

# It Takes Two

Special ID Grand Rounds  
April 6, 2017

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Nothing to disclose

# Case

- **Consult reason:** Pre-transplant evaluation for pulmonary *Mycobacterium avium intracellulare* infection and multiple warts
- **History:**
  - 36 yo male with myelodysplastic syndrome
  - Healthy till his late teens
    - Warts on his hands and feet
    - *S. aureus* skin soft tissue infections on his legs
      - Required IV treatment for some episodes
    - Frequent pneumonia and bronchitis

## Recurrent and recalcitrant warts



- Developed pancytopenia-
  - WBC 1,000-2,000 (Normal 3,700-10,500 /mm<sup>3</sup>)
  - Hgb 7-10 (Normal 13.2-17.7 g/dL)
  - PLT 70,000 (Normal 150,000-400,000/mm<sup>3</sup>)
  
- Immunologic work-up
  - Slight ↓ in B cells and NK cells
  - Slight ↑ in T cells
  - NK cell activity non-detectable
  - No response to pneumococcal vaccination
  - Slight decrease in IgG and IgA
  
- Bone marrow biopsies in his early 20s-
  - Hypocellular marrow (20-30%)
  - Mildly decreased megakaryocytes
  - Markedly decreased granulopoiesis
  - No increase in blasts, no clonal abnormality
  - Normal karyotype, 46XY

- In his early 30s,
  - sepsis due to acute cholecystitis s/p cholecystectomy
  - disseminated VZV infection
    - acyclovir treatment followed by prophylaxis
  - *Mycobacterium avium intracellulare* infection
    - fever and night sweats
    - PET-CT showed FDG-avid mediastinal lymphadenopathy
    - Mediastinoscopy with biopsy- MAI infection
    - Treated for 12 months- rifampin, ethambutol and azithromycin
    - Fevers with night sweats after discontinuing treatment
    - Restarted on treatment with resolution of symptoms

- Cytopenias worsened-
  - Packed RBCs every 3-4 weeks
  - Intermittent injections of granulocyte colony stimulating factor
  
- Repeat bone marrow biopsy:
  - Mildly hypocellular (20-30%) with markedly decreased granulopoiesis and mild to moderate reticulin fibrosis

- **PMH:**
  - Migraines
  
- **Family History:**
  - Mother- healthy. No h/o recurrent infections or hematologic or immunologic diseases in family
  - Father- healthy. Family history unknown
  - Sister- healthy
  
- **Social History:** Office jobs. H/o smoking, quit 11 years ago. No alcohol or illicit drugs

- **Physical exam:** Vital signs stable. Thin, pale. No lymphadenopathy. Multiple warts



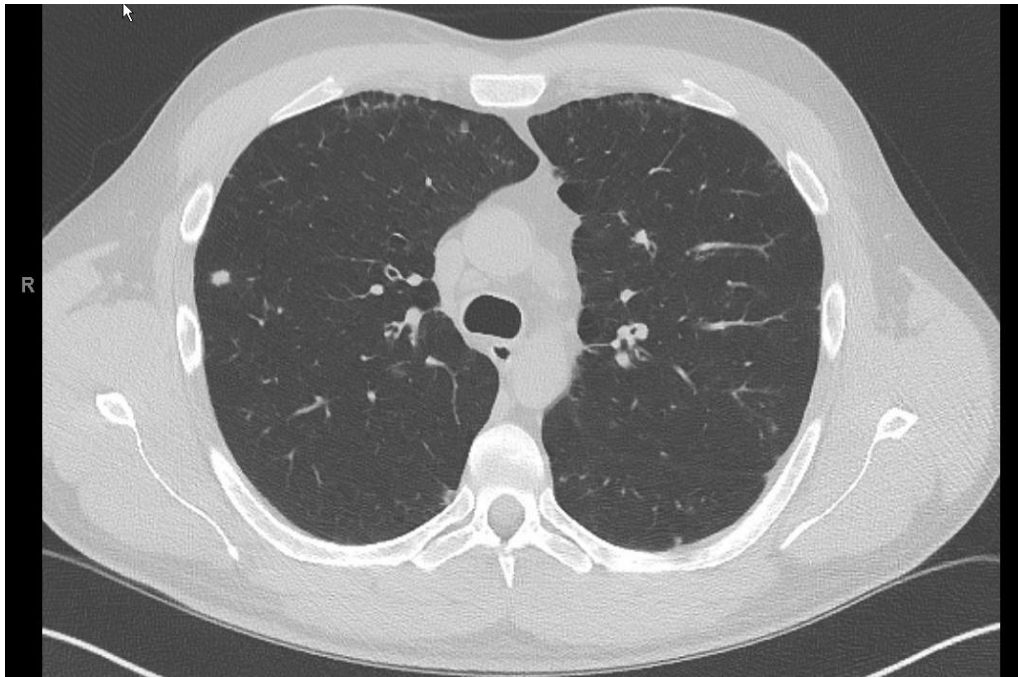
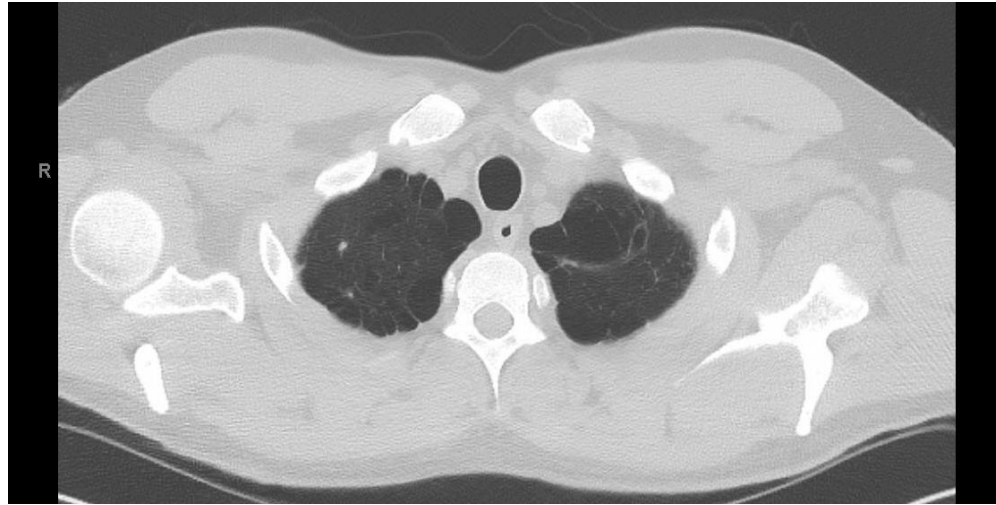


# LABS

		1/27/2016 1206
<b>CBC AND BLOOD SMEAR</b>		
WBC Count	Latest Range: 3.7-10.5 K/MM3	<i>1.0</i> ▼
RBC Count	Latest Range: 4.50-6.20 M/MM3	<i>2.53</i> ▼
Hemoglobin	Latest Range: 13.2-17.7 g/dL	<i>9.2</i> ▼
Hematocrit	Latest Range: 40-52 %	<i>30</i> ▼
MCV (Mean Corpuscu...)	Latest Range: 82-99 FL	<i>120</i> ▲
MCH (Mean Corpuscu...)	Latest Range: 25-35 PG	<i>36</i> ▲
MCHC (Mean Corpuscu...)	Latest Range: 32-36 %	<i>30</i> ▼
Platelet Count	Latest Range: 150-400 K/MM3	<i>78</i> ▼
MPV (Mean Platelet...)	Latest Range: 9.4-12.3 FL	<i>12.9</i> ▲
RBC Dist Width-STD	Latest Range: 35.1-43.9 FL	<i>91.2</i> ▲
RBC Distrib Width	Latest Range: 9.0-14.5 %	<i>20.3</i> ▲
Nucleated RBC	Latest Units: /100 WBC	<i>0</i>
Smear Review, Path	No range found	
Smear Review, Path	No range found	
Neutrophils-Manual	Latest Range: 2188-7800 /MM3	<i>293</i> ▼
Lymphocytes-Manual	Latest Range: 875-3300 /MM3	<i>693</i> ▼
Monocytes-Manual	Latest Range: 130-860 /MM3	<i>4</i> ▼
Eosinophils-Manual	Latest Range: 40-390 /MM3	

# Chest CT

- Mixed emphysema with bullous disease and bleb formation in upper lobes
- Numerous small noncalcified nodules in both lungs



## **Pulmonary function test**

- Mild obstructive pulmonary disease

**DIAGNOSIS ?**

## HEMATOPOIESIS AND STEM CELLS

# **GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics, and immunity**

Michael A. Spinner,<sup>1</sup> Lauren A. Sanchez,<sup>1</sup> Amy P. Hsu,<sup>1</sup> Pamela A. Shaw,<sup>2</sup> Christa S. Zerbe,<sup>1</sup> Katherine R. Calvo,<sup>3</sup> Diane C. Arthur,<sup>4</sup> Wenjuan Gu,<sup>5</sup> Christine M. Gould,<sup>6</sup> Carmen C. Brewer,<sup>7</sup> Edward W. Cowen,<sup>8</sup> Alexandra F. Freeman,<sup>1</sup> Kenneth N. Olivier,<sup>1</sup> Gulbu Uzel,<sup>1</sup> Adrian M. Zelazny,<sup>1</sup> Janine R. Daub,<sup>1</sup> Christine D. Spalding,<sup>1</sup> Reginald J. Claypool,<sup>1</sup> Neelam K. Giri,<sup>9</sup> Blanche P. Alter,<sup>9</sup> Emily M. Mace,<sup>10</sup> Jordan S. Orange,<sup>10</sup> Jennifer Cuellar-Rodriguez,<sup>1</sup> Dennis D. Hickstein,<sup>1</sup> and Steven M. Holland<sup>1</sup>

Blood. 2014; 123: 809-21

**GATA2 mutation in exon 7 of the GATA2 gene, p.R396Q**

# Four syndromes associated with GATA2 deficiency

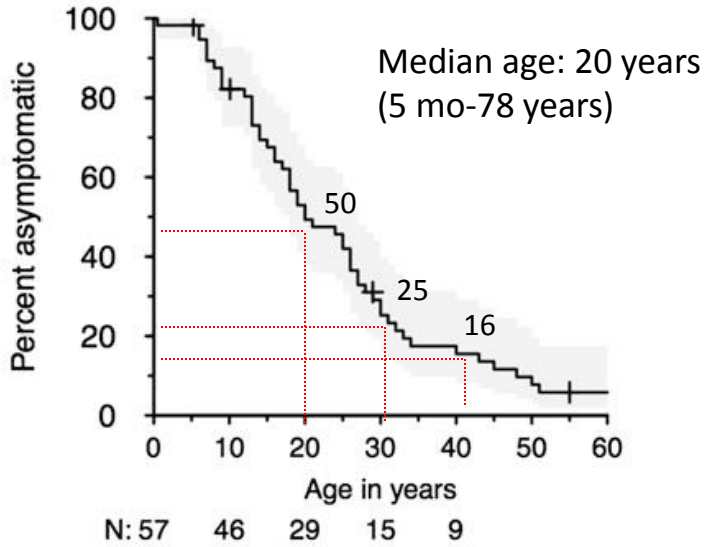
- MonoMAC syndrome-
  - monocytopenia and atypical mycobacterial infections
  - Increased incidence of myelodysplastic syndrome (MDS)
  - Recurrent viral and fungal infections
- Familial MDS/AML
- Dendritic cell, monocyte, B- and NK-cell (DMCL) deficiency
- Emberger syndrome-
  - primary lymphedema
  - MDS
  - deafness

# GATA2 deficiency also detected in...

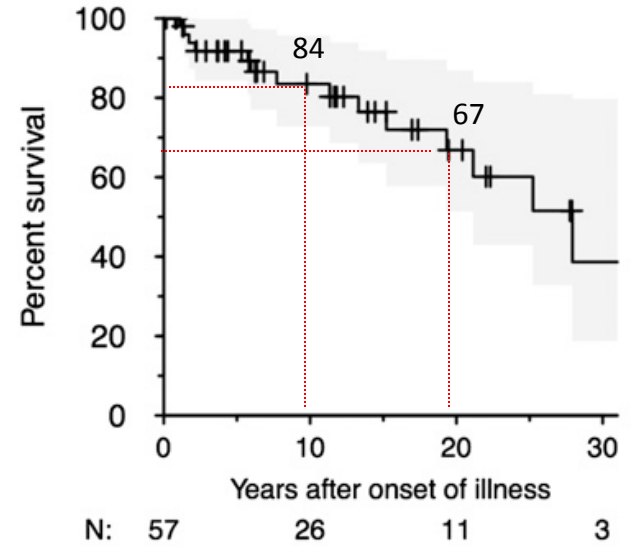
- Congenital neutropenia
- Aplastic anemia
- Chronic myelomonocytic leukemia
- Severe EBV infections and EBV related cancers
- NK cell deficiency
- Idiopathic bone marrow failure

# Onset of Disease and Survival

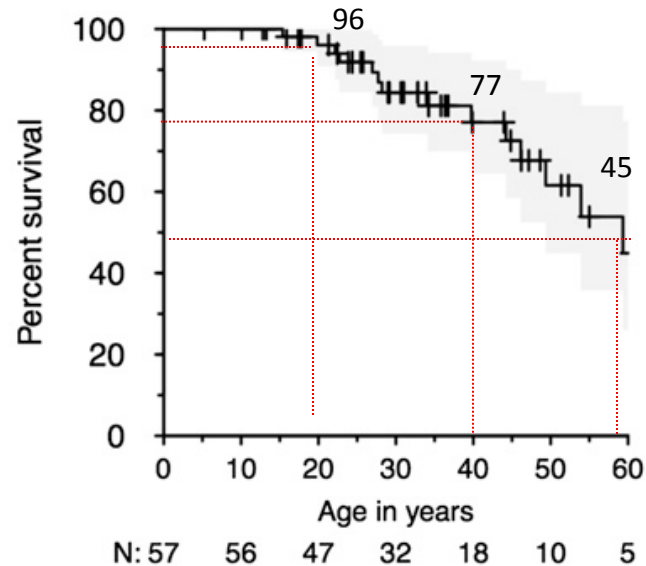
## Onset of Illness



## Survival After Onset of Illness



## Survival



# Clinical Features

## Hematologic

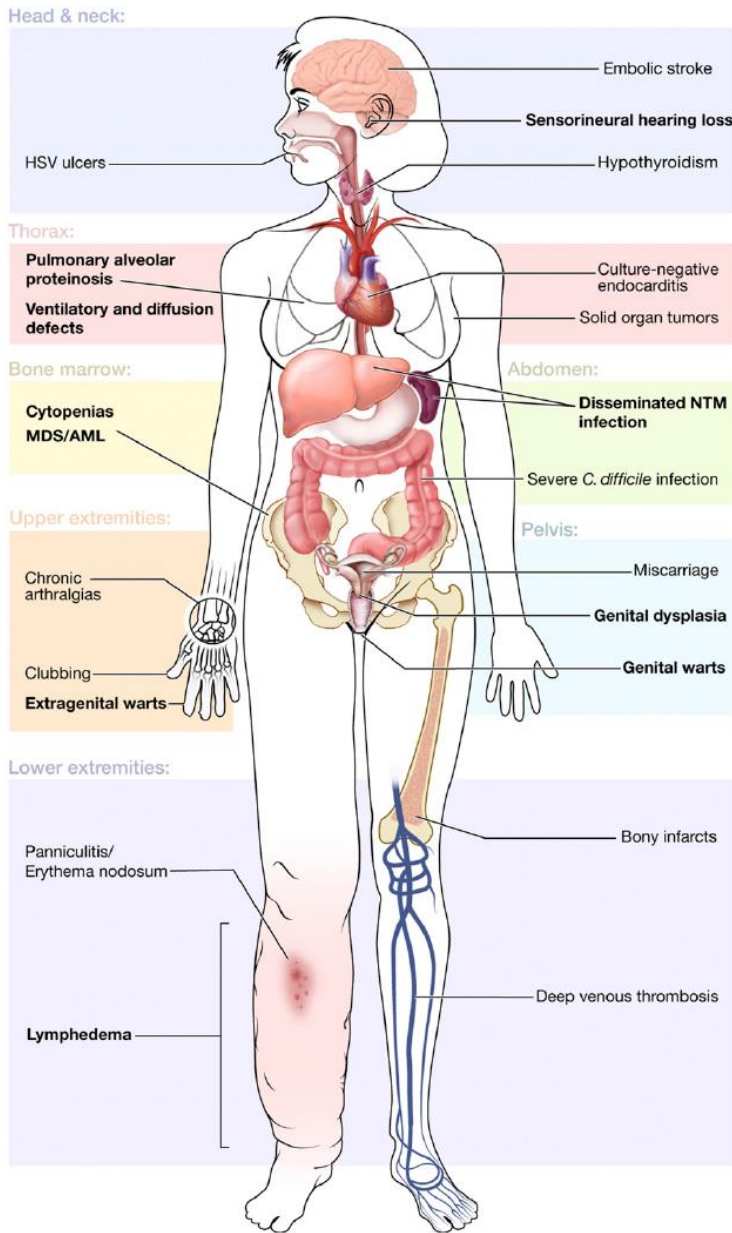
- Cytopenias
  - B- cell 86 %
  - NK cell 82 %
  - Monocytopenia 78 %
  - CD4 51 %
  - Neutropenia 47 %
- Malignant blood disorders
  - MDS 84 %
  - AML 14 %
  - CMML 8 %

## Infectious

- Viral (70%)
  - HPV 63 %
  - Herpesvirus 35 %
    - HSV 16 %
    - VZV 11 %
    - EBV 11 %
    - CMV 4 %
- Bacterial
  - Disseminated atypical mycobacteria 53 %
  - Other severe bacterial 49 %
- Fungal (16%)
  - Aspergillosis 9 %
  - Histoplasmosis 5 %
  - Severe candidiasis 5 %



# Common Clinical Features



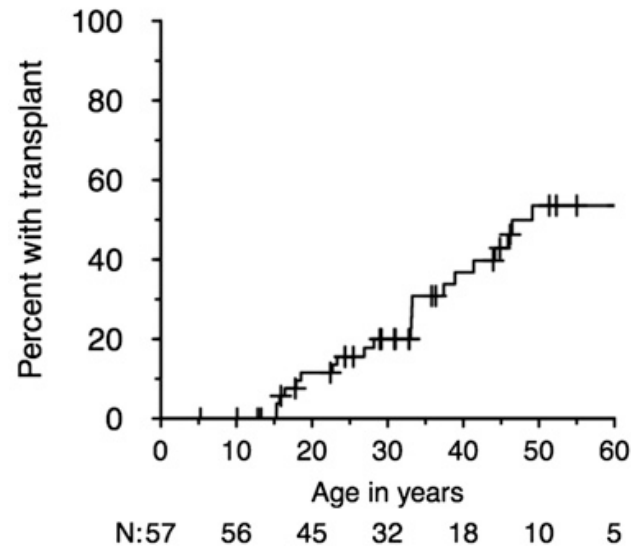
- Solid tumors
  - HPV related 35%
  - EBV related
  - Breast cancer 22%
- Pulmonary
  - Pulm. alveolar proteinosis 18%
  - PFT abnormalities 79%
- Lymphedema 11%
- Venous thrombosis 25%
  - (DVT, PE, catheter related)
- Sensorineural hearing loss 76%
- Miscarriage 33%
- Hypothyroidism 14%

Spinner MA, et al. Blood. 2014; 123: 809-21

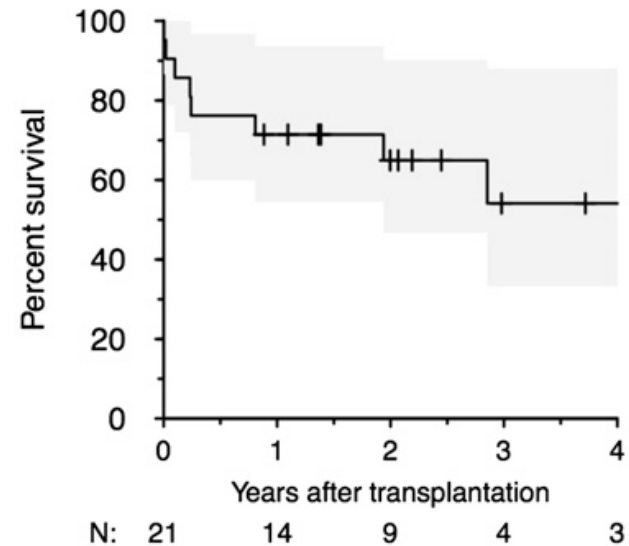
Crispino JD, Horwitz MS. Blood 2017 Feb 8. pii:blood-2016-09-687889

# Definitive Treatment-Stem Cell Transplant

**Cumulative Incidence of Transplantation**



**Survival After Transplantation**



# Screening and Treatment

- Initially, focus on
  - control of infections
  - management of pulmonary disease
- Vaccinate in childhood against HPV
- Azithromycin prophylaxis for MAI infection and other bacterial infections
- Monitor blood counts every 3-6 months

# Case

- Allogeneic SCT (mismatched unrelated)- April 2016
- Continued on azithromycin and ethambutol
- Antifungal and antiviral prophylaxis
- Disseminated HSV2 infection at time of SCT
- Vancomycin resistant enterococcus bacteremia and thrombophlebitis
- Skin GVHD- on steroids
- Has had multiple URTIs

# LABS

		<b>3/31/2017</b>
		<b>1326</b>
WBC Count	Latest Range: 3.7-10.5 K/MM3	<i>6.7</i>
RBC Count	Latest Range: 4.50-6.20 M/MM3	<i>3.32</i> ▼
Hemoglobin	Latest Range: 13.2-17.7 g/dL	<i>12.4</i> ▼
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RBC Dist Width-STD	Latest Range: 35.1-43.9 FL	<i>59.2</i> ▲
RBC Distrib Width	Latest Range: 9.0-14.5 %	<i>14.2</i>
Nucleated RBC	Latest Units: /100 WBC	<i>0</i>
Neutrophils-Auto Diff	Latest Range: 2188-7800 /MM3	
Lymphocytes-Auto Diff	Latest Range: 875-3300 /MM3	
Monocytes-Auto Diff	Latest Range: 130-860 /MM3	
Eosinophils-Auto Diff	Latest Range: 40-390 /MM3	
Basophils-Auto Diff	Latest Range: 10-136 /MM3	
Immature Granulocy...	Latest Units: /MM3	
Neutrophils-Manual	Latest Range: 2188-7800 /MM3	<i>5802</i>
Lymphocytes-Manual	Latest Range: 875-3300 /MM3	<i>352</i> ▼
Monocytes-Manual	Latest Range: 130-860 /MM3	<i>527</i>
Eosinophils-Manual	Latest Range: 40-390 /MM3	<i>59</i>

# Questions

- What is the role of GATA2?
- How does GATA2 mutations make patients prone to certain infections and malignancies?