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February 2023 Pulmonary Case of the Month: SCID-ing to a Diagnosis

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History of Present Illness

A 40-year-old man was referred for management of respiratory symptoms of cough, sputum production and shortness of breath. He has a history of respiratory infections that began in early childhood. Sputum cultures were positive for *Pseudomonas*. He is currently using oxygen at night and occasionally during the day.

Past Medical History, Family History and Social History

- Childhood diagnosis of asthma.
- Multiple colds and pneumonias in the past.
- No family history of a similar problem.
- He has never smoked.
- Denies any occupational exposure.

Physical Examination

- Vital Signs: O2 Sat 88% on RA
- Chest: diminished breath sounds, no wheezes
- Heart: regular rate and rhythm without murmur
- Extremities: mild clubbing present, no edema

Pulmonary Function Testing

Pulmonary function testing (PFTs) was performed with results as below (Figure 1).

Figure 1. Pulmonary function testing.

	PREDICTED		CONTROL		POST-DILATOR**	
	Expd	LLN	Actual	%Pred	Actual	%Chng
- LUNG VOLUMES -						
TLC (Pleth) (L)	6.51	3.21	6.04	92		
SVC (L)	4.98	4.16	*2.24	*44		
RV (Pleth) (L)	1.65	1.32	*3.81	*250		
RV/TLC (Pleth) (%)	26.11	20.89	*62.98	*241		
- SPIROMETRY -						
FVC (L)	4.98	4.16	*2.25	*45	*2.19	-2
FEV1 (L)	4.04	3.37	*1.06	*26	*1.05	-1
FEV1/FVC (%)	81.26	67.85	*47.18	*58	*47.90	+1
PEF 25-75% (L/sec)	3.99	2.20	*0.27	*6	*0.26	-3
PEF Max (L/sec)	9.83	7.37	*6.34	*66	*6.31	-3
MVV (L/min)	164	137	*56	*43		
- DIFFUSION -						
DLCOinc (ml/min/mmHg)	32.57	26.05	*15.28	*46		
DLCOcor (ml/min/mmHg)	32.57	26.05				
VA (L)	6.51	5.44	*2.96	*45		

To view Figure 1 in a separate enlarged window click [here](#).

Thoracic CT Scan

A thoracic CT was performed (Figure 2).

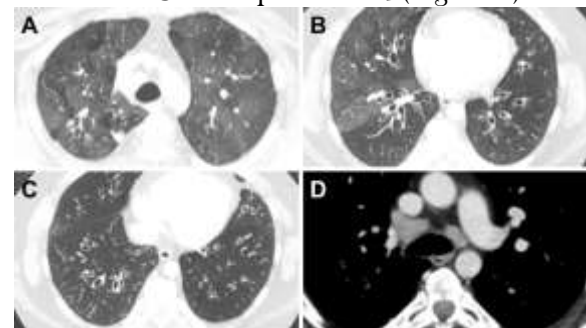


Figure 2. Representative images from the thoracic CT in lung windows (A-C) and soft tissue windows (D). To view Figure 2 in a separate enlarged window click [here](#).

Which of the following is/are true?

1. PFTs show severe obstructive disease
2. The thoracic CT shows a normal mediastinum
3. Bronchiectasis is shown in the CT scan lung windows
4. 1 and 3
5. All of the above

Correct!

4. 1 and 3

The spirometry on the PFTs show very severe obstruction without reversibility. The reduced forced vital capacity (FVC) suggests the possibility of restriction in addition. The total lung capacity is normal but the residual volume is markedly elevated suggesting the possibility of a combined obstruction and restriction. The diffusion is moderately reduced at 46% of predicted. The thoracic CT shows septal thickening with mosaicism, extensive lower lung bronchiectasis with mucus plugging, tree-in-bud nodularity, signet rings and mediastinal lymphadenopathy (Figure 3).

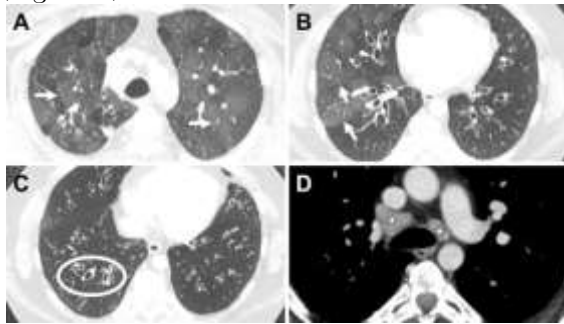


Figure 3. Thoracic CT showing septal thickening (arrows in A and B), signet rings (circle in C) and enlarged mediastinal lymph nodes (starred in D). To view Figure 3 in a separate enlarged window click [here](#).

Which of the following are diagnostic considerations?

1. Cilia abnormalities
2. Cystic fibrosis
3. Immunodeficiency
4. 1 and 3
5. All of the above

Correct!

5. All of the above

Adult bronchiectasis can result from several abnormalities including cystic fibrosis or repeated infections because of an immunodeficiency or abnormal mucus transport from cilia abnormalities (1). The patient had previously had negative genetic testing for a mutation associated with cystic fibrosis and did not have cilia abnormalities. However, previous testing had demonstrated low immunoglobulins, including IgG, and he was receiving Hizentra® or subcutaneous IgG. His IgG was normal while receiving Hizentra® (1378 mg/dL) although his IgA remained low (<10 mg/dL).

What other testing should be done?

1. Interleukin-2 receptor subunit
2. Interleukin-5 receptor
3. Interleukin -8 receptor
4. 1 and 3
5. All of the above

Correct!

1. Interleukin-2 receptor subunit

The common gamma chain, also known as interleukin-2 receptor subunit gamma or IL-2RG, is a cytokine receptor sub-unit that is common to the receptor complexes for at least six different interleukin receptors: IL-2, IL-4, IL-7, IL-9, IL-15 and interleukin-21 receptor (2). The IL-2RG proteins encoded by the IL2RG gene located on the long (q) arm of the X chromosome. A mutation in this gene is associated with X-linked severe combined immunodeficiency (X-SCID). Since this mutation is on the X chromosome, it is almost exclusively seen in males, either due to inheriting an X chromosome with this mutation from their mother who is heterozygous for the mutation, or due to a germ cell mutation on the X-chromosome. Germ cell mutations seem to be the more common cause as only 1/3 of patients are reported to have a positive family history.

What other *immune defects should be tested* should be tested in evaluating for x-linked severe combined immunodeficiency (X-SCID)?

1. T cells
2. B cells
3. NK cells
4. 1 and 3
5. All of the above

Correct!

4. 1 and 3 or 5. All of the above

Our patient was tested for T cells, NK cells and B cells (Figure 4).

ABS B Cells (CD19)	11/02/22	142	142	176
% CD16+CD56 (NK cells)	09/16/21	1		
% NK (CD16)	11/02/22	<1	<1	1
CD16+CD56 (NK cells)	09/16/21	11		
ABS NK (CD16)	11/02/22	7	7	28
4/5 Ratio	09/16/21	0.8		
HS Ratio	11/02/22	0.56	0.56	0.33

Figure 4. Patient's immune cell panel. To view Figure 4 in a separate enlarged window click [here](#).

In SCID the body produces very few T cells and NK cells. B cells become defective in the absence of T cells. Most patients with X-SCID died before the age of 2 without treatment until universal screening identified those patients. Treating the patient with IgG allows the patients to usually live until adulthood. However, this patient also has mediastinal lymphadenopathy and a restrictive pulmonary function defect and has likely developed granulomatous and lymphocytic ILD (GLILD) as a complication of their X-SCID (3).

How is *GLILD best treated*?

- Rituximab
- Azathioprine
- Mycophenolate
- 1 and 2
- 1 and 3

Correct!

4 1 and 2 or 5. 1 and 3

GLILD occurs in 20 to 30% of patients with SCID and may occur in other patients with a primary immunodeficiency. The disease results from lymphocytic infiltration and/or granulomas in the lungs in which other causes are excluded. It may be a pulmonary manifestation of a more diffuse lymphoproliferative disorder as lymphadenopathy and splenomegaly are common. Biopsy in our patient was thought to be overly risky and currently he is being monitored for progression with a plan to treat with rituximab and azathioprine or mycophenolate should he progress.

References

1. Lomni S, Chalmers JD, Goeminne PC, *et al*. Etiology of Non-Cystic Fibrosis Bronchiectasis in Adults and Its Correlation to Disease Severity. *Ann Am Thorac Soc*. 2015 Dec;12(12):1764-70. [\[CrossRef\]](#) [\[PubMed\]](#)
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3. Verbsky JW, Hintermeyer MK, Simpson PM, *et al*. Rituximab and antimetabolite treatment of granulomatous and lymphocytic interstitial lung disease in common variable immunodeficiency. *J Allergy Clin Immunol*. 2021 Feb;147(2):704-712.e17. [\[CrossRef\]](#) [\[PubMed\]](#)