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%, FEV₁ of 88% with 8% reversibility, FEF₂₅-₇₅ 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

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


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


Medical Complications in Patients With CVID

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
IFNγR1 Deficiency

Recessive vs Dominant

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AR (complete)</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNγR1 display</td>
<td>none</td>
<td>high</td>
</tr>
<tr>
<td>Circulating IFNγ</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>IFNγ responsiveness</td>
<td>none</td>
<td>low</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>disseminated</td>
<td>local</td>
</tr>
<tr>
<td>Granulomata</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>rare</td>
<td>~100%</td>
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<tr>
<td>Survival</td>
<td>most die</td>
<td>good</td>
</tr>
</tbody>
</table>

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

Defects prevent IFNγ induced DNA transcription

Anhidrotic Ectodermal Dysplasia

Abnormal or sparse hair
Conical/peg teeth
Absent sweat glands
NFκB activation is critical for:
normal immune response and ectodermal development

NEMO = NFκB Essential MODulator

NFκB activation is involved in ectodermal development; defect results in EDA