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Case Report

Atypical Case of Autosomal Recessive Agammaglobulinemia Presenting with Mild Hypogammaglobulinemia and Follow Up Findings

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Abstract

Autosomal recessive Agammaglobulinemia (ARA) is an uncommon type of congenital Agammaglobulinemia characterized by the absence of any of the molecules that constitutes the pre-B cell receptor complex at the B lymphocyte developmental stages. ARA is defined by profound hypogammaglobulinemia of all immunoglobulin isotypes and absence of circulating B lymphocytes. Herein, we report an atypical case of ARA with λ5/14.1 deficiency due to homozygous mutation in the IGLL1 gene with absence of B lymphocytes and normal levels of IgA and IgM and her follow up findings.

Keywords: Agammaglobulinemia; Hypogammaglobulinemia; Neutrophil

Introduction

λ5/14.1 deficiency was first reported by Minegishi et al. [1] at 1998 as an autosomal recessive cause of agammaglobulinemia. The λ5/14.1 chain is encoded in the *IGLL1* gene located at chromosome 22q11.23 [2]. Genetic mutations of autosomal recessive Agammaglobulinemia (ARA) have only been described in a few families in the literature. We report a rare case of ARA caused by homozygous mutation in the *IGLL1* gene with normal levels of IgA and IgM and her follow up findings.

Case Presentation

A 13-month-old female patient presented at our hospital with a history of recurrent pneumonia since 40 days old. She had been vaccinated appropriate of her age. There was consanguineous marriage between the mother and father. She had a healthy 7 years old sister. There was no growth and developmental delay. Tonsillar tissue was hypoplasic. Immunologic evaluation at presentation revealed an IgG level of 290 mg/dl (<2SD of the normal level for the age) with normal IgA and IgM levels. Antibody responses to diphtheria toxoid and hepatitis B were completely absent. Tuberculin skin test was evaluated as negative. Chest X-ray revealed radiological evidence of a thymus. Peripheral lymphocyte phenotyping by flow cytometry revealed absent B cells with normal T and NK cell counts (Figure 1). Genetic mutation analyses were performed for autosomal recessive inherited molecular defects due to the absence of B lymphocyte, the female sex and the parental consanguinity. Genetic analysis of the patient was performed at Research Center for Molecular Medicine of the Austrian Academy of Sciences. Next generation sequencing based gene panel screening revealed a homozygous mutation of c.425C>T (p.Pro142Leu) in the *IGLL1* gene and confirmed by Sanger Sequencing. A diagnosis of ARA due to λ5/14.1 deficiency was made. The patient's parents were heterozygous for the same mutation and there was no mutation at her sister.

Since the age of 13 months, she has been treated with intravenous replacement immunoglobulin therapy (400 mg/kg every 4 weeks) and a progressive normalization of the absolute neutrophil count was observed within 2 months. Neutropenia was considered to be secondary to the infection episode and did not recurred during follow up. During the 6 years follow-up, the frequency of infection decreased significantly with no serious infections or hospitalization except upper respiratory tract infections less than 1-2/year. Pulmonary and any other complication did not observed during follow up. Her growth and development are appropriate for age. Her B cells remained undetectable with normal blood IgA and IgM levels (Table 1).

Discussion

In general, the autosomal recessive forms of agammaglobulinemia tend to show a more severe and early onset than X-linked Agammaglobulinemia (XLA). Both forms are characterized by recurrent respiratory and/or gastrointestinal tract infections caused mostly by encapsulated bacteria such as *Haemophilus influenzae* and *Streptococcus pneumonia* [2,3]. Our patient's history of recurrent pneumonia and the absence of tonsils were remarkable. She was suffered from recurrent respiratory infections starting early of life at age 40 days.

There have been sporadically reported atypical cases of XLA that were diagnosed as teenagers or adults exhibiting normal levels of one or two Ig isotypes such as IgM or IgA deficiency or presenting as

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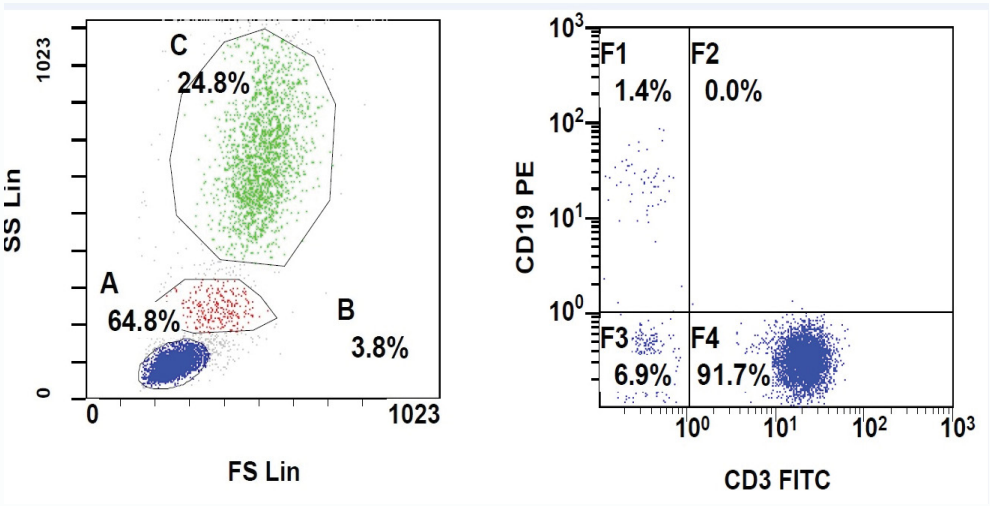

Figure 1: Flow cytometric analysis of B cells.

Table 1: Immunological results at the time of presentation and annual assesment of immunological tests.

Test results at the time of presentation					
Parameters	**Patient**	**Normal referans values for age**			
Complete blood count					
White blood cells, cells/ml	7850	6000-17500			
Neutrophils, cells/ml	1100	1500-8500			
Lymphocytes, cells/ml	5830	2300-5600			
Immunoglobulin values					
IgG(mg/dL)	290	715 ± 181			
IgA, (mg/dL)	50	47.72 ± 18.33			
IgM, (mg/dL)	76	94.41 ± 40.34			
IgE, (ku/L)	1.9	0-100			
Lymphocyte subsets					
CD3+ Cells, cells/mm^3, n (%)	5350 (91.9)	1400-4500			
CD4+ Cells, cells/mm^3, n (%)	2279 (58.9)	700-2000			
CD8+ Cells, cells/mm^3, n (%)	1540 (26.5)	500-1400			
CD19+ Cells, cells/mm^3, n (%)	50 (0.9)	400-1500			
NK Cells, cells//mm^3, n (%)	370 (6.4)	100-700			
Specific antibodies					
Anti Hbs IgG	Negative				
Anti Diphtheria IgG	Negative				
C3 (mg/dl)	116	73-180			
C4 (mg/dl)	27	Dec-39			
Annual assesment of immunological tests					
Parameters	**2 years old**	**3 years old**	**4 years old**	**5 years old**	**6 years old**
Neutrophils, cells/ml	2740	5140	4170	5390	4160
Lymphocytes, cells/ml	6140	3750	3680	3000	3500
CD3+cells, %	91.7	91.9	89.4	94.4	91.9
CD4+cells, %	60.6	63.3	52.6	58.9	63.5
CD8+cells, %	29.2	26.5	34.4	31	26.3
CD19+cells, %	1.4	0.9	1.1	1	0.8
NK cells, %	6.3	6.4	9	3.1	6.5
IgG (mg/dl)*	571	797	733	683	849
IgA (mg/dl)	62	80	65	74	75
IgM (mg/dl)	38	52	53	56	122

*with IVIG replacement

transient hypogammaglobulinemia of infancy. Genotype–phenotype correlations in XLA have not been established clearly but some studies suggest that missense mutations or splice site mutations that allow the production of some functional Bruton tyrosine kinase were associated with less severe clinical findings and mild hypogammaglobulinemia [4-6]. Previously reported patients with ARA exhibits profound hypogammaglobulinemia of all immunoglobulin isotypes and absence of circulating B lymphocytes and the small number of reported ARA patients does not allow evaluation of genotype–phenotype correlations [1-3,7-10]. Although in our case, at initial evaluation IgG level was below the 2 standard deviation by age, IgA and IgM levels were within normal ranges and peripheral CD19+B cells were detected low by flow cytometry. If the immunoglobulin values were evaluated only, this patient could have been diagnosed with transient

hypogammaglobulinemia of infancy. Genetic analysis performed due to absence of B cells has been revealed homozygous mutation in the gene encoding the λ5/14.1 light chain.

The essential and life-saving treatment for ARA patients is immunoglobulin replacement therapy with antibiotic therapy for any documented and/or suspected infection [2]. Our patient was treated and continues to receive intravenous immunoglobulin replacement therapy and she has had no any lower respiratory tract infection during 6 year follow up. Our patient's IgA and IgM levels remained within normal limits and B cells remained low over the next 6 years.

Recognizing the clues of primary immunodeficiency with anamnesis and careful physical examination such as recurrent pneumonia and the absence of tonsils will provide early diagnosis and prevent severe complications. Our patient also emphasize the importance of analyzing the B-lymphocyte surface markers and further molecular analyses in patients with mild hypogammaglobulinemia in the presence of clinical findings because as seen in XLA patients, ARA patients may be also presented with milder and atypical phenotypes.

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References

1. Minegishi Y, Coustan-Smith E, Wang YH, Cooper MD, Campana D, Conley ME. Mutations in the human λ5/14.1 gene result in B cell deficiency and agammaglobulinemia. J Exp Med. 1998;187(1):71-7.

2. Berglöf A1, Turunen JJ, Gissberg O, Bestas B, Blomberg KE, Smith CI. Agammaglobulinemia: causative mutations and their implications for novel therapies. Expert Rev Clin Immunol. 2013;9(12):1205-21.

3. Khalili A, Plebani A, Vitali M, Abolhassani H, Lougaris V, Mirminachi B. Autosomal recessive agammaglobulinemia: a novel non-sense mutation in CD79a. J Clin Immunol. 2014;34(2):138-41.

4. Fujioka T, Kawashima H, Nishimata S, Ioi H, Takekuma K, Hoshika A, et al. Atypical case of X-linked agammaglobulinemia diagnosed at 45 years of age. Pediatr Int. 2011;53(4):611-2.

5. Lim LM, Chang JM, Wang IF, Chang WC, Hwang DY, Chen HC. Atypical X-linked agammaglobulinaemia caused by a novel BTK mutation in a selective immunoglobulin M deficiency patient. BMC Pediatr. 2013;13:150.

6. Carrillo-Tapia E, García-García E, Herrera-González NE, Yamazaki-Nakashimada MA, Staines-Boone AT, Segura-Mendez NH, et al. Delayed diagnosis in X-linked agammaglobulinemia and its relationship to the occurrence of mutations in BTK non-kinase domains. Expert Rev Clin Immunol. 2018;14(1):83-93.

7. Ferrari S, Zuntini R, Lougaris V, Soresina A, Sourková V, Fiorini M, et al. Molecular analysis of the pre-BCR complex in a large cohort of patients affected by autosomal-recessive agammaglobulinemia. Genes Immun. 2007;8(4):325-33.

8. Gemayel KT, Litman GW, Sriaroon P. Autosomal recessive agammaglobulinemia associated with an IGLL1 gene missense mutation. Ann Allergy Asthma Immunol. 2016;117(4):439-41.

9. Lougaris V, Vitali M, Baronio M, Moratto D, Tampella G, Biasini A, et al. Autosomal recessive agammaglobulinemia: the third case of Igβ deficiency due to a novel non-sense mutation. J Clin Immunol. 2014;34(4):425-7.

10. Tang P, Upton JEM, Barton-Forbes MA, Salvadori MI, Clynick MP, Price AK, et al. Autosomal Recessive Agammaglobulinemia Due to a Homozygous Mutation in PIK3R1. J Clin Immunol. 2018;38(1):88-95.