A 17 YEAR OLD FEMALE WITH PROGRESSIVE DYSPNEA AND PULMONARY NODULES

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CHIEF COMPLAINT

Fever and Dyspnea

HISTORY OF PRESENT ILLNESS

17 y/o female presented to the ER with fever, dyspnea, and shortness of breath for 2 days, associated with diarrhea and abdominal pain

History of dyspnea with exertion for the last 3 years, with progression over the previous two months
HPI

Respiratory symptoms

8 years

Pneumonia

13 years

Dyspnea

16 years

Pulmonary nodules
HPI

12 years
Gastrointestinal symptoms
13 years
Celiac Disease
15 years
Weight loss
17 years
Autoimmune Enteropathy
REVIEW OF SYSTEMS (ROS)

- HEENT
- CV
- MSK

- Neurologic
- Endocrine
- Skin
OTHER PAST MEDICAL HISTORY

IMMUNIZATIONS: Complete

SURGICAL: Appendectomy at age 5

EXPOSURES: None

SOCIAL HISTORY: Lives with parents and sister

NEURODEVELOPMENT: Adequate

FAMILY HISTORY: Non-contributory

UNREMARKABLE
VITAL SIGNS AND MEASUREMENTS

BP: 100/51 mmHg
MAP: 75 mmHg
HR: 84-103
RR: 19-22
T: 97.7-98.6 Fº
SpO₂: 92-98% (2600 Mt above sea level)

Weight 29.6 Kg/66 lb (-4 z score)
Height 147 cm/57 inch (-3 z score)
BMI: 14.08 (-4 z score)
Alert and oriented, NAD, good color, very thin
HEENT: Non-icteric sclera, dry oral mucosa
Chest: Normal to palpation and percussion with clear lung sounds. Normal heart sounds without murmurs.
Abdomen: Non-tender, non-distended without organomegaly
EXTREMITIES: Clubbing
Multi-systemic disease with respiratory and GI involvement

Teenage Patient

Chronic dyspnea, increasing with exertion

Pulmonary nodules

History of gastrointestinal symptoms

Autoimmune enteropathy

Chronic malnutrition
Is the dyspnea:

• A new problem?
• An exacerbation of a chronic problem?
• A combination of the two?
### Table 3 Laboratory Testing for Dyspnea

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary Function</strong></td>
<td>spirometry pre- and post-bronchodilators, lung volumes, diffusing capacity,</td>
</tr>
<tr>
<td></td>
<td>respiratory muscle strength</td>
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<tr>
<td><strong>Oxygen saturation by pulse oximeter</strong></td>
<td></td>
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<tr>
<td><strong>Chest radiograph</strong></td>
<td></td>
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<tr>
<td><strong>Complete Blood Count and differential</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Capillary blood gas</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Electrolytes, urea nitrogen, creatinine, Thyroid Stimulating Hormone</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Formal exercise testing</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Provocation testing</strong></td>
<td></td>
</tr>
<tr>
<td><strong>(Cardiology: ECG and echo)</strong></td>
<td></td>
</tr>
</tbody>
</table>
SPIROMETRY

<table>
<thead>
<tr>
<th>Test</th>
<th>Ref</th>
<th>Pre Measure</th>
<th>Pre % Ref</th>
<th>CI Post Measure</th>
<th>Post % Ref</th>
<th>Chg %</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>2.50</td>
<td>2.12</td>
<td>85</td>
<td>2.17</td>
<td>87</td>
<td>2</td>
</tr>
<tr>
<td>FEV1</td>
<td>2.35</td>
<td>1.99</td>
<td>85</td>
<td>2.04</td>
<td>87</td>
<td>3</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>86</td>
<td>94</td>
<td>109</td>
<td>94</td>
<td>110</td>
<td>0</td>
</tr>
<tr>
<td>FVC</td>
<td>1.74</td>
<td>3.66</td>
<td>134</td>
<td>1.79</td>
<td>133</td>
<td>-0</td>
</tr>
<tr>
<td>FEF25-75%</td>
<td>2.74</td>
<td>5.80</td>
<td>111</td>
<td>6.14</td>
<td>117</td>
<td>6</td>
</tr>
<tr>
<td>PEF</td>
<td>5.24</td>
<td>4.65</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Flow

Volume

IC = Interval de Confianza

prebroncodilatador
postbroncodilatador
# Bronchoprovocation Test

<table>
<thead>
<tr>
<th>Dose</th>
<th>Ref Meas</th>
<th>Pre Meas</th>
<th>Level 1 Meas</th>
<th>Level 2 Meas</th>
<th>Level 3 Meas</th>
<th>Level 4 Meas</th>
<th>Level 5 Meas</th>
<th>Post Meas</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC Liters</td>
<td>2.45</td>
<td>2.48</td>
<td>2.47</td>
<td>2.48</td>
<td>2.48</td>
<td>2.43</td>
<td>2.40</td>
<td>2.50</td>
</tr>
<tr>
<td>mg/ml</td>
<td>101</td>
<td>101</td>
<td>101</td>
<td>101</td>
<td>99</td>
<td>98</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>% Chg</td>
<td>-0</td>
<td>0</td>
<td>-0</td>
<td>-2</td>
<td>-3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 Liters</td>
<td>2.31</td>
<td>2.17</td>
<td>2.15</td>
<td>2.16</td>
<td>2.15</td>
<td>2.07</td>
<td>2.03</td>
<td>2.23</td>
</tr>
<tr>
<td>% Ref</td>
<td>94</td>
<td>93</td>
<td>94</td>
<td>93</td>
<td>90</td>
<td>88</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>% Chg</td>
<td>-1</td>
<td>-0</td>
<td>-1</td>
<td>-5</td>
<td>-6</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>86</td>
<td>87</td>
<td>87</td>
<td>87</td>
<td>87</td>
<td>85</td>
<td>84</td>
<td>89</td>
</tr>
<tr>
<td>FEF25-75%</td>
<td>2.70</td>
<td>2.62</td>
<td>2.63</td>
<td>2.51</td>
<td>2.56</td>
<td>2.25</td>
<td>2.22</td>
<td>3.00</td>
</tr>
<tr>
<td>% Ref</td>
<td>97</td>
<td>97</td>
<td>93</td>
<td>95</td>
<td>83</td>
<td>82</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>% Chg</td>
<td>0</td>
<td>-4</td>
<td>-2</td>
<td>-14</td>
<td>-15</td>
<td>14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BRONCHOPROVOCATION TEST

PC 20 FEV1: ---

Pre 0.06 250.25 1. 4. 16. Post

PC 20 FEV1 ---
DIFFUSING CAPACITY OF CARBON MONOXIDE IN THE LUNG (DL,CO)

CAPACIDAD DE DIFUSIÓN MONOXIDO DE CARBONO (DLCO)

<table>
<thead>
<tr>
<th>Parámetro</th>
<th>Pred</th>
<th>LLN</th>
<th>Result.</th>
<th>%Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLCO [ml/min/mmHg]</td>
<td>17,6</td>
<td>14,1</td>
<td>15,3</td>
<td>87</td>
</tr>
<tr>
<td>DLat [ml/min/mmHg]</td>
<td>17,6</td>
<td>14,1</td>
<td>13,4*</td>
<td>76</td>
</tr>
<tr>
<td>VA sb [L]</td>
<td>3,15</td>
<td>2,87</td>
<td>3,02</td>
<td>96</td>
</tr>
<tr>
<td>DLadj/VA [ml/min/mmHg/L]</td>
<td>5,58</td>
<td>4,87</td>
<td>4,42*</td>
<td>79</td>
</tr>
<tr>
<td>VI [L]</td>
<td>-</td>
<td>-</td>
<td>2,35</td>
<td>-</td>
</tr>
</tbody>
</table>

* Indica valor situado fuera del rango normal o cambio posterior significativo.
22/04/16

- Normal LV dimension
- Normal cardiac valves
- Normal LV systolic function
- Normal PAP
- No pericardial effusion
- Absence of pulmonary hypertension
ADDITIONAL TESTING

1. Chest X Ray
2. High-resolution CT
3. Blood work
4. Bronchoscopy with bronchoalveolar lavage
What is the differential diagnosis of pulmonary nodules in children?

How does the differential diagnosis change given the clinical history of this patient?
Approach to Pulmonary Nodules in Children

- In comparison to adults there are not specific guidelines for the evaluation of pulmonary nodules.

- Pulmonary nodules are **NOT** an incidental finding in a **symptomatic patient**.

- Evaluation should be planned based on the clinical history.

- Look for evidence of immunodeficiency, connective tissue disease, immune dysfunction, h/o malignancy, or h/o congenital pulmonary malformation.

Differential Diagnosis

- Infection
- Malignancy
- Other
- Inflammatory
WORK UP

- Low complement levels
- Low vaccine titers
- Normal IgG, A, M, E
- T-cell lymphopenia
- Negative PPD and HIV testing
• Normal findings on inspection
• Bronchoalveolar lavage and brushings
  – Negative cultures
  – BAL cell differential: Ly-93%, N-5%, M-2%
Open biopsy of pulmonary nodules
alveolar space
DIAGNOSIS:
FOLLICULAR BRONCHIOLITIS (FB)
Follicular Bronchiolitis

- Rare, benign lymphoproliferative disorder
- Hyperplasia of bronchial associated lymphoid tissue
- More common in adults
- CT findings include
  - Peribronchial & centri-lobular nodules
  - Ground glass opacities
- Symptoms
  - Shortness of breath
  - Cough
  - Fever
  - Recurrent LRTI
- Most often associated with
  - Connective tissue disease
  - Immunodeficiency
  - Hypersensitivity
  - Infection

Carrillo J, et al. (2013) Seminars in Ultrasound, CT, and MRI.
Pulmonary Complications of Primary Immunodeficiencies (PID)

Common Variable Immunodeficiency & Lung Disease

• Most common symptomatic humoral PID
• Genetic defects found to cause in some cases
• Recurrent respiratory tract infections
• Inflammatory complications
• Autoimmune manifestations
  – Most common hemolytic anemia or thrombocytopenia
Given the diagnosis of FB and autoimmune enteropathy, what further evaluation is recommended in this patient?
## PID Associated With Autoimmune Disease

<table>
<thead>
<tr>
<th>PID</th>
<th>Defect</th>
<th>Autoimmune GI Disease</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Variable Immunodeficiency</td>
<td>Polygenetic</td>
<td>X</td>
<td>Lymphoproliferation, other autoimmunity</td>
</tr>
<tr>
<td>X-Linked Agammaglobulinemia</td>
<td>BTK</td>
<td>X</td>
<td>Neutropenia in setting of infection</td>
</tr>
<tr>
<td>Autoimmune Lymphoproliferative Syndrome (ALPS)</td>
<td>FAS, FASL, CASP 10</td>
<td>X</td>
<td>Lymphoproliferation, other autoimmunity</td>
</tr>
<tr>
<td>Partial DiGeorge</td>
<td>22q 11.2</td>
<td>X</td>
<td>Craniofacial anomalies, cardiac anomalies, hypocalcemia, other autoimmunity</td>
</tr>
<tr>
<td>Cytotoxic T-lymphocyte antigen 4</td>
<td>CTLA4</td>
<td>X</td>
<td>Lymphoproliferation, other autoimmunity</td>
</tr>
<tr>
<td>LPS- responsive vesicle trafficking, beach &amp; anchor containing protein</td>
<td>LRBA</td>
<td>X</td>
<td>Growth retardation, eczema, lymphoproliferation, other autoimmunity</td>
</tr>
<tr>
<td>Immune dysregulation polyendocrinopathy enteropathy X linked syndrome</td>
<td>FOXP3</td>
<td>X</td>
<td>Failure to thrive, dermatitis, lymphoproliferation, other autoimmunity</td>
</tr>
<tr>
<td>Signal transducer and activator of transcription 3</td>
<td>STAT3</td>
<td>X</td>
<td>Short stature, eczema, lymphoproliferation, other autoimmunity</td>
</tr>
<tr>
<td>Signal transducer and activator of transcription 1</td>
<td>STAT1</td>
<td>X</td>
<td>Aneurysms, eczema, carcinomas, other autoimmunity</td>
</tr>
<tr>
<td>Wiskott –Aldrich syndrome</td>
<td>WAS</td>
<td>X</td>
<td>Microthrombocytes with low count &amp; poor function, eczema, mucosal bleeding, renal disease</td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
<td>CYBB, CYBA, NCF1, NCF2, NCF4</td>
<td>X</td>
<td>Lymphoproliferative pathology with severe multi-organ granulomatous disease</td>
</tr>
</tbody>
</table>

*Adapted from Walter J. et al. (2016) J. Allergy Clinical Pract.*

*Boston Children’s Hospital
Until every child is well*

*Harvard Medical School
Teaching Hospital*
What would be the suggested treatment approach of FB in this patient?
Treatment Approach

• IVIG
• Preventative antibiotics
• Prevent & treat infections
• Consider airway clearance
• Nutritional therapy
• Anti-inflammatory therapies
  – No RTC
• Targeted therapies if underlying disorder found
• Monitor progression
TREATMENT

- Systemic glucocorticoids
- Tacrolimus
- IVIG
CONSIDER FOLLICULAR BRONCHIOLITIS IN PATIENTS WITH

- Chronic cough
- Recurrent upper respiratory tract infections
- Unexplained progressive dyspnea

Not an easy diagnosis

Patients with an immunodeficiency

Heterogeneous group, often presenting with peripheral eosinophilia, suggesting an underlying hypersensitivity reaction

With an underlying connective tissue disease

Primary

Secondary

Groups

1

2

3
<table>
<thead>
<tr>
<th>Connective tissue disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sjögren’s syndrome [13,14]</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis [15,16]</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus [17,18]</td>
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</tr>
<tr>
<td>Other immunological disorders</td>
<td></td>
</tr>
<tr>
<td>Evans Syndrome (Autoimmune haemolytic anaemia and immune thrombocytopenia) [19,20]</td>
<td></td>
</tr>
<tr>
<td>Pernicious anaemia [21]</td>
<td></td>
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<tr>
<td>Immunodeficiency</td>
<td></td>
</tr>
<tr>
<td>AIDS, particularly in children [22]</td>
<td></td>
</tr>
<tr>
<td>Common variable immunodeficiency (CVID) [23,24]</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Pneumocystis Jiroveci pneumonia [25]</td>
<td></td>
</tr>
<tr>
<td>Legionella pneumonia [26]</td>
<td></td>
</tr>
<tr>
<td>Active hepatitis [27]</td>
<td></td>
</tr>
<tr>
<td>Interstitial lung diseases [24, 28-30]</td>
<td></td>
</tr>
<tr>
<td>LIP</td>
<td></td>
</tr>
<tr>
<td>Respiratory bronchiolitis-ILD (RB-ILD)</td>
<td></td>
</tr>
<tr>
<td>Desquamative interstitial pneumonia (DIP)</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis (HP)</td>
<td></td>
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<tr>
<td>Cryptogenic organizing pneumonia (COP)</td>
<td></td>
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<tr>
<td>Granulomatous lymphocytic-ILD (GLILD)</td>
<td></td>
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<tr>
<td>Airway inflammatory diseases [10,11]</td>
<td></td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td></td>
</tr>
<tr>
<td>Familial [31,32]</td>
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<tr>
<td>Idiopathic (primary)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>[Table/Fig-2]: Diseases associated with follicular bronchiolitis</td>
<td></td>
</tr>
<tr>
<td>Histologic classification [6]</td>
<td>Clinical features</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Cellular bronchiolitis</td>
<td>Mild dyspnea ± cough in adults; acute onset in infants; obstructive and/or restrictive pattern; good prognosis</td>
</tr>
<tr>
<td>Nonspecific chronic bronchiolitis</td>
<td>Obstructive and/or restrictive pattern; variable prognosis</td>
</tr>
<tr>
<td>Follicular bronchiolitis</td>
<td>Progressive dyspnea, chronic cough, recurrent URTI; obstructive and/or restrictive; generally good prognosis</td>
</tr>
<tr>
<td>Diffuse panbronchiolitis</td>
<td>Chronic productive cough, dyspnea, sinusitis; progressive airflow obstruction</td>
</tr>
<tr>
<td>Constrictive bronchiolitis obliterans</td>
<td>Chronic cough, dyspnea, wheeze; irreversible airflow obstruction on pulmonary function tests</td>
</tr>
<tr>
<td>Respiratory (smoker's) bronchiolitis</td>
<td>Usually asymptomatic/incidental; excellent prognosis</td>
</tr>
</tbody>
</table>

IBD, inflammatory bowel disease; RA, rheumatoid arthritis; CVID, common variable immunodeficiency syndrome; AIDS, acquired immunodeficiency syndrome.
More progressive disease and higher mortality in patients:

- Under 30
- With underlying immunodeficiency
EL HOSPITAL CON ALMA

Pablo Tobón Uribe
Thank you!
CHEST RADIOGRAPHY IS MOST OFTEN NORMAL IN PATIENTS WITH FOLLICULAR BRONCHIOLITIS, BUT HIGH RESOLUTION CHEST COMPUTED TOMOGRAPHY (HRCT) SCAN CAN BE USEFUL

WHICH OF THE FOLLOWING ARE THE MOST COMMON HRCT FINDINGS NOTED IN CHILDREN WITH FOLLICULAR BRONCHIOLITIS

A. Smallcentrilobularnodulesassociatedwithbilateral patchy ground glass opacities

B. Peripheral sub-pleural small nodules associated with cysts

C. Bronchial wall thickening and mild interlobular septal thickening

D. Bronchiectasis associated with mosaic attenuation pattern

E. Honeycombing and peribronchovascular consolidation
IN A 8 YEAR OLD GIRL PRESENTS WITH CHILDREN'S INTERSTITIAL LUNG DISEASE (CHILD) SYNDROME AND IS FOUND TO HAVE AN HISTOPATHOLOGIC DIAGNOSIS OF FOLLICULAR BRONCHIOLITIS ON LUNG BIOPSY. WHICH OF THE NEXT OPTIONS, WOULD BE THE LEAST HELPFUL IN FINDING A SECONDARY CAUSE FOR THE DISEASE

A Autoimmune profile.

B Immunoglobulin levels and lymphocyte subsets

C HIV testing

D Testing for adenovirus, Legionella, mycoplasma pneumonia, and hepatitis

E Eosinophil count
WHICH OF THE FOLLOWING IS A MAIN CHARACTERISTIC OF THE BIOPSY FOR THE DIAGNOSIS OF FOLLICULAR BRONCHIOLITIS?

A. Chronic pleuritis overlying cellular non-specific interstitial pneumonia pattern.
B. Fibrotic non-specific interstitial pneumonia pattern
C. Peribronchovascular cysts
D. Presence of well formed lymphoid follicles in the walls of bronchioles and narrowing or complete obliteration of the bronchiolar lumen.
E. Uniform thickening of all of the alveolar walls and scant chronic inflammation