Asia Pac Allergy. 2021 Jan;11(1):e7
https://doi.org/10.5415/apallergy.2021.11.e7
pISSN 2233-8276·eISSN 2233-8268

Asia Pacific allergy

Case Report

Primary immunodeficiency from B-cell defect: a case series of 6 patients seen in a national tertiary hospital in the Philippines

Carol Stephanie C. Tan-Lim * **and Mary Anne R. Castor**

Department of Pediatrics, Section of Allergy and Immunology, Philippine General Hospital, Manila, the Philippines

Received: May 1, 2020
Accepted: Jan 24, 2021

***Correspondence to**
Carol Stephanie C. Tan-Lim
University of the Philippines Manila, Philippine General Hospital, Taft Avenue, Ermita, Manila, 1000, the Philippines.
Tel: +639178331196
Email: cctan7@up.edu.ph

ORCID iDs
Carol Stephanie C. Tan-Lim
https://orcid.org/0000-0001-8815-4191
Mary Anne R. Castor
https://orcid.org/0000-0003-2291-4615

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Carol Stephanie C. Tan-Lim, Mary Anne R. Castor. Formal analysis: Carol Stephanie C. Tan-Lim. Investigation: Carol Stephanie C. Tan-Lim. Methodology: Carol Stephanie C. Tan-Lim. Project

ABSTRACT

Primary immunodeficiency disorders, although rare, pose a significant burden in the quality of life of afflicted patients and their families. The most common of these disorders are caused by B-cell defects. A total of 6 patients were seen and diagnosed in a national tertiary hospital in the Philippines from 1996 to 2018. These patients were admitted due to various infections, and were subsequently diagnosed to have B-cell defects. Four out of the 6 patients have genetic studies confirming the diagnosis of X-linked agammaglobulinemia. One patient succumbed to sepsis at 10 years of age, while the rest are on follow-up at the Philippine General Hospital for intravenous immunoglobulin infusion.

Keywords: Immune deficiency syndromes; B-lymphocytes; Agammaglobulinemia

INTRODUCTION

Primary immunodeficiency is a group of rare disorders of immune system dysfunction affecting 1 in 2,000 live births [1]. Based on reports from various countries, B lymphocyte defects account for 50% to 58% of primary immunodeficiency disorders [2, 3].

In the Philippine Pediatric Society registry, there have been 50 reported cases of hereditary hypogammaglobulinemia, 4 cases of selective IgA deficiency, 1 case of selective IgG deficiency, and 2 cases of hyper IgM syndrome [4].

This case series describes the 23-year experience of a national tertiary hospital in the Philippines, during which 6 patients with primary immunodeficiency from B-cell defects were seen and diagnosed.

administration: Carol Stephanie C. Tan-Lim. Writing - original draft: Carol Stephanie C. Tan-Lim. Writing - review & editing: Mary Anne R. Castor.

CASE REPORTS

In our institution, 6 patients were seen and diagnosed with primary immunodeficiency from B-cell defects from 1996 to 2018. The summary of the patients' data is shown in **Table 1**. All patients were male and were admitted in the Philippine General Hospital due to a variety of infections. The age of onset of their first infections ranged from 11 months to 27 months, with a mean age of 17 months.

The age at the time of diagnosis of B-cell immunodeficiency varied widely, from 2 years to 16 years of age, with a mean age of 5 years. The longest interval from the age of onset of first infection to the age of diagnosis of B-cell immunodeficiency was 15 years. The shortest interval was 3 months.

Only 4 patients had definitive diagnosis made through genetic studies. One patient expired without genetic studies being conducted. The other patient has not had genetic testing done due to financial constraints. The youngest patient to have had genetic testing done was at 2.5 years old, 3 months after the onset of his infections. The oldest patient was at 17 years old, which was 16 years after the onset of clinical manifestations.

The first clinical presentation of the 6 patients varied from upper respiratory tract infection, diarrhea, skin infections, oral sores, meningitis, to pneumonia. Other clinical manifestations included sepsis, septic arthritis, otitis media, and tuberculosis. **Table 2** shows the frequency distribution of the various infections.

Three out of the 6 patients had a positive family history of early death, all of which involved male family members (brother, uncle). Two patients had negative family history of early death, while data was not available for 1 patient.

Table 1. Clinical, laboratory, and molecular profile of patients with B-cell immunodeficiency.

Patient No.	Sex	Age at onset of infections (mo)	Age at diagnosis of B-cell defect (yr)	Age at definitive diagnosis (yr)	Family History	First clinical manifestation	IgG (mg/dL)	IgM (mg/dL)	IgA (mg/dL)	B cell (%)	Genetic studies	Mother's status	Final diagnosis	Outcome
1	M	12	5	N/A	+ (brother)	URTI	554 (low)	33.4 (low)	60.5 (low)	0	*BTK* mutation (exon 18 c.G1751A)	N/A	XLA	On follow-up, 27 years old
2	M	12	16	17	-	Meningitis	288 (low)	58.6 (low)	68.7 (low)	0	*BTK* mutation (exon 1 g.35420G>A)	Carrier	XLA	On follow-up, 26 years old
3	M	13	2	9	+ (brother)	Skin infection	284 (low)	34.4 (low)	60.5	0	*BTK* mutation (R520X)	N/A	XLA	On follow-up, 12 years old
4	M	26	2.5	No definitive diagnosis	-	Diarrhea	33 (low)	5.16 (low)	6.67 (low)	0.73	Not done	Not done	B-cell defect	On follow-up, 12 years old
5	M	11	1.5	No definitive diagnosis	N/A	Oral sores	390 (low)	85.9	68.7	2.64	Not done	Not done	B-cell defect	Died at 10 years old from sepsis
6	M	27	2.5	2.5	+ (brother, maternal uncle)	Pneumonia	688 (low)	48.6 (low)	114.2	0.64	*BTK* mutation (exon 8 c.895>T)	N/A	XLA	On follow-up, 2.5 years old

N/A, data not available; *BTK*, Bruton tyrosine kinase; URTI, upper respiratory tract infection; XLA, X-linked agammaglobulinemia.

https://doi.org/10.5415/apallergy.2021.11.e7

Table 2. Frequency distribution of clinical manifestations of patients with B-cell immunodeficiency

Clinical manifestation	First clinical manifestation (n)	Manifestations up until diagnosis was made, n (%)
Skin infection	1	5 (83)
Pneumonia	1	4 (67)
Otitis media	0	3 (50)
Abscess, deep-seated	0	3 (50)
Upper respiratory tract infection	1	2 (33)
Sepsis	0	2 (33)
Tuberculosis	0	2 (33)
Oral sores	1	1 (17)
Diarrhea	1	1 (17)
Meningitis	1	1 (17)
Pericarditis	0	1 (17)
Septic arthritis	0	1 (17)

The serum IgGs of all 6 patients were below normal range. Five patients had concomitantly low IgMs, while 3 patients had concomitantly low IgAs. All patients had normal T cell and natural killer cell counts. B-lymphocytes were less than 1% in 5 patients. Out of these 5 patients, 4 were able to undergo genetic analysis for *BTK* mutation which confirmed the diagnosis of X-linked agammaglobulinemia. One patient had a B lymphocyte of 2.64%. Unfortunately, this patient expired before genetic analysis could be performed.

Only 1 patient had available results of the other family members, with results showing that the mother was heterozygous for the mutated allele.

Out of the 6 patients, 1 succumbed to sepsis at 10 years of age. The rest are on follow-up at our institution for intravenous immunoglobulin infusion. One patient has cognitive and motor deficits as a complication of viral encephalitis. Another patient has chronic lung disease, specifically bronchiectasis, which necessitated tracheostomy.

Although the recommended dose of intravenous immunoglobulin is 400–600 mg/kg every 3–4 weeks, all 5 patients are unable to comply with this recommendation due to financial constraints. The usual average interval of their intravenous immunoglobulin infusion is 3 months. All patients are provided antibiotic prophylaxis and supportive care, and are monitored for possible complications such as chronic lung disease, autoimmunity, and malignancy.

DISCUSSION

B-cell defects are characterized by disorders in the number or function of B-lymphocytes, resulting in the inability to produce normal antibodies. These manifest as recurrent and severe infections occurring during early childhood, after the maternally derived antibodies wane over 6 to 12 months [5]. This is consistent with the experience of our institution, with all patients first manifesting with infections at ages 1 to 2 years old.

Based on the 2019 International Union of Immunological Societies classification of primary immunodeficiencies, B-cell defects can be classified as hypogammaglobulinemia or other antibody deficiencies [6]. The most common cause of congenital hypogammaglobulinemia is X-linked agammaglobulinemia (XLA), which accounts for 85% of the cases [7]. In our case series, 4 out of the 6 patients had mutations in the *BTK* gene, confirming the diagnosis of XLA. All our patients were male and 3 patients had male relatives with early deaths from infection,

https://doi.org/10.5415/apallergy.2021.11.e7

which is consistent with the X-linked mode of inheritance. One patient still needs to undergo genetic studies to confirm the diagnosis. The patient who expired most likely did not have XLA, since his B cell was greater than 1%. He manifested with recurrent oral sores, pneumonia, septic arthritis, cellulitis, and *Enterobius* infection. His serum IgG, CD19, and CD20 levels were below normal range. His serum IgM, IgA, CD3, CD4, CD8, CD16/56, absolute neutrophil counts, and absolute lymphocyte counts were normal. This patient may have isolated IgG subclass deficiency. Although patients with isolated IgG subclass deficiency are usually asymptomatic, a minority can manifest with recurrent viral and bacterial infections. Another differential diagnosis is CD20 deficiency, although this is extremely rare [6].

B-cell defects cause significant economic and psychosocial difficulties among patients and their families [8]. The older patients in the case series had long intervals from the onset of manifestations to the age of diagnosis of B-cell immunodeficiency, during which repeated infections, physician consults, and antibiotic treatments drained the finances of the family. In fact, one patient already developed chronic lung disease necessitating tracheostomy before the diagnosis of B-cell defect was made. The younger patients had shorter interval from the onset of manifestations to the age of diagnosis, reflecting the positive results of increased awareness and early referral among the Philippine physicians. However, there may be patients with B-cell defects whose diagnosis were missed because of various reasons such as (1) they succumbed to infections complications before they could be screened for primary immunodeficiency, (2) inability to perform diagnostic tests such as serum immunoglobulins and B-cell enumeration due to financial constraints, and (3) they were lost to follow-up [9].

Currently, the cost and accessibility of genetic studies and intravenous immunoglobulin are significant obstacles in achieving optimal outcome for these patients.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Aimee Lou M. Nano and Dr. Addah S. de Peralta for their assistance in providing pertinent patient data for this case series.

REFERENCES

1. Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, Kobrynski LJ, Levinson AI, Mazer B, Nelson RP Jr, Orange JS, Routes JM, Shearer WT, Sorensen RUAmerican Academy of Allergy, Asthma and ImmunologyAmerican College of Allergy, Asthma and ImmunologyJoint Council of Allergy, Asthma and Immunology. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 2005;94(5 Suppl 1):S1-63.
PUBMED | CROSSREF
2. Zelazko M, Carneiro-Sampaio M, Cornejo de Luigi M, Garcia de Olarte D, Porras Madrigal O, Berrón Perez R, Cabello A, Rostan MV, Sorensen RU. Primary immunodeficiency diseases in Latin America: first report from eight countries participating in the LAGID, Latin American Group for Primary Immunodeficiency Diseases. J Clin Immunol 1998;18:161-6.
PUBMED | CROSSREF
3. Stray-Pedersen A, Abrahamsen TG, Frøland SS. Primary immunodeficiency diseases in Norway. J Clin Immunol 2000;20:477-85.
PUBMED | CROSSREF
4. ICD 10 Registry [Internet]. Manila (the Philippine): Philippine Pediatric Society, Inc. [cited 2019 Mar 26]. Available from: https://pps.org.ph/icd-10-registry/

5. Niewiesk S. Maternal antibodies: clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. Front Immunol 2014;5:446.
PUBMED | CROSSREF

6. Bousfiha A, Jeddane L, Picard C, Al-Herz W, Ailal F, Chatila T, Cunningham-Rundles C, Etzioni A, Franco JL, Holland SM, Klein C, Morio T, Ochs HD, Oksenhendler E, Puck J, Torgerson TR, Casanova JL, Sullivan KE, Tangye SG. Human inborn errors of immunity: 2019 update of the IUIS phenotypical classification. J Clin Immunol 2020;40:66-81.
PUBMED | CROSSREF

7. Shillitoe B, Gennery A. X-linked agammaglobulinaemia: outcomes in the modern era. Clin Immunol 2017;183:54-62.
PUBMED | CROSSREF

8. Guaní-Guerra E, Jiménez-Romero AI, García-Ramírez UN, Velázquez-Ávalos JM, Martínez-Guzmán E, Sandoval-Ramírez E, Camacho-Meza I. Disease burden for patients with primary immunodeficiency diseases identified at reference hospitals in Guanajuato, Mexico. PLoS One 2017;12:e0175867.
PUBMED | CROSSREF

9. Marco NM, de Leon JC, Castor MR, Recto MT, Sumpaico MW. Clinical profile of pediatric patients referred for immunodeficiency at the UP-PGH Medical Center: a five-year review. Philippine J Allergy Asthma Immunol 2009;14:14-23.