Bridging diagnosis of a rare hematological disorder through genetic testing in a young girl with persistent panleukopenia

Himanshi Chaudhary[1], Sanjib Mondal[2], Ariba Zaidi[2], Pandiarajan Vignesh[1], Man Updesh Sachdeva[2], and Amit Rawat[1]

[1]PGIMER
[2]Post Graduate Institute of Medical Education and Research

September 11, 2020

Title Page

Manuscript type: Letter to editor

Title: Bridging diagnosis of a rare hematological disorder through genetic testing in a young girl with persistent panleukopenia

Running title: Young girl with persistent panleukopenia

Authors:

1. Dr. Himanshi Chaudhary, MD, Senior Resident, Allergy Immunology unit, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India-160012. Email: chaudhary.himanshi1434@gmail.com
2. Dr. Sanjib Mondal, MD Senior Resident, Allergy Immunology unit, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India-160012. Email: drsanjib87@gmail.com
3. Dr. Ariba Zaidi, MD, Senior Resident, Department of Hematology, Postgraduate Institute of Medical Education and Research, Chandigarh, India-160012. Email: draribazaidi@gmail.com
4. Dr. Vignesh Pandiarajan, DM, Assistant Professor, Allergy Immunology unit, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India-160012. Email: vigimmc@gmail.com
5. Dr. Man Updesh Singh Sachdeva MD, Professor, Department of Hematology, Postgraduate Institute of Medical Education and Research, Chandigarh, India-160012.

Email: drmanupdeshpgi@yahoo.co.in

Dr. Amit Rawat, MD, Professor, Allergy Immunology unit, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India-160012.

Email: rawatamit@yahoo.com

Author contribution:

Dr. Himanshi Chaudhary: Patient management, draft of manuscript, conception of the study, data analysis and editing.

Dr. Sanjib Mondal: Patient management, draft of manuscript

Dr. Ariba Zaidi: Examination of peripheral smears, bone marrow examination, review of literature

Dr. Vignesh Pandiarajan: Patient management, Clinician- in charge, concept of manuscript, review of literature, approval of manuscript

Dr. Man Updesh Singh Sachdeva: Examination of bone marrow slides, diagnosis of myelokathexis and WHIMS

Dr. Amit Rawat: Patient management, immunological investigations, critical review of manuscript for important intellectual content

Name of institution :

Advanced Pediatrics Centre,

Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India

Disclaimers : Nil

Correspondence:

Dr. Vignesh Pandiarajan

Assistant Professor, Allergy Immunology unit, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India-160012.

Email: vigimmc@gmail.com

Telephone: +91-9592047009

Funding/ Support: None declared

Declaration on competing interest: Nil

Word count: 500

No. of tables: 1

No. of figures: 1

No. of supplementary figures: 1

Keywords : Warts, Hypogammaglobulinemia, Infections and Myelokathexis syndrome (WHIMS), primary hypogammaglobulinemia, neutropenia, panleukopenia

Bridging diagnosis of a rare hematological disorder through genetic testing in a young girl with persistent panleukopenia

A 9-year-old girl was referred for evaluation of fever for 2 months without any systemic complaints. She was first born to a non-consanguineously married couple with no significant family history. She had past history of 3 episodes of pneumonia requiring intravenous antimicrobials and hospital admissions. She was noted to have panleukopenia in her blood counts and underwent bone marrow examination twice (reported as normal). However, in view of recurrent infections and chronic persistent leukopenia, she was referred to our center. Systemic examination was unremarkable. Laboratory investigations showed persistently low total white cell counts (TLC) (table 1). Repeat bone marrow aspiration showed hypercellular marrow with no atypical cells. With a suspicion of underlying inborn error of immunity (IEI), genetic analysis was done which showed a heterozygous novel mutation in exon 1 of *CXCR4* (c.1012C>T, p. Arg338Ter). A fresh and detailed re-look at the bone marrow aspirate revealed evidence of myelokathexis (Fig. 1). A diagnosis of Warts, Hypogammaglobulinemia, Infections and Myelokathexis syndrome (WHIMS) was made and she was treated with 1 µg /kg/day of subcutaneous granulocyte colony-stimulating factor (G-CSF) therapy for 2 weeks and prophylactic dose of co-trimoxazole (5 mg/kg/day). Since there was not much improvement in cell counts, G-CSF was gradually hiked to 5 µg /kg/day. After hiking of dose, her TLC started improving

(supplemental figure S1). At 10 months of follow up, she has normal leukocyte counts and there has been no breakthrough infections.

Discussion:

WHIMS is an autosomal dominant IEI caused by a gain of function mutation in CXC chemokine receptor 4 (CXCR4) [1]. CXCR4 chemokine receptor binds to its ligand CXCL-12 and has a role in leukocyte trafficking, signaling, survival and proliferation [2]. Clinical spectrum of WHIMS includes recurrent infections, susceptibility to human papilloma virus (HPV) infection, and immunodeficiency characterized by neutropenia, hypogammaglobulinemia, and lymphopenia.

Common hematological manifestations observed in WHIMS include neutropenia, lymphopenia, and mild thrombocytopenia[3,4]. Neutrophils are typically sequestered within the bone marrow that show myeloid hyperplasia and cytoplasmic abnormalities like vacuolization, chromatin hyper condensation and hyper segmented nuclei, traditionally labelled as myelokathexis [3].

Because of rarity of this condition, WHIMS is often overlooked and missed by hematologists during the evaluation of panleukopenia or neutropenia [5]. In majority of centers, *CXCR4* is not included in the panel for genetic evaluation of leukopenia/ neutropenia. Our patient was evaluated for chronic leukopenia for months elsewhere. The bone marrow examination also missed myelokathexis and genetic testing finally clinched the diagnosis of WHIMS.

Treatment involves antimicrobial therapy, removal of warts and immunoglobulin replacement in patients with hypogammaglobulinemia. Leucocyte mobilizing agents like G-CSF and specific *CXCR-4* antagonists like plerixafor are advised in patients with severe neutropenia and recurrent infections [6]. Definitive cure strategies include allogenic hematopoietic stem cell transplant and gene therapy [4] .

In conclusion, WHIMS is an important differential diagnosis to be considered in evaluation of leukopenia in childhood. A careful look at marrow for myelokathexis or a genetic work-up can clinch the diagnosis of WHIMS in children with leukopenia. Genetic confirmation is essential for counselling of the affected families.

References:

1. Tangye SG, Al-Herz W, Bousfiha A, et al. Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. *Journal of Clinical Immunology* . 2020;40(1):24-64. doi:10.1007/s10875-019-00737-x

2. Kawai T, Malech HL. WHIM syndrome: congenital immune deficiency disease. *Curr Opin Hematol* . 2009;16(1):20-26. doi:10.1097/MOH.0b013e32831ac557

3. Beaussant Cohen S, Fenneteau O, Plouvier E, et al. Description and outcome of a cohort of 8 patients with WHIM syndrome from the French Severe Chronic Neutropenia Registry. *Orphanet Journal of Rare Diseases* . 2012;7(1):71. doi:10.1186/1750-1172-7-71

4. Heusinkveld LE, Majumdar S, Gao J-L, McDermott DH, Murphy PM. WHIM Syndrome: from Pathogenesis Towards Personalized Medicine and Cure.*Journal of Clinical Immunology* . 2019;39(6):532-556. doi:10.1007/s10875-019-00665-w

5. Walter JE, Ballow M. The WHIM Syndrome Is No Longer a Whim. *The Journal of Allergy and Clinical Immunology: In Practice* . 2019;7(5):1578-1579. doi: 10.1016/j.jaip.2019.03.001

6. Dotta L, Tassone L, Badolato R. Clinical and genetic features of Warts, Hypogammaglobulinemia, Infections and Myelokathexis (WHIM) syndrome. *Curr Mol Med* . 2011;11(4):317-325. doi:10.2174/156652411795677963

Legends to Figure 1 : Bone marrow aspirate smears of patient with WHIMS (A) neutrophils (arrows) showing abnormal nuclear lobation with presence of extremely thin chromatin threads connecting the nuclear lobes (Magnification 40x); (B) similar neutrophils (magnification 100x).

Legends to Supplemental Figure S1 : Trend of total leucocyte count, absolute neutrophil count and absolute lymphocyte count after GM-CSF therapy

Hosted file

TABLE 1.docx available at https://authorea.com/users/333860/articles/479498-bridging-diagnosis-of-a-rare-hematological-disorder-through-genetic-testing-in-a-young-girl-with-persistent-panleukopenia