Università degli Studi di Padova

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Chair Internal Medicine

Deficit Immunitari e Malattie Respiratorie

Disclosure

In relation to this presentation, I declare the following, real or perceived conflicts of interest:

- C.A. participated in advisory board meetings for Intermune/Roche, Inc, CSL Behring GmbH, Inc, Baxter Int, Inc, LFB, Inc.
- C.A. received consultancy fees from Intermune, Inc, Baxter Int., Boehringer Ingelheim, Centocor, Inc
- C.A. received travel grants from CSL Behring GmbH, Inc, Boehringer Ingelheim, Intermune/Roche, Inc
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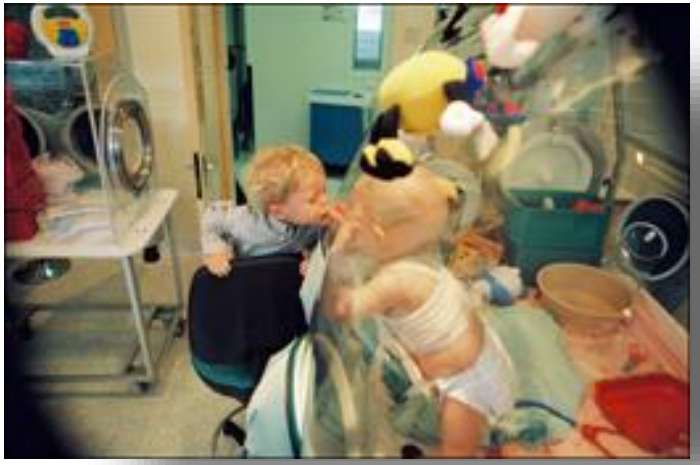
- No other fees or grants relevant to this lecture are reported

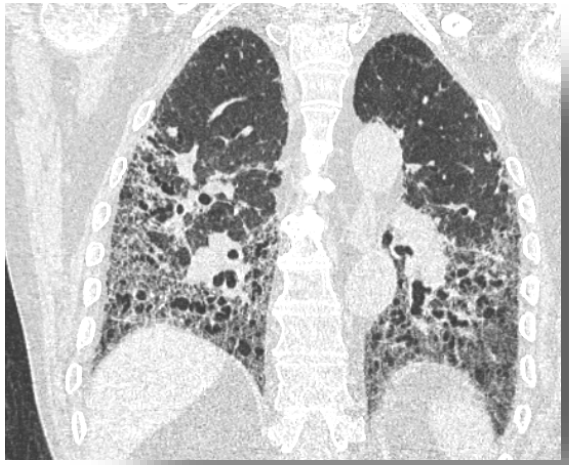
Structural Department of Medicine
Internal Medicine 1 - Postgraduate School of Allergy and Clinical Immunology
Regional Centre for Immune Mediated and Allergic Diseases

Diagnosis and treatment of immunological and allergic diseases, including patients with severe asthma, primary and secondary immunodeficiency, autoimmune diseases, autoinflammatory disorders, immunomediated and other rare interstitial lung diseases, including sarcoidosis

Treviso Ca' Foncello Padua University Hospital

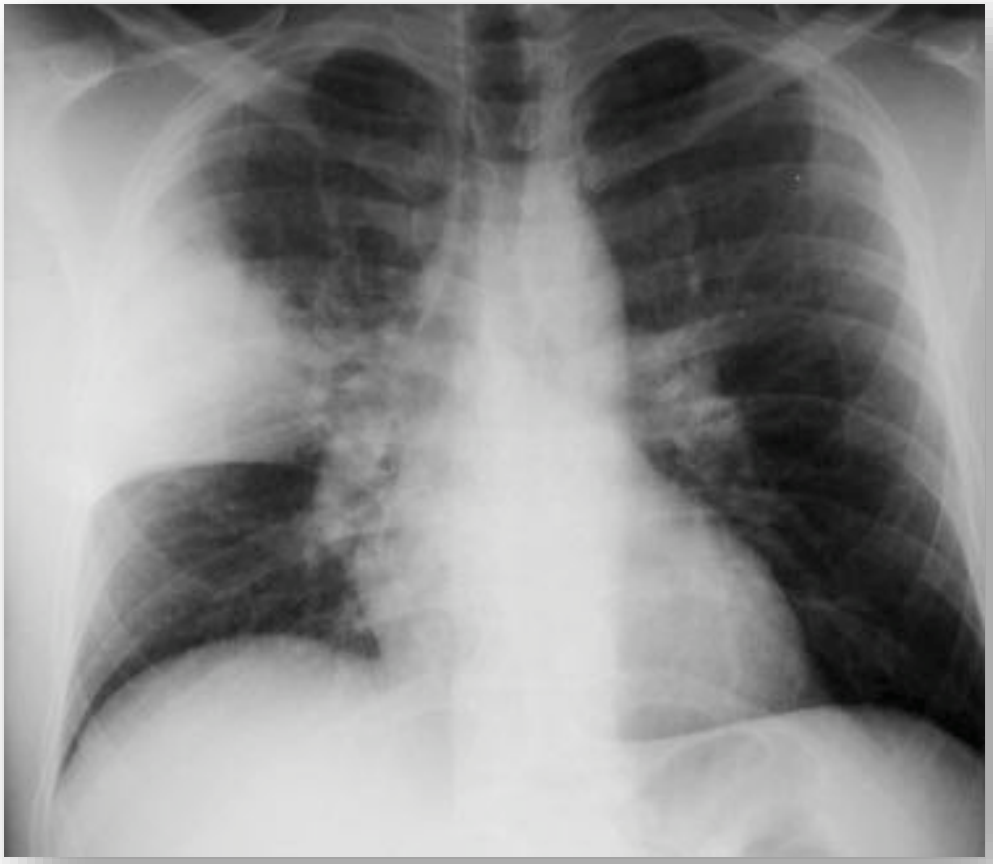
Immunodeficiency: state in which the immune system's ability to fight infectious disease is compromised or entirely absent





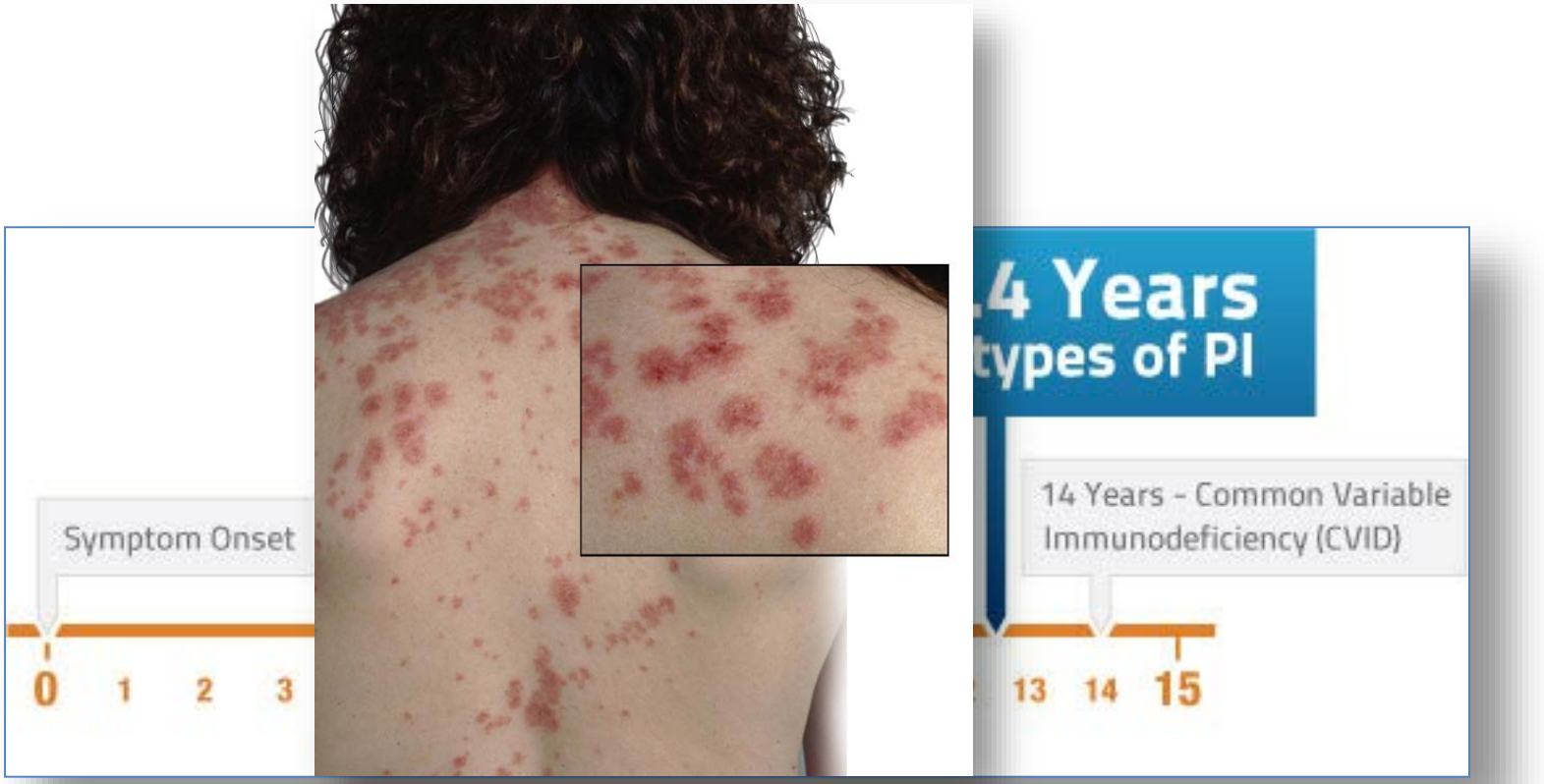
Primary Immune Deficiency Diagnosis: My Disease Has a Name, Now Let the Fight Begin

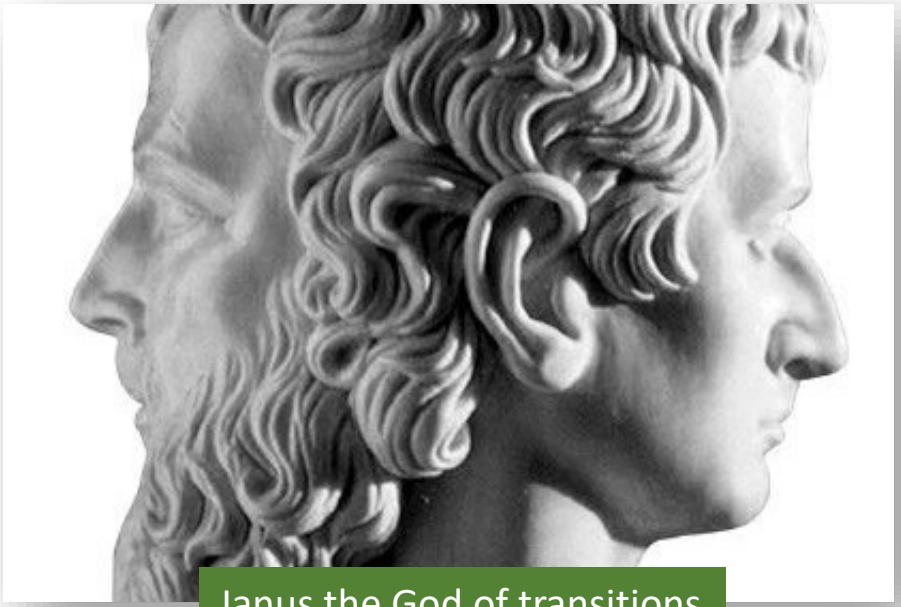
RC: In 2005 I was diagnosed with CVID. The diagnosis was the culmination of years of suffering through scores of serious infections...multiple penumonias, upper respiratoric tract infections, urinary tract infections, ear, nose, throat, eyes, and the list goes on. And on...



Primary Immune Deficiency Diagnosis: My Disease Has a Name, Now Let the Fight Begin

SA: In 2010 I was diagnosed with Sweet's Syndrome in CVID. Years of full body rashes, flu-like symptoms, and high fevers went unchallenged and undiagnosed. I was told on multiple occasions that the rashes were allergic reactions to mosquito bites.





Janus the God of transitions

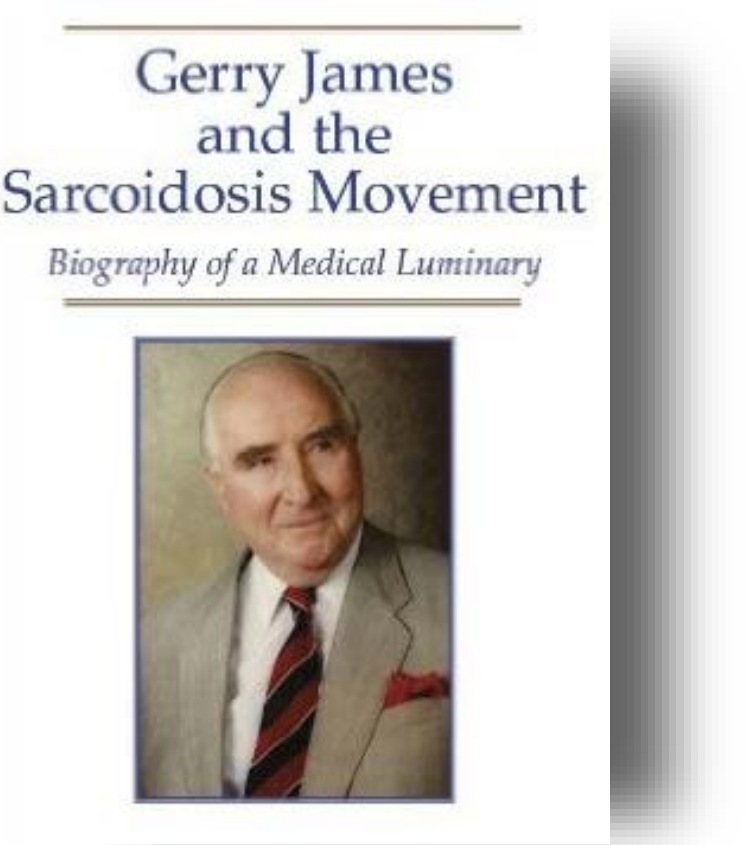
THE EXPANDING CLINICAL SPECTRUM OF PRIMARY DEFECTS OF IMMUNE SYSTEM INCLUDES THE LUNG

- AUTOIMMUNITY
- ALLERGY
- AUTOINFLAMMATION

- **Allergy**: state arising from an hypersensitivity reaction initiated by IgE or non-IgE antibody reactions or by T-cell mediated mechanisms

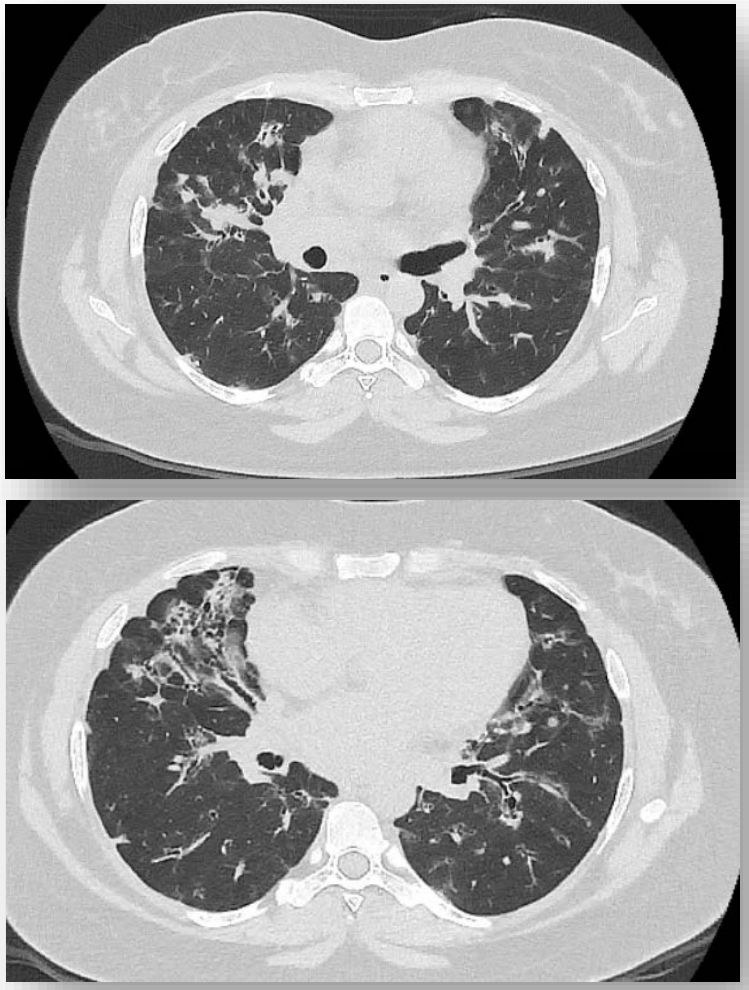
- **Autoimmunity**: state arising from an exaggerated adoptive B and T immune response againts substances and tissues normally present in the body
- **Autoinflammation**: state arising from a determined innate immune activation driven by endogenous danger signals, metabolic mediators and cytokines

Making the diagnosis: All that glitters is not sarcoidosis

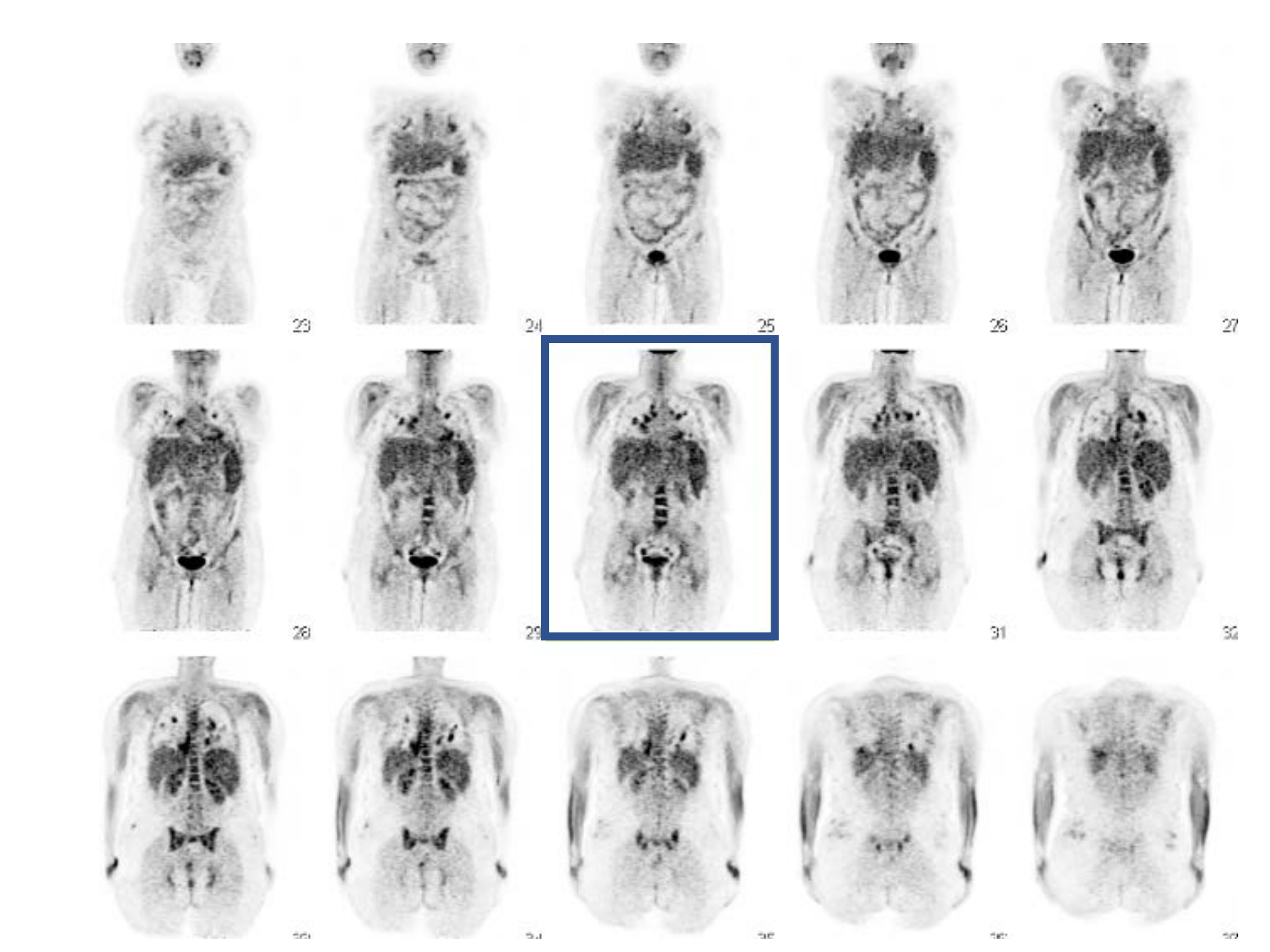


William W J: All that glitters is not sarcoidosis. Sarcoidosis 1984; 1: 16-23

Making the diagnosis: All that glitters is not sarcoidosis



- ✓ Woman, 38 anni
- ✓ Long history of multiple upper and lower respiratory tract infections
- ✓ Ex smoker
- ✓ Office worker
- ✓ Fever, night sweats
- ✓ Arthralgia, mild exertional dyspnea
- ✓ Suspected IBD (calprotectine ↑)
- ✓ Chest X ray: bilateral ilar lympadenopaties, mild interstitial thickening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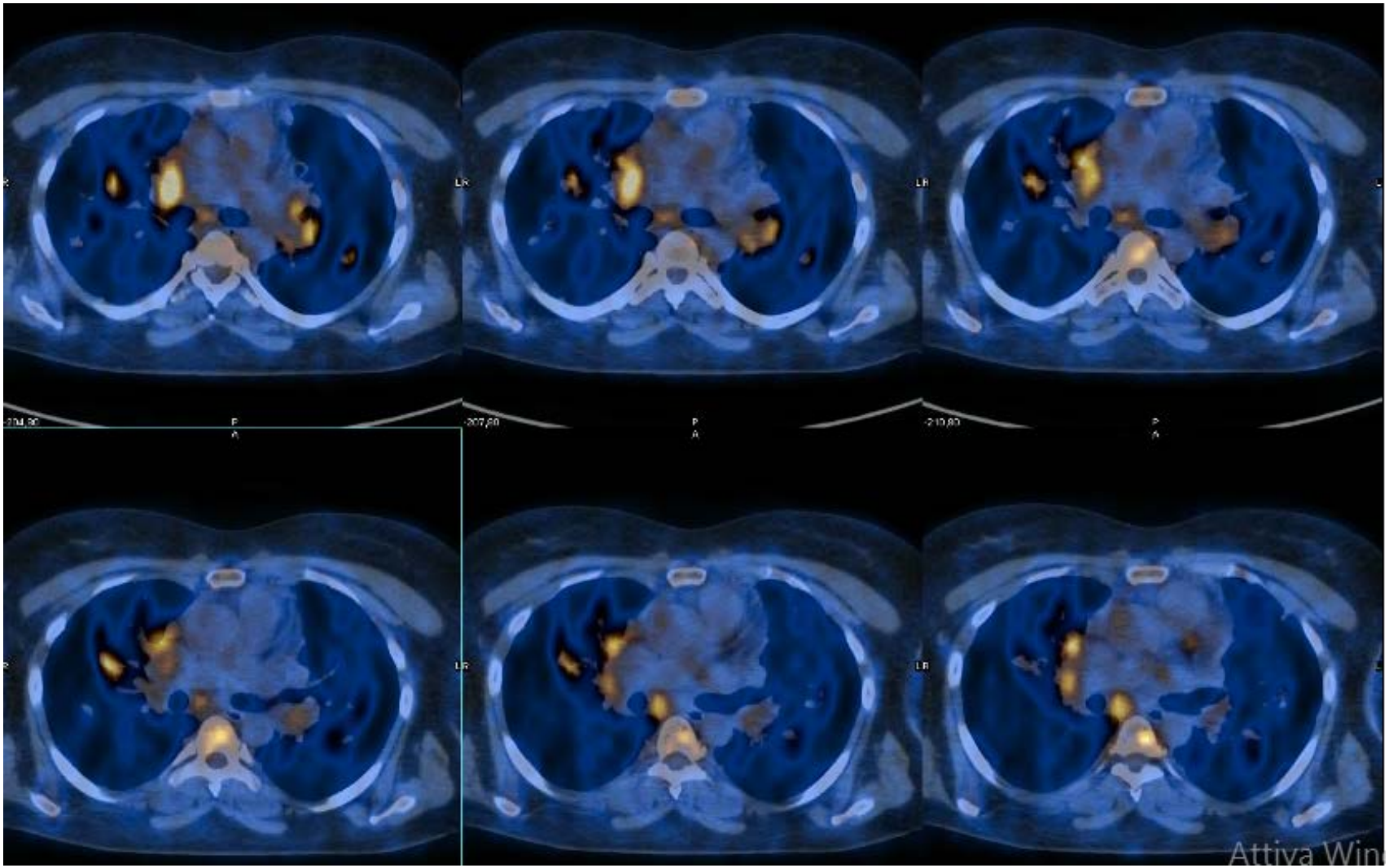

Attiva Win

Bronchoscopy: TBB and BAL

Bronchoalveolar lavage

Alveolar Macophages	65%
Lymphocytes	20%
Neutrophils	13%
Eosinophils	2%

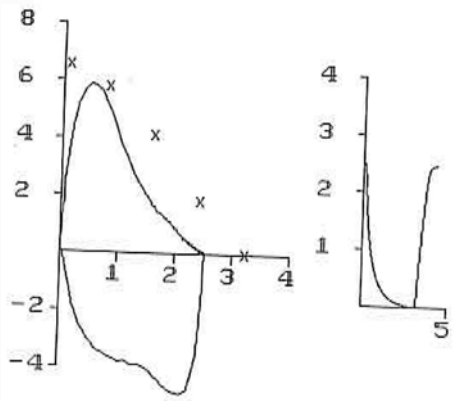
Flow cytometric analysis

CD3	88%
CD4	46%
CD8	41%
CD4/CD8	1.1
CD19	9% (polyclonal)
CD16	1%

Spirometry

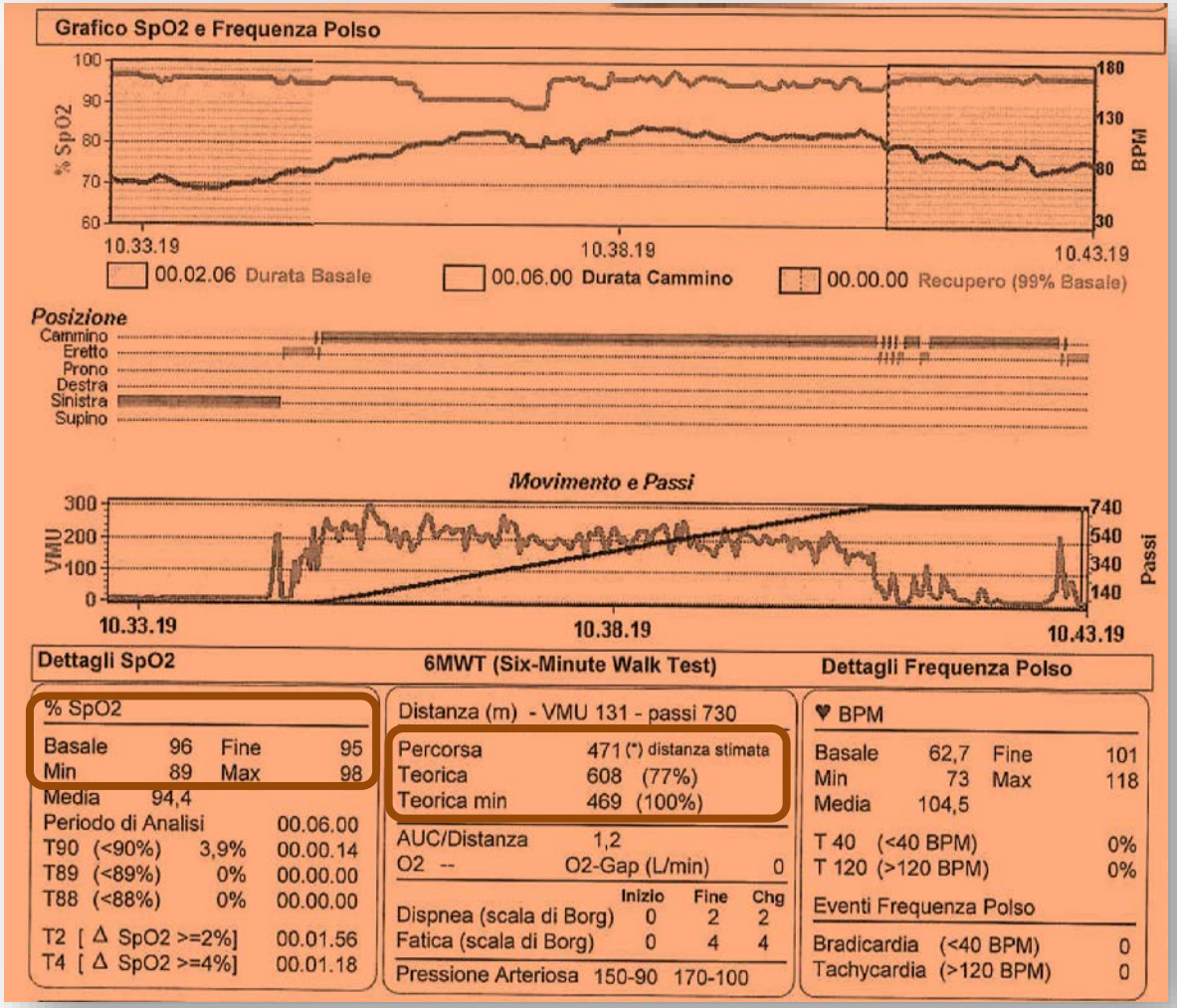
		oss.	teorici	%	lim.
VC	l	2.56	3.22	79	2.53-3.91
FVC	l	2.52	3.23	78	2.52-3.94
FEV1	l	2.19	2.80	78	2.18-3.42
FEV1/VC	%	85.80	82.00	105	71.3-92.7
FEV1/FVC	%	86.96			
FEF25-75	l/s	2.60	3.67	71	2.27-5.07
FEF25-75/VC	l/s	1.02			
PEF	l/s	5.88	6.59	89	5.11-8.07
IC	l	2.15			
FIV1	l	2.51			
FEV1/FIV1	%	87.21			
RV	l	1.20	1.49	81	0.91-2.07
FRC	l	1.60	2.63	61	1.81-3.45
ERV	l	0.41			
TLC	l	3.76	4.77	79	3.78-5.76
RV/TLC	%	32.01	31.35	102	21.8-41.0
FRC/TLC	%	42.65	51.02	84	41.2-60.8
TLCO(Va)	ml/(min*mmHg)	17.38	25.48	68	19.7-31.2
KCO	*	5.10	5.34	95	2.94-7.74

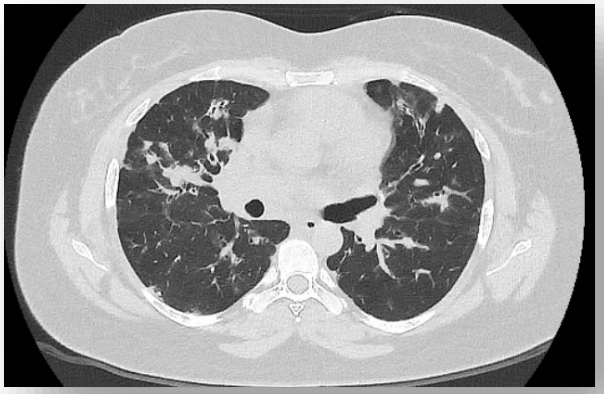
Teorici di Riferimento: Polgar 71 (6<eta'<18) ERS93 (18<=eta')



Mild restrictive. Mild DLCO reduction

Six Minute Walk Test





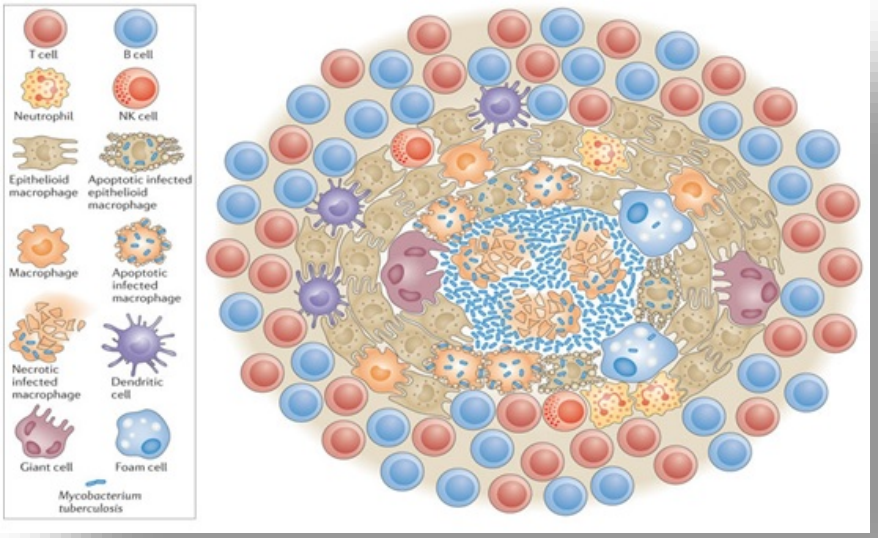
- ✓ **Diagnosis**: sarcoidosis
- ✓ **Therapy**: Steroids with slight improvement
- ✓ **Complications**: CMV uveitis

Electrophoretic protidogram

Total proteins	**55.5 g/L**
Albumine	**69.70%**
Alpha1	**5.80%**
Alpha 2	**11.5%**
Beta 1	**6.9%**
Beta 2	**3.2%**
Gamma	**2.7%**
S-IgG	**1.44 g/L**
S-IgA	**0.08 g/L**
S-IgM	**0,28 g/L**

Hypogammaglobulinemia was present since 1999!

Making the diagnosis: All that glitters is not……

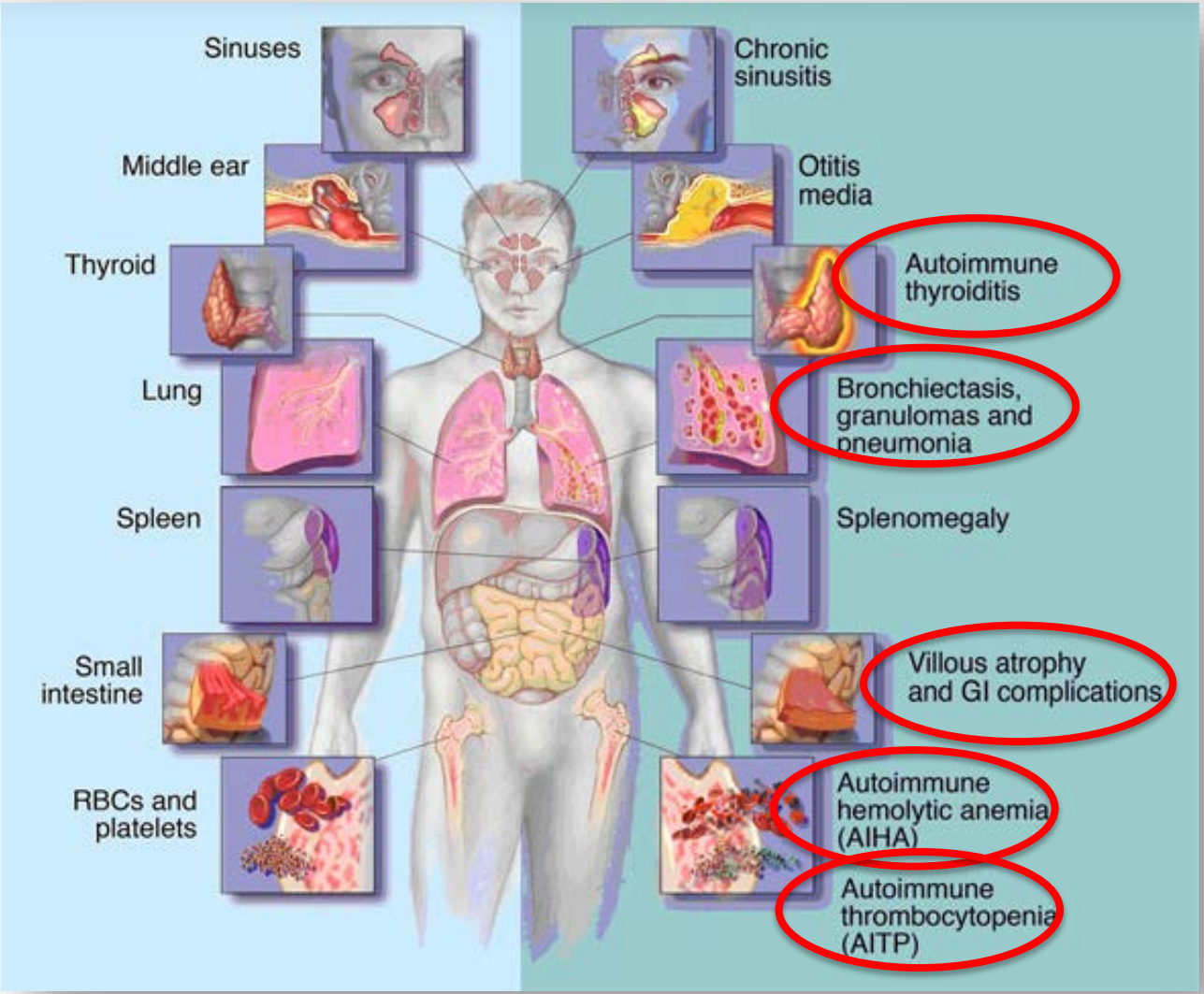


but may be a primary immunodeficiency ……..

COMMON VARIABLE IMMUNODEFICIENCY

- the most frequent diagnosis of PID in adults. In 70% of cases diagnosis is made between 20 and 40 yrs.
- more than 90% of documented CVID patients are lacking a definite molecular genetic diagnosis or other causal explanation for their disease
- only 10 to 20% of CVID patients have a positive family history, while most cases occur sporadically
- genes associated with a CVID phenotype are ICOS (inducible costimulator) TACI (transmembrane activator and calcium-modulating cyclophilin ligand interactor) CD19, BAFF-R , CD81, CD20, CD21 and LRBA (lipopolysaccharide responsive beige-like anchor protein)

CVID: Clinical features



Causes of Death in CVID

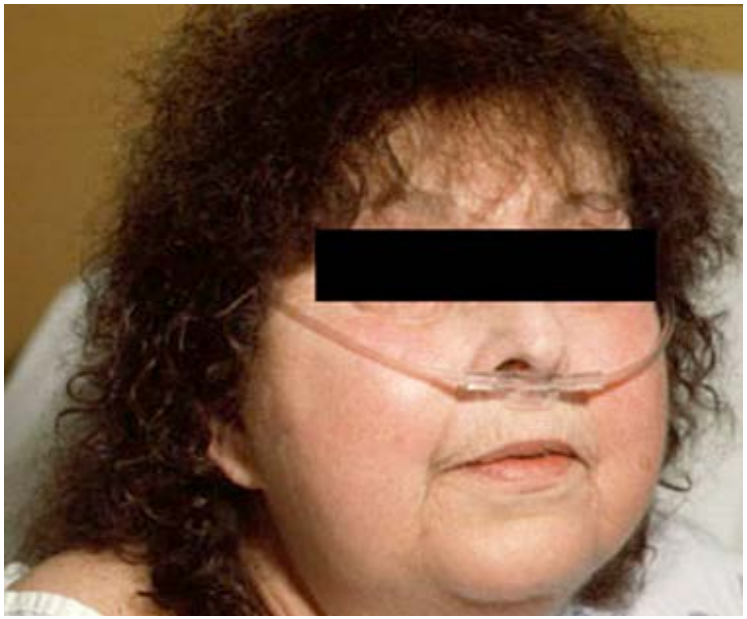
	Cunningham-Rundles 1999	Quinti 2007	Resnick 2012
Deaths/Patients	57/248	13/224	93/473
Cancer	30%	46%	37%
Chronic Lung Diseases	23%	31%	29%
Liver	9%	2 (15%)	9%

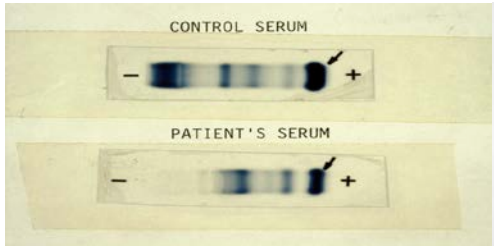
Cunningham-Rundles & Bodian, 1999. *Clin Immunol* 92: 34-48
Quinti et al, 2007. *J Clin Immunol* 27: 308-16
Resnick et al, 2012. *Blood* 119: 1650-7

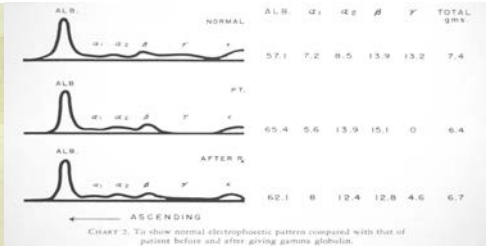
Chronic Lung Diseases in CVID

Manifestations	PFT
Chronic bronchitis/Emphysema	Mild airflow obstruction
Asthma	Moderate airflow obstruction
Bronchiectasis	Mild airflow obstruction
Recurrent infections	Mild airflow restriction Mild airflow obstruction
NSIP, COP	Moderate airflow restriction
Granulomatous & other lymphocytic lung diseases	Moderate airflow restriction
B cell lymphoproliferative disorders	

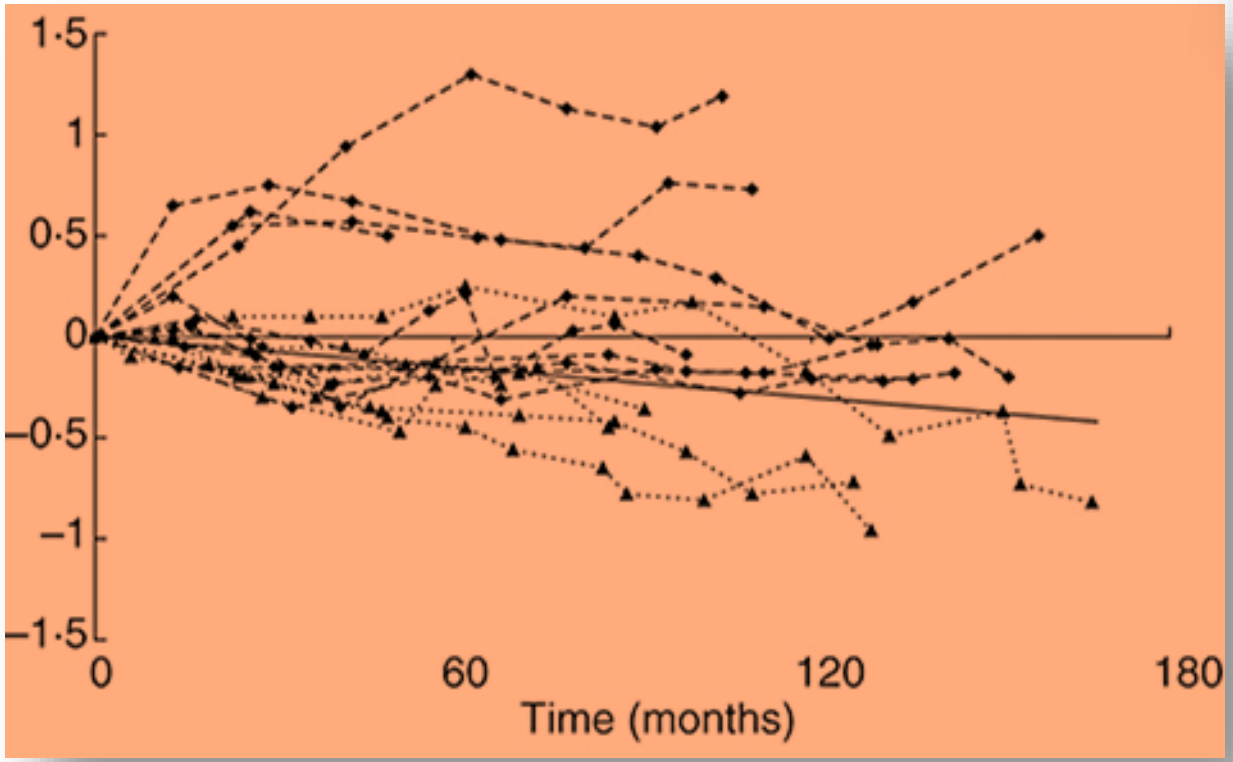
Diagnostic delay is a characteristic feature of CVID



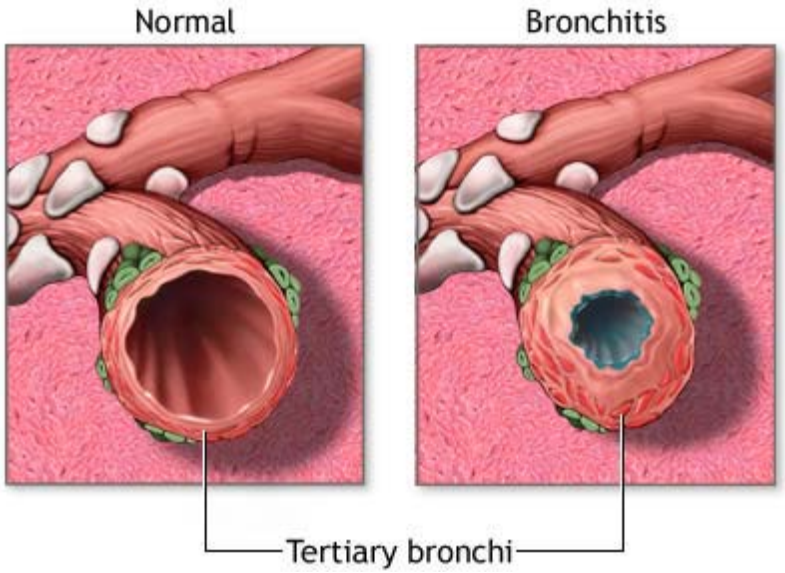


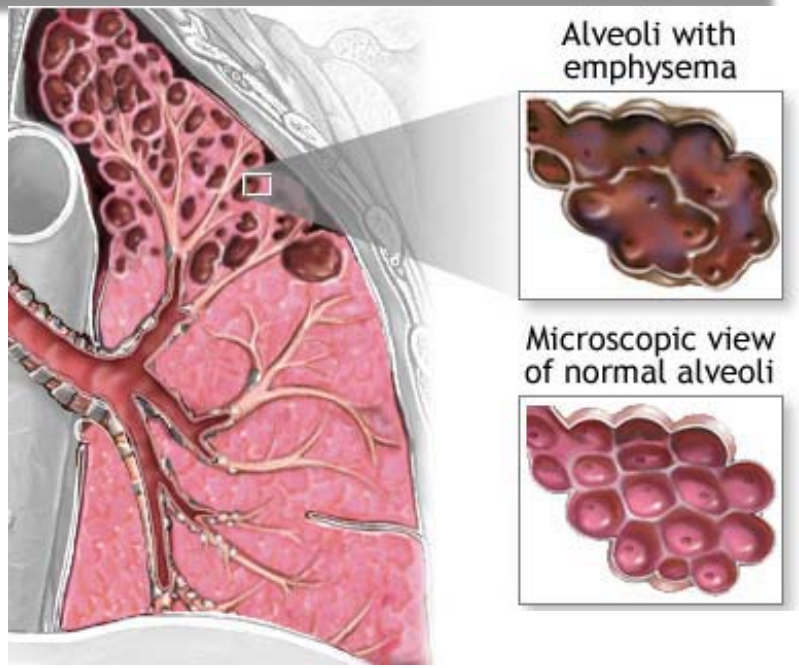


Absolute change in forced expiratory volume in 1 second (FEV1) in a cohort of patients with CVID:
most patients show a progressive early onset obstructive pattern

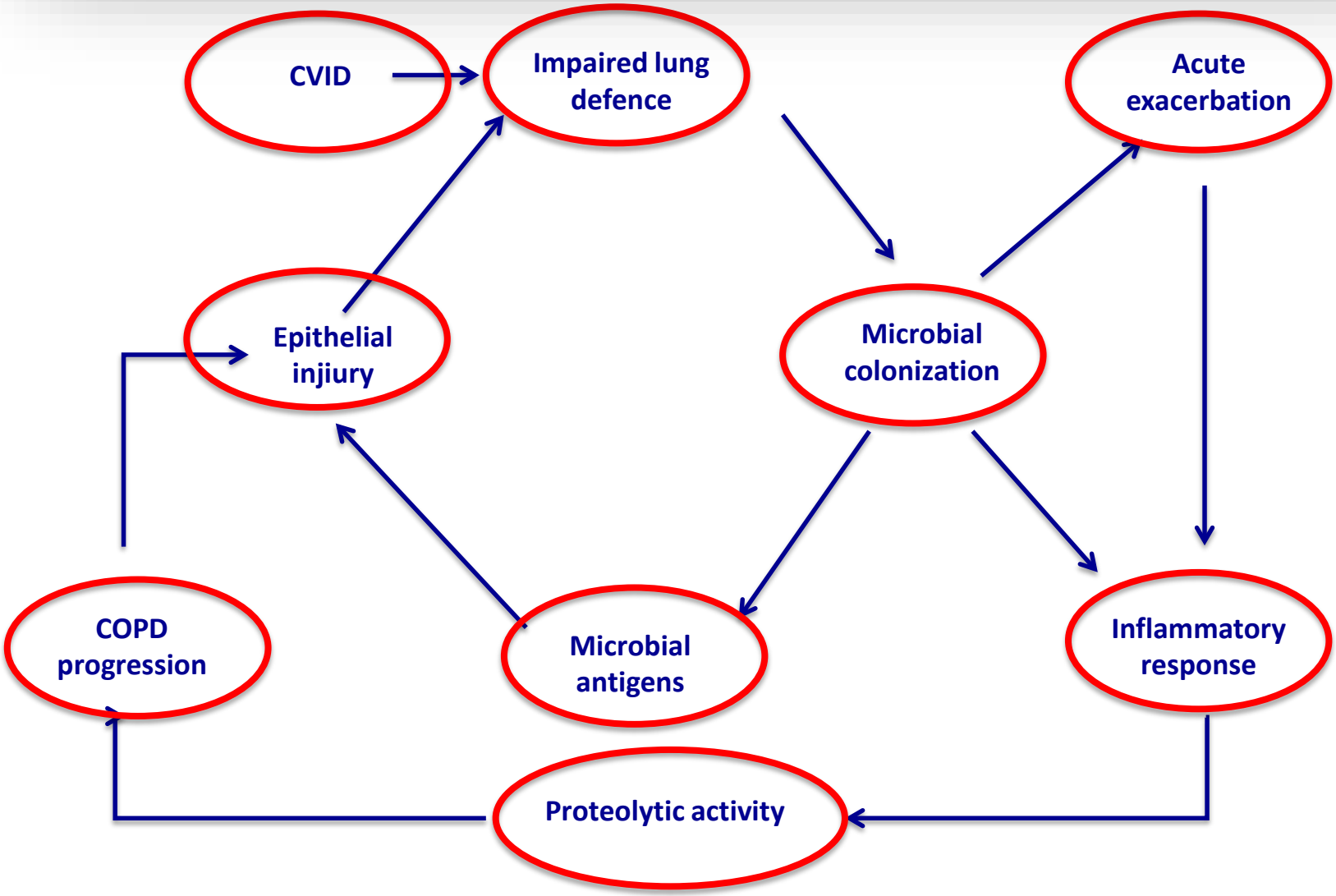


Chronic Obstructive Pulmonary Disease in CVID is Characterized by Early Development but does not Differ from "Classic" Forms





COPD Exacerbations in CVID



Why COPD Exacerbations in CVID?

- COPD patients maintain the capability to produce specific antibody response to strain-specific epitopes on the P2 outer membrane protein of non-typeable *Haemophilus influenzae*;
- For year these antibodies provide protection against mucosal colonization.
- Exacerbations of bronchitis in COPD are usually due to a new strain with a different P2 epitope
- In CVID patients the quantities of IgG antibodies to P2 epitopes are to be small and inadequate for protection against H. influenzae bronchitis
- Ig replacement therapy contains antibodies from at least 5,000 donors and contain **a wide repertoire of IgG antibodies to P2 epitopes**

Chronic Lung Diseases in CVID

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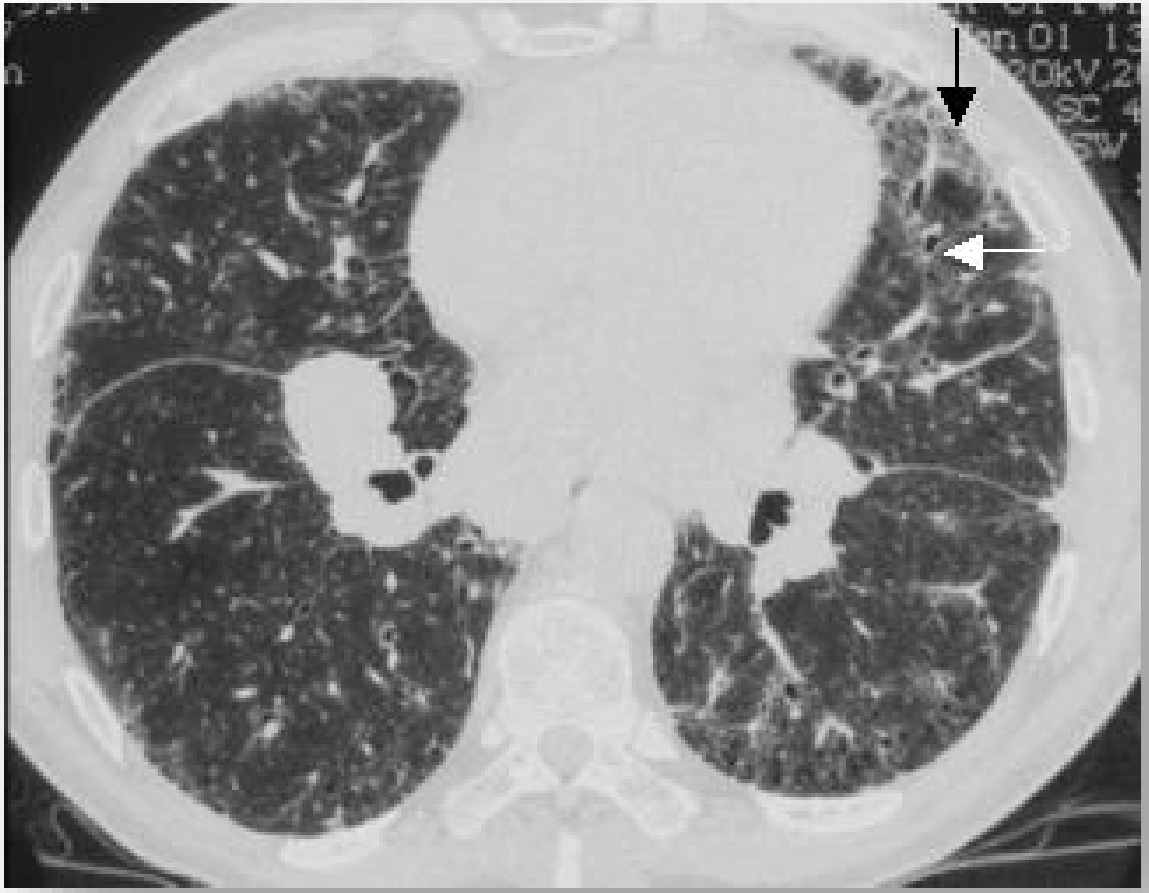
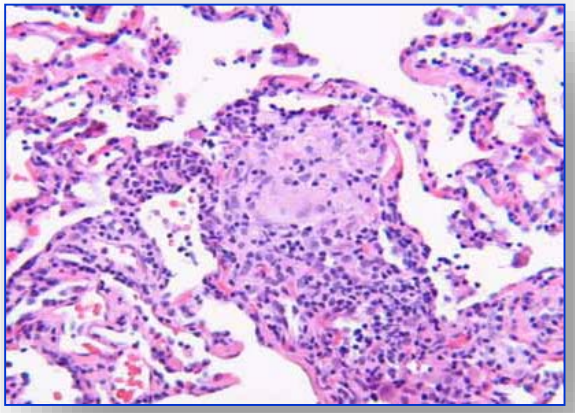
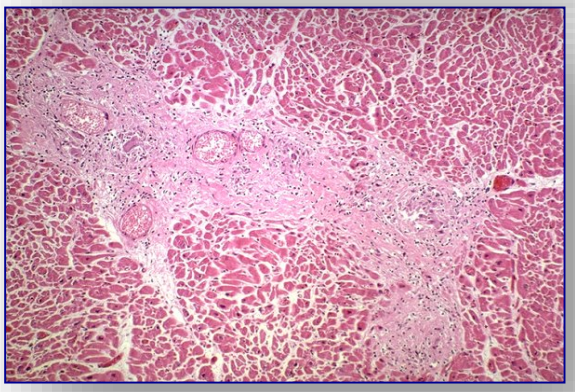


Mediastinoscopia con biopsie multiple: Linfoadenopatia granulomatosa non necrotizzante con diffusi aspetti di istiocitosi reattiva dei seni.
Diagnosi: Sarcoidosi
Avviata terapia steroidea senza successo

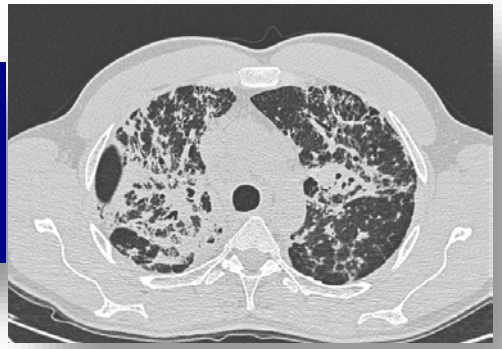
Parallelism between GLILD in CVID and sarcoidosis

- About 30% of CVID patients develop granulomatous lesions in various organs including the lung, spleen and liver
- The onset of granulomatous lung disease is insidious, the patient complaining nonproductive cough, dyspnea, deterioration in exercise tolerance.
- **Granulomatous disease and fibrosis coexist in bronchiectasic areas**
- The diagnosis is based on the deteriorating CO gas transfer on lung function tests and on chest HRCT imaging
- **Fall in serum IgG levels in patients on Ig replacement suggests the presence of a granulomatous process somewhere in the body** (hypercatabolism of IgG by activated macrophages)

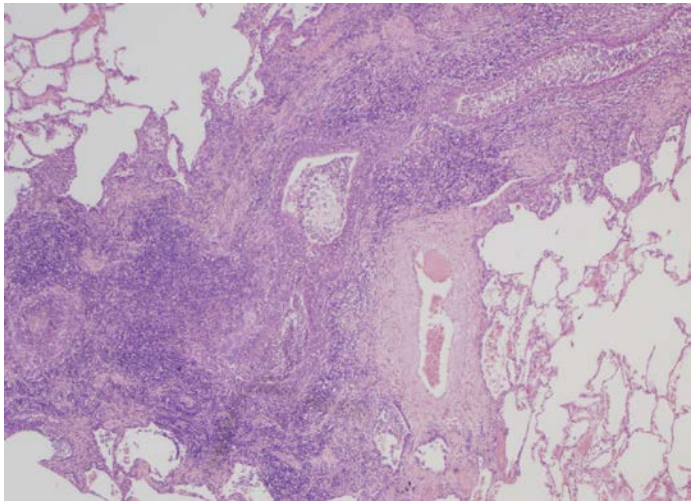




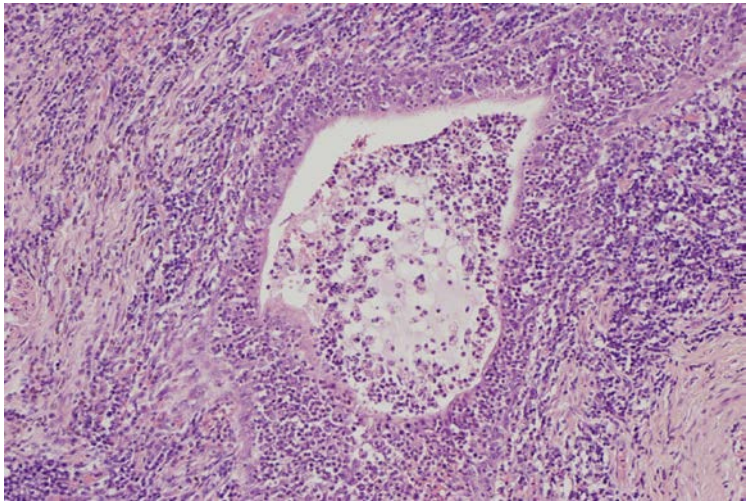
Characteristics of 30 patients with GLILD & lung disease



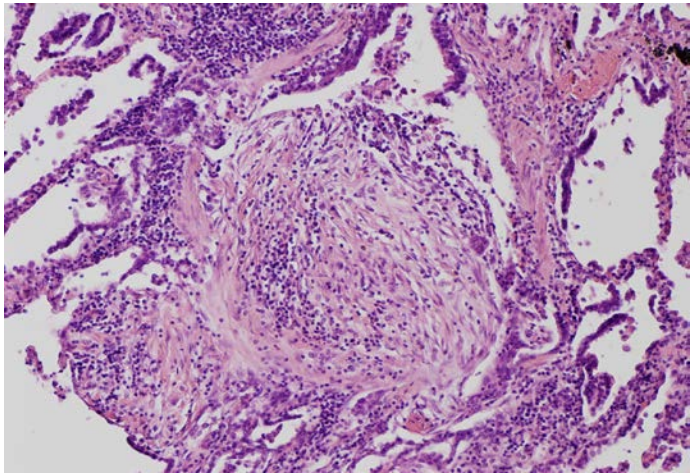
	Characteristics	Number of patients (n. 30)
PFTs	- Obstructive pattern	6 (20%)
	- Restrictive pattern	5 (17%)
	- Decreased DLCO	10 (33%)
Symptoms/ Signs	- Cough	16 (53%)
	- Dyspnea	16 (53%)
	- Chest pain	1 (3%)
	- Hypoxemia	3 (10%)
HRCT	- Disseminated micronodules	29 (97%)
	- Ground glass attenuation	16 (53&)
	- Mediastinal / hilar adenopathy	28/22 (93%/73%)
	- Interlobular thickening	19 (63%)
	Positive biopsy for sarcoid like pulmonary granuloma	**23 (72%)**



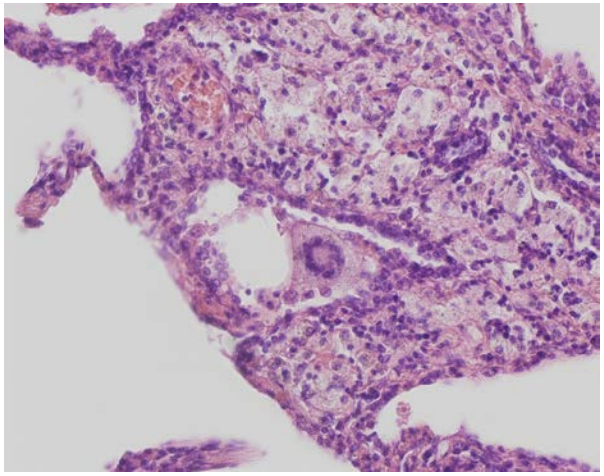
Bronchiolar and peribronchiolar inflammation with follicular bronchiolitis



Bronchiolar lymphocytic and granulocytic inflammation with abscess of the adjacent parenchyma

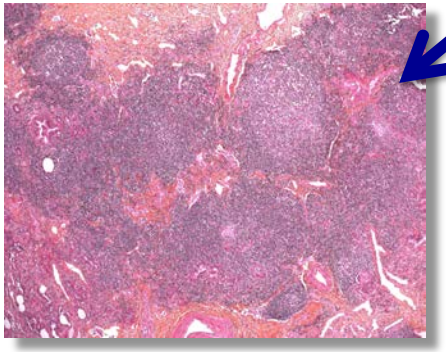


Intra-alveolar plugs of granulation tissue (organizing pneumonia)

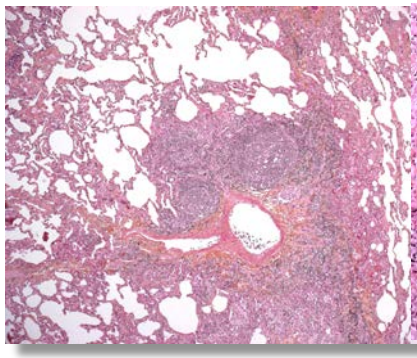


Microgranuloma with a giant cell surrounded by foamy and epithelioid macrophages

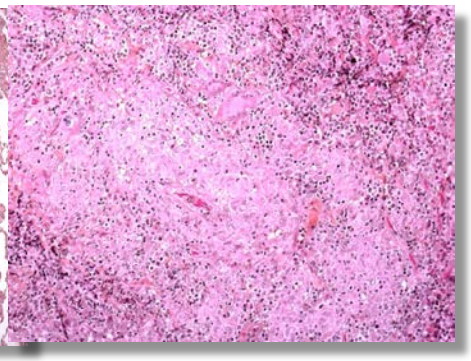
Granulomatous-lymphocytic interstitial lung disease (GLILD): a sarcoid like inflammatory process



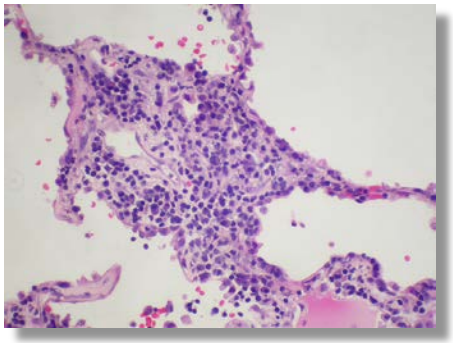
Nodular lymphocytic infiltrate



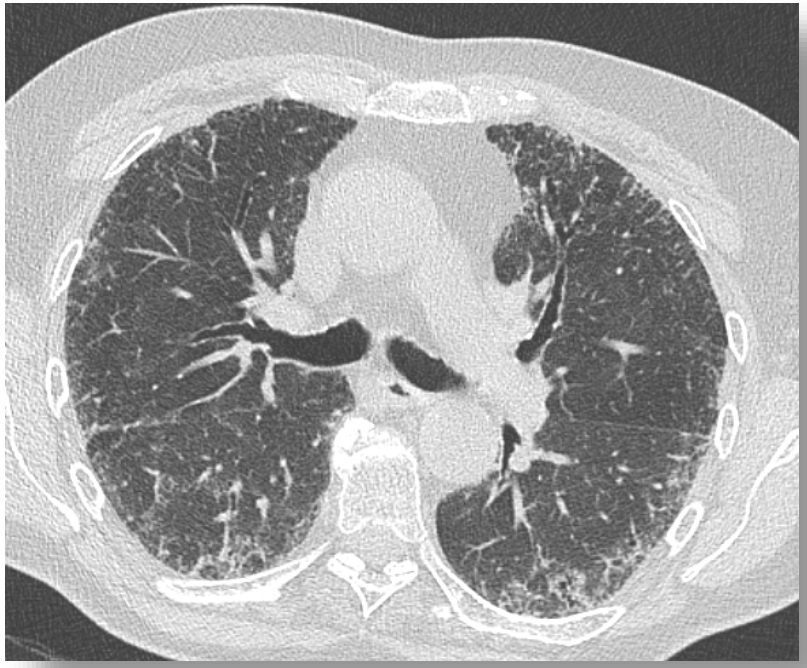
BALT hyperplasia and peribronchiolar lymphocytic infiltrate

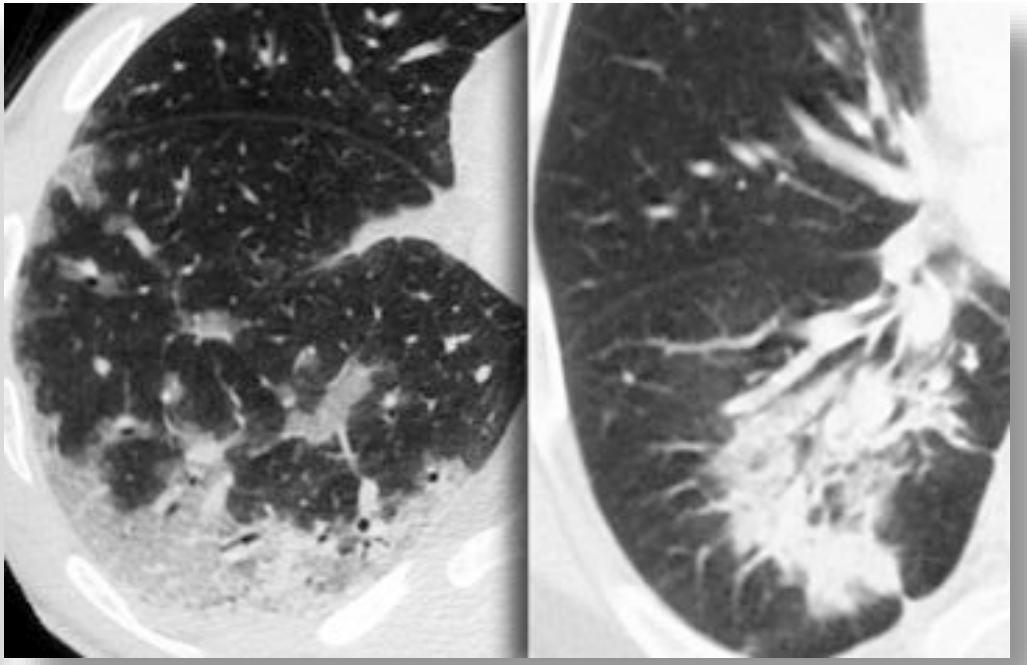


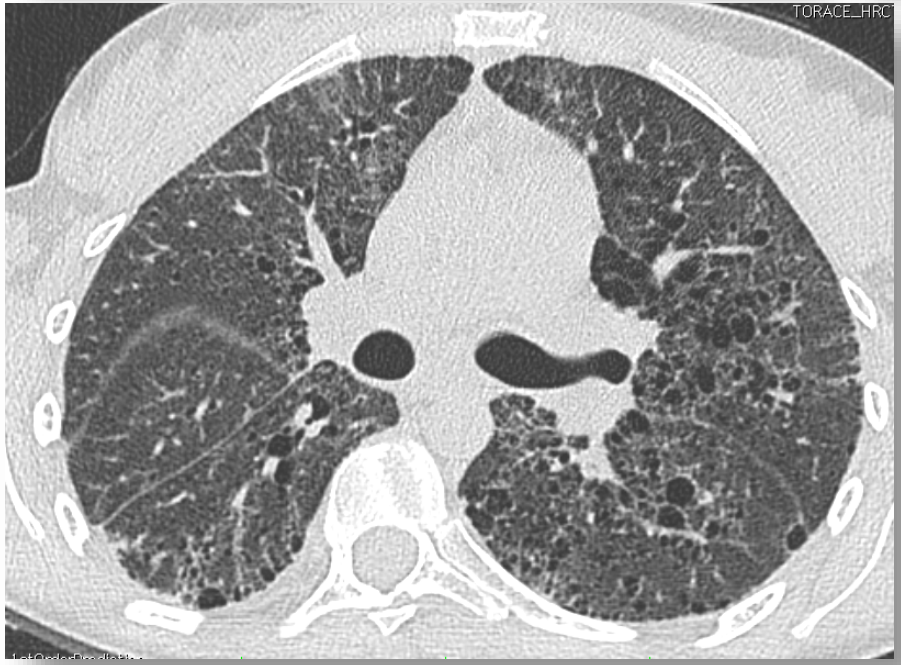
Perivascular granuloma

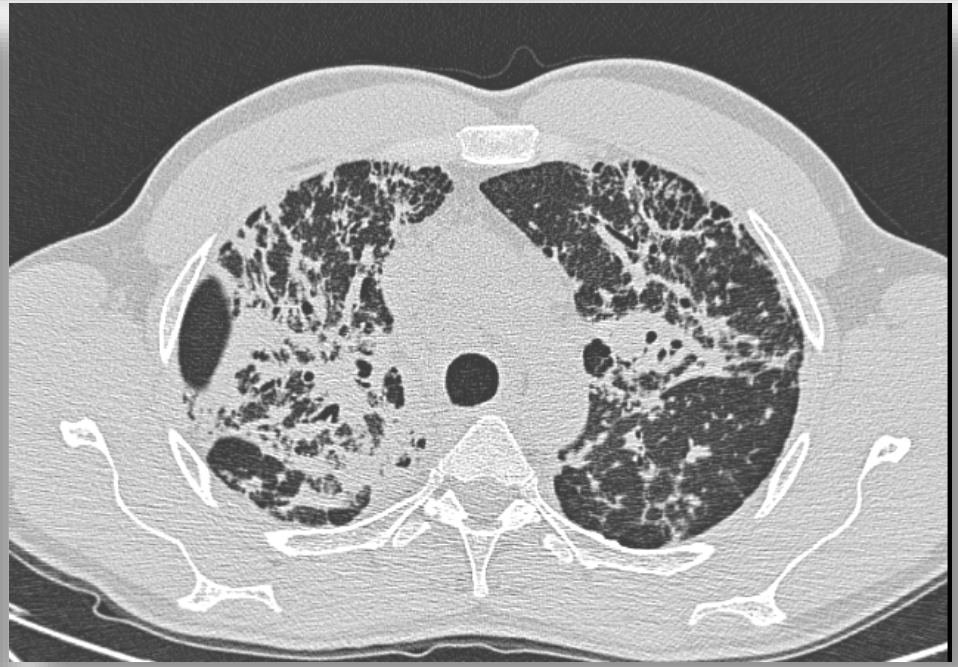


Lymphocytic interstitial pneumonia






TORACE_HRC



Location of granuloma in patients with GLILD

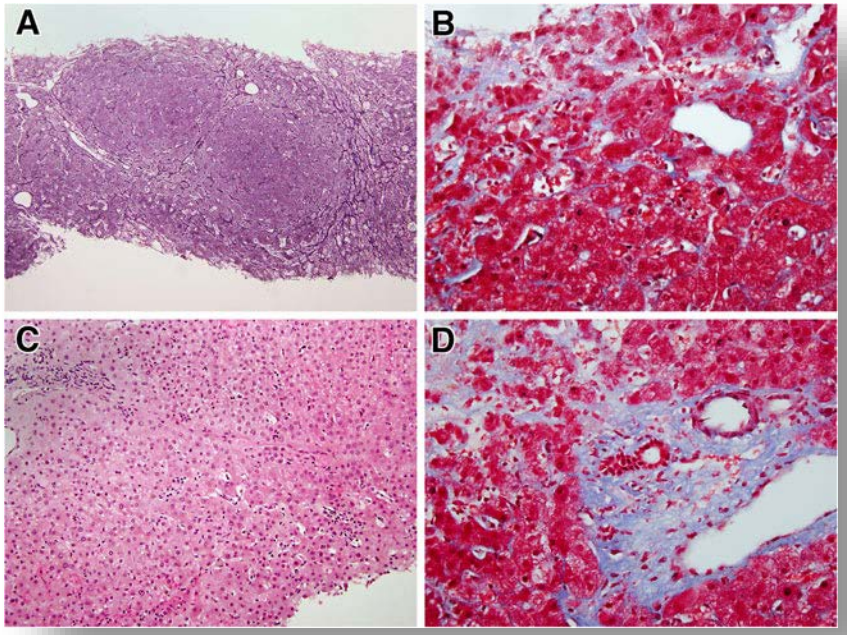
Organ	Localized (1 organ)	Multisystemic (≥ 2 organs)	Total (%)
Lung	8	22	30 (51)
Spleen and lymph nodes	8	19	27 (46)
Liver	9	15	29 (41)
GI tract	1	7	9 (15)
Bone Marrow	1	4	5 (8)
Skin	1	3	4 (7)
Central nervous system	1	2	3 (5)
Accessory glands eye, kidney	1	4	5 (8)
	31	28	59

The DEFI Group, J Clin Immunol (2013) 33:84–95

Hepatic Nodular Regenerative Hyperplasia in Common Variable Immunodeficiency

- presenting with elevated alkaline phosphatase level
- in some patients the disease remain static
- in a larger proportion a more severe disease develop with portal hypertension, hypersplenism with neutropenia and thrombocytopenia and, in some cases, ascites
- histologic pattern is characterized by superimposed interface hepatitis, lymphocytic infiltration and fibrosis

characteristic nodularity



periportal fibrosis and portal inflammation

lobular inflammation

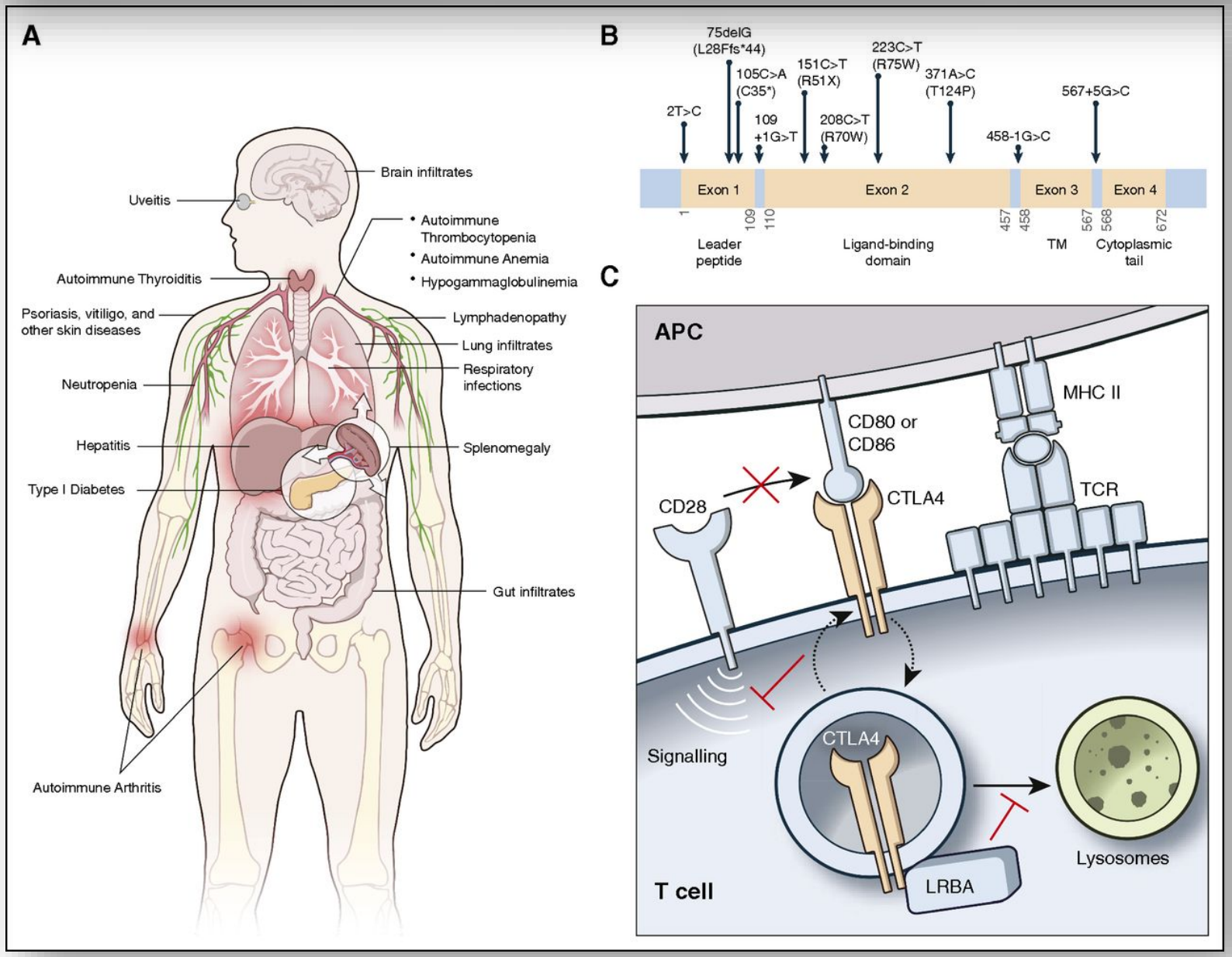
Fuss IJ et al., 2013 J Clin Immunol DOI 10.1007/s10875-013-9873-6

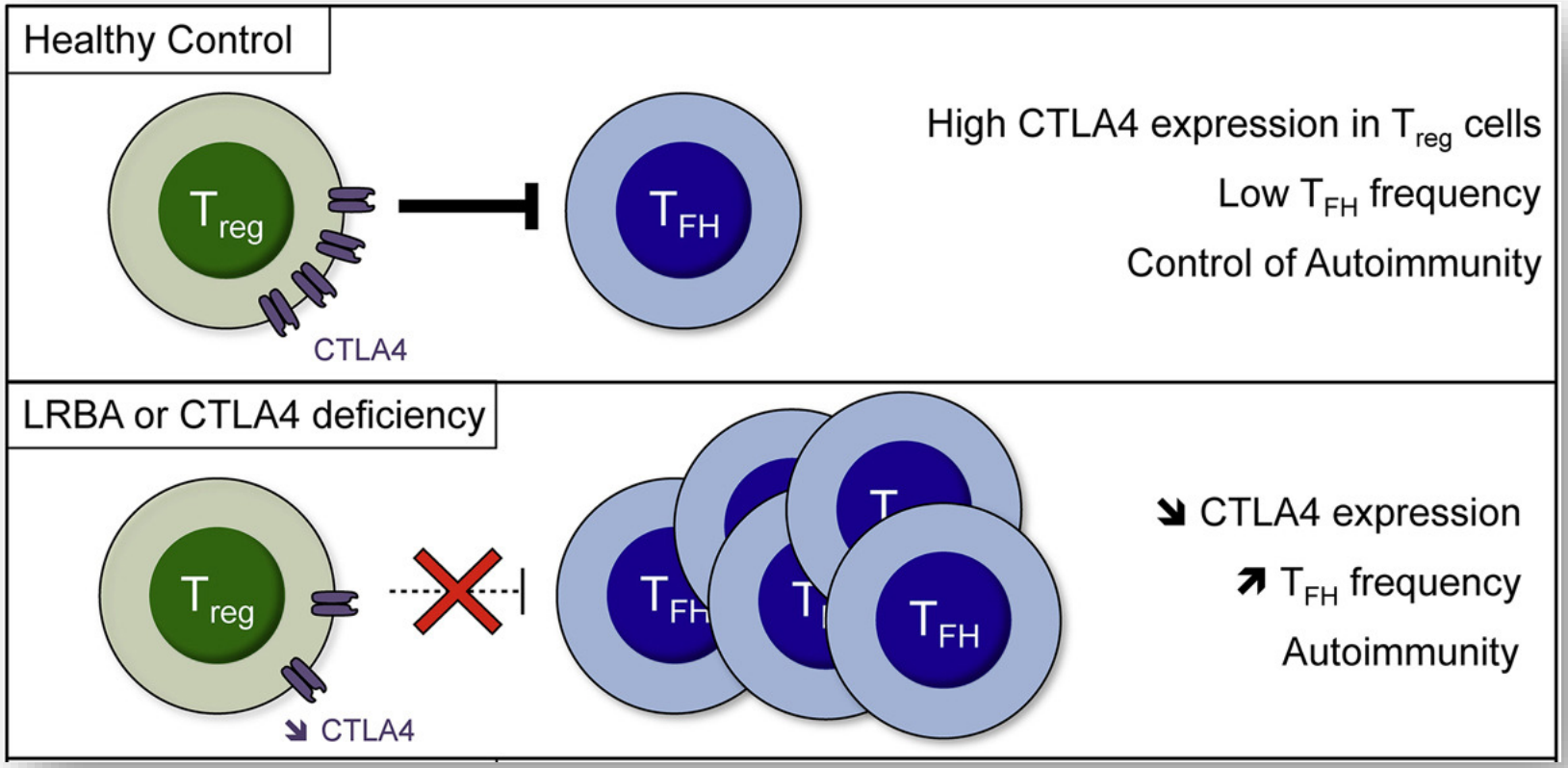
Main features	GLILD	SARCOIDOSIS
Gamma globulin	Generally decreased, may be normal in IgG subclass deficiency	Normal or increased. No specific Ig class or subclass level alteration
ACE	Generally normal	Often increased
BALF lymphocytosis	frequent	frequent
Elevated BALF CD4:CD8 ratio	Reported in a small case series	Typical in acute Lofgren Syndrome
Recurrent infections	Generally reported	infrequent
Autoimmune cytopenia	frequent	Not associated. Cytopenia may be due to bone marrow granulomatosis
Splenomegaly	frequent	Spleen may be involved
Nodular regenerative hyperplasia of the liver	Increased likelihood	Liver involvement is often asymptomatic; biopsies may show granulomatous hepatitis
G.I. involvement	Reported in 15%	rare
Eye involvement	Not reported	frequent
PLH histologic and radiologic evidence	typical	Not present
Hilar adenopathy	May be present	Typical feature
Lung nodules size and distribution on HRCT	Often > 1 cm, with random or predominantly basal distribution	Typically < 1 cm, with mainly apical and peri-lymphatic distribution
Bronchiectasis	frequent	Traction bronchiectasis may be found in advanced fibrotic disease
Prognosis	Slowly progressing restrictive lung disease with poor prognosis	Generally good prognosis; spontaneous remission may frequently occur

COMMON VARIABLE IMMUNODEFICIENCY

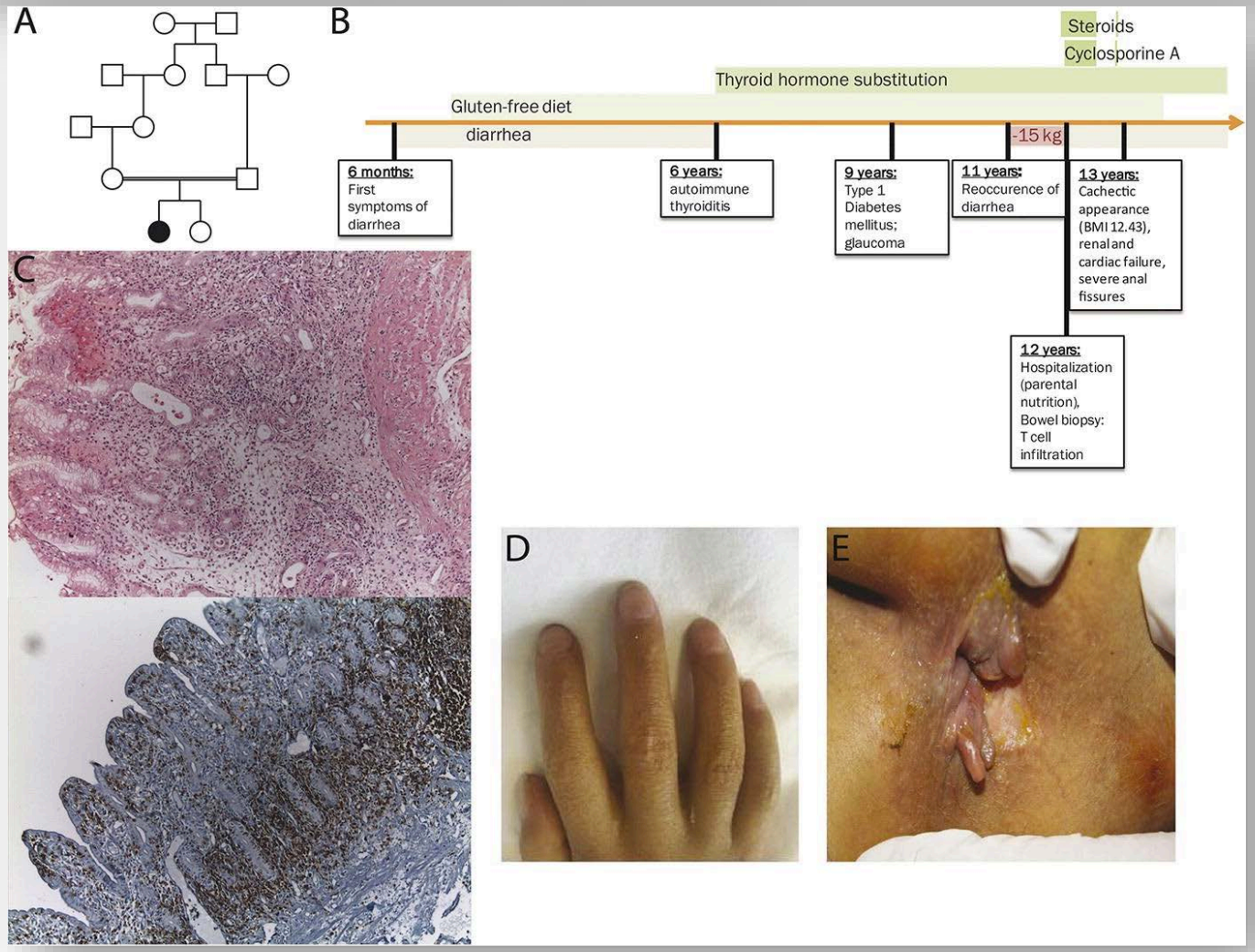
- the most frequent diagnosis of PID in adults. In 70% of cases diagnosis is made between 20 and 40 yrs.
- more than 90% of documented CVID patients are lacking a definite molecular genetic diagnosis or other causal explanation for their disease
- only 10 to 20% of CVID patients have a positive family history, while most cases occur sporadically
- genes associated with a CVID phenotype are ICOS (inducible costimulator) TACI (transmembrane activator and calcium-modulating cyclophilin ligand interactor) CD19, BAFF-R , CD81, CD20, CD21 and **LRBA (lipopolysaccharide responsive beige-like anchor protein)**

Deleterious mutations in LRBA gene deficiency are associated with a syndrome of immune deficiency, infiltrative inflammation, granuloma formation & autoimmunity

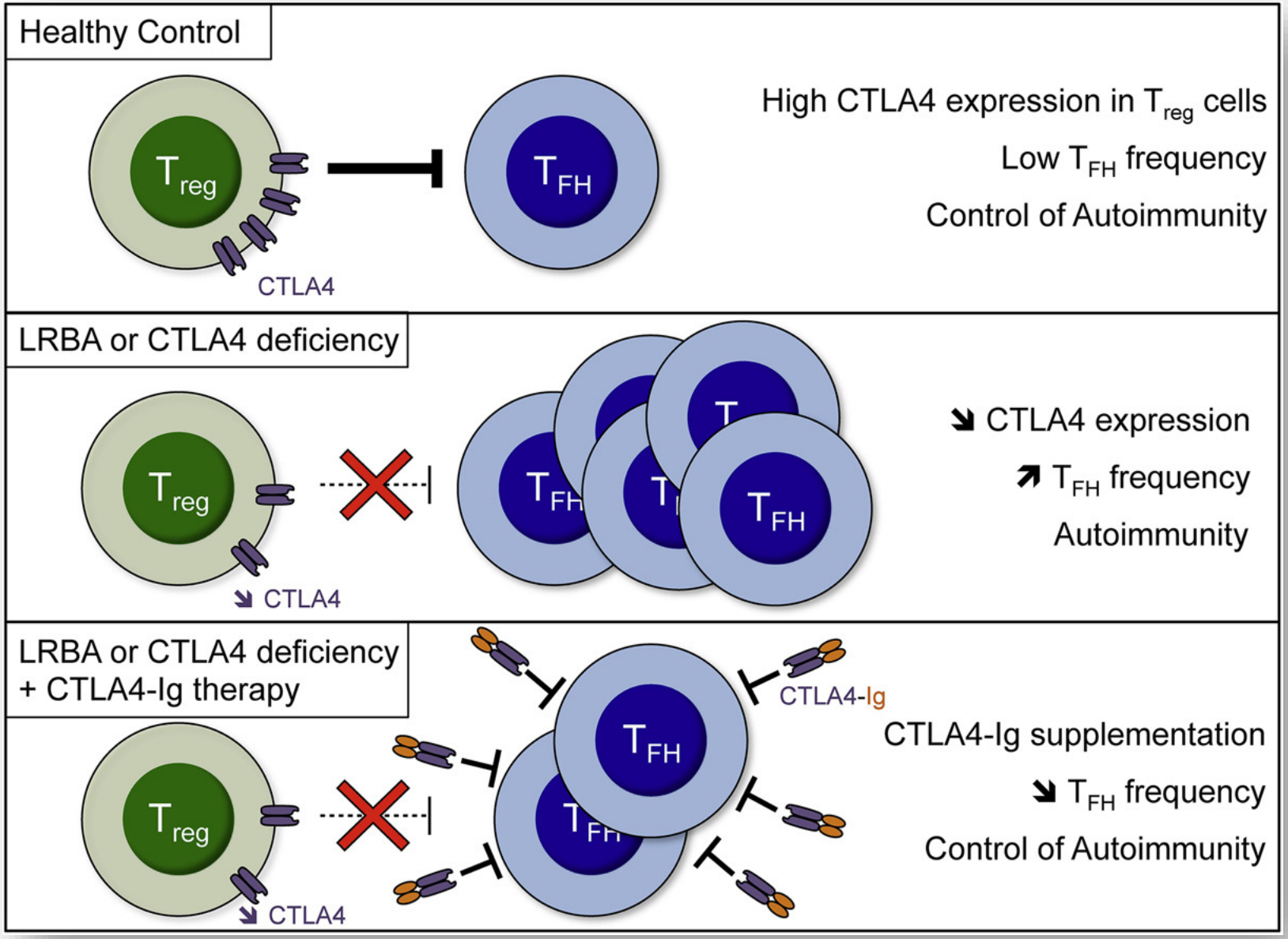



Healthy Control
T_{reg}
T_{FH}
CTLA4
High CTLA4 expression in T_{reg} cells
Low T_{FH} frequency
Control of Autoimmunity
LRBA or CTLA4 deficiency
T_{reg}
T_{FH}
↘ CTLA4
↘ CTLA4 expression
↗ T_{FH} frequency
Autoimmunity

Clinical history and presentation of a LRBA deficiency with IBD-like phenotype diagnosed after 15 yrs

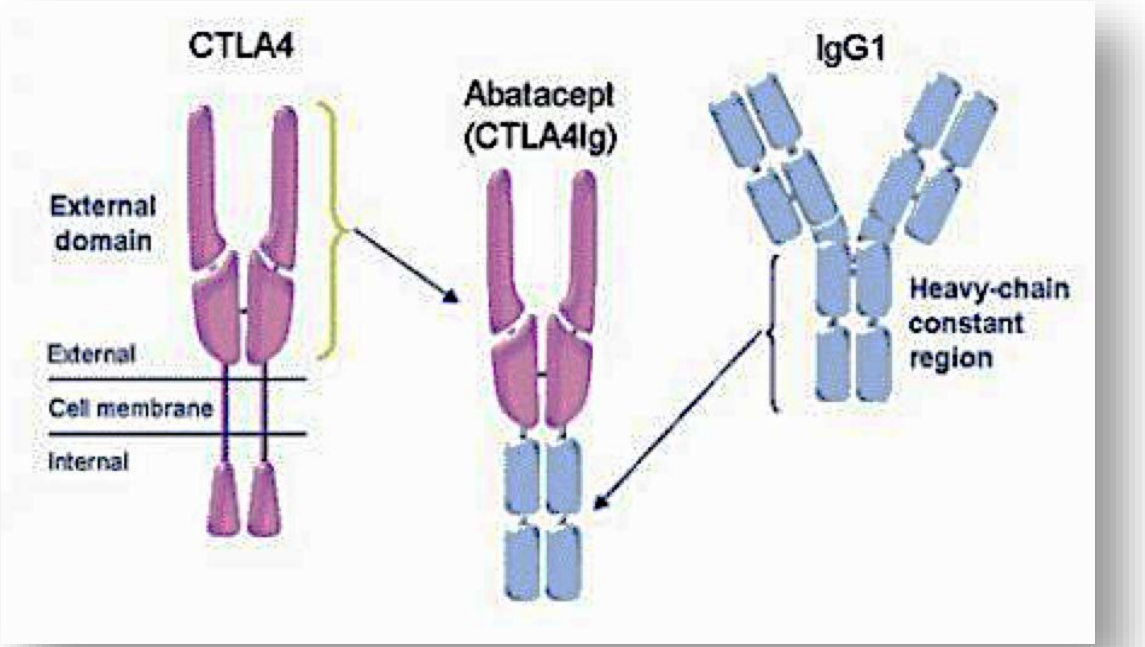


Inflammatory Bowel Diseases doi: 10.1097/MIB.0000000000000266


Healthy Control
T reg
T FH
CTLA4
High CTLA4 expression in T reg cells
Low T FH frequency
Control of Autoimmunity
LRBA or CTLA4 deficiency
T reg
T FH
CTLA4
↘ CTLA4 expression
↗ T FH frequency
Autoimmunity
LRBA or CTLA4 deficiency
+ CTLA4-Ig therapy
T reg
T FH
CTLA4
CTLA4-Ig
CTLA4-Ig supplementation
↘ T FH frequency
Control of Autoimmunity

An example of how fundamental investigations into the mechanisms of disease can lead to new treatment concepts

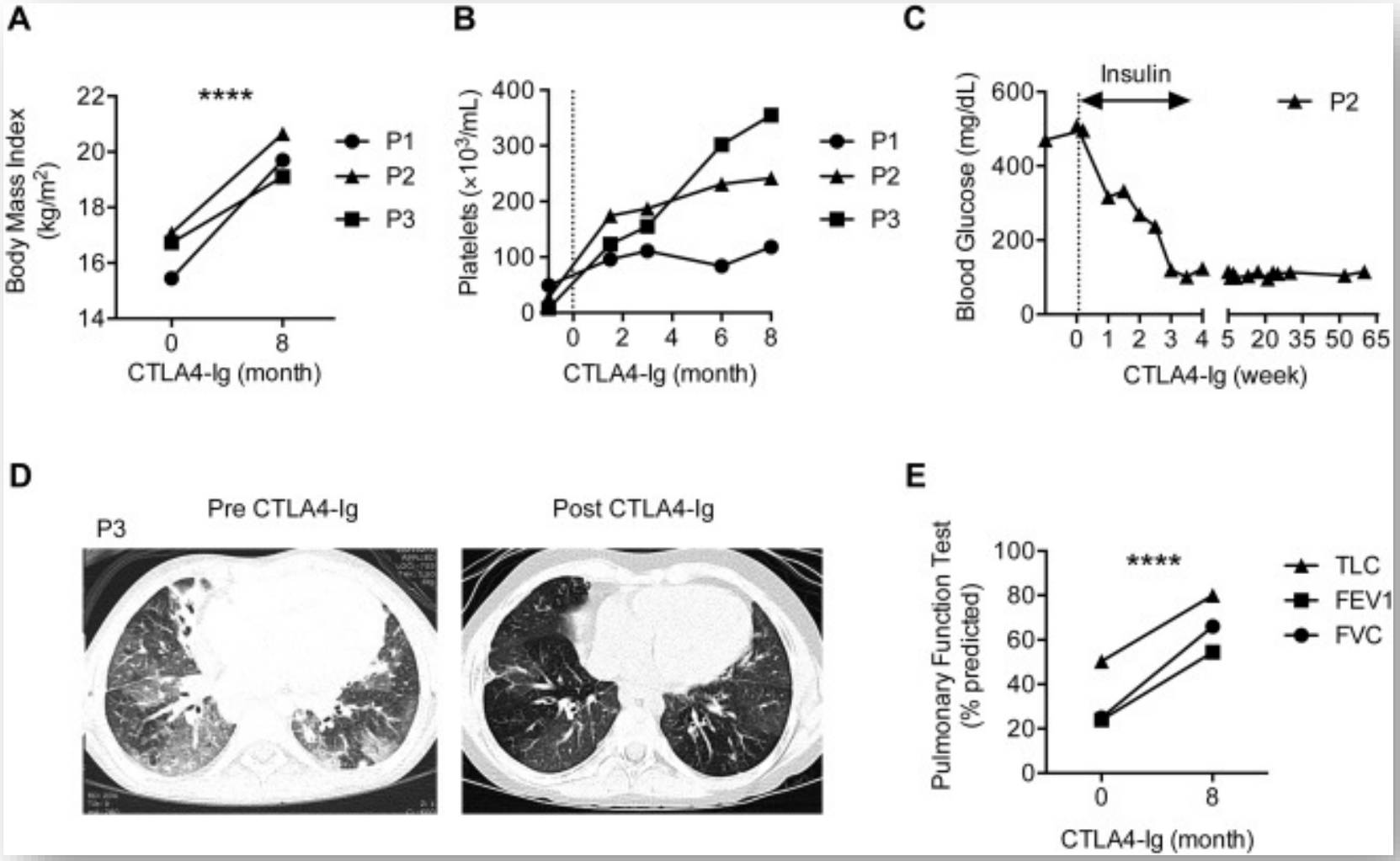
Abatacept a chimeric fusion protein that consists of the extracellular domain of the human CTLA4 molecule and the heavy-chain constant region of human IgG1



induces dramatic and sustained improvement of LRBA immunodeficiency

Science 2015: DOI:10.1126/science.aaa1663

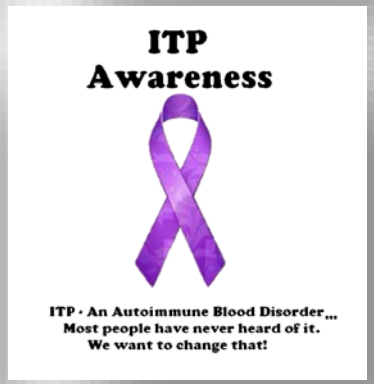
Resolution of exaggerated pulmonary helper T-cell responses after CTLA4-Ig treatment



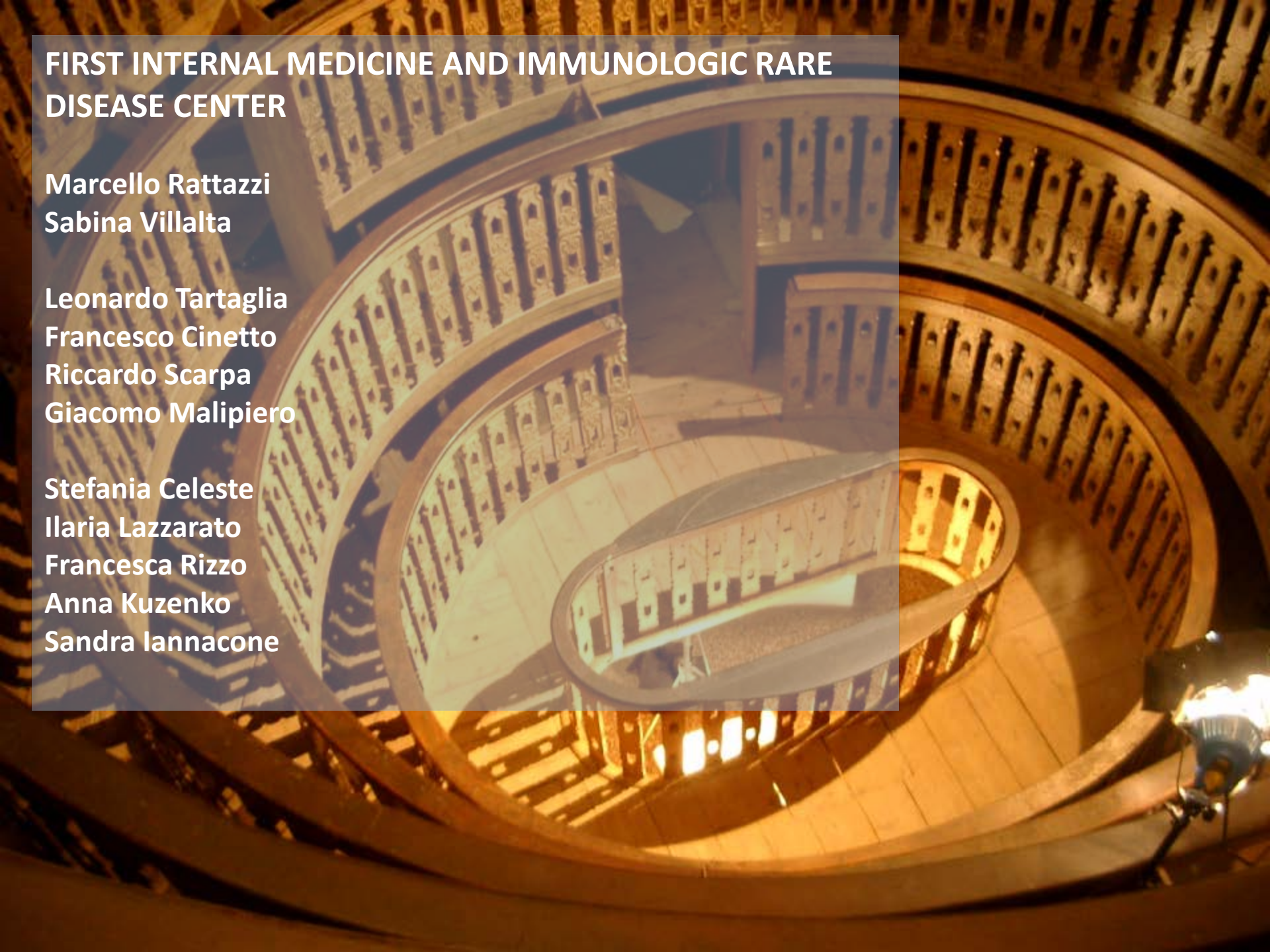
Take home message

- A early onset COPD or a multisystemic infiltrative granulomatous disease may occur in the context of PID
- Be careful the lung is one of the target organs. It is mandatory a global evaluation of the patient.
- Treatment should be considered if there is evidence of organ dysfunction, in particular in patients with progressive involvement
- Steroids are the initial drug of choice but response to treatment is often unsatisfactory;
- If this is the case consider immunosoppressants (azathioprine, mycophenolate) and/or biologic drugs (rituximab, infliximab)

Making the diagnosis: All that glitters is not…….



Do not forget PID and pick up the signs. A correct treatment is life-saving



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