We describe a 4 year old boy, of consanguineous parents, with Schimke Immuno-osseous Dysplasia. At the age of 2 years, he was found to have a deletion of 2q35 with deletion of exons 13 and 14 of SMARCAL-1 gene on microarray after being investigated for facial dysmorphism, solitary right kidney with nephrotic range proteinuria and hypertension, bicuspid aortic valve & mitral stenosis, skeletal dysplasia with short stature and developmental delay. He also had a history of prematurity (ex-25 weeks gestation) with intra-uterine growth restriction. He had an older brother, born at 26 weeks gestation, who died at 5 months of age with unclear cause, and an older sister who was well. At presentation to immunology, he had a mild infection history with approximately 2 upper respiratory tract infections and 1 gastroenteritis episode per year. He had tolerated his vaccines including live vaccines.

Immune investigations showed T cell lymphopenia with reduced naïve T-cells and reduced anti-CD3 proliferation. Immunoglobulin levels were normal with poor pneumovax response. He had progressive decline in T cell function with increasing frequency of infections. He was commenced on immunoglobulin replacement with marked reduction in frequency of infections.

More recently, he presented with acute kidney injury. While some initial improvement with conservative management, his renal function continued to decline until he passed away with complications of renal failure.

Schimke Immuno-osseous dysplasia (SIOD) is an autosomal recessive condition, caused by a mutation in the gene encoding SMARCAL1, with over 40 different known mutations. The prevalence is unknown, estimated at 1:1,000,000. The SMARCAL-1 protein encodes a chromatin remodeling enzyme which participates in gene regulation. The genotype does not predict disease severity or outcome with reports of intra-familial variation.

There is a wide spectrum of clinical manifestations but is characterized by spondyloepiphyseal dysplasia with short stature, nephropathy and T cell deficiency. Almost all affected individuals have proteinuria with the majority (86%) with progressive steroid-resistant nephropathy, which generally evolves into end-stage renal disease. Patients with SIOD may have neurological disease, most commonly migraines and cerebral ischaemic events.

Approximately 80% of affected individuals have a T-cell deficiency with reduction in both CD4 and CD8 T cells. T cells are predominantly of a memory surface phenotype, rather than a naïve phenotype. Analysis of thymic capacities in individuals with SIOD has shown that those affected have reduced TRECs and T-cell receptor rearrangements. SIOD has also been associated with a lack of interleukin 7 receptor alpha expression on the T cells of patients with SIOD. These findings indicate that there is an underlying defect in thymus histology with reduction in thymic output and activity, but also defective T cell development.

B cell numbers are usually normal to slightly elevated with normal IgG in 70% of patients. About 20% of individuals with SIOD have features of autoimmune disease including immune thrombocytopenia, haemolytic anaemia, enteropathy, pericarditis and Evans syndrome.

There is large variation in severity of SIOD, ranging from in utero growth restriction and early death to a slowly progressive course with survival into adulthood. The mean age of death is 11 years, with the most common causes of death including infection (23%), stroke (13%), pulmonary hypertension & congestive cardiac failure (13%) and renal failure (11%). Treatment is largely supportive.

There have been five reports of haematopoietic stem cell transplant in SIOD, one of which survived, at last report, to the age of 21 years. This patient developed renal deterioration post HSCT, and received subsequent renal transplantation from the same donor, now with good bone marrow and renal function. The other four patients died of complications including sepsis, pulmonary oedema and cardiac tamponade, pulmonary embolism and cerebral ischaemia and haemorrhage.
SIOD is a multi-system disorder with a wide variable phenotype. Unfortunately, it is associated with a poor prognosis with limited treatment options. While HSCT, with or without renal transplantation, may be an option of treatment, there is a reported high mortality rate.

References: