# WHIM Syndrome and CXCR4 Variants: New Insights into Cellular Changes That Can Impact Patient Treatment Plans

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# Resource Information

## About This Resource

These slides are one component of a continuing education program available online at MedEd On The Go titled WHIM Syndrome (A Chronic Neutropenic Disorder): Uncouple the Complex for HCPs and Patients

**Program Learning Objectives:**

- Gain an understanding of WHIM syndrome as a rare PID/ chronic neutropenic disorder with diverse clinical presentations
- Implement strategic measures to improve the early identification of WHIM syndrome patients for prompt assessment and diagnosis to avoid potential complications and long-term sequelae
- Understand the CXCR4 pathway dysregulation and how it relates to the underlying causes of WHIM syndrome
- Garner an understanding of the limitations of current approaches for WHIM syndrome and potential new approaches for patients

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# WHIM Syndrome: Family History

- WHIM syndrome is an autosomal dominant disorder caused by mutations in the *CXCR4* gene
- The *CXCR4* mutation that causes WHIM syndrome may be inherited from an affected parent or may occur de novo as a new mutation in a patient whose parents do not carry the mutation
- One study found that 59% of WHIM syndrome mutations occurred de novo
- Therefore, a family history of immunodeficiency, such as recurrent infections, is frequently not present in patients with WHIM syndrome
- Patients with a family history were diagnosed earlier, received earlier treatment, experienced less hospitalization, and had less end-organ damage

Geier CB, et al. *J Clin Immunol*. 2022;42(8):1748-1765.

# WHIM Syndrome: Clinical Signs

- The cardinal clinical features used to recognize and diagnosis WHIM syndrome include those for which WHIM syndrome takes its name: Warts, Hypogammaglobulinemia, Infections, and Myelokathexis, along with neutropenia and lymphopenia
- However, the clinical features are variable in their occurrence and age of onset, often resulting in delayed diagnosis

| Clinical feature | Reported frequency | Reported age at clinical detection (years) |
|---|---|---|
| Warts | 40-79% | 12 |
| Hypogammagl-obulinemia | 65-90% | 7.3 |
| Infections | 92-100% | 1.6 |
| Neutropenia | 92-98% | 3.5 |
| Lymphopenia | 88% | 5.3 |

Geier CB, et al. *J Clin Immunol*. 2022;42(8):1748-1765; Kawai T & Malech HL. *Curr Opin Hematol*. 2009;16(1):20-26.

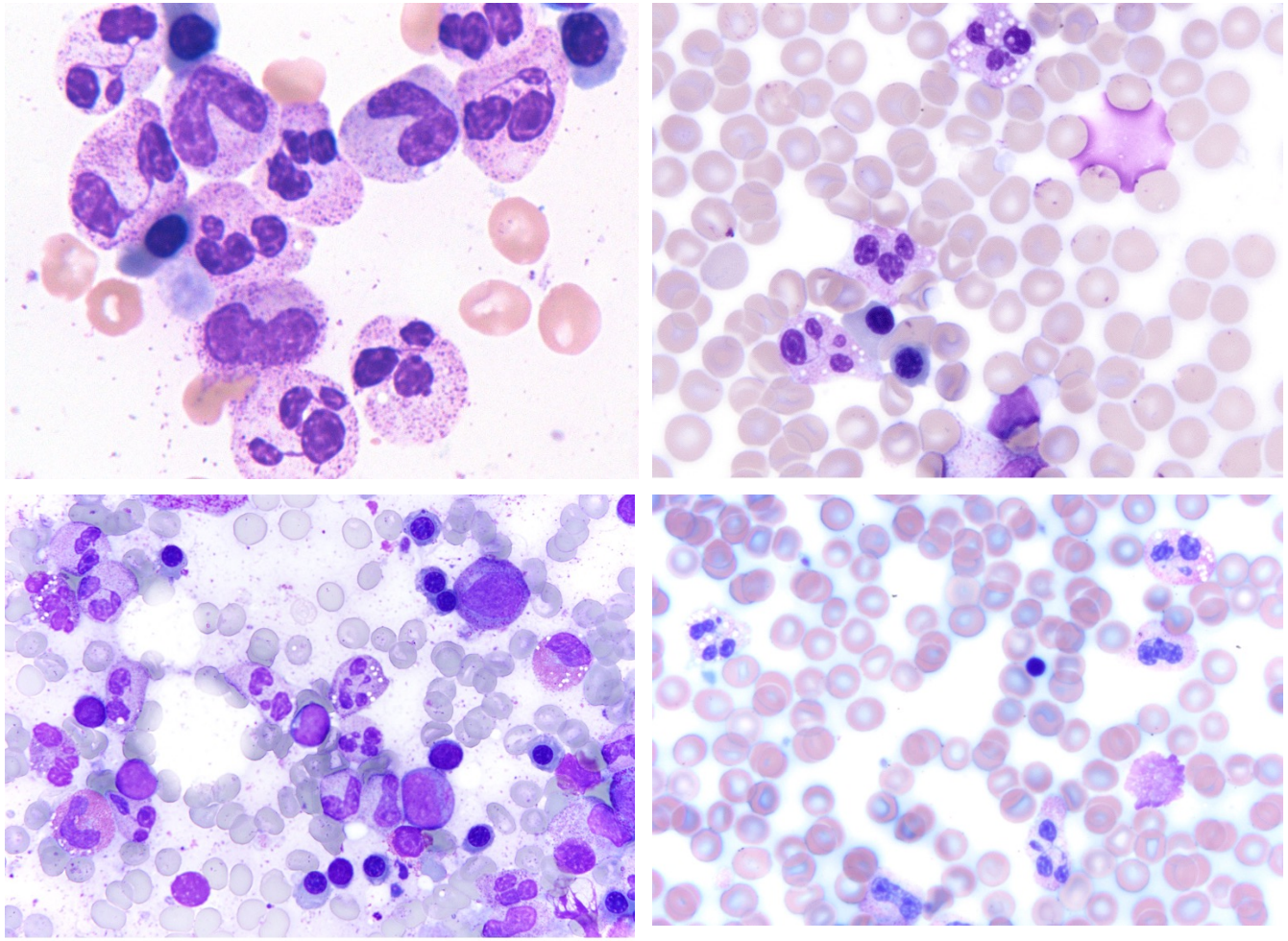
# Reasons for Delayed Diagnosis

- Most patients present with one or more of these findings before 1 year of age. However, delayed diagnosis is common and some patients are not diagnosed until well into adulthood
- Reasons for delayed diagnosis:
  1. The clinical features are variable
  2. WHIM syndrome is rare, and physicians may not be familiar with pertinent features that facilitate its recognition
  3. Infections result in an increase in neutrophil count that may mask neutropenia at the time of clinical presentation
  4. Demonstration of myelokathexis is best accomplished by bone marrow biopsy and the extent of morphologic changes is variable. Myelokathexis is less apparent on peripheral blood smear evaluation

Geier CB, et al. *J Clin Immunol*. 2022;42(8):1748-1765; Cohen SB, et al. *Orphanet J Rare Dis*. 2012;25(7):71.

# Variability in Myelokathexis Morphology

- In a study of 13 WHIM patients, the percentage of neutrophils with myelokathexis morphologies varied greatly, from 32 to 80% (median 66%)
- Most pathologists are not experienced in WHIM syndrome
- The morphology may be subtle, and diagnostic features may not be recognized, resulting in delayed diagnosis



Bledsoe JR, et al. *Blood*. 2022;140(Suppl 1):5487-5489.

# Importance of Early Diagnosis

- Earlier treatment: Decreased risk of severe infection
- Decreased rates of hospitalization
- Less end-organ damage including bronchiectasis and hearing loss from pulmonary and ear infections, respectively
- Increased surveillance for tumors
  - Patients with WHIM syndrome have an increased risk of HPV-driven squamous cell carcinomas and EBV-driven lymphomas

EBV, Epstein-Barr virus; HPV, human-papilloma virus.

Geier CB, et al. *J Clin Immunol*. 2022;42(8):1748-1765; Moulin C, et al. *Br J Haematol*. 2024.

# Delayed Diagnosis Needs to Change

How can we diagnosis WHIM syndrome in a timelier fashion?

- Increase clinician and pathologist familiarity with the disorder
- Develop new assays to evaluate for abnormal leukocyte retention in the bone marrow
  - Evaluation of CXCR4 expression by leukocyte subsets in patients with unexplained neutropenia
  - In addition to WHIM syndrome, myelokathexis may play a role in other neutropenia syndromes including germline *G6PC3* and *CXCR2* mutations
- Utility of early germline sequencing for patients with unexplained and persistent neutropenia or other suspicion for immunodeficiency

McDermott DH, et al. *Blood*. 2010;116(15):2793-802; Marin-Esteban V, et al. *Haematologica*. 2022;107(3):765-769.

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