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BRIEF REPORT

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Membranous nephropathy in Schimke immuno-osseous dysplasia

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Abstract Schimke immuno-osseous dysplasia is a rare autosomal recessive multi-system disorder, with clinical features of growth retardation, spondylo-epiphyseal dysplasia, nephrotic syndrome and immunodeficiency beginning in childhood. Here, we report a new case, in a 10-year-old boy with characteristic symptoms of Schimke immuno-osseous dysplasia. The patient presented with short stature and, later, developed nephrotic syndrome and peritonitis. In addition, he had perinuclear anti-neutrophilic cytoplasmic antibody (p-ANCA)-positive arthritis. Renal pathology of the patients with this disease usually show focal segmental glomerulonephritis, whereas our patient had membranous nephropathy, which has not previously been reported.

Keywords Schimke immuno-osseous dysplasia · Membranous nephropathy · Spondylo-epiphyseal dysplasia · Nephrotic syndrome · Growth failure

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Introduction

Schimke immuno-osseous dysplasia (SIOD) (MIM 242900) is a rare autosomal recessive disorder characterised by growth retardation, spondylo-epiphyseal dysplasia (SED), nephrotic syndrome (NS) with focal segmental glomerulonephritis, defective immunity and dysmorphic facial features [1–5]. SIOD was first described by Schimke et al. in 1971 [1] and, since then, 42 cases have been reported [6]. We present a new case with characteristic symptoms of SIOD with membranous nephropathy (MN).

Case report

Our patient was the 10-year-old son of first-degree consanguineous Turkish parents. He had a healthy brother, but his mother and grandmother had type 1 diabetes mellitus. He was delivered at term after a pregnancy complicated by diabetes mellitus. At birth he was small for gestational age [weight 2,420 g (<3rd centile)], and he subsequently grew below the 3rd percentile. He had a normal intellectual and neurological development. He received routine immunisation, with no unusual reactions. There was no history of transient lymphopenia or frequent infections. He had had atopic dermatitis when he was 4 years old.

At the age of 5.5 years he was examined for short stature. His height was 99 cm (<3rd centile) and weight was 16 kg (10–25th centile). He was disproportionately short, with a short neck and trunk and a waddling gait. His other features included a triangular face, broad, low, nasal bridge, bulbous nasal tip, small palpebral fissures, microdontia, clindo-

dactly, lumbar lordosis and a protruding abdomen. He had fine, coarse, hair and a high-pitched voice. There were no hyperpigmented macules. Endocrinological work-up revealed normal results of thyroid function tests and a normal, random, growth hormone level and somatomedin C level. Growth hormone stimulation test showed a normal growth hormone response. Bone age at the age of 5.5 years was delayed to 3 years.

At the age of 7 years he developed NS complicated by hypertension and peritonitis. Antinuclear antibody (ANA) and anti-DNA values were negative; C3, C4 levels were low. Accordingly, a renal biopsy was performed. Under light microscopy, thickened basement membrane (H&E stain) and characteristic spikes in the capillary loops of the glomeruli [periodic acid–methenamine silver (PAMS)] were seen (Fig. 1). Immunofluorescence study showed intense granular staining of IgG and C3; there was weaker staining of C4 in the basement membrane. There was weak and granular segmental mesangial deposition of IgM. Under electron microscopy, thickening of glomerular basement membrane and large electron-dense deposits in the subepithelial aspects of capillary walls were observed. There was vacuolisation in epithelial cell cytoplasm, transformation of microvilli and marked obliteration of podocytes. The pathology was consistent with MN. Methylprednisolone treatment was initiated. C3 and C4 levels returned to normal in 5 months, and proteinuria, hypoalbuminuria and oedema improved. Corneal opacity was detected at ophthalmological examination on follow-up. At 9 years of age, he had an NS relapse complicated by peritonitis again and was rehospitalised. He was treated with pulse steroids, antibiotics and angiotensin-converting enzyme inhibitors for persistent and severe hypertension.

Six months later, he was referred to our hospital for further evaluation of his severe infections and renal disease. Immunological analysis demonstrated an inverse CD4/CD8 ratio. Absolute B-cell (CD19) (7%) count was reduced. He had a BCG vaccination, and his purified protein derivative (PPD) enduration was 5×7 mm. Immunoglobulins G, M, A and G3 serum levels were low. Extremity X-rays taken for disproportionately short stature showed marked broadening and flattening of the metaphyses of the femur, humerus, tibia and fibula. Metaphyseal dysplasia was also noted in the distal radius and ulna, and epiphyseal dysplasia was observed in the proximal fibula. Capital femoral heads were displaced antevertly. Osteopenia was observed in all extremity bones. Radiolucent nodular lesions were noted in the distal diaphyses of the right radius and ulna, in the proximal diaphyses of the left humerus and in all fibular metaphyses. Physiological cervical lordosis was flattened. Lumbar and cervical vertebrae were shortened, with low, elongated, vertebral bodies. He was diagnosed as having SIOD on the basis of these clinical and laboratory features.

At the age of 10 years he was referred with complaints of pain and hyperaemia in his right ankle. He was hospitalised with the diagnosis of cellulitis and arthritis. A week later he developed arthritis in his left ankle. Repeated ANA, ds-DNA titers and cytoplasmic anti-neutrophilic cytoplasmic antibody (c-ANCA) were negative, perinuclear anti-neutrophilic cytoplasmic antibody (p-ANCA) was positive. MPO and proteinase 3 (PR3) were negative. A few months later he developed diffuse and severe oral thrush. There was no lymphopenia during his complaint.

He is now 10.5 years old; his height is 120 cm (<3rd percentile), and his weight is 25.5 kg (10–25th percentile). Immunoglobulin levels show normal for Ig M (0.706 g/l),

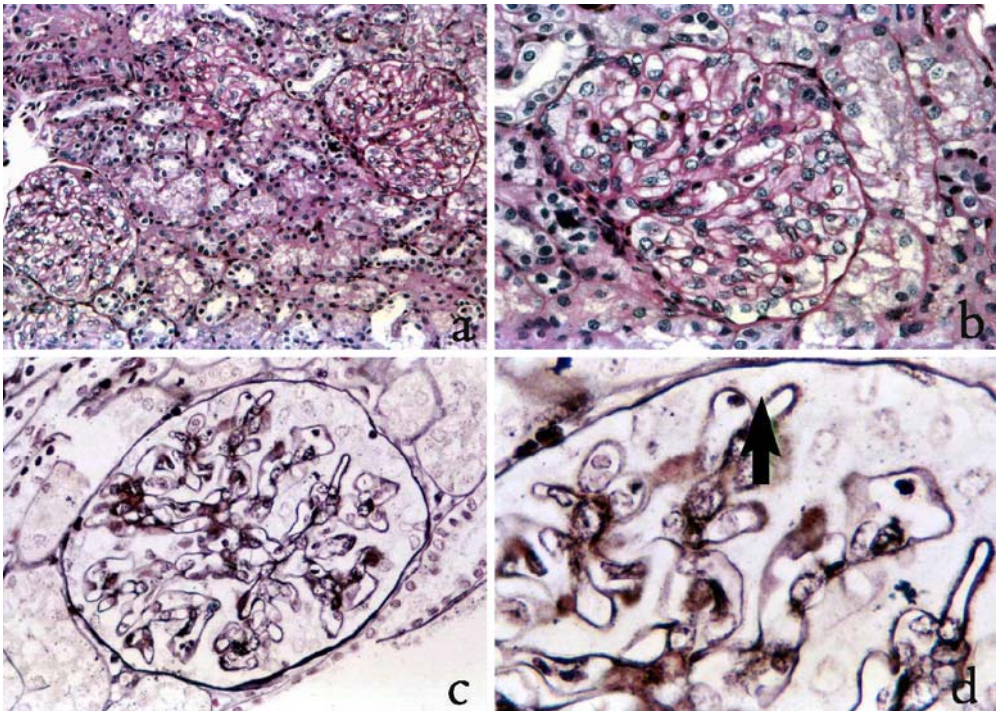

Fig. 1 Microscopy of renal biopsy from patient. **a** Basement membrane thickening in the glomerulus. Periodic acid–Schiff (PAS) stain, ×100. **b** Basement membrane thickening, high-power field appearance. PAS, ×400. **c** Basement membrane thickening in the glomerulus. PAMS, ×200. **d** The capillary loops show the characteristic spikes in the glomeruli. PAMS, ×1,000

high for Ig G (25.3 g/l), and low for Ig A (0.442 g/l) (−2SD). Serum Ig G levels were positive for mumps, rubella and hepatitis B vaccination. T-cell subset analysis revealed an inverse CD4/CD8 ratio and a reduced absolute B-cell count (CD19) (7%). On his last routine control, massive proteinuria (3.41 g/24 h) was detected. There was no oedema on physical examination. His renal function test results and electrolyte, albumin and lipid levels were normal. He is still on alternate-day low-dose methyl prednisone therapy.

Discussion

SED, renal dysfunction, immunodeficiency and facial dysmorphism occur in all patients with SIOD. Growth failure, episodic lymphopenia, cerebral ischaemia, ectodermal abnormalities, hypothyroidism, ocular abnormalities, autoimmune disorders and bone marrow hypoplasia are other features with variable expression [7]. Although most cases of SIOD are sporadic, consanguinity is common among reported patients. The pathogenesis of this disease is unknown. Recent genetic studies by Boerkoel et al. showed that mutations in chromatin remodelling protein *SMARCAL 1* (SW1/SNF2-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like 1) cause SIOD [8, 9]. Direct DNA testing of the *SMARCAL 1* gene is available on a research basis only.

Morbidity of SIOD is mainly due to renal failure. Boerkoel et al. reviewed cases and found that all the patients had proteinuria and renal pathology, mostly showing focal segmental glomerulonephritis; one patient had minimal change disease, one patient nephrophthisis, and two patients mesangial proliferative glomerulonephritis [7]. Our patient had NS who showed MN on biopsy.

Autoimmune findings have been noted in patients with SIOD before; however, no consistent inflammatory or serological marker suggestive of an autoimmune disorder was reported. There is also a strong correlation between autoimmune diseases and MN [10]. Our patient had atopic dermatitis, and his mother had type 1 diabetes mellitus. He had biopsy proven MN and also a positive p-ANCA level detected later, which would suggest an unrecognised related autoimmune disorder.

Patients with SIOD are prone to viral, fungal and bacterial infections, and recurrent infections are noted in approximately one half of the patients [11]. Although defective T cell-mediated immunity and lymphopenia are frequently noted in patients with SIOD, it is not universal and may be missed because it is episodic. Our patient had severe infections under immunosuppression, and he has had one episode of severe oral thrush so far. The B-cell count was low, and he had hypogammaglobulinaemia when he was in remission.

Prenatal growth retardation, disproportionately short stature with radiological evidence of SED, proteinuria, biopsy proven MN and defective immunity confirmed the diagnosis of SIOD in our patient. Characteristic facial dysmorphism, microdontia, unusual hair, short neck and trunk, protruding abdomen, high-pitched voice, normal intelligence and neurological development, and corneal opacity are supportive findings. Genetic diagnosis is not available, since cell culture cannot be done in our laboratory.

SIOD is a rare multi-system disease with variable expression and should be kept in mind in patients with growth failure, skeletal dysplasia and renal disease.

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