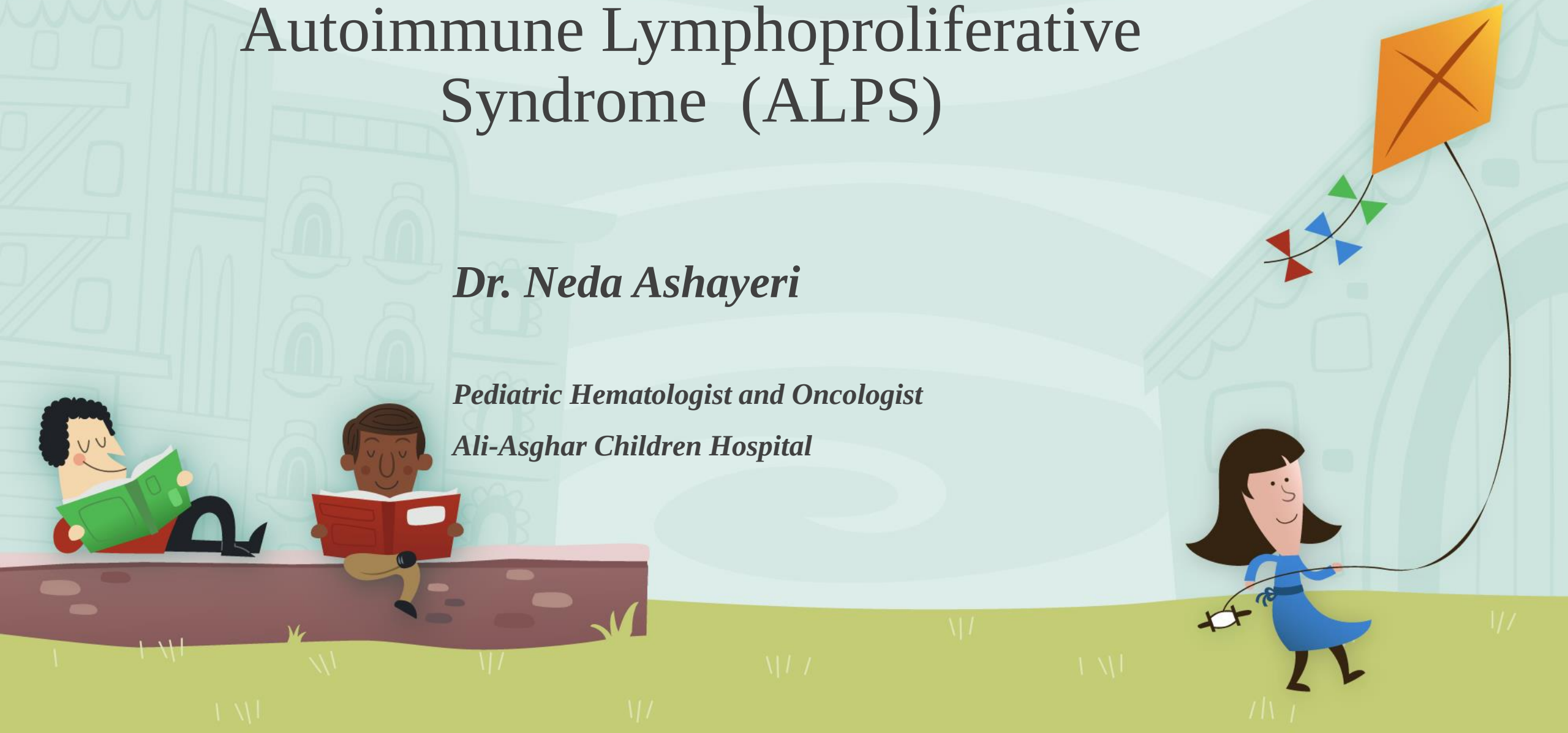
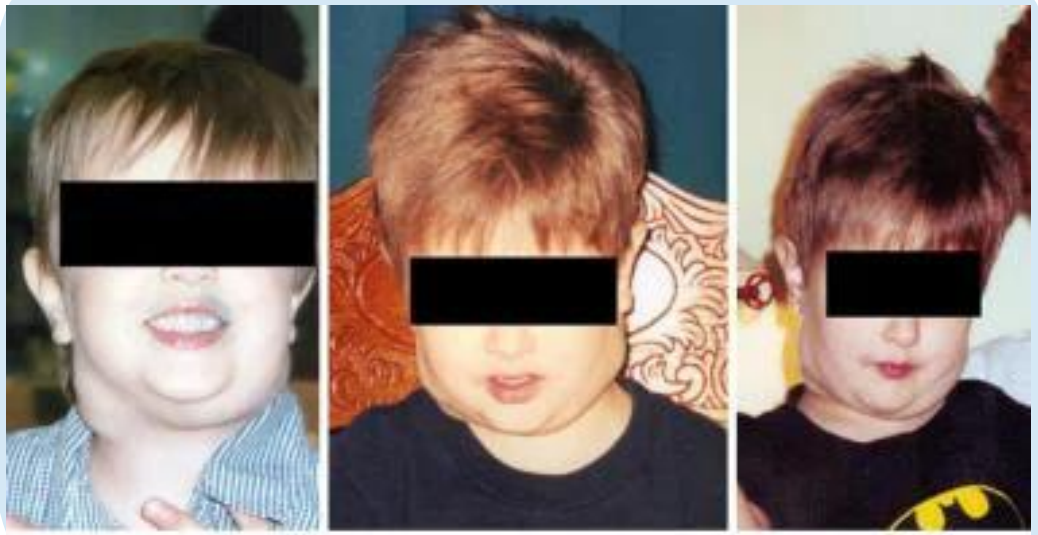
Autoimmune Lymphoproliferative Syndrome (ALPS)

Dr. Neda Ashayeri

Pediatric Hematologist and Oncologist

Ali-Asghar Children Hospital





Pathology

- A disorder of disrupted lymphocyte homeostasis caused by defective Fas-mediated apoptosis.
- Normally, as part of the downregulation of the immune response:

1. activated B and T lymphocytes upregulate Fas expression

2. activated T lymphocytes upregulate expression of Fas ligand.

3. Fas and Fas ligand interact triggering the caspase cascade, leading to cellular apoptosis.

- Patients with ALPS have a defect in this apoptotic pathway leading to chronic lymphoproliferation, autoimmunity, and secondary malignancies.

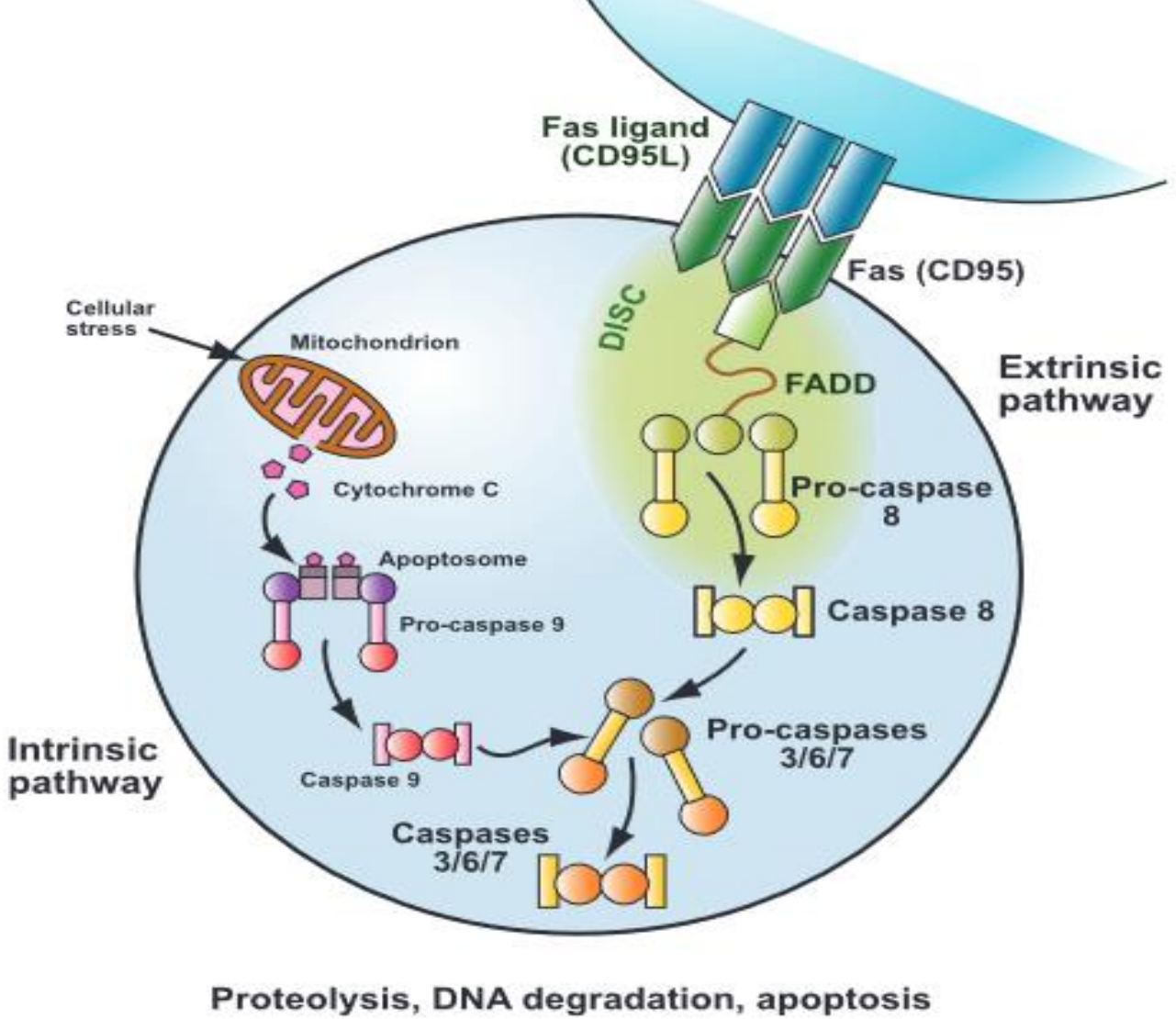


Fig 1. Fas apoptotic pathway. Patients with ALPS have defective Fas-mediated apoptosis. During downregulation of the immune response, activated B and T lymphocytes upregulate expression of Fas ligand, and activated T lymphocytes up-regulate expression of Fas. Fas ligand and Fas interact, activating the intracellular Fas-associated death domain (FADD) and triggering the caspase cascade with subsequent proteolysis, DNA degradation, and apoptosis. Apoptotic signalling mediated by Fas is part of the extrinsic pathway as it is activated through engangement of cell surface death receptors. The intrinsic apoptotic pathway is activated by cellular stressors, leading to alterations in mitochondrial membrane permeability and release of apoptosis-inducing substances. © Sue Seif, MA (used with permission).

Clinical manifestations

- 1. **Chronic (>6 months) nonmalignant lymphoproliferation:**

  lymphadenopathy

  and/or hepatomegaly

  and/or splenomegaly.

Lymphoproliferation may be massive and tends to wax and wane. The majority of patients present with lymphoproliferation prior to 2 years of age;

however, lymphoproliferation may not occur until adult years in rare cases.

Clinical manifestations

2. **Autoimmune disease**

> 80% of patients develop autoimmune disease.

The most common manifestation is autoimmune destruction of blood cells (autoimmune cytopenias), including immune thrombocytopenia, autoimmune hemolytic anemia, and autoimmune neutropenia.

Urticaria occurs in ~10% of patients.

Patients may also develop autoimmune disease of almost any organ system, including autoimmune hepatitis, nephritis, gastritis, colitis, and bronchiolitis obliterans;

however, these manifestations are rare and suggest an ALPS-like disease.

Clinical manifestations

3. **Secondary malignancy**.

10% of ALPS patients,

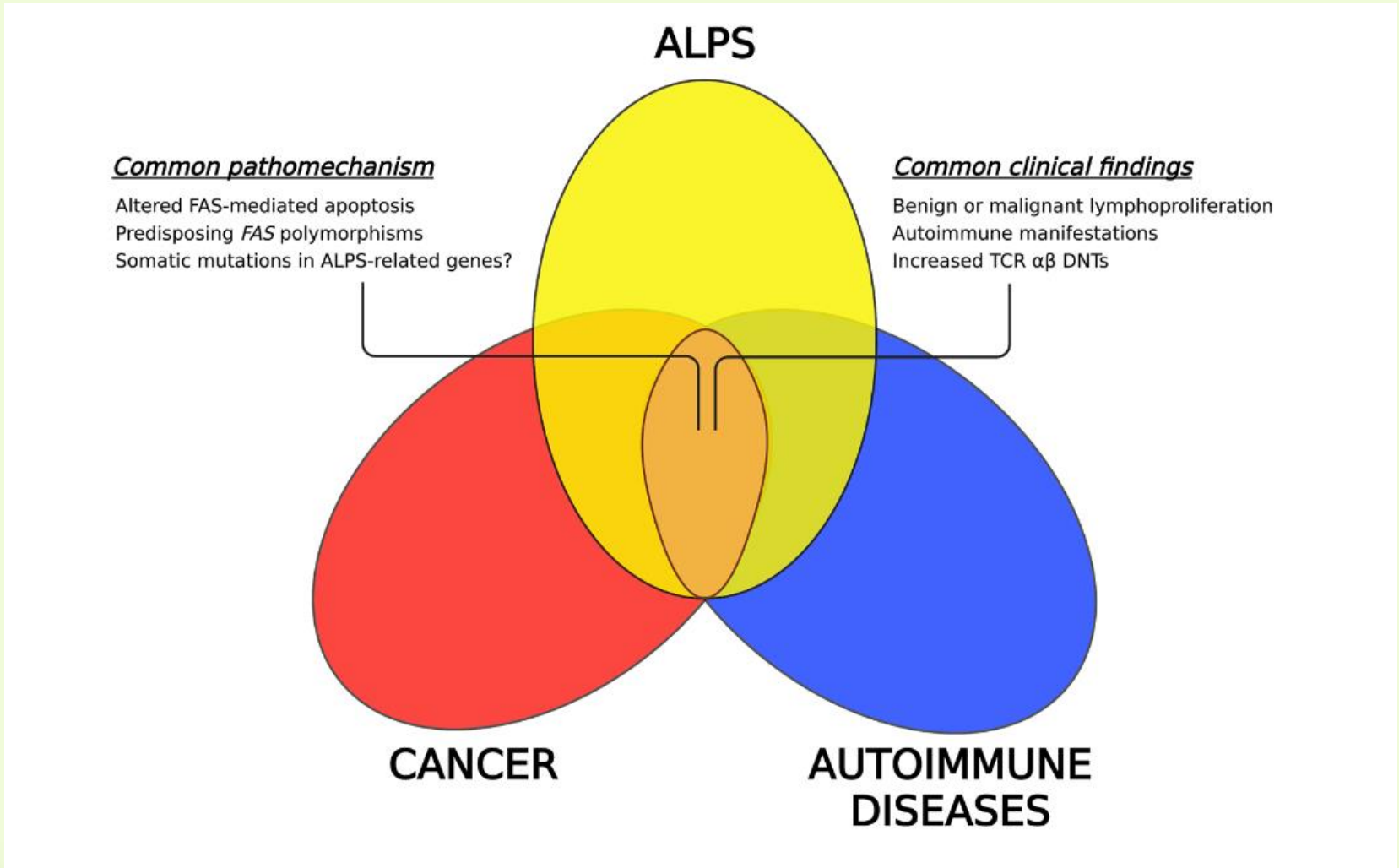
Most commonly lymphoma.

Most occur in FAS mutant ALPS.

4. **CVID.**

A subset of ALPS develops secondary CVID;

This is usually a sign of an ALPS-like disease.


ALPS
Common pathomechanism
Altered FAS-mediated apoptosis
Predisposing FAS polymorphisms
Somatic mutations in ALPS-related genes?
Common clinical findings
Benign or malignant lymphoproliferation
Autoimmune manifestations
Increased TCR αβ DNTs
CANCER
AUTOIMMUNE DISEASES

Laboratory manifestations

1. Elevated double-negative T cells (DNTs);

cell phenotype CD3+ /TCRα/β1 /CD4- /CD8-

DNTs are a rare population, representing ,1% of circulating T lymphocytes in normal individuals.

When markedly elevated, DNTs are usually pathognomonic for ALPS.

Mild elevations can be found in SLE, other autoimmune diseases, and many ALPS-like conditions.

Laboratory manifestations

2. In vitro evidence of defective Fas-mediated apoptosis. Only performed in a few specialized laboratories.

3. Elevated gamma/delta DNTs, CD57+ T-cells, CD5+ B-cells, CD8+ T-cells and HLA-DR+ T-cells.

4. Elevated serum IL-10.

5. Increased soluble Fas ligand.

6. Increased vitamin B12.

7. Hypergammaglobulinemia (or hypogammaglobulinemia).

8. Autoantibodies (DAT, antiplatelet, antineutrophil, ANA, Rf, antiphospholipid).

9. Eosinophilia.

10. The current gold standard test to diagnosis ALPS is genetic testing for mutations in FAS, FASL, or CASP10. FAS mutations can be germline or somatic.

Pathophysiology

ALPS has been attributed to defective apoptosis of lymphocytes, most often arising as a result of mutations in the gene encoding the lymphocyte apoptosis receptor FAS/APO-1/CD95.

Because of the failure of the affected lymphocytes to die after their response to antigen has been completed, there is an accumulation and buildup of an excessive number of polyclonal lymphocytes, which leads to hepatosplenomegaly and lymphadenopathy.

ALPS is classified into subtypes based on genotype.

Classification

In 2009 an international consensus conference was held at the NIH to develop a gene-based nomenclature mirroring the WHO classification

ALPS-FAS

- The most common type of ALPS
- 60-70% of patients
- Germline mutations or deletions in FAS
- These can be homozygous mutations (ALPS-0) or heterozygous mutations (ALPS 1a)
- Homozygous: rare and lead to a complete absence of functional Fas protein.
- Heterozygous: can exert a transdominant effect on wild-type FAS, leading to absent to near-absent functional Fas protein or can lead to haploinsufficiency and a partial defect in Fas protein function.

ALPS-sFAS

The second most common type of ALPS (~10% of patients) with an identifiable genetic mutation.

ALPS-sFAS (formerly ALPS-1s) is caused by somatic mutations in FAS restricted to the DNT compartment.

Similar clinical features as ALPS-FAS with the exception that these patients tend to develop disease at an older age.

The average age of presentation for ALPS-FAS is ~18 months.

The average age of presentation for ALPS-sFAS is over 5 years.

Thus the former “gold standard” test to diagnosis ALPS, the Fas-mediated apoptosis assay (described later) is normal (false negative).

ALPS-FASL

ALPS-FASL (formerly ALPS-1b) is caused by mutations in FASL (Fas ligand).

Clinically, it manifests with features of SLE.

However, it often lacks the classical features of ALPS, that is, expansion of DNT cells and splenomegaly.

It is quite rare, with only a handful of reported cases.

Nevertheless, as the phenotype of ALPS-FASL mirrors SLE, it may be more common as a subset of patients diagnosed with SLE who may in fact have ALPS-FASL.

ALPS-CASP10

ALPS-CASP10 (formerly ALPS-II) is caused by caspase 10 deficiency.

Very rare and represents ~2%

Clinically similar to ALPS-FAS;

Less prominent lymphoproliferation

Comorbid CVID

ALPS-U (formerly ALPS-III)

The molecular defects: unknown;

20-30% of ALPS patients are type III

Clinically they are indistinguishable from other ALPS variants.

Should undergo comprehensive genomic profiling either with targeted next-generation sequencing panels or whole-exome sequencing.

Many patients previously classified as ALPS-U have an ALPS-like disease.

Patients with somatic mutations of NRAS and KRAS in lymphocytes used to be classified as having ALPS IV. These patients, however, are considered to have a distinct disease termed Ras-associated autoimmune leukoproliferative disease.

Other ALPS-like conditions include CTLA4 haploinsufficiency with autoimmune infiltration (CHAI), p110delta activating mutation causing senescent T-cell lymphadenopathy and immunodeficiency (PASLI or APDS), and lipopolysaccharide-responsive vesicle trafficking, beach- and anchor-containing (LRBA) deficiency with autoantibodies, regulatory T-cell defects, autoimmune infiltration and enteropathy (LATAIE), gain-of-function (GOF) signal transducer and activator of transcription 3 (STAT3) mutations. This list of genetic alternations that can present with an ALPS-like phenotype is growing as new disorders are identified frequently.

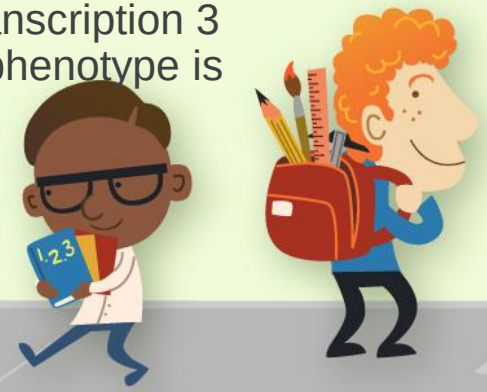


Table 2. Diagnostic Subtypes of Autoimmune Lymphoproliferative Syndrome (ALPS)[a]

Diagnosis	Definition
ALPS-FAS	Meets clinical criteria for ALPS plus germline *FAS* mutation
ALPS-sFAS	Meets clinical criteria for ALPS plus somatic *FAS* mutation
ALPS-FASL	Meets clinical criteria for ALPS plus germline *FASL* mutation
ALPS-CASP10	Meets clinical criteria for ALPS plus germline *CASP10* mutation
ALPS-U	Meets clinical criteria for ALPS but no detected genetic lesion

Abbreviations: CASP10, caspase 10; FAS, first apoptosis signal receptor; FASL, first apoptosis signal receptor ligand; sFAS, somatic FAS; U, unknown.

Diagnostic criteria

- Required criteria

1. Chronic nonmalignant lymphoproliferation
2. Elevated blood DNTs

- Primary accessory criteria

1. Defective in vitro Fas-mediated apoptosis (verified in two separate assays)
2. Somatic or germline mutation in ALPS causative gene (FAS, FASL, CASP10)

- Secondary accessory criteria

1. Elevated biomarkers (any of the following):

    a. Plasma sFASL>200 pg/mL

    b. Plasma IL-10 >20 pg/mL

    c. Plasma or serum vitamin B12 >1500 ng/L

    d. Plasma IL-18 >500 pg/mL

    e. Family history of ALPS or nonmalignant lymphoproliferation

2. Immunohistochemical findings consistent with ALPS as determined by experienced hematopathologist

3. Autoimmune cytopenias and polyclonal hypergammaglobulinemia

In order to diagnose ALPS, a patient must have the two required criteria plus one primary accessory criteria (definitive diagnosis)

or the two required criteria plus one secondary accessory criteria (probable diagnosis).

A probable diagnosis mandates more extensive testing for ALPS-like disorders, including RALD, CHAI, LATAIE, and PASLI. The 2010 criteria are arguably in need of revision as genetic testing has become more common and is the gold standard for diagnosis.

ORIGINAL ARTICLE

WILEY

Clinical, immunological, and genetic features in 780 patients with autoimmune lymphoproliferative syndrome (ALPS) and ALPS-like diseases: A systematic review

Nasim Hafezi[1] | Majid Zaki-Dizaji[2] | Matineh Nirouei[3,4] |
Gelayol Asadi[5] | Niusha Sharifinejad[3,4] | Mahnaz Jamee[6,7] |
Seyed Erfan Rasouli[3,4] | Haleh Hamedifar[8,9] | Araz Sabzevari[8,10] |

- Totally, 720 patients with ALPS (532 genetically determined and 189 genetically undetermined ALPS) and 59 cases with ALPS-like phenotype due to mutations in genes other than ALPS genes were assessed.
- Splenomegaly was the most common clinical presentation followed by autoimmune cytopenias and ymphadenopathy.
- Respiratory tract infections were significantly higher in ALPS-like patients than ALPS.
- Lower serum level of IgA, IgG, and lymphocyte count in ALPS-like patients compared to ALPS.
- Most (85%) of the ALPS and ALPS-like cases with determined genetic defects carry mutations in the FAS gene.
- About one-third of patients received immunosuppressive therapy with conventional or targeted immunotherapy
- A small fraction of patients (3.3%) received HSCT with successful engraftment

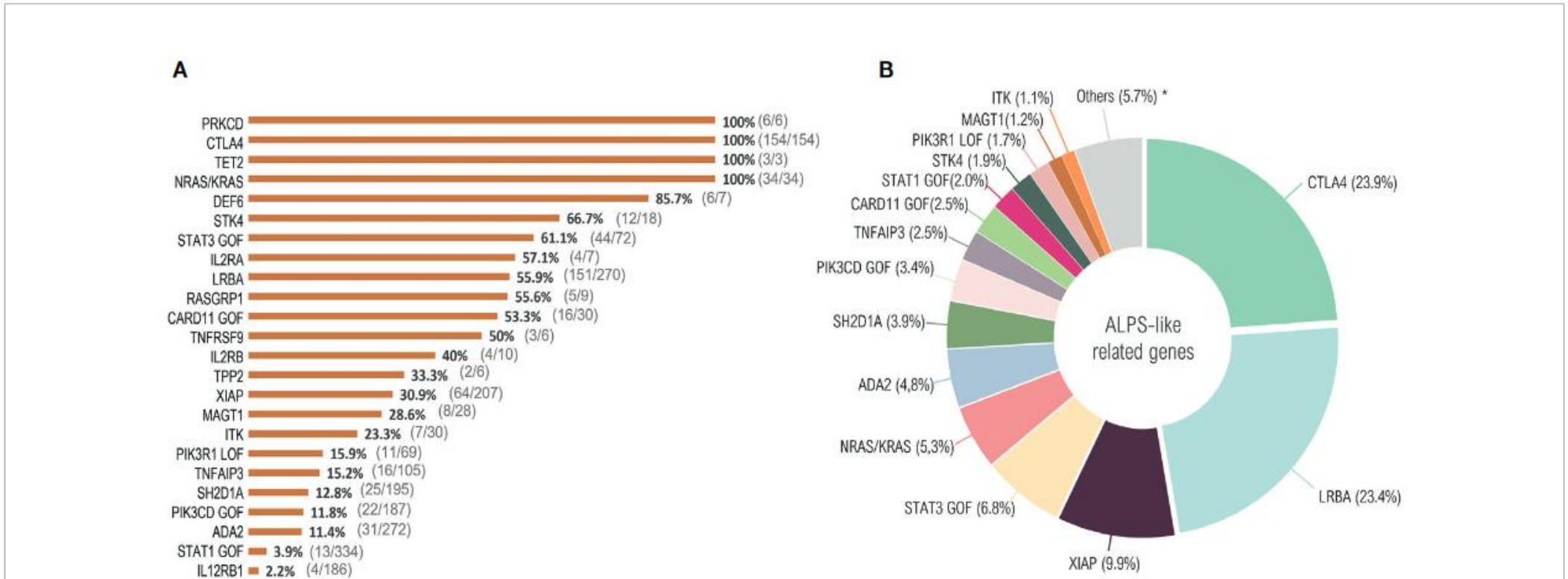


FIGURE 1 | ALPS-like related cases. Twenty-four distinct genetic defects with immune dysregulation, lymphoproliferation and autoimmunity were identified in the literature until October 2020. More than 2000 total cases were reported. After filtering according to the ALPS-like inclusion criteria, 645 patients were selected. **(A)** percentage of patients that fulfill clinical ALPS-like phenotype criteria. The number of ALPS-like patients with respect to the total number of patients counted in each genetic defect is indicated in parentheses. **(B)** ALPS-like related genes prevalence. *ALPS-like related genes with a prevalence less than 1%: *PRKCD* (0.9%), *DEF6* (0.9%), *RASGRP1* (0.8%), *IL2RA* (0.6%), *IL2RB* (0.6%), *TNFRSF9* (0.5%), *TET2* (0.5%), *TPP2* (0.3%).

López-Nevado M, González-Granado LI, Ruiz-García R, et al. Primary Immune Regulatory Disorders With an ***Autoimmune Lymphoproliferative Syndrome-Like Phenotype****: Immunologic Evaluation, Early Diagnosis and Management. Front Immunol.* ***2021*** *Aug 10;12:671755*

Treatment

Lymphoproliferation rarely requires treatment unless patients develop hypersplenism and/or organ compression, in which case it should be treated with immunosuppressive agents similarly to autoimmune disease.

Splenectomy should be avoided because ALPS patients have a high risk of postsplenectomy sepsis.

Other treatments include:

Short-term treatment for flares:

Corticosteroids

Most commonly used and very effective.

Steroid side effects.

Should be used short term (days to weeks) only.

Treatment

Chronic therapy first-line:

Sirolimus is the drug of choice

Targeting a serum trough of 5-15 ng/mL.

DNTs have abnormal activation of the PI3K/Akt/mTOR signaling pathway.

Sirolimus is effective for both lymphoproliferation and autoimmune disease in most patients.

Well tolerated

Common side effects: mucositis and hyperlipidemia.

Requires therapeutic drug monitoring.

Chronic therapy second-line:

*M*ycophenolate mofetil [MMF (CellCept)].

Effective at treating autoimmune disease but not effective at treating lymphoproliferation.

Does not require therapeutic drug monitoring and thus often used in patients who have difficulty obtaining more frequent laboratory testing or who develop side effects from sirolimus. MMF may cause lymphopenia.

Chronic therapy third-line:

other agents that may be effective include azathioprine, tacrolimus, mercaptopurine, methotrexate, vincristine, and cyclosporine.

Rituximab may be effective; however, a percentage of ALPS patients treated with rituximab have developed CVID and it should be avoided if possible.

Allogeneic stem cell transplantation is occasionally used but very rarely necessary with modern immune suppression.

Many ALPS-like disorders have targeted therapies, including MAPK inhibitors such as trametinib for patients with KRAS and NRAS mutations, abatacept for patients with CTLA4 and LRBA mutations, and tocilizumab for STAT3 GOF mutations.

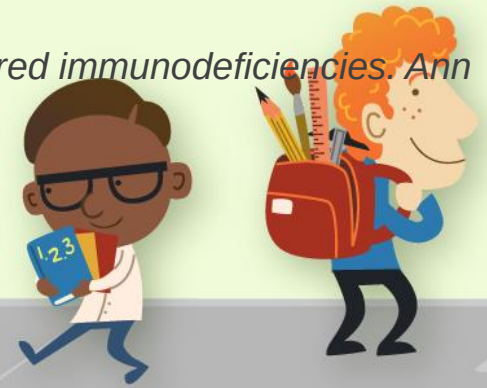
- Autoimmune cytopenias in ALPS have been classically treated as sporadic immune cytopenias, using corticosteroids and intravenous immunoglobulins (IVIG) as first-line options
- Due to refractoriness to these treatments, cytopenias in ALPS often require the use of second-line agents
- Evidence revealed a dramatic effectiveness of Sirolimus, which may be considered a targeted treatment for ALPS with the high degree of remission achieved and the significant reduction of ALPS biomarkers after 6 months of therapy
- For these reasons, Sirolimus may be considered as a first-line treatment option

- *Consonni F, Gambineri E, Favre C. ALPS, FAS, and beyond: from inborn errors of immunity to acquired immunodeficiencies. Ann Hematol.* ***2022*** *Mar;101(3):469-484*

Treatment

- Treatment of isolated benign lymphoproliferation for cosmetic reasons is not usually indicated
- In case of symptoms or concomitant cytopenias, the only drug that demonstrated to significantly diminish lymphoproliferation is Sirolimus , consistently with the description of a hyperactive mTOR pathway in ALPS.
- Splenomegaly should be carefully managed using spleen guards, in order to avoid splenic rupture, allowing children to participate to sport programs
- ALPS is characterized by poor anti-polysaccharide response and disorganized splenic marginal zone, correlated with a high risk of streptococcal sepsis.

Consonni F, Gambineri E, Favre C. ALPS, FAS, and beyond: from inborn errors of immunity to acquired immunodeficiencies. Ann Hematol. ***2022*** *Mar;101(3):469-484.*



Prognosis

Excellent with modern therapy

ALPS often improves with age and many adults who required chronic immune suppression as children are able to wean off medication.

The prognosis for ALPS-like conditions is more guarded.

The severity of ALPS varies from mild to severe within the same family.

The following malignancies have been reported in ALPS families:

1. Burkitt lymphoma, T cell rich B-cell lymphoma, and atypical lymphoma;
2. Nodular lymphocyte-predominant Hodgkin lymphoma;
3. Breast cancer, lung cancer, basal cell carcinoma of the skin, squamous cell carcinoma of the tongue, and colon cancer

Table 2 Clinical criteria for a probable diagnosis of ALPS (2019) as defined in 2019 by the European Society for Immunodeficiencies (ESID) registry's working definitions for clinical diagnosis of Primary immunodeficiencies (PID) [12].

At least one of the following:

1. Splenomegaly
2. Lymphadenopathy (> 3 nodes, > 3 months, non-infectious, non-malignant)
3. Autoimmune cytopenia (≥ 2 lineages)
4. History of lymphoma
5. Affected family member

AND at least one of the following:

1. $CD3^+TCR\alpha\beta^+CD4^-CD8^-$ of $CD3^+TCR\alpha\beta^+$ T cells > 6%
2. Elevated biomarkers (at least 2 of the following):
   - sFASL > 200 pg/ml
   - Vitamin B12 > 1500 ng/L
   - IL-10 > 20 pg/ml
   - Impaired FAS-mediated apoptosis

Consonni F, Gambineri E, Favre C. ALPS, FAS, and beyond: from inborn errors of immunity to acquired immunodeficiencies. Ann Hematol. **2022** Mar;101(3):469-484.

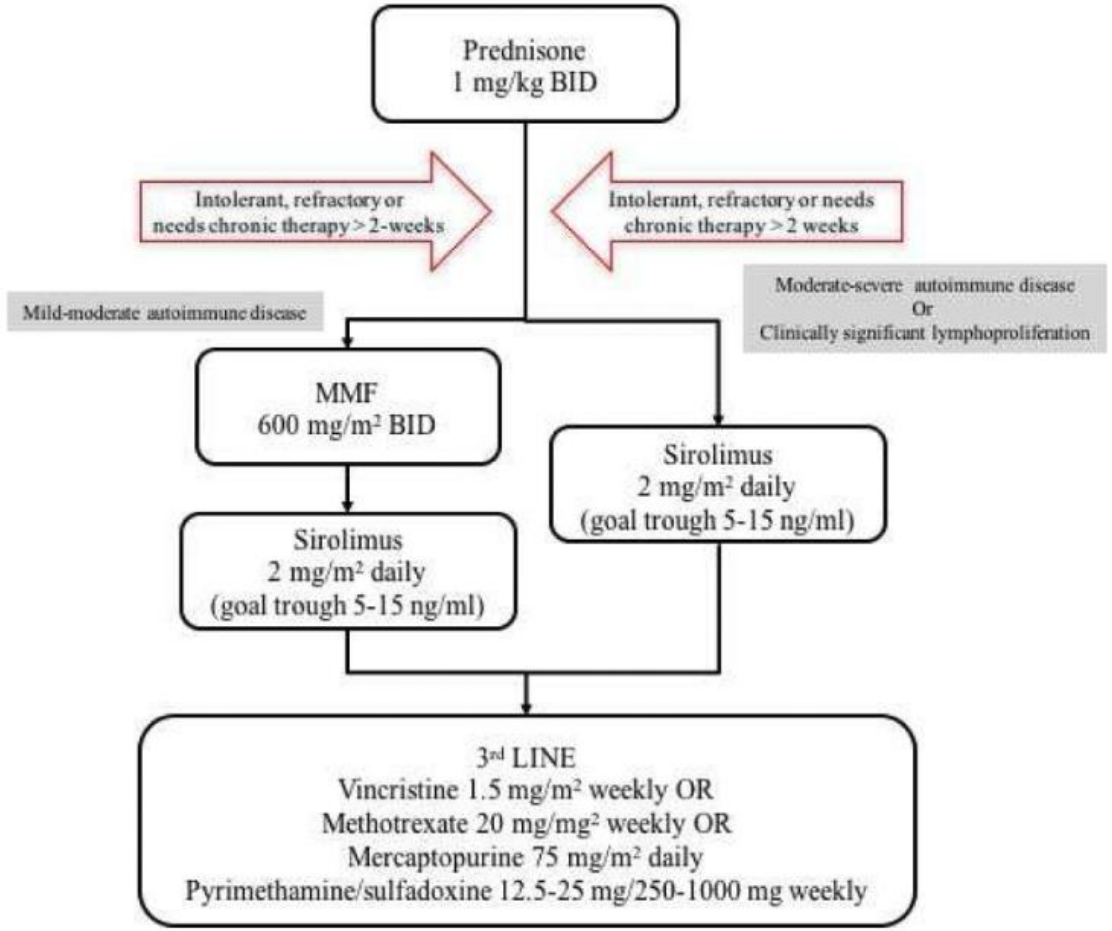


Figure 2. Proposed algorithm of our approach to the treatment of patients with autoimmune lymphoproliferative syndrome (ALPS) and associated mild-moderate and moderate-severe autoimmune disease, with or without clinically significant lymphoproliferation. Adapted from George *et al.*[1]. BID, twice daily.

Bride K, Teachey D. Autoimmune lymphoproliferative syndrome: more than a FAScinating disease. F1000Res. ***2017*** *Nov 1;6:1928*

- ALPS patients exhibit an increased risk of lymphoma;

- Conventional multiagent chemotherapy and radiation are usually effective, and no specific treatment protocols are available for ALPS-related lymphoma

- *Consonni F, Gambineri E, Favre C. ALPS, FAS, and beyond: from inborn errors of immunity to acquired immunodeficiencies. Ann Hematol.* ***2022*** *Mar;101(3):469-484*

- The most important goals of therapy are to resolve life-threatening cytopenias and avoid splenectomy.
- Fluorodeoxyglucose–positron emission tomography (FDG-PET) is not particularly helpful in distinguishing lymphoma from ALPS since both are PET-avid

Matson DR, Yang DT. Autoimmune Lymphoproliferative Syndrome: An Overview. Arch Pathol Lab Med. 2020 Feb;144(2):245-251


Thank You