Case Report

Schimke immune osseous dysplasia: a rare case report

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ABSTRACT

Schimke immune-osseous dysplasia (SIOD) is primarily characterized by the combination of spondyloepiphyseal dysplasia (SED), unique clinical phenotype, immune complex nephropathy (focal segmental glomerulosclerosis) and progressive immune defects with T-cell immunodeficiency. SIOD is caused by mutations in SMARCAL1 gene. Here we report a case of a 6-year-old girl who presented to us with disproportionate short stature, short neck kyphoscoliosis, hyper pigmented macules and severe herpes zoster. On further evaluation, she had evidence of T cell deficiency and nephrotic range of proteinuria. Renal histopathology documented focal segmental glomerular sclerosis. Genetic analysis confirmed homozygous missense mutation of SMARCAL gene on exon 8 variant c1358G>c. On extensive literature survey, this is noted to be the first case of SIOD reported from India. These children need close surveillance to watch for infections and progressive renal failure and require special care during administration of certain drugs and live vaccines.

Keywords: Immunodeficiency, Schimke immune-osseous dysplasia, Short stature, Steroid resistant nephrotic syndrome

INTRODUCTION

Schimke immune-osseous dysplasia (SIOD) is a rare autosomal recessive disorder characterised by typical facial features, disproportionate short stature, nephropathy and T cell deficiency.1 Other associated features include hypothyroidism, protruding abdomen, hyper pigmented macules (lentigenes), progressive atherosclerosis, transient ischemic attacks or strokes, severe migraine like headaches, pulmonary complications such as pulmonary emboli, pulmonary hypertension, dental malformation, bone marrow aplasia and autoimmune conditions.2 No definitive treatment is available. Regular monitoring of renal functions, immune functions and hematological parameters is recommended.

CASE REPORT

Our index case is a 6-year-old girl who presented for evaluation of short stature and had evidence of severe herpes zoster skin lesions lasting 5 days. She was the first born to consanguineous parents, delivered by elective LSCS (indications: oligohydramnios; low birth weight of 1.75 kg) with an uneventful postnatal period. Her development was normal. There was no family history of short stature.

Her midparental height was 150.8 cm. Her parents had noticed that over the previous three years, she had poor height gain as compared to the younger sibling. Several skin lesions in the form of fluid filled vesicles were present in the right hand and back.

There was no history recurrent infections or varicella infection in the past or clinical symptoms suggestive of hypothyroidism.

On examination, the child was alert, cheerful and had multiple dysmorphic features, viz., triangular facies, thin upper lip, and broad philtrum, multiple hyper pigmented macules all over the body, protruded abdomen, and kyphoscoliosis (Figure 1).
Figure 1: Triangular facies, thin upper lip, prominent philtrum, kyphoscoliosis, protuberant abdomen, hyper pigmented macules in lower abdomen, limb length discrepancy.

Bilateral acute suppurative otitis media was noted. Systemic examination was normal with no organomegaly. Her blood pressure was 98/54 mmHg (50th to 90th). There were fluid filled vesicular lesions over the ventral aspect of the left forearm and extending to the back of the chest, confined to the right side, suggestive of Herpes zoster (Figure 2).

She had waddling gait and mild periorbital puffiness. Her weight was 15 kg (<3rd centile), and her height 98 cm (<3rd centile; >2 SD from her MPH). Her US/LS ratio was 0.9, suggestive of disproportionate short stature. In view of the appearance of rashes and typical dermatomal distribution, the clinical diagnosis of herpes zoster was made, though there was no history of chicken pox in the past.

On investigation, complete blood count was normal, nephrotic range proteinuria (8 g / 24 hrs) was observed, with urinary spot protein: creatinine ratio of 27.

Ultrasound abdomen was suggestive of nephropathy with mild ascites, and normal uterus and ovaries for her age. Her serum albumin was 1.5 g/dl, total cholesterol 350 mg/dl, and triglycerides 250 mg/dl. Renal biopsy was done which was suggestive of focal segmental glomerulosclerosis (FSGS). Blood urea, serum creatinine, electrolytes and thyroid function tests were normal. Skeletal survey showed kyphoscoliosis, ovoid vertebra and shallow dysplastic right acetabula (Figure 3). Immunodeficiency workup was done in view of severe form of herpes zoster. HIV test was negative and immunoglobulin profile was normal but CD4, CD8 counts, were low, suggestive of T cell immunodeficiency.

Figure 2: Short neck, kyphoscoliosis, healing herpes zoster skin lesions on backs of neck, and arm.

In the presence of typical facial features, disproportionate short stature, nephrotic involvement (FSGS), and T cell deficiency, a clinical diagnosis of Schimke immune osseous dysplasia was made. Exome sequencing revealed homozygous missense mutation of SMARCAL gene on exon 8 variant c1358G>c, which confirmed the diagnosis of SIOD.

Figure 3: Ovoid vertebra and shallow dysplastic right acetabula.
DISCUSSION

Schimke immune-osseous dysplasia (SIOD) is a rare progressive multisystem disorder which was first described by Schimke et al, as a combination of chondroitin-6-sulfate mucopolysaccharidosis defective cellular immunity and nephrotic syndrome. SIOD is a very rare disorder with prevalence less than one per million. It is an autosomal recessive inheritance condition due to biallelic mutations in SMARCAL1 gene. The protein encoded by this gene is a member of the SWI/SNF family of proteins which regulate transcription of certain genes by altering the chromatin structure around those genes. Saraiva et al, reported 25 new cases and Boerkoelet al, reported 14 cases in 2000, and detected mutant chromatin remodeling protein SMARCAL1 in 2002. Clewling proposed that SMARCAL1 protein regulates proliferation of chondrocytes, lymphocytes, spermatooza and maintenance of cardiocytes. Basiratnia and Fallahzadeh reported two cases in southern Iran. They also reported an 8-year-old boy with SIOD and non-Hodgkin lymphoma. SIOD could also present as autoimmune diseases, neurological complications such as transient cerebral ischemia, chronic headache, cancer such as non-Hodgkin’s lymphoma or osteosarcoma, dental malformations, bone marrow aplasia and hypothyroidism.

Based on clinical manifestations and age of disease onset, it is classified into severe early-onset/infantile and milder late-onset/juvenileile forms. The outcomes of the two forms are early death for severe forms and survival into adulthood for the mild form.

Mean age of onset of growth failure reported in SIOD patients is 2 years, ranging from 0-13 years. Current evidence indicates that poor growth is not the consequence of renal dysfunction in SIOD patients. The difference between patients with SIOD, from those with non SIOD chronic kidney diseases that the leg length reduction is more significant than trunk length reduction. SIOD related nephropathy mainly develops within five years after its diagnosis and before 12 years of age. Most of the patients with SIOD have hyper pigmented macules more commonly on the trunk and less frequently on the face, neck and extremities. Although most of the early onset and severe form of the SIOD usually die at a younger age and those with milder form often survive to adulthood, there are also documented cases which show that severity and age of onset could not definitely predict the survival in SIOD. The most common causes of death in SIOD in order of frequency are infection, cerebrovascular events, congestive heart failure, pulmonary hypertension and renal failure. Other causes of death are organ transplant complication, complications of lymph proliferative disease, gastrointestinal hemorrhage, bone marrow aplasia and acute restrictive lung disease.

The mutations SMARCAL1 (SWI/SNF1-related, matrix-associated, actin-dependent regulator of chromatin) are responsible for SIOD. New mutations of SMARCAL1 are revealed recently. Santangelo et al reported in missense change (P. Arg 247 Pro); Point mutation with alternation of arginine 247 residue to prolineas well-known non-sense mutation (P. Glu 848); and point mutation of glutamine 848 residue as a mild phenotype. Barraza-Garcia et al identified a new mutation in a six year old SIOD patient with severe symptoms who died of nephropathy. The splicing alternation point (Leu 539-Ile 548 deletion), causes 10 amino acids loss in HARP-ATPase catalytic domain and the RPA-binding domain (HepA-related protein-ATPase is a member of the SNF 2 family of ATP-driven molecular motor proteins). Boerkoelet al also observed that some missense mutations results in retention of partial SMARCAL1 function and cause milder disease, whereas nonsense, frameshift or splicing mutations causes severe disease.

Management includes Acyclovir for recurrent herpes infections, immune response modifiers like Imiquimod and cidovir (an antiviral) for severe papilloma virus infections of the skin, standard treatment of hypothyroidism, and scoliosis. Kidney dialysis or transplant, bone marrow transplant, hip replacement, treatment of neutropenia with granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor, medications to suppress the immune system for those with autoimmune symptoms and drugs to improve blood flow or decrease blood clotting to treat transient ischemic attacks. Certain drugs like ergotamine should be avoided in these cases. In addition, proper short-interval follow up is recommended for cases with diagnosis of SIOD to facilitate better evaluation and management of the disease related complication.

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REFERENCES


