- A 6 years old boy suspected to PID with chronic diarrhea

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- A 6 Y.O boy
- Consanguineous parent (cousin)
- He has one sister older than him without any remarkable history

The presentation is started from the 8th hospitalization 3 month ago

- A6 Y.O boy suspected to primary immunodeficiency was admitted due to fever and cough.
- He had close contact with his father with positive covid-19 PCR
- He had positive covid-19 PCR and remdisivir was started
- At the 6 day of admission he developed watery diarrhea
- His diarrhea lasted for about 3 months and according to his history of immunodeficiency , the etiology was deeply investigated

The remarkable finding of his assays

- GI tissue PCR: CMV+
- Blood CMV PCR: weakly positive

- Val ganciclovir was started
- After 1 week diarrhea was significantly diminished.

- Let`s start with his significant past medical history

First admission: (15month old)

- He was first admitted in 15 month age, due to seizure+ fever and watery diarrhea
- He had mild splenomegaly at that time

- Without any evaluation he was discharged with febrile convulsion diagnosis

second admission (18 month old)

- 3 month later he was admitted due to petechial purpura and low platelet
- **ITP** was diagnosed and IVIG and prednisolone was started

Third admission (2 years old)

- 4 month later when he was 2 years old
- He developed fatigue and pallor

- RETIC=9%,,,HB=6,,ESR=110
- He had splenomegaly
- He was admitted to rule out: leukemia or MDS

First assay	
Peripheral blood	Bone marrow
WBC 3670	Blast 9%
RBC 3.91	Promyelocyte9%
Hb 11.1	Myelocyte13%
Plt 138000	Metamyelocyte 5%
Band 1% Segment 8% Lymphocyte 70% Monocyte 21%	Band 3% Segment5% Lymphocyte5%
	Cellular marrow with shift to lef

Second assay	
Peripheral blood	Bone marrow
WBC 3230	Blast 2%
RBC 3.62	Promyelocyte9%
Hb 10	Myelocyte14%
Plt 181000	Metamyelocyte 7%
Band - Segment 5% Lymphocyte 60% Monocyte 26% Eosinophil 9%	Band 10% Segment 10% Lymphocyte11%
	Cellular marrow with increased number of immature precursor cell

Bone marrow biopsy	
CD34	Positive in 3-4 cluster of immature precursor cells
CD117	Positive in scattered marrow cells
TdT	Positive in some cluster of immature precursor cells
CD20	Positive in some mature lymphocytic and immature cells
CD3	Positive in some mature lymphocytic and immature cells

BCR-ABL	undetectable
ETV6-RUNX1	undetectable
AML1-ETO T(8-21)(q22-q22)	undetectable

he had 3 times bone marrow aspiration

BONE MARROW FLOWCYTOMETRY	HLA-DP,DQ, DR	CD2	CD3	CD4	CD5	CD7	CD8	CD10	CD13	CD14	CD19	CD20	CD33	CD34	CD64	CD 117	CD4/ 8	CD2/ 19	CD3/ HLADR
1	35.6	25.5	61.9	33.3	41.7	31.1	39.5	24.4	25.9	2.4	36.5	16.8	15.5	8.7	23.4	16.1	8.3	3.2	13.5
2	22	9.5	25		12.5	14.7		5.1	10	9	10.7	9.3	8.6	1.6	34.2	3.6		0.1	4.4
3	34.4	12.3	16.3	10.5	12.7	11.7	7.4	5	4.3	5	21.3	14.4	5.8	5.5	26.5	2.9	1	0.6	3.5

- MDS and leukemia was excluded .
- ALPS was suggested for him.

Forth admission (2 years old+10 day)

- He returned to the hospital 10 days later with: cough, respiratory distress

- CXR: normal
- Antibiotic + supportive care
- he was discharged

- He was treated with the diagnosis of ALPS until 3y 6m
- He received 2 doses of rituximab+ many courses of prednisolone
- Some course of azathioprine and irregular IVIG

5 admission (3 years +6 month)

- At the age 3.5 y after the second dose of rituximab
- he was admitted just one day after the injection due to:
- Fever, weakness, confusion and back pain
- Antibiotic and acyclovir was started
- Brain MRI: periventricular masses were reported
- Brain mass biopsy: non specific inflammation,
- negative for malignancy
- Negative for: TB, toxoplasma, JC virus and fungal

- During this admission he had not respiratory symptoms
- But chest CT scan showed: a non erosive mass with internal echo was reported in the posterior mediastina beside T7-8

- Biopsy done, we have tow different report

- 1- necrotizing granulomatous inflammation with negative acid fast staining

- 2-malignant undifferentiated tumor(granulocytic sarcoma)
- CD45:+, CD3-, CD20-, MPO+, CD117 weakly +, CD34 + in few dispersed cell, Vimentin:+, CD30-, TLE-1 -, Ki-67 + in 15% of cells, EMA-, CD15-,CD1a-, s-100-, B-Catenin-

6 admission (4 years old)

- At the age 4 y.o he was admitted due to pancytopenia, ecchymosis and cough+ fever
- Abdominal sonography: some lesion in liver
- Splenomegaly
- Pleural thickening
- Chest CT: A LOCULATED EFFUSION IN PLEURA
- Pleural tap was done: not empyema
- Pathology: non specific inflammation, no malignancy
- He was treated with antibiotic, prednisolone and azathioprine

7 admission (5 years old)

- At the age 5 he was admitted due to seizure and loss of consciousness
- brain MRI: multiple periventricular lesion
- Biopsy: non specific inflammation, no malignancy,
- One of them showed necrotizing granuloma
- TB ,toxoplasma, fungal all the PCR negative

- Immunology consult was done

Peripheral blood	PERCENTAGE	ABSOLUTE COUNT
CD3	**94.2**	**838**
CD4	**52.3**	**465**
CD8	**36.5**	**325**
CD4/CD8	**1.43**	**-**
CD19	**0.1**	**1**
CD20	**1.3**	**11**
CD27	**76.3**	**679**
CD20+CD27+	**1.1**	**10**
CD16	**3.11**	**28**
CD56+CD16+	**1.81**	**16**
CD56	**2.82**	**25**
CD45	**98.3**	**875**
TCRà.ß+ CD4- CD8-	**2.25**	**20**

- IgG: 41 (500-800 mg/dl)
- IgA: not detectable (>70 mg/dl)
- IgM:10 (50-240 mg/dl)
- IgE=5 (<100 IU)
- LTT: mitogen normal but candida, BCG were abnormal
- NBT and DHR flowcytometry: normal

- Primary immunodeficiency (PID) was suspected for him
- Prophylactic co-trimoxazol, acyclovir, itraconazol and regular monthly IVIG was started

Additional findings

- Ferritin: >2000, vitamin B12: 330(normal)
- Triglyceride: 318
- Fibrinogen: 298 (350- 400)

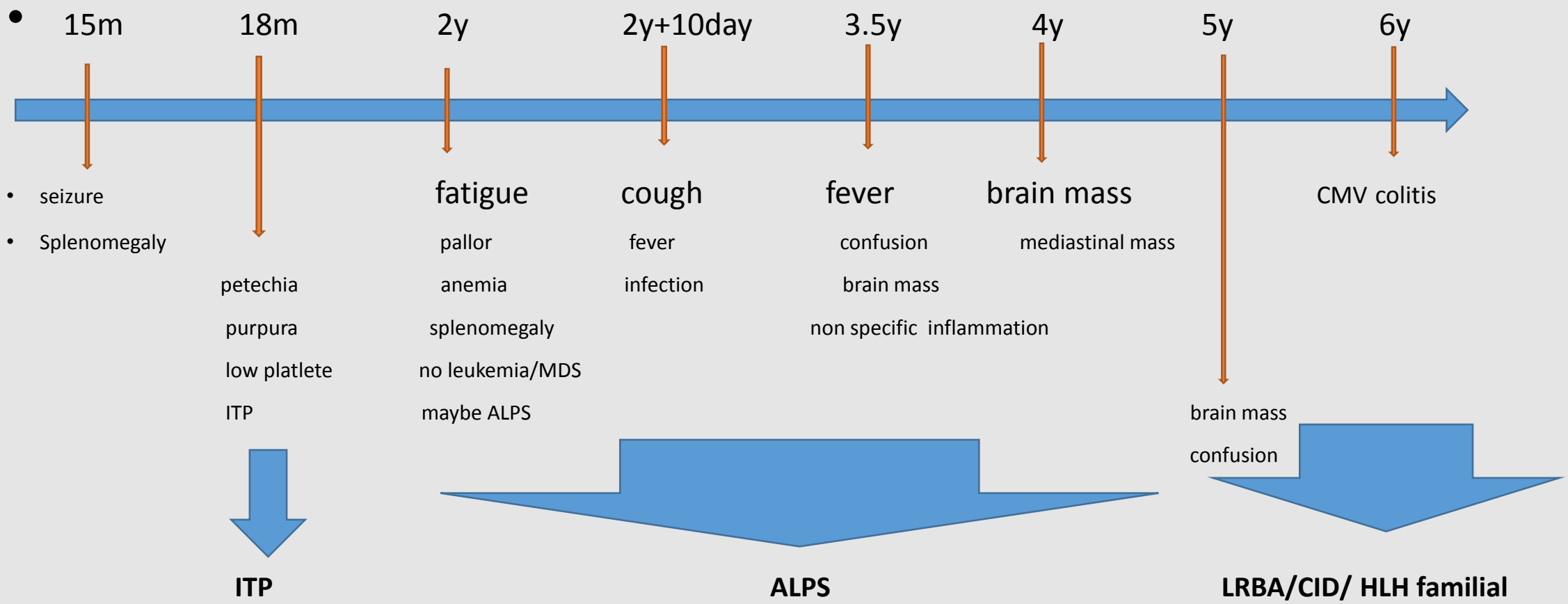
Most probable diagnosis for him

- Immune dysregulation disease especially **LRBA**
- Combined immunodeficiency(CID)
- And Less likely, familial HLH
- NGS was requested but we do not have the result.

The main questions?

- Is it necessary to think the immune system?
- What is the diagnosis?
- How to approach?
- Do you recommend BMT?
- Do you recommend another therapeutic option?

Let`s review this case



The rule of unusual

- Unusual age of onset
- Unusual frequency
- Unusual severity
- Unusual response to treat
- Unusual complication
- Unusual organism
- Unusual site of involvement

} think to immunodeficiency primary or secondary

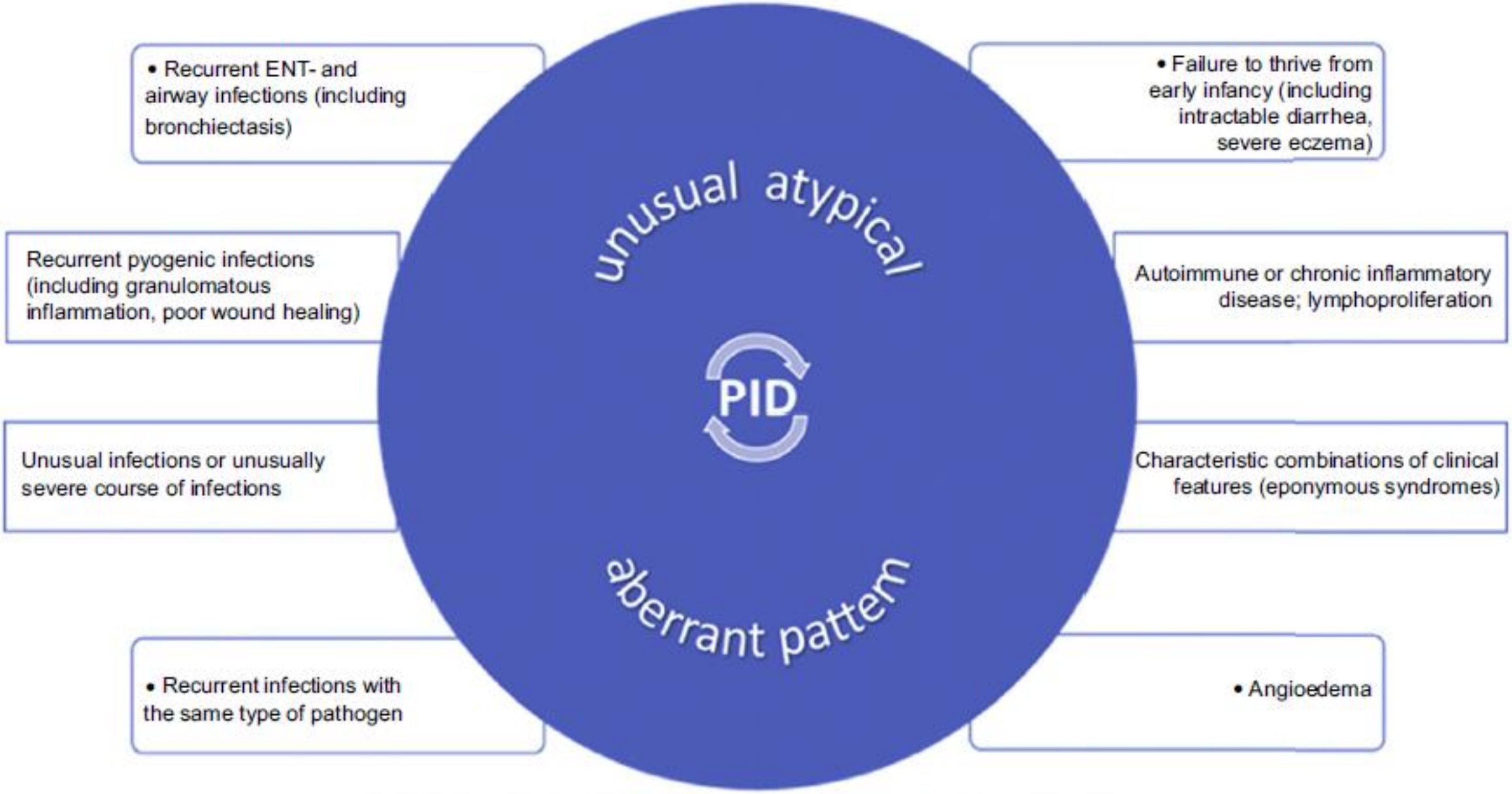


FIG. 1.1 Various clinical presentations of primary immune deficiencies.

TABLE 1.1 Eight common clinical presentations of primary immune deficiency.

Clinical presentation[a]	Overlap with IUIS classification
Recurrent ENT- and airway infections (including bronchiectasis)	Predominantly antibody deficiencies
Failure to thrive from early infancy (including intractable diarrhea, severe eczema)	Immunodeficiencies affecting cellular and humoral immunity
Recurrent pyogenic infections (including granulomatous inflammation, poor wound healing)	Congenital defects of phagocyte number or function
Unusual infections or unusually severe course of infections	Immunodeficiencies affecting cellular and humoral immunity
Recurrent infections with the same type of pathogen	Defects in intrinsic and innate immunity
Autoimmune or chronic inflammatory disease; lymphoproliferation	Diseases of immune dysregulation; autoinflammatory disorders
Characteristic combinations of clinical features (eponymous syndromes)	Combined immunodeficiencies with associated or syndromic features
Angioedema	Complement deficiencies

The major non-infectious manifestations

- a) Allergic: severe asthma, chronic urticaria, atopic eczema;
- b) Gastrointestinal: inflammatory bowel disease, autoimmune enteropathy, chronic non-infectious diarrhea, celiac disease;
- c) Hematologic: hemorrhages (plaquetopenia with chips), autoimmune cytopenias (thrombocytopenia, anemia, neutropenia);
- d) Rheumatologic: immunocomplex mediated autoimmune diseases;
- e) Endocrinopathies: type I diabetes mellitus, thyroid disease, hypoparathyroidism;
- f) Neoplastic (lymphohematopoietic system);
- g) Non-allergic angioedema (without urticaria).

The primary clues for approach

- Is the main concern infection or immune dysregulation?
  - If infection-are the main infections bacterial, viral, fungal, mycobacterial or mixed?
  - If immune dysregulation-are the features autoantibody-driven, lymphoproliferation, granulomatous?
- Are there any laboratory studies already that help point toward a category of deficits?
- Are there any somatic features (i.e., short stature, microcephaly, poor wound healing)?

- Is there a family history of malignancy, infection, autoimmunity?
- Are the exposures unusual?

IV. Diseases of immune dysregulation. b: Syndromes with Autoimmunity and Others

Syndromes with Autoimmunity

Increased $CD4^-$ $CD8^-$ TCR $\alpha\beta+$ (double negative (DN) T cells) ?

Yes:
ALPS
Autoimmune
Lymphoproliferative Sd

Chronic adenopathy
Splenomegaly, defective lymphocyte apoptosis.

ALPS-FAS. ***TNFRSF6.*** AD or AR.

Autoimmune cytopenias, increased lymphoma risk, IgG and IgA Nl or increased, elevated serum FasL, IL-10, vitamin B12.

ALPS-FASLG. ***TNFSF6.*** *AR.*

Autoimmune cytopenias, SLE, soluble FasL is not elevated

ALPS-Caspase10*. ***CASP10.*** AD.

ALPS-Caspase 8**. ***CASP8.*** *AR.*

Bacterial and viral infections, Hypogammaglobulinemia. Defective lymphocyte activation. Slightly increased DNT cells.

FADD deficiency.** ***FADD.*** AR.

Functional hyposplenism, bacterial and viral infections, recurrent episodes of encephalopathy and liver dysfunction.

No :
Regulatory T Cell Defects ?

No

Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy: APECED (APS-1) .

AIRE. AR/ AD.

Hypoparathyroidism hypothyroidism, adrenal insufficiency, diabetes, gonadal dysfunction and other endocrine abnormalities, chronic mucocutaneous candidiasis, dental enamel hypoplasia, alopecia, enteropathy, pernicious anemia.

ITCH deficiency. ***ITCH.*** *AR.*

Early-onset chronic lung disease (interstitial pneumonitis), thyroiditis, type I diabetes, chronic diarrhea/enteropathy, and hepatitis, developmental delay, dysmorphic facial features .

Tripeptidyl-Peptidase II Deficiency**. ***TPP2.*** *AR.*

Variable lymphoproliferation, severe autoimmune cytopenias, hypergammaglobulinemia, recurrent infections.
Decreased Tc and Bc.

JAK1 GOF**. ***JAK1.*** AD GOF.

HSM, eosinophilic enteritis, thyroid disease, poor growth, viral infections. Eosinophilia,

Prolidase deficiency. ***PEPD.*** AR.

Chronic skin ulcers, eczema, infections. Auto-antibodies common.

Yes

IPEX, immune dysregulation, polyendocrinopathy, enteropathy X-linked. ***FOXP3.*** Autoimmune enteropathy, early onset diabetes, thyroiditis hemolytic anemia, thrombocytopenia, eczema, elevated IgE, IgA. Lack and/or impaired function of $CD4^+$ $CD25^+$ $FOXP3^+$ regulatory T cells (Tregs).

CD25 deficiency*. ***IL2RA.*** AR. Lymphoproliferation, autoimmunity, impaired Tc proliferation. No CD4+C25+ cells with impaired function of Tregs cells.

CTLA4 deficiency (ALPSV). ***CTLA4.*** AD. Autoimmune cytopenias, enteropathy, interstitial lung disease, extra-lymphoid lymphocytic infiltration recurrent infections . Impaired function of Tregs. Tc and Bc decreased.

LRBA deficiency. ***LRBA.*** AR. Recurrent infections, inflammatory bowel disease, autoimmunity. Reduced IgG and IgA in most. Low or normal numbers of Bc. Normal or decreased CD4 numbers, Tc dysregulation.

STAT3 GOF mutation. ***STAT3.*** AD. Lymphoproliferation, solid organ autoimmunity, recurrent infections. Enhanced STAT3 signaling, leading to increased Th17 cell differentiation, lymphoproliferation and autoimmunity. Decreased Tregs and impaired function. Tc and Bc decreased.

BACH2 deficiency. ***BACH2.*** AD. Lymphocytic colitis, sinopulmonary infections. Impaired memory Bc development. Progressive Tc lymphopenia.

CD122 deficiency. ***IL2RB.*** Lymphoproliferation, lymphadenopathy, HSM, AIHA, dermatitis, enteropathy. Hypergammaglobulinemia, recurrent viral (EBV, CMV) infections

DEF6 deficiency*. ***DEF6.*** HSM, enteropathy, cardiomyopathy, recurrent infections. Low Tc, low or normal Bc

FERMT1 deficiency. ***FERMT1.*** Dermatosis (congenital blistering, skin atrophy, photosensitivity, skin fragility, and scaling). Intracellular accumulation of IgG, IgM, IgA, and C3 in colloid bodies under the basement membrane

Immune Dysregulation with Colitis: IBD

IL-10 deficiency*. ***IL10.*** AR.
Folliculitis, recurrent respiratory diseases, arthritis. No functional IL-10 secretion.

IL-10R deficiency. AR. Folliculitis, recurrent respiratory diseases, arthritis, lymphoma.
IL10RA Leukocytes unresponsive to IL-10.
IL10RB. Leukocytes unresponsive to IL10, IL22, IL26, IL28A, IL28B, IL29

NFAT5 haploinsufficiency**. ***NFAT5.***
AD. Recurrent Sinopulmonary infections. Decreased memory Bc and plasmablasts.

TGFB1 deficiency*. ***TGFB1.*** AR.
Recurrent viral infections, microcephaly, and encephalopathy. Decreased T cell proliferation in response to anti-CD3

RIPK1 deficiency*. ***RIPK1.*** AR.
Recurrent infections, progressive polyarthritis. Low Tc , low or nl Bc.

I. Immunodeficiencies affecting cellular and humoral immunity
b- Combined Immunodeficiencies Generally Less Profound than Severe Combined Immunodeficiency

Low CD4: MHCII Expression ?

Absent

MHC-II def ***RFXANK,CIITA, RFX5, RFXAP***

AR, Failure to thrive, respiratory and gastrointestinal infections, liver/biliary tract disease

Present

LCK def. ***LCK.*** ***AR,*** Immune dysregulation, auto-immunity. Low Treg, restricted T cell repertoire, poor TCR signaling.↑IgM.

Polymerase δ def*. AR. **POLD1** or **POLD2.** Recurrent respiratory tract infections, skin infections, warts and molluscum, short stature, intellectual disability. Low Bc, Low Ig.

*AD :***UNC119 def** ***UNC119***

Low CD8

CD8 def *. ***CD8A***

Recurrent infections .Maybe asymptomatic.CD8 Absent.

Nl MHC -I on lymphocytes.

ZAP-70 def. ***ZAP70*** May have immune dysregulation, autoimmunity. Nl Ig. CD4: Low function

Combined hypomorphic and activating mutations: Severe autoimmunity . Nl or decreased CD4 and Bc. Nl IgA, low IgM, IgG Nl or low.

Absent MHC -I on lymphocytes.

MHC-I def .

TAP2, TAP1 **or** ***TAPBP :*** Vasculitis, pyoderma gangrenosum. Nl Ig.

B2M *: Sinopulmonary infections, cutaneous granulomas. Nl Ig. Hypoprotidemia. Absent β2m associated proteins MHC-I, CD1a, CD1b, CD1c.

Low Bc:

Omenn sd (hypomorphic mutations). Erythroderma, Alopecia, Adp, HSM, Eo ↑, IgE↑

DOCK8 def. ***DOCK8.*** Severe Eczema. Cutaneous viral and staphylococcal infections; severe atopy; cancer ,diathesis. High IgE, Low IgM, eosinophilia.↓NK with poor function.↑Bc, ↓memory Bc Poor peripheral Bc tolerance. ↑ exhausted CD8+ TEM cells

STK4 def . ***STK4.*** Intermittent neutropenia, bacterial, viral (HPV, EBV, molluscum), candidal infections, lymphoproliferation, autoimmune cytopenias, lymphoma, congenital heart disease. ↓ : CD4 Tc, naïve Tc, ↑ TEM and TEMRA cells, poor proliferation. ↓: memory Bc, IgM & Ab responses. ↑IgG, IgA, IgE.

IL21 def.** ***IL21.*** Severe early onset colitis. Tc : NL / low function. Hypogammaglobulinemia, poor specific antibody responses;↑ IgE

NIK def.** ***MAP3K14.*** Bacterial, viral and Cryptosporidium infections.↓: NK, Ig levels & switched memory Bc. Tc :Ag poor proliferation

Moesin def.* ***MSN.*** XL, Recurrent infections with bacteria, varicella; neutropenia. ↓ Ig over time. Tc: defective migration, proliferation.

C-REL def.** ***REL. :*** Recurrent infections with bacteria, mycobacteria, salmonella and opportunistic organisms. Defective innate immunity. Low Ig. Tc: decreased memory CD4, poor proliferation.

ICOSL def.** ***ICOSL.*** Recurrent respiratory tract viral infections. hypogammaglobulinemia, and Low Tc, slowly progressive neutropenia

IKAROS def*. (CD154). AD DN, ***IKZF1.*** Opportunistic infections, including P.jirovecii, bacterial, viral and other fungal infections. Increased risk fo T-ALL. Agammaglobulinemia, high recent thymic emigrant (naive/Th0 cells; low-absent memory T cells

Ig : often NL

CD3γ def*. ***CD3G*** TCR low. Autoimmunity

RHOH def.** ***RHOH.*** HPV infection, lung granulomas, molluscum contagiosum, lymphoma. Low naive T cells, restricted repertoire, poor proliferation to CD3.

TCRα def* . ***TRAC.*** Recurrent viral, bacterial, fungal infections; diarrhea; immune dysregulation and autoimmunity. Absent TCRαβ except for a minor CD3-dim TCRαβ population; poor proliferation.

OX40 def.** ***OX40.*** Kaposi's sarcoma, impaired immunity to HHV8. Low memory Bc. Tc : low Ag specific memory CD4+.

FCHO1 def*. ***FCHO1*** Lymphoproliferation, failure to thrive. . Tc: Low. Bc & Ig : Nl Increased activation-induced T-cell death, defective clathrin-mediated endocytosis

RelA haploinsufficiency.** ***RELA,*** AD, Chronic mucocutaneous ulceration. Impaired NFkB activation; reduced production of inflammatory cytokines

ITK deficiency. ***ITK*** . EBV associated Bc lymphoproliferation, lymphoma, immune dysregulation. Nl or low IgG. Progressive CD4 T cell lymphopenia; reduced T cell activation

Ig Low

DOCK2 def. ***DOCK2.*** Early invasive herpes viral, bacterial infections, Nl NK number, but defective function. Poor interferon responses. IgG NL or low; poor antibody responses.

CARD11 deficiency (LOF). ***CARD11.*** *Pneumocystis jirovecii* pneumonia, bacterial & viral infections .Ig:Absent/low.Tc:NL number, poor proliferation .

BCL10 def.** ***BCL10.*** Recurrent bacterial and viral infections, candidiasis, gastroenteritis. Tc: few memory T and Treg cells, poor Ag and anti-CD3 proliferation. Bc: Decreased memory and switched Bc

IKBKB def. ***IKBKB.*** Recurrent bacterial, viral and fungal infections. Opportunistic infections. Bc : poor fonctions. absent Treg and γδ T cells; impaired TCR activation.

ICOS def. ***ICOS.*** Recurrent infections, autoimmunity, gastroenteritis, granulomas.

TFRC deficiency* ***TFRC.*** Recurrent infections. Neutropenia, thrombocytopenia. Bc:Nl number, low memory Bc. Tc: Nl number, poor proliferation .

CD40 ligand def. (CD154). XL, ***CD40LG***. or **CD40 def.** AR, ***CD40.*** Opportunistic infections, biliary tract and liver disease, *Cryptosporidium*.. Neutropenia, HIGM: IgM normal or high, other Ig isotypes low. Bc: $sIgM^+$, IgD^+ cells present, absent $sIgG^+$, IgA^+ and IgE^+ cells. Tc: NL to low.

IL21R def* . ***IL21R.*** Recurrent infections; Pneumocystis, Cryptosporidium, liver disease. Tc: low cytokine production; poor antigen proliferation. Decreased memory and switched B cells. Poor specific antibody responses; increased IgE

Normal Ig but Poor Specific Antibody response

MALT1 def*. ***MALT1.*** Bacterial, fungal and viral infections. Impaired Tc proliferation.

RelB def.** ***RELB.*** Recurrent infections Tc:poor diversity, ↓ proliferation to mitogens; no response to Ag; Bc: marked increase

IV. Diseases of immune dysregulation.
a : Hemophagocytic Lymphohistiocytosis HLH & EBV susceptibility

Hemophagocytic Lymphohistiocytosis (HLH)

Hypopigmentation:

Partial albinism . Decreased NK and CTL activities(cytotoxicity and/or degranulation). Bc and Tc: NI

Chediak Higashi Sd. *LYST*

Recurrent infections, fever, HSM, bleeding tendency, progressive neurological dysfunction. Giant lysosomes (WBC), neutropenia, cytopenias, Specific hair shaft anomaly. Increased activated Tc.

Griscelli Sd type 2. *RAB27A.*

Fever, HSM, cytopenias; Specific hair shaft anomaly

Hermansky Pudlak sd type 2. *AP3B1.*

Recurrent infections, pulmonary fibrosis, increased bleeding, neutropenia; Specific hair shaft anomaly.

Hermansky-Pudlak syndrome, type 10. *AP3D1.***

Oculocutaneous albinism, severe neutropenia, recurrent infections, seizures, hearing loss and neurodevelopmental delay .

Familial Hemophagocytic Lymphohistiocytosis Syndromes:

Fever, HSM, cytopenias, NI Bc. Increased activated Tc. Decreased to absent NK and CTL activities (cytotoxicity and/or degranulation)

Perforin deficiency (FHL2).*PRF1.*

UNC13D / Munc13-4 deficiency (FHL3). *UNC13D.*
Syntaxin 11 deficiency (FHL4). *STX11.*
STXBP2 / Munc18-2 deficiency (FHL5) *STXBP2.* Enteropathy

FAAP24 deficiency. *FAAP24.*** EBV-driven lymphoproliferative disease. Increased activated Tc. Failure to kill autologous EBV transformed Bc. NI NK cell function.

SLC7A7 deficiency. *SLC7A7.*
Lysinuric protein intolerance, bleeding tendency, alveolar proteinosis Hyper-inflammatory response of macrophages. NI Tc and NK cell function

Susceptibility to EBV

RASGRP1 deficiency*. *RASGRP1.* Recurrent pneumonia, herpes virus infections, EBV associated lymphoma. Decreased NK cell function; high IgA. Bc and Tc: Poor activation, proliferation, motility

CD70 deficiency*. *CD70 (TNFSF7).* Hodgkin lymphoma, autoimmunity in some patients. Reduced IgM, IgG, IgA (75%) and reduced Ag-specific Ab responses (50%). Bc:poor antibody and memory responses. Tc:low Treg, poor activation and function

CTPS1 deficiency. *CTPS1.*
Recurrent/chronic bacterial and viral infections (EBV, VZV), EBV lympho-proliferation, B cell non-Hodgkin lymphoma. Tc: poor proliferation to Ag

CD137 deficiency*. *TNFRSF9.* EBV lymphoproliferation, B cell lymphoma, chronic active EBV infection. Low IgA and IgG, poor response to antigens, decreased T cell proliferation

RLTPR (CARMIL2) deficiency. RLTPR. Recurrent bacterial, fungal and mycobacterial infections, viral warts, molluscum and EBV lymphoproliferative and other malignancy, atopy. Ig NI to ↓, poor T dependent antibody response. NI Bc. Tc: ↓ Treg, high CD4, poor function.

XL magnesium EBV and neoplasia (XMEN)*. *MAGT1.XL.* EBV infection, lymphoma, viral infections, respiratory and GI infections. Glycosylation disorder. Some patients can present with neurological manifestations. Low CD4 Low recent thymic emigrant cells, poor proliferation to CD3. High B cells, high DN T cells..

PRKCD deficiency*. *PRKCD.* Recurrent infections, EBV chronic infection, lymphoproliferation, SLE-like autoimmunity (nephrotic and antiphospholipid Sd). Low IgG. Low memory Bc high CD5 Bc

EBV associated HLH

XL, **XLP1. *SH2DIA.***

Clinical and immunologic features triggered by EBV infection:
lymphoproliferation, Aplastic anemia, Lymphoma.

Hypogammaglobulinemia, Absent iNKT cells. Impaired NK cell and CTL cytotoxic activity . Reduced Memory B cells .

SAP deficiency (FCM).

XL, **XLP2. *XIAP.***

Splenomegaly, lympho-proliferation, Colitis, IBD, hepatitis.

Hypogammaglobulinemia, Low iNKT cells. Increased T cells susceptibility to apoptosis to CD95 and enhanced activation-induced cell death (AICD). Normal NK and CTL cytotoxic activity. XIAP def (FCM)

AR, **CD27 deficiency . *CD27 (TNFRSF7).***

Features triggered by EBV infection, aplastic anemia,

low iNKTc lymphoma. Low Ig

Thank you