CASE REPORT
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Disseminated Intravascular Coagulation Associated with Large Deletion of Immunoglobulin Heavy Chain

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ABSTRACT

Although the majority of monogenic defects underlying primary immunodeficiency are microlesions, large lesions like large deletions are rare and constitute less than 10% of these patients. The immunoglobulin heavy chain (IGH) locus is one of the common regions for such genetic alterations. This study describes a rare case of autosomal recessive agammaglobulinemia with a homozygous large deletion in chromosome 14q32.33 (106067756-106237742) immunoglobulin heavy chain clusters with an unusual and severe skin infection and disseminated intravascular coagulopathy.

Keywords: Agammaglobulinemia; Disseminated intravascular coagulation; Immunoglobulin mu-chain; Primary immunodeficiency diseases

INTRODUCTION

Autosomal recessive agammaglobulinemia (ARA) is a rare inborn error of immunity that is characterized by severe hypogammaglobulinemia and absent peripheral B-cells without *BTK* gene mutation.[1] ARA is reported to present with more severe and earlier manifestations compared with X-linked agammaglobulinemia due to BTK deficiency.[2]

Deleterious biallelic mutations in several genes encoding for *Igα*, *Igβ*, *μ heavy chain*, *BLNK*, *SLC39A7*, *FNIP1*, *CTNNBL1*, *p85α,* and *p110δ* (PI3K signaling) are associated with ARA.[3]

Besides these proteins, intact membrane-bound mu heavy chain is important for early B-cell development so any defect in gene encodes this component can cause ARA in humans with low peripheral B cells.[4]

Of note, the immunoglobulin heavy chain constant region (IGH) locus is a multigene family composed of highly homologous segments often involved in unequal crossings that lead to deleted and duplicated haplotypes.[5] In this study, we described a case of ARA with a large deletion mutation in the IGH locus who presents with a severe skin infection and disseminated intravascular coagulation.

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Case Report

The patient was a 2-years old girl who was born to a consanguineous family. Her sibling died due to leukemia. She was referred to our center with fever; severe skin infection and necrotic abscess (Figure1).

After several days, her condition deteriorated and the clinical picture of sepsis and disseminated intravascular coagulation appeared. Microscopic examination of skin lesions revealed ecthyma gangrenosum. But we do not have any positive skin or blood culture in our evaluations. Subsequently, she was treated with an empirical broad spectrum of antibiotics targeting *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Ceftazidime and vancomycin were antibiotics that we used in the patient. Recovery was achieved after several days and the patient was discharged with good condition and recommendation for intravenous immunoglobulin replacement therapy.

Because of severe and unusual infection in this patient immunologic profile was evaluated. Laboratory data at this admission are shown in Table 1.

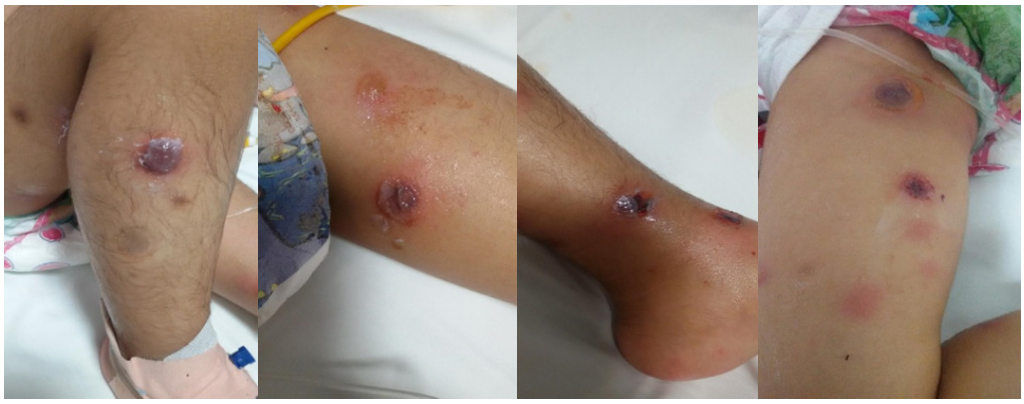

Figure 1. Severe skin infection and necrotic abscess in a patient with immunoglobulin heavy chain deficiency

Table 1. Immunologic profile and laboratory data of a patient with immunoglobulin heavy chain deficiency

Parameters	Patient	Normal values
IgG (mg/dL)	<50	295-1156
IgA (mg/dL)	9	27 -246
IgM (mg/dL)	10	37 -184
IgE (IU/mL)	<0.100	0-60
Specific antibodies		
Anti-diphtheria antibody (IU/mL)	0.001	>0.01
Anti-tetanus antibody (IU/mL)	0.001	>0.01
Complete blood count		
White blood cells, cells/mL	31400	5200-11000
Neutrophils, cells/ml (% of WBC)	26376 (84%)	1500-9000
Lymphocytes, cells/ml (% of WBC)	5024 (16%)	2300-5400
Lymphocyte subsets		
$CD3^+$ T cells/uL (%)	3964 (79.5%)	1400-3700
$CD3^+CD4^+$ T cells	2210 (44%)	700-2200
$CD3^+CD8^+$ T cells	2059 (41.6%)	490-1300
$CD19^+$ B cells	200 (4.5%)	390-1400
$CD20^+$ B cells	452 (9.9%)	300-900
$CD16/56^+$ NK cells	502 (10.6%)	480-1300

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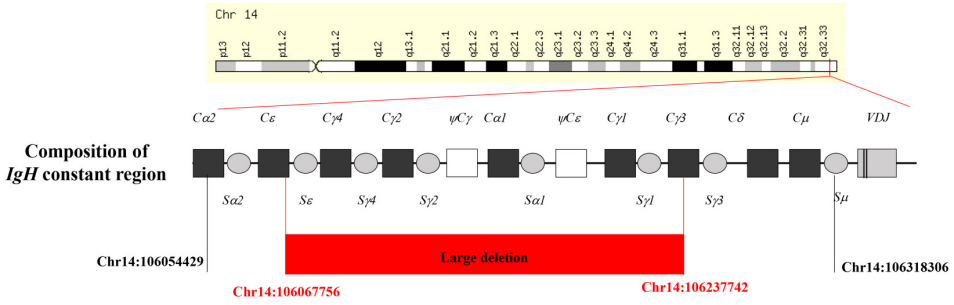
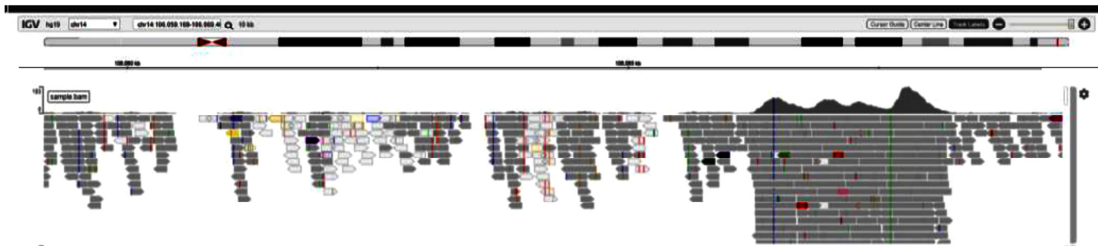
Written informed consent was obtained from the patient's parents for genetic evaluation and anonymized publication (Code: 1399-03-25-1951). Whole exome sequencing (WES) was performed using a qualified genomic DNA sample which was randomly fragmented by Covaris technology (Covaris, USA) and the size of the library fragments was mainly distributed between 150bp and 250bp. The end-repair of DNA fragments was performed, and an "A" base was added at the 3'-end of each strand. Adapters were then ligated to both ends of the end-repaired/dA-tailed DNA fragments for amplification and sequencing. Size-selected DNA fragments were amplified by ligation-mediated PCR (LM- PCR), purified, and hybridized to the exome array for enrichment (using Sureselect kit, Agilent Technologies, UAS). Non-hybridized fragments were then washed out. Captured products were then circularized. The rolling circle amplification (RCA) was performed to produce DNA Nanoballs (DNBs). Each resulting qualified captured library was then loaded on BGISEQ-500 sequencing platforms (Shenzhen, China), and high-throughput sequencing for each captured library was performed to ensure that it met the desired average sequencing coverage.

The average sequencing depth on target was 147.5 and the fraction of target covered >4X was 99.8%. WES analysis using a previously published pipeline,[6,7] revealed a homozygous large deletion in chromosome 14q32.33 (106067756-106237742) immunoglobulin heavy chain clusters compatible with residual counts of B cells in the patient. Even though the large deletion does not affect the Cμ the severe impact on the regulatory elements of the IGH region can explain the low level of IgM in this patient (Figure 2).

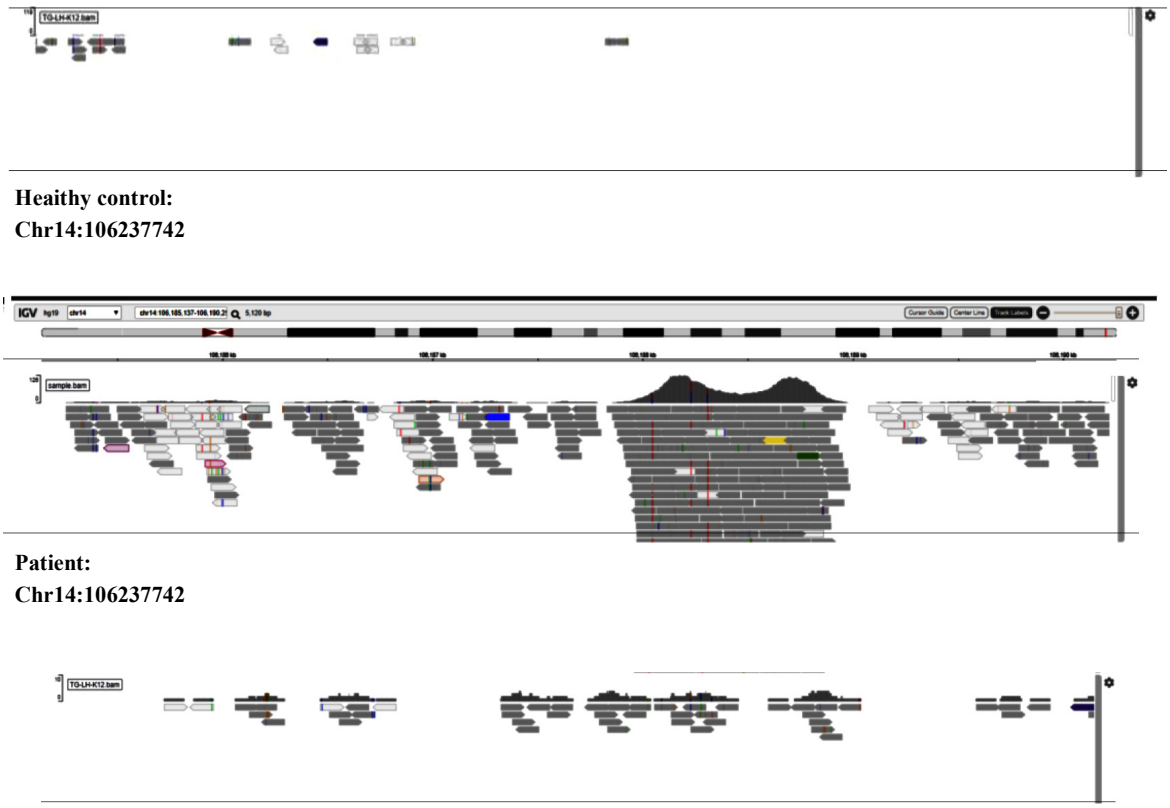
These deletions were confirmed by Sanger sequencing compared to healthy individuals. The genetic findings in combination with the clinical and immunological data were consistent with the definitive diagnosis of IGH deficiency.



Healthy control:
Chr14:106067756



Patient:
Chr14:106067756



Heaithy control:
Chr14:106237742

Patient:
Chr14:106237742

Figure 2. Large deletion of immunoglobulin heavy chain region from Cγ3 till Cε on chromosome 14 of a patient presenting with autosomal recessive agammaglobulinemia

DISCUSSION

Agammaglobulinemia is associated with significant morbidity and mortality in the absence of appropriate treatment. Patients with congenital agammaglobulinemia present with infections caused by encapsulated bacteria, mainly *Streptococcus pneumoniae* and *Haemophilus influenzae*. The most common clinical manifestations are acute or chronic otitis media, sinusitis, and pneumonia, and skin infections. Other infections that lead to hospitalizations are meningitis, meningoencephalitis, vaccine-associated polio, arthritis, and mastoiditis.[8] One of the most important and prominent clinical features of agammaglobulinemia patients are respiratory tract complications such as pneumonia and bronchiectasis.[9,10]

The majority of patients with agammaglobulinemia are not recognized to have primary immunodeficiency until they are admitted for infection.[11] Of note, many proteins are required for immunoglobulin production and the IGH heavy chain is at the center of this process and several gene mutations can lead to profound immunodeficiency.[1,4] We described a rare case of ARA that genetic analysis showed large deletion in chromosome 14q32.33 (106067756-106237742) immunoglobulin heavy chain clusters.

Disseminated intravascular coagulopathy (DIC) is a rare presentation of patients with ARA. There are few reports of pseudomonas and staphylococcal sepsis associated with neutropenia in patients with agammaglobulinemia.[11,12] But to the best of our knowledge, there is no evidence about IGH deficiency and susceptibility to DIC. Interestingly the literature review of all reported patients with IGH deficiency indicates that the majority of IGH patients (17 patients, almost 50% of all reported cases globally, Table 2) are due to deleting gross deletion breakpoints were located in or close to transposable elements-derived repeats.

Table 2. Previously reported patients with immunoglobulin heavy chain (IGH) deficiency due to homozygous large deletion and antibody deficiency

Description	Phenotype	Year	Reference
125 kb (IGV6-1 to Cδ)	Hypogammaglobulinaemia	2002	16
165-265 kb (described at genomic DNA level)	Hypogammaglobulinaemia	2002	17
300 kb (described at genomic DNA level)	Hypogammaglobulinaemia	2002	16
40 kb (described at genomic DNA level)	Hypogammaglobulinaemia	2002	16
578 kb (IGV3-20 to Cγ4)	IGHM-deficiency	2008	13
732 kb (IGV3-41 to Cα1)	IGHM-deficiency	2008	13
75-100 kb (IGD to Cμ)	Hypogammaglobulinaemia	1996	18
117 kb (IGV6-1 to Cδ)	IGHM-deficiency	2019	19
320 kb (Cγ1 to Cα1)	IgG subclass deficiency	1982	20, 21

Interestingly, the involved elements (particularly LINEs and LTR retrotransposons) have been evident to be overrepresented in the IGH locus compared to the average in the human genome. Gastrointestinal and neurologic complications due to polio vaccine are common in reported IGH deficient cases due to large deletion but were absent in our current studied patient.[13]

Several studies have tried to establish a genotype-phenotype correlation in patients with agammaglobulinemia, especially in BTK mutations. But the result was controversial. Aghamohammadi et al in one study showed that there is a correlation between clinical phenotype and the category of agammaglobulinemia (XLA, ARA). Comparison of XLA and ARA showed that the age at onset of the clinical presentation was lower in ARA, mainly IGH deficiency. They also showed that the variation of BTK mutation does not correlate with the clinical phenotype.[14] In another study, 54 patients with agammaglobulinemia were evaluated (48 patients with BTK mutation and 6 patients with mu heavy chain mutation). The most common presentation in both groups was pneumonia. Meningitis was seen in 16 patients with BTK mutation. However, in patients with mu heavy chain, the most frequent diseases were pneumonia, otitis media, autoimmunity, and sinusitis respectively.[15]

IGH deficiency is one of the forms of AAR that could be presented in the early childhood period with very severe and unusual manifestations such as DIC, so early diagnosis and replacement therapy with intravenous immunoglobulin and appropriate antibiotic prophylaxis lead to control of severe and catastrophic complications.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

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REFERENCES

1. Ben-Ali M, Kechout N, Mekki N, Yang J, Chan KW, Barakat A, et al. Genetic Approaches for Definitive Diagnosis of Agammaglobulinemia in Consanguineous Families. J Clin Immunol. 2020;40(1):96-104.
2. 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.
3. Khalili A, Plebani A, Vitali M, Abolhassani H, Lougaris V, Mirminachi B, et al. Autosomal recessive agammaglobulinemia: a novel non-sense mutation in CD79a. J Clin Immunol. 2014;34(2):138-41.
4. Yel L, Minegishi Y, Coustan-Smith E, Buckley RH, Trübel H, Pachman LM, et al. Mutations in the mu heavy-chain gene in patients with agammaglobulinemia. New Eng J Med. 1996;335(20):1486-93.
5. Brusco A, Cariota U, Bottaro A, Boccazzi C, Plebani A, Ugazio AG, et al. Variability of the immunoglobulin

heavy chain constant region locus: a population study. Hum Gen. 1995;95(3):319-26.
6. Abolhassani H, Aghamohammadi A, Fang M, Rezaei N, Jiang C, Liu X, et al. Clinical implications of systematic phenotyping and exome sequencing in patients with primary antibody deficiency. Genet Med. 2019;21(1):243-51.
7. Abolhassani H, Hammarstrom L, Cunningham-Rundles C. Current genetic landscape in common variable immune deficiency. Blood. 2020;135(9):656-67.
8. Bagheri Y, Vosughi A, Azizi G, Yazdani R, Hafezi N, Alimorad S, et al. Comparison of clinical and immunological features and mortality in common variable immunodeficiency and agammaglobulinemia patients. Immun lett. 2019;210(6):55-62.
9. Fekrvand S, Yazdani R, Olbrich P, Azizi G, Shirzadi R, Modaresi M, et al. Evaluation of respiratory complications in patients with X□linked and autosomal recessive agammaglobulinemia. Ped Allergy Immunol. 2020;31(4):405-17.
10. Pashangzadeh S, Yazdani R, Nazari F, Azizi G, Abolhassani H, Aghamohammadi A. Agammaglobulinemia: Epidemiology, Pathogenesis, Clinical Phenotype, Diagnosis, Prognosis and Management. Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders). 2020;20(9):1434-47.
11. Conley ME, Howard V. Clinical findings leading to the diagnosis of X-linked agammaglobulinemia. J Pediatrics. 2002;141(4):566-71.
12. Granados EL, Porpiglia AS, Hogan MB, Matamoros N, Krasovec S, Pignata C, et al. Clinical and molecular analysis of patients with defects in μ heavy chain gene. J Clin Invest. 2002;110(7):1029-35.
13. van Zelm MC, Geertsema C, Nieuwenhuis N, de Ridder D, Conley ME, Schiff C, et al. Gross deletions involving IGHM, BTK, or Artemis: a model for genomic lesions mediated by transposable elements. Am J Hum Genet. 2008;82(2):320-32.
14. Abolhassani H, Vitali M, Lougaris V, Giliani S, Parvaneh N, Parvaneh L, et al. Cohort of Iranian patients with congenital agammaglobulinemia: mutation analysis and novel gene defects. Expert Rev Clin Immunol. 2016;12(4):479-86.
15. Mohsenzadeh A, Yazdani R, Abolhassani H, Kiaee F. Comparison of Common Monogenic Defects in a Large Predominantly Antibody Deficiency Cohort. J Allergy Clin Immunol Pract. 2019;7(3):864-878.
16. Lopez Granados E, Porpiglia AS, Hogan MB, Matamoros N, Krasovec S, Pignata C, et al. Clinical and molecular analysis of patients with defects in micro heavy chain gene. J Clin Invest. 2002;110(7):1029-35.
17. Milili M, Antunes H, Blanco-Betancourt C, Nogueiras A, Santos E, Vasconcelos J, et al. A new case of autosomal recessive agammaglobulinaemia with impaired pre-B cell differentiation due to a large deletion of the IGH locus. Eur J Pediatr. 2002;161(9):479-84.
18. Yel L, Minegishi Y, Coustan-Smith E, Buckley RH, Trubel H, Pachman LM, et al. Mutations in the mu heavy-chain gene in patients with agammaglobulinemia. N Engl J Med. 1996;335(20):1486-93.
19. Yazdani R, Abolhassani H, Kiaee F, Habibi S, Azizi G, Tavakol M, et al. Comparison of Common Monogenic Defects in a Large Predominantly Antibody Deficiency Cohort. JAllergy Clin Immunol. 2019;7(3):864-78.
20. Lefranc G, Chaabani H, Van Loghem E, Lefranc MP, De Lange G, Helal AN. Simultaneous absence of the human IgG1, IgG2, IgG4 and IgA1 subclasses: immunological and immunogenetical considerations. Europ Journal Immunol. 1983;13(3):240-4.
21. Lefranc MP, Lefranc G, Rabbitts TH. Inherited deletion of immunoglobulin heavy chain constant region genes in normal human individuals. Nature. 1982;300(5894):760-2.