GATACA

A Real Life Story of a Genetic Deficiency

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Meanings of the Word Gata

- English – Armenian Pastry
- Catalan – female cat
- Fijian – snake
- Hiligaynon – coconut milk
- Icelandic – street (noun), to pierce (verb)
- Norwegian – gate
- Portuguese – female cat, very beautiful woman
- Romanian – ready (adj), readily (adv)
- Spanish – carjack
- Swedish – street
- Urban Dictionary – Get After That A$$
GATA2 deficiency

- Genetics and mechanism of disease (haploinsufficiency)
- Clinical syndromes
  - Immunodeficiency and hematologic finding
  - Non-hematopoietic manifestations
- Diagnosis
- Management
Patient Presentation

- 45yo woman started having fevers and malaise in Spring 2015
  - Initially treated with mtx, pred, and adalimumab for possible ANA+ MCTD

- July 2015, admitted to hospital in AK with fever, found to be pancytopenic with profound monocytopenia and lymphopenia

- Diagnosed with MAC in marrow, liver, and lung, as well as pulmonary aspergillosis

- Immunologist suspected immunodeficiency, and pt was transferred to UWMC for further evaluation
Patient Presentation

- Originally from Brazil
- Recurrent ear infections and asthma exacerbations
- G4P2 – 3 miscarriages ~12-15 weeks
- Diagnosed with anti-phospholipid syndrome
- Extensive cervical and vulvar dysplasia
  - Hysterectomy
- Fever, infection d. 31
- Colon cancer d. 36
- Prolonged illness 7
- 45
- d. early unknown
- d. ? stroke
Patient Presentation

- WBC 2.4
  - ANC 2.24
  - Lymph 0.05
    - CD4 0.049
  - Mono 0
  - Immature Gran 0.12
- HCT 22, Plt 36
- GATA2 sequencing – R398W
- Oncoplex
  - GATA2, STAG2 mutations
  - ? splice alteration of PALB2
  - ? frameshift mutation in ASXL1
GATA2

- Key transcriptional regulator of hematopoiesis
- Homozygous knock-out is lethal, while haplo-insufficiency results in defects of hematopoiesis
- Decreased GATA2 expression promotes stem cell division and differentiation

Collin et al, BJH. 2015;169:173-87
GATA2 Haploinsufficiency

- First reported in humans in 2011
- At least 50 distinct mutations
  - Gene deletions, frameshifts, regulatory mutations, nonsense and missense mutations
- 2/3 involve zinc finger domains
- 1/3 inherited, 2/3 de novo
- Functional effects are due to haploinsufficiency
Clinical Syndromes

- MonoMac Syndrome
  - Vinh et al, *Blood*. 2010;115;1519-29

- DCML Deficiency

- Familial MDS/AML

- Emberger Syndrome
Immunodeficiency and hematologic findings

Immunodeficiency and hematologic findings

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Immunodeficiency and hematologic findings

- Typically arise with increasing age
- Decrease in B cells, NK cells, monocytes
- Progressive, leading to bone marrow failure
- Often confused with aplastic anemia
  - GATA2 patients typically have higher HCT and Plt
  - Severely reduced monos, B, and NK cells in marrow
  - Atypical Monocytes
  - Megakaryocyte atypia
  - Abnormal Cytogenetics
Immunodeficiency and hematologic findings

• Bone marrow often shows multilineage dysplasia

• Typically hypocellular

• Megakaryocyte atypia is a prominent feature

• Fibrosis is common

• Cytogenetic abnormalities
90% of patients develop MDS by age 60

Often associated with trisomy 8, monosomy 7

ASXL1 mutation in 30% of patients with MDS

5-10% of pediatric MDS/AML patients have germline GATA2 mutations, higher in more advanced disease

GATA2 is infrequently mutated in sporadic MDS/AML

Non-hematopoietic Manifestations

- HPV – warts, condylomata, dysplasia
- HSV, CMV, EBV
- Disseminated NTM infections
- Fungal Infections
  - Invasive aspergillosis, histoplasmosis, candidiasis
- Bacterial
  - SSTI, PNA, URTI
Non-hematopoietic Manifestations

- PAP
  - No anti-GM-CSF antibodies
  - Adequate alveolar macrophages in BAL
  - No response to whole-lung lavage or GM-CSF

- Lymphedema
  - GATA2 is expressed in lymphatic valves

- Thrombosis
  - APLS, endothelial dysfunction

- Solid Tumors
  - HPV, EBV

- Hearing Loss
  - Confounded by aminoglycoside use

- Miscarriage

Genotype/Phenotype Correlation

- Certain clinical manifestations cluster together
  - PAP, NTM, MDS
  - Emberger Syndrome – Lymphedema, MDS

- Lymphedema associated only with null mutations

- Severe, early onset viral infections also associated with null mutations

- Significant clinical variation within families

Diagnosis of GATA2 Deficiency

- When to suspect GATA2 Deficiency?
  - Monocytopenia may be the first laboratory abnormality
  - Lymphopenia and neutropenia are also common
  - Recurrent or unusual infections
    - HPV-related neoplasia/dysplasia is often very profound
  - Family history of MDS/AML, particularly pediatric
Diagnosis of GATA2 Deficiency

- **Is it germline?**
  - Inferred by a 1:1 ratio of variant to reference sequencing reads
  - 50% variant allele fraction

- **Complexity**
  - Acquired clonal hematopoiesis can approach 1:1 ratio of variant to reference sequencing reads

- **Resolution**
  - Sequence non-hematopoietic tissue
  - Sequence parents/children

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**Variant Allele Fraction**

0.50

(variant reads/total reads)

(249 / 500)
Diagnosis of GATA2 Deficiency

- Order MarrowSeq on marrow or peripheral blood
  - Will be held by lab med until prior auth is obtained

- Genetics Consult
  - CPOE order for genetic counseling

- Have TC enter prior auth referral in EPIC
  - Use MarrowSeq CPT code – MRW
  - Sign consent for genetic testing

- Document medical necessity
Management of GATA2 Deficiency

- Testing for family members
- Serial CBC
- Annual BM exam
- Dermatologic and gynecologic monitoring
- HPV vaccination
- Prophylactic azithromycin
- Immunoglobulins, if necessary
- Prudent use of aminoglycosides with audiology testing
Management of GATA2 Deficiency

- Allogeneic transplant is the only curative treatment

- Indications for transplant
  - MDS/AML
  - Immunodeficiency
  - Progressive Marrow Failure
  - PAP

- NIH – 21 patient with allogeneic HCST
  - 54% of patients alive 4 yrs after transplant
  - No major infectious issues

- 50 pediatric patients with MDS and GATA2 mut
  - 66% 5 year survival, TRM 24%

Back to our patient…

- Progressive decline with weight loss, inability to clear infections
- Double Umbilical Cord Blood Transplant
  - RIC consisting of hydroxyurea, alemtuzumab, fludarabine, melphalan, and thiotepa
    - Used in children with non-malignant diseases
    - 85% engraftment, 27% GVHD, 77% 1yr OS
    - Median day of engraftment +20
- Neutrophil recovery at day 16, 100% donor chimerism d+28
- Post-transplant course complicated by hypercapneic respiratory
Conclusions

- GATA2 haploinsufficiency is a heterogeneous disorder associated with cytopenias, recurrent/atypical infection, and MDS/AML

- Can be either inherited or sporadic

- Requires frequent monitoring from multiple specialties

- HSCT is the only curative treatment
Thanks!
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