Host Defense: Where the Rubber of Immunology Hits the Road of Life

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Disclosures of Financial Relationships with Relevant Commercial Interests

- None

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Concepts of Hell

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Host Immune Defense

Humoral
- Complement
- Mannose binding lectin
- Antibody

Cellular
- Neutrophils
- Monocytes
- Eosinophils
- Lymphocytes (NK, T, B)
- Other (erythrocytes, platelets)

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Basic Principles

Patients with impaired inflammation:

- May be unable to tell you they are sick (feel fine)
- Are often sicker than they look
- Often have more extensive disease than is apparent
- May require longer treatment than normals
- May have unusual infections

In vitro testing is tricky and variable, genetics is not

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Who's Got a Problem?

Abnormal frequency of infections

- Recurrent *Neisseria* bacteremia
- Recurrent pneumonia

Abnormal presentation of infections

- Necrotic cutaneous ulcers (not anthrax)
- *Aspergillus* pneumonia

Specific unusual infections

- *Pneumocystis jiroveci*
- *Burkholderia cepacia* complex
- *Nontuberculous mycobacteria.*

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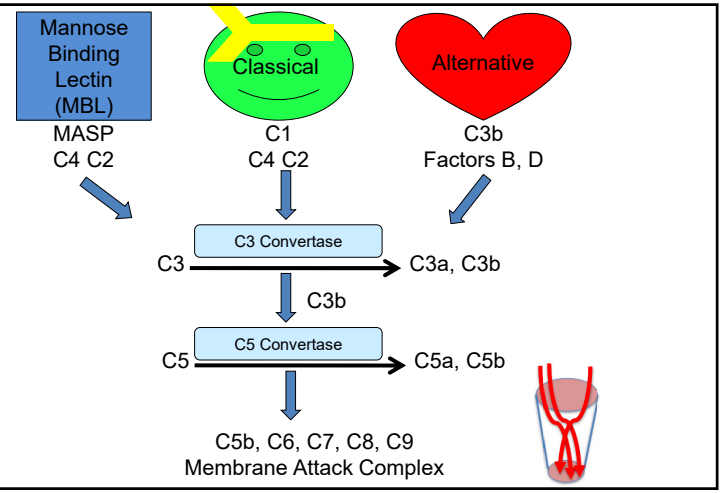

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Complement Deficiencies

Classical Pathway (C1-C9) (AR)

- Antibody *de*pendent bacterial lysis
- Deficiency leads to recurrent bacteremia and meningitis

Alternative Pathway (Factors I, H, Properdin, C3) (Properdin X-linked, others AR)

- Antibody *in*dependent bacterial lysis
- More severe than classical defects

Mannose Binding Lectin (MBL) Pathway

- Very modest IF ANY defect, mild effect in infancy

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Complement Defects

C5-C9 Defects
- Recurrent *Neisseria* bacteremia and meningitis
- Average age of onset 17 y, milder CNS sequelae
- High rates of relapse and reinfection

C1-C4 Defects
- Autoimmune disease (SLE, DLE) more common

Dx - CH_{50} (Classical), AH50 (Alternative)

Rx - treat infections, prophylaxis if needed, hypervaccination?

J Clin Immunol 2020 May;40(4):576-591

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Antibody Deficiencies

IgA Deficiency (AR)
- Common (1/700 adults)
- Probably not a pathologic condition *per se*
- Frequently associated with other deficits, such as common variable immunodeficiency (CVID), Ig subclass deficiencies, allergies, etc.

Dx - Low IgA

Rx - None

J Transl Autoimmun 2019 Nov 23:2:100025

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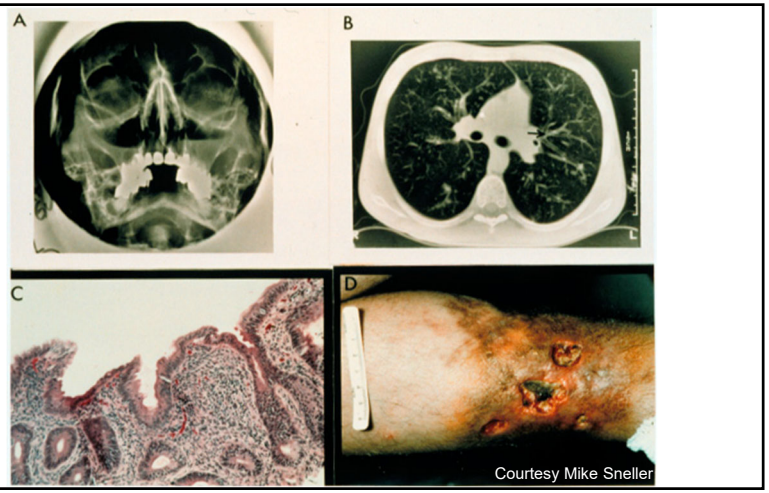

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Common Variable Immunodeficiency (CVID)

Recurrent sino-pulmonary bacterial infections

Chronic enteric *Giardia, Campy, Salmonella, Shigella*

Severe enteroviral meningitis/encephalitis/myositis

Nodular regenerative hyperplasia

Dx - ↓ IgG (total and subclasses 1,3 or 2,4), IgA, IgM, isohemagglutinins, DTH, Impaired response to new or recall immunization

↑ Autoimmunity and cancer

Rx - Treat infections, Ig replacement

Cunningham-Rundles C. Immunol Rev. 2019 Jan;287(1):145-161.

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Question #1

PREVIEW QUESTION

47-year-old woman

- Recurrent episodes of bronchitis, recently more exacerbations; tired
- One episode of documented bacterial pneumonia and sinusitis
- Immunoglobulin levels:
  - IgG 500 (normal 523-1482)
  - IgA <10 (normal 51-375)
  - IgM 165 (normal 37-200)

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Question #1

PREVIEW QUESTION

What is the next step?

A. IgG subclasses and titers against tetanus and pneumococcus. If low, consider IVIG.
B. Repeat IgG levels. If low, consider IVIG.
C. Skin tests for DTH. If anergic, consider IVIG.
D. Titers against tetanus and pneumococcus, immunize, and repeat. If low, consider IVIG.
E. Check MBL levels. If low, consider IVIG.

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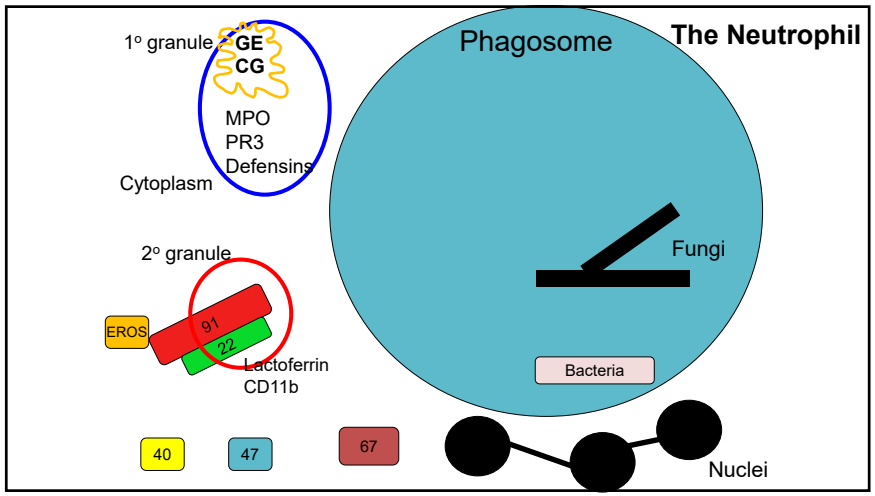

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Neutrophils: They're a Big Deal!

- Average count 5000/mcl
  - (5,000,000/ml)
  - (5,000,000,000/L)
- Make around 10^{11}/day
- Most are in bone marrow
- Can go up 10-fold in emergency
- Circulating half life 7 hours
- About 50% marginated

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Cyclic and Severe Chronic Neutropenias

Cyclic and SCN: *ELANE* mutations (AD)

Kostmann SCN: *HAX1* mutations (AR)

– Digital, oral, perineal infections, usually self-healing with recovery of counts, bacteremia uncommon

– Relatively low baseline PMN count with profound neutropenia, about every 3-4 weeks

Dx - Molecular; periodicity, family history, genetics

Rx - G-CSF, BMT

Hematol Oncol Clin North Am. 2019;33:533-551

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Other Causes of Neutropenia

X-linked	Recessive	Drugs
WAS	G6PC3	
GATA1	HAX1	**Splenomegaly/ sequestration**
TAZ	JAGN	
	USB1	Autoimmunity
Dominant	CSF3R	
GFI1	VPS45	
ELA2	GSD1B	
GATA2	SBDS	
DNM2		
SRP54		
CXCR4		

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Case Study

52-year-old man

- Referred from his Family Practitioner
- Recurrent digital and oral ulcers occurring every month or so for the last 4 months
- One CBC showed an ANC of 100, but on repeat several days later was normal
- Previous health good
- Took “some antibiotic for a cold a few months ago”
- Spleen tip felt

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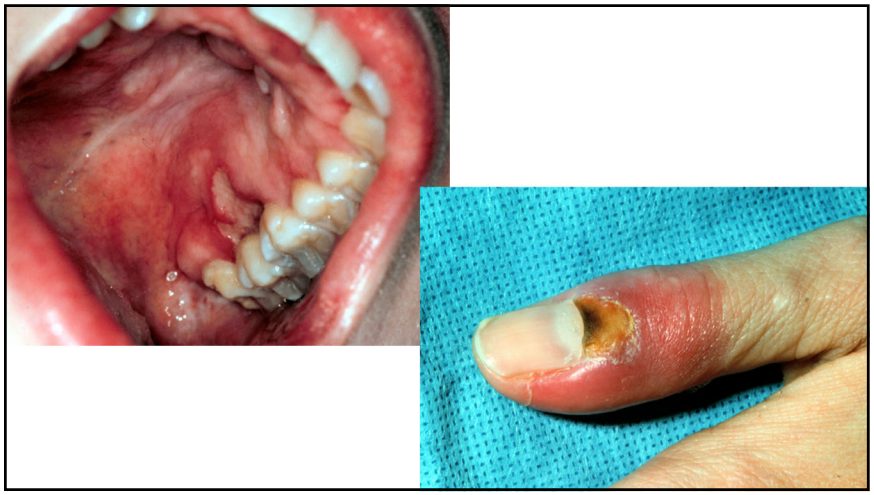

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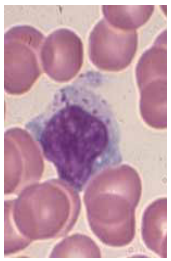
Acquired Neutropenia in Adults

- Drugs, lupus, etc.
- Acquired cyclic neutropenia
  (Large Granular Lymphocytosis, LGL)
  Splenomegaly, often associated with
  Rheumatoid arthritis (Felty Syndrome)



Dx - Clonal CD3+/8+/57+ lymphs (LGL)
(Gain of Function mutations in *STAT3*)

Rx - Treatment of the abnormal clone can be curative
(cyclosporine, MTX, steroids, alemtuzumab)
G-CSF may lift both nadir and baseline

Hematol Malig Rep. 2020 Apr;15(2):103-112.

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Myeloperoxidase (MPO) deficiency (AR)

Most common neutrophil disorder (1/2000)

- Not a pathologic condition *per se*
- Failure of H_2O_2 -----MPO-----> HOCl
- Compensated by increased H_2O_2 production
- Appears to need another condition to potentiate, such as diabetes mellitus

Dx - Absence of peroxidase positive granules due to mutations in *MPO* gene

Rx - Treat invasive infections (*Candida*), no specific therapy

J Leukoc Biol. 2013 Feb;93(2):185-98

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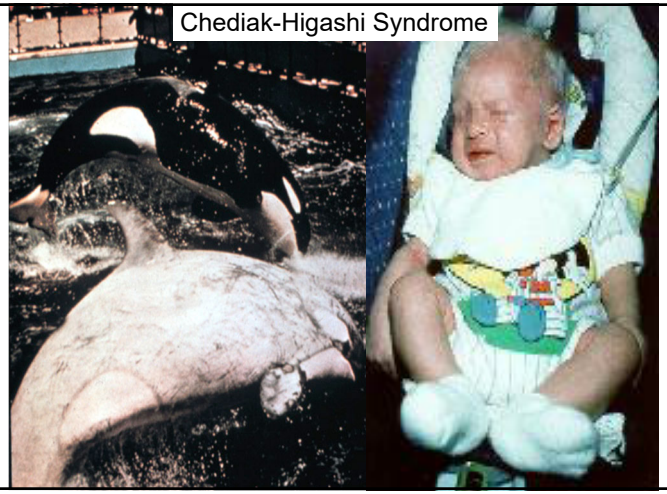

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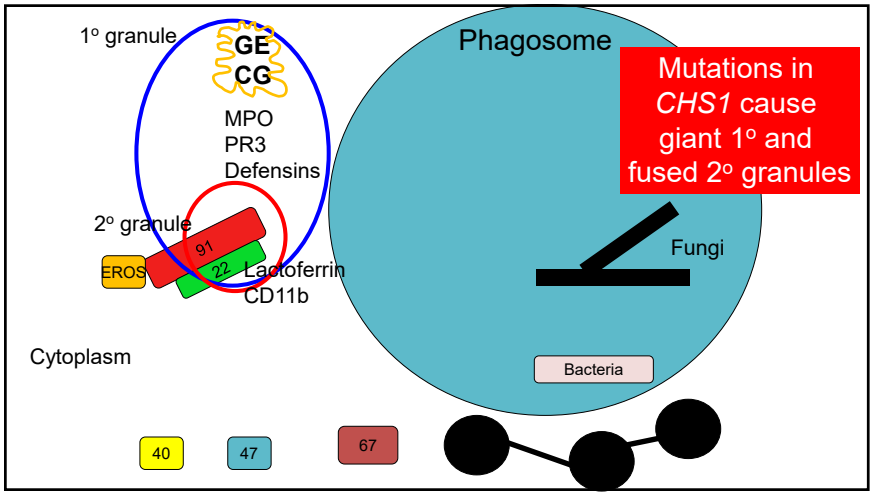

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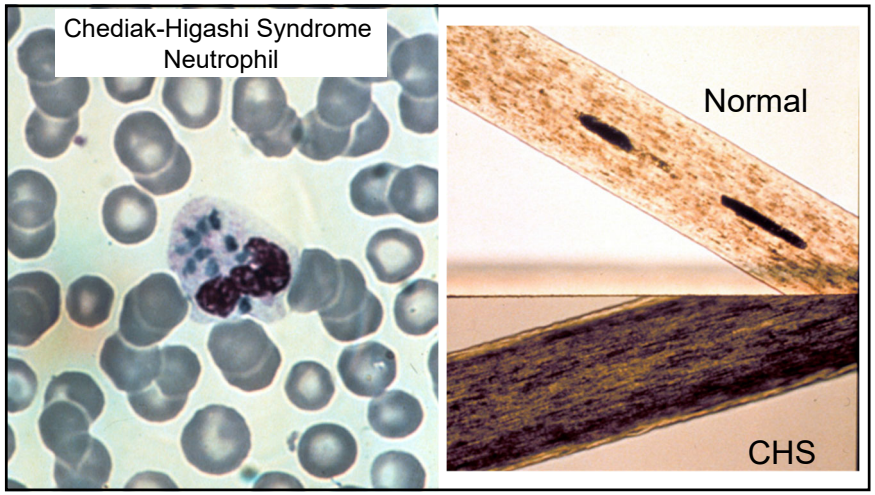

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Chediak-Higashi Syndrome (AR)

Recurrent cutaneous, sino-pulmonary infections
- GNR, staph, strep, no fungi
- Mild neutropenia (intramedullary destruction)

Partial oculocutaneous albinism,
Mental retardation, neuropathy (late)
Lymphoma or HLH-like "accelerated phase" (late)
Dx - Giant blue PMN granules or chaotic hair granules due to mutations in *CHS1*, encodes LYST
Rx - Prophylaxis**,** treatment of infections, BMT

Drug Discov Today Dis Models. 2020;31:31-36

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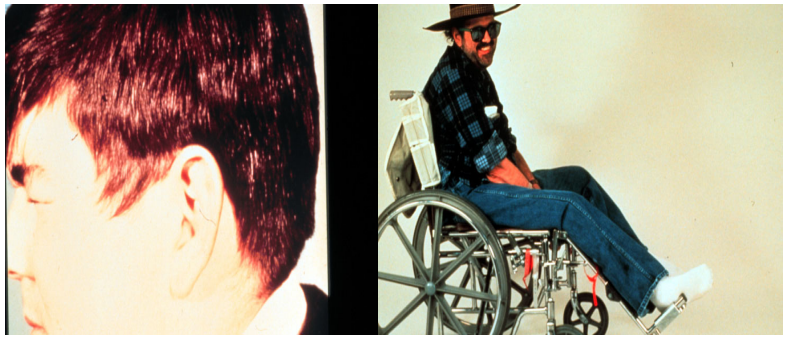
Silvery Sheen **Peripheral Neuropathy**



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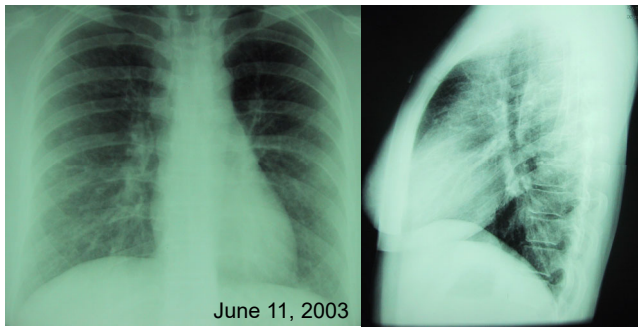
Case Study

23-year-old woman; athletic coach

Previously healthy; short of breath 4 hours after 3-mile run



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ER Presentation

- Recent weekend with friends in NYC
- Anxious, chest pressure, febrile
- Acute mononucleosis?

PMH

- Respiratory infections in infancy
- Cat scratch disease 8-year-old: resolved with antibiotics

Family History

- 1 brother with two episodes Cat scratch cervical nodes
- 2 sibs well

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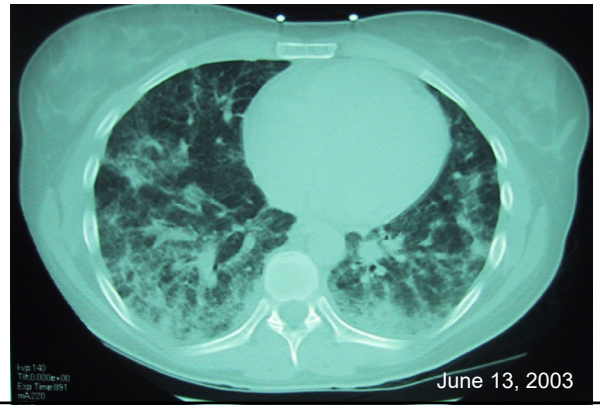
2 Days Later, Hypoxia And Fever



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Hospital Course

- Progressive dyspnea, fever, leukocytosis
- Refractory to antibiotics and steroids
- Bronchoscopy uninformative
- Visually Assisted Thoracoscopic Surgery (VATS) necrotizing granulomata and hyphae

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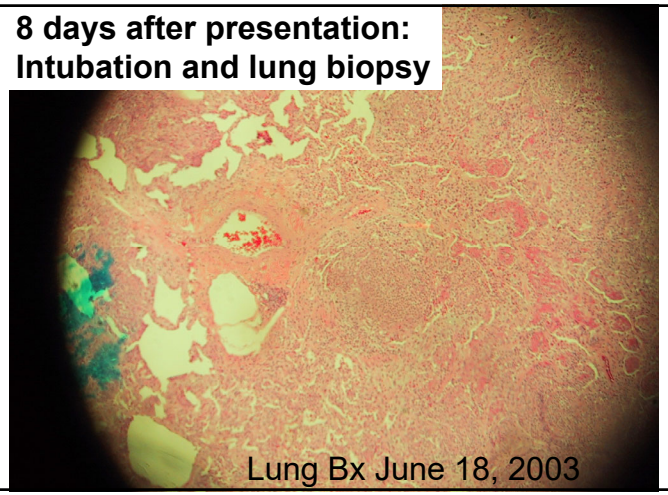
8 days after presentation: Intubation and lung biopsy



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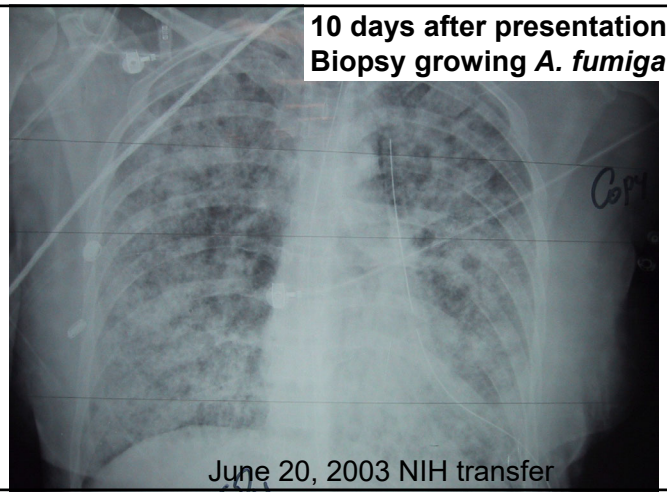

10 days after presentation:
Biopsy growing *A. fumigatus*

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Question #2

Which of the following is a cause of invasive aspergillosis in an otherwise normal host?

A. Allergic bronchopulmonary aspergillosis
B. Cystic fibrosis
C. Lymphocyte dysfunction (SCID)
D. Phagocyte defect
E. Acute HIV

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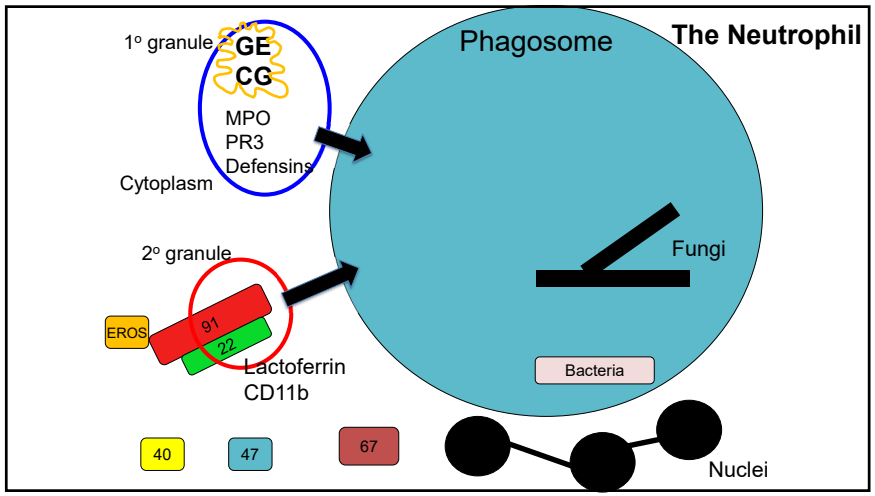

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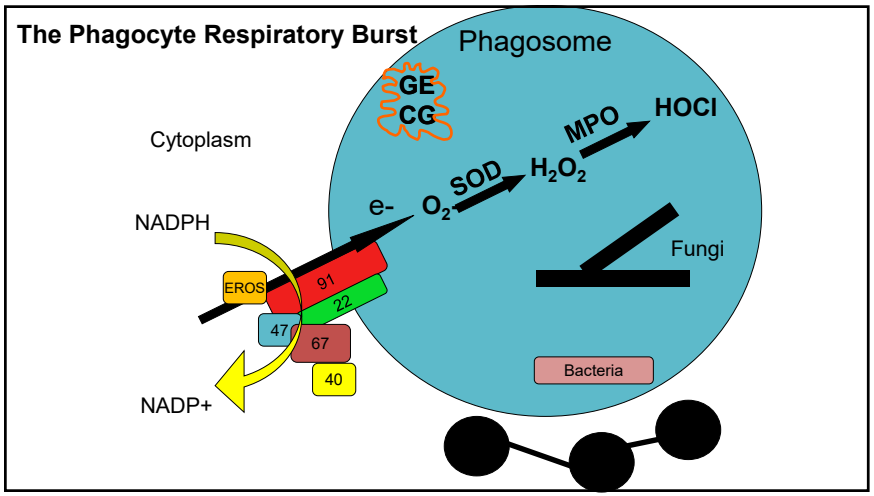

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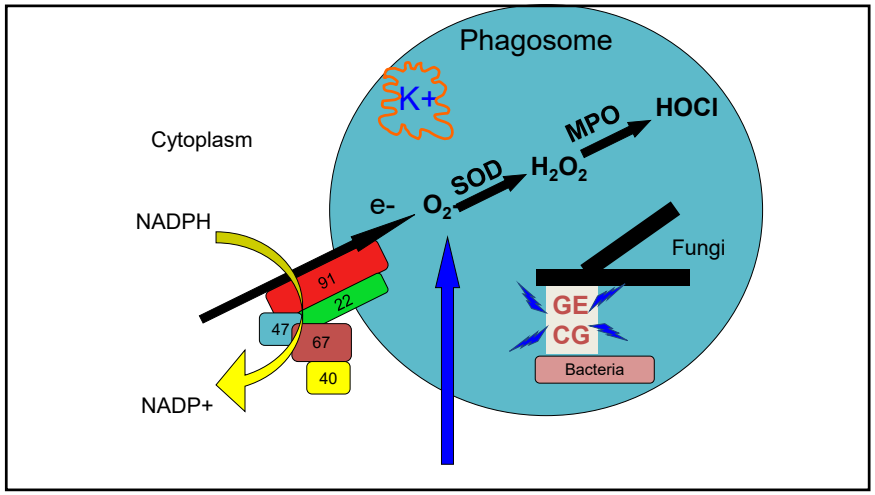

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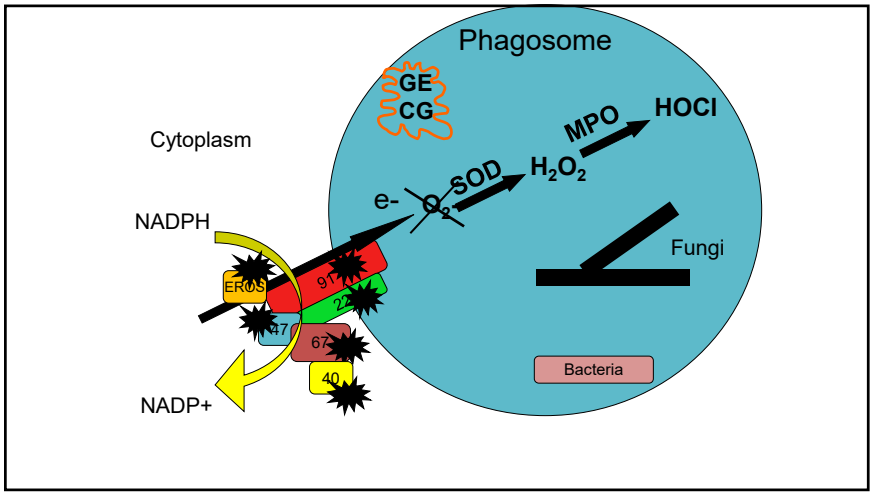

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Chronic Granulomatous Disease (X, AR)

Failure to make the phagocyte respiratory burst

Frequency 1/100,000 - 1/200,000 live births

- Presentation usually in childhood; more adults recognized

Recurrent life-threatening infections

- Catalase-positive bacteria, fungi (nuanced)
- Tissue granuloma formation

Infections: Lung, liver, lymph nodes, skin, bone

Bacteremia: Uncommon but bad

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Infections in CGD

S. Aureus	(liver, lymph nodes, osteo)
S. Marsescens	(skin, lung, lymph nodes)
B. Cepacia	(pneumonia, bacteremia)
Nocardia spp.	(pneumonia, brain, liver)
Aspergillus spp.	(lung, esp. miliary, spine)
Salmonella	(enteric, bacteremia)
BCG	(local/regional infections)

Chromobacterium violaceum *(warm brackish water, soil, e.g., Disney World)*

Francisella philomiragia *(brackish water, Chesapeake Bay, Sounds)*

Burkholderia gladioli *(causes onion rot)*

Granulibacter bethesdensis *(necrotizing LN, hard to grow, likes CYE)*

Paecilomyces spp.

Pediatric Health Med Ther 2020 Jul 22;11:257-268.

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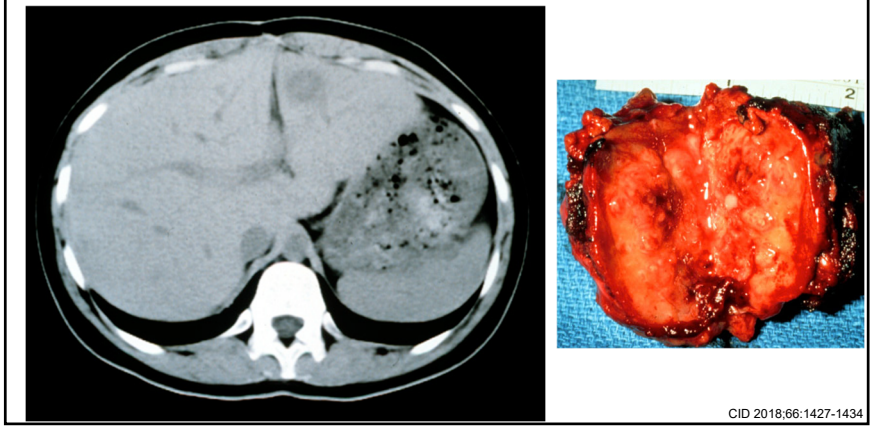
Staphylococcal Liver Abscess in CGD



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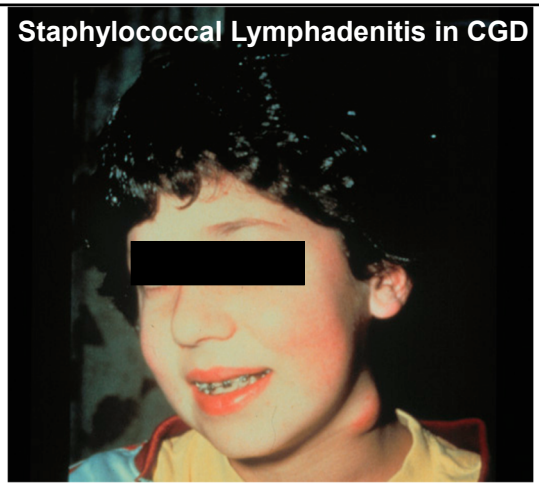
Staphylococcal Lymphadenitis in CGD



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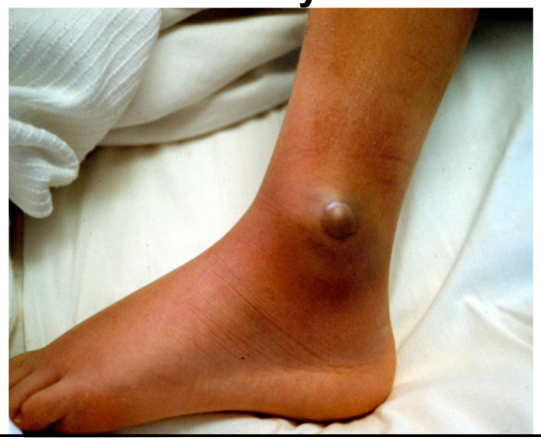
Staph aureus Osteomyelitis in CGD



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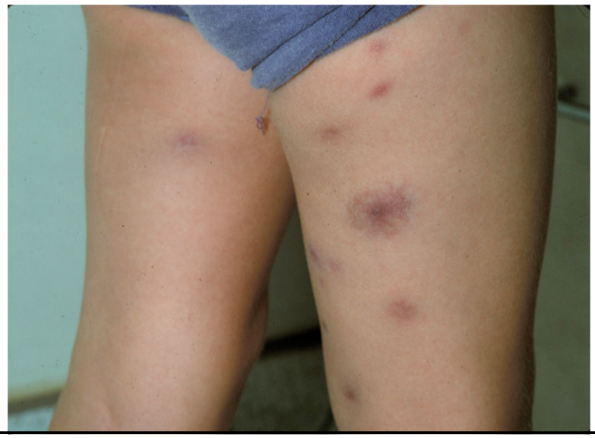
Burkholderia cepacia Complex Bacteremia in CGD



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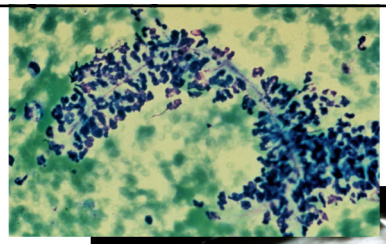
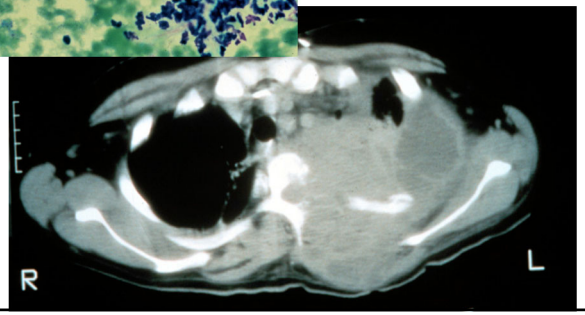


CGD
Aspergillus nidulans
Pneumonia



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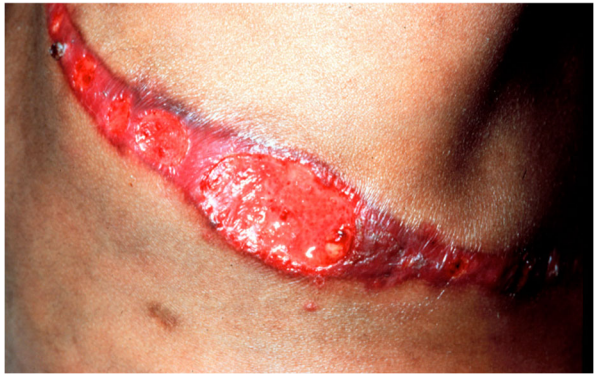
Thoracotomy 10 Days Postop



CGD Granulomatous Wound Dehiscence

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CGD Granulomatous Esophageal Obstruction

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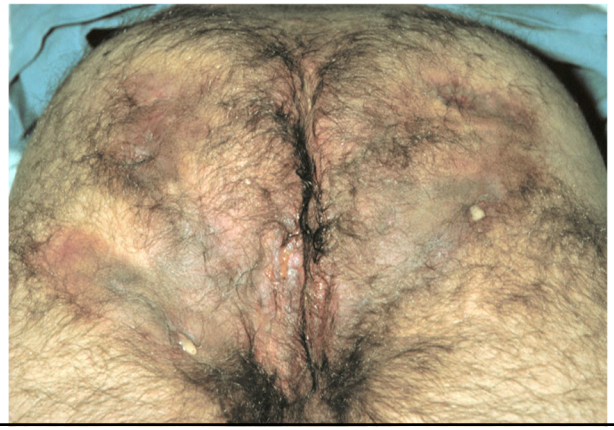
CGD Inflammatory Bowel Disease



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Chronic Granulomatous Disease

- X-linked, chr. Xp21 (70% of US cases)
  - Carrier females are mosaic (Lyonization)
  - 1/2 of offspring of carrier Mom will receive the gene
    - ~1/3 of carriers are sporadic, from sperm
  - X-linked male: all daughters carriers, no sons affected
- Autosomal recessive (30% of cases)

Dx - PMN dihydrorhodamine 123 oxidation (DHR)
[PMN nitroblue tetrazolium reduction (NBT) is the old test]
(MPO Deficiency gives a FALSE ABNORMAL DHR)

BE CAREFUL ABOUT THE LAB AND HOW YOU DISCUSS IT!

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CGD Management and Treatment

- 90% overall long-term survival
- Follow CRP, radiographs
- Prophylactic antibiotics and antifungals
  - TMP/SMX, itraconazole
- Prophylactic interferon gamma
  - 50 µg/m2 subcutaneously three times weekly
- Aggressive search for and treatment of infections
- BMT (gene therapy)

Hematol Oncol Clin North Am. 2013 Feb;27(1):89-99

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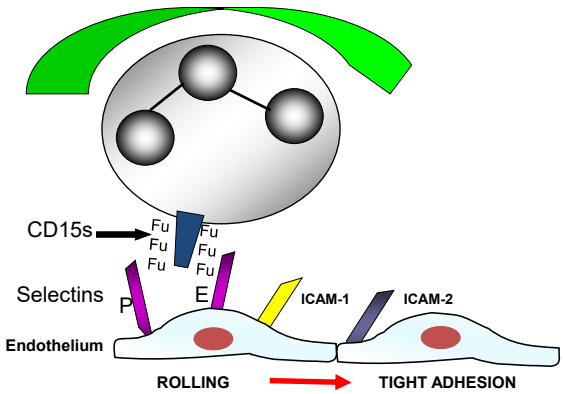
Neutrophil Rolling



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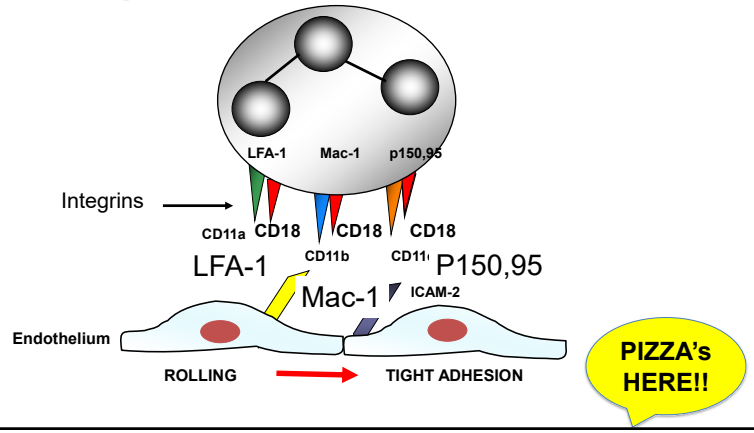
Neutrophil Adhesion



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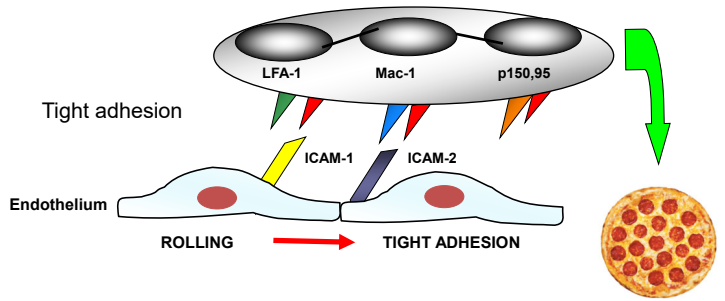
Neutrophil Tissue Entry (Diapedesis)



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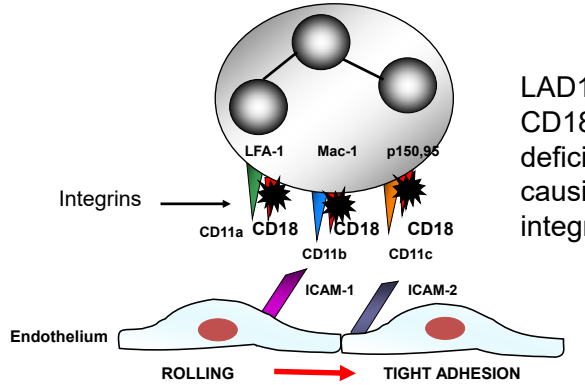
Leukocyte Adhesion Deficiency Type 1



LAD1 is due to CD18 deficiency, causing loss of integrins

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Leukocyte Adhesion Deficiency Type 1 (AR)

- Failure to attach to the endothelium due to mutations CD18
- Recurrent necrotizing infections: skin, perineum, lung, gut
- Enteric GNR, GPC, NOT fungi or *Candida*
- Baseline leukocytosis, further WBC increase to infection
- Rare, consanguinity common

Dx - FACS for CD18,
Complement dependent opsonization
Rx - Treatment of infections, BMT

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Leukocyte Adhesion Deficiency I

- Delayed umbilical stump separation
- Dystrophic, "cigarette paper" scars
- Gingivitis with tooth loss, alveolar ridge resorption
- Biopsies: no neutrophils at sites of infection, rare monocytes and eosinophils
- Severe and moderate forms of disease

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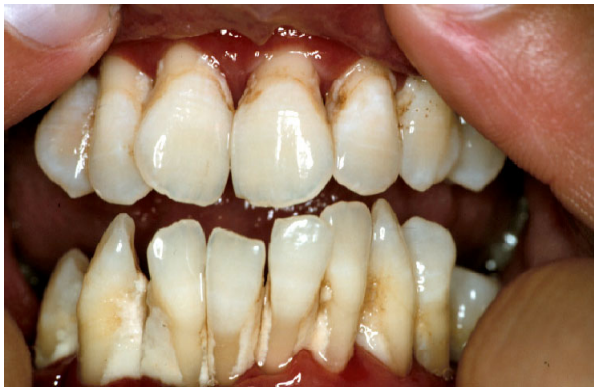
Almost Universal Tooth Loss in LAD1 By Adulthood



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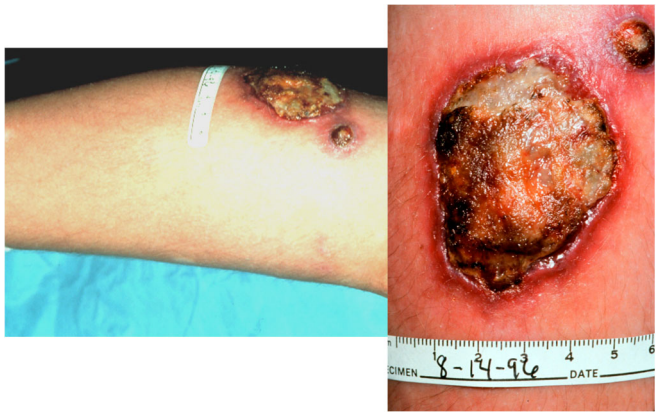
Impaired Wound Healing in LAD1



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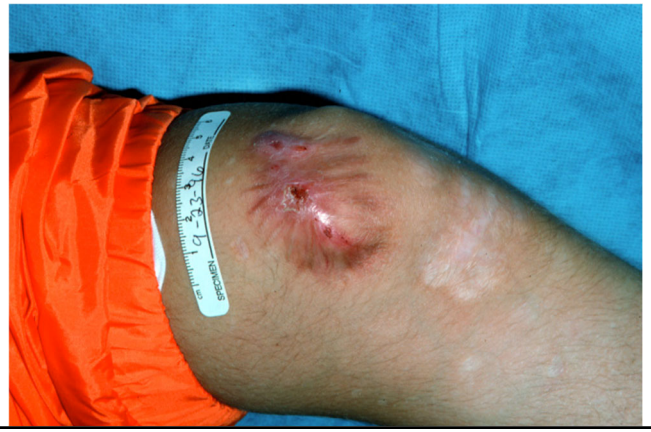
Cigarette Paper Scarring



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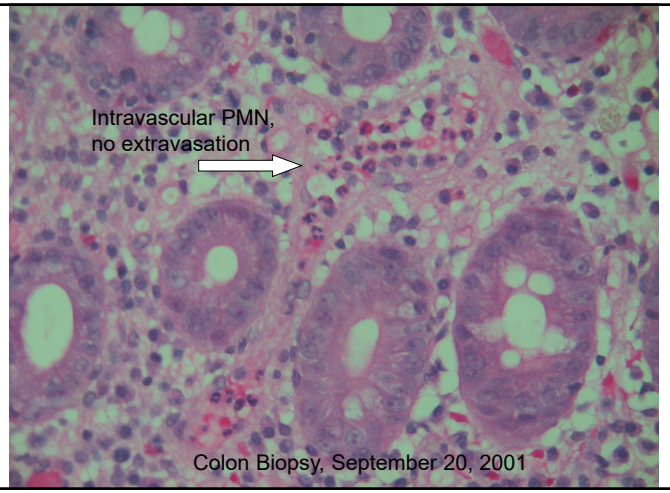

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Question #3

19-year-old boy with Pneumonia

- Admission WBC 43,000, looked OK
- Ceftriaxone, good response
- Medical student: WBC never <11,000/mcl
- Left shin ulcer not inflamed
- Not healed in > 2 mos
- She raises the possibility of Leukocyte Adhesion Deficiency (LAD1)

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Question #3

Which of the following would lead to a ruling <u>against</u> LAD1?

A. Gingivitis, tooth loss, and alveolar ridge resorption

B. FACS showing 5% of normal expression of CD18 and CD11a-c on granulocytes

C. He is the product of a first cousin union

D. Extensive neutrophil infiltration in the left shin ulcer

E. Multiple dystrophic scars over the legs from previous ulcers

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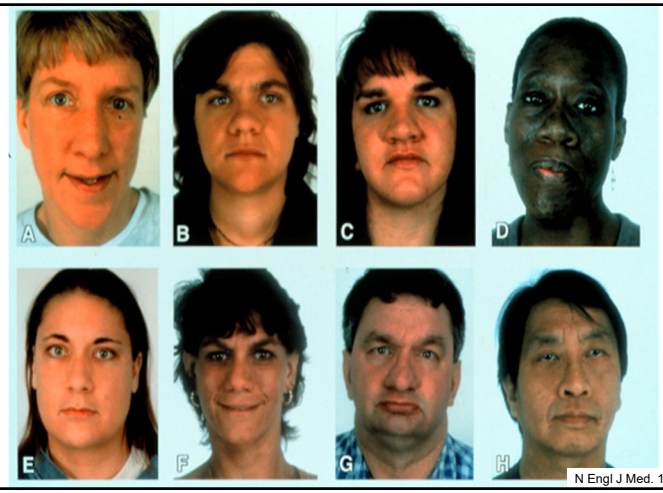
27-year-old Woman with Boils

Referred from her internist for recurrent boils with *S. aureus*

- IgE of 12,376 IU
- "Bronchitis and sinusitis at least once a year"
- Persistent eczema requiring topical steroids
- Never hospitalized but having "more trouble" lately

63



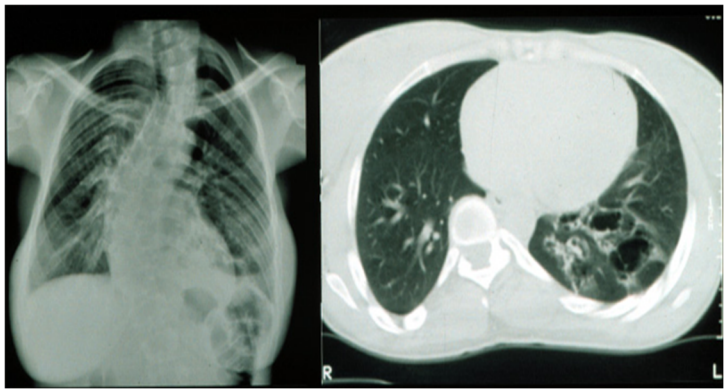
N Engl J Med. 1999;340:692-702

64

HIE (Job's) Syndrome History and Exam

Eczema	100%
Facies	100% (≥16y)
Boils	87%
Pneumonia	87%
Mucocutaneous Candidiasis	83%
Pulmonary Cysts	77%
Scoliosis	76% (≥ 16y)
Delayed dental deciduation	72%
Coronary artery aneurysms	65%
Pathologic fractures	57%

65



66

Pulmonary Pathogens in HIE

Primary pathogens:

- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- *Hemophilus influenzae*

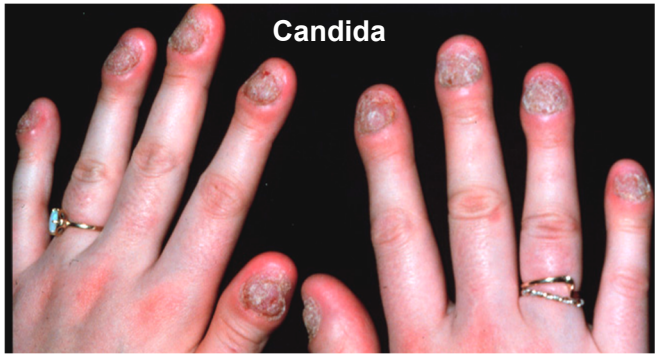
Secondary pathogens:

- *Pseudomonas aeruginosa*
- *Aspergillus fumigatus*

Others:

- *Pneumocystis jiroveci, M. avium* complex

67



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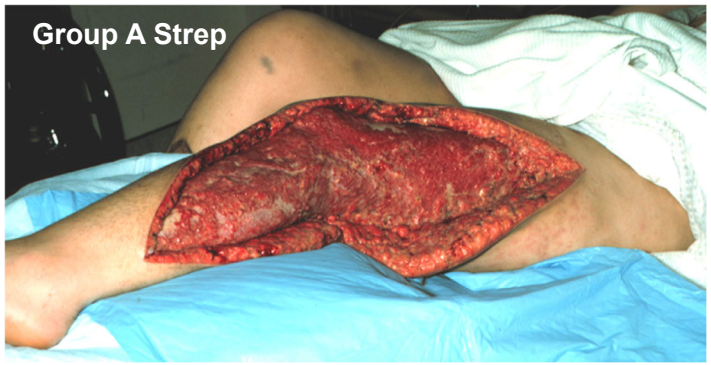
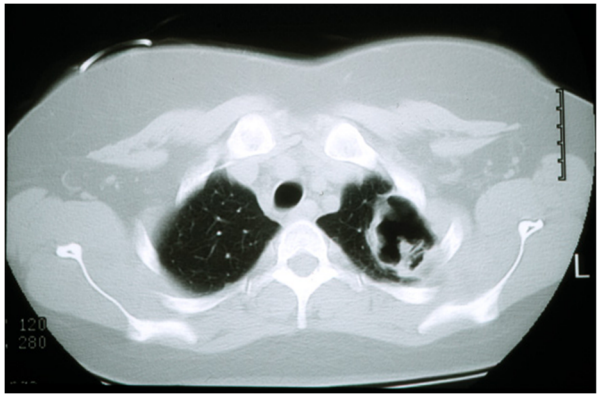


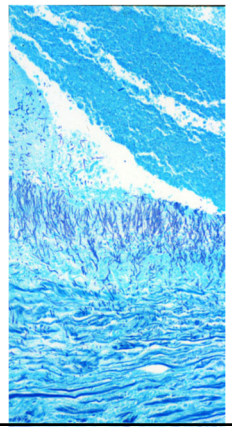
69

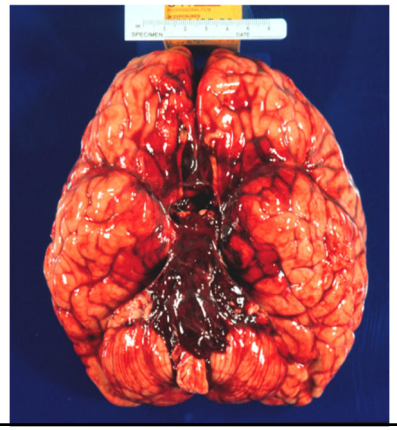
Aspergillus Lung Infection



70

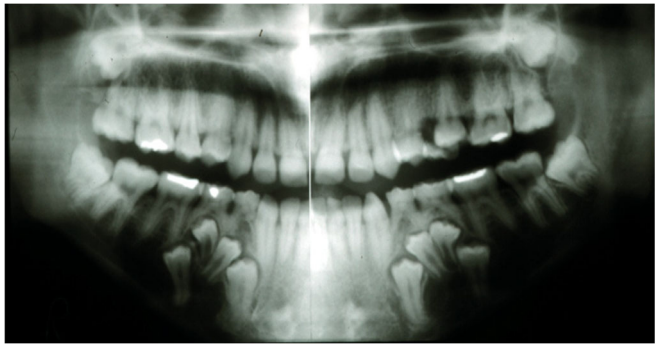
Metastatic *Aspergillus* Brain Infection





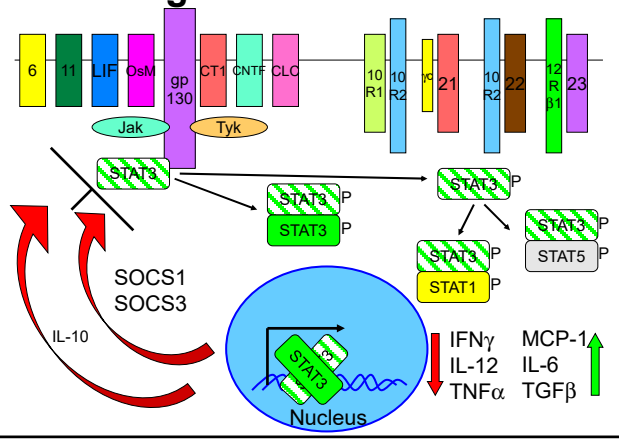
71

Failure Of Primary Dental Deciduation



72

Dominant Negative Mutant STAT3



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Hyper IgE Recurrent Infection (Job's)

- Recurrent sinopulmonary infections *S. aureus, S. pneumo, H. flu*
- Post-infectious pulmonary cyst formation
- Recurrent *S. aureus* skin abscesses
- Characteristic facies, eczema, scoliosis, fractures
- Very elevated IgE (>2000 IU), eosinophilia

DDx - Atopic dermatitis is a close mimic
Job's: pneumonia, lung cysts, skeletal, mutations in *STAT3*

Rx - Treatment of infections, prophylactic antibiotics, antifungals
BMT

J Clin Immunol. 2021;41:864-880

74

DOCK8 Deficiency

Autosomal Recessive hyper IgE syndrome

Eczema, allergies, asthma, high IgE

Staph, Strep, H. flu, Acinetobacter, Pseudomonas

Candida, Cryptococcus, Histoplasma

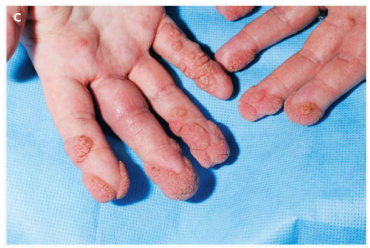
HPV, HSV, molluscum

Squamous cell carcinomas, lymphoma

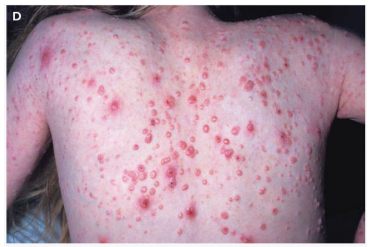
J Clin Immunol 2021 May 1. doi: 10.1007/s10875-021-01051-1.

75

DOCK8 Deficiency



HPV

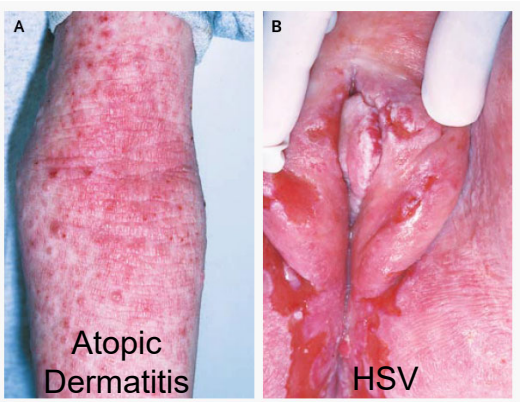


Molluscum contagiosum

N Engl J Med. 2009;361:2046-55

76

DOCK8 Deficiency



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DOCK8 vs. STAT3 Hyper IgEs

	DOCK8 (Recessive)	STAT3 (Dominant)
Pneumonia	+	+++
Pneumatoceles	-	+++
Retained teeth	-	+++
Fractures	-	+++
Viral infections	+++	-
Fungal infections	+	++
Allergies	+++	-
IgM	Low	Normal
Eosinophils	+ to ++	+

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Question #4

15-year-old girl with recurrent infections

- Infancy: eczema, recurrent pneumonias, skin infections
- IgE 14,574 IU/ml
- Allergist: use bed covers to avoid dust mites

Going over the allotted 15 minutes you elicit points trying to establish whether she has hyper-IgE recurrent infection syndrome (Job's).

79

Question #4

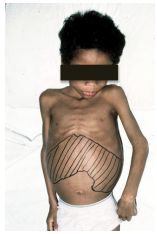
Which one of the following is not supportive of the diagnosis of Job's?

A. Pneumatoceles
B. Scoliosis
C. Severe warts
D. Retained baby teeth
E. Recurrent fractures

80

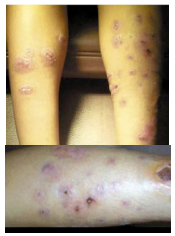
Clinical Spectrum of NTM Infections

Disseminated
Severe, Young
IFNg/IL-12 defects
NEMO, STAT1



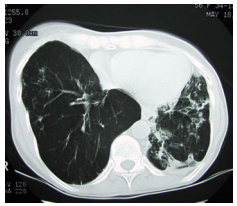
IMMUNE

Skin
Exposure
Inoculation



EXPOSURE

Pulmonary
Chronic, Older
Bronchiectasis
Cystic fibrosis (CF)
Ciliary dyskinesia (PCD)

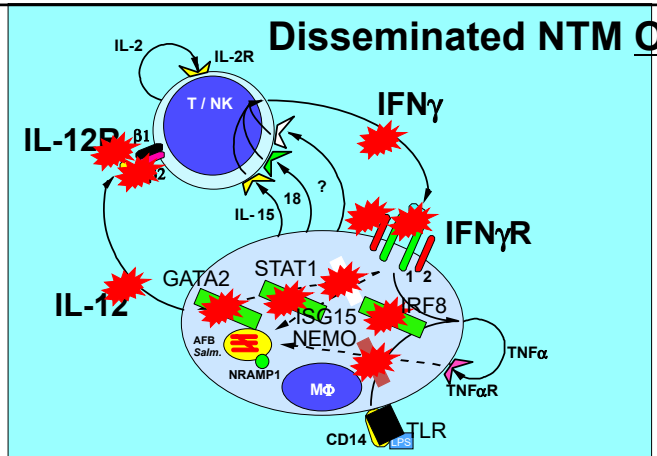


EPITHELIAL

Lancet Infect Dis. 2015;15:968-80

81

Disseminated NTM Only



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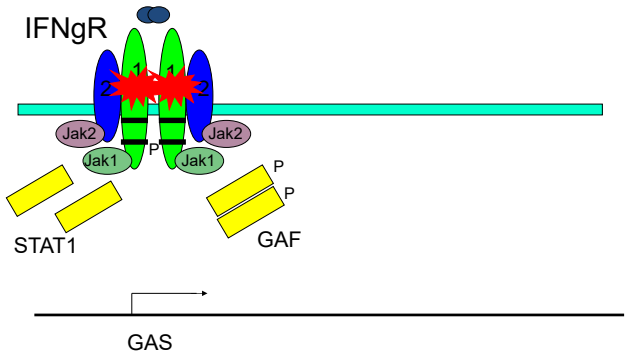
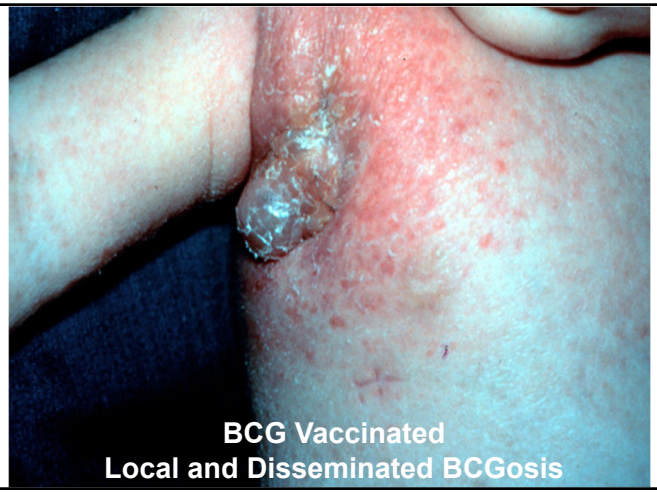
Autosomal Recessive IFNGR1 (Both Alleles)



83



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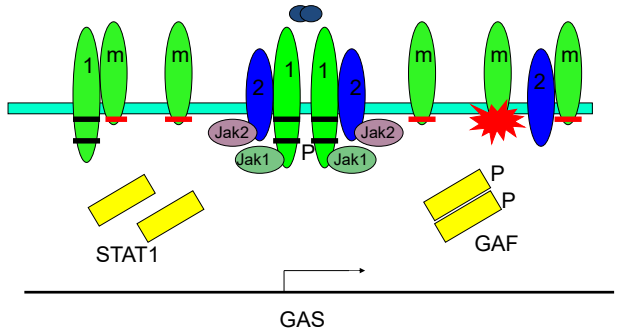
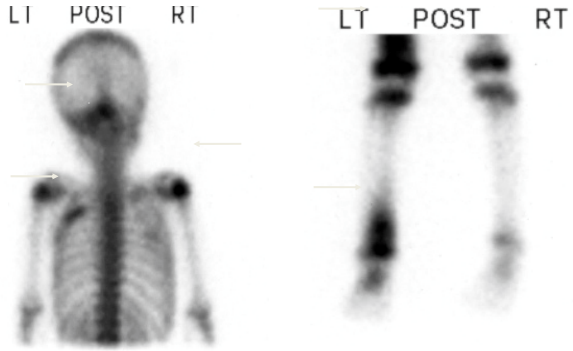
Autosomal Dominant IFNGR1 (One Allele)



85

Mycobacterial Osteomyelitis in Dominant IFNγR1 Deficiency



Ann Allergy Asthma Immunol 2002;89:239-43.

86

Pathogens in Human IFNγR Deficiencies

M. avium	*Salmonella*
M. intracellulare	*Listeria*
M. chelonae	
M. abscessus	CMV
M. smegmatis	HSV
M. fortuitum	VZV
M. tuberculosis	RSV
Bacille Calmette Guerin	HHV-8
	Coccidioides
	Histoplasma

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IFNGR1: Dominant vs. Recessive

Characteristic	AD	AR
IFNγR1 display	High	None
IFNγ responsiveness	Low	None
Clinical presentation	Local	Disseminated
Granulomata	Present	Absent
Osteomyelitis	100%	Rare
Survival	Excellent	Most die

Lancet. 2004;364:2113-21

88

Interferon γ Receptor Deficiencies

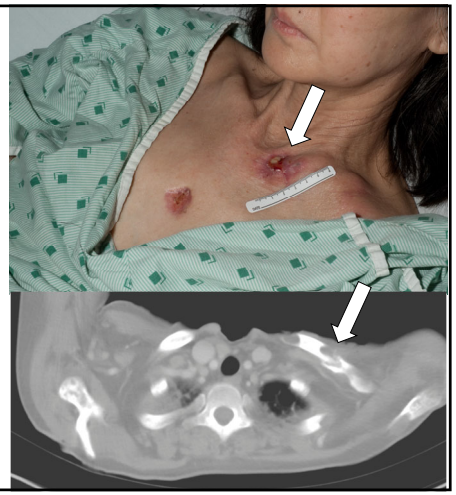
- Absent or defective IFNγR1
  - MAC and other NTM, *Salmonella*, TB, viruses
  - Complete defects present in childhood
  - Partial defects present later in life
  - May be misdiagnosed as malignancy!
  - NOT a cause of isolated lung disease in adults
- Dx - genetics, flow cytometry for IFNγR1
- Rx - antimycobacterials (BMT)

N Engl J Med. 2017;377:1077-1091.

89

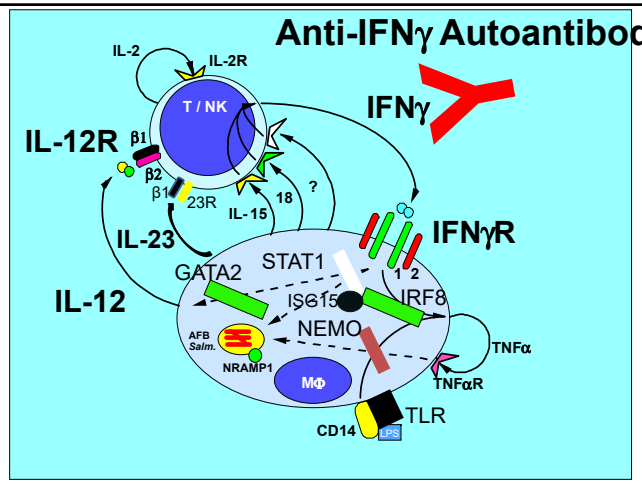
60-year-old Vietnamese woman

- USA 1970s
- 1 year recurring disseminated *M. avium* complex
- Numerous fistulae



90

Anti-IFNγ Autoantibodies



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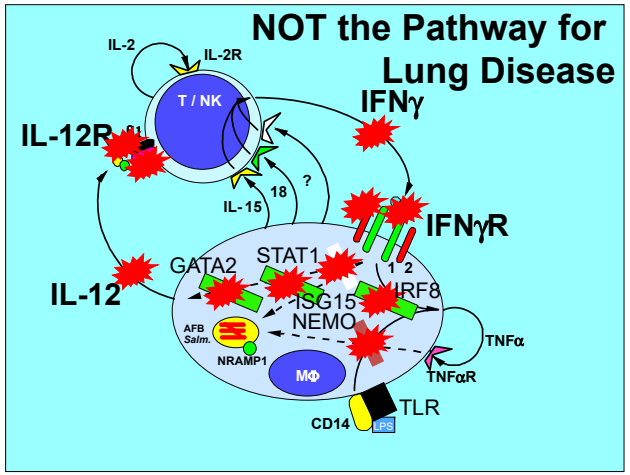
Anti-IFNγ Autoantibody Syndrome

- *Disseminated* NTM later in life also TB, *Talaromyces*, *Burkholderia*, VZV
- Predominantly female, mostly East Asian
- Dx-anti-IFNg autoantibody detection
  Quantiferon is often INDETERMINATE
- Rx- antimycobacterials, possibly rituximab

NEJM 2012;367:725

92



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Question #5

30-year-old Thai Woman with Back Pain

- 2 months pain and weight loss
- HIV-, normal CBC and chemistries, normal CD4
- Biopsy: osteomyelitis, MAC growing
- Quantiferon indeterminate
- You suspect that she has the anti-interferon gamma autoantibody syndrome

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Question #5

Supporting this diagnosis, what should you do?

A. Check complements and total IgG
B. Determine anti-IFNγ antibody levels
C. Determine anti-GM-CSF autoantibody levels
D. Determine anti-IFNα autoantibody levels
E. Determine her cellular response to IFNγ

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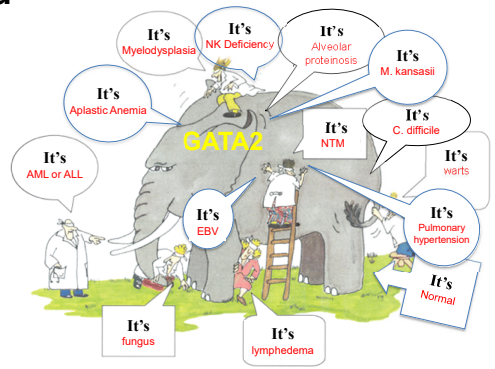
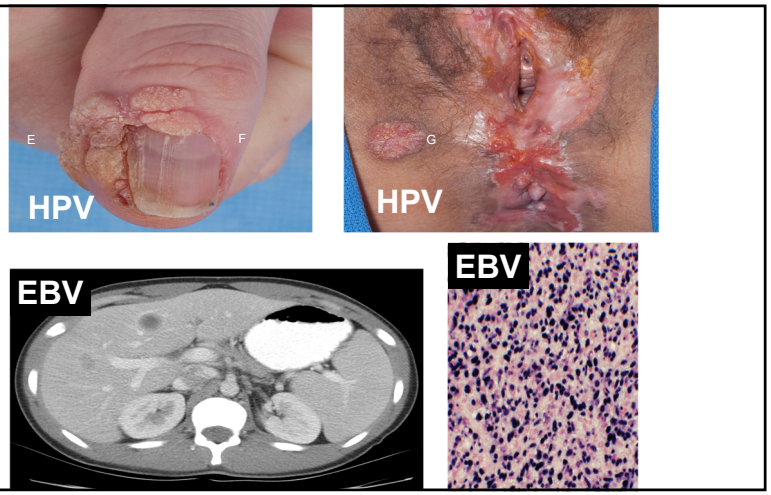
The Blind



The Elephant

96



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GATA2 Deficiency

- Heterozygous mutations in *GATA2*, a critical hematopoietic gene
- Adolescent to adult onset
  - HPV (hands, genitals, cervical, vulvar)
  - Disseminated NTM (mediastinal *M. kansasii*)
  - Pancytopenia
- Labs: profound monocytopenia, low B, low NK
- CT: subpleural blebs
- Autosomal dominant
- Dx: genetics, hypocellular marrow, abnormal megakaryocytes
- Rx: antibiotics, BMT

Blood 2014; 123:809-21

98

Idiopathic CD4+ T-lymphocytopenia

- Idiopathic CD4+ T-lymphocytopenia (ICL)
  - ≤ 300 CD4+/µl
  - Associated with AIDS-like infections (crypto, PCP, MAC)
    - Exclude HIV infection (PCR, bDNA, p24, culture)
    - Often older onset than HIV associated OI
    - Surprisingly stable, consider incident cancers
- **Dx -** Determination of ICL (FACS)
  Often due to an underlying defect, so LOOK
- **Rx -** Treat infections (follow CD4+, ?cytokines)

N Engl J Med. 2023;388:1680-1691

99

Screening Laboratories

- For Lymphocytes
  - Ig levels
  - Immunization status (tetanus, pneumovax)
  - CD4+ number
  - *Genetics* (exome studies, panels)

100

Screening Laboratories

- Phagocytes
  - DHR for CGD
  - Genetics for everything else
- Complement
  - CH_{50} (classical pathway)
  - AH_{50} (alternative pathway)
  - Think about the gene involved!
  - Use Pubmed OMIM
  - Sequence is faster and cheaper than you think

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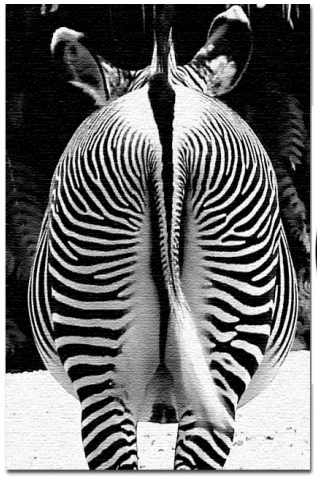

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