2019 FOCUSED MEETING OF THE
EUROPEAN SOCIETY FOR IMMUNODEFICIENCIES

BRUSSELS, BELGIUM | SEPTEMBER 18-21, 2019

MALIGNANCY AND PID

Pitfalls in PID: Expect the unexpected

Faculty Disclosure

X	No, nothing to disclose
	Yes, please specify:

PITFALLS IN PID: EXPECT THE UNEXPECTED

- First daughter of non-consanguineous parents, no relevant family history.

- 2 months old (positive findings):

- **Lymphoproliferation** (cervical lymphadenopathy and splenomegaly) +

autoimmune pancytopenia (Bone marrow aspirate: hypercellular, Coombs test +)

without response to IVIG.

- **CMV: viruria +, IgM -, IgG +, whole blood PCR negative** (Mother: CMV -). No other infectious triggers detected.

- Positive antithyroid autoantibodies and other signs of autoimmunity (ASMA +, anticardiolipin IgG and IgM).

Starts treatment with steroids + gancyclovir with a good response.

Question 1: What's your initial diagnosis?

a) Possible SCID

b) Possible immune dysregulation: ALPS

c) Possible immune dysregulation: HLH

d) Lymphoma

Immunological assessment

Antibody-mediated immunity

*	2 mo	5 yo
IgG (mg/dL)	**1970 (> 2 DS)**	752 (normal)
IgA (mg/dL)	**242 (> 2 DS)**	70 (normal)
IgM (mg/dL)	**400 (> 2 DS)**	**750 (> 2 DS)**
IgE (UI/ml)	**-**	<5 **(<2 DS)**
% CD19 (/mm^3)	13%: **525** (1080-2544)	**3%: 93** (411-658)
% CD19+ CD27+	-	**2.97%**
% CD19+ CD27+ IgD+		**1.83%**
% CD19+ CD27+ IgD-		**1.14%**
% CD19+ CD10+		**49%**
% CD19+ CD21+		75% **CD21low: 45%**
Anti-HBS Anti-HAV ATT (UI/ml) IgG Anti-Measles IgG Anti-Rubella		**-** **-** 0,9 **-** +
Antipneumococcus (mg/L)		**<3**
Allohaemagglutinins		**1/1**

Cell-mediated immunity

T Cell Subsets	2 mo	5 yo
ALC (/mm^3)	4046 (2920-8840)	3102 (2400-5810)
% CD3 + (/mm^3)	58% : **2346** (3302 – 4050)	92%: 2853 (2054-3169)
% CD4+ (/mm^3)	32.5% : **1314** (2059 – 2932)	52%: 1613 (1129-1581)
% CD8+ (/mm^3)	23%: 930 (850-1394)	34%: 1054 (711-1121)
%CD3+ HLADR+	41% (7.9-16.7%)	**25%** (9.7-20.6%)
% CD4+ CD45RA+	-	**19%** (65-80.6%)
%CD4+ CD45RO+		**91%** (31.8-51.4%)

NK- mediated immunity

NK	2 mo	5 yo
% CD16/56 (/mm^3)	21%: 850 (336-897)	**3%: 93** (246-461)

ALPS criteria

ALPS criteria	2 mo	1 y 9 m	2 y 6 m
% αβ DNTs	2.76% (B220: 65%)	3.04% (B220: 52%)	-
Vitamin B12 (pg/ml)	-	>2000 (supplemented)	-
sFasL (pg/ml)	**347** (<200 pg/ml)	-	-
Fas-mediated Apoptosis	-	Normal	-
Fas sequencing (germline)	-	**Normal**	-
Fas sequencing (somatic)	-	-	**Normal**

ALPS-like syndromes

ALPS-like syndromes	3 yo
Monocyte count	No persistent monocytosis
LRBA expression	Normal
CTLA-4 expression	Normal
CD25 expression	Normal

Follow-up

- Multiple relapses of autoimmune cytopenias.
- 1 yo 4 m: Acute toxoplasmosis (IgM +). Normal fundus.
- 1 yo 9 m: **Autoimmune hepatitis**
- 2 yo: **Acute right facio-brachio-crural paresis + acute bilateral coriorretinis** (under low dose hydrocortisone).

*CNS biopsy: CD8+ lymphohistiocytic infiltrate with calcifications. **PCR EBV and HHV-6 +**

Persistent positive serology for *T. gondii
(IgM and IgG)

Starts treatment for CMV and Toxoplasmosis.

Continues with valgancyclovir prophylaxis until 5 yo

Starts sirolimus and G-CSF → Normal blood counts.

- 5 yo: Persistent thrombocytopenia refractory to immunosuppresion (IV IG, sirolimus, steroids, rituximab) and antiviral treatment (CMV viremia)

Starts HLA typification: identical brother, with persistent mild hepatitis (unknown etiology)

Genetic diagnosis

Possible genes?

PIK3R1, PIK3CD, STAT3, CTLA4, LRBA, NFKB1, NFKB2, TNFSF6, TNFRSF13C, CASP8, CASP10, FADD, TNFRSF13B, CD27, FOXP3, KRAS, NRAS, RAG1, RAG2, STAT1, TPP2, CD25

Question 2: What would be your therapeutical strategy?

1) **Continue immunosuppresion and wait for genetic diagnosis.**

2) Don’t wait for genetic diagnosis: HSCT with HLA-identical brother

3) Don’t wait for genetic diagnosis: HSCT with MUD.

4) Don’t wait for genetic diagnosis: HSCT with haploidentical donor

WES:

Heterozygous variant in ***CARD11***

(deletion + inframe insertion in exon 6)

c.732_733insATGGAGGAGGAATGTAAG

(p.L245delinsMEEECKL)

Sanger sequence of *CARD11* (brother and parents): normal.

Confirmed by Sanger sequencing

Question 3: How do you interpret these results?

1) The variant is not relevant for the clinical picture.

2) **The variant could correspond to *CARD11* CID.**

3) The variant could correspond to *CARD11* LOF dominant negative

4) The variant could correspond to *CARD11* GOF (BENTA disease)

Follow-up

- The patient persisted with severe thrombocytopenia and multiple infectious complications (esophageal candidiasis, BK cystitis, HHV-6 reactivation).

Develops respiratory distress (CT: bilateral micronodules) and acute encephalitis (CT: multiple hypodense bilateral lesions)

Deceased due to multiorgan failure

PCR + for *Toxoplasma gondii* in whole blood and BAL