CASE REPORT
Iran J Allergy Asthma Immunol
April 2022; 21(2):219-227.
Doi: 10.18502/ijaai.v21i2.9230

Lipopolysaccharide Responsive Beige-like Anchor Protein Deficiency in a Patient with Autoimmune Lymphoproliferative Syndrome-like Disease Phenotype: A Case Report and Literature Review

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Received: 21 July 2021; Received in revised form: 2 November 2021; Accepted: 6 November 2021

ABSTRACT

LPS-responsive beige-like anchor protein (LRBA) deficiency is a primary immunodeficiency caused by a mutation in the LRBA gene. Affected individuals present with a variety of clinical symptoms including hypogammaglobulinemia, recurrent infections, splenomegaly, hepatomegaly, and autoimmune cytopenias. Except for hypogammaglobulinemia, the remaining features resemble autoimmune lymphoproliferative syndrome (ALPS). Here, we report the case of a 14-year-old boy with the ALPS phenotype, eventually diagnosed with LRBA deficiency. He presented with lymphadenopathy and hepatosplenomegaly, along with autoimmune cytopenia. Due to recurrent infections and worsening gastrointestinal symptoms, whole-exome sequencing was conducted and revealed a novel homozygous pathogenic variant in the LRBA gene (c.534del; p.9Asp179IIef*16). The patient recently suffered from clinical deterioration due to SARS-COV-2 which appears to have triggered an acute worsening of his existing Cytomegalovirus colitis leading to an eventual demise. A literature search for reported LRBA deficient patients with ALPS-like phenotype revealed 11 patients. The most common clinical presentations in LRBA patients with ALPS-like phenotype included autoimmunity (100%), splenomegaly (91%), lymphadenopathy (36.4%), and respiratory tract infections (63.6%). LRBA deficiency is unique in the fact that it encompasses immune deficiency, autoimmunity, and lymphoproliferation. In children with multiple symptoms related to these domains, a genetic diagnosis is necessary to ensure tailored and precise medical therapy.

Keywords: Autoimmunity; Autoimmune lymphoproliferative syndrome; COVID-19; Human LRBA protein; Primary immunodeficiency diseases; SARS-CoV-2

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INTRODUCTION

LPS-responsive and beige-like anchor protein (LRBA) deficiency were described as a novel primary immunodeficiency (PID) in 2012.[1] This autosomal recessive condition has become one of the most commonly reported genetic defects in patients previously considered to have a common variable immune deficiency (CVID).[2] The biallelic mutations in the *LBRA* gene usually abrogate the protein expression of LRBA. This leads to immunodeficiency, specifically of B cells, and leads to hypogammaglobulinemia with low numbers of switched memory and increased numbers of CD21low B cells. B cells are low along with an imbalance in CD4+ T cells subsets, mainly in the regulatory T cell (Treg), helper T (Th)1, Th1-like, and Th17 cells. These factors are important in the immunopathogenesis of enteropathy and autoimmunity.[3]

Patients with LRBA deficiency present with a broad spectrum of clinical phenotypes including autoimmunity, enteropathy, hypogammaglobulinemia, and recurrent infections.[3] In some patients, this clinical presentation occurs along with a high frequency of double-negative ($CD3^+CD4^-CD8^-$) T-cells resembling clinical features of the autoimmune lymphoproliferative syndrome (ALPS).[3,4]

Here we report a case of a 14-year-old deceased male who was first diagnosed as a case of ALPS but whole-exome sequencing revealed a homozygous pathogenic variant in the *LRBA* gene.

CASE PRESENTATION

A 14-year-old boy first presented with prolonged fever, respiratory distress, hepatosplenomegaly, lymphadenopathy as well as thrombocytopenia, and anemia at the age of six months. A complete history at the time revealed an unremarkable birth history and first-degree parental consanguinity along with two older healthy male siblings. Moreover, there was no history of oncological or immune-related disorders within his family. This study was approved by the ethics committee of Alborz University of Medical Sciences, Karaj, Iran (IR.ABZUMS.REC.1399.336).

He was initially diagnosed with immune thrombocytopenic purpura (ITP) and was admitted multiple times in the first year of his life. The rare possibility of Evans syndrome was also entertained due to the combination of anemia and thrombocytopenia. Treatment included intravenous immune globulin (IVIg) and corticosteroids. Additionally, he was admitted for severe pneumonia requiring intensive care and mechanical ventilation within the same year. A bone marrow biopsy was normal at the time.

After a period of stability, his condition worsened at the age of three years when he required admission to the pediatric intensive care unit (PICU) for epistaxis, lymphadenopathy, hepatosplenomegaly, and severe thrombocytopenia (platelet count: 5.0×10^9/L) along with low hemoglobin (67 g/L). Investigations revealed a warm immunoglobulin (Ig) G-associated autoimmune hemolytic anemia (AIHA) and positive Epstein Barr Virus (EBV)in serum (118, 250 copies/mL). A chest computerized tomography (CT) showed multiple lymph nodes in both lungs distributed in the hilar, mediastinal, and right axillary regions (Figure 1 A). Of note, a repeated bone marrow biopsy only suggested a diagnosis of consumptive or ITP. Despite multiple transfusions and IVIg therapy, at a dose of 1 gram per kg, the child ultimately required urgent splenectomy to treat the refractory ITP. He was discharged with a presumed diagnosis of ALPS triggered by the EBV infection. Over the following eight years he continued to be admitted repeatedly with recurrent pulmonary and gastrointestinal infections (Figure 2) suggestive of an underlying immune deficiency related to a lymphoproliferative disorder. Figure 3 is a graphic representation of the various infections he suffered from over his lifetime. His immune deficiency presented in the form of hypogammaglobinemia and increased susceptibility to various infections. Laboratory evidence (Table 1) of low immunoglobulin levels was noted specifically due to an IgG of 4.05 g/L, an IgM level less than 0.05 g/L, and an IgA level less than 0.04 g/Las well as a low CD19 B-lymphocyte count (0.003×10^9/L) and an increased frequency of peripheral TCRαβ+CD3+CD4-CD8double-negative cells (4.8%). Infections included Escherichia Coli bacteremia, septic arthritis, recurrent cases of pneumonia leading to bronchiolitis obliterans (Figure 1B), chronic sinusitis, and most recently, *Cytomegalovirus (CMV)* positive colitis (Figures 2 and 3). Treatment consisted of antimicrobials specific to each infection episode as well as regular IVIg infusions and Pentamidine as prophylaxis against *Pneumocystis Jirovecci*. In terms of pulmonary care, he received an extensive daily nebulization regime for the

management of Bronchiolitis Obliterans. Of note, the multi-drug resistant *CMV* colitis is only responsive to Cidofivir and has been the most distressing and prolonged of all his infections. Next-generation sequencing performed on the CMV strain revealed multiple mutations leading to resistance against *Foscarnet* and *Ganciclovir*. Colitis symptoms have spanned over two years and in late 2020 this was further complicated by profuse rectal bleeding and rectal prolapse.

The lymphoproliferative manifestations included the aforementioned hepatosplenomegaly, lymphadenopathy, and an episode of leukocytosis with a total white blood cell count of 66.0×10^9/L.

Immune dysregulation and autoimmunity were initially evident with the onset of ITP, followed by hypothyroidism, interstitial lung disease (ILD), drug allergies to penicillin and cephalosporin as well as atopic dermatitis and arthritis. These pathologies were treated with Sirolimus and Mycophenolate Mofetil which are believed to be particularly useful in ALPS. Various other immune suppressants were also used including Azathioprine, repeated courses of steroids, and four cycles of Rituximab at the age of four years. The arthritis responded to intra-articular steroid injections.

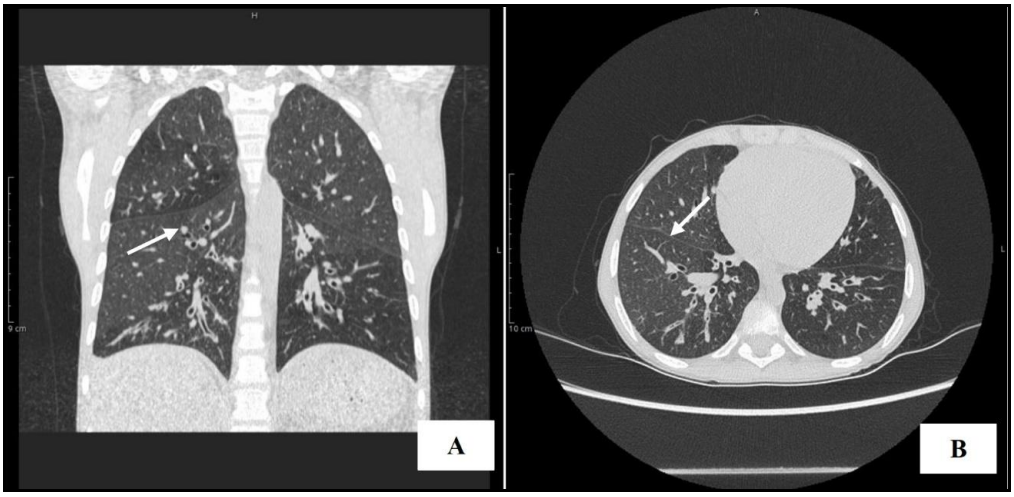

Figure 1. Chest computerized tomography (CT) of a patient at age of 3 years with LPS- responsive beige-like anchor protein (LRBA) deficiency showing multiple lymph nodes in both lungs (A) and Bronchiolitis Obliterans (B). Specifically, both images exhibit bilateral lower lobe and right upper lobe peribronchial thickening and mild bronchiectasis change with tree-in-bud appearance.

Table 1. Immunologic profile of ALPS-like patient with a mutation in *LRBA* gene, sampled at age 12 years

Parameters	Patient	Normal ranges
$CD3^+$ T cells (% of lymphocytes)	96.7	55.0-82.0
$CD3^+ CD4^- CD8^-$ T cells (% of CD3+ lymphocytes)	4.8	$\leq 2.5\%$
$CD4^+$ T cells (% of T cells)	53.9	27.0-57.0
$CD8^+$ T cells (% of T cells)	37.4	14.0-34.0
$CD19^+$ (% of lymphocytes)	0.08	9.0-29.0
$CD16^+56^+$ (% of lymphocytes)	2.1	2.0-19.0
IgG (g/L)	4.05	5.7-14.7
IgA (g/L)	<0.04	0.34-3.05
IgM (g/L)	<0.05	0.31-2.08
IgE (IU/mL)	< 1.0	<= 90.0

CD; Cluster of differentiation, Ig; Immunoglobulin, ALPS; Autoimmune lymphoproliferative syndrome, LRBA; LPS- responsive beige-like anchor protein.

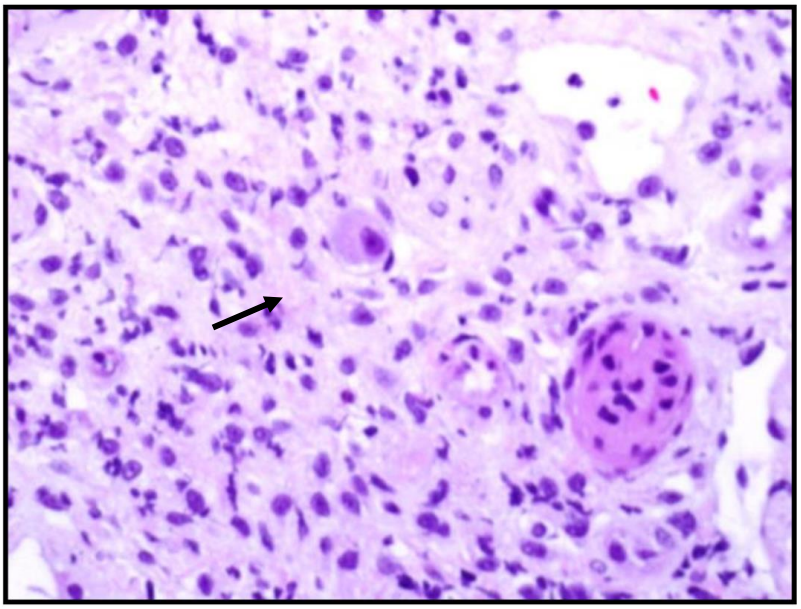

Figure 2. Histopathology specimen from the sigmoid colon at age 13 years. Sigmoidoscopy was done to diagnose Cytomegalovirus-positive colitis. This specimen shows colonic mucosa exhibiting some active chronic inflammation. Immunohistochemistry for Cytomegalovirus was positive. Arrow points to a Cytomegalovirus inclusion body.

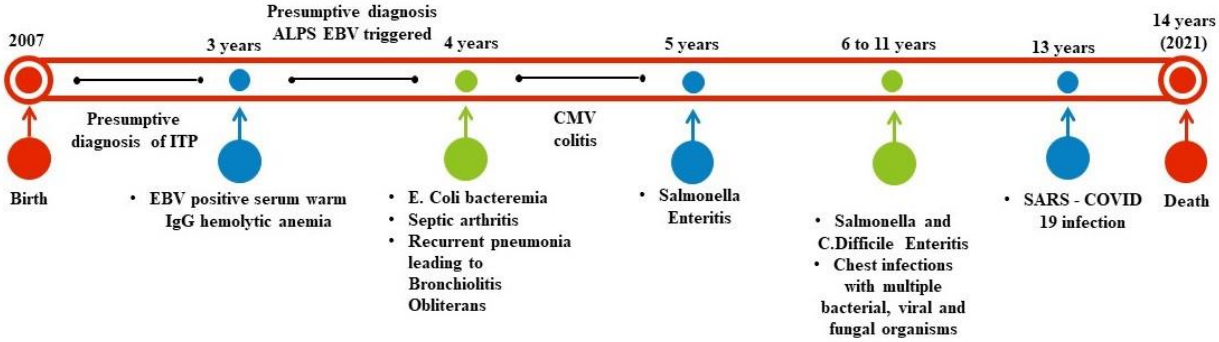

Figure 3. A timeline depicting various infections suffered throughout the lifetime of a patient diagnosed with LRBA deficiency.

ALPS; Autoimmune lymphoproliferative syndrome, EBV; Epstein-Barr virus, ITP; Immune thrombocytopenic purpura, CMV; Cytomegalovirus, Ig; Immunoglobulin.

An additional manifestation of the immune dysregulation included the possibility of inflammatory bowel disease (IBD) due to chronic diarrhea and high fecal calprotectin levels on two occasions. An initial calprotectin level was over 2100 µg/mL in December 2018, and was later found to be 360 µg/mL in February 2019 (normal range<50 ug/mL). However, IBD was ruled out after a colonoscopy conducted in February 2019, which was only indicative of CMV colitis. IBD was never fully excluded since the biopsy sample may have been insufficient and further sampling would have been needed specifically from colonic crypts.

His multidisciplinary team sought to prove the suspected diagnosis of ALPS via genetic confirmation in light of recent advances in the fields of immunology and the wider availability of genetic testing. A whole-exome sequencing performed in May 2019 identified a novel homozygous frameshift mutation in the *LRBA* gene (c.534del; p.9Asp179IIef*16).

Table 2. An overview of the clinical, immunological and genetic findings in reported LRBA patients with ALPS like phenotype

Article	Sex	Con	Age (M)	AOO(M)	AOD(M)	AIHA	ITP	Other autoimmune diseases	Splenomegaly	Lymphoadenopathy	RTI	Enteropathy	HSCT	Steroids therapy	mTOR inhibitor	Immunosuppressive	Elevared_DNT cell	Lym (Cell/μL)	CD4	CD8	CD19	IgG	IgA	IgM	Mutation	Zygosity
Fernandez et al, [14]	M	NA	48	48	168	+	+	-	-	+	-	-	-	+	+	MMF, Rituximab, Tacrolimus, Sirolimus, Abatacept	-	NA	NA	NA	NA	NA	NA	NA	c.1931dupC	Homo
Cagdas et al, [5]	M	-	78	48	60	-	+	-	+	NA	+	-	-	+	-	Cyclosporin, Abatacept	+	2600	NA	NA	NA	Hi	NA	NA	c.5805delT p.C1935Wfs*4	CH
	M	+	108	54	84	+	+	IBD, AIT	+	NA	+	+	+	+	-	Cyclosporin, MMF, Abatacept	+	2000	NA	NA	NA	Hi	NA	NA	c.675G>A p.W225*	Homo
	M	+	180	72	156	+	-	IBD, AIT	+	NA	+	+	+	+	-	Cyclosporin, MMF, Abatacept	+	9644	NA	NA	NA	Hi	NA	NA	c.5527delT p.C1843Afs*2	Homo
	M	+	54	54	108	+	+	-	+	NA	+	-	-	+	-	Cyclosporin, MMF, Abatacept	+	12500	NA	NA	NA	Hi	NA	NA	c.3396_3397delA p.N1132Lfs*8	Homo
	F	+	210	132	168	-	+	-	+	NA	+	-	+	+	-	Cyclosporin, MMF, Abatacept	+	1400	NA	NA	NA	Hi	NA	NA	c.7042C>T p.R2348*	Homo
	M	+	228	108	120	-	-	CD	+	NA	+	+	+	+	-	Cyclosporin, MMF, Abatacept	+	1800	NA	NA	NA	Hi	NA	NA	c.IVS6+1delT	Homo
	F	+	132	84	132	-	+	AIT	+	NA	+	-	-	+	-	Cyclosporin,	+	1900	NA	NA	NA	Hi	NA	NA	c.501+1_502-1	Homo

															Abatacept									p.G75_W183*
Revel-Vilk et al,[4]	M	+	36	36	36	+	NA	-	+	+	-	-	NA	+	+	MMF, Sirolimus	+	1400	1	Nor	Lo	Lo	Nor	Nor	c.7937T>G p.Ile2646Ser	Homo
	M	+	42	18	18	+	+	-	+	+	-	-	NA	+	+	MMF	+	1400	1	Nor	Lo	Nor	Nor	Nor	c.8139_8142dup C p.N2715Hfs*13	Homo
	M	+	106	72	84	+	+	-	+	+	-	-	NA	+	+	MMF, Sirolimus	+	1200	1	Nor	Lo	Nor	Nor	Nor	c.8139_8142dup C p.N2715Hfs*13	Homo

LRBA; LPS responsive beige-like anchor protein, M, Male; F, Female; Ig; Immunoglobulin, NA; Not available, RTI; respiratory tract infection, AIHA; Autoimmune hemolytic anemia, ITP; idiopathic thrombocytopenic purpura, Homo; Homozygote, CH; compound heterozygotes, Con; Consanguinity, AOO; Age of onset, AOD; Age of diagnosis, AIT; Autoimmune thyroiditis, CD; Celiac disease, MMF; Mycophenolate mofetil. * All cases are alive.

In terms of treatment, Abatacept was offered to the patient; however, the family did not consent to its use due to concerns for side effects. They did agree for him to continue receiving monthly IVIg infusions Trimethoprim/sulfamethoxazole as a thrice-weekly prophylactic antibiotic. In the interim, his care teams remained hopeful for curative allogeneic hematopoietic stem cell transplantation (HSCT) with a human leukocyte antigen (HLA) matched donor. Unfortunately, the patient recently suffered from further clinical deterioration and ultimate demise. In January 2021, he was admitted initially for safe isolation when he tested positive for COVID-19 while remaining asymptomatic from a respiratory standpoint. During admission, he eventually developed another episode of *Escherichia coli* bacteremia that required intravenous antibiotics. Of note, whilst he remained SARS-CoV-2 positive for one month after initial detection, he did not develop any respiratory or other COVID-19 related complications. Soon after, In March 2021, he was readmitted in hypovolemic shock due to severe rectal bleeding and required intensive care. Following these recent prolonged hospital stays and recurrent severe rectal bleeding episodes, our patient deteriorated from an already precarious baseline in terms of nutrition and general wellbeing. Unfortunately, he passed away in July 2021 in his hometown due to a fulminant CMV infection.

The Reported LRBA Patients with an ALPS-like Phenotype

Literature searches for reported LRBA patients with ALPS-like phenotype revealed 11 LRBA deficient patients of which two were females and nine were males. The median (IQR) age of onset of symptoms and age of diagnosis were 4.5 (4.0-7.0) and 9.0 (5-13.0) years, respectively (Table 2). The most common clinical presentations in LRBA patients with ALPS-like phenotype included autoimmunity (100%; [ITP in 80% and AIHA in 63.6%]), splenomegaly (91%), lymphadenopathy (36.4%), and respiratory tract infections (63.6%). Elevated double negative T cell was present in 10 patients (91%). Among 8 patients with available data, four patients underwent HSCT with a matched sibling donor at the median age of 16.0 (8.5-25.0) years. All patients were alive and engraftment was achieved during the median follow-up of 30.0 (19.5-45.0) months. The only reported complications after HSCT were autoimmune cytopenia and CMV infection in one patient.

DISCUSSION

Patients with LRBA deficiency exhibit heterogeneous clinical phenotypes including autoimmunity, enteropathy, hypogammaglobulinemia, and recurrent infections. In a systematic review of 109 patients, the most commonly reported clinical manifestations were autoimmunity (82%), enteropathy (63%), splenomegaly (57%), pneumonia (49%), and lymphadenopathy (43%).[4] ALPS patients demonstrate a spectrum of signs and symptoms as a consequence of lymphoid hyperplasia and the progressive accumulation of autoreactive B and T lymphocytes.[4] Immune dysregulation in ALPS patients leads to a lymphoproliferative disease with different clinical manifestations including lymphadenopathy, hepatomegaly, splenomegaly, and autoimmune disease.[5]

Similarly, our patient presented with lymphadenopathy and hepatosplenomegaly, along with refractory ITP and AIHA resembling an ALPS-like phenotype. Similarly, through a review of the literature, we found 11 reported LRBA patients who initially manifested as ALPS.[4] Moreover, ALPS is characterized by elevated double-negative T cell count as reported in 91% of LRBA patients with ALPS-like phenotype, and this feature was also observed in our patient. Furthermore, Revel-Vilk et al, reported LRBA deficient patients who presented with autoimmune cytopenia, splenomegaly, lymphadenopathy, elevated double-negative T cells, enhanced FAS mediated apoptosis, and raised serum FAS ligand levels resembling ALPS.[4] Therefore, patients with LRBA deficiency may be clinically diagnosed as ALPS, however, a progressive decrease in B cells, switched memory B cells, and IgG, as well as enteropathy, should raise the suspicion for LRBA deficiency. Analysis of the LRBA protein by either western blotting or flow cytometry is also useful in patients with missense LRBA variants.[5] Finally, the necessity of genetic diagnosis to provide early correct diagnosis and subsequent care should not be overlooked.

The most common mutation leading to LRBA deficiency is homozygous and this remains the case in the reported patient who had a frameshift homozygous

mutation in chromosome 4. The frequency of consanguinity, chronic diarrhea, bronchiectasis, and hepatomegaly is higher in homozygous patients than in patients with compound heterozygosity.[3] The type of mutation plays a role in terms of disease phenotype with nonsense mutations being more pathogenic than splicing or missense mutations.[3] Additionally, the location of the mutation is also of consequence with those closest to the 5' end of the gene holding a higher risk of absent or reduced protein function.[3] Nevertheless, there is no apparent genotype-phenotype correlation, as patients with the same mutation in LRBA, may present with different clinical phenotypes or even be asymptomatic.[6]

With regards to the impact of SARS-CoV-2 on such patients, existing literature remains sparse and anecdotal. Patients with immune disorders such as CVID, Wiskott - Aldrich syndrome, and severe combined immunodeficiency have been reported after being infected by SARS-CoV-2.[7-9] Apparently, SARS-CoV2 can trigger a cytokine storm in pulmonary tissue by releasing inflammatory mediators and leads to acute respiratory distress syndrome (ARDS). Therefore, whilst PID patients may not have a significantly higher mortality rate when compared to the general population and in fact, often their presentation may be mild, caution is necessary to ensure better survival rates.

In terms of novel treatments, Abatacept has been reported to improve symptoms in eight of eleven reported LRBA cases with an ALPS phenotype, while also causing significant fungal infections in some patients due to its immunosuppressive action.[10,11] It is designed to modulate the T-cell costimulatory signal mediated through the CD28-CD80/86 pathways. Essentially, Abatacept inhibits T cell activation by binding to CD80/CD86 on antigen-presenting cells and therefore prevents interaction with CD28, which in turn, prevents the complete co-stimulatory signal needed to activate T lymphocytes. Abatacept has been reported to successfully and rapidly improve autoimmune and inflammatory symptoms as well as significantly improve refractory ILD.[12] However, *Bal et al.* note that Abatacept does not always resolve all symptoms while long-term efficacy and safety data are still awaited. They suggest HSCT as a valid and successful alternative and possibly curative treatment.[13] Tesch et al, compared the clinical course of LRBA patients who had undergone HSCT to those who had not through an international retrospective study. They concluded that lifelong disease activity, which would necessitate the need for immunosuppression and risk of malignancy, must be weighed against the equally concerning risks of HSCT and required post-transplant care.[11]

The recent discovery of LRBA deficiency has allowed for accurate diagnoses in patients previously diagnosed as having a CVID clinical presentation. LRBA deficiency is unique in the fact that it encompasses immune deficiency, autoimmunity, enteropathy, and lymphoproliferation and is similar to the autosomal dominant condition, CTLA-4 deficiency. In children with multiple symptoms related to these domains, a genetic diagnosis is necessary to avoid delayed diagnosis and ensure tailored and precise medical therapy. Current research suggests the immune modulator Abatacept as well as HSCT as possible treatment modalities. This case report emphasizes the key role of a molecular diagnosis to reach a precise diagnosis in patients with suspected ALPS or ALP-like disorders to avoid delayed diagnosis and appropriately treat with disease-modifying agents such as the immune modulator Abatacept.

CONFLICT OF INTEREST

The authors do not have any conflicts of interest to disclose.

ACKNOWLEDGEMENTS

We wish to thank the patient, his family members, and staff from all the units that participated in the study. This work was supported by the vice chancellor for research, Alborz University of Medical Sciences.

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