Case Discussion on Patients with Possible Immune Deficiency

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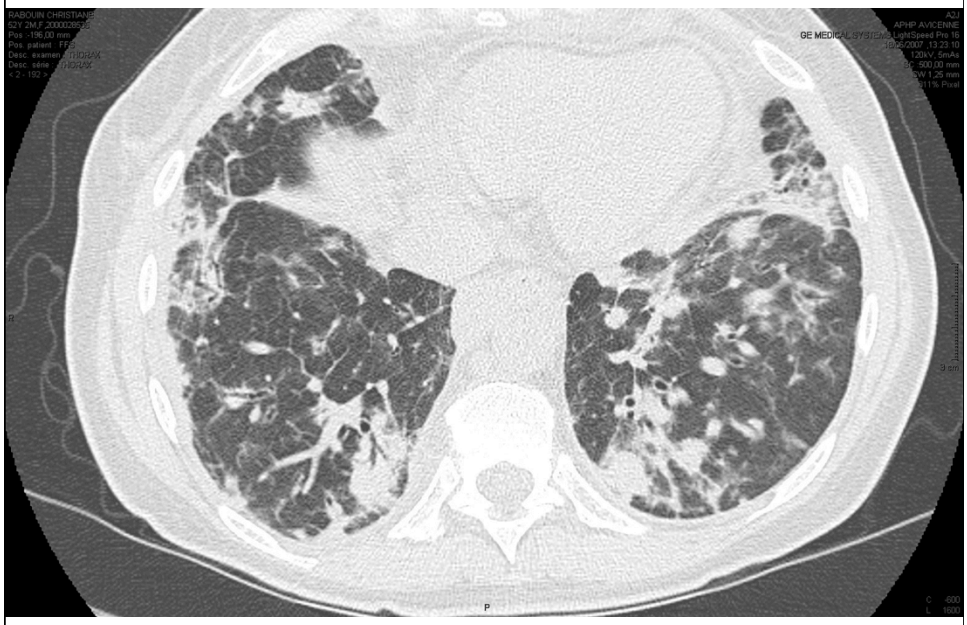
Case Presentation

- A 45 year old women with Common Variable Immunodeficiency (CVID) complains of more difficulty with shortness of breath when she climbs stairs.
  - Spirometry shows an FVC of 80%, FEV_1 of 88% with 8% reversibility, FEF_{25-75} of 60%, and DLCO of 50% reduction/corrected for hemoglobin.



Pulmonary Findings in CVID

- Bronchitis/bronchiectasis
  - Serum IgG level at diagnosis does not predict subsequent pneumonias or bronchiectasis
- Granulomatous lung disease
  - 8%-12% of patients
  - May be diagnosed years before the hypogglobulinemia
    - Well-formed, non-caseating granuloma with epitheloid giant cells
    - Often misdiagnosed as sarcoid
  - Lung (54%); lymph nodes and spleen (43%); liver (32%)
  - Autoimmune disorders are commonly associated (54%)
    - Autoimmune thrombocytopenia, hemolytic anemia most common
    - Have low number of switched memory B cells

Ardeniz O, Cunningham-Rundles C. *Clin Immunol*. 2009;133(2):198-207.
Chapel H et al. *Blood*. 2008;112(2):277-286.
Mechanic LJ et al. *Ann Intern Med*. 1997;127(8 Pt 1):613-617.

Pulmonary Findings in CVID (cont'd)

- Lymphoid interstitial pneumonia (LIP)
  - Lymphoma
- Granulomatous lymphocytic interstitial lung disease (GLILD)
  - HHV8
  - Poorer prognosis, T-cell deficiency, B-cell lymphoproliferative disease
    - Median survival - 13.7 yrs vs. 28.8 yrs
    - MALT

Wheat WH et al. *J Exp Med*. 2005;202(4):479-484.
Bates CA et al. *J Allergy Clin Immunol*. 2004;114(2):415-421.

Pulmonary Disease Management

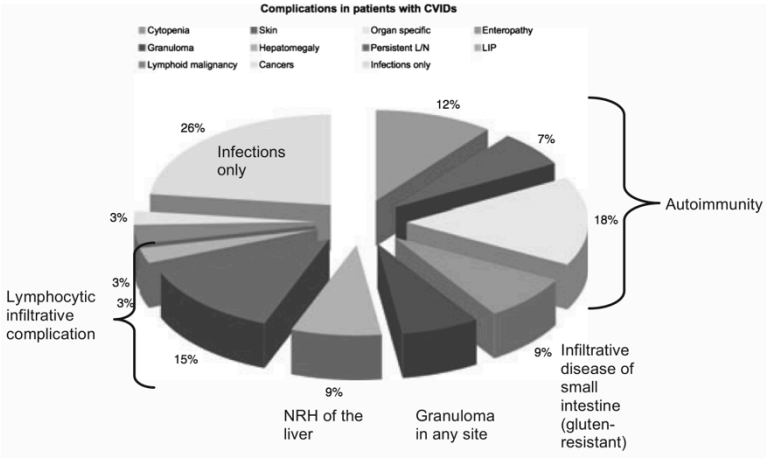
- Baseline high-resolution chest CT
  - Chest x-rays
  - Spirometry
- If lung disease present:
  - Sputum cultures/sensitivities
  - Spirometry – DLCO
  - Pulmonary care
  - Biopsies
    - Flow cytometry
    - Clonality for MALT

Pulmonary Disease Management (cont'd)

- Therapy
  - Bronchiectasis
    - Adequate IVIG/SCIG replacement therapy
    - Prophylactic antibiotics
    - Pulmonary toilet
  - Granulomatous disease
    - Oral steroids/inhaled corticosteroids
    - Hydroxychloroquine
    - TNF inhibitors

Hatab AZ, Ballas ZK. *J Allergy Clin Immunol*. 2005;116(5):1161-1162.
Lin JH et al. *J Allergy Clin Immunol*. 2006;117(4):878-882.

Medical Complications in Patients With CVID



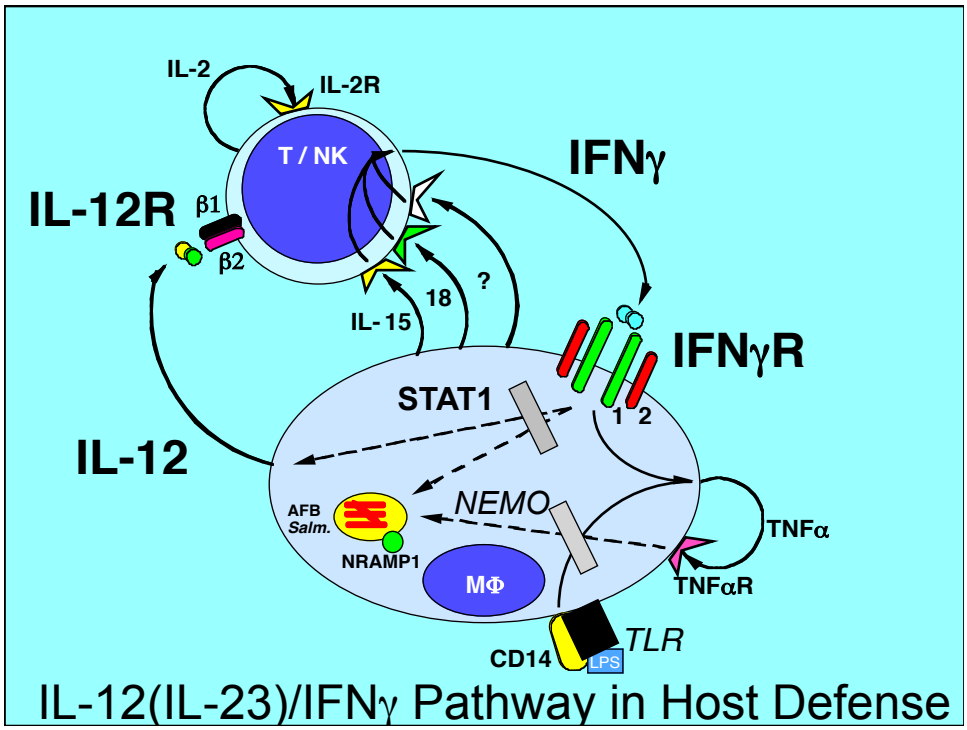
Chapel H, Cunningham-Rundles C. *Br J Haematol*. 2009;145(6):709-727.

Case Presentation

- a 7-year old African-American male patient with juvenile dermatomyositis and selective IgA deficiency presenting with a recurrent left-sided *Mycobacterium szulgai* pleural effusion for the past 5 months.
  - antimycobacterial regimen for the atypical mycobacterial infection
  - He is currently on IVIG (x1 year), methotrexate, and prednisone for dermatomyositis

- He has not had any problems with infections in the past.
- There is no family history of consanguinity
- Labs –
  - IgA<7, IgG 2240, IgM 73
  - IgG1=1764,IgG2=387,IgG3=64 IgG4=66

- Labs –
  - CD3 – 210, CD4 – 159, CD8 – 43
  - CD19 – 703 (NL), CD56 – 108
  - normal lymphocyte proliferative response to PHA, CON-A, PWM
  - lymphocyte proliferative responses to Tetanus, MMR, Streptolysin, Candida were present



IL-12(IL-23)/IFNγ Pathway in Host Defense

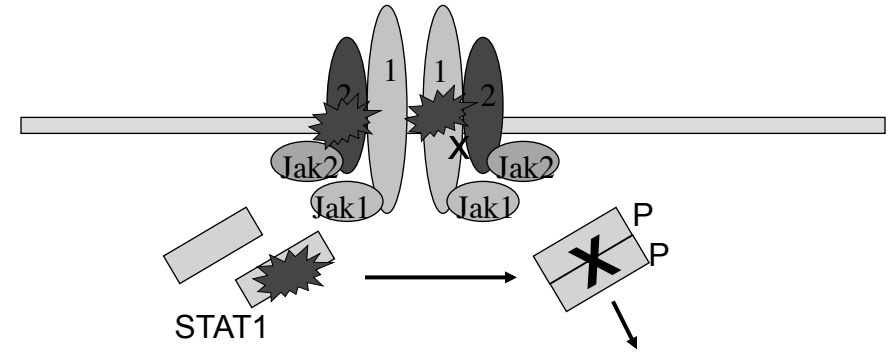
IFNγR1 Deficiency Recessive vs Dominant

Characteristic	AR (complete)	AD
IFNγR1 display	none	high
Circulating IFNγ	high	low
IFNγ responsiveness	none	low
Clinical presentation	disseminated	local
Granulomata	absent	present
Osteomyelitis	rare	~100%
Survival	most die	good

Other Genetically Defined Defects Involving IFNγR Signaling

- Complete IFN-γR2 defect: (recessive) results in severe disease
- Partial IFN-γR2 defect results in mild disease
- Complete STAT1 defect: severe disease, often have life threatening viral disease
- Partial STAT1 defect (recessive, dominant): mild disease similar to the clinical picture of the partial IFN-γR defects
- These defects have a very low frequency

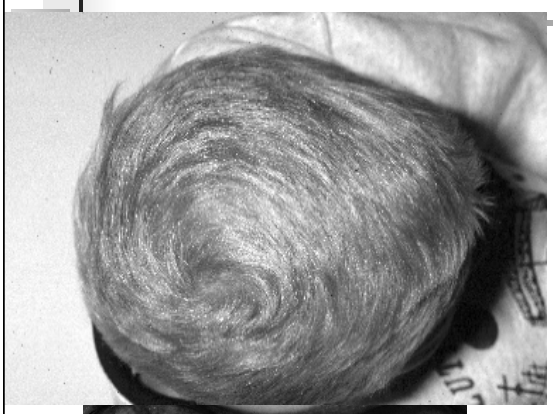
Summary of Defects Affecting Interferon-γ Receptor Signaling

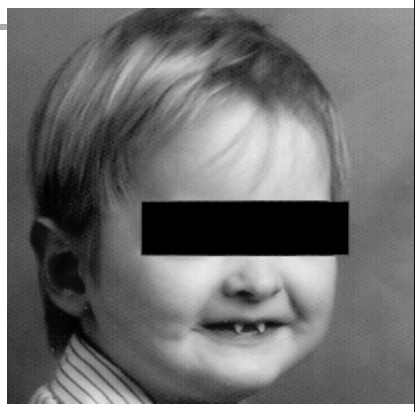


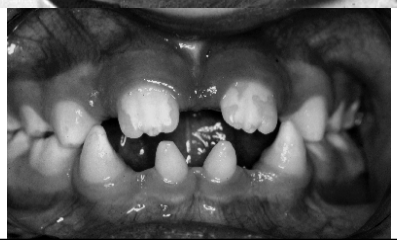
Sites of defects

Defects prevent IFNγ induced DNA transcription

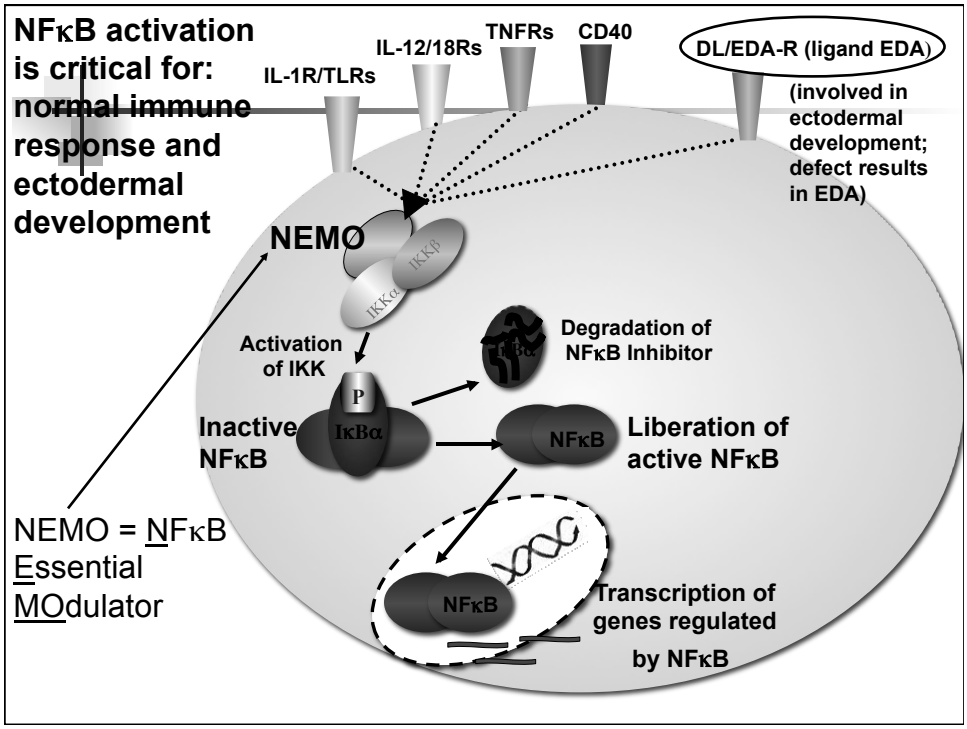
Anhidrotic Ectodermal Dysplasia







Abnormal or sparce hair
Conical/peg teeth
Absent sweat glands


NFκB activation is critical for: normal immune response and ectodermal development
IL-1R/TLRs
IL-12/18Rs
TNFRs
CD40
DL/EDA-R (ligand EDA)
(involved in ectodermal development; defect results in EDA)
NEMO
IKKβ
IKKα
Activation of IKK
Degradation of NFκB Inhibitor
P
IκBα
Inactive NFκB
NFκB
Liberation of active NFκB
NEMO = NFκB Essential MOdulator
NFκB
Transcription of genes regulated by NFκB