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Case Report

De novo *CXCR4* Mutation in WHIM Syndrome: Report of a 4-Year-Old Case without Wart and Myelokathexis

Shayan Roshdi[1,2]†, Sepideh Shahkarami[3,4]†, Samaneh Zoghi[4,5], Elham Rayzan[4], Rasol Molatefi[6], Meino Rohlfs[3], Christoph Klein[3], Nima Rezaei[4,7*]

[1] *School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*
[2] *Medical Genetics Network (MeGeNe), Universal Scientific Education and Research Network (USERN), Munich, Germany*
[3] *Department of Pediatrics, Dr. von Hauner Children's Hospital, Ludwig-Maximilians-Universität München, Munich, Germany*
[4] *Research Center for Immunodeficiencies, Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran*
[5] *St. Anna Children's Cancer Research Institute (CCRI), Vienna, Austria*
[6] *Pediatric Department of Bou-Ali Educational Hospital, Ardabil University of Medical Sciences, Ardabil, Iran*
[7] *Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran*

† These authors contributed equally.

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Abstract

WHIM syndrome (Warts, Hypogammaglobulinemia, Immunodeficiency, and Myelokathexis syndrome), a type of severe congenital neutropenia (SCN), involves Warts, Hypogammaglobulinemia, Infections, and Myelokathexis as its main components of clinical presentation, which results from mutations in the *C-X-C chemokine receptor type 4* (*CXCR4*) gene.

Here, we present an Iranian 4-year-old girl with severe congenital neutropenia without warts and normal bone marrow examination, lacking evidence of myelokathexis. Whole Exome Sequencing (WES) was performed for the patient. Subsequently, Sanger segregation/validation was done of the patient and her parents. Whole exam sequencing identified a heterozygous stop variant mutation in *CXCR4* (NM_001008540.2:c.1012C>T; p.Arg338Ter) in the patient. Two of the main clinical criteria in WHIM syndrome, including warts and myelokathexis, were not observed in our patient. So, the absence of warts is not deceptive in ruling out the disease. This case report also represents the high importance of genetic analysis as a primary tool for the accurate differential diagnosis of patients with neutropenia.

Keywords: WHIM Syndrome, Severe Congenital Neutropenia, CXCR4, Whole Exome Sequencing

***Corresponding Author:** Nima Rezaei, MD, PhD
Research Center for Immunodeficiencies, Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran
E-mail: rezaei_nima@tums.ac.ir

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Introduction

Severe congenital neutropenia (SCN), one type of primary immunodeficiency disorder, is defined as absolute neutrophilic count (ANC) of <0.5 x 109/L for at least three months. This immune deficiency makes patients prone to multiple infectious events during early childhood that are severe enough to cause hospital admissions (1,2). Recent genetic analysis reveals more than one hundred genes attributing to SCN, although

the exact pathogenesis of many of them is not understood well (2,3). Some of these mutations accompany non-hematological presentations as a syndrome that can help physicians shorten their differential diagnosis list (2).

WHIM syndrome, a subtype of SCN, is a congenital immunodeficiency characterized by susceptibility to human papilloma virus-induced Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (4,5). This syndrome is caused by an autosomal dominant mutation in the gene encoding *C-X-C chemokine receptor type 4* (*CXCR-4*) (6). Herein, we present a case of SCN with absent warts and normal bone marrow associated with a de novo mutation in *CXCR4*. With this case, we aim to question the consideration of warts and myelokathexis as constant elements of WHIM syndrome in the pediatric population.

Case Presentation

A 4-year-old Iranian girl was referred to the Pediatrics Center of Excellence of the Children's Medical Center Hospital, Tehran, Iran, due to persistent neutropenia and lymphopenia. The patient was the first and only child born via normal vaginal delivery of non-consanguineous parents, who were healthy with a history of neither primary immune deficiency nor other diseases. The patient's birth history was favorable, with a born weight of 2.7 Kg and a normal Apgar score. She reached developmental milestones at appropriate ages, and her cognitive function status was also normal. The diagnosis of neutropenia was firstly established at 1 year of age during the workup of abscess formation in the vaccine injection site. From then on, the patient suffered from chronic diarrhea, multiple bronchopulmonary bacterial infections, and episodes of prolonged fever that rarely exceeded 38.5° C. The patient only consumed a Salbutamol inhaler for her reactive airway disease and iron supplements.

Her physical examination was unremarkable except for failure to thrive (FTT) and tenderness in her legs and thighs. In her medical profile, a bone marrow biopsy was taken at the age of 3, demonstrating normal bone marrow tissue with 90% cellularity composed of a polymorphic population of hematopoietic cells and a normal level of megakaryocytes. CBC exams in our center approved previously reported neutropenia several times. Results of all CBC exams sorted by age are listed in **Table 1**. Considering the patient's previous medical history of multiple infectious events and lab tests confirming consistent neutropenia, primary immune deficiency diseases were suggested at the top list of differential diagnosis. A quantitative serum immunoglobulin test was performed, and the result was consistent with IgG in the lower normal range (IgG: 516 mg/dl) and an increased IgE level (645.5 IU/ml)**(Table 2)**. Blood flow cytometry on 1200 WBC/μL revealed CD-3 lymphocyte 82%, CD-4 lymphocyte 74%, CD-8 lymphocyte 7.6%, CD-19 lymphocyte 3%, and CD-16-56 NK cells 6.5 %. To assay the functional status of IgG, we performed the Isohemagglutinin titer test, and we detected a defect in the function of IgG (Iso-Anti-A: 1/2 and Iso-Anti-B: negative, BG: B). A trial course of G-CSF was initiated but failed to increase the ANC number to a favorable count. We performed whole Exome Sequencing (WES) for the patient. Agilent V6+UTR library preparation and an Illumina NextSeq 500 sequencing platform were used. The bioinformatics analysis pipeline uses Burrows-Wheeler Aligner (BWA 0.7.15), Genome Analysis Toolkit (GATK 3.6), Variant Effect Predictor (VEP 89), and frequency filters with public and in house databases (e.g. ExAC, GnomAD and GMEl). WES identified a heterozygous stop variant (NM_001008540.2:c.1012C>T; p.Arg338Ter)

Table 1. CBC exams sorted by age in years.

Age (year)	WBC* (10^9/L)	ANC* (10^9/L)	lymphocytes (10^9/L)	Monocytes (10^9/L)
4	1.2	0.15	0.94	0.09
4	1.07	0.07	0.88	0.1
6	1.5	0.5	0.8	0.2
6	1.2	0.38	0.76	0.01
6	1.8	1	0.75	0.01

***WBC, white blood cell count; ANC, absolute neutrophilic count**

Table 2. Quantitative serum immunoglobulin test

Type	Result	Unit	Normal Range
IgM*	94	mg/dl	37-224
IgA*	90	mg/dl	25-134
IgE*	645.5	IU/ml	<135
IgG*	516	mg/dl	386-1470

***IgM, Immunoglobulin M; IgA, Immunoglobulin A; IgE, Immunoglobulin E; IgG, Immunoglobulin G**

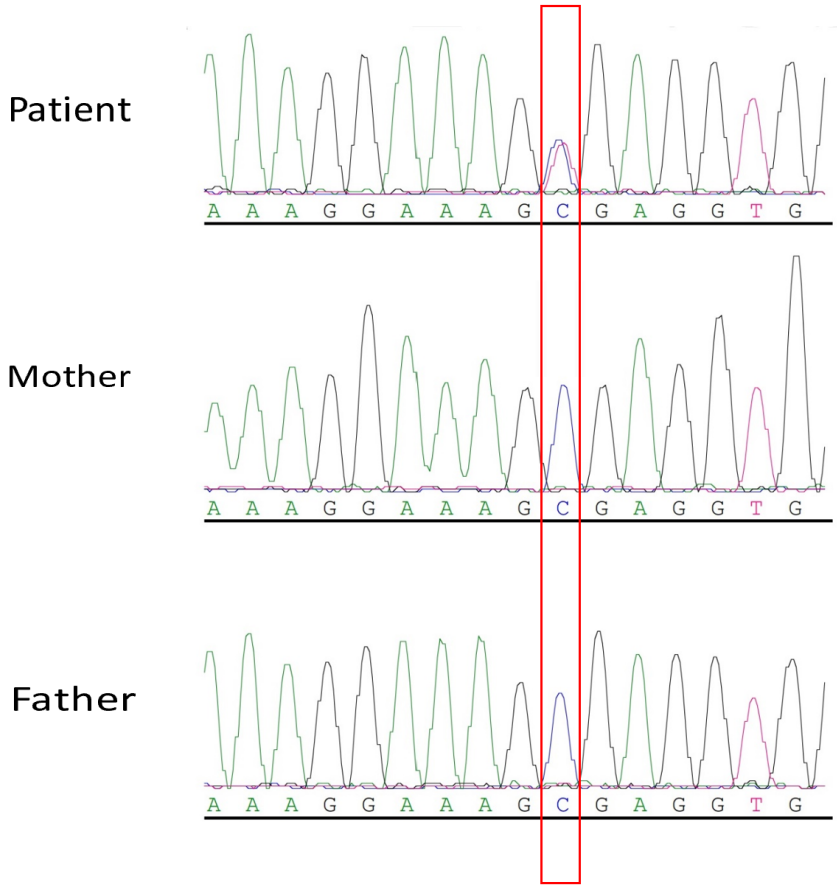

Figure 1. Sanger validation/segregation in the patient and parents.

in the *CXCR4* (*CXC chemokine receptor 4*) gene, which was described before (rs104893624) to cause autosomal dominant WHIM syndrome (OMIM#193670). This mutation is a de novo event in the patient since both parents were normal for this variant **(Figure 1)**.

Discussion

Severe congenital neutropenia encompasses a large group of genetically inherited disorders, and the prompts diagnosis of the causative disease is necessary to administer appropriate treatments and avert severe complications. As some of the diseases leading to SCN manifest with phenotypes more than neutropenia, accompanying features seen in patients with SCN can guide physicians to confine the differential diagnosis (2). It should be noted that although genetic analysis confirms the diagnosis of the presumed disease, some cases may fulfill the criteria of a syndrome with no gene detection, and it can make the diagnosis more difficult (7).

Variations in the clinical presentation of a syndrome may delay diagnosis and result in misclassification of the disease to other primary immune deficiency groups unless a responsible gene is detected (6). The case we presented has genetic confirmation for WHIM syndrome but doesn't have warts in her clinical presentation and didn't depict characteristics of myelokathexis in the bone

marrow examination. As the first component represented in the acronym of WHIM syndrome, Warts are less likely to be found in early ages since the pediatric population has low sexual and cutaneous exposure to the *Human Papillomavirus* (*HPV*)(7–9). Therefore, it may raise the doubt about the absence of warts to be considered a diagnostic clue to rule out WHIM syndrome.

Myelokathexis, a Greek word meaning bone marrow retention, was first described by Zuelzer in 1964 in a patient that was later believed to be the first patient affected by WHIM syndrome (9). Thanks to molecular biology, the pathology behind the myelokathexis in affected patients is explained now. Mutations in *CXCR4*, the primary gene associated with WHIM syndrome, impairs cell trafficking and hemostasis through hypo-function in interaction with its unique ligand CXCL12. This impairment results in the retention of bizarre matured neutrophils in bone marrow (9–11). The cell retention in bone marrow (myelokathexis) is considered as a component of the WHIM acronym since it was a common finding among the WHIM patients guiding the physician toward the clinical suspicion for this syndrome in neutropenic patients (4).

Despite what is declared as characteristic clinical features of WHIM syndrome, warts were not found in our patient, and bone marrow biopsy didn't demonstrate features of myelokathexis. However, genetic analysis proved the *CXCR4* mutation responsible for WHIM syndrome. This heterogeneity in phenotypic presentation adds support for recommending gene analysis utilization as a primary tool for accurate diagnosis instead of relying on the presence or absence of phenotypic traits in PID patients. In addition, clinicians should be informed that the absence of these components is not convincing to exclude WHIM syndrome as a causative disease in neutropenic patients.

Conclusion

This article and other similar cases add support for further investigations on early presentations of WHIM syndrome to guide physicians for more reliable diagnosis when the definite genetic analysis is not performed yet. Since warts are a late complication of whim syndrome, we suggest not to consider it as a main component for diagnosing WHIM syndrome. Considering the importance of immediate and precise diagnosis of congenital immunodeficiency disorders in the pediatric population, we emphasize performing genetic analysis early in our workup to confirm the definite diagnosis instead of relying on phenotypical presentations of the patient.

Consent for Publication

Samplings were done according to the Ethics Committee of TUMS (Tehran University of Medical Sciences). After describing the unique presentation of the patient's disease to her family, they consented to the authors to publish their child's medical records for research purposes, and written informed consent has been taken from patient's parents (approval number: 98-3-205-46257).

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Conflict of Interest

The authors declare that there is no conflict of interest.

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