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CASE REPORT

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Immunodeficiency in a Child Presenting with Ecthyma Gangrenosum and Normal Immunoglobulin Levels

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ABSTRACT

Primary immunodeficiency diseases (PID) are genetic defects of the immune system that result in chronic, serious and often life-threatening infections if not diagnosed and treated appropriately. Antibody deficiency is the most common PID, accounting for 50% of all cases. X-linked agammaglobulinemia (XLA) with Bruton tyrosine kinase (BTK) deficiency is the most common antibody deficiency.

XLA presenting with ecthyma gangrenosum is rare and was only noted in a few case reports. Here we present a one-year-old Filipino male who was previously well until he was admitted at ten months old due to a first bout of severe pneumonia with concomitant ecthyma gangrenosum. No similar case has been reported in the Philippines yet. This patient also presented with normal immunoglobulin levels and a reactive antibody to a vaccine. His older brother died at the age of 1 year and 4 months due to pneumonia and sepsis and his stepbrother also died at the early age of 1 year old again due to pneumonia.

XLA may be suspected in patients with ecthyma gangrenosum, especially if there is a strong family history of early deaths among males on the maternal side, despite normal serum immunoglobulin levels. It is therefore imperative to include XLA in the differential diagnosis of a child with an increased susceptibility to infection and neutropenia.

Keywords: ecthyma gangrenosum, agammaglobulinemia, XLA, PID, child

BACKGROUND

Primary immunodeficiency diseases (PID) are genetic defects of the immune system that result in chronic, serious and often life-threatening infections if not diagnosed and treated appropriately. The common presentations of PID are recurrent or unusually severe infections, unusually persistent infections and infections attributable to organisms that do not ordinarily cause disease in immunocompetent children or adults, such as opportunistic infections. Antibody deficiency is the most common PID, accounting for 50% of all cases.[1] X-linked agammaglobulinemia (XLA) with Bruton tyrosine kinase (BTK) deficiency is the most common antibody deficiency, with a total number of 2,064 reported cases and 230 of these patients are Asians.[2] In a study done at the University of the Philippines, Philippine General Hospital (UP-PGH), published in 2010, the majority of the referrals for PID were due to recurrent pneumonia.[1] According to Stiehm, the most common etiologies of pneumonia were due to *Haemophilus influenzae* (58%), *Streptococcus pneumoniae* and *Staphylococcus* (17% each) and *Pseudomonas aeruginosa* (8%).[3] Ecthyma gangrenosum (EG) is a characteristic dermatologic manifestation of severe and invasive infection caused most commonly by *Pseudomonas aeruginosa*.[4] From our review of literature, there are only a few cases of XLA that initially presented with ecthyma gangrenosum and no case has yet been reported in the Philippines. Herein, we describe a case of ecthyma gangrenosum caused by *Pseudomonas aeruginosa*, which led to the recognition and diagnosis of XLA.

CASE

A 10-month-old Filipino male was initially admitted to a local hospital and was managed as a case of pneumonia; wherein unrecalled antibiotics were given. He had a fever with a maximum temperature of 39°C with occasional non-productive cough and postprandial vomiting (~3x/day) nine days before admission to our institution. Five days prior to admission, there was a note of a reddish maculopapular lesion on the left shoulder. There was a progression of the erythematous macules all over the extremities, which morphed into vesicles and then became hemorrhagic bullae. There was also involvement of the perianal area. The patient was given unrecalled topical antibiotics with noted improvement. One day before admission, the patient had difficulty breathing and a decrease in sensorium. The patient's family was apprised of the need for intubation; however, they declined and opted to transfer the patient to the Philippine General Hospital. The patient was brought to the emergency room due to dyspnea. He has no known allergies, no previous surgeries or hospitalizations and no tuberculosis or blood dyscrasia.

The patient's maternal uncle died at a young age due to pneumonia. His older brother had a cough and abscesses in the scalp, shoulders and arms at 7 months old and died at the age of 1 year and 4 months due to pneumonia and sepsis. He also had a half-brother who died at 1 year old, also due to pneumonia (Figure 1).

He was born full term via spontaneous vaginal delivery without any fetomaternal complications and no maternal infections during the pregnancy. He was given one dose each of BCG and MMR and three doses each of hepatitis B vaccine, DPT, oral polio virus and H influenza vaccines, with no adverse reactions noted.

On physical examination at the ER, vital signs were as follows: BP 90/60 mm Hg, heart rate 140/min, respiratory rate 30/min and SpO_2 99%. He was sedated, slightly agitated when moved, intubated, in cardiorespiratory distress with bilateral crackles, right greater than the left lung fields, with note of multiple lesions described as circular with sharply demarcated borders and central necrosis,

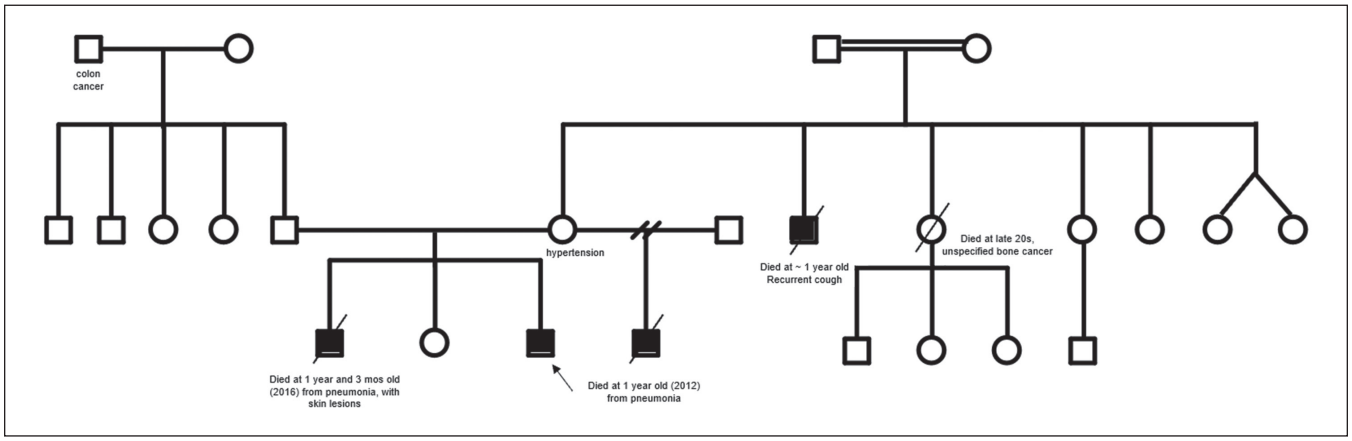

Figure 1. Family genogram.

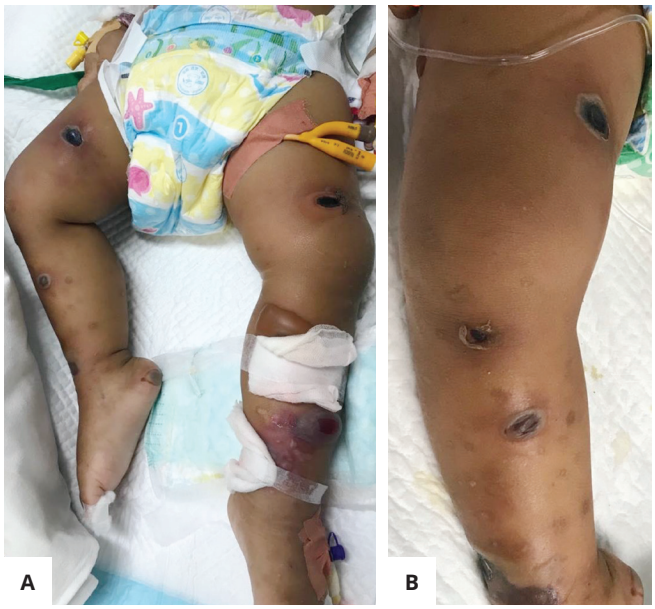

Figure 2. Skin lesions of the patient showing **(A)** both lower extremities; **(B)** right lower extremity.

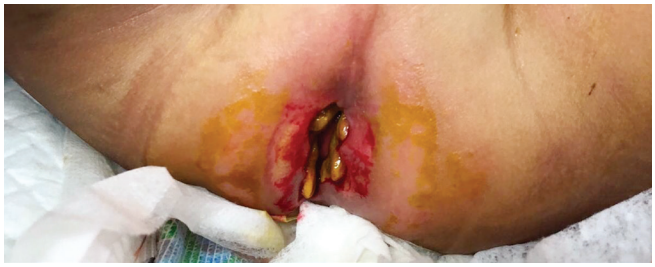

Figure 3. Perianal abscess.

located on bilateral lower extremities (Figure 2). During the examination, the anesthetic's effect was already waning, which led to the patient's agitation. He was admitted to the pediatric intensive care unit (PICU) and was hooked on a mechanical ventilator. He was started on multiple antibiotics. He was immediately referred to the Section of Allergy and Immunology, with initial consideration of PID, likely XLA. Immunologic workups, namely serum immunoglobulins and lymphocyte subset enumeration, were requested but were not done immediately due to financial constraints. On the fifth hospital day, a perianal abscess (Figure 3) was noted and the pediatric surgeons advised colostomy, but the family refused.

Investigations

Initial laboratory evaluation showed leukopenia at 2.20 x 10^9/L, with neutrophils 5%, lymphocytes 29% and monocytes 29%; absolute neutrophil count (ANC) was 1,100 and absolute lymphocyte count (ALC) was 638, both low. Hemoglobin 100 g/dL, platelets 113 x 10^9/L. Anti-HBs was reactive (26.23); HIV screening was negative. Endotracheal aspirate culture and sensitivity (CS) and tissue CS revealed *Pseudomonas aeruginosa.*

While awaiting funds for immunologic testing, serum protein electrophoresis was done revealing a marked decrease in the gamma globulin fraction at 0.2% (11.1-18.8), albumin 43.9% (55.8-66.1%), alpha 1 22.9% (2.9-4.9%), alpha 2 24.6% (7.1-11.8%), beta 1 5.9% (4.7-7.2%) and beta 2 2.5% (3.2-6.5%). On the succeeding days, Ceftazidime was given and daily wound care was done. Once funding was secured, lymphocyte subset enumeration was done which showed a CD19 of 20 mm^3 (NV: 600-3,100), CD3 of 1,859 (NV: 1,400-8,000), CD4 of 1,859 (NV: 900-5,500), CD8 of 945 (NV: 400-2,300) and CD16+CD56: 213 (NV: 100-1,400). The serum immunoglobulins were as follows: IgG 688 IU/mL (NV: 650-1,600), IgA 114.2 IU/mL (NV: 40-350), IgM 48.6 IU/mL (NV: 50-300) and IgE 840 (NV: 0.6-220). Genetic testing was done, which showed an X-linked substitution (nonsense) mutation in Exon 8 of the BTK gene, confirming the diagnosis of XLA.

Differential diagnosis

The patient's skin lesions appeared vasculitic, so he was also evaluated for possible vasculitis; however, p-ANCA and c-ANCA tests were negative. Job's syndrome was also considered in this patient because of an elevated serum IgE level. Still, given the clinical presentation and family history, XLA was the primary working diagnosis, later confirmed by genetic testing. The genetic testing had to be done outside of the country, as no PID genetic tests are available in the Philippines as of this writing.

Treatment

The patient was initially given empiric antibiotics and later was shifted to Ceftazidime for *Pseudomonas* coverage. When the lymphocyte subset enumeration test showed low B cell numbers, he was given intravenous immunoglobulin (IVIG) at 400mg/kg during the 16th and 22nd hospital days. After more than a month of admission, he improved and was eventually extubated. The perianal abscess and the skin lesions have already healed.

Outcome and follow-up

He was discharged improved after 2 months. Currently, the patient is healthy with good weight gain. There have been no new skin lesions or repeated admissions despite receiving irregular IVIG infusions. IVIg infusions were irregularly given due to financial constraints and the distance from the institution where they were administered.

DISCUSSION

XLA is a primary humoral immunodeficiency typically characterized by severe hypogammaglobulinemia and recurrent bacterial infections. It is caused by mutations

in the BTK gene. BTK is a signal transduction molecule essential for B-cell lineage development and its loss impairs the progression of pre-B cells to mature B cells. The lack of mature B lymphocytes results in insufficient immunoglobulin levels and affected patients are unable to mount an appropriate antibody response to infection.[5] Infections usually start at four to six months of age, coinciding with the catabolism of IgG of maternal origin. In a study done by de Leon et al., the majority of patients suspected of PID were in the age range of 0 to 6 months (37%) and 1 to 6 years old (36%); and they were predominantly males (72%), which was comparable to that reported by Stiehm.[1] In XLA, infection was the most common initial clinical presentation (85%), followed by a positive family history (41%) and neutropenia (11%). The organisms commonly found in XLA infections were encapsulated, as antibodies neutralize encapsulated microbes. Most strains of *P. aeruginosa* are non-encapsulated, but some produce an extracellular polysaccharide capsule. *Pseudomonas* species are catalase-positive organisms commonly encountered in patients with phagocytic defects. XLA is not a phagocytic disorder, but neutropenia is present in about 25% of patients; In a US registry report, neutropenia occurred in 21 patients, but only at the time of diagnosis.[6] A survey done in Japan showed 16/87 (18%) patients with XLA had neutropenia before initiation of IVIG, with two fatal cases of *Pseudomonas* sepsis. There were, however, no episodes of neutropenia after IVIG.[7] A case report of a 1 year and 7 months old twin Hispanic male in the US who had ecthyma gangrenosum and septicemia. His twin died of septic shock, purpura fulminans and disseminated intravascular coagulation. The authors reported that although uncommon, there have been case reports of patients presenting with *P. aeruginosa* septicemia and ecthyma gangrenosum that were subsequently diagnosed with XLA.[8] Although rare, in addition to our patient, there have been three case reports of patients presenting with *Pseudomonas aeruginosa* septicemia and ecthyma gangrenosum that were subsequently diagnosed with XLA.[8-10] Ecthyma gangrenosum (EG) secondary to *P aeruginosa* is an uncommon and aggressive infection that can be linked with agammaglobulinemia.[9] Ecthyma gangrenosum is a cutaneous infection most commonly associated with Pseudomonas. EG usually occurs in patients who are critically ill and immunocompromised. The characteristic lesions are erythematous macules that progress to hemorrhagic bluish bullae that rupture to form necrotic ulcers. This lesion represents a formidable skin sign of a possible fatal sepsis. The main site of EG lesions is the gluteal or perineal region (57%), although these lesions can spread to other body sites, as occurred in our patient. In two case reports, all patients with EG were immunocompromised, leading to severe neutropenia and an absolute neutrophil count of less than 500/mm^3 was strongly associated with clinical outcome.[8,9] BTK is also expressed in myeloid cells, monocytes and platelets.[10] Recently, there has been growing evidence suggesting multiple roles for BTK in innate immunity. Neutrophils are arrested at the myelocyte/promyelocyte stage and phagocytosis and chemotaxis are reduced.[11]

There was some difficulty with blood typing for this patient. Isohemagglutinins are naturally occurring IgM antibodies to the ABO blood group substances. By 1 year of age, 70% of infants have positive isohemagglutinin titers, depending, of course, on their blood type. Blood typing relies on the ability of this antibody to cross-link RBC by interacting with the antigens on the surface of the RBC. Forward blood typing is not a problem, but reverse typing, which relies on the patient's IgM function, would show discrepancies.

Most patients with XLA have dysgammaglobulinemia, meaning they cannot produce a specific antibody response to antigens. Antibody response to vaccines is a qualitative assessment of immunoglobulin. Our patient presented with reactive anti-HBs and, from the history, had no adverse reactions to live vaccines. This is possibly because the patient is still producing antibodies. This phenotypic diversity is attributed to variable disease penetrance, expression variability and interactions between genetic and environmental factors.

A case report from New Zealand described a 22-month-old male with normal immunoglobulin levels and vaccine seroconversion. There are no rigid diagnostic criteria for immunoglobulin deficiency. However, an IgG value below 3 g/L (300 mg/dL) in an adolescent or adult, as well as values clearly below the age-appropriate reference range (95% CI) in an infant or child, should trigger further evaluation. Protective antibody levels to the immunizations were demonstrated in this patient. Further investigation showed low B-cell numbers and genetic testing confirmed the diagnosis. This patient had a subsequent drop in immunoglobulin level with deteriorating B-cell function. The authors concluded that XLA is not excluded by normal immunoglobulin levels or by apparent “protective” IgG titers following vaccination.[12]

The other problem encountered in this patient was the need for a colostomy. Rokhsar et al., conducted a 13-year retrospective review of immunocompromised children with intestinal stomas treated at the Children's Hospital in Los Angeles. The patients were assessed regarding their diagnoses, surgical indications, stoma type, postoperative complications, ostomy-related complications and survival. Six children had immunodeficiency and 12 were immuno-compromised from chemotherapy treatment for cancer. Among those with immunodeficiency, the indications were for colitis or ulcerative colitis (1 case of Hirschsprung’s disease). Neutropenic patients had serious post-operative

infectious complications. The authors suggested that collaboration between the surgical and medical staff can maximize patient care by facilitating the more intensive treatment these children need compared with immunocompetent children.[13]

Learning points

This case report highlights the need for increasing awareness and education so that patients with PID can receive early and appropriate diagnosis. Early recognition is key to avoiding associated morbidity and mortality. In conclusion, our patient initially manifested as pneumonia with ecthyma gangrenosum, which led to Pseudomonas sepsis. Ecthyma gangrenosum can be a presentation of XLA, especially if there is a strong family history. Therefore, XLA should be included in the differential diagnosis of a child with an increased susceptibility to infection and neutropenia. Currently, no national registry of PID exists in the Philippines and we need epidemiological data to support the public health benefits of early diagnosis and treatment.

CONCLUSION

Primary immunodeficiency diseases (PID) are genetic defects of the immune system that result in chronic, serious and often life-threatening infections if not diagnosed and treated appropriately. Antibody deficiency is the most common PID, accounting for 50% of all cases. X-linked agammaglobulinemia (XLA) with Bruton Tyrosine Kinase (BTK) deficiency is the most common antibody deficiency. XLA presenting with ecthyma gangrenosum is rare and was only noted in a few case reports. Here we present a one-year-old Filipino male who was previously well until he was admitted at ten months old due to a first bout of severe pneumonia with concomitant ecthyma gangrenosum. No similar case has been reported in the Philippines yet. This patient also presented with normal immunoglobulin levels and a reactive antibody to a vaccine. XLA may be suspected in patients with ecthyma gangrenosum, especially if there is a strong family history of early deaths among males on the maternal side, despite normal serum immunoglobulin levels. Therefore, XLA should be included in the differential diagnosis of a child with an increased susceptibility to infection and neutropenia.

Ethical Consideration

The parents' consent was obtained before the manuscript was submitted.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

The authors declared no conflict of interest.

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REFERENCES

1. Marco NM, de Leon JC, Castor MAR, Recto MT, Sumpaico MW. Clinical profile of pediatric patients referred for immunodeficiency at the UP-PGH medical center: a five-year review. Phil J Allergy Asthma Immunol. 2010;14(2):14-23.
2. Modell V, Knaus M, Modell F, Roifman C, Orange J, Notarangelo LD. Global overview of primary immunodeficiencies: a report from Jeffrey Modell Centers worldwide focused on diagnosis, treatment, and discovery. Immunol Res. 2014;60(1):132-44. PMID: 24668296 DOI: 10.1007/s12026-014-8498-z
3. Sullivan KE, Stiehm ER, editors. Stiehm's immune deficiencies. Amsterdam, Netherlands: Elsevier Inc.; 2015.
4. Pseudomonas and related species. In: Feigin RD, Cherry JD, eds Textbook of Pediatric Infectious Diseases. 8th ed. Philadelphia, PA: WB Saunders; 1998.
5. Ochs HD, Smith CI. X-linked agammaglobulinemia. A clinical and molecular analysis. Medicine (Baltimore). 1996;75(6):287-99. PMID: 8982147 DOI: 10.1097/00005792-199611000-00001
6. Winkelstein JA, Marino MC, Lederman HM, et al. X-linked agammaglobulinemia: report on a United States registry of 201 patients. Medicine (Baltimore). 2006;85(4):193-202. PMID: 16862044 DOI: 10.1097/01.md.0000229482.27398.ad
7. Kanegane H, Taneichi H, Nomura K, Futatani T, Miyawaki T. Severe neutropenia in Japanese patients with x-linked agammaglobulinemia. J Clin Immunol. 2005;25(5):491-5. PMID: 16160918 DOI: 10.1007/s10875-005-5370-x
8. Sanford E, Farnaes L, Batalov S, et al. Concomitant diagnosis of immune deficiency and Pseudomonas sepsis in a 19 month old with ecthyma gangrenosum by host whole-genome sequencing. Cold Spring Harb Mol Case Stud. 2018;4(6):a003244. PMID: 30559311 PMCID: PMC6318772 DOI: 10.1101/mcs.a003244
9. Almeida JF, Sztajnbok J, Troster EJ, Vaz FAC. Pseudomonas aeruginosa septic shock associated with ecthyma gangrenosum in an infant with agammaglobulinemia. Rev Inst Med Trop Sao Paulo. 2002;44(3):167-9. PMID: 12163911 DOI: 10.1590/s0036-46652002000300010
10. Nussinovitch M, Frydman M, Cohen HA, Varsano I. Congenital agammaglobulinemia presenting with ecthyma gangrenosum. Acta Paediatr Scand. 1991;80(6-7):732-4. PMID: 1867095 DOI: 10.1111/j.1651-2227.1991.tb11938.x
11. López-Herrera G, Vargas-Hernández A, González-Serrano ME, et al. Bruton's tyrosine kinase--an integral protein of B cell development that also has an essential role in the innate immune system. J Leukoc Biol. 2014;95(2):243-50. PMID: 24249742 DOI: 10.1189/jlb.0513307
12. Preece K, Lear G. X-linked agammaglobulinemia with normal immunoglobulin and near-normal vaccine seroconversion. Pediatrics. 2015;136(6):e1621-4. PMID: 26527549 DOI: 10.1542/peds.2014-3907
13. Rokhsar S, Harrison EA, Shaul DB, Phillips JD. Intestinal stoma complications in immunocompromised children. J Pediatr Surg. 1999;34(12):1757-61. PMID: 10626848 DOI: 10.1016/s0022-3468(99)90306-8