03 - Clinical Immunology and Host Defense

Speaker: Steven Holland, MD

Clinical Immunology and Host Defense

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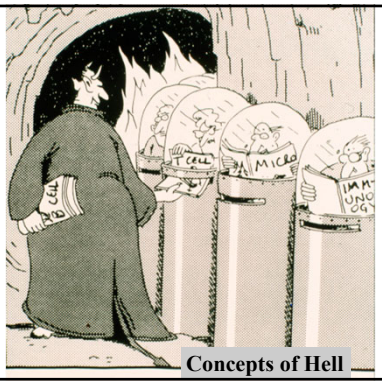
NIAID, NIH

7/1/2024

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**



Concepts of Hell

Host Immune Defense

Humoral
- Complement
- Mannose binding lectin
- Antibody

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

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

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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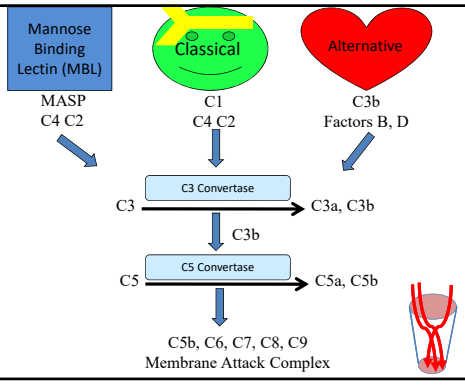


Complement Deficiencies

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

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), AH_{50} (Alternative)

Rx- treat infections, prophylaxis if needed, hypervaccination?

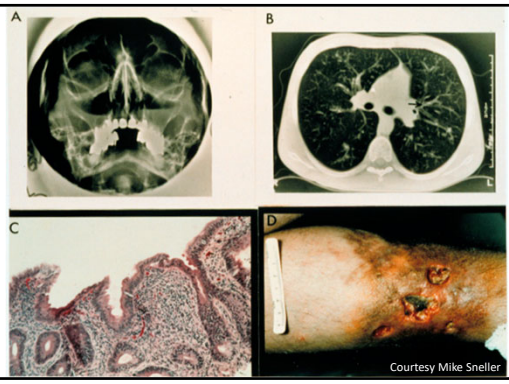
J Clin Immunol 2020 May;40(4):576-591

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

Dx- low IgA

Rx- none



Common Variable Immunodeficiency (CVID)

- recurrent sino-pulmonary bacterial infections
- chronic enteric infections with *G. lamblia, Campylobacter, Salmonella, Shigella*
- severe echoviral meningitis/encephalitis/myositis

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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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)

Preview Question

Next step?

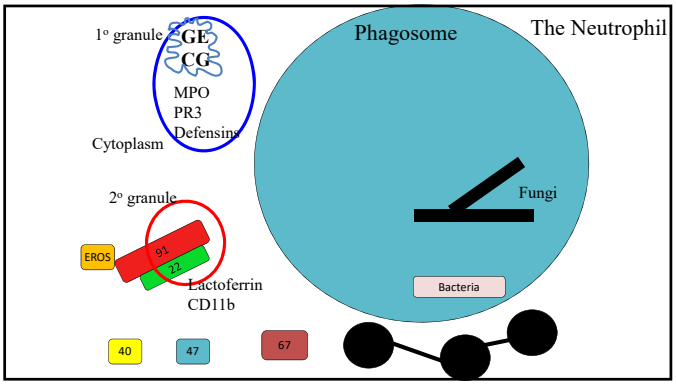
a) IgG subclasses and titers against tetanus and pneumococcus. If low consider IVIG

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.



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

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

Other Causes of Neutropenia

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

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52 year old man

referred from his Family Practitioner.

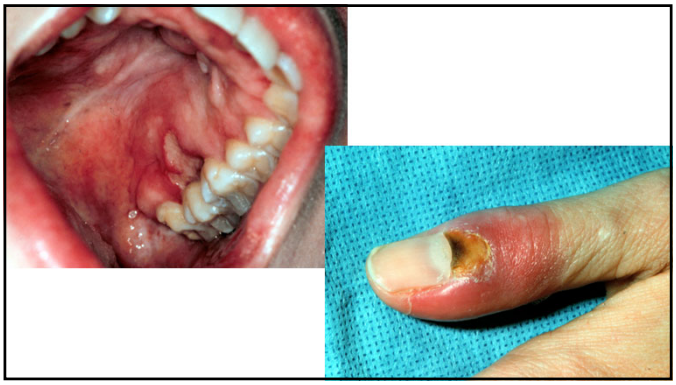
Recurrent digital and oral ulcers occurring every month or so for the last 4 months.

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.



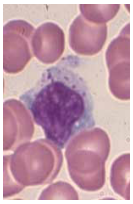
Acquired Neutropenia in Adults

-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 is curative (cyclosporine, MTX, steroids)

G-CSF may lift both nadir and baseline

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

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

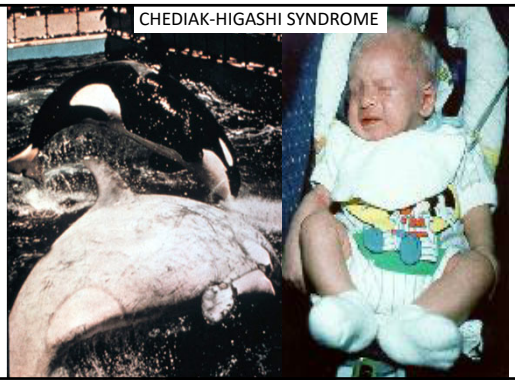
Dx- absence of peroxidase positive granules

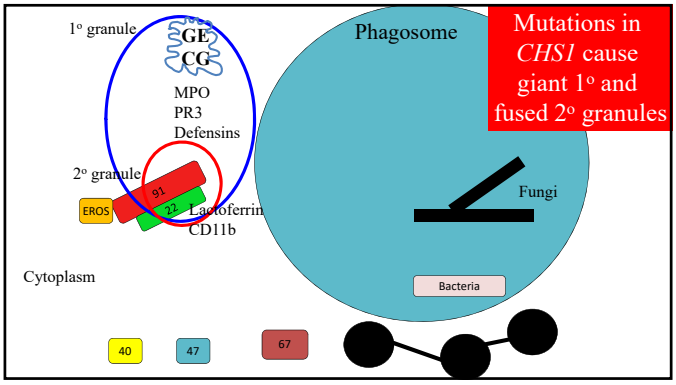
due to mutations in *MPO* gene

Rx- treat invasive infections (*Candida*),

no specific therapy

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

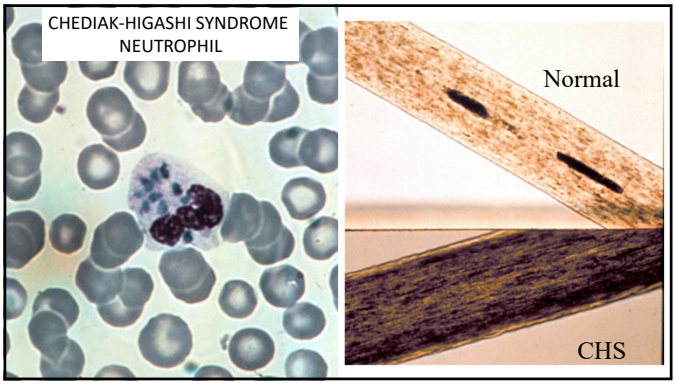




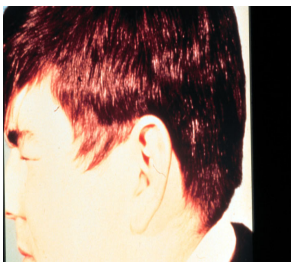
Chediak-Higashi Syndrome (AR)

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 granules; killing and chemotactic defects
  due to mutations in *CHS1*, encodes LYST
Rx- prophylaxis**,** treatment of infections, BMT

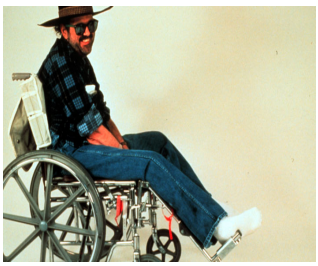
Drug Discov Today Dis Models. 2020;31:31-36



SILVERY SHEEN

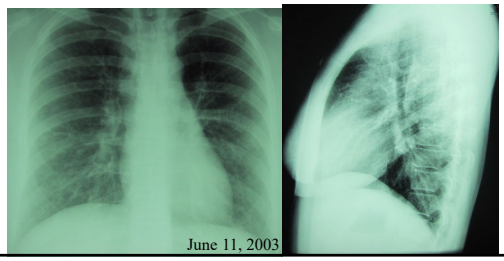


PERIPHERAL NEUROPATHY



23 yo woman; athletic coach

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



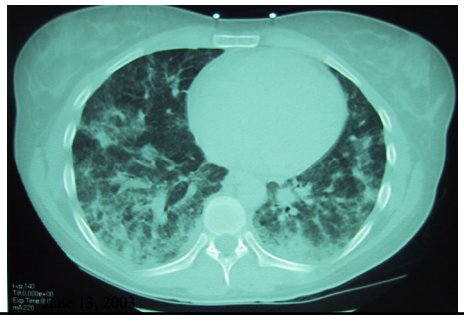
ER presentation

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

PMH
Respiratory infections in infancy
Cat scratch disease 8 yo: resolved with antibiotics

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

2 days later, hypoxia and fever



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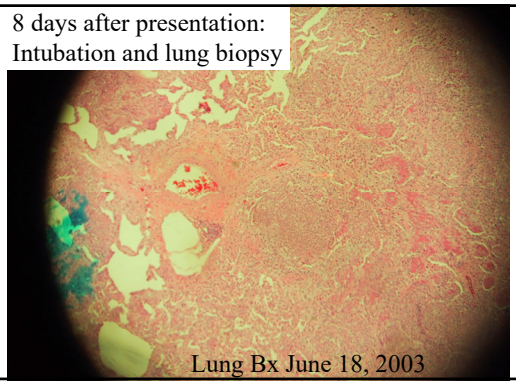
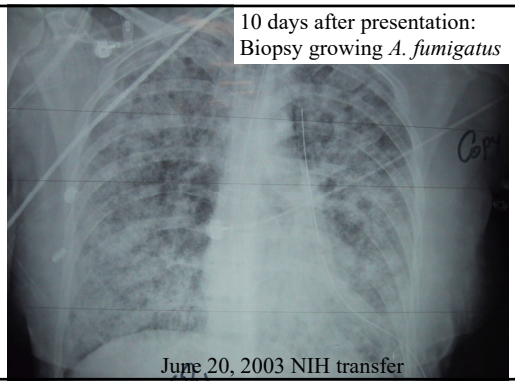
Hospital Course

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

8 days after presentation:
Intubation and lung biopsy





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

Preview Question

Invasive aspergillosis in an <u>otherwise normal host</u>

a) Allergic bronchopulmonary aspergillosis

b) Cystic fibrosis

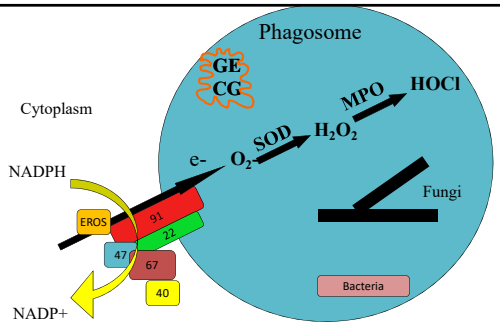
c) Lymphocyte dysfunction (SCID)

d) Phagocyte defect

e) Acute HIV

What is so special about phagocytes?

- neutrophils, monocytes, macrophages, eosinophils, basophils
- Preformed cytoplasmic granules with stored enzymes
- Normal humans make how many neutrophils/d?
  10^{11}
- Half life of neutrophils in the circulation?
  7 hours



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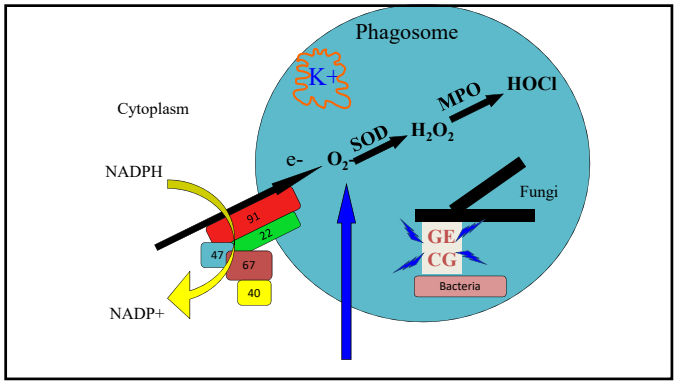
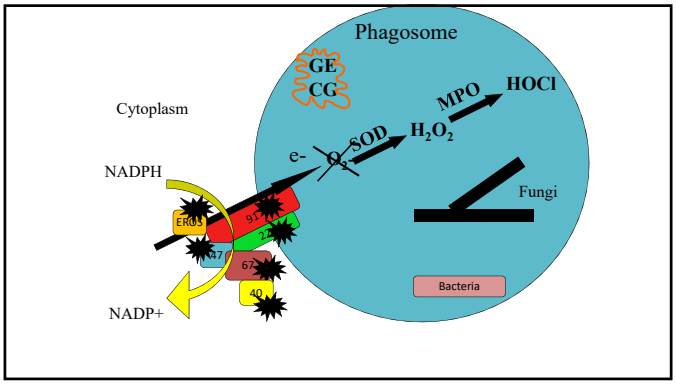




Chronic Granulomatous Disease (X, AR)

Failure to make the phagocyte respiratory burst

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

- presentation usually in childhood,
  - but more adult cases being recognized

recurrent life-threatening infections

- catalase-positive bacteria, fungi (nuanced)
- tissue granuloma formation
- **infections**: lung, liver, lymph nodes, skin, bone
- **Bacteremia:** uncommon but bad

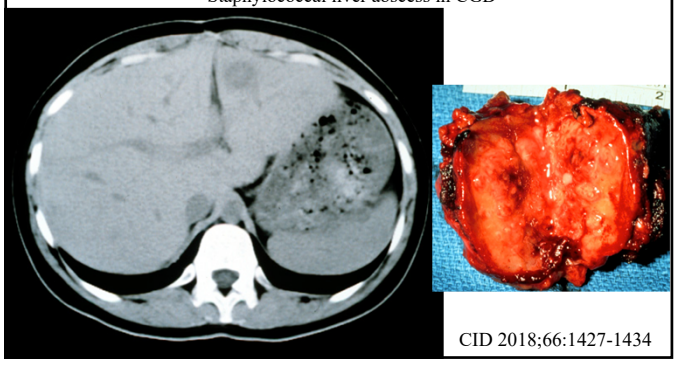
Infections in CGD

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.

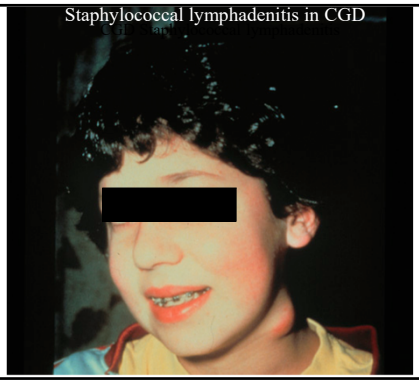
Pediatric Health Med Ther 2020 Jul 22;11:257-268

Staphylococcal liver abscess in CGD



CID 2018;66:1427-1434

Staphylococcal lymphadenitis in CGD



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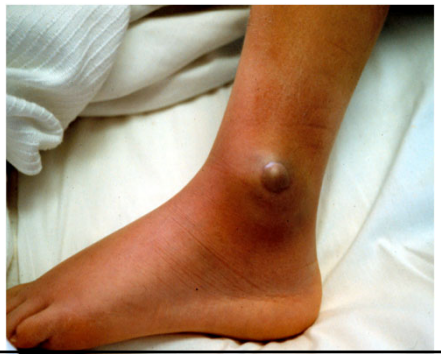
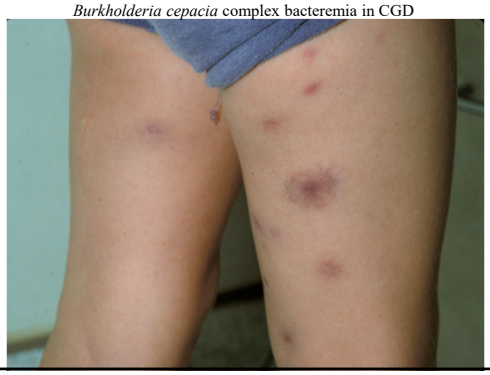
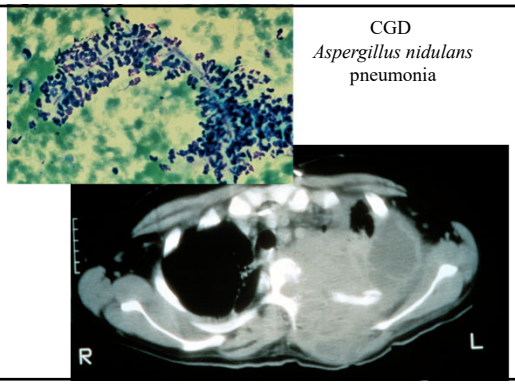
Staph aureus osteomyelitis in CGD



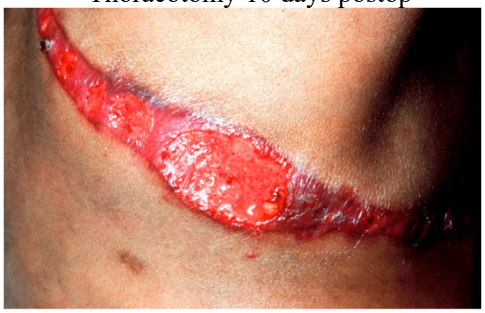
Burkholderia cepacia complex bacteremia in CGD



CGD
Aspergillus nidulans
pneumonia



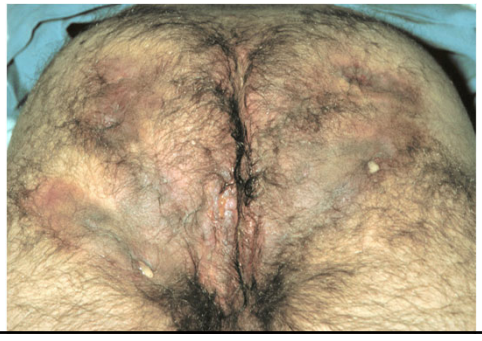
Thoracotomy 10 days postop



CGD granulomatous wound dehiscence

CGD
granulomatous
esophageal
obstruction

CGD Inflammatory Bowel Disease



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Chronic Granulomatous Disease

X-linked, chr. Xp21 (70% of cases)
- carrier females are mosaic (Lyonization)
- 1/2 of offspring of carrier Mom will receive the gene
  - about 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!

CGD Management and Treatment

90% overall long-term survival

follow CRP, radiographs

prophylactic antibiotics and antifungals
- TMP/SMX, itraconazole

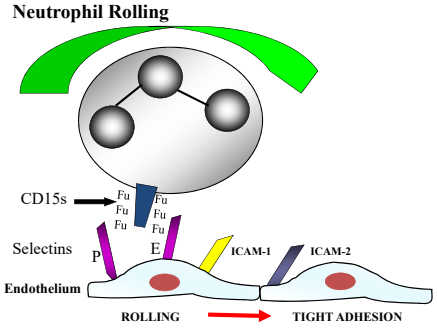
prophylactic interferon gamma
- 50 µg/m2 subcutaneously three times weekly

aggressive search for and treatment of infections

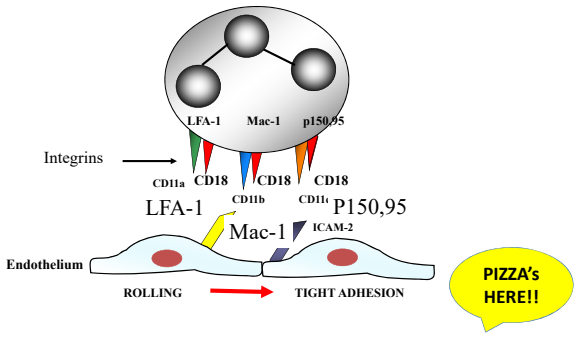
BMT (gene therapy)

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

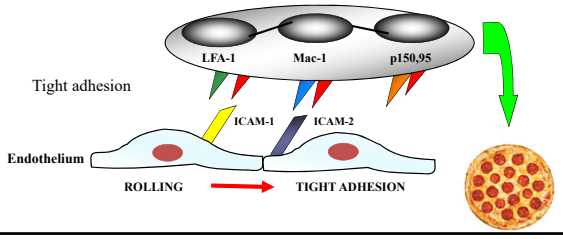
Neutrophil Rolling



Neutrophil adhesion

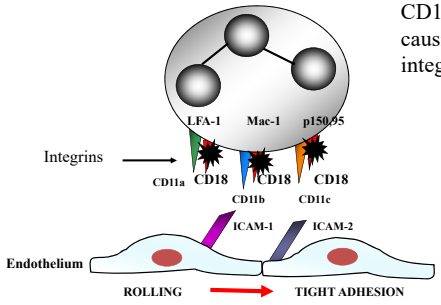


Neutrophil tissue entry (diapedesis)



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)

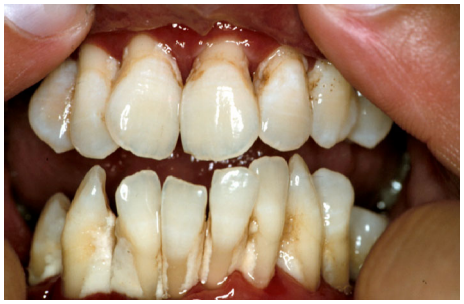
Failure to attach to the endothelium due to mutations CD18
Recurrent necrotizing infections: skin, perineum, lung, gut
Enteric GNR, GPC, NOT fungi or *Candida*
baseline leukocytosis, further WBC increase to infection
rare, consanguinity common

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

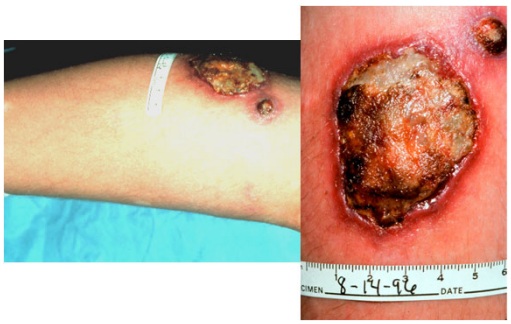
Leukocyte Adhesion Deficiency I

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

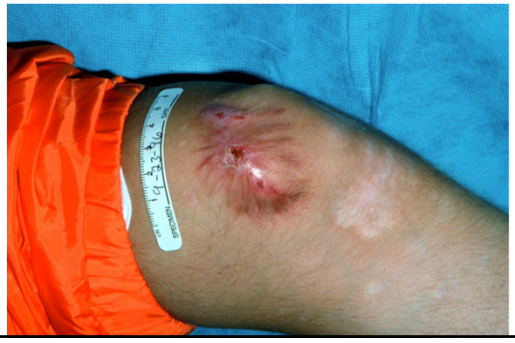
Almost universal tooth loss in LAD1 by adulthood

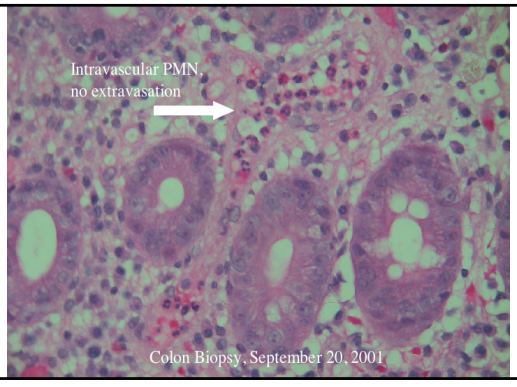


Impaired wound healing in LAD1



Cigarette paper scarring





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Preview Question

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)

Ruling against LAD1 would be:

a) Gingivitis, tooth loss, and alveolar ridge resorption.

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

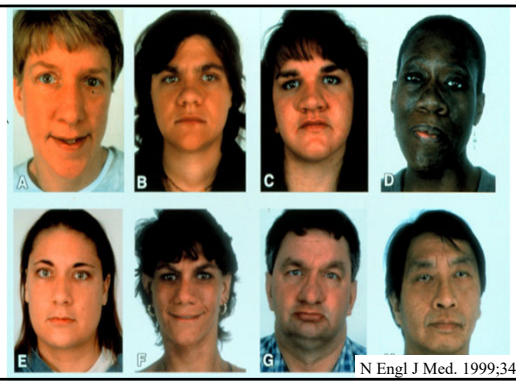
c) He is the product of a first cousin union.

d) Extensive neutrophil infiltration in the left shin ulcer.

e) Multiple dystrophic scars over the legs from previous ulcers

27 year old woman with boils

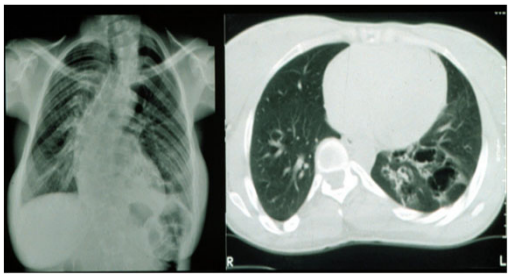
Referred from her internist for recurrent boils with *S. aureus*
IgE of 12,376 IU.
"Bronchitis and sinusitis at least once a year"
Persistent eczema requiring topical steroids.
Never hospitalized but having "more trouble" lately.



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

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%



03 - Clinical Immunology and Host Defense

Speaker: Steven Holland, MD

Pulmonary Pathogens in HIE

Primary pathogens:

Staphylococcus aureus

Streptococcus pneumoniae

Hemophilus influenzae

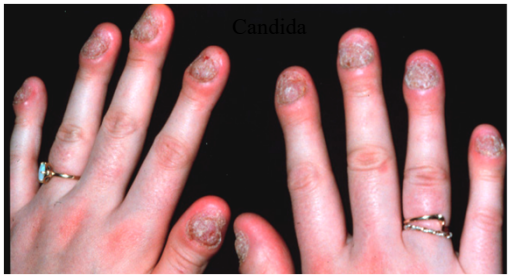
Secondary pathogens:

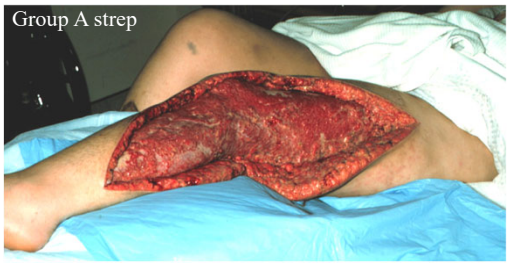
Pseudomonas aeruginosa

Aspergillus fumigatus

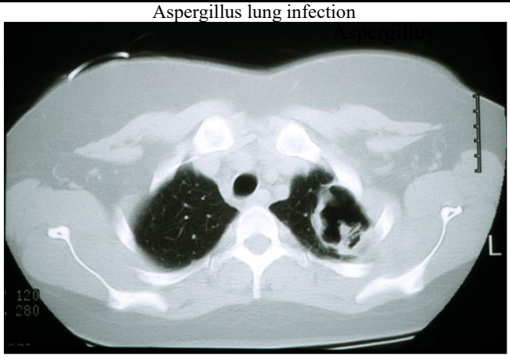
Others:

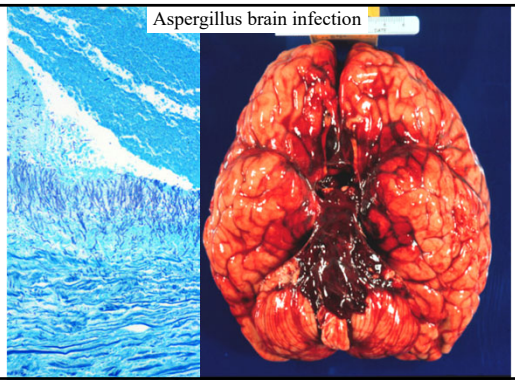
Pneumocystis jiroveci, M. avium complex



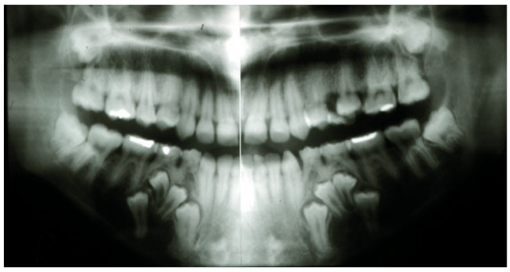


Aspergillus lung infection





Failure of primary dental deciduation



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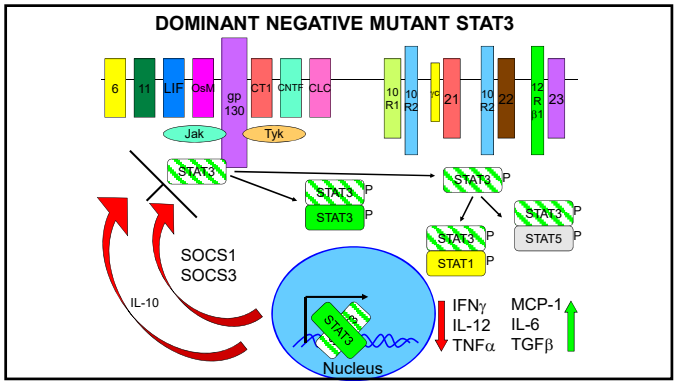


Hyper IgE Recurrent Infection (Job's)

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

DOCK8 Deficiency

Autosomal Recessive hyper IgE syndrome
Eczema, allergies, asthma, high IgE
Staph, Strep, H. flu, Acinetobacter, Pseudomonas

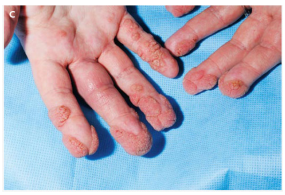
Candida, Cryptococcus, Histoplasma

HPV, HSV, molluscum

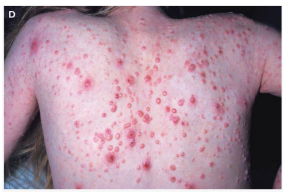
Squamous cell carcinomas, lymphoma

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

DOCK8 Deficiency



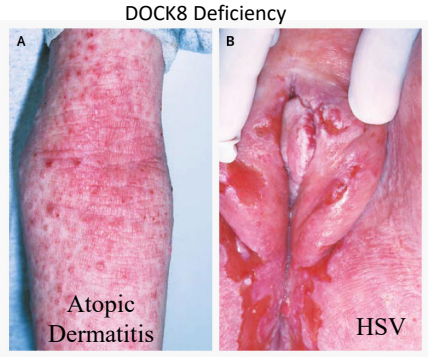
HPV



Molluscum contagiosum

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

DOCK8 Deficiency



DOCK8 vs. STAT3 Hyper IgEs

	DOCK8 (Recessive)	STAT3 (Dominant)
Pneumonia	+	+++
Pneumatoceles	-	+++
Retained teeth	-	+++
Fractures	-	+++
Viral infections	+++	-
Fungal infections	+	++
Allergies	+++	-
IgM	low	normal
eosinophils	+ to +++	+

03 - Clinical Immunology and Host Defense

Speaker: Steven Holland, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW COURSE Preview Question

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.

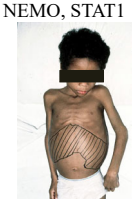
Going over the allotted 15 minutes you elicit points trying to establish whether she has hyper-IgE recurrent infection syndrome (Job's).

Which one of the following is <u>not</u> supportive of the diagnosis of Job's:

a) Pneumatoceles
b) Scoliosis
c) Severe warts
d) Retained baby teeth
e) Recurrent fractures

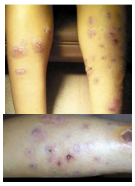
Clinical Spectrum of NTM Infections

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



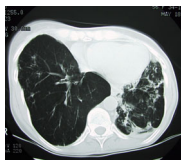
IMMUNE

Skin
Exposure
Inoculation



EXPOSURE

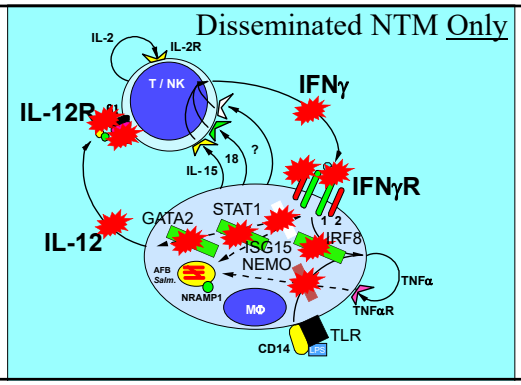
Pulmonary
Chronic, Older
Bronchiectasis
Cystic fibrosis (CF)
Ciliary dyskinesia (PCD)



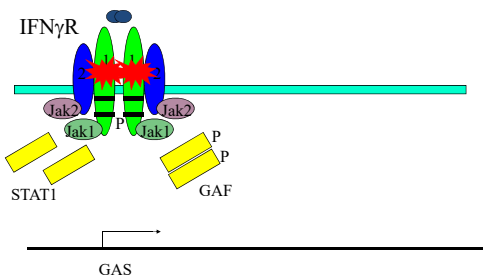
EPITHELIAL

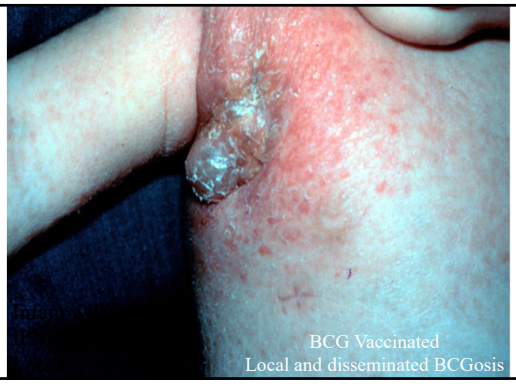
Lancet Infect Dis. 2015;15:968-80

Disseminated NTM Only



Autosomal Recessive IFNGR1 (both alleles)





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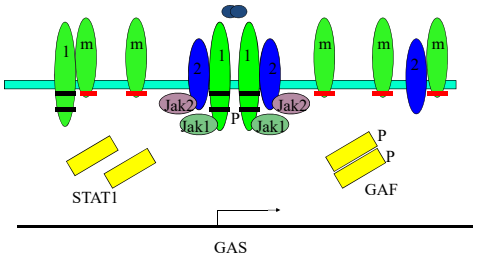
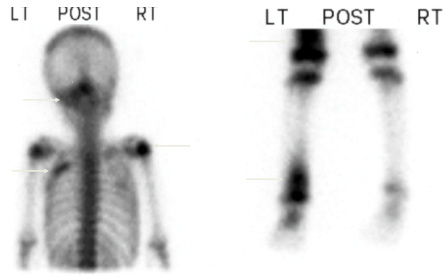
Autosomal Dominant IFNGR1 (one allele)



Mycobacterial Osteomyelitis in Dominant IFNγR1 Deficiency



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

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

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

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)

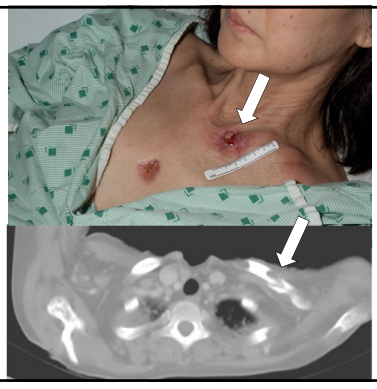
N Engl J Med. 2017;377:1077-1091.

60 yo Vietnamese woman

USA 1970s

1 year recurring disseminated *M. avium* complex

Numerous fistulae



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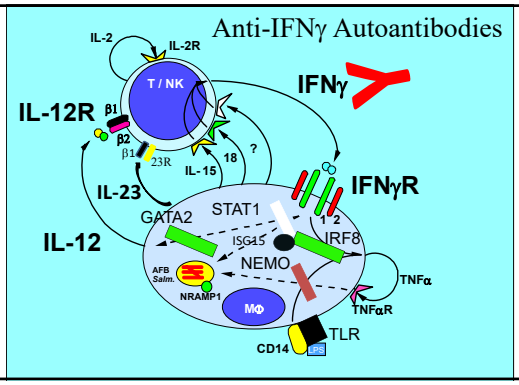


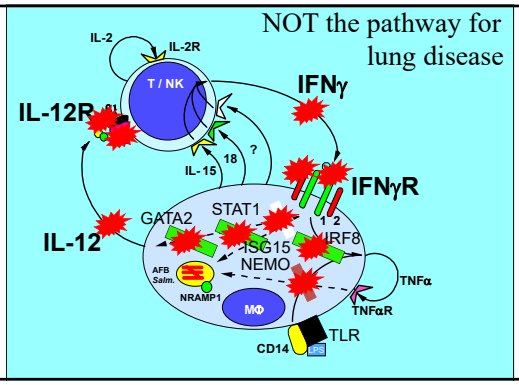
Anti-IFNγ autoantibody syndrome

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



IDBR INFECTIOUS DISEASE BOARD REVIEW COURSE Preview Question

30 yo Thai woman with back pain

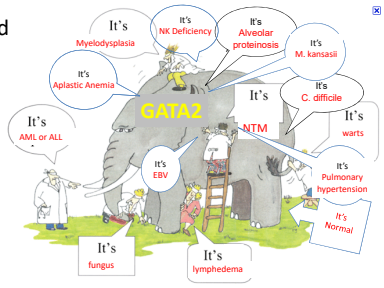
2 months pain and weight loss
HIV-, normal CBC and chemistries, normal CD4
Biopsy: osteomyelitis, MAC growing
Quantiferon indeterminate

You suspect that she has the anti-interferon gamma autoantibody syndrome

Supporting this diagnosis, you should:

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

The Blind



The Elephant

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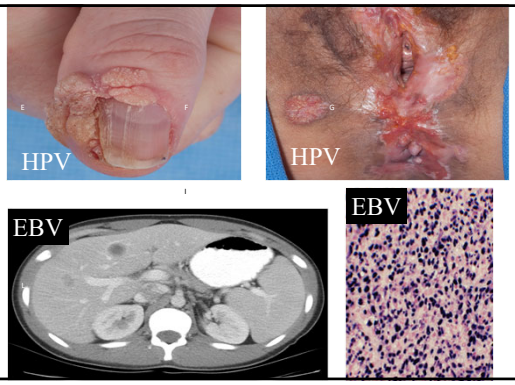

GATA2 Deficiency

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
Rx: antibiotics, BMT

Blood 2014; 123:809-21

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

Screening Laboratories

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

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