

CASE REPORT

Pediatrics

Streptococcal pneumonia meningitis as an initial presentation of X-linked agammaglobulinemia: A case report and discussion

Daniel Kadden MD | Grace Fowler BS, BM | Elissa Engel MD | Casey Logan MD |
 Kalyani Marathe MD, MPH | Craig Gosdin MD, MSHA

UC College of Medicine, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA

Correspondence

Daniel Kadden, MD, UC College of Medicine, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA.
 Email: daniel.kadden@cchmc.org

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Abstract

X-linked agammaglobulinemia (XLA) is a primary immunodeficiency caused by mutations in the gene for Bruton's tyrosine kinase (*Btk*), with affected males most commonly presenting with recurrent bacterial infections during the first few years of life. Here we present a 17-month-old male with a chief complaint of worsening rash and fever, whose history of streptococcal pneumonia meningitis at 5 months of age prompted suspicion for an underlying immunodeficiency and subsequent diagnosis of XLA. Bacterial meningitis is a rare initial presentation of XLA, and therefore physicians may easily overlook any underlying immunodeficiency. Prompt workup for immunodeficiency should be initiated in any vaccinated patient with a history of pneumococcal meningitis outside of the newborn period. Further discussion surrounding the various presentations of XLA, their related clinical manifestations and laboratory findings, and the importance of thorough chart review may encourage earlier diagnosis and initiation of treatment of this disease.

KEYWORDS

absolute neutrophil count, bacterial meningitis, Bruton's tyrosine kinase, ecthyma gangrenosum, *Staphylococcus aureus*, X-linked agammaglobulinemia

1 | NARRATIVE

A 17-month-old fully immunized male with a history of *Streptococcus pneumoniae* meningitis at age 5 months and subsequent cochlear implants presented to the emergency department with complaint of fever to 100.6°F, cough, nasal congestion, and worsening "boils." Symptoms began 5 days before presentation with the onset of red spots on his legs, abdomen, and buttock area. Per mother, these lesions would "blister and boil," followed by the centers of each spot turning black. He was seen at an urgent care and prescribed a course of Bactrim and Bactroban ointment. However, the lesions worsened in the following days.

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In the emergency department (ED), he had multiple, scattered vesicular and necrotic lesions with surrounding erythema involving his legs, abdomen, and back (Figure 1). He was otherwise well appearing with appropriate vital signs for age. Of note, a complete blood count (CBC) at this time showed an absolute neutrophil count (ANC) of 0, white blood cell (WBC) count of 7.6, hemoglobin of 10.3, and platelets at 300. Lymphocytes, monocytes, and basophils were all within normal limits.

Chart review revealed the cause of the patient's meningitis and bacteremia at 5 months of age to be *Streptococcal pneumoniae serotype 19F*, a strain covered in the Prevnar vaccine (PCV13), which the patient previously received on schedule. He was treated with a 14-day course of ceftriaxone and recovered without complication other than hearing loss. A CBC with differential during that admission was normal with an absolute neutrophil count (ANC) of 11.91×10^3 . The patient had no

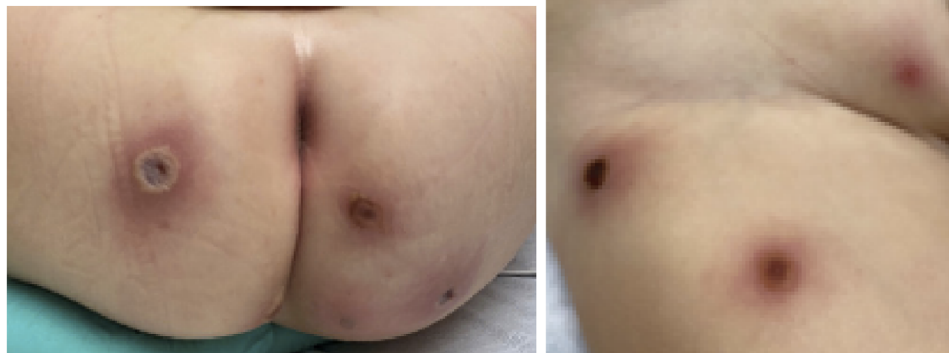


FIGURE 1 The patient on day 1 of hospitalization

history of otitis media, recurrent infections, infections related to his cochlear implants, family history of immunodeficiency, or death of a family member at a young age.

Upon admission to the floor, the patient was started on vancomycin, cefepime, and acyclovir for empiric coverage of staphylococcus, pseudomonas, and herpes simplex virus (HSV).

Lesion biopsy confirmed the diagnosis of ecthyma gangrenosum (EG). Vancomycin and cefepime were continued for 3 days until the biopsy culture grew pan-sensitive staphylococcus aureus. At that time, the patient was switched to cefazolin for 7 days before being transitioned to cephalexin. Acyclovir was discontinued when HSV polymerase chain reaction resulted negative.

Hematology was consulted concerning the patient's ANC of 0. This remained under 200 through day 9 of admission, at which time he was given 5 mcg/kg of granulocyte colony-stimulating factor. By hospital day 10, his ANC was found to be 580, and by day 11, 1340. At time of discharge (day 11 of hospitalization), ANC was 4940 and has since remained above 1500 at future outpatient checks.

History of vaccine-preventable pneumococcal meningitis in combination with EG and ANC of 0 prompted an immunodeficiency workup. His newborn screen was normal. Immunoglobulin levels revealed very low levels of IgA, IgG, IgM, and IgE. Lymphocyte subpopulations demonstrated normal levels of T-cells but absent B cells, suggesting diagnosis of XLA. Further studies showed no antibody response to diphtheria and tetanus and very minimal IgG response to pneumococcus serotypes, despite receiving age appropriate diphtheria, tetanus, and pertussis vaccines. Phytohemagglutinin assay showed decreased response to phytohemagglutinin mitogen, candida, and tetanus. *Btk* protein expression in B cells was not obtained due to lack of B cells

but was found to be decreased in monocytes at 1.21 (normal control of 3.77), confirming the diagnosis.

2 | DISCUSSION

XLA is a primary immunodeficiency caused by mutations in the gene for *Btk*, a signal transduction molecule and non-receptor tyrosine kinase critical for development and differentiation of myeloid and erythroid precursor cells.^{1,2} The disease manifests in an array of laboratory findings, including a profound decrease in levels of mature B lymphocytes, all classes of immunoglobulins, and antibody response to vaccines.^{3,4} Individuals present with an increased susceptibility for severe, recurrent, or abnormal bacterial infections, including those of the lower respiratory tract, otitis media, skin infections, and diarrhea. Additional findings can include severe neutropenia, scant lymphoid tissue, failure to thrive in younger patients, and a family history of immunodeficiency with X-linked recessive inheritance. XLA, primarily a disorder of B cell development, can also be associated with profound neutropenia. In a case series of 50 patients with XLA, 26% were noted to have profound neutropenia.⁵ A combination of clinical presentation, laboratory findings, and family history drive clinical suspicion, with the presence of a pathogenic variant of the *Btk* gene identified via molecular genetic testing confirming diagnosis.²

XLA remains relatively rare, with the most recent estimation from birth rate data gathered from a registry of 201 patients diagnosed with XLA between 1988 and 1997 suggesting a minimum birth rate of 1 in 379,000 within the United States.⁶ Infection is by far the most common initial presenting symptom of XLA,^{7,8} as seen in 85% of enrolled

patients.⁶ The onset of recurrent infections typically emerges after age 3 months, following the waning protection from maternal IgG antibodies delivered transplacentally during the third trimester. Approximately 50% of patients will develop presenting symptoms by 1 year of age, with nearly all symptomatic by age 5 years.⁶ The variable presentation makes diagnosis challenging as patients will not always present with recurrent infections in infancy that would alert a physician to consider an immunodeficiency.

Central nervous system (CNS) infections also occur at substantial rates, with reports ranging from 4% to 38% of patients at various centers worldwide,^{4,6,8,9,10} including 19.65% of 174 Chinese patients with XLA in a study by Chen et al.⁷ The most common bacterial etiologies of CNS infections include *Streptococcus pneumoniae* and *Haemophilus influenzae* type b.⁶ Only 11% of patients with untreated XLA had a history of meningitis; current literature shows that meningitis at initial clinical presentation is rare, with no patients in a registry of 201 patients reporting CNS infection at initial presentation in a 2006 study by Winkelstein et al.⁶

Current mainstays of treatment incorporate regular intravenous immunoglobulin substitution therapy, continued surveillance for sequelae of infections, avoidance of live vaccines, and prophylactic antibiotic use. These together have proven crucial in improving outcomes in affected males.^{2,6,9} Early diagnosis allows timely implementation of therapy and better management of disease burden.^{3,4,9} Recent literature suggests a need for additional education of physicians regarding typical and atypical presentations of XLA and related best practices.⁴

EG classically describes the skin manifestations of gram-negative septicemia, frequently in the setting of neutropenia or malignancy.¹¹ Although *Pseudomonas aeruginosa* is the most commonly identified species, other organisms have also been reported.¹² In the classic form of EG, patients have preceding *P. aeruginosa* bacteremia, with skin lesions developing from hematogenous spread to the skin. A localized, non-septicemic form can also occur in which lesions develop from direct inoculation.¹³ In addition to immunodeficiency, other risk factors include hematologic or other malignancies, severe burns, malnutrition, diabetes mellitus, systemic antibiotics, recent viral respiratory illness, and preceding urologic or gastrointestinal surgeries (resulting in bacteremia).

Skin findings are initially characterized by asymptomatic erythematous or purpuric macules. Over the proceeding 12–24 hours, the lesions rapidly progress to painful, indurated, hemorrhagic pustules or bullae, eventually becoming necrotic ulcers with a central black eschar and surrounding erythema. The most common locations are the gluteal and perineal region or extremities, as seen in our patient, though they can appear on any part of the body.¹⁴ Skin biopsies should be performed for histology and tissue cultures obtained to investigate for bacterial, fungal, or mycobacterial infection. Blood cultures also should be obtained alongside prompt initiation of broad-spectrum empiric antimicrobials.

Although EG is increasingly recognized in immunocompetent patients in literature,¹⁴ most cases are seen in neutropenic or otherwise immunosuppressed patients. A 2015 review of 167 cases of

EG from 1975 to 2014 found that at least 103 of 167 patients with EG (62%) were known to be, or subsequently found to be, immunocompromised.¹⁴ Furthermore, in a 2002 review, many previously healthy children diagnosed with EG were found to have a variety of risk factors, including appendicular abscesses, ruptured bowel, hypogammaglobulinemia, cyclic or transient neutropenias, prior antibiotic exposure, or other recent illnesses such as meningitis or pneumonia.¹⁵

3 | CONCLUSION

Aside from his history of a previous vaccine-preventable infection and presenting skin lesions, our patient did not display characteristic signs of an underlying immunodeficiency, such as family history of immunodeficiency or history of recurrent infections. Furthermore, he was overall well appearing and hemodynamically stable throughout his hospitalization. The unique and striking finding of vaccine-preventable meningitis is important to identify as it can be a relevant clinical clue toward identification of an underlying primary immunodeficiency and direct initial workup. A prior history of pneumococcal meningitis outside of the newborn period in a vaccinated patient should prompt a thorough workup for fever or other signs of bacterial infection. Furthermore, even in patients who are otherwise well appearing and without apparent risk factors, EG warrants a CBC with differential, blood culture, lesion biopsy, and prompt initiation of antimicrobial therapy as there is a high rate of underlying immunodeficiency in patients with this condition. In atypical presentations of XLA, thorough chart review, directed history-taking, and immunologic workup can elucidate subtle signs and symptoms that may uncover the presence of disease. Greater knowledge among clinicians regarding the various presentations of XLA may contribute to early diagnosis, a process critical in allowing timely initiation of treatment, disease management, and prevention of known complications.

CONFLICTS OF INTEREST

None.

REFERENCES

1. Pal Singh S, Dammeijer F, Hendriks RW. Role of Bruton's tyrosine kinase in B cells and malignancies. *Mol Cancer*. 2018;17(1):57.
2. López-Granados E, Pérez de Diego R, Ferreira Cerdán A, et al. A genotype-phenotype correlation study in a group of 54 patients with X-linked agammaglobulinemia. *J Allergy Clin Immunol*. 2005;116(3):690-697.
3. Smith CIE, Berglöf A. *X-Linked Agammaglobulinemia*. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews*®. Seattle (WA): University of Washington, Seattle; 2001.
4. El-Sayed ZA, Abramova I, Aldave JC, et al. X-linked agammaglobulinemia (XLA): phenotype, diagnosis, and therapeutic challenges around the world. *World Allergy Organ J*. 2019;12(3):100018.
5. Farrar JE, Rohrer J, Conley ME. Neutropenia in x-linked agammaglobulinemia. *Clin Immunol Immunopathol*. 1996;81(3):271-276.
6. Winkelstein JA, Marino MC, Lederman HM, et al. X-linked agammaglobulinemia: report on a United States registry of 201 patients. *Medicine*. 2006;85(4):193-202.

7. Chen XF, Wang WF, Zhang YD, et al. Clinical characteristics and genetic profiles of 174 patients with X-linked agammaglobulinemia: report from Shanghai, China (2000-2015). *Medicine (Baltimore)*. 2016;95(32):e4544.
8. Lederman HM, Winkelstein JA. X-linked agammaglobulinemia: an analysis of 96 patients. *Medicine (Baltimore)*. 1985;64(3):145-156.
9. Chun JK, Lee TJ, Song JW, et al. Analysis of clinical presentations of Bruton disease: a review of 20 years of accumulated data from pediatric patients at severance hospital. *Yonsei Med J*. 2008;49(1):28-36.
10. Pac M, Bernatowska EA, Kierkuś J, et al. Gastrointestinal disorders next to respiratory infections as leading symptoms of X-linked agammaglobulinemia in children—34-year experience of a single center. *Arch Med Sci*. 2017;13(2):412-417.
11. Greene SL, Su WPD, Muller SA. Ecthyma gangrenosum: report of clinical, histopathologic and bacteriologic aspects of eight cases. *J Am Acad Dermatol* 1984;11:781-787.
12. Reich HL, Fadeyi DW, Naik NS, et al. Nonpseudomonal ecthyma gangrenosum. *J Am Acad Dermatol* 2004;50:S114-S117.
13. Huminer D, Siegman-Igra Y, Morduchowicz G, et al. Ecthyma gangrenosum without bacteremia. *Arch Intern Med* 1987;147:299-301.
14. Vaiman M, Lazarovitch T, Heller L, et al. Ecthyma gangrenosum and ecthyma-like lesions: review article. *Eur J Clin Microbiol Infect Dis* 2015;34:633-699.
15. Zomorodi A, Wald ER. Ecthyma gangrenosum: considerations in a previously healthy child. *Pediatr Infect Dis J*. 2002;21(12):1161-1164.

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