Pulmonary Manifestations of Primary Immunodeficiencies (PID)

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SPUR: When to Suspect a PID

- **Severe**: complicated pneumonias (multilobar, pneumatoceles, cavities, empyema) and/or unusual mediastinal/hilar adenopathy
- **Prolonged/Persistent**: failure to respond to usual therapy in a expected manner
- **Unusual**: unusual or opportunistic pathogens, lymphadenopathy
- **Recurrent**: repeated episodes of pneumonia
Diagnostic Studies in Patients with PID

• DO NOT use serological assays for dx in pts. with PID: many forms of PID decreased/absent ability to make specific Abs

• Serological assays: measure antibodies in gammaglobulin in patients receiving IVIG

• Dx of infectious disease MUST be done by culture, PCR or other direct methods to directly test the presence of the pathogen
Severe Combined Immunodeficiency (SCID)
Combined Immunodeficiencies
SCID

- Group of syndromes characterized by a profound decrease in T cells and concomitant B cell defects

- Pulmonary infections are common: opportunistic pathogens (*P. jirovecii*), viruses (AD, CMV, herpes virus, RSV, PIV-3 and others), atypical mycobacteria, fungi (aspergillus, scedosporium etc.) and common pathogens as well

- Absence of lymphoid tissue, absence thymic shadow and ALC<2500/mm3 (most)

- Newborn screening using TREC assay-early diagnosis and improved prognosis
SCID

- Normal CXR neonate
- Prominent thymic shadow

- SCID with diffuse infection secondary to *P. jiroveci* (PCP)
- Absent thymic shadow
ADA Deficiency-SCID

• Increased incidence of non-infectious pulmonary abnormalities compared to X-SCID (metabolic abnormalities due to ADA deficiency leading to pulmonary problems)

• Pulmonary alveolar proteinosis, squaring of the scapula, cupping of ribs

• Reversible with definitive Rx (HSCT, gene therapy, ADA-replacement)
Squared off scapula (white arrows) that normalize with ADA-replacement therapy

Immunodeficiency due to Gain of Function (GOF) Mutations in Phosphatidylinositol-3-OH kinase-Activated PI3KD Syndrome (APDS)
Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110δ result in T cell senescence and human immunodeficiency


Phosphoinositide 3-Kinase δ Gene Mutation Predisposes to Respiratory Infection and Airway Damage

Phosphatidylinositol-3-OH kinase (PI3K)

- Function: Phosphorylation of PIP2 to generate PIP3, which leads to activation of AKT-mTOR pathways
- \( p110^\delta-PI3K^\delta \) catalytic subunit: only expressed in lymphocytes
- PI3K\( ^\delta \) is activated by ligation of BCR and TCR and essential for T cell and B cell function
- Primary immunodeficiency disease (PI) due to activating mutations (gain of function-GOF) mutations of PI3KD
- Autosomal dominant-termed Activated PI3KD Syndrome (APDS)
## Clinical Features APDS

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Sinopulmonary Infections</td>
<td>100%</td>
</tr>
<tr>
<td>Lymphadenopathy/splenomegaly</td>
<td>~75%/60%</td>
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<tr>
<td>Bronchiectasis/Bronchiolitis</td>
<td>~50%</td>
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<tr>
<td>EBV/CMV infections (also HSV, VZV)</td>
<td>~50%</td>
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<tr>
<td>Mucosal lymphoidal aggregates</td>
<td>~50%</td>
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<tr>
<td>Skin, salivary gland, lacrimal gland or dental carries</td>
<td>~40%</td>
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<tr>
<td>Other: Autoimmune cytopenias, IBD, EBV-induced lymphomas</td>
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## Immunological Abnormalities

<table>
<thead>
<tr>
<th>Assay</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Serum IgG/IgA/IgM</td>
<td>Variable: IgG, IgA, ↑ IgM 80%</td>
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<tr>
<td>Low B cell numbers</td>
<td>~75%</td>
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<tr>
<td>Increased transitional B cells (CD19+CD38+ IgM(^{lo})), decreased isotype class switched B cells</td>
<td>88% / 50%</td>
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<tr>
<td>Decreased specific Ab H.Infl./S. Pneum.</td>
<td>~70%</td>
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<tr>
<td>Decreased T cells (either CD4 or CD8)</td>
<td>~70%</td>
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Pulmonary Findings
APDS

Mosiac Attenuation
(air trapping)

Bronchiectasis

Lymphoproliferation in APDS

Lymphocytic Infiltrates Airway

Lymphocytic Infiltrates Gut

Hodgkin Lymphoma

LMP1 (EBV Ag)

Treatment of APDS

• Prognosis and optimal treatment is unknown
• PI3KD only in hematopoietic cells--HSCT in one patient, alive and well
• Inhibitor mTOR pathway (rapamycin) clinical improvement in small number patients
Antibody Deficiencies: CVID and Inherited Agammaglobulinemias
RT Pathogens in Antibody Deficiencies

- Encapsulated bacterial organisms (e.g. H. influenzae, S. pneumoniae)
  - Infection with other GNR (pseudomonas and others) may occur esp. in pts. Rx’d repeatedly with broad spectrum Abx
- Atypical bacteria: Mycoplasma /Ureaplasma sp.
  - Unique susceptibility--Antimicrobial Rx MUST cover “atypical” bacteria (URTI/LRTI)
- Viruses (enteroviruses, CMV, RV)
Lungs-the Good and the Bad in CVID

N=69 pts.

Non-infectious Pulmonary Cxns of CVID

- Predominantly Obstructive lung disease
  - Bronchiectasis
  - Asthma/COPD
  - Bronchiolitis obliterans
- Predominantly restrictive lung disease and diffuse
  - Granulomatous and lymphocytic interstitial lung disease (GLILD)
  - Cryptogenic organizing pneumonia
  - Lymphoma (BALT, NHL) or metastatic carcinoma
  - Hypersensitivity pneumonitis
Our Approach to Diagnosis of Lung Disease in CVID
Chest X ray is NOT Sensitive for Lung Disease in CVID

Normal CXR

Abnormal HRCT scan
HRCT Chest

Abnormal

Nodular/ground glass opacities
Thoracoscopic open lung bx

Normal

Other
(Bronchiectasis etc.)
Rx based on cause
Bronchiectasis in CVID

- 31 year-old female with hx “asthma”
- Frequent pneumonias
- Partial lobectomy of right lower lobe.
- CT scan: severe bronchiectasis.
- Patient died of progressive pulmonary failure.
- MOST COMMON pulmonary abnormality in CVID
Bronchiectasis in CVID

- Most common lung abnormality in CVID (20-35% overall)
- Abnormal mucous clearance-predisposes recurrent pneumonias
- Bronchiectasis may progress or occur despite IVIG/SCIG
- Requires higher dose replacement Ab
- Rx in manner similar to cystic fibrosis
  - Daily chest physiotherapy (acapella, vest in severe cases) w hypertonic saline if tolerated
  - Hospitalization with IV Abx for acute exacerbations
  - Chronic azithromycin Rx—decreases infectious exacerbations for bronchiectasis not associated with PID. (Lancet 2012;380:660-7; JAMA 2013;309:1251-9; Respiratory medicine 2013;107:800-15)
  - Culture for MAI prior to institution of chronic azithromycin
GLILD in CVID

- Different histological patterns in same biopsy
  - Granulomatous disease
  - Lymphocytic interstitial pneumonitis
  - Follicular bronchiolitis
  - Frequently large areas of organizing pneumonia
- Granulomas lung, liver, lymph nodes, bone marrow
- Enlarged spleen and diffuse adenopathy
- Increased autoimmunity, B cell lymphomas
- Multisystemic lymphoproliferative disease

GLILD-Histology

Lymphocytic interstitial pneumonitis

Follicular Bronchiolitis

Granuloma

Organizing pneumonia
GLILD vs Sarcoidosis

GLILD
- Macronodular disease
- Hilar adenopathy less common
- Lower lung zone predominance
- Bronchiectasis in 20-40%

Sarcoid
- Micronodular disease and
- Marked hilar adenopathy
- Upper lung zone predominance
- Bronchiectasis uncommon

Semin Respir Crit Care Med. 2014 Jun;35(3):330-5
PMN Defects: CGD
Chronic Granulomatous Disease (CGD)

- Mutation in one of four subunits of NADPH oxidase: essential for respiratory burst: gp91phox (x-linked)-70%; others autosomal recessive; p47 phox (20%), p22 and p67phox (5% each)

- 5 organisms cause the bulk of the infections developed countries that do not use BCG: *Staphylococcus aureus*, *Burkholderia cepacia*, *Serratia marcescens*, *Nocardia sp.*, *Aspergillus sp.*

- BCG, TB and Salmonella in other parts of the world
Chronic Granulomatous Disease (CGD)

- Recurrent severe, complicated pneumonias
- Mulch pneumonitis—inhalaion of decaying organic matter leads to fulminant pneumonitis: appropriate antimicrobial Rx AND corticosteroids needed
- Advise patients to avoid outside jobs with exposure to organic material (e.g. raking leaves, hay)
- Progressive interstitial lung disease (rare)
Chronic Granulomatous Disease

Mulch pneumonitis with aspergillus infection before and after Rx steroid and antifungal
Clinical Infectious Diseases 2007; 45:673–81

ILD in AR CGD (p47) before and 1 year post HSCT (JR paper in preparation)
Well Defined Syndromes with Immunodeficiency
Ataxia Telangiectasia

- Mutation in ATM gene (DNA repair): immune deficiency, increased cancer, neurodegeneration, premature aging and telangiectasias

- T cell lymphopenia common, variable hypogammaglobulinemia and poor specific Ab response to PS antigens in some

Ataxia Telangiectasia

- Bronchiectasis due to recurrent infection, interstitial lung disease/interstitial fibrosis and lung disease secondary to neurological sequela (weak cough and difficulty clearing secretions)
- ILD may be responsive to corticosteroids
- Radiation sensitivity limits and muscle weakness can limit pulmonary evaluation of patients
- Consider MRI in pulmonary evaluation of patients
Ataxia Telangiectasia

Severe bronchiectasis

ILD and pulmonary fibrosis
AD Hyper IgE Syndrome

- DN mutation in STAT3: impaired TH17 response and dysregulated inflammatory response
- Eczema, cold abscesses, MCC, recurrent pneumonia with pneumatoceles
- The most common pathogens of acute pneumonia are S. aureus, H. influenzae, and S. pneumoniae
- ~75% of AD-HIES pts: long-term pulmonary complications (pneumatoceles, bronchiectasis, cysts)-major cause of morbidity and mortality
- Chronic infection: non-tuberculous mycobacterium, GNR (Pseudomonas aeruginosa) and molds (Aspergillus fumigatus, Scedosporium sp)
- DOCK8 deficiency: Bronchiectasis common but pneumatoceles are rare—more diverse pathogens (viral and bacterial, as well as PCP)
AD Hyper IgE Syndrome

A. Cavities with areas of consolidation; B. Pneumatocoele complicated by aspergilloma; C. Diffuse bronchiectasis; D. Staphylcoccus abscess
AD Hyper IgE Syndrome

- Chest CT showing the characteristic pneumatoceles.
- The pneumatoceles are prone to infection with fungi and gram-negative bacteria. Arrow indicates an aspergilloma.