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Evaluating a Newborn Infant with Pancytopenia for WHIM Syndrome

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Introduction

- Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome is an autosomal dominant immunodeficiency, with about 200 cases reported to date
- Myelokathexis is the retention of neutrophils in the bone marrow which results in peripheral neutropenia and can increase the risk of fatal infections
- In addition to severe neutropenia, most patients with WHIM suffer from pan-leukopenia
- Patients are susceptible to Human Papillomavirus (HPV) infections, resulting in recalcitrant warts and occurs usually in the 2nd decade of life
- Other complications include hearing loss, bronchiectasis, Epstein-Bar virus (EBV) or HPV associated malignancies, autoimmune disease, and heart defects

Initial Presentation

- Full-term male born by urgent cesarean section due to non-reassuring fetal heart tones
- Delivery was complicated by hypoxia initially requiring non-invasive positive pressure ventilation, but was able to be transitioned to high flow nasal cannula
- Admitted to the neonatal intensive care unit (NICU) for therapeutic cooling for concerns of hypoxic ischemic encephalopathy (HIE) and empiric antibiotics for neonatal sepsis
- Initial labs were significant for pancytopenia, but it was suspected to be due to stress, HIE, or infection
- Infectious evaluation including Toxoplasma, Cytomegalovirus, Herpes Simplex Virus, Enterovirus, Parvovirus, Paraechovirus, EBV, CSF and blood cultures were all negative
- Due to the significant pancytopenia without an identifiable infectious etiology, Hematology/Oncology and Immunology were consulted for additional evaluation

Initial Labs

White Blood Cell Count	1.01 x10^3/ mcL
Hemoglobin	7.7gm/dL
Platelet	120x10^3/mcL
Absolute Neutrophil Count	0.17 x10^3/mcL
Absolute Lymphocyte Count	0.80 x10^3/mcL
Absolute Monocyte Count	0.03 x10^3/mcL
Absolute Eosinophil Count	0.02x10^3/mcL
Absolute Basophil Count	0
Total T Cells (CD3+)	1325 mm3
T-Helper Cells (CD4+)	920 mm3
T-Cytotoxic Cells (CD8+)	390 mm3
Total B Cells (CD19+)	42 mm3
Total NK Cells (CD16+)	28 mm3
Naïve CD4+ Cells	817 mm3
Naïve CD8+ Cells	359 mm3
Immunoglobulin G	775 mg/dL
Immunoglobulin A	<7 mg/dL
Immunoglobulin M	12 mg/dL
Immunoglobulin E	5 mg/dL
Lymphocyte Proliferation to Mitogen Stimulation	Normal lymphoproliferative response to PHA and PWM
Newborn Screen for Severe Combined Immunodeficiency	Normal
Blueprint Flex Comprehensive Gene Hematology Panel	Heterozygous for *CXCR4* c.1000C>T,p. (Arg334*)

Clinical Course

- For his anemia, he received a transfusion of packed red blood cells and thrombocytopenia resolved without intervention
- Initial immunology evaluation with lymphocyte subsets showed significantly decreased T, B, and NK cells, including naïve CD4+ and CD8+ cells
- He did not require prophylactic anti-microbials despite his significant T cell lymphopenia and was maintained on neutropenic precautions during his hospitalization
- While in the NICU, he had poor oral motor skills resulting in failure to thrive which prolonged his hospitalization
- Repeat lymphocyte subsets 1 month after the initial continued to show significantly decreased T and B cells
- At 1-month-of age, he was discharged from the NICU without a unifying diagnosis for persistent leukopenia & severe neutropenia
- After discharge, his comprehensive hematology panel identified a pathogen variant in *CXCR4*, establishing a diagnosis of WHIM syndrome
- At 2-years-of-age, he remains persistently leukopenic with severe neutropenia (ANC of 50/mcL)
- Despite his neutropenia, he continues to have infrequent infections, with an episode of thrush and episodes of viral illness, but no recurrent bacterial infections
- He is not currently on immunoglobulin replacement therapy (IgRT) or receiving granulocyte- colony stimulating factor (G-CSF)

Discussion

- Although the pathogenesis of WHIM syndrome is not fully understood, it is believed that the gain-of-function mutation in *CXCR4* results in increased signaling of the CXCR4 receptor
- This mutation results in myelokathexis and lymphocyte dysfunction, which can also affect immunoglobulin class switching
- There is significant variability in the presenting symptoms of WHIM syndrome, especially in children who may be asymptomatic which can delay diagnosis
- For diagnosis of WHIM, a bone marrow biopsy may be done showing myelokathexis or genetic testing
- Treatment options for WHIM syndrome may include G-CSF, IgRT, prophylactic antibiotics, and wart removal
- Curative treatment would include stem cell transplant, but there are significant risks associated with this intervention
- An FDA approved medication plerixafor, is a competitive antagonist of CXCR4 receptor
- In a phase III trial comparing plerixafor to G-CSF, it was not superior to G-CSF for maintaining an ANC greater than 500 cells/µL
- Our patient was referred to the bone marrow transplant team for evaluation of a stem cell transplant, but it was deferred at this time due to the patient doing clinically well

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