REVIEW

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Expanding the Clinical Features of Schimke Immuno-osseous Dysplasia: a New Patient with a Novel Variant and Novel Clinical Findings

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Abstract

Schimke immuno-osseous dysplasia (SIOD) (MIM:242900) is an ultra-rare, autosomal recessive, pan-ethnic pleiotropic disease. Typical findings of this syndrome are steroid-resistant nephrotic syndrome, cellular immunodeficiency, spondyloepiphyseal dysplasia (SED) and facial dysmorphism. Biallelic variants in the *SMARCAL1* gene cause SIOD. The five-and-a-half-year-old female patient was evaluated because of short stature, dysmorphism, hypercalcemia, hypophosphatemia, and elevated follicle-stimulating hormone (FSH) levels. Karyotype analysis and array-CGH testing were normal. Clinical exome sequencing (CES) was performed to analyze genes associated with hypophosphatemia. No pathogenic variant was detected. The subsequent detection of proteinuria during follow-up for cross-fused ectopic left kidney ultimately facilitated the diagnosis of SIOD, although no obvious SED was detected. Re-analysis of CES revealed a novel homozygous c.2422_2427 + 9delinsA pathogenic variant in the *SMARCAL1*. The literature on *SMARCAL1* gene pathogenic variants, including 125 SIOD cases from 38 articles was reviewed to investigate whether hypercalcemia, hypophosphatemia, and elevated FSH levels had been previously reported in SIOD patients. This review revealed that this was the first report of these findings in a patient with SIOD. Thus, this report expands both the phenotypic and genotypic spectrum of SIOD.

Keywords: *SMARCAL1*, hypercalcemia, hypophosphatemia, ectopic kidney, gonadal dysfunction

Introduction

Schimke immuno-osseous dysplasia (SIOD) (MIM: 242900) is an ultra-rare, autosomal recessive, pan-ethnic pleiotropic disease. The prevalence of SIOD is estimated to be 1 in 1-3 million live births in the USA (1). This syndrome was first described as chondroitin-6-sulfate mucopolysaccharidosis (2). However, after further studies, mucopolysaccharidosis was excluded (3). The main findings of this syndrome are steroid-resistant nephrotic syndrome, immunodeficiency, and spondyloepiphyseal dysplasia (SED). The short stature observed in almost all patients is due to the SED (4). Renal disease, mostly due to focal segmental glomerulosclerosis (FSGS), is progressive and eventually leads to end-stage renal failure. Defective cellular immunity is the cause of the associated immunodeficiency. Patients also exhibit typical phenotypic features, such as fine hair, a triangular face, a depressed nasal bridge, a bulbous nasal tip, microdontia, a short neck, a short trunk, hyperpigmented macules, and a protruding abdomen. In 2002, it was discovered that

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biallelic pathogenic variants in the SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, *subfamily A-like 1* gene (*SMARCAL1*) caused this syndrome (5).

Herein, we present a patient with SIOD who exhibited an atypical clinical presentation characterized by hypercalcemia and hypophosphatemia, resembling osteopenia of prematurity, along with elevated follicle-stimulating hormone (FSH) levels indicative of primary gonadal failure. Furthermore, we conducted a review of all genetically confirmed cases of SIOD, providing an occurrence ratio of clinical and laboratory findings in comparison with our patient.

Diagnostic Insights in Schimke Immuno-osseous Dysplasia

A one-and-a-half-year-old female was referred to the medical genetics outpatient clinic with disproportionate short stature and renal failure. She was the second child of a 33-year-old mother and 36-year-old father, both of whom were healthy. Although there was no consanguinity between her parents, they both came from the same small village. Family history was unremarkable. She was born at 30 gestational weeks with a birth weight of 945 g [-2.1 standard deviation score (SDS)] and birth length of 35 cm (-2 SDS), and was hospitalized in the neonatal intensive care unit (NICU) for three months due to prematurity. At that time, patent ductus arteriosus, patent foramen ovale, and atrial septal defect were detected by echocardiography. Her cranial ultrasonography (USG) was normal. She passed the hearing test and her ophthalmologic examination revealed no retinopathy of prematurity.

The timeline of the patient's medical history and diagnostic procedures, and results are shown in Figure 1. At the initial presentation, at the age of 7 months, she was referred to the pediatric endocrinology clinic for hypercalcemia. On physical examination, height was 58 cm (-3.9 SDS), weight was 4.5 kg (-4.4 SDS), and head circumference was 38 cm (-4.2 SDS), while mid-parental height was at -1 SDS. The dysmorphic examination revealed that she had fine and sparse hair, microcephaly, prominent forehead, synophrisis, upslanting palpebral fissures, malar hypoplasia, depressed nasal bridge, bulbous nasal tip, long philtrum, thin upper lip, retrognathia, everted lower lip, microdontia, posteriorly rotated and low set ears, anteverted ears, short neck, short trunk, hyperpigmented macules on the trunk, protruding abdomen, tapering fingers, and brachydactyly (Figure 2). External genitalia were normal.

The laboratory evaluation revealed the following results: calcium (Ca) of 11.6 mg/dL [normal range (NR) 8.7-11], PO_4 of 3.2 mg/dL (NR 5.0-7.8), alkaline phosphatase (ALP) of 1122 U/L (NR 116-450), 25-OH vitamin D of 24.4 µg/L (NR 30-100), parathyroid hormone of 6.2 ng/L (NR 15-65), creatinine (Cre) of 0.19 mg/dL (NR 0.0-0.42), magnesium of 2.4 mg/dL (NR 1.8-2.6), urinary Ca/Cre ratio of 0.4 mg/mg (NR 0.03-0.8), tubular phosphate resorption of 98% (NR 85-100), and tubular maximum for phosphate/glomerular filtration rate of 5.45 (NR 4.8-8). The laboratory and wrist X-ray were consistent with the osteopenia of prematurity and rickets, which were related to phosphate deficiency. Phosphate replacement therapy was initiated and continued for five months, resulting in the normalization of biochemical parameters and improvement in radiological findings (Figure 2).

The patient had not demonstrated catch-up growth and exhibited poor growth velocity. She began to sit independently at 10 months old and started walking at 18 months. She also had her first words at 18 months.

Endocrinological evaluation of short stature at the age of 19 months revealed low levels of insulin-like growth factor-1 (IGF-1) (-2 SDS) and IGF binding protein-3 (IGFBP-3) (-2.4 SDS) along with an elevated FSH level (24 U/L). Biochemical parameters, including renal function and celiac-associated antibodies showed no abnormality. The bone age was consistent with the chronological age (Figure 2a.3). Turner syndrome was considered as a potential diagnosis due to the presence of short stature, an ectopic kidney, and elevated FSH levels. However, karyotype analysis and array-CGH testing demonstrated a 46,XX karyotype with no deletion or duplication. Furthermore, a growth hormone (GH) stimulation test with glucagon showed a high basal GH level (17.6 ng/mL) and an exaggerated peak GH response (32 ng/mL) with consistently elevated GH levels throughout the test. One year after the first elevated FSH measurement, FSH was 14.1 U/L, luteinizing hormone was <0.2 U/L and estradiol was 13.3 ng/L at the age of 2.5 years. The first The first elevation in thyroid-stimulating hormone (TSH) was detected at age 3 years and had worsened by the age of 3.5 years, with levels of 6.44 mIU/L and 12.80 mIU/L (NR 0.70-5.97), respectively.

Furthermore, USG of the urinary tract showed a cross-fused ectopic left kidney at initial evaluation. The patient was referred to pediatric nephrology. At nephrological follow-up of the patient, she had experienced recurrent urinary tract infections. She was diagnosed with nephrotic syndrome at the age of 1.5 years. She was treated with albumin infusions, diuretics, angiotensin-converting enzyme inhibitors, and corticosteroids but failed to respond. The patient presented with severe decompensation of nephrotic syndrome that required peritoneal dialysis for 10 months and she received

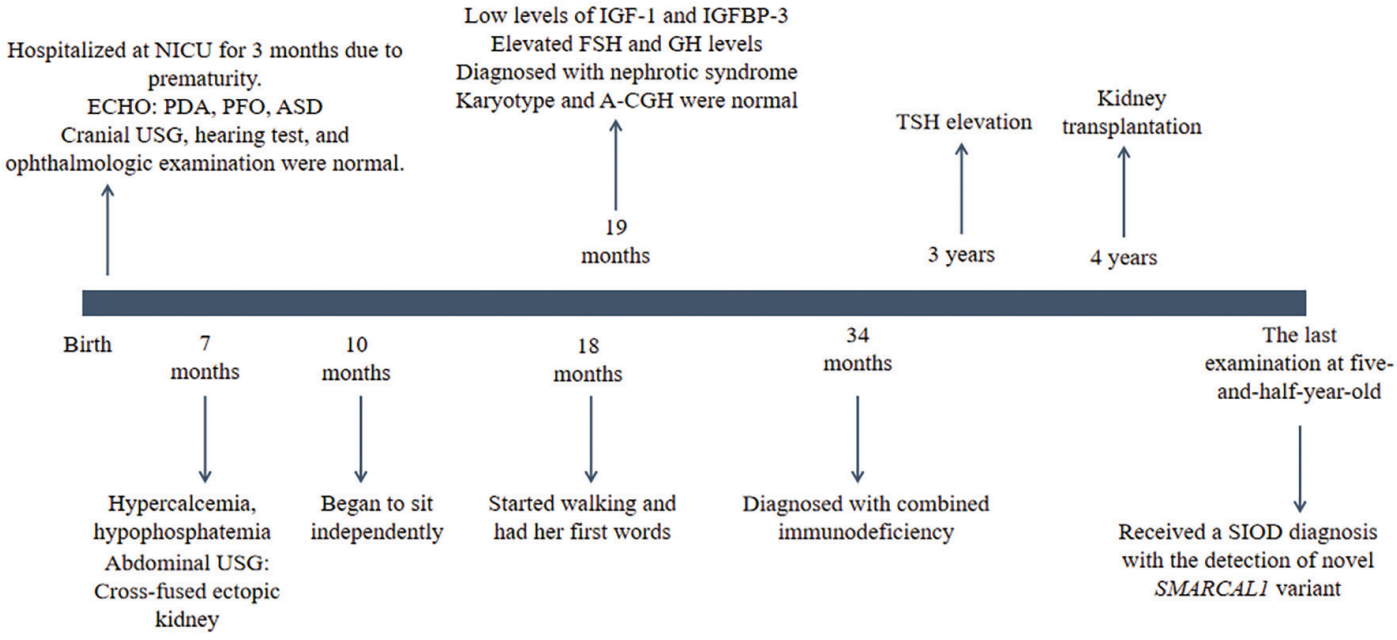

Figure 1. The timeline of the patient's medical history and diagnostic procedures, and results

NICU: neonatal intensive care unit, IGF-1: insulin-like growth factor-1, IGFBP-3: IGF binding protein-3, TSH: thyroid stimulating hormone, USG: ultrasonography

a kidney transplant from her uncle when she was 4 years old. The patient was not deemed to need a renal biopsy since she had received a genetic diagnosis. The patient's initial blood pressure measurement was 92/54 mmHg, while at the last measurement, it was 118/84 mmHg (NR 105/63).

Nephrological evaluation revealed hemoglobin 15.6 g/dL (NR 12-16), hematocrit 46.7% (NR 36-48%), mean corpuscular volume 80.9 fL (NR 80-100), white blood cell $7.3x10^3$/µL (NR 4.5-11$x10^3$), mild lymphopenia of $1x10^3$/µL (NR 2.1-7.8$x10^3$) (5), platelet count $293x10^3$/µL (NR 150-450$x10^3$), hypoalbuminemia with an albumin of 2.2 g/dL (NR 3.4-5.4), high total cholesterol level of 382 mg/dL (NR < 200) and hypertriglyceridemia of 253 mg/dL (NR < 150). Urinalysis demonstrated 3+ proteinuria. Spot urine protein was 1043 mg/dL (NR 0-10), urine Cre 37 mg/dL (NR 20-275), and the urine protein/Cre ratio was calculated as 28.1 mg/mg Cre (NR < 0.5). Serum complement C3 level was 197 mg/dL (NR 80-120) and C4 level was 59 mg/dL (NR 10-40).

Although no obvious bone dysplasia was initially detected on hand X-rays, SIOD was considered as a potential diagnosis after the development of nephrotic syndrome. However, a more comprehensive skeletal survey revealed certain skeletal abnormalities, including ovoid vertebral bodies and shallow acetabular fossae with laterally displaced femoral heads (Figure 2c, 2d). Notably, there were no epiphyseal changes observed. Subsequent X-rays taken at the age of five-and-a-half-years displayed mild platyspondyly, metaphyseal widening of the long bones, and osteopenia with metaphyseal sclerosis (Figure 2d.1).

Immunological analyses at the age of 34 months revealed mild lymphopenia of $1.3x10^3$/µL, low serum IgG of 157 mg/dL (NR 604-1921), but normal levels of IgA 58 mg/dL (NR 26-228), and IgM 167 mg/dL (NR 71-235). Serum IgE level was moderately elevated as 149 IU/mL. The patient also had anemia and thrombocytopenia. Responses to protein antigens, including hepatitis B, mumps IgG were negative, and measles, varicella, and rubella IgG were positive. Lymphocyte subgroup analysis showed severe CD3+ T, CD4+ T, and CD8+ T lymphopenia accompanied by decreased naive and increased memory CD4+ and CD8+ T cells. Elevated CD19+ B lymphocyte numbers were detected, while CD16+ CD56+ NK cell numbers were normal. Although the patient had no history of recurrent infections other than recurrent urinary tract infections, concomitant prophylactic antibiotics and immunoglobulin infusions were administered every 3 weeks with a diagnosis of combined immunodeficiency. The clinical findings of the patient are summarized in Table 1.

After obtaining informed written consent from the patient's parents, DNA was isolated from her peripheral blood using QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). Clinical

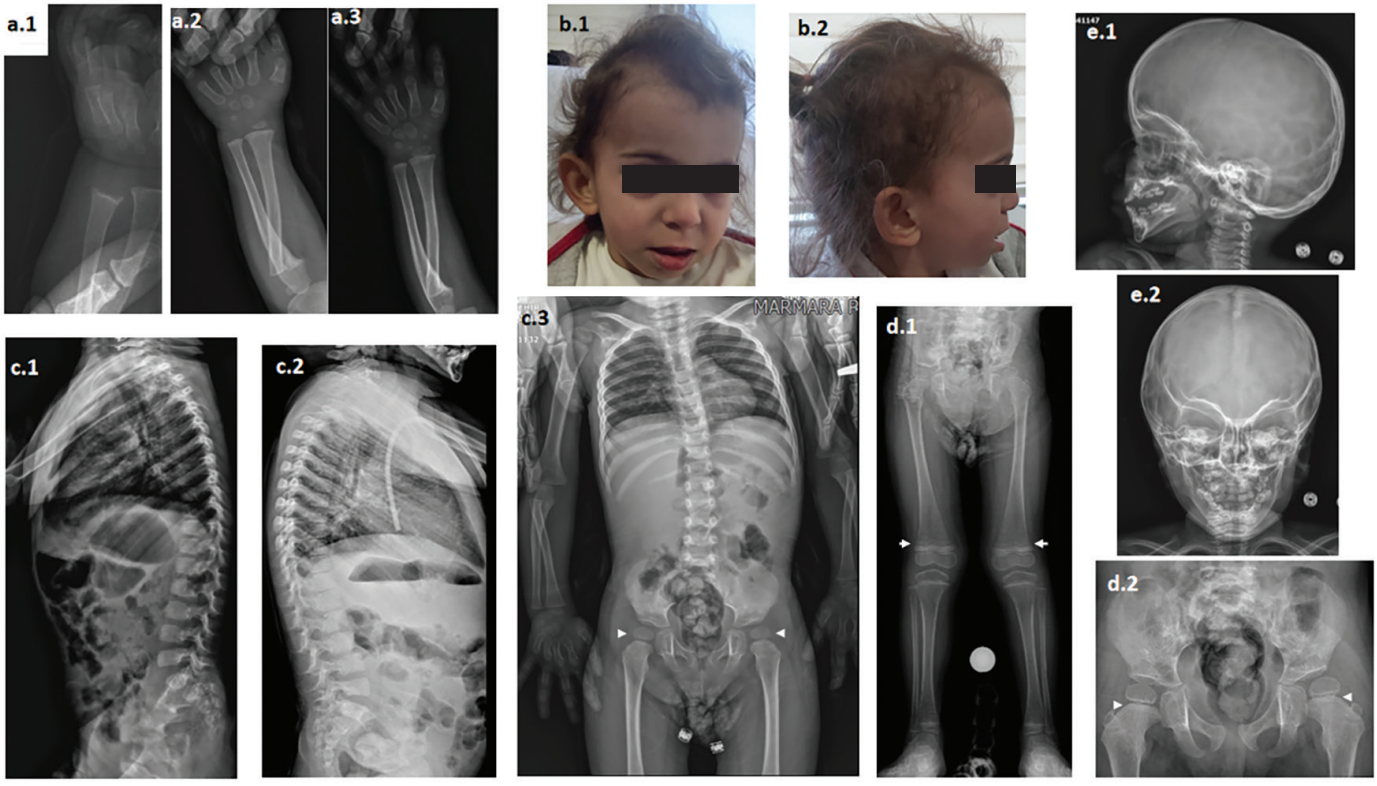

Figure 2. a) Hand radiograph at 7 months of age reveals osteopenia and cupping of distal ulna (a.1). By the age of 19 months, complete resolution of rickets findings and osteopenia, and, bone age is consistent with that of a 2-year-old (a.2). At the age of 32 months, bone age is 3-year-old (a.3). b) Facial pictures display various dysmorphic features including; fine and sparse hair, microcephaly, prominent forehead, synophrisis, upslanting palpebral fissures, malar hypoplasia, depressed nasal bridge, bulbous nasal tip, long philtrum, thin upper lip, retrognathia, everted lower lip, posterior rotated and low set, anteverted ears, short neck. c) Spinal radiographs shows mild ovoid vertebra (c.1) with mild lumbar scoliosis (c.3) at the age 33 months, and, mild platyspondyly at the age of five-and-half-years. d) At the age of five-and-half-years, long leg radiographs demonstrate mild coxa valga deformity with metaphyseal widening of long bones, resembling an Erlenmeyer flask deformity, metaphyseal sclerosis (arrow) and osteopenia (d.1), shallow acetabular fossae and lateral displacement of capital femoral epiphysis (Arrowhead) (d.2), which is more pronounce compared to the finding at 33 months of age (c.3). There is no obvious epiphyseal involvement. e) Cranial radiographs show J-shaped Sella turcica

exome sequencing (CES) was performed via next-generation sequencing (Illumina Nextseq 500) using Sophia Clinical Exome Solution V2. Data were analyzed through the Sophia DDM-V4 platform. Non-synonymous (missense, nonsense, in-frame, frameshift) variants with minor allele frequency less than 1.0% in population studies (1000 Genomes-1000G, Exome Aggregation Consortium database-ExAC, and Genome Aggregation Database-gnomAD) were filtered. American College of Medical Genetics and Genomics (ACMG) criteria were also applied. Retained variants were searched for in ClinVar and the Human Genome Mutation Database (HGMD). Segregation analyses were also performed via Illumina Nextseq 500. Molecular analysis revealed a novel homozygous c.2422_2427+9delinsA (NM_001127207) variant in the *SMARCAL1* gene (Figure 3a). It was localized at the donor site of the 15th exon. This variant was not reported in Clinvar and HGMD. According to ACMG criteria, this variant was pathogenic (PVS1, PM2, PP3). Segregation analysis revealed that her parents were heterozygous for this variant (Figure 3b, 3c). Given the presentation at the age of seven months with hypophosphatemia requiring phosphate replacement, genetic causes of hypophosphatemia were considered. No variant was detected in the customized panel containing *PHEX, DMP1, FGF23, ANKH, CYP27B1, CYP2R1, VDR, CYP3A4, CYP24A1, SLC34A1, SLC34A3, KL, GALNT3, CLCN5, SLC2A2, OCRL, FAM20C, FGFR1, ABCC6, ALPL, EXT1, SLC9A3R1, AVPR2* genes selected from CES.

Discussion

SIOD is a pleiotropic disorder with typical clinical findings of short stature, SED, immune deficiency, renal involvement, and typical dysmorphic findings. However, the diagnosis of SIOD can be challenging before the occurrence of renal

Table 1. A comprehensive overview of all reported findings with *SMARCAL1* variant in the literature along with the details of our case

	Patients in literature	Present case	Reference
Sex	71 M/54 F	F	
Age (year)	9.3 mean	5.5	
Growth and endocrine features			
Short stature, disproportionate	55/55 (100%)	+	1, 4, 7-19, 22-25, 26-41
Intrauterine growth retardation	68/72 (94.4%)	+	1, 4, 7-15, 18, 19, 22-24, 27, 30, 32, 37-39, 41, 43, 44
Elevated TSH	31/61 (50.8%)	+	1, 4, 9, 10, 14, 15, 22-24, 31-34, 42
Head and neck			
Short neck	20/22 (90.9%)	+	7, 9-11, 13, 14, 16, 18, 23, 24, 29, 30, 32, 33, 37, 39, 42, 44
Corneal opacities	4/9 (44.4%)	-	10, 24, 32
Depressed nasal bridge	48/55 (87.2%)	+	1, 6, 7, 9, 10, 12, 15, 16, 22, 30, 32, 37, 38, 40, 44
Bulbous nasal tip	48/55 (87.2%)	+	6, 7, 9, 10, 12, 14, 16, 22, 30-32, 37, 38, 40, 44
Dental anomalies (including microdontia)	13/19 (68.4%)	+	9, 10, 13, 14, 29, 31, 32, 38, 44
Hyperpigmented macules	46/55 (83.6%)	+	6, 7, 10-14, 16, 17, 23, 24, 30-32, 38, 40, 44
Fine hair	7/9 (77.7%)	+	1, 16, 30-32, 40
Abdomen			
Protruding abdomen	16/18 (88.8%)	+	7, 9, 10, 14, 16, 22-24, 30, 32, 38, 39, 42, 44
Renal			
Nephrotic syndrome	81/83 (97.5%)	+	1, 6, 8-19, 21-24, 26-31, 33, 35-39, 42, 44
Focal segmental glomerulosclerosis	55/65 (84.6%)	N/A	1, 4, 9-13, 15, 17-19, 22, 23, 28, 29, 33, 35-39, 44
Perihilar mesangial deposition of proteinaceous material	2/2 (100%)	N/A	10, 29
Renal failure	39/49 (79.5%)	+	10-15, 17-19, 21, 24, 26, 27, 31, 33–35, 37, 38, 40, 43
Hypertension	23/28 (82.1%)	+	10-16, 19, 26–29, 33, 38, 40, 42, 44
Proteinuria	84/84 (100%)	+	1, 4, 6-19, 21-24, 26-39, 42, 44
Skeletal			
Spondyloepiphyseal dysplasia	52/55 (94.5%)	-	6, 12, 13, 17, 19, 22, 23, 26, 29, 30–32, 35–39, 41–44
Osteopenia	6/8 (75%)	+	9, 12, 14, 18, 42
Lumbar lordosis	6/7 (85.7)	-	10, 13, 18, 22, 37
Platyspondyly	15/20 (75%)	+	7, 10, 12-14, 18, 22, 24, 29, 30, 32, 42, 43
Ovoid vertebral bodies	4/8 (50%)	+	7, 12, 29, 30
Thoracic kyphosis	3/6 (50%)	-	10, 23, 39
Short, broad iliac bones	3/3 (100%)	-	1, 22, 43
Slanted acetabular roofs/Shallow acetabular fossae/Small capital femoral epiphyses/Laterally displaced femoral heads/Hip dysplasia	28/30 (93.3%)	+	10, 12-15, 18, 21-24, 26, 27, 29–32, 35, 38, 42–44
Neurologic			
Normal intelligence	15/19 (78.9%)	+	1, 7, 8, 10, 11, 13, 14, 19-32, 37, 39, 43, 44
Motor delay	18/50 (36%)	-	4, 9, 16, 19, 24, 31, 41
Transient ischemic attacks	20/33 (60.6%)	-	10-15, 18, 19,27, 28, 31, 34, 38, 44
Moyamoya	4/11 (36.3%)	-	12, 13, 15, 18
Cerebral infarcts	44/94 (46.8%)	-	4, 6, 10-12, 18, 19, 24, 26, 29, 33, 34, 38, 44
Hematology			
Neutropenia	27/51 (52.9%)	-	6, 7, 10, 12, 16, 17, 19, 24, 35, 38, 40, 44
Lymphopenia	69/79 (87.3%)	+	1, 6, 7, 10-13, 16-19, 24, 28, 32, 35, 37–41, 44
Thrombocytopenia	19/46 (41.3%)	+	6, 10, 12, 16, 18, 19, 38, 40
Anemia	22/45 (48.8%)	+	6, 10-13, 16-19, 37, 38, 44

Table 1. Continued

	Patients in literature	Present case	Reference
Immunology			
Recurrent infections	65/104 (62.5%)	+	4, 6, 7, 10-13, 15-19, 21, 24, 29, 33, 36, 38, 40, 41, 44
Defective cellular immunity	8/8 (100%)	+	7, 8, 10, 16, 24, 29
T-cell deficiency	31/31 (100%)	+	1, 7-10, 13, 16, 18, 19, 23, 24, 26, 28, 29, 31–33, 35, 36, 38, 39, 41, 42
Decreased CD4+ and CD3+/CD4+ lymphocytes	24/24 (100%)	+	7-10, 13, 16-18, 23, 28, 29, 35, 36, 38, 39, 41, 42
Abnormal immunoglobulin levels	7/12 (58.3)	+	23, 24, 29, 32, 38, 41
Additional findings			
Fused crossed ectopic kidney	2/125 (1.6%)	+	19, 23
Hypercalcemia	0/125 (0%)	+	
Hypophosphatemia	0/125 (0%)	+	
Elevated FSH levels	0/125 (0%)	+	

TSH: thyroid stimulating hormone, FSH: follicle-stimulating hormone, M: F: male, F: female, N/A: non-applicable

findings, as observed in the presented case. The presented patient was born prematurely with intrauterine growth retardation (IUGR) and required prolonged hospitalization in the NICU. Subsequently, she presented with hypercalcemia related to the hypophosphatemia and needed prolonged (5 months) phosphate replacement. Genetic analysis for hypophosphatemia found no etiology, and she was accepted as having osteopenia of prematurity. Later follow-up demonstrated no catch-up growth and the presence of elevated FSH, along with an ectopic kidney, suggested Turner syndrome. However, further investigation, including a normal female karyotype and array-CGH testing did not confirm this diagnosis. Nephrological follow-up for the patient, focusing on her cross-fused ectopic left kidney and recurrent urinary tract infections, ultimately led to the early diagnosis of proteinuria and SIOD.

When we reviewed all published genetically-confirmed cases of SIOD, all cases exhibited short stature, and almost all (94.4%) had IUGR. In addition, proteinuria was a consistent feature in all cases, serving as the primary indicator leading to the diagnosis of SIOD, as observed in the presented case. Although short stature is a universal feature of SIOD, only a few patients have had their GH/IGF-1 axis evaluated. Almost all of the evaluated cases demonstrated normal GH levels on GH stimulation tests (7,8,9,10). Furthermore, when the patients were treated with GH, they responded poorly to GH treatment (4,6,11,12,13) even in the case of low GH levels at GH stimulation tests (14). The presented patient, however, showed high basal GH levels and an exaggerated peak GH response to stimulation, along with low IGF-1 and IGFBP-3 levels, indicative of GH resistance. When all reported patients were evaluated from this perspective, although most GH stimulation tests were described as normal (exact values not provided), at least one patient had GH levels similar to ours (9). However, IGF-1 and IGFBP-3 levels were not mentioned in any of the other patients. In light of the poor response to GH treatment, normal or high GH levels, and low IGF-1 and IGFBP-3 levels in our case, SIOD may be considered a condition of GH resistance related to the primary disease. Furthermore, the final height of patients with SIOD ranged from 110 to 165 cm for males and from 107 cm to 143 cm for females (6,15). Table 1 presents a comprehensive overview of all reported findings in the literature, along with the details of the presented case.

Primary gonadal failure and elevated FSH levels had not been previously reported in any SIOD patients. The FSH level was reported only once in a 14-year-old male patient and was found to be normal (9). However, cryptorchidism has been reported in five patients and may be a sign of hypogonadism (12,15,16,17,18). Furthermore, SMARCAL1 expression has been reported in fetal ovaries and testis (20). Therefore, pathogenic variants in this gene may plausibly lead to gonadal dysfunction. The reason for gonadal failure remaining unrecognized in SIOD could be due to the severity of renal or other systemic diseases and renal transplantation. More detailed laboratory studies are required in other cases of SIOD for further explanation of this issue. Unfortunately, although our patient had persistently elevated FSH levels, we did not measure anti-Mullerian hormone.

The other features we report for the first time here are hypercalcemia, hypophosphatemia and rickets in SIOD. However, these features may not be inherent to SIOD and could be a co-occurrence related to prematurity and insufficient phosphate intake.

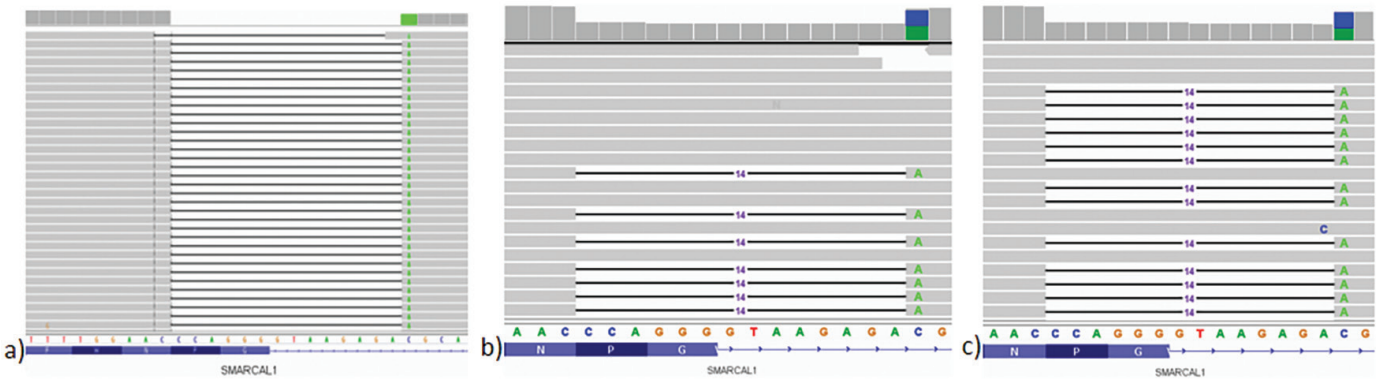

Figure 3. (a) Integrative genomics viewer visualization of novel homozygous c.2422_2427 + 9delinsA (NM_001127207) variant in the *SMARCAL1* gene detected in the patient. b, c) Her parents were heterozygous for this variant

The renal phenotype of SIOD is steroid-resistant nephrotic syndrome, which is progressive and often leads to end-stage renal failure. The main renal histopathology is FSGS; however, minimal glomerular lesions and podocytic infolding glomerulopathy have also been detected (21,22). Our patient exhibited an additional renal phenotype, namely crossed-fused ectopic kidney. Our literature review of a total of 125 genetically confirmed patients revealed crossed-fused ectopic kidney in two other SIOD patients (19,23). Furthermore, one patient with an ectopic kidney (24) and another patient with unilateral renal agenesis (10) have been reported. SMARCAL1 expression is known to be high in fetal kidneys and collecting ducts (23). Therefore, the association between *SMARCAL1* pathogenic variants and renal malformations is an expected finding. As suggested by Dekel et al. (23), this finding may have been overlooked in some reports. Evaluating SIOD patients for renal malformations will contribute to our understanding of whether renal malformations are incidental findings or a rare component of SIOD.

The clinical presentation or progression of SIOD is classified as either severe or mild (4). In severely affected patients, IUGR, neurologic manifestations such as cerebral infarction and transient ischemic attack, hypothyroidism, and bone marrow failure are observed more frequently (6). End-stage renal failure can occur at an earlier age in severely affected patients and most die within the first 15 years of life (6). The most common causes of death are severe infections, cerebral ischemia, and renal failure (4). The immune phenotype is predominantly characterized by lymphopenia and T cell failure, leading to recurrent infections, which are one of the most important causes of death (4). The presence of IUGR, early-onset renal failure, elevated TSH levels, and immunodeficiency in our patient, consistent with a severe phenotype, leads us to anticipate that the patient could experience neurological complications in the future. Moreover, the detection of a truncating variant in the presented patient indicated a severe phenotype. Patients with biallelic non-truncating variants tend to have a milder phenotype, although a strict genotype-phenotype correlation has not been found in SIOD patients. There was no significant difference observed between patients carrying truncating and non-truncating variants, particularly concerning the renal phenotype. However, it has been demonstrated that patients with biallelic truncating mutations exhibit higher mortality rates than those with biallelic missense variants (4). Furthermore, different clinical severities have been observed in two siblings carrying the same variant, indicating intra-familial variability (11).

The *SMARCAL1* gene contains 18 exons and encodes a 954 amino acid protein. SMARCAL1 protein is highly conserved and belongs to the sucrose non-fermenting 2 (SNF2) family (25). It functions as an ATP-dependent chromatin remodeling protein involved in various biological activities, such as replication, transcription, and DNA damage response. The protein contains four functionally important domains: HepA-related protein 1 (HARP1, 226-303 amino acids), HARP2 (327-398 amino acids), helicase ATP-binding domain (445-600 amino acids), and helicase C-terminal domain (716-869 amino acids). As of June 25, 2023, the HGMD lists 150 pathogenic variants in the *SMARCAL1* gene, with the majority being truncating variants. SIOD-related variants are depicted in Figure 4 with many pathogenic variants located within two helicase domains, similar to the variant detected in our report.

In conclusion, we present a patient with SIOD who exhibited an atypical clinical presentation characterized by hypercalcemia and hypophosphatemia, resembling osteopenia of prematurity, along with elevated FSH levels indicating primary gonadal failure. We identified a novel, homozygous indel variant in the donor splice site of the

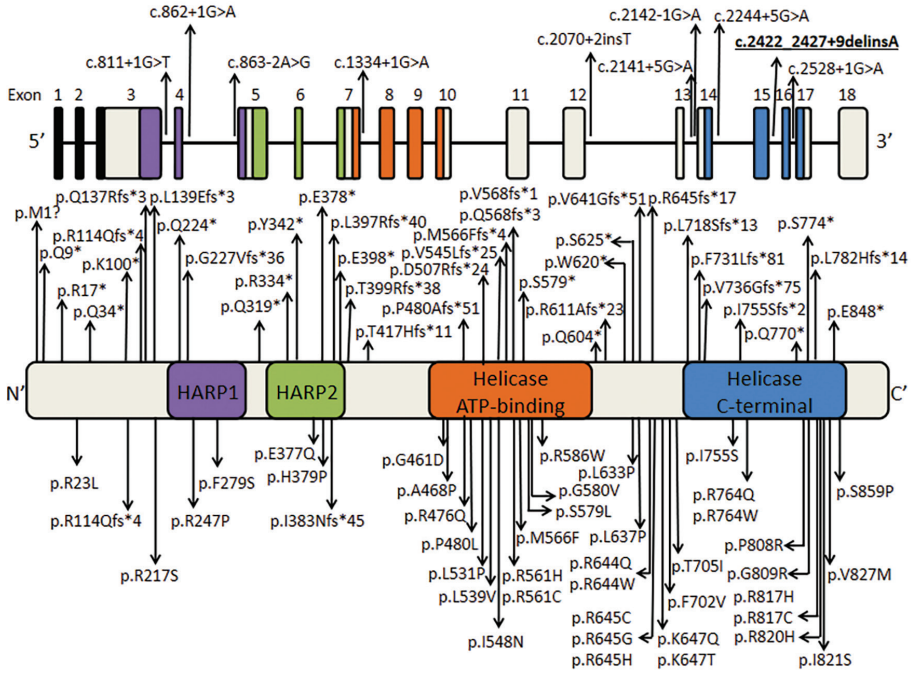

Figure 4. Schematic representation of *SMARCAL1* gene structure and its protein with the reported variants. The novel variant in the patient is indicated in bold. SMARCAL1 protein has 4 domains: HepA-related protein 1 (HARP1), HARP2, helicase ATP-binding and helicase C-terminal

SMARCAL1 gene. This report expands both the phenotypic and genotypic spectrum of SIOD.

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Footnotes

Authorship Contributions

Concept: Ceren Alavanda, Serap Turan, Design: Serap Turan, Data Collection or Processing: Serçin Güven, Mehmet Eltan, Sevgi Bilgiç Eltan, Asena Pınar Sefer, Serim Pul, Tülay Güran, Harika Alpay, Ahmet Arman, Pınar Ata, Analysis or Interpretation: Ceren Alavanda, Şenol Demir, Pınar Ata, Literature Search: Ceren Alavanda, Writing: Ceren Alavanda, Serap Turan.

Conflict of Interest: One author of this article, Serap Turan, is a member of the Editorial Board of the Journal of Clinical Research in Pediatric Endocrinology. However, she did not involved in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions.

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