WHIM Syndrome Diagnosis in a Parent and Child

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Warts, Hypogammaglobulinemia, Immunodeficiency, Myelokathexis (WHIM)

- WHIM Syndrome is a rare autosomal dominant primary immunodeficiency(PID) caused by defects in the C-X-C motif chemokine receptor 4(CXCR4) gene.
- This defect results in retained leukocytes in the bone marrow and reduced peripheral leukocytes, particularly neutrophils.
- Manifestations of WHIM syndrome include warts due to predisposition to HPV, hypogammaglobulinemia, and immunodeficiency/infections.
- These Cases demonstrate a father and son with WHIM syndrome and their respective presentation, evaluation, and management.

Discussion

- WHIM is a PID that can have a milder phenotype and not present with severe manifestations until adulthood.
- Case 1 demonstrates a patient with severe manifestations later in life, with history of recurrent cutaneous manifestations and chest imaging suggestive of bronchiectasis from recurrent pneumonias.
- Case 2 demonstrates the milder phenotype seen early in life, with warts and recurrent otitis media.
- Mavorixafor is a CXCR4 antagonist that can improve white blood cell migration from bone marrow into serum, currently approved for 12 years and older.

Key Take Aways

- PIDs with milder phenotypes are often not considered in adult patients until severe manifestations occur, as seen in Case 1.
- Diagnosis of PIDs should prompt early immune evaluation with consideration of genetic testing in family members.

CASE 1

History of Presenting Illness

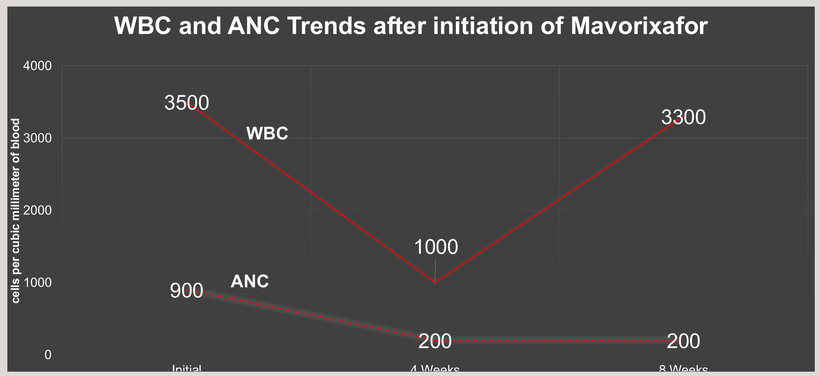
- 39-year-old male with WHIM syndrome presented after being lost to follow up.
- Infectious history: frequent warts, rashes, and recurrent pneumonia since his early 20's occurring 5-6 times a year.
- Recent chest CT showed tree-in-bud opacities in the right middle lobe and posterior left lower lobe with mediastinal lymphadenopathy.
- Genetic Testing via FOUNDATION ONE
  - CXCR4 mutation (T322fs*26 and C1012dup with protein sequence change pser338Phefs*6).
- Started pegfilgrastim 6 months prior through outside hematologist but had no improvement with infection frequency.

Initial Workup

- Reduced WBC, CD4, CD8, CD19 counts, and low pneumococcal antibody titers.
- Normal tetanus antibody titers, CBC, CMP, and total immunoglobulins.

Management and Follow up

- Received pneumococcal polysaccharide vaccine, with mild improvement in protective pneumococcal titers after 8 weeks.
- Mavorixafor was started and pegfilgrastim discontinued.
- Eight weeks after initiation, he had no sinopulmonary infections or hospitalizations. However, had increased skin rashes and developed an axillary abscess requiring trimethoprim-sulfamethoxazole and cephalexin therapy.



CASE 2

History of Presenting Illness

- 8-year-old male presented for evaluation of WHIM syndrome due to father's (Case 1) diagnosis.
- Infectious history: warts and recurrent acute otitis media requiring 2 bilateral myringotomy and tube procedures.

Initial Workup

- Absent ANC, and reduced WBCs, ALC, CD4, CD8, IgG, and pneumococcal antibody titers.
- Normal tetanus antibody titers and CMP.
- Genetic Testing via Invitae IEI panel
  - CXCR4 c.952dup (p.Thr318Asnfs*26) heterozygous variant
  - RNU4ATAC n.48G>A (RNA change) heterozygous variant
  - AP3D1 c.3400A>C (p.Ile1134Leu) heterozygous variant of uncertain significance.

Management and Follow up

- Received pneumococcal polysaccharide vaccine, with adequate response in protective pneumococcal titers after 8 weeks.
- Filgrastim was started.
- Eight weeks following initiation, WBCs, ALC and ANC increased to normal values.
- Patient with no infections, hospitalizations, or need for antibiotics since initiation.