



# XVIII IPOPI GLOBAL PATIENTS' MEETING

an **IPOPI** event

16-19 OCTOBER 2024  
MARSEILLE, FRANCE

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# PIDs/SIDs what are the commonalities?

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## overview

vignette #1: primary vs secondary antibody deficiency

vignette #2: primary immune deficiency masquerading as SID, ADA deficiency

vignette #3: primary immune deficiency masquerading as SID, X-linked lymphoproliferative syndrome 1

vignette #4: primary immune deficiency masquerading as SID, unknown genetic cause

vignette #5: a case of severe and fatal secondary immune deficiency

# What are immune deficiencies?

## impaired immune response:

- to pathogens : susceptibility to infections
- impaired regulation (of immune cell proliferation)
- autoimmunity / inflammation
- risk of cancer

## primary immune deficiencies: > 450 syndromes (IUIS classification)

- first manifestation: infection in  $\approx$  70%
- syndromal manifestations

## secondary immune deficiencies: mostly Ab deficiency

- first manifestation: usually not infection
- related to the cause of SID: malignancy, autoimmune, therapy related, ...

# Clinical vignette #1 (1)

**Secondary** vs **primary** antibody deficiency

45 year-old female diagnosed with **lymphocytic lymphoma** ( $\simeq$  CLL), enlarged lymph nodes

4 cycles of **rituximab** (anti B-cell antibody)

develops frequent ENT infections

**low antibody levels**: gammaglobulins 2.5 g/l (N 7-8 g/l)

started on **Ig replacement therapy (IgRT)**

progression of lymphoma: **ibrutinib (BTK inhibitor)**

complete response. Discontinued after 3 years

> 2 years later, in remission, requires IgRT

## Clinical vignette #1 (2)

48 year-old male, **no prior medical history**

2001: **pneumonia**. **Normal Ig levels:** IgG 9.9, IgA 2.5, IgM 0.56

2002: **persistant bronchitis**. **Low Ig levels:** IgG 5.5, IgA 0.54, IgM <0.04

started on **IgRT**.

immunological work-up: normal T-cells, B-cells in the low normal range

**no genetic cause of PID**

latest Ig levels: IgG (on IgRT), IgA 0.06, IgM <0.04

diagnosis of **common variable immune deficiency** (CVID, most common PID in adults)

without further complications

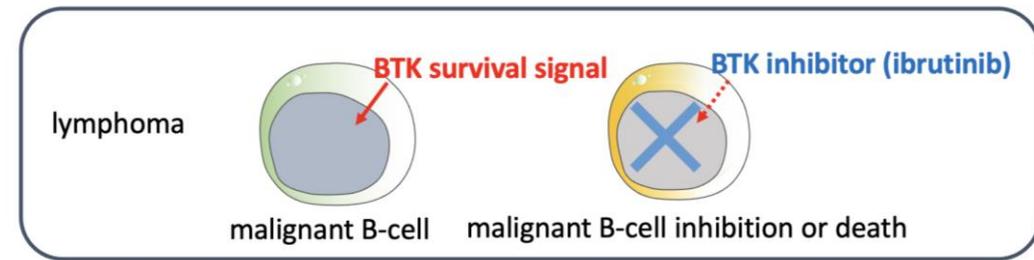
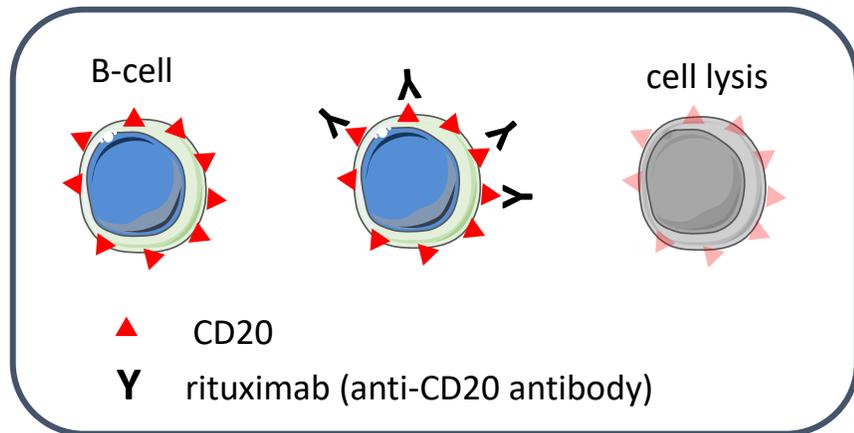
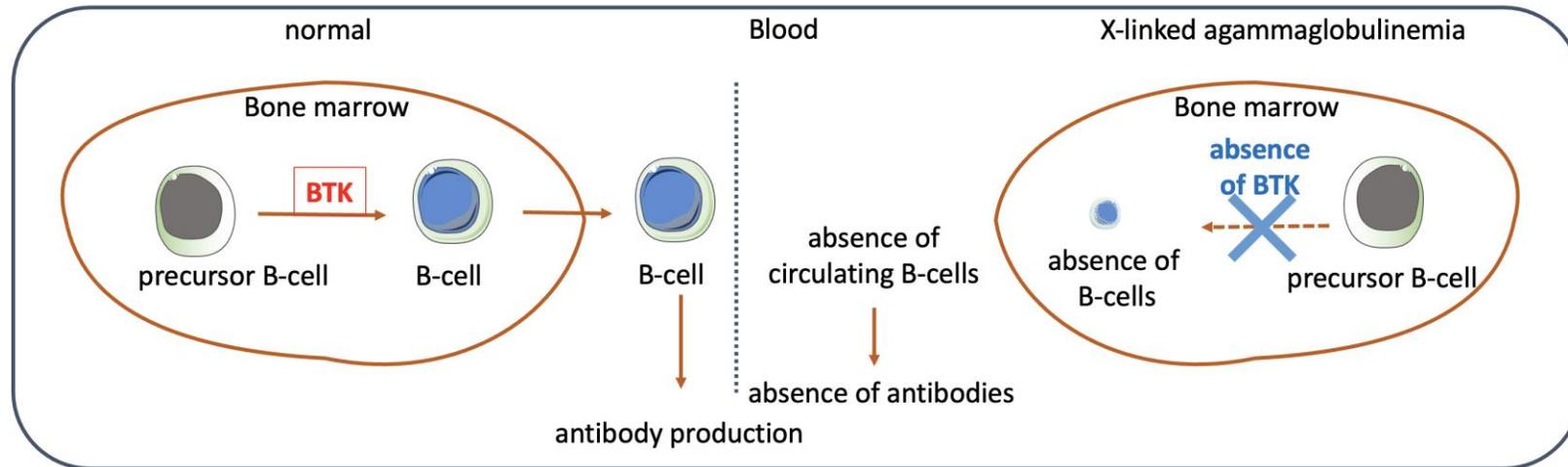
## Clinical vignette #1 (3)

primary vs secondary antibody deficiency

most common immune deficiency

	primary	secondary
agammaglobulinemia	XLA (bruton)	rituximab
→ global hypogammaglobulinemia	CVID	CLL, myeloma, chemo, rituximab
partial	other PAD	CLL, myeloma, chemo, rituximab
hyper-IgM	CD40L	
normal Ig / impaired response	various	chemo, rituximab, lymphoma

**antibody deficiency in B-cell malignancies** often precedes therapy and can be aggravated by the latter



pharmacologic inhibition ≠ genetic disease:  
 no B cell or antibody deficiency in patients treated with iBTK

# PID masquerading as SID

by convention, diagnosis of PID requires the exclusion of patients with prior cancer treatment (SID)

does it always hold ?

## Clinical vignette #2 (1)

**index patient:** 25 y old male, of italian and Vietnamese descent

no prior medical history other than **recurrent bronchitis** in the context of asthma

developed since his early twenties recurrent and **extensive warts** (HPV27 and 57)

normal monocytes, **low lymphocytes (0.5 G/L)**, CD4/CD8 and naïve T-cells, low B-cells, low NK cells.

IgG 10 g/l, IgA 0.55, **IgM 0.12**.

**older brother:**

treated 10 years before for **B-cell lymphoma** (autologous stem cell transplantation).

no significant medical history prior to the lymphoma

developed a few years **after transplantation, recurrent bronchitis and warts** (to a lesser extent than the index).

normal lymphocytes, low CD4, high CD8, low B-cells, low NK cells,

IgG 20, **IgA <0.05**, IgM 0.66

healthy younger sister

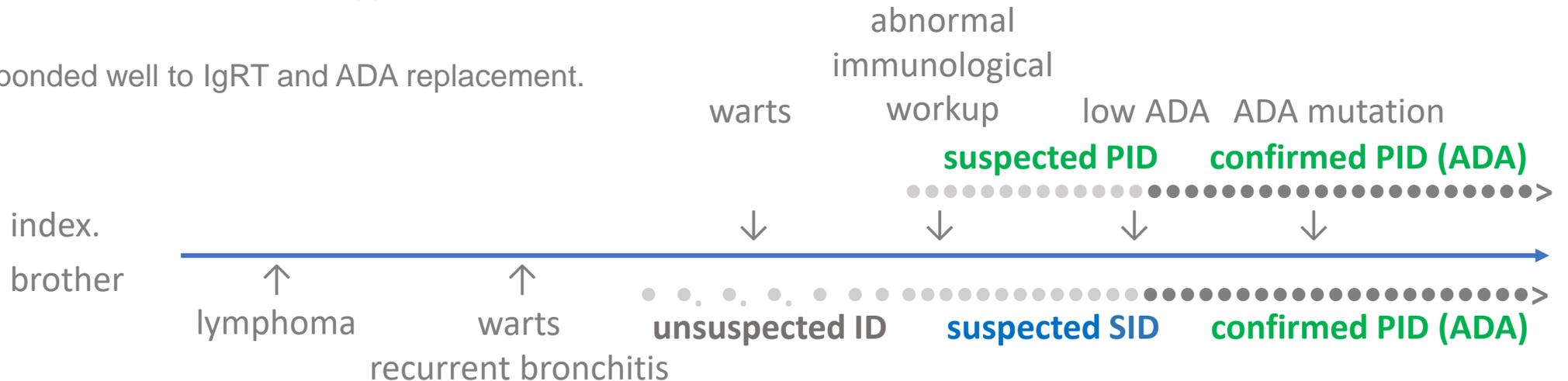
# Clinical vignette #2 (2)

presentation consistent with **combined immune deficiency** (low T-cells, extensive warts)

**undetectable ADA (adenosine deaminase)** in index patient, very low in brother  
 both were found to harbor **bi-allelic mutation in the ADA gene**.

conclusion: **adult-onset ADA deficiency**  
 in the index patient (Warts, abnormal B-cell response, lymphopenia)  
 brother: preceded 10 years before by aggressive lymphoma.

follow-up: both responded well to IgRT and ADA replacement.





## Clinical vignette #4

index patient: female born in 1973

no prior medical history before 2008

2008: classical **Hodgkin's lymphoma**, chemotherapy

2015: **EBV+ diffuse large B-cell lymphoma**, chemotherapy followed by autologous stem cell transplantation

2016: pancytopenia following parvovirus B19 infection. Recovers after high dose immunoglobulins

2017: **recurrent bronchitis**

2017: **Low IgG (3.29 g/l) and low IgA (0.13 g/l)** ; normal IgM (0.68 g/l)

2017: Normal T-cells. **Normal-low B-cells, low memory B-cells.**

2017: **started on IgG replacement** therapy, clinical improvement

2023 : after summer discontinuation, IgG 3, IgA <0.05, IgM <0.18

reason for **high suspicion of PID** despite absence of genetic diagnosis?

**2 ≠ lymphomas**, second lymphoma **EBV-associated**

**progressive** antibody deficiency, **persistant** over several years (unusual for chemo even with rituximab)

## Clinical vignette #5 (1)

67 year-old male

2007 : diagnosed with **chronic lymphocytic leukemia** (lymphocytes 14 G/L). Normal Ig levels. **Binet stage A**. No therapy required

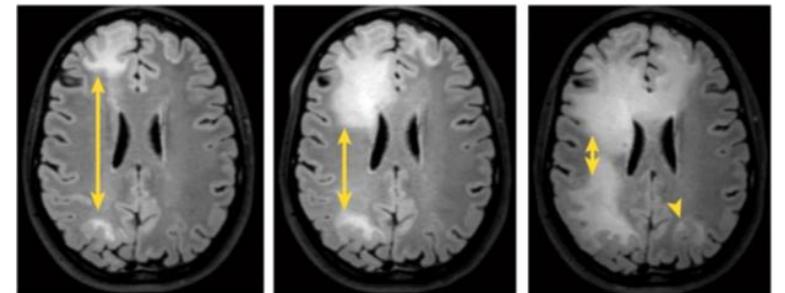
2016 : lymphocytes 26 G/L

2018 : lymphocytes 18 G/L . Slightly decreased Ig (gammaglobulins 5.5 g/L)

2021 : lymphocytes 4.8 G/L. **Gammaglobulins 3.7 g/L. No symptoms.**

12/2021 : cognitive and motor impairment.

Diagnosis of **progressive multifocal leukoencephalopathy** (JC virus) leading to death



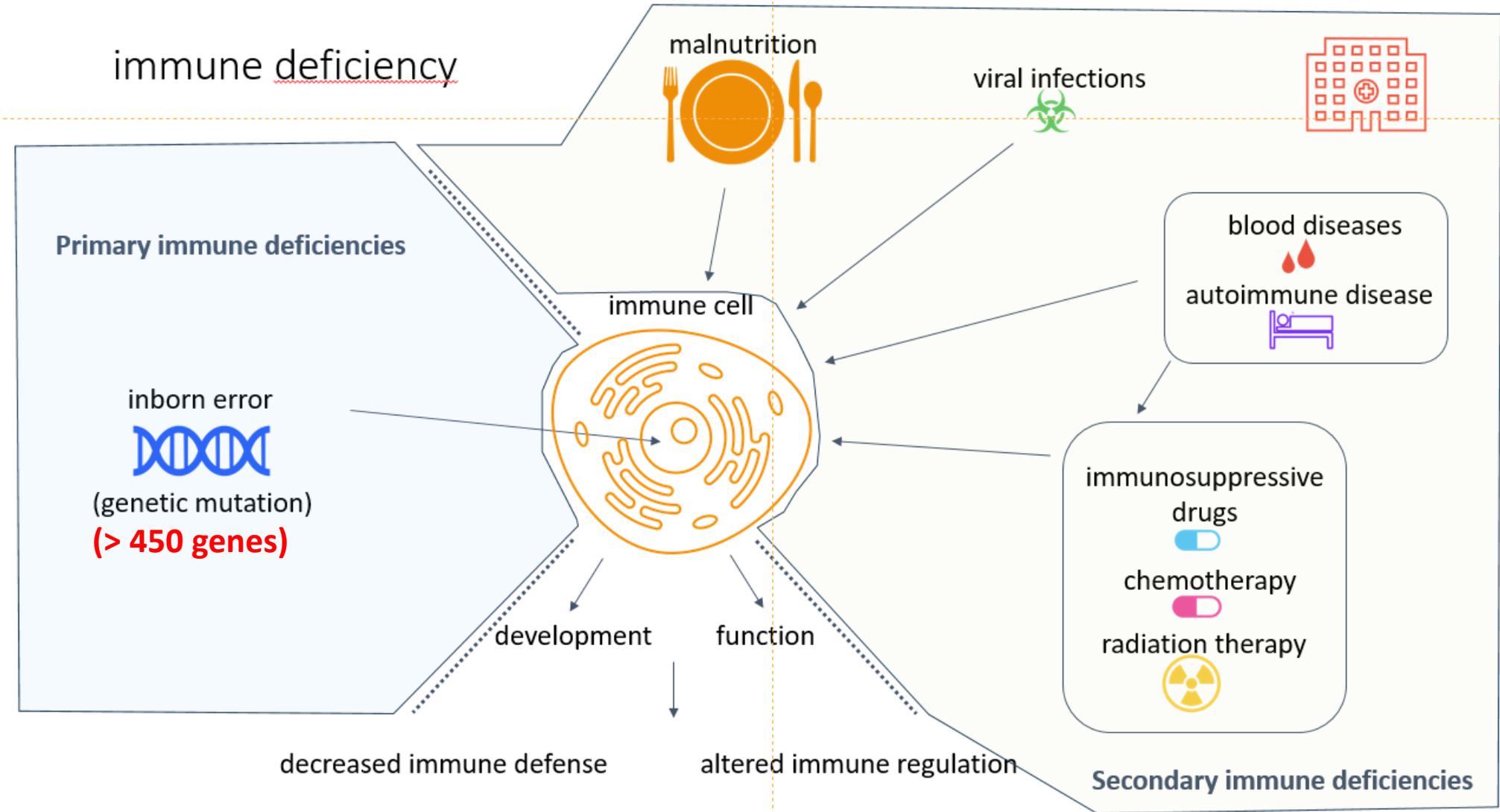
## Clinical vignette #5 (2)

untreated CLL over the course of 14 years: **very common**

**spontaneously** develops JC positive PML: **very rare, fatal opportunistic infection** associated with profound immunodeficiency (HIV, transplantation)

no other evidence of severe immunosuppression (very common moderate asymptomatic antibody deficiency) prior to PML

**profound immune deficiency induced by CLL itself**



# Comparing PID and SID

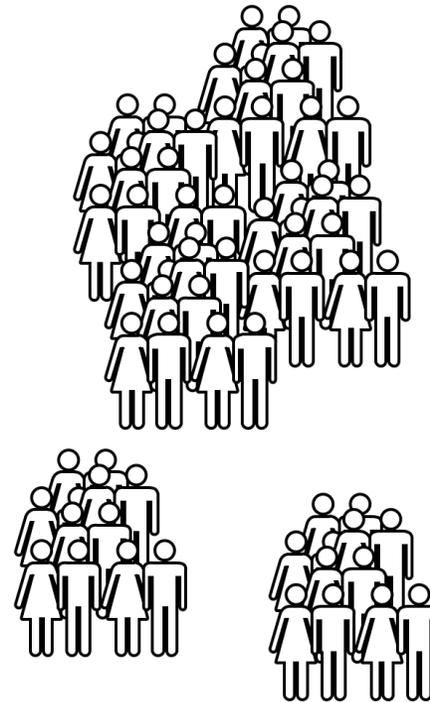
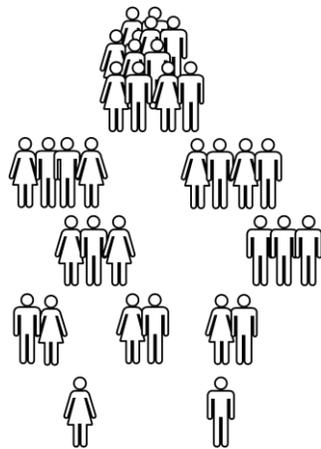
70 million people living in France

- ≈ 7,000 patients with PID (10/100,000)
- ≈ 500 new patients/year
- ≈ 4,000 patients with a known mutation

3,8 million living with cancer  
≈ 400,000 new patients with cancer  
+ autoimmune disorders and IS treated

how many with SID ? (X30 ?)

10 large categories  
> 450 genetic conditions  
**large number of clinical phenotypes**  
few patients / category



fewer primary causes  
**fewer clinical phenotypes**  
many patients / category

# Conclusion

SID may be overlooked (mild)

SID can be severe

SID can turn out to be PID (even without a genetic diagnosis): awareness

SID largely outnumber PID: access to immunoglobulin substitution

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