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Clinical presentation and management challenges of sphingosine-1-phosphate lyase insufficiency syndrome associated with an SGPL1 variant: a case report

Vahid Saeedi[1], Nahid Rahimzadeh[2], Fahimeh Ehsanipour[1], Neda Shalbaf[5], Amirhosein Farahi[1], Khalil Rashidi[3] and Leila Kamalzadeh[4*]

Abstract

Background This case report describes a unique presentation of sphingosine-1-phosphate lyase insufficiency syndrome (SPLIS) caused by a rare SGPL1 variant, highlighting the diagnostic and management challenges associated with this condition.

Case presentation A 2-year-old Iranian female presented with steroid-resistant nephrotic syndrome (NS), primary adrenal insufficiency (AI), growth delay, seizures, and hyperpigmentation. Laboratory evaluation revealed hypoalbuminemia, significant proteinuria, hyperkalemia, and elevated adrenocorticotropic hormone (ACTH) levels. The patient was diagnosed with SPLIS through genetic testing, revealing a c.1018 C>T variant in SGPL1. Despite supportive treatment, including corticosteroids and cyclosporine, the patient's condition deteriorated, leading to end-stage renal disease and sepsis, ultimately resulting in death.

Conclusions This case underscores the clinical heterogeneity of SPLIS and the importance of early genetic evaluation in patients with combined NS and AI. Personalized management approaches and increased awareness among clinicians are essential to improve patient outcomes.

Keywords Sphingosine-1-phosphate lyase insufficiency syndrome (SPLIS), Sphingosine-1-phosphate lyase 1 (SGPL1), Sphingolipids, Nephrotic syndrome, Adrenal insufficiency, Case report

*Correspondence:
Leila Kamalzadeh
Kamalzadeh.l@iums.ac.ir; lkamalzadeh@gmail.com
[1]Pediatric Growth and Development Research Center, Institute of Endocrinology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[2]Department of Pediatrics, School of Medicine, Hazrate-e Rasool General Hospital, Iran University of Medical Sciences, Tehran, Iran
[3]Cancer Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[4]Geriatric Mental Health Research Center, Department of Psychiatry, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[5]Endocrine Research Center, Institute of Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

Background

The concurrent presentation of nephrotic syndrome (NS) and adrenal insufficiency (AI) in pediatric populations represents a complex clinical entity with significant diagnostic challenges. While NS typically presents with proteinuria, hypoalbuminemia, edema, and hyperlipidemia, extrarenal manifestations, such as AI, can complicate the clinical picture, necessitating comprehensive evaluations to elucidate underlying etiologies [1]. AI encompasses a spectrum of disorders affecting adrenal hormone production and manifests with a variety of symptoms, including fatigue, weight loss, electrolyte imbalances, and hyperpigmentation. It can be life-threatening due to the lack of cortisol and aldosterone [2].

The identification of mutations in the sphingosine-1-phosphate lyase 1 (SGPL1) gene has provided a novel link between NS and AI [3]. As discovered in 2017, sphingosine-1-phosphate lyase insufficiency syndrome (SPLIS), also known as nephrotic syndrome type 14, is a rare autosomal recessive disorder caused by mutations in the SGPL1 gene [4]. Approximately thirty pathogenic mutations have been identified in the SGPL1 gene, contributing to diverse phenotypes, including NS, AI, skin, neurological, and immune dysfunctions [5]. Despite the limited number of reported cases, the true prevalence of SPLIS is likely underestimated because of undiagnosed cases and limited clinical awareness [5, 6].

The pathogenesis of SPLIS is complex and not fully understood. The accumulation of sphingolipids disrupted Sphingosine-1-phosphate (S1P) signaling, and the loss of sphingosine phosphate lyase (SPL) products are likely involved in the development of the disorder. These mechanisms can lead to damage to various organs and tissues, resulting in the diverse clinical manifestations observed in SPLIS [7, 8].

Early diagnosis and management of SPLIS are crucial for preventing severe complications. Given the potential for irreversible organ damage, genetic testing and comprehensive evaluation are essential for patients with suspected SPLIS [9]. This case report presents a patient with a novel SGPL1 variant not previously reported in Iran, contributing to the growing body of knowledge on the genetic basis and clinical spectrum of this rare disorder.

Case presentation

Patient information

A 2-year-old Iranian female with an upper respiratory tract infection presented at Rasoul Akram Hospital, affiliated with Iran University of Medical Sciences, Tehran, Iran. She was the second child of consanguineous parents. Her elder sibling died at one year of age due to gastroenteritis. The patient was born at term via cesarean section and had a normal birth weight and length. The patient exhibited normal developmental progress, meeting age-appropriate milestones until the age of one year, when growth retardation commenced.

Approximately one month prior to the current admission, she was hospitalized at another facility due to failure to thrive and urinary symptoms. During that stay, laboratory tests revealed anemia, urinary tract infection, hematuria, and proteinuria. She was treated with a course of iron drops and antibiotics, but there was no significant response to the treatment.

Clinical findings

On admission, the patient presented fever, dehydration, tachycardia, productive cough, loss of appetite, and failure to thrive, with weight and length significantly below the 3rd percentile. Hyperpigmentation, noted by parents to have started a year prior, was present. Periorbital and peripheral edema occurred following intravenous rehydration.

Diagnostic assessment

The laboratory results revealed microcytic hypochromic anemia, and an elevated erythrocyte sedimentation rate (ESR), alongside mild hyperkalemia, elevated creatinine (Cr), and an estimated glomerular filtration rate (eGFR) of 15.4 mL/min/1.73 m2. The lipid profile was abnormal, indicating hypertriglyceridemia and hypercholesterolemia. Additional findings included hypoalbuminemia, significant proteinuria, and elevated levels of plasma lactate and ammonia. Hormonal assays revealed low cortisol (8 AM) and markedly elevated adrenocorticotropic hormone (ACTH) levels, with low 17-hydroxyprogesterone and low dehydroepiandrosterone sulfate (DHEA-S) levels. The laboratory results are detailed in Table 1.

Ultrasound findings revealed an infantile uterus without signs of Müllerian agenesis or a bicornuate uterus. The liver and gallbladder appeared normal, and no adrenal hyperplasia or calcification was observed. Increased renal echogenicity was detected. Echocardiography revealed normal cardiac anatomy with minor, clinically insignificant valve regurgitation. In the Technetium-99 m DMSA (Dimercapto Succinic Acid) renal scan, decreased uptake was observed in the lower poles of both kidneys, along with cortical defects in both kidneys. Brain magnetic resonance imaging (MRI) revealed increased signal intensity in the right cerebral hemisphere, bilateral occipital regions, and brainstem.

Given the significant proteinuria, hypoalbuminemia, edema, and dyslipidemia, the patient was diagnosed with nephrotic syndrome, and prednisolone treatment was initiated. A renal biopsy was recommended if no improvement was observed after four weeks. Concurrent hyperpigmentation and electrolyte imbalances raised concerns about adrenal insufficiency, with laboratory tests confirming low serum cortisol and significantly

Table 1 Laboratory data

Parameter	Result	Reference Range	Units
White Blood Cell Count (WBC)	12.0	5.0–14.5	$10^3/mm^3$
Segment	45.4%		
Lymphocytes	34.7%		
Monocytes	14.6%		
Eosinophil	4.3%		
Red Blood Cell Count (RBC)	4.77	3.7–5.3	$10^6/mm^3$
Hemoglobin (Hb)	**8.6**	10.5–14.0	g/dL
Mean Corpuscular Volume (MCV)	**75**	76.0–90.0	fL
Mean Corpuscular Hemoglobin (MCH)	24.2	23.0–31.0	pg
Mean corpuscular hemoglobin concentration (MCHC)	**29.0**	30.0–34.0	g/dL
Platelet Count	372	140–440	$10^3/mm^3$
Erythrocyte Sedimentation Rate (ESR)	**74**	< 20	mm/hr
Blood Urea Nitrogen (BUN)	**74**	5–25	mg/dL
Creatinine (Cr)	**2.7**	0.12–1.06	mg/dL
Fasting Blood Sugar	**75**	80–180	mg/dL
Serum Glutamic Oxaloacetic Transaminase (SGOT)	45	6–45	IU/L
Serum Glutamate Pyruvate Transaminase (SGPT)	40	20–60	IU/L
Alkaline phosphatase (ALP)	281	145–320	IU/L
Calcium (Ca)	9.2	8.7–9.8	mg/dL
Inorganic Phosphate (P)	5.5	3.5–6.8	mg/dL
Serum Sodium (Na)	136	136–145	mEq/L
Serum Potassium (K)	**5.8**	3.5–5.5	mEq/L
Serum Chloride (Cl)	**109**	95–105	mEq/L
Triglycerides	**213**	< 150	mg/dL
Total Cholesterol	**264**	< 200	mg/dL
Total Protein	**5.5**	6.0–8.0	g/dL
Albumin	**2.4**	3.5–5.5	g/dL
Total Iron Binding Capacity (TIBC)	238	230–440	µg/dL
Ferritin	36	20–120 ng/mL (women), 30–400 ng/mL (men)	ng/mL
Lactate (plasma)	**10.3**	0.5–2.2 mmol/L	mmol/L
Ammonia	**153**	68–136	µg/dL
C-Reactive Protein (CRP)	1	< 0.8 mg/dL	mg/dL
Free Thyroxine (T4)	0.89	0.7–1.8	ng/dL
Thyroid Stimulating Hormone (TSH)	5.1	0.7–6.4	µIU/mL
Anti TPO Antibody	9.52	Up to 35.0	IU/mL
17-Hydroxyprogesterone	**< 0.1**	0.2–0.8	ng/mL
Cortisol (8 AM)	**< 1**	3.7–19.4	µg/dL
Dehydroepiandrosterone Sulfate (DHEA-S)	**< 0.1**	37–271	µg/dL
Testosterone	0.1	0.1–1.2	ng/dL
Adrenocorticotropic Hormone (ACTH)	**> 2000**	10–60 pg/mL	pg/mL
Serum IgA	69	19–395	Mg/dL
Transglutaminase (tTG) IgA	3.1	< 12	U/mL
Transglutaminase (tTG) IgA	1.5	< 12	U/mL
Endomysial IgA	1.0	< 12	U/mL
Endomysial IgG	2.2	< 12	U/mL
Anti-Leishmania IgA	0	< 1/100	ELISA Units
Anti-Leishmania IgM	0	< 1/100	ELISA Units
Anti-Leishmania IgG	0	< 1/100	ELISA Units
Urine Volume/24 Hours	860	800–2000	mL
Urine Creatinine/24 Hours	10	10–15	mg/kg/day
Urine Protein/24 Hours	**51**	<4	$mg/m^2/hr$
Urine Random Protein	**95**	5–24	mg/dL
Urine Random Creatinine	35	20–140	mg/dL

Table 1 (continued)

Parameter	Result	Reference Range	Units
Urine Protein: Creatinine ratio	**2.71**	< 0.2	
Urine Analysis			
Color	Yellow		
Appearance	Clear		
pH	6	4.5–8.0	
Specific Gravity	1.007	1.003–1.030	
Protein	**+ 3**	Negative	
Blood	Negative	Negative	
Glucose	Negative	Negative	
White Blood Cells (WBC)	1–2	0–3	WBCs/hpf
Red Blood Cells (RBC)	0–1	0–2	RBCs/hpf
PCR COVID-19	Negative	Negative	
PCR Influenza Virus	Negative	Negative	
Stool Exam	Normal	Normal	

Note: Abnormal values are in bold

elevated ACTH levels. Although congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is the most common cause of adrenal insufficiency at this age, the patient's unexpectedly low 17-hydroxyprogesterone levels prompted the consideration of alternative etiologies for primary adrenal insufficiency.

Genetic evaluation

Owing to the familial history, consanguinity of the parents, and the unusual combination of nephrotic syndrome and adrenal insufficiency, genetic evaluation was warranted. Whole-exome sequencing identified a homozygous missense variant in the SGPL1 gene (NM_003901.4: Exon 11: c.1018 C>T, p.Arg340Trp). Based on ACMG/AMP guidelines [10], the variant was classified as a variant of uncertain significance (VUS), supported by the following evidence:

> *PM2 (Moderate): The variant is extremely rare in population databases, with a minor allele frequency (MAF) of 0.000007954 in gnomAD.*
> *PP3 (Supporting): In silico prediction tools and conservation analysis suggest a deleterious effect on protein function, supported by a BLOSUM score of -3 and alteration of a highly conserved residue across species.*
> *PP4 (Supporting): The patient's phenotype, including nephrotic syndrome and adrenal insufficiency, is highly specific to sphingosine-1-phosphate lyase insufficiency syndrome (SPLIS), a monogenic disorder caused by SGPL1 mutations.*

Further structural modeling of the SGPL1 protein revealed significant differences between the wild-type (p.Arg340) and mutant (p.Arg340Trp) forms. The p.Arg340Trp substitution introduces a bulky, aromatic tryptophan residue in place of the conserved arginine,, as shown in comparative crystallographic models (Fig. 1). This change alters the local physico-chemical properties, including steric and electrostatic interactions, in a highly conserved region of the protein. The structural model underscores the potential impact of this variant on SGPL1 function and aligns with computational predictions of pathogenicity.

Despite strong computational and phenotype-based evidence, functional validation and additional clinical data are required to reclassify this variant as "likely pathogenic" or "pathogenic."

To confirm the results of whole-exome sequencing, Sanger sequencing was performed on the patient and both parents. The analysis revealed that the patient was homozygous for the c.1018 C>T variant in the SGPL1 gene, while both parents were heterozygous carriers of the mutation, consistent with autosomal recessive inheritance. A normal control sample confirmed the absence of the variant (Fig. 2).

Therapeutic intervention

During hospitalization, the patient was treated with corticosteroids (prednisolone, 60 mg/m²/day), diuretics, and albumin infusions to manage adrenal insufficiency, nephrotic syndrome, and acute kidney injury (AKI Stage 3). Fluid management included balanced fluid administration to correct dehydration and maintain hemodynamic stability, diuretic therapy with furosemide to alleviate edema and prevent fluid overload, and judicious albumin infusions to address severe hypoalbuminemia while avoiding intravascular volume expansion. This comprehensive approach aimed to stabilize renal function and mitigate complications associated with nephrotic-range proteinuria and AKI. Despite treatment, she continued to experience hypertensive crisis and focal status epilepticus, necessitating additional

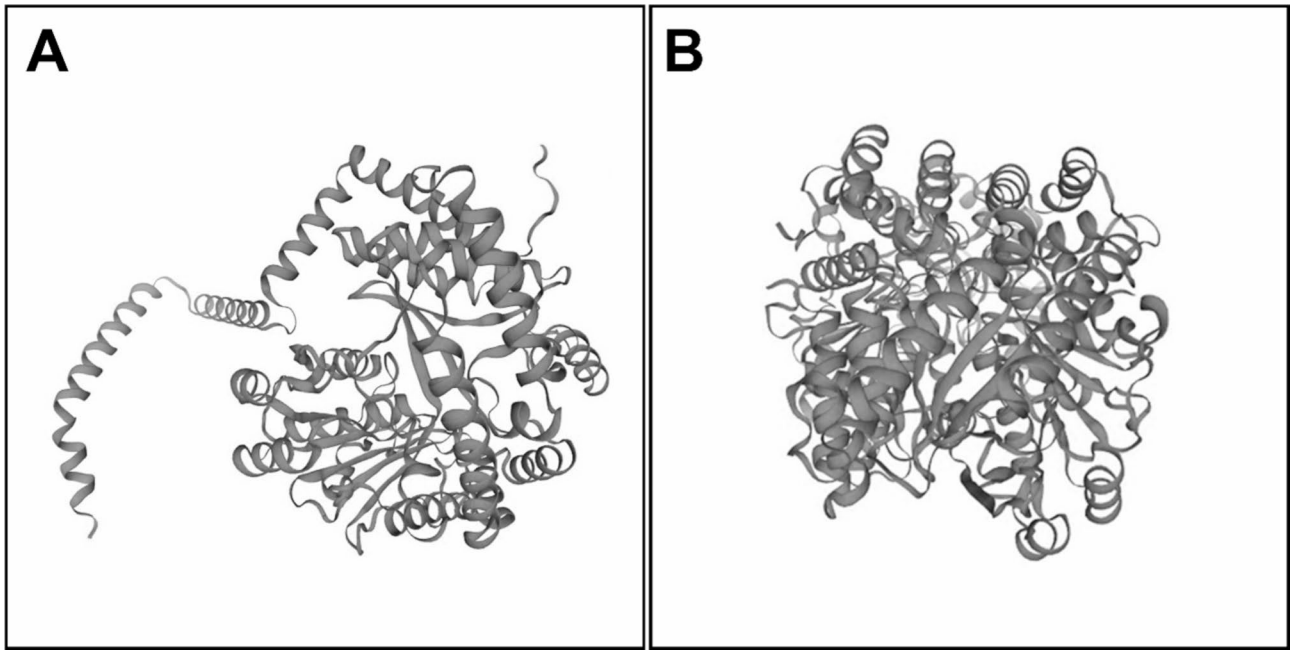

Fig. 1 **A** (Wild 340 SGPL1): Crystal structure of the wild-type SGPL1 protein showing the conserved arginine (Arg340) in its native configuration within the catalytic domain. **B** (Mutant 340 SGPL1): Crystal structure of the SGPL1 protein with the p.Arg340Trp mutation, highlighting the structural disruption caused by the introduction of a bulky, aromatic tryptophan residue

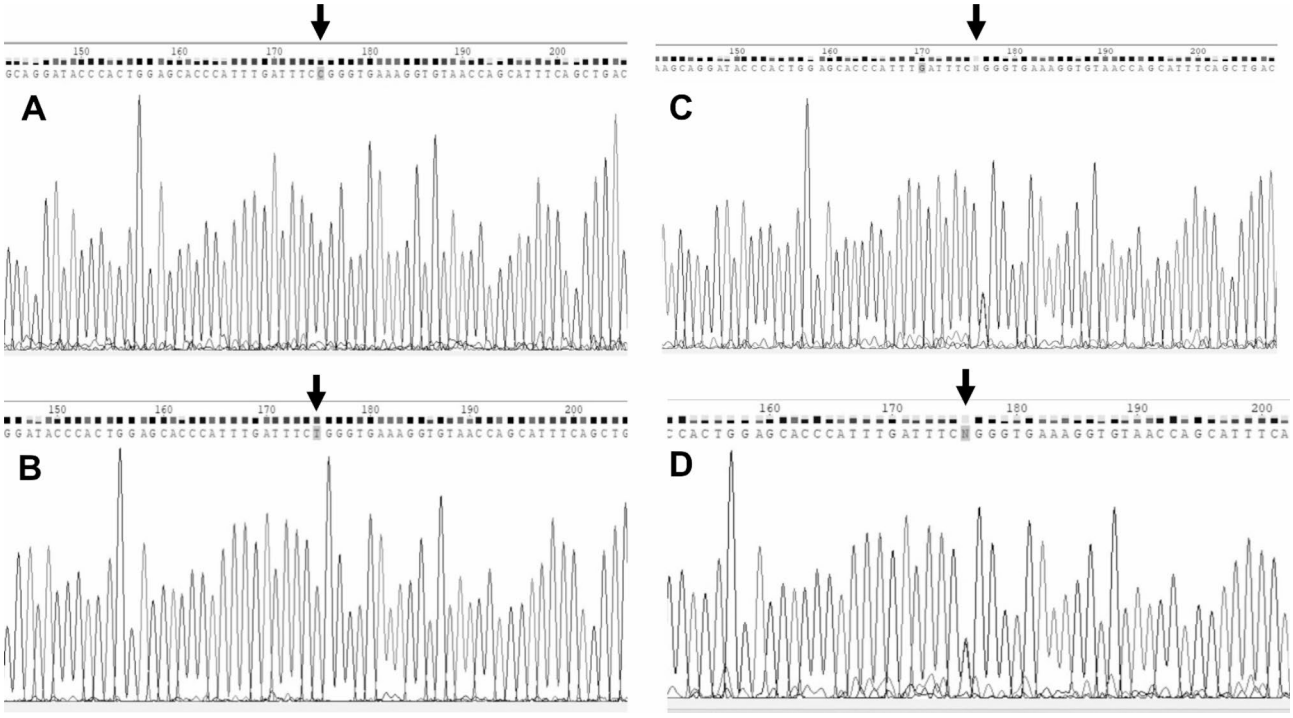

Fig. 2 Sanger Sequencing Results for SGPL1 Variant (c.1018 C > T, p.Arg340Trp). (**A**) Normal Control (Wild-Type): Homozygous wild-type sequence (C at position 1018). (**B**) Patient (Homozygous): Homozygous for the c.1018 C > T variant (T at position 1018). (**C**) Father (Heterozygous): Heterozygous for the c.1018 C > T variant, showing overlapping C (wild type) and T (mutant) peaks. (**D**) Mother (Heterozygous): Heterozygous for the c.1018 C > T variant, showing overlapping C (wild type) and T (mutant) peaks

antihypertensive and anticonvulsant medications. She was eventually discharged with prescriptions for furosemide, prednisolone, levetiracetam, atenolol, amlodipine, and calcium carbonate.

Follow-up and outcomes

Four weeks postdischarge, due to persistent generalized edema and nonresponse to treatment with steroids, a renal biopsy was performed, confirming the diagnosis of nephrotic syndrome with a histopathological pattern consistent with focal segmental glomerulosclerosis (FSGS). Immunofluorescence of the renal biopsy sample was negative for immunoglobulins and complement components (total Ig, IgG, IgM, IgA, C3, and C1q). Cyclosporine was added to the patient's treatment regimen.

Despite ongoing treatment efforts, the patient passed away due to renal function deterioration and sepsis approximately six months after hospital discharge.

Discussion and conclusions

This case report illustrates the diagnostic complexities associated with SPLIS in a pediatric patient who presented with steroid-resistant NS, primary AI, developmental delay, and seizures. The c.1018 C>T variant identified in our patient is novel in Iran and has not been reported in major databases, such as ClinVar [11], the Leiden Open Variation Database (LOVD) [12], or the Human Gene Mutation Database (HGMD) [13]. Although SGPL1 mutations have been reported in the Iranian population, such as c.932 C>G, p.Pro311Arg by Tran et al. [14] and c.1_27del (start loss) by Najafi et al. [15], these variants differ from the one described in our patient. The identification of this novel variant contributes to expanding the genetic spectrum of SPLIS in Iranian patients. Linhares et al. previously described this variant in a Brazilian child with congenital NS and Addison's disease [16]. Despite the shared mutation, the clinical presentations differed significantly, while the Brazilian case involved congenital NS, our patient developed NS after one year and did not exhibit thyroid abnormalities, underscoring the clinical heterogeneity of SPLIS. Such phenotypic variability is a hallmark of SPLIS, even among individuals with the same genetic mutation. For example, a recent case series highlighted that the most common SPLIS variant, p.R222Q, affected 11 children from different families, each presenting distinct endocrine and renal involvement levels. This variability reflects the syndrome's unpredictable genotype–phenotype correlations and varying disease penetrance within families [6]. A systematic review of 55 SPLIS cases further highlighted this variability, revealing endocrine manifestations (86.5%), kidney disorders (80.8%), and neurological dysfunctions (57.7%) as the most prevalent clinical features [5]. Endocrinopathies typically include adrenal insufficiency, hypothyroidism, hyperparathyroidism, and hypogonadism. Kidney disorders, primarily nephrotic syndrome, usually present early, often by 5 months, and are commonly associated with FSGS and rapid progression to end-stage kidney disease in more than one-third of cases. Neurological issues include seizures, microcephaly, neurodevelopmental delays, and peripheral neuropathy [5, 6]. Our patient exhibited many of these features but lacked hypothyroidism, lymphopenia, adrenal calcifications, and peripheral neuropathy. Notably, her renal biopsy confirmed FSGS, which was consistent with approximately 36% of reported SPLIS cases [5]. The variability in the severity and onset of organ failure in SPLIS suggests the influence of genetic and environmental factors, including polymorphisms in genes related to sphingolipid and vitamin B6 metabolism or dietary influences [17, 18]. This phenotypic diversity complicates the diagnosis, highlighting the need to consider SPLIS in pediatric patients with concurrent nephrotic syndrome and adrenal insufficiency.

Recent findings from a natural history study of 76 SPLIS patients by Keller et al. underscore the phenotypic heterogeneity of the condition and key survival determinants, including age and organ involvement at presentation, SGPL1 genotype, and access to kidney transplantation. High-risk subgroups, such as those diagnosed with nephropathy in the first year of life or with prenatal findings, had survival rates below 30% at two years, while those diagnosed after one year showed markedly better outcomes (over 70% survival). The study also highlighted the critical role of kidney transplantation in improving prognosis and noted genotype-specific differences, with the SPL R222Q variant associated with longer survival. Although our patient carried the novel p.Arg340Trp variant, the rapid progression to end-stage renal disease and subsequent fatality are consistent with the high-risk features identified in early-onset nephropathy [19].

Treatment options for SPLIS have expanded from supportive care to include targeted therapies such as mutant SGPL1 repair, enzyme replenishment, and bone marrow transplantation [7, 18]. Although not utilized in our patient, recent studies have introduced vitamin B6 supplementation, which has shown promise in some patients with specific SGPL1 missense mutations, improving lymphocyte counts and reducing sphingolipid levels. However, its efficacy in preventing end-organ damage remains unclear [18, 20]. Gene therapy via adeno-associated virus (AAV) vectors has shown promise in animal studies, but further research is needed to establish its clinical utility [21].

Conclusions

This case highlights the diagnostic challenges of SPLIS, emphasizing its clinical variability and the need for genetic evaluation in pediatric patients with nephrotic syndrome and adrenal insufficiency. The diverse presentations, even among patients with the same mutation, underscore the importance of personalized management. Early recognition,

genetic counseling, and targeted therapies are crucial for improving outcomes. Increased clinical awareness and further research are essential to refine the diagnosis and enhance care for SPLIS patients.

Abbreviations

AVV	Adeno-associated virus
AI	Adrenal insufficiency
ACTH	Adrenocorticotropic hormone
CAH	Congenital adrenal hyperplasia
DMSA	Dimercapto succinic acid
FSGS	Focal segmental glomerulosclerosis
HGMD	Human Genome Mutation Database
LOVD	Leiden Open Variation Database
MRI	Magnetic Resonance Imaging
NS	Nephrotic Syndrome
S1P	Sphingosine-1-Phosphate
SPL	Sphingosine Phosphate lyase
SGPL1	Sphingosine-1-Phosphate Lyase 1
SPLIS	Sphingosine-1-Phosphate Lyase Insufficiency Syndrome

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Author contributions
NR, FE, and NSh contributed to the literature review and patient data acquisition. VS, AF, KhR, and LK participated in patient data acquisition, data interpretation, consent, and manuscript preparation. All the authors read and approved the final manuscript.

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Data availability
Functional genomics data were deposited into the ClinVar database under accession number [VCV003362888.1] and are available at the following URL: https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV003362888.1.

Declarations

Ethics approval and consent to participate
Informed consent for participation was obtained from the patient's parents. The study adhered to the principles of the Declaration of Helsinki and received approval from the Institutional Review Board of Iran University of Medical Sciences (IR.IUMS.REC.1403.607). Rigorous measures were implemented to ensure anonymization.

Consent for publication
Informed consent for publication was obtained from the patient's parents.

Clinical trial number
Not applicable.

Competing interests
The authors declare no competing interests.

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