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Review Article

Monogenic Disorder Associated with Autoimmune Lymphoproliferative Syndrome-Like Phenotype: A Systematic Review

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Abstract

Background: Autoimmune lymphoproliferative syndrome (ALPS) is a congenital disorder that results in an apoptosis impairment of lymphocytes, leading to chronic lymphoproliferation and autoimmunity, mainly autoimmune cytopenia. Some of autoreactive T cells cannot become apoptosis in activation-induced cell death (AICD) pathway; therefore, they have accumulation of autoreactive TCRαβ+CD4−CD8− double-negative T (αβ- DNT) cells, leading to cytopenia, splenomegaly, lymphadenopathy, autoimmune disorders and a greatly increased lifetime risk of lymphoma. *FAS, FASL, CASP8* and *CASP10* gene defects are often responsible for the disease, the phenotype of which can vary from asymptomatic/mild forms to severe disease. More rarely, defects are associated to other genes involved in ALPS-like phenotype.

Methods: A systematic literature search was performed in Web of Science, PubMed and Scopus from the earliest available date to march 2021 with standard keywords to find patients with ALPS-like phenotypes. Demographic, clinical, immunological and molecular data were extracted.

Results: In this systematic review we reported 61 patients with genetically determined ALPS-like. Most of ALPS-like cases carry mutations in the *STAT3* (n=15), *LRBA* (n=11) and *CARD11* (n=8) genes. The most common presentation was splenomegaly and lymphadenopathy followed by hepatomegaly. The most common autoimmunity was autoimmune hemolytic anemia and immune thrombocytopenic purpura followed by auto immune neutropenia. Elevated serum immunoglobulin was reported especially in IgG, IgM and IgA.

Conclusion: In the present study, 61 patients with genetically determined ALPS-like were examined. Our results showed that most of ALPS-like cases carry mutations in the *STAT3*. We reported that the most common presentations were splenomegaly and lymphadenopathy. Elevated serum immunoglobulin, IL-10, vitamin B12 and increased proportion of DNT cells were reported.

Keywords: Primary Immunodeficiency; ALPS; Autoimmune Lymphoproliferative Like Syndrome; Lymphoproliferation; Autoimmunity; LRBA; STAT3

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Introduction

Autoimmune Lymphoproliferative syndrome (ALPS) is a primary immunodeficiency (PID) that caused impaired apoptosis in lymphocytes. Defect in lymphocyte apoptosis make lymph proliferation in multiple organs. Chronic accumulate of nonmalignant lymphocytes in organs caused hepatomegaly, splenomegaly and lymphadenopathy with an increase in the number of TCRαβ+CD4−CD8− double-negative T (αβ- DNT) cells (1-3).Oncogenic potential lymphocyte survived that it caused an increased risk of B-cell lymphoma and T cell lymphoma in ALPS patients (4).

Autoimmune manifestations in ALPS is immune cytopenia (like autoimmune hemolytic anemia (AIHA), thrombocytopenia and autoimmune neutropenia) and hyperglobulinemia (4, 5). Polyclonal hypergammaglobulinemia and autoimmune cytopenia with elevated plasma-soluble FAS ligand levels, elevated vitamin B12, elevated plasma IL10 or IL18 levels, typical histological findings and family history of a nonmalignant lymphoproliferation provide accessory criteria for the diagnosis of ALPS (6).

ALPS which is resulted from the mutation in *FAS, FASL, CASP8* and *CASP10* genes cause defects in apoptotic signaling pathway. Patients who didn't fulfill the criteria established for the diagnosis of ALPS, classified as ALPS-like patients (2, 7). Genes responsible for ALPS-like include PI3KD, *STAT3, LRBA deficiency, CTLA4* haploinsufficiency and Tumor necrosis factor (TNF) alpha-induced protein 3 (TNFAIP3) (7).

In this study, we have reviewed all case reports or case series that describe ALPS-like patients until March 2021 and we report their clinical, immunological and genetic findings.

Materials and methods

Search strategy

The literature search was performed in 3 main databases including PubMed, Web of Science and Scopus, using the following search keywords: "Autoimmune lymphoproliferative like syndrome", "ALPS-like syndrome" in combination with subsequent genes: "Cytotoxic T-lymphocyte associated protein 4 or CTLA4", "KRAS proto-oncogene", "TNF alpha induced protein 3 or TNFAIP3", "NRAS proto-oncogene", "Phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit delta or PIK3CD", "signal transducer and activator of transcription 3 or STAT3", "LPS responsive beige-like anchor protein or LRBA", "recombination-activating *genes* or *RAGs*", "adenosine deaminase 2 or ADA2", "unc-13 homolog D or UNC13D", "RAS guanyl releasing protein 1 or RASGRP1","serine/threonine kinase 4 or STK4","protein kinase C delta or PRKCD", "caspase recruitment domain family member 11 or *CARD11*" "*RELA* proto-oncogene, NF-KB *subunit* or RELA "phosphatidylinositol 3-kinase delta or PIK3D". Reference lists of all full-text articles and major reviews were manually searched for additional studies.

Study selection and Data extraction

As described previously(8), in the first step, the articles were screened based on the title and abstract and then all full-text manuscripts were assessed for eligibility criteria; the articles were written in English and conducted on human subjects. All of the articles reported that at least one patient with ALPS-like syndrome was diagnosed. Studies using animal models, reviews and articles in languages other than English were excluded.

In the next step, one researcher extracted the data from all included studies. The following data were collected from all identified studies: name of the first author, publication year, and the number of participants, demographic, clinical, laboratory and molecular data.

Statistical analy.sis

Data analysis was performed with simple data pooling. In accordance with this, an overall summary of subgroup data or data from several related studies was combined without weighting. Central and descriptive statistics were reported for quantitative data. For variables with abnormal distribution, median and interquartile ranges (IQR) were calculated. All statistical analyses were performed using the SPSS software (v. 25.0, Chicago, IL).

Results

Study characteristics

The literature search identified 29 related articles. A total of 61 ALPS-like patients were reported in these 29 articles.

Epidemiologic characteristics

In this systematic review, the researchers reported 61 patients with genetically determined ALPS-like. In this study, 29 female and 31 male were included. The median (IQR) age of onset, age of clinical diagnosis and the diagnostic delay was 3 (0.9- 5), 7 (4.2-11.7) and 2.5 (1- 4.5) years old, respectively. The precise demographical data is summarized in **Table 1**. The most common origins were Japanese and Indian (6.6%) and Palestine (4.9%). The life status of 44 cases was available; 37 cases (84.1%) were alive at the time of publication and 7 (15.9%) were passed away.

Molecular findings

Most of ALPS-like cases carry mutations in the *STAT3* gene (24.6%), including both germline (76.2%) and somatic (23.6%) mutations. Other most frequent mutations were *LRBA* (18.0%), *CARD11* (13.1%), *KRAS* (8.2%), *CTL4* (4.9%), *ADA2, RASGRP1, STK4, NRAS, PIK3CD* each in 3.3% of patients and *UNC13D, TNFAIP3, PRKCD, RAGs, A20, RELA,* in each in 1.6% of patients. In a digenic patient mutation, both *LRBA* and *STAT3* were reported. **Figure 1** represents the detailed distribution of reported genes in ALPS-like patients.

Inheritance, in 20 (74.1%) cases of ALPS-like syndrome was autosomal recessive (AR) ,in 7 (25.9%) cases was autosomal dominant (AD) and in 34 cases was not available. Mutation type in 29 cases (56.9%) was heterozygote, in 18 (35.3%) cases was homozygote, in 4 (7.8%) cases was compound heterozygote and data were not available in 10 cases. 35 unique reported mutations in DNA (Deoxyribonucleic Acid) level were detected. These variants consisted of 28 missenses, 2 splice sites and 5 indels (2 mutations with exon deletion).

Clinical spectrum

The first most common presentations were lymphadenopathy (34.5%) and splenomegaly (20.7%), followed by infection (10.3%) and autoimmune hemolytic anemia (10.3%). **Figure 2** summarizes the first most common presentations in ALPS-Like patients.

The most common clinical manifestation was splenomegaly in 50 (86.2%) cases and autoimmunity in 46 (83.6%) cases followed by lymphadenopathy in 42 (79.2%) cases. **Figure 3** represents the detailed distribution of clinical manifestation in ALPS-Like patients. Autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura (8) are the most common autoimmune disorders in ALPS-like patients respectively. **Figure 4** summarizes autoimmune disorders in patients with ALPS-like syndrome.

A large proportion of patients with ALPS-like syndrome [83.6% (46 of 55)] were affected by autoimmune complications. The most common

Table 1. Demographic data of patients with ALPS-like syndrome

Parameters	***ALPS-like (n=61)***
Sex ratio, M/F, (n=60)	31/29
Consanguinity, % (n=30)	13 (43.3)
Dead/Alive ratio, % (n=44)	7/37
Age at onset, y, median (IQR) (n=45)	3.0 (0.9-5.0)
Age at clinical diagnosis, y, median (IQR) (n=24)	7.0 (4.25-11.75)
Age at genetic diagnosis, y, median (IQR) (n=22)	7.0 (3.75-11.25)
Delay in diagnosis, y, median (IQR) (n=23)	2.5 (1.0-4.5)
Age at presentation of first autoimmunity, y, median (IQR), (n=9)	3.0 (1.4-5.5)
Age at presentation of second autoimmunity, y, median (IQR), (n=6)	7.0 (3.0-87)
Age at first lymphoproliferation, y, median (IQR), (n=14)	3.5 (1.0-8.5)
Age at first infection, y, median (IQR), (n=5)	1.4 (0.1-5.5)

M, Male; F, Female; N, Count; Y, Year.

The median is shown [with 25th and 75th percentiles].

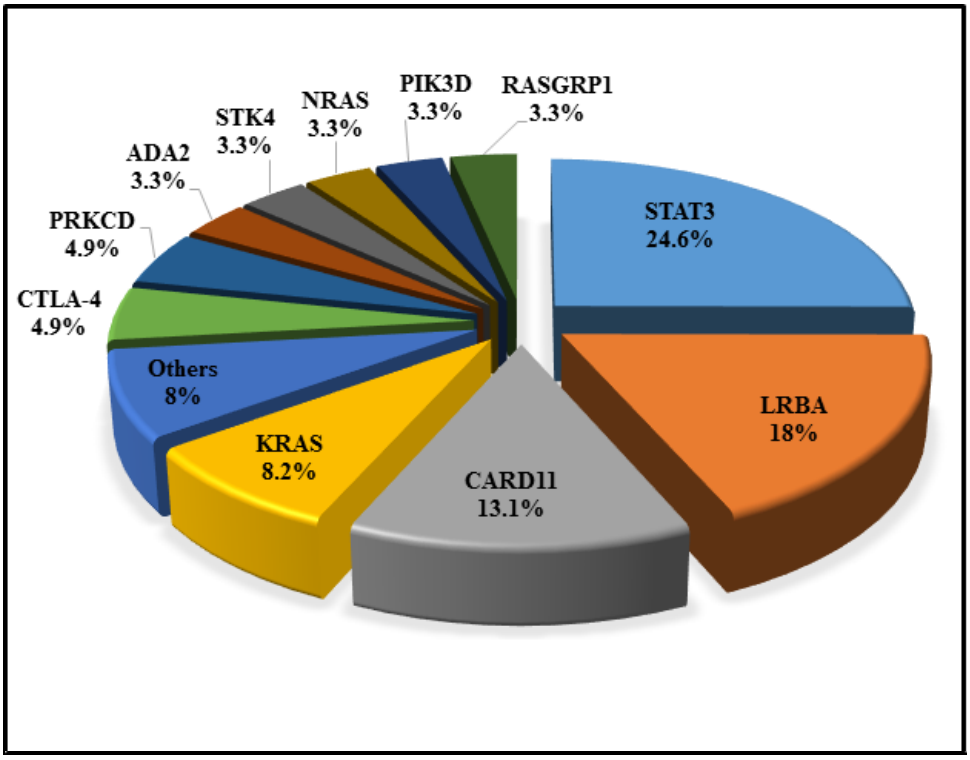

Figure 1. Distribution of reported genes in ALPS-like patients; others: UNC13D, TNFAIP3, Rag, A20, RELA

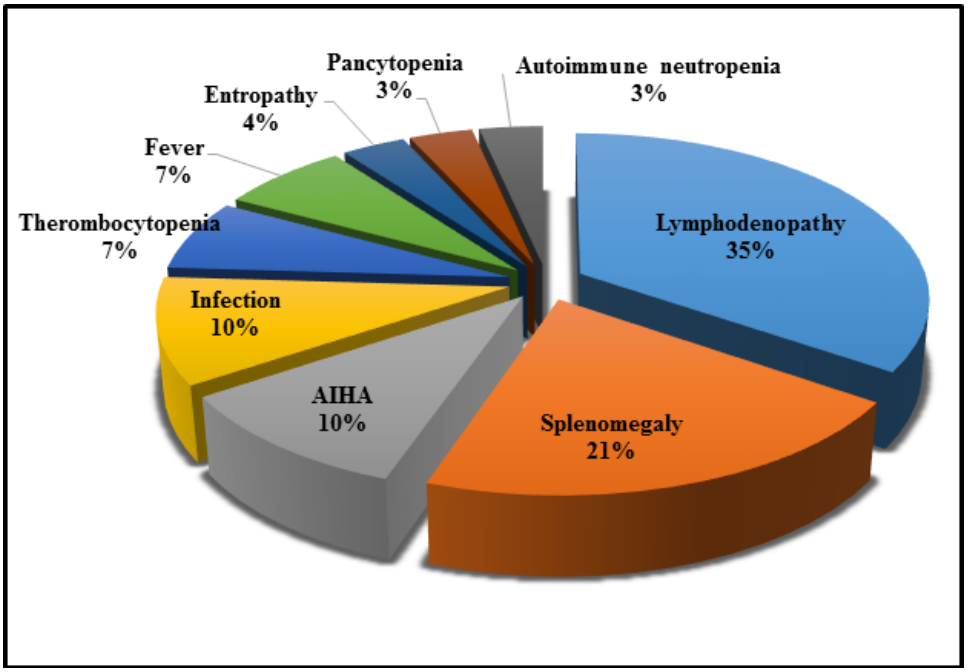

Figure 2. The first presentation in ALPS Like patients. The most common first presentation in ALPS Like patients were Lymphadenopathy and splenomegaly.

and the first autoimmunity was AIHA 51.9% (14 of 27). In this regard, immune thrombocytopenia (ITP) and thyroiditis [64.3% (9 of 14) and 66.7% (2 of 3)] are the second and third occurring autoimmunity respectively.

The first presentations of autoimmunity in patients with ALPS-like syndrome was started at median (IQR) age of 3.0 (1.4-5.5) years old followed by second autoimmune manifestations at 7.0 (3.0-87) years old **(Table 1)**. The rate of

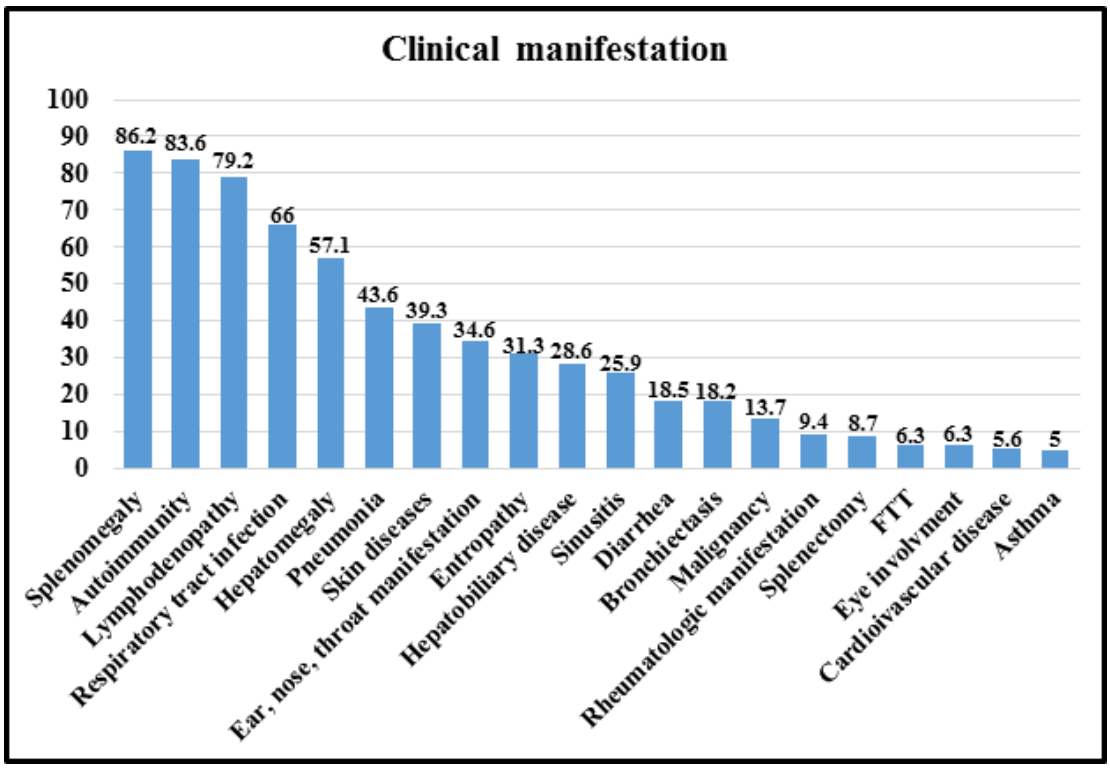

Figure 3. Distribution of clinical manifestation in ALPS Like patients.

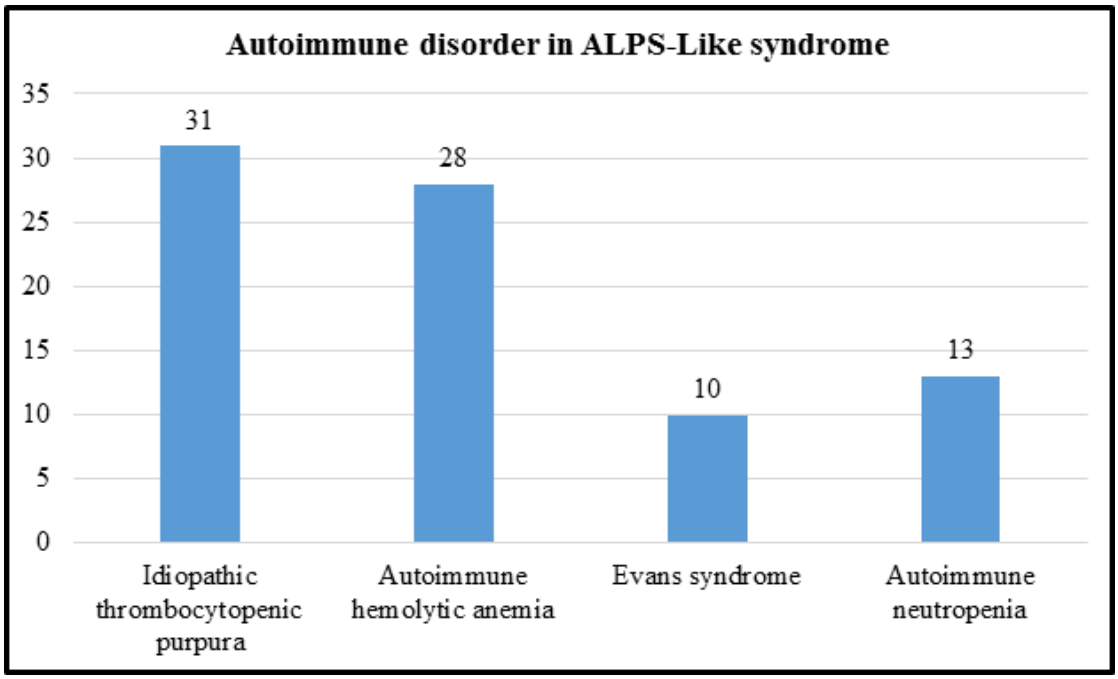

Figure 4. Autoimmune disorders in ALPS-like syndrome

malignancy was reported 13.7% (7 of 51) and the most common form was Hodgkin lymphoma. Skin disorders including eczematous, cellulitis, urticaria, macular rash, livedo reticularis, Molluscum contagiosum, skin HPV(Human Papilloma Virus) as well as herpes zoster were presented 39.3% [11 of 28] of ALPS-like individuals.

Other manifestations were respiratory tract infection (66.0%) [31 of 47], including

pneumonia (43.6%) [17 of 39], sinusitis (25.9%) [7 of 27], bronchiectasis (18.2%) [4 of 22] and asthma (5.0%) [1 of 20]. **Table 2** summarized Clinical manifestations of patients with ALPS-like syndrome.

Infection was reported in 72.9% [35 of 48] of patients that included viral infection in 51.2% [21 of 41], bacterial infection in 35.7% [10 of 28] and fungal infection in 21.9% [7 of 32] of patients. Viral infection mostly occurs with EBV (Epstein - Barr virus) in 52.3% of patients [11 of 21] and CMV (Cytomegalovirus) in 33.3% [7 of 21] of patients. Bacterial infection mostly occurs with Staphylococcus aureus and Hemophillus influenza in 30% [3 of 10] of patients. Moreover, fungal infection mostly occurs with Candida Albicans in 71.4% [5 of 7] of patients.

Immunological findings

Lymphocyte count [13 of 28] was in a normal range (46.4% of patients) but lymphocytosis was 11 of 21 which represented 52.4% of patients. Neutrophil count was normal [7 of 14] (50.0% of patients) but neutropenia occurred in [7 of 11] 50% of cases.

Elevated serum IgG (83.3%) [20 of 24], IgM (73.3%) [11 of 15], and IgA (61.5%) [8 of 13] were reported. Increased proportion of DNT cells was reported in 72.3% of cases [34 of 47]. Elevated IL-10 was detected in 72.7% of cases [8 of 11].

Elevated vitamin B12 level was presented in 28.6% of patients [4 of 14]. Apoptosis assays showed a defect in 78.3% of patients [18 of 23].

The most frequently detected auto-antibodies were anti-thyroid peroxidase, antinuclear

Table 2. Clinical manifestations of patients with ALPS-like syndrome

Parameters	***ALPS-like (n=61)***
Splenomegaly (%) (n=58)	50 (86.2)
Hematologic disease (%) (n=43)	36 (83.7)
Autoimmunity (%) (n=55)	46 (83.6)
Lymphadenopathy (%) (n=53)	42 (79.2)
Respiratory tract infection (%) (n=47)	31 (66)
Hepatomegaly (%) (n=42)	24 (57.1)
Anemia (%) (n=13)	6 (46.2)
Pneumonia (%) (n=39)	17 (43.6)
Skin disease (%) (n=28)	11 (39.3)
Ear nose throat disorders (%) (n=26)	9 (34.6)
Sinusitis (%) (n=27)	7 (25.9)
Bronchiectasis (%) (n=22)	4 (18.2)
Malignancy (%) (n=51)	7 (13.7)
Asthma (%) (n=20)	1 (5)
Fungal infection (%) (n=32)	7 (21.9)
Bacterial infection (%) (n=28)	10 (35.7)
Viral infection (%) (n=41)	21 (51.2)
Rheumatologic manifestation (%) (n=32)	3 (9.4)
Diarrhea (%) (n=27)	5 (18.5)
Enteropathy (%) (n=32)	10 (31.3)
Failure to thrive (%) (n=16)	1 (6.3)
Cardiovascular disease (%) (n=18)	1 (5.6)
Eye involvement (%) (n=16)	1 (6.3)

Table 3. Immunologic profile of patients with ALPS-like syndrome

Parameters	*ALPS-like (n=61)*
WBC × 10^3 (cell/uL), median (IQR) (n=19)	6800 (3200-9200)
Absolute lymphocytes counts × 10^3 (cells /μL), median (IQR) (n=31)	2600 (1400-9644)
Absolute neutrophils counts × 10^3 (cells /μL), median (IQR) (n=14)	2020 (661-3345)
$CD3^+$ T cells × 10^3 (cell/μL), median (IQR) (n=18)	1893.5 (909.03-3511.75)
$CD4^+$ T cells × 10^3 (cell/μL), median (IQR) (n=17)	525 (429.5-948)
$CD8^+$ T cells × 10^3 (cell/μL), median (IQR) (n=17)	551 (315.18-898.5)
$CD19^+$ (cell/μL), median (IQR) (n=18)	630 (241.5-5558.75)
$CD20^+$ (cell/μL), median (IQR) (n=6)	541.5 (46.19-1572.25)
CD16+56+ cells (cell/μL), median (IQR) (n=16)	296.5 (58.61-597.25)
IgG, mg/dL, median (IQR) (n=36)	1187 (660.75-1863.5)
IgA (mg/dL), median (IQR) (n=25)	93 (29.4-261.5)
IgM (mg/dL), median (IQR) (n=26)	154 (46.75-301.5)
IgE (mg/dL), median (IQR) (n=13)	70 (38.5-817.5)

Ig, Immunoglobulin; WBC, White blood cell.
The median is shown [with 25th and 75th percentiles].

antibody, anti-thyroglobulin autoantibodies, anti-phospholipid antibody and anti-neutrophil cytoplasmic antibodies [5 of 7 (71.4%), 18 of 26 (69.2%), 4 of 6 (66.7%), 5 of 8 (62.5%) and 4 of 7 (57.1%), respectively]. Moreover, 65% of patients (13 of 20) was direct coombs positive.

The therapeutic approach in ALPS-like patients

Patients who underwent steroid therapy were 29 of 30 (96.7%) of patients. 20.0% of patients (4 of 20) didn't have improvement and 60.0% of patients (12 of 20) had improvement after steroid therapy. Of note, four patients (20%) relapsed after reducing the dose of drugs.

IVIG (Intravenous Immune Globulin) treatment applied in 21 of 28 (75 %) of patients. 21 (35.6%) patients had improvement but eventually 5 (8.5%) patients didn't have improvement. Unfortunately, splenectomy was occurred in 8.7% [2 of 23] of patients.

MTOR-inhibitor (Mammalian Target of Rapamycin) was used in [10 of 33] 30.3% of patients. Mycophenolate Mofetil was used for 18 patients (28.9%), Cyclosporine for 10 patients (17%), Sirolimus for 7 patients (11.9%) and Rituximab for 4 patients (6.8%).

Moreover, 22.2% of patients [10 of 45] underwent hematopoietic stem cell transplantation (HSCT).

Discussion

Autoimmune lymphoproliferative syndrome (ALPS) is a rare genetic secondary disorder to a defective FAS-mediated apoptotic pathway of lymphocytes (9). The major diagnostic criteria are non-malignant lymphoproliferation, hepatomegaly, splenomegaly and autoimmune manifestations mainly autoimmune cytopenia (8, 10). Most of our data were obtained from USA (40%), Japan (15%), Turkey (11.7), Germany (6.7%) and India (6.7%). It is important to note that most of these countries have an efficient database and registry system.

Somatic or germline pathogenic mutation in FAS, FASL, or CASP10 reported in ALPS patients. Whereas, in this study, we collected all new pathogenic mutations in ALPS-like patients. These genes include STATT3, LRBA, CARD11, *KRAS*, *CTL4*, ADA2, RASGRP1, STK4, TNFAIP3, PRKCD, NRAS, PIK3CD, UNC13D, RAGs, RELA and PIK3CD (1-7, 11-31). According to our findings, most of ALPS-like cases carried mutations in the *STAT3* (24.6%), *LRBA* (18.0%), *CARD11* (13.1%) genes. Previous studies on the frequency of genes involved in APLS patients have reported the highest prevalence (8). Therefore, in patients with clinical manifestations similar to ALPS, who don't have mutations in the main

genes such as FAS, FASL, CASP8 and CASP10, evaluation of STAT3, LRBA and CARD11 genes can be considered.

The most common presentation was splenomegaly in 86.2% and hematologic disease in 83.7% of cases followed by autoimmunity in 83.6% of cases, this is the same as what had been observed in the previous studies (16, 32, 33). Shaili Shah Et.al reported that the earliest and the most common clinical manifestation of ALPS is chronic lymphadenopathy and/or splenomegaly. It is in concordance with our study that the first presentations were lymphadenopathy (35.0%) and splenomegaly (21.0%) of cases (34). Of note, livedo reticularis reported in ALPS-like patient, whereas ALPS patients didn't represent such a thing. It can be a new finding in ALPS-like patients(16).

In this regard, the most common autoimmunity was ITP in 31 (64.6%) cases and AIHA in 28 (60.9%) cases followed by autoimmune neutropenia in 13 (39.4%) cases. This finding is in concordance with Be´ ne´ dicte Neven et. al published in 2021. They reported that AIHA was the most frequent event (n =30), ITP was diagnosed in 23 patients and autoimmune neutropenia was diagnosed in 7 cases (35). Furthermore shaili Shah et al reported the most autoantibodies may be present in ALPS include positive Combs' direct antiglobulin test, rheumatoid factor (RF), or ANA. In our study the most frequently detected auto-antibodies were antinuclear antibody in 18 (29.5%), Antiphospholipid antibody in 5 (8.3%), and anti-thyroid peroxidase in 5 (8.2%) anti-thyroglobulin autoantibodies and anti-neutrophil cytoplasmic antibodies in 4(6.6%) of patients. Moreover, 13 (21.7%) of patients was direct coombs positive. It may be because ALPS-like patients has different mutation with ALPS patients (34).

In immunological finding, Serum IL-10, soluble FAS ligand, and vitamin B12 are commonly elevated in ALPS patients with FAS mutations but in our study elevated IL-10 was detected in 8 (13.1%) cases and elevated vitamin B12 level was present in 4 (6.7%) of patients. It might be because in ALPS-like patients other mutations than FAS, FASL and CASP 10 occurs(34). Also in our study in our study elevated serum IgG (33.3%) IgM (18.3%), and IgA (13.3%) were reported. In previous study, Be ´ne´ dicte Neven et.al reported that almost all patients presented hyper-IgG (71 of 73) and hyper-IgA serum levels(35). However, it seems that hypergammaglobulinemia is less common in ALPS-like patients.

Increased proportion of DNT cells is a required criterion in ALPS diagnosis whereas in our study only in half of patients (56.7%) elevated DNT cells was reported. In our study, elevated DNT cells didn't reported in patients with *RASGRP1*, *KRAS,* and *ADA2* mutation(31, 32).

ALPS is characterized by childhood onset; in this study, the median (IQR) age of onset was 3 (0.9- 5). It is in accordance with Be ´ne´ dicte Neven et.al that reported the median age at symptom onset was 3 years old (range: 0-35) (35, 36). These findings demonstrate that onset of ALPS-like and ALPS patients are manifested in the childhood and these patients need to the early diagnosis and treatment.

Patients with ALPS have an increased risk of developing malignancies. Most common malignancies which have been described are lymphoma (non-Hodgkin ,Hodgkin), leukemia and a number of solid tumors (thyroid, breast and liver carcinoma) (37). Be 'ne´ dicte Neven et.al reported3 cases of Hodgkin lymphoma and 4 cases of B-cell non Hodgkin lymphoma. In addition, they reported the cumulative risk of developing lymphoid malignancy before the age of 30 years old which was calculated to be 15% in ALPS patients with *TNFRSF6* mutation (35). In our study, malignancy was reported in 8 patients including Hodgkin lymphoma in 3 patients and non-classical B cell lymphoma, independent Hodgkin lymphoma, leiomyoma, intramucosal adenocarcinoma, Histiocytosis, childhood leukemia, non-Hodgkin's B cell lymphoma, abdominal mass in each individual. It demonstrated that malignancy is more common in ALPS-like patients.

In our study, 29 (47.5%) patients underwent steroid therapy. 4 (6.6%) patients didn't have improvement and 4 (6.6%) patients after dose reduction, their symptoms increased. But 12 (19.7%) patients had improvement after steroid therapy. IVIG treatment applied in 28 (45.9%) patients so that 21 (35.6%) patients had improvement but eventually 5 (8.5%) patients didn't have improvement. Unfortunately, splenectomy was done in 2 patients. MTOR-inhibitor was used in 9 (15%) patients. Mycophenolate Mofetil was

used for 18 (28.9%), Cyclosporine for10 (17%) patients, Sirolimus for 7 patients (11.9 %) and Rituximab for 4 (6.8%) patients. Moreover, 10 (16.9%) patients underwent hematopoietic stem cell transplantation (HSCT).

In the first step of treatment, patients usually responded to short bursts of corticosteroids. In the next step, some patients responded to IVIG but some others don't. After corticosteroid treatment, the most studied medication in ALPS is Mycophenolate Mofetil. Patients who underwent Mycophenolate Mofetil treatment demonstrated over 80% improvement in autoimmune diseases. The next step of treatment in ALPS, is Sirolimus (rapamycin). Sirolimus has been used with clinicians over 20 years (37).

Two patients with diagnosis of ALPS-like and clinical presentation of DADA2 disease have been reported and were successfully treated with HSCT and anti-TNF medications respectively(14, 16).

Conclusion

In this study, we have described clinical and laboratory features of genetically determined ALPS-like. Most of ALPS-like cases carry mutations in the *STAT3* gene. The common first presentations were lymphadenopathy and splenomegaly followed by infection .The most common clinical manifestations were splenomegaly. In laboratory data, lymphocytosis and neutropenia occurred in some of the patients. Moreover, elevated serum IgG, IgM and IgA were reported. The study showed that the increased proportion of DNT cells and the elevated IL-10 can be found in more than half of the cases. In addition, elevated vitamin B12 level was presented in most of patients.

Conflict of interest

The authors declare that they have no conflicts of interest.

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