Boy: A Case Report

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## ABSTRACT

A previously healthy 16-month-old boy presented with 5 days of fever, a limp favoring his right side, and swelling and erythema of the dorsal left foot and left great toe. Contrasted magnetic resonance imaging revealed septic arthritis of the left knee, the interphalangeal joint of the left great toe, and the left subtalar and ankle joints. He had osteomyelitis of the left talus and intraosseous abscess formation in the left calcaneus. Cultures of the blood, left knee synovial fluid, and abscess fluid all showed growth of *Pseudomonas aeruginosa*. He was subsequently diagnosed with X-linked agammaglobulinemia with a novel mutation in the Bruton's tyrosine kinase gene. He had a promising recovery after intravenous immune globulin and antimicrobial therapy. Unusually severe infections in children, particularly with atypical organisms, should prompt suspicion of an underlying immunodeficiency.

**Keywords:** Osteomyelitis, *Pseudomonas Aeruginosa*, X-linked Agammaglobulinemia

## INTRODUCTION

Osteoarticular infections in otherwise healthy children are typically caused by a limited number of pathogens, most notably *Staphylococcus aureus*.<sup>1</sup> Pseudomonas osteoarticular infections are rare and primarily limited to individuals with pre-existing risk factors (eg, postoperative nosocomial infections).<sup>2</sup> Primary immunodeficiency disorders, such as X-linked agammaglobulinemia, may present with atypical pathogens. However, to our knowledge, pseudomonas osteoarticular infections have not been previously described with this condition.

## CASE REPORT

A previously healthy, fully-immunized, 16-month-old, Native American boy presented to a hospital in Northern New Mexico with a 5-day fever of up to 103°, anorexia, and irritability. Two days into his fever, his family noted swelling and redness over his left foot's dorsum and left great toe, with a worsening limp and unwillingness to bend his left knee. He had undergone drainage of a paronychia of his left great toe 2 months before admission, which never fully healed. He also received five courses of antimicrobial therapy with three different antibiotics for recurrent acute otitis media in the 3 months before admission. Thrush was noted at the time of presentation to the emergency department. Blood cultures from admission grew *Pseudomonas aeruginosa*, which prompted a transfer to our facility.

His initial laboratory investigations revealed a white blood cell count of  $25.5 \times 10^3$  cells/ $\mu$ L. A C-reactive protein level was 16.3 mg/dL, with an erythrocyte sedimentation rate of 55 mm per hour. Plain films of the lower extremities showed diffuse soft-tissue swelling. Over the first 4 days of his hospitalization, his blood cultures grew *Pseudomonas aeruginosa*. A contrasted magnetic resonance image (MRI) of the lower extremities revealed synovial tissue inflammation in the left knee and the interphalangeal joint of the left great toe, bilateral quadriceps myositis, and a 2.0 x 1.0 x 1.5 cm soft-tissue abscess adjacent to the left tibia. The patient underwent arthrotomy of the left knee and the interphalangeal joint of the left great toe, with drainage of the peri-tibial abscess. Intraoperative cultures of the synovial fluid from the left knee and the abscess grew *Pseudomonas aeruginosa*. He began therapy with cefepime.

An immunological evaluation demonstrated undetectable antibody responses to tetanus, pneumococcal, and diphtheria immunization, along with an undetectable response to toll-like receptor-three stimulation. His CD3-19+ level was 0.0% (normal range, 11.0% - 45.0%), in addition to low levels of IgG (155 mg/dL; normal range, 413 - 1200 mg/dL). DNA sequencing of the Bruton's Tyrosine Kinase (BTK) gene revealed a novel mutation with a six-base pair deletion in exon 11, consistent with X-linked agammaglobulinemia.

Due to persistent fevers 2 weeks into his hospitalization, a repeat contrasted MRI of the lower extremities was performed. It revealed osteomyelitis of the left talus and left calcaneus, a 1.0 cm abscess of the proximal right calf, and new septic arthritis in the left ankle and subtalar joints (Figures 1 and 2). He underwent operative drainage of these sites 2 days later.

The patient was admitted to the hospital for 73 days. He completed 134 days of total anti-pseudomonal therapy, with 69 days of parenteral therapy and 2 months of oral ciprofloxacin. He received intravenous immune globulin infusions every 3 weeks during his hospital stay, which continued after discharge. His IgG

levels increased to 521 mg/dL (normal range, 413 - 1200 mg/dL) 3 weeks after instituting this therapy.

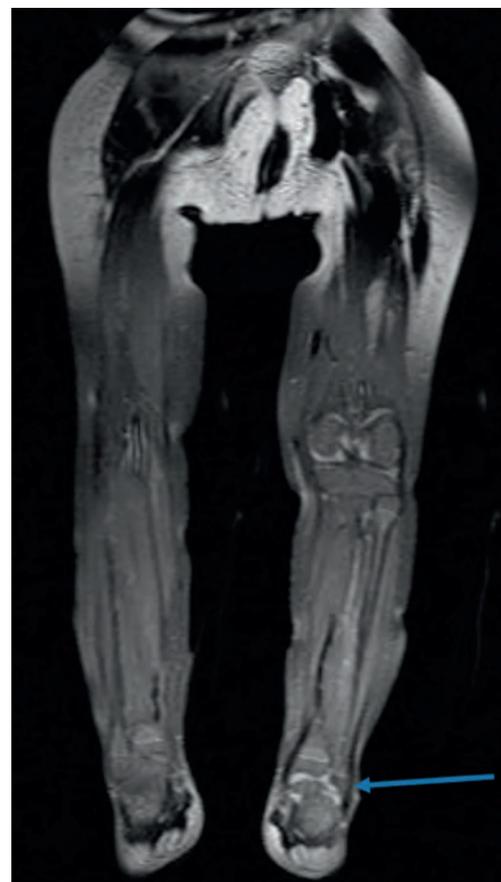
No leg-length discrepancy was present on follow-up imaging 10 months after his hospitalization. The patient made a good recovery with no orthopaedic concerns 7 years after his initial diagnosis.

## DISCUSSION

X-linked agammaglobulinemia is caused by a mutation in the BTK gene on the long arm of the X-chromosome, which results in a near absence of mature B lymphocytes in circulation and produces a lack of circulating antibodies.<sup>3</sup> Approximately 15.0% to 20.0% of mutations in the BTK gene arise de novo.<sup>3,4</sup> Given the mode of inheritance, the onset is almost entirely in young boys, who may present with recurrent bacterial infections. The onset typically occurs before the patient's first birthday when transplacentally transferred antibody levels decline.<sup>3-5</sup> Children with family histories of this disorder have a mean age of diagnosis of 2.6 years. However, large registries of patients with this disorder have shown that patients without a family history of X-linked agammaglobulinemia typically have a delayed diagnosis, with a mean age of diagnosis of 5.4 years.<sup>6</sup> The absence of complete ethnicity



**Figure 1.** Magnetic resonance image 2 weeks into the patient's hospital stay showing diffusion-weighted abnormalities in the left calcaneus consistent with osteomyelitis (red arrow) and an abscess formation in the proximal right calf (blue arrow).



**Figure 2.** Contrasted magnetic resonance image 2 weeks into the hospital stay showing enhancement of the tibio-talar joint concerning for septic arthritis (blue arrow).

data in many data registries may also lead to an underestimation of the prevalence of this disease in underrepresented minorities, such as our patient.<sup>6</sup>

Osteoarticular infections are rarely reported in patients with X-linked agammaglobulinemia.<sup>4,6,7</sup> *Pseudomonas* has been described in patients with X-linked agammaglobulinemia presenting with sepsis, though to our knowledge, it has not been described as an agent of osteoarticular infections before.<sup>4,6</sup>

Treating X-linked agammaglobulinemia consists of replacing antibodies with intravenous immune globulin every 3 to 4 weeks. Using intravenous immune globulin has had a profound effect on mortality, with mortality rates now less than or equal to 1.0%, compared with historical rates of approximately 25.0%.<sup>5</sup> Daily prophylaxis with trimethoprim-sulfamethoxazole may also help prevent infections with bacterial organisms, though data on this is inconclusive.<sup>3,5</sup>

Several features of our case increased suspicion of an immune deficiency. The patient had a history of recurrent acute otitis media, reports of a poorly healing paronychia despite adequate drainage, and history of thrush. He presented with bilateral leg involvement and developed septic arthritis in four joints and concurrent osteomyelitis. Though the involvement of multiple joints and bones may occur in the setting of certain pathogens (most notably disseminated disease with *Staphylococcus aureus*), such a presentation is atypical for an osteoarticular infection in an immunocompetent child.<sup>18</sup> Lastly, the organism involved (*Pseudomonas aeruginosa*) was highly unusual for a community-associated osteoarticular infection in a presumably otherwise healthy child. Osteoarticular infection with this organism is essentially confined to rare case reports.<sup>2,9</sup> Thus, these findings should raise suspicion of a primary immune deficiency. It is possible that the frequent use of antimicrobial therapy may have selected for colonization with *Pseudomonas*, with the poorly healing paronychia serving as the nidus of infection.

Surgeons and medical providers caring for children with osteoarticular infections should be aware of clinical presentations that may herald an undiagnosed, underlying immunodeficiency. They should recognize that such patients may require more aggressive medical and surgical treatment.

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