Stanford Alliance for Primary Immunodeficiency

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Adult onset of primary immune deficiency

- Is it really adult onset?
- Adult onset genetic disorders
  - Hypomorphic mutations
  - Age-related unskewing of X-inactivation
  - Partial somatic reversion
- CVID
- Good Syndrome

Primary Immune Deficiency

- *Any* patient with severe, unusual, recurrent, or opportunitistic infections
- Any patient with autoimmunity
- Any patient with severe or unusual allergic diseases

Case

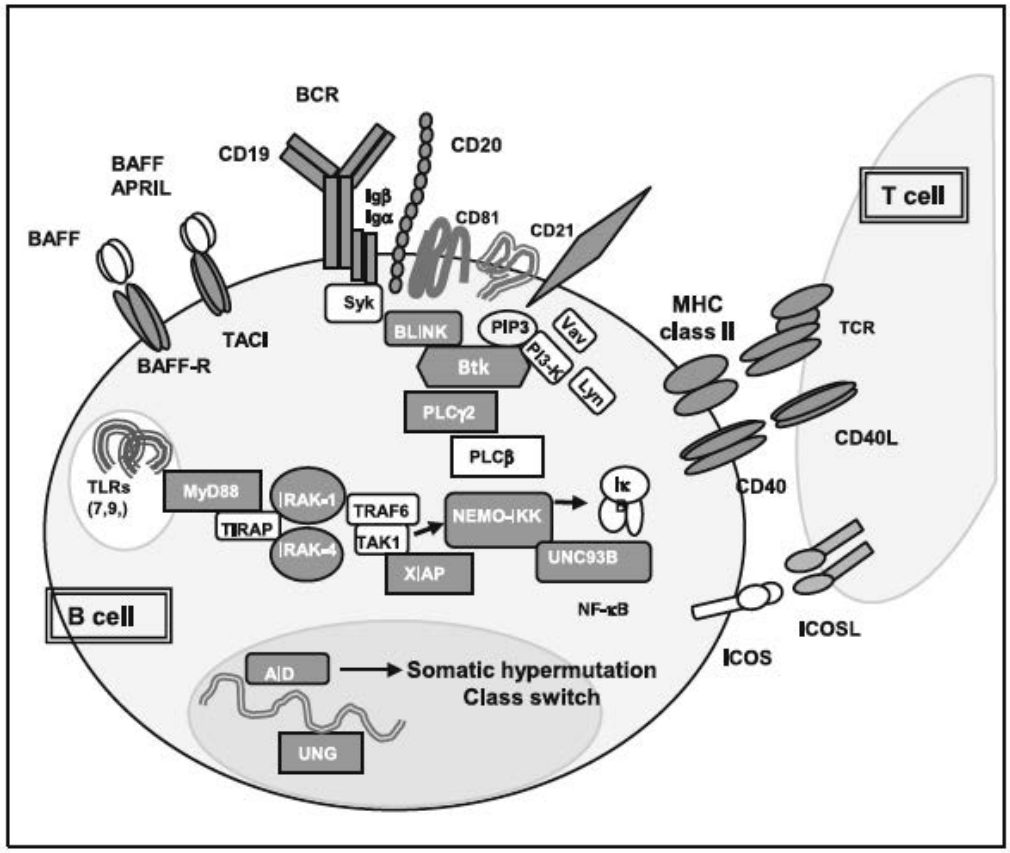
- 26 year old woman
- Environmental allergies as young adult
- Sudden onset left chest pain upon waking up
- Recent history of productive cough, not bloody, no trauma
- PMH history of anxiety treated with Effexor, few outpatient pneumonias treated with Zpak
- Tm 100.7
- No travel, no surgeries, no OCP, no CA
- FH nothing relevant
- SH lives with family

Work up

- WBC 24K, Hgb 12.9, Plt 305
- T 36.9, HR 122, RR 36, 95% on RA
- Exam ill appearing, tachypneic, lower lobe consolidation
- CXR showed a pneumonia with effusion
- Chest tube placed, cultured *H. flu*+
- Improved on Levofloxacin
- HIV negative
- IgG 0, IgA 0, IgM 0, IgE 0 (!)
- SPEP: hypo-proteinemia
- Bone marrow: normal

Common Variable Immune Deficiency

- Two peaks of incidence: age 6 and age 26 (80% over age 20). incidence 1/25000
- Diagnosis: hypo-IgG, usually IgA too, lack of specific antibodies
- Typically 2 or more protein vaccines (tetanus, diptheria) or polysaccharide vaccines
- **Defect in B cell memory and T cell function**



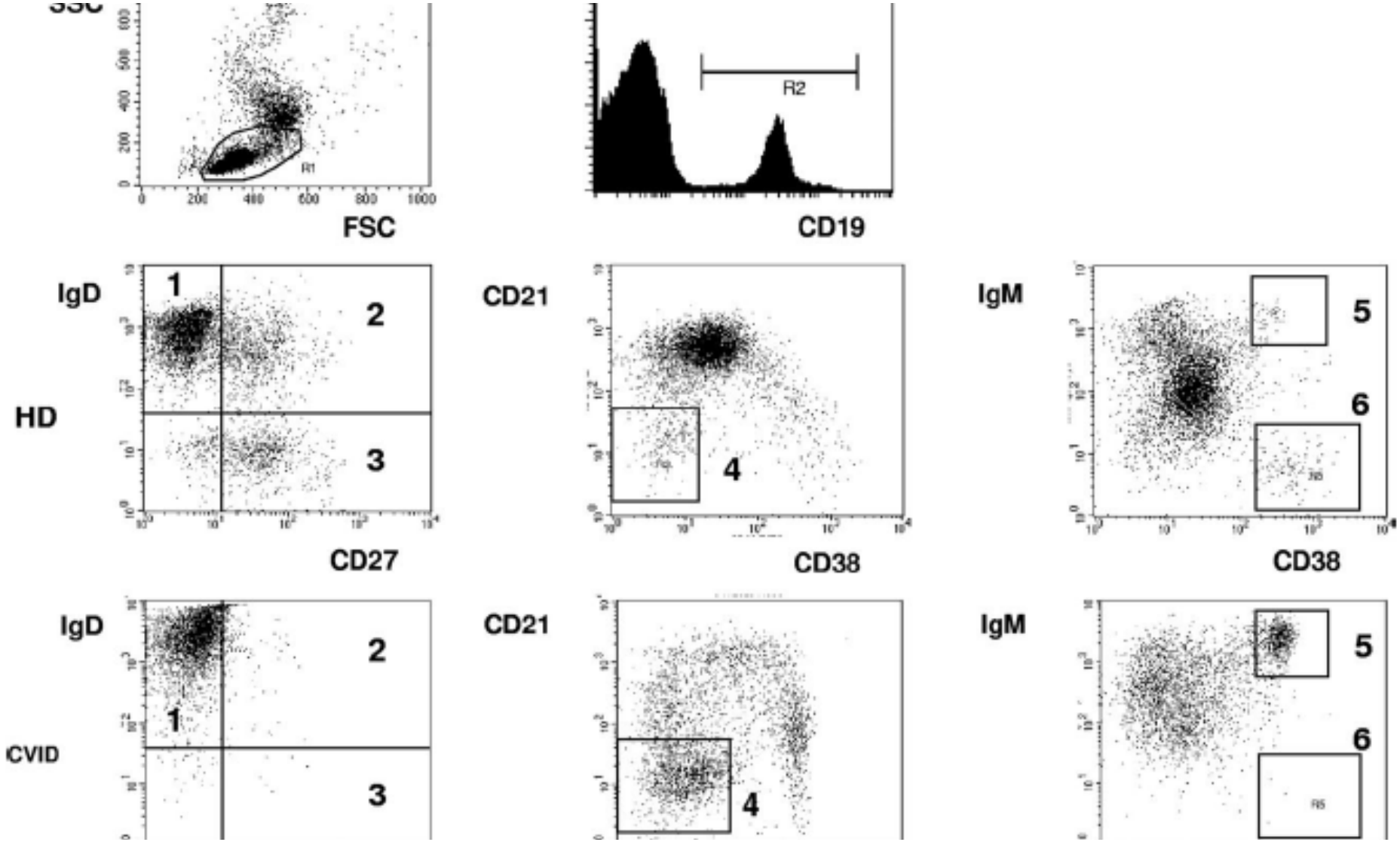
Cunningham-Rundles, Imm Res 2012

Table 1. Suggested template evaluation to verify lack of IgG antibody

Serum IgG < 150 mg/dL	Repeat serum immune globulins for verification; no antibody testing required
Serum IgG between 150 and 250 mg/dL	Repeat serum immune globulins for verification; Consider testing antibodies to tetanus and diphtheria or other protein based vaccines; optional, non conjugated pneumococcal vaccine and test 4 weeks after vaccination.
Serum IgG between 250 and 450 mg/dL	Repeat serum immune globulins for verification. Test antibodies to tetanus and diphtheria or other protein-based vaccines; also nonconjugated pneumococcal vaccine and test 4 weeks after vaccination.
Serum IgG between 450 and 600 mg/dL	Repeat serum immune globulins for verification. Test antibodies to tetanus and diphtheria and also other protein-based vaccines (measles mumps rubella, H zoster) also nonconjugated pneumococcal vaccine and test 4 weeks after vaccination

Cunningham-Rundles, Blood 2010

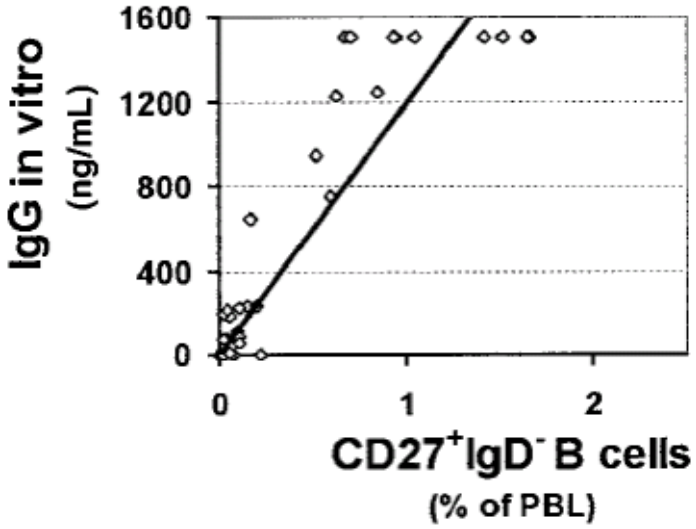
CVID: B cell subsets



Wehr, et al, Blood 2008

Memory B cells in CVID

- Warnatz et al, Blood 2002



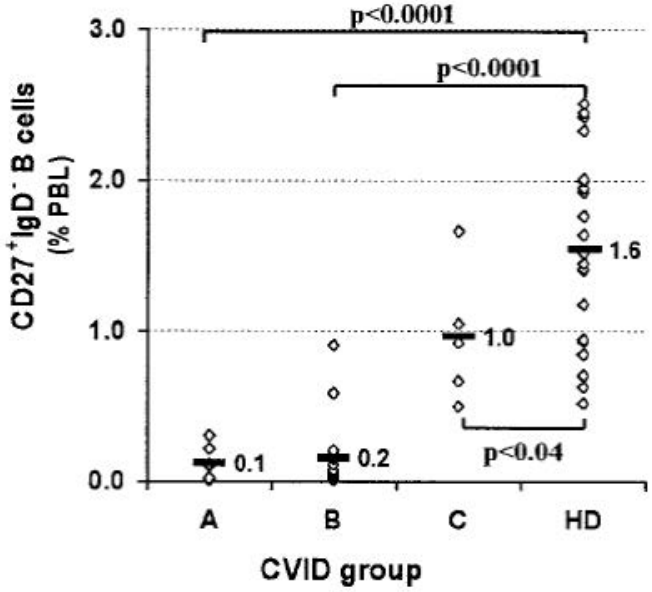
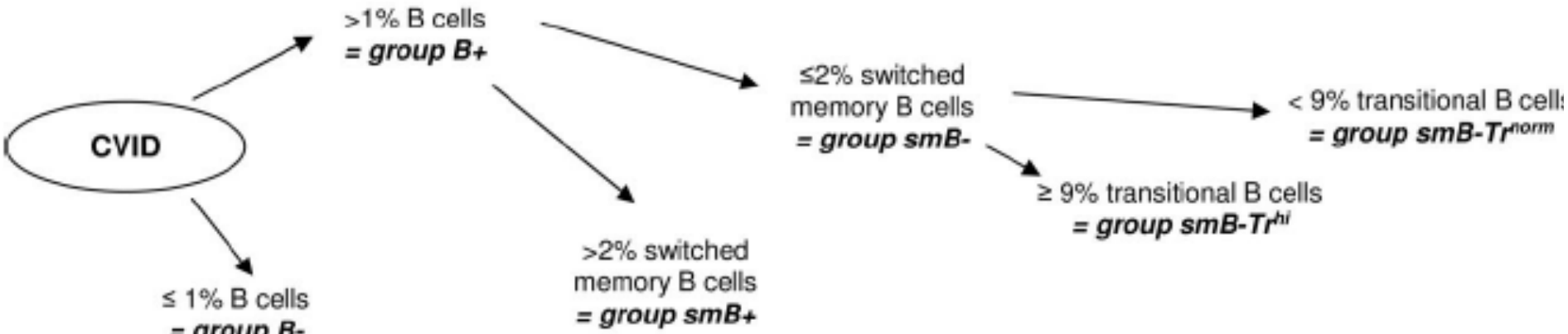


Table 4. New classification of CVID

CVID	Subgroup	No. of patients	CD19+ B cells, % of PBLs	CD27− IgM/D+, % of PBLs	CD27+IgM/D+, % of PBLs	CD27+IgM/D−, % of PBLs	CD21−, % of B cells	Bryant classification	Splenomegaly	Autoimmunity*	Vaccination†
Group I	a	10	4.9 ± 2.6‡	3.5 ± 1.8	1.2 ± 0.9	0.1 ± 0.1§	44.7 ± 11.0§	A/B	10/10 (100%)	6/10	Neg.
	b	13	7.8 ± 3.6	6.5 ± 3.2‖	0.9 ± 0.4‡	0.1 ± 0.1§	9.9 ± 5.7	A/B	5/12 (42%)	6/13	Interm.
Group II		7	12.6 ± 4.7‖	7.6 ± 4.3	3.8 ± 1.9‖	0.9 ± 0.4¶	12.6 ± 9.0#	C	1/7 (14%)#	3/7	Pos.
HD		22	7.7 ± 2.7	4.3 ± 1.6	1.6 ± 1.1	1.6 ± 0.6	7.0 ± 2.7	NA	NA	NA	NA

CVID classification

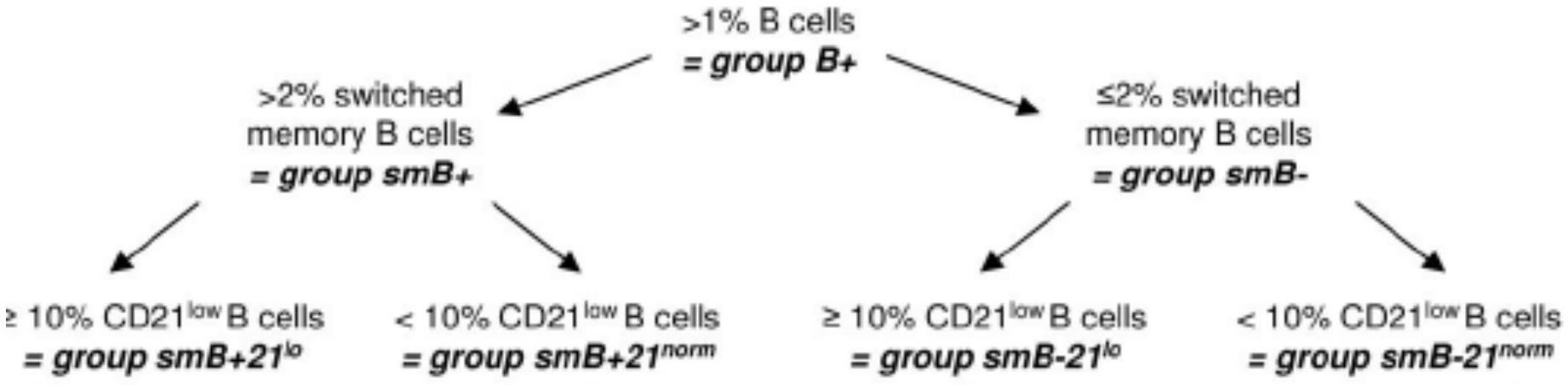
A **European consensus classification for CVID: EUROClass**



	B+	smB+	smB-	smB-Tr^{hi}	smB-Tr^{norm}
Number of patients	303	127 42% of total	176 58% of total	25 19% of smB-	108 81% of smB-
Incidence of (%)					
splenomegaly	115/284 pts./ 41%	28/116 pts./ 24%	**87/168 pts./ 52%***	13/24 pts./ 54%	55/107 pts./ 51%
lymphadenopathy	68/260 pts./26%	23/106 pts./ 22%	45/154 pts./ 24%	**12/21 pts./ 57%‡**	21/95 pts./ 22%
granuloma	35/303 pts./12%	5/127 pts./ 4%	**30/176 pts./ 17%+**	6/25 pts./ 24%	17/108 pts./ 16%
autoimmune cytopenia	43/213 pts./ 20%	22/117 pts./ 19%	36/169 pts./ 21%	4/21 pts./ 19%	24/93 pts./ 26%

Wehr, et al, Blood 2008

CVID classification



smB+21^{lo}	smB+21^{norm}		smB-21^{lo}	smB-21^{norm}
29 33% of smB+	60 67% of smB+	**Number of patients**	69 49% of smB-	71 51% of smB-
		Incidence of (%)		
13/26 pts./ 50%§	8/57 pts./ 14%	**splenomegaly**	**41/68 pts./ 60%¶**	30/71 pts./ 42%
4/23 pts./ 17%	10/50 pts./ 20%	**lymphadenopathy**	24/63 pts./ 38%	15/61 pts./ 25%
4/29 pts./ 14%‖	1/60 pts./ 2%	**granuloma**	**14/69 pts./ 20%#**	11/71 pts./ 15%
3/20 pts./ 15%	4/40 pts./ 10%	**autoimmune cytopenia**	16/60 pts./ 27%	14/59 pts./ 24%

Wehr, et al, Blood 2008

CVID complications

Table 2. Summary of complications and incidence*

	Numbers	Percentage
Infections	428	90
Autoimmunity	97	25
Lung impairment	88	24
Gastrointestinal disease	51	14
Malabsorption	31	5
Lymphoid malignancy	36	10
Previous splenectomy	31	8
Granulomatous disease	31	8
Other cancers	21	6

*On the basis of on a cohort of 476 subjects.

Cunningham-Rundles, Blood 2010

Autoimmunity in CVID

Table 3. Hematologic autoimmunity*

Condition	Number	Percentage
Thrombocytopenia	44	9.0
Evans syndrome	11	2.3
Acute hemolytic anemia	8	2.0
Anti-IgA antibodies	6	1.0
Neutropenia	2	0.4
Pernicious anemia	2	0.4

IgA indicates immunoglobulin A.
*On the basis of a cohort of 476 subjects.

Cunningham-Rundles, Blood 2010

Autoimmunity breakdown

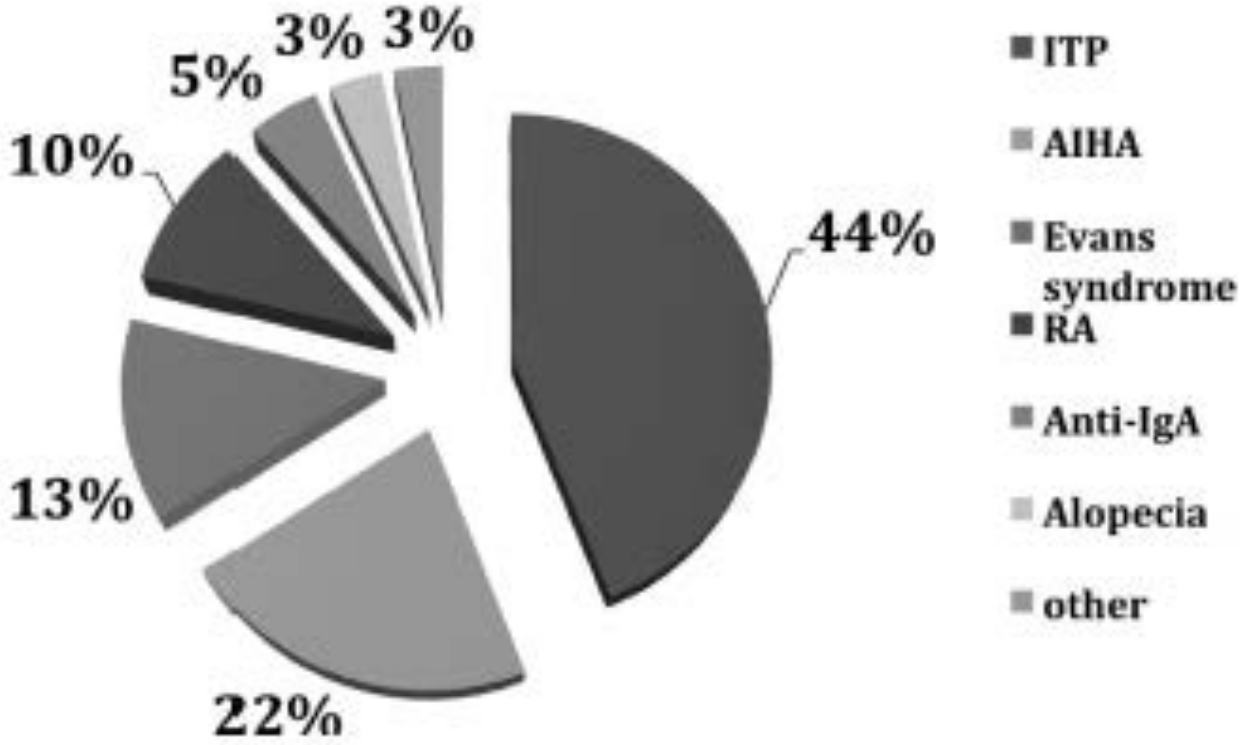


Figure 1. Autoimmunity in CVID. Of 473 patients with CVID, 134 (28.6%) had autoimmunity.[6] The main autoimmune diseases are shown here. In the category "other" are included neutropenia, pernicious anemia, anticardiolipin Ab, antiphospholipid syndrome, diabetes mellitus, juvenile rheumatoid arthritis, uveitis, multiple sclerosis, systemic lupus erythematosus, autoimmune thyroid disease, lichen planus, vasculitis, vitiligo, and psoriasis. ITP indicates immune thrombocytopenia; AIHA, autoimmune hemolytic anemia; RA, rheumatoid arthritis.

Cunningham-Rundles, ASH 2012

Splenectomy in CVID

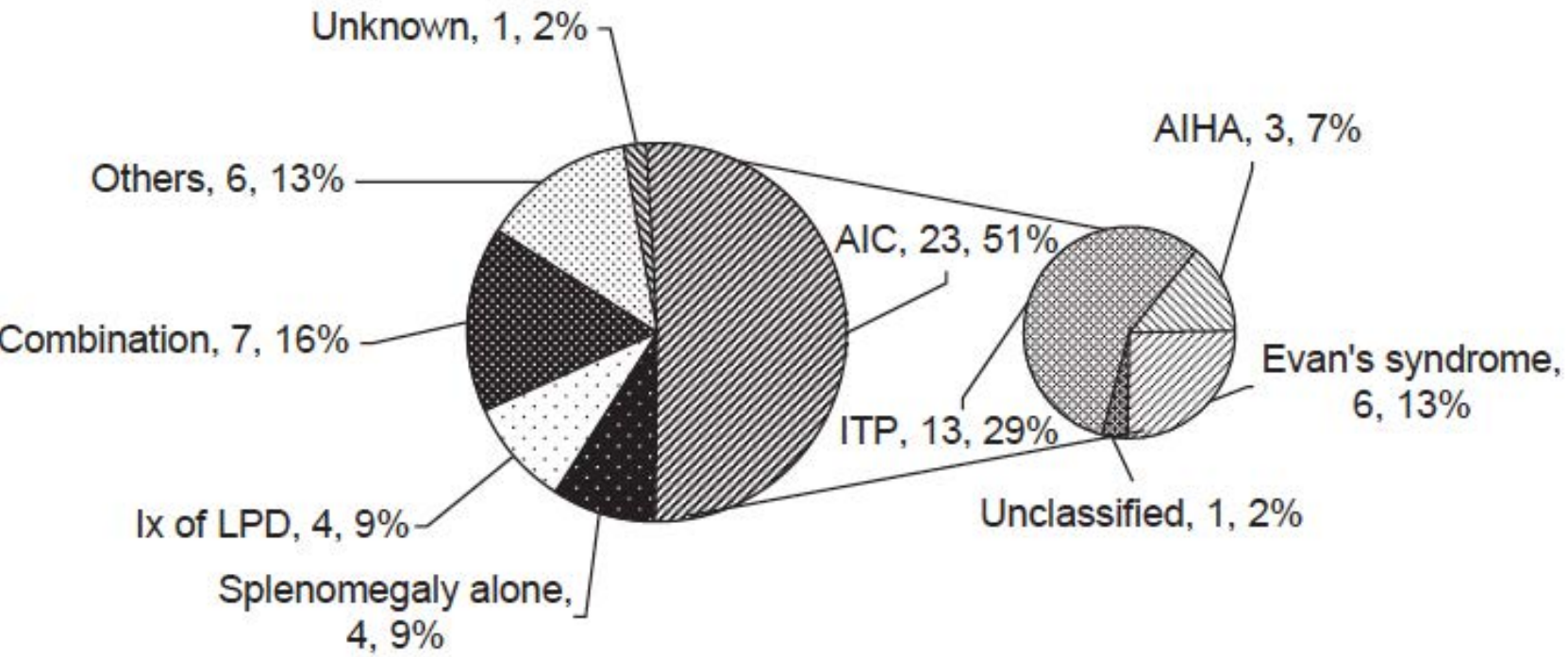


Table 3. Summary of 26 histological reports.

Histological findings	Frequency (of 26)
Granulomatous inflammation	13
Congestive red pulp	8
Lymphoma/lymphoma-like	Highly malignant B cell NHL × 1 Plasmoblastic lymphoma × 1 Low-grade B cell lymphoma × 1 Castleman's disease-like × 1
Follicular hyperplasia	3
Atrophic germinal centres/white pulp	3

Approximately 78% effective for AIC across 6 studies

Wong, Clin Exp Imm 2012

Granulomatous complications

Table 3. Granulomatous disease by location

Tissue location	No. (n = 46)
Lung	20
Multiple locations (ie, liver, lung, and spleen)	7
Lymph node	6
Liver	4
Skin	3
Spleen	2
Bone marrow	1
Brain	1
Neck tissue	1
Operative site	1

Resnick et al, Blood 2012

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IVIg Immune Reconstitution Treatment Alleviates the State of Persistent Immune Activation and Suppressed CD4 T Cell Counts in CVID

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