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Schimke immuno-osseous dysplasia in a boy with generalized edema; a case report

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ABSTRACT

Schimke immuno-osseous dysplasia (SIOD) is a rare disease diagnosed by skeletal malformations, steroid-resistant nephrotic syndrome (SRNs), and T-cell immunodeficiency. Proteinuria with focal segmental glomerulosclerosis (FSGS) is the most common renal pathologic finding in SIOD. In this case report, we present an 8-year-old boy with generalized edema, kyphosis, and nephrotic syndrome who was eventually diagnosed with SIOD.

Keywords: Schimke immuno-osseous dysplasia, Nephrotic syndrome, Immunodeficiency

Case Report

Implication for health policy/practice/research/medical education:
Schimke immuno-osseous dysplasia is rare and manifests as skeletal malformations, SRNS, and T-cell immunodeficiency. The most common renal pathology in SIOD is proteinuria with FSGS.

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Introduction

Schimke immuno-osseous dysplasia (SIOD) is a rare multisystemic disease with an autosomal recessive tendency characterized by growth retardation, spondyloepiphyseal dysplasia, and renal dysfunction (1,2). SIOD can increase the risk of undifferentiated carcinoma, osteosarcoma, and non-Hodgkin's lymphoma (3,4). Patients with SIOD are at risk of premature death due to opportunistic infection and end-stage renal disease (ESRD) (5). Bi-allelic variations in the SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin and subfamily A-like 1 (SMARCAL1) result in SIOD. SMARCAL1 has a few roles like DNA stabilization. This deficiency leads to impaired cell function, DNA damage, and progressive systemic disease (6,7).

The SIOD accounts for about one in 1 000 000 to 3 000 000 live births in the US (8-11). Standard clinical and laboratory manifestations in SIOD include steroid-resistant nephrotic syndrome (SRNS), progressive renal failure, T-cell immunodeficiency, spondyloepiphyseal dysplasia, and hypothyroidism. In this study, we reported an 8-year-old boy with renal impairment and treatment-resistant kidney disease who was diagnosed with SIOD.

Case Presentation

An 8-year-old boy with generalized edema was referred to the nephrology clinic affiliated with the Shahid Beheshti University of Medical Sciences. The patient had a low birth weight at birth and intrauterine growth disorders. There was no history of recurrent infectious diseases. The patients' parents were cousins. The patient was short in stature, had a Dove's chest, and had mild kyphosis. All vital signs were also normal. Severe proteinuria was observed on urinalysis. Initially, the patient was diagnosed with nephrotic syndrome. Table 1 shows the laboratory findings.

Ultrasonography of the kidney revealed a horseshoe kidney with reduced corticomedullary differentiation and mild hydronephrosis. The voiding cystourethrogram was normal. The patient was resistant to steroid treatment. Therefore, a kidney biopsy and focal segmental glomerulosclerosis (FSGS) were performed. Additionally,

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ciclosporin was administered, but the patient was resistant to all treatments. After three months, the patient suffered from ESRD and underwent hemodialysis. Finally, after eleven months, the patient received a kidney transplant.

Blood samples from the patient and his parents were collected in EDTA tubes. After informed consent, DNA was extracted using the standard salting-out method. Whole exome sequencing was performed using a custom-designed NimbleGen chip-capturing array. In addition, sequencing was performed on the Illumina HiSeq 4000 platform (Illumina, San Diego, CA, USA). Paired-end sequence reads were aligned to the human reference genome (UCSC hg19/GRCh37) using the Burrows-Wheeler Aligner.

A new homozygous variant was identified in exon 11 of the *SMARCAL1* gene (NM_014140.4). This variant (c.1754C>T, S.S585F) is classified as probable pathogenic (PP3, PM2) according to ACMG standards and guidelines. This variant is a missense mutation that leads to a physicochemical change in an evolutionarily conserved amino acid on the *SMARCAL1* protein (Table 2).

The bioinformatic test suggested it could damage protein structure and function. The frequency of this variant in 1000G, ExAC, and Iranome databases was zero. Results were verified by Sanger sequencing using the ABI Prism3130 Genetic Analyzer (Applied Biosystems). Targeted sequencing of the parents showed that both were heterozygotes for the detected variant. A mutation in the *SMARCAL1* gene is associated with SIOD. The diagnosis was SIOD with a new mutation.

After the preparation of the genetic test, the patient was again asked to take an anamnesis, and an immunological evaluation of the patient was carried out. The patient was hospitalized twice a month for three years for diarrhea and pneumonia. The patient had a syndromic facial appearance (broad nasal tip, depressed nasal bridge, microdontia). Immunologic testing revealed leukopenia, hypogammaglobulinemia, weak antibody response, and an inverted CD4/CD8 ratio (Table 1).

After kidney transplantation, the patient was stable, symptom-free, and within the standard laboratory range. After six months of transplantation, the BK virus screening test was positive. Very low-dose cyclosporine and mechanistic target of rapamycin (mTOR) inhibitor therapy was started. Due to the high viral load, the patient also received intravenous immunoglobulin (IVIG) and cidofovir. Finally, the biopsy of a transplanted kidney showed more than 50% interstitial fibrosis/tubular atrophy (IF/TA). The serum creatinine value was 2.8 mg/dL.

Table 1. Result of the immunologic tests, leukopenia, hypogammaglobulinemia, weak antibody response, and an inverse ratio of CD4/CD8

Variable	Value	Normal range
WBC (cell/mm^3)	4300	5000-13000
Lymphocyte (%, cell count)	23% (989)	22-50%
Neutrophil (%, cell count)	72%	38-80%
Hb (g/dL)	13.8	11-14.7
PLT (×10^3 cells/mm^3)	258000	150000-450000
Ig G(mg/dL)	559	600-1100
IgA (mg/dL)	139	51-297
IgE (IU/mL)	430	Up to 144
IgM (mg/dL)	40	40-150
CD3 (%, cells/mm^3)	51% (504)	35-78%
CD4 (%, cells/mm^3)	19% (187)	22-62%
CD8 (%, cells/mm^3)	28% (276)	12-36%
CD19 (%, cells/mm^3)	9.5% (93)	3-14%
CD20 (%, cells/mm^3)	9.7% (95)	3-15%
CD16 (%, cells/mm^3)	23.7% (229)	5-19%
CD56 (%, cells/mm^3)	4.5%(45)	3-15%
CD4/CD8	0.67	1.5-2
Anti D	0.01	≥ 0.01
Anti T	0.08	≥0.1

WBC, White blood cell; Hb, Hemoglobin; PLT, Platelets; Ig, Immunoglobulin; Anti-D, Anti-diphtheria; Anti-T, Anti-tetanus.

Discussion

Schimke immuno-osseous dysplasia is a rare multisystemic autosomal recessive disease. The SIOD accounts for about one in 1 000 000 to 3 000 000 live births in the US (8-11). The etiology of SIOD needs to be clarified in more detail. Mutations in the *SMARCAL1* gene have been identified in approximately 50% to 60% of patients diagnosed with SIOD (8). In our case, whole exome sequencing (WES) showed a mutation in the *SMARCAL1* gene.

Schimke immuno-osseous dysplasia exhibits heterogeneous phenotypes. The severity of SIOD varies from mild to severe. Patients with severe SIOD die before the age of five. Severe disease is characterized by facial abnormalities, bone dysplasia, and T-cell deficiency, leading to recurrent infections and chromosomal fragility (12,13). In our report, the patient did not have severe SIOD since he was eight years old, had no recurrent infections, and had no history of T-cell deficiency, and all components of the immune system were normal. Growth retardation is one of the most common manifestations of SIOD and was observed in our case report (14).

Along with FSGS, proteinuria is the most common pathologic finding in SIOD. FSGS in a patient with SIOD is recognized when the patients are between 1 and 14 years of age and progress rapidly to ESRD (15). FSGS is the leading cause of SRNS, membranous nephropathy,

Table 2. Result of immunologic work-ups and laboratory diagnostic tests

Gene & transcript	Variant	rs	ACMG	SIFT	CADD Score	gnomAD (Aggregated)	Iranome
SMARCAL1 NM_014140.4	Exon11 c.1754C>T p.S585F	rs1574465627	Likely pathogenic	Pathogenic	29.6	N/A	N/A

minimal change disease, and mesangial proliferative glomerulonephritis. In these patients, previous research shows that prescribing angiotensin-converting enzyme inhibitors or cyclosporin A reduces proteinuria (8). In our report, the patient was resistant to all drugs, such as steroids and ciclosporin. SRNS is one of the major manifestations of SIOD, but our case was resistant to all drugs. Cerebrovascular and neurological disorders are the leading causes of morbidity and mortality in SIOD. In addition, hypertension and hyperlipidemia due to kidney disease associated with immunodeficiency may predispose these individuals to atherosclerosis and subsequently predispose the patient with SIOD to cerebrovascular disorders (5). Our patient had no history of neurological manifestations.

Recent advances in dialysis and transplantation are increasing the life expectancy of patients with SIOD (15). Kidney transplantation is one of the treatment methods for SIOD. In our report, the patient's condition was stable for months after kidney transplantation, but the function of the transplantation deteriorated due to BK virus nephropathy. It appears that patients with this new mutation are more susceptible to immunosuppressive side effects such as opportunistic infections leading to BK virus nephropathy with treatment problems that have been resistant to conventional treatments.

Conclusion

In conclusion, we reported an eight-year-old boy with SIOD and a new mutation who was presented with rapidly progressive SRNS and ESRD. The patient underwent renal transplantation. It appears that a lower immunosuppressive dose is better than a standard dose in reducing opportunistic infections, particularly with this new mutation.

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Author's contribution

Conceptualization: SHM, Paniz Pourpashang, and Nasrin Esfandiar.
Data curation: Nasrin Esfandiar, Paniz Pourpashang.
Formal analysis: Paniz Pourpashang and Nasrin Esfandiar.
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Methodology: Paniz Pourpashang.
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Supervision: Nasrin Esfandiar.
Validation: Nasrin Esfandiar.
Visualization: Nasrin Esfandiar.
Writing-original draft: Nasrin Esfandiar and Paniz Pourpashang.
Writhing-review & editing: Nasrin Esfandiar, Paniz Pourpashang and Samin Sharafian.

Conflicts of interest

The authors declare that they have no conflict of interest.

Data availability statement

Not applicable.

Ethical issues

This case report was conducted in accordance with the World Medical Association Declaration of Helsinki. Informed consent was obtained from the parents of the patient prior to their child's inclusion in the study. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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