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CASE REPORT

When rarity meets complexity – Schimke immuno-osseous dysplasia with nephrotic syndrome: a 15-year longitudinal case report

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ABSTRACT

Schimke immuno-osseous dysplasia (SIOD) is an exceptionally rare autosomal recessive disorder caused by pathogenic variants in the *SMARCAL1* gene and characterised by spondyloepiphyseal dysplasia, immunodeficiency, and progressive renal disease, often presenting as steroid-resistant nephrotic syndrome. Fewer than 100 cases have been reported worldwide. This manuscript describes a male patient with genetically confirmed SIOD, monitored age 4.5–19 years. Early features included growth failure, hyperpigmentation, skeletal abnormalities, moderate T-cell lymphopaenia, and biopsy-proven focal segmental glomerulosclerosis. In adolescence, the disease transitioned to a severe phenotype with end-stage renal disease, recurrent infections, bone marrow failure, and Evans syndrome, reflecting profound immune dysregulation. Despite multidisciplinary management, including renal-replacement therapy and individualised immunological care, the patient's condition progressively deteriorated and he ultimately died from multi-organ failure. This long-term observation illustrates the evolving natural history of SIOD and the shift from renal disease in childhood to combined immunodeficiency and haematological complications in adolescence.

KEY WORDS:
paediatrics, nephrotic syndrome, rare disease, *SMARCAL1***, Schimke immuno-osseous dysplasia.**

INTRODUCTION

Schimke immuno-osseous dysplasia (SIOD) is an extremely rare autosomal recessive multisystem disorder caused by pathogenic variants in the *SMARCAL1* gene, which encodes a chromatin-remodelling adenosine triphosphate essential for DNA replication fidelity, replication-fork stability, and DNA repair [1]. Clinically, SIOD is characterised by a triad of disproportionate short stature, spondyloepiphyseal dysplasia, and progressive renal impairment, most commonly presenting as steroid-resistant nephrotic syndrome (SRNS) [2]. Additional manifestations include facial dysmorphism, diffuse skin hyperpigmentation, T-cell lymphopaenia, and increased susceptibility to infections due to impaired cellular immunity [3].

Although approximately 100 cases have been described worldwide, SIOD remains markedly underrecognised, and the clinical spectrum continues to expand. Recent analyses by Castellano-Martínez *et al.* [4] have demonstrated significant phenotypic variability even among patients carrying the same pathogenic variant. Larger cohort studies have provided additional insight into genotype-phenotype correlations and long-term outcomes [5, 6]. In Poland, only isolated cases have been reported to date.

An early clinical description of the patient presented in this manuscript was published by Zachwieja *et al.* [7] in 2013, when he was 4.5 years old. That report documented the initial phase of steroid-resistant nephrotic syndrome, early skeletal dysplasia, characteristic hyperpigmentation,

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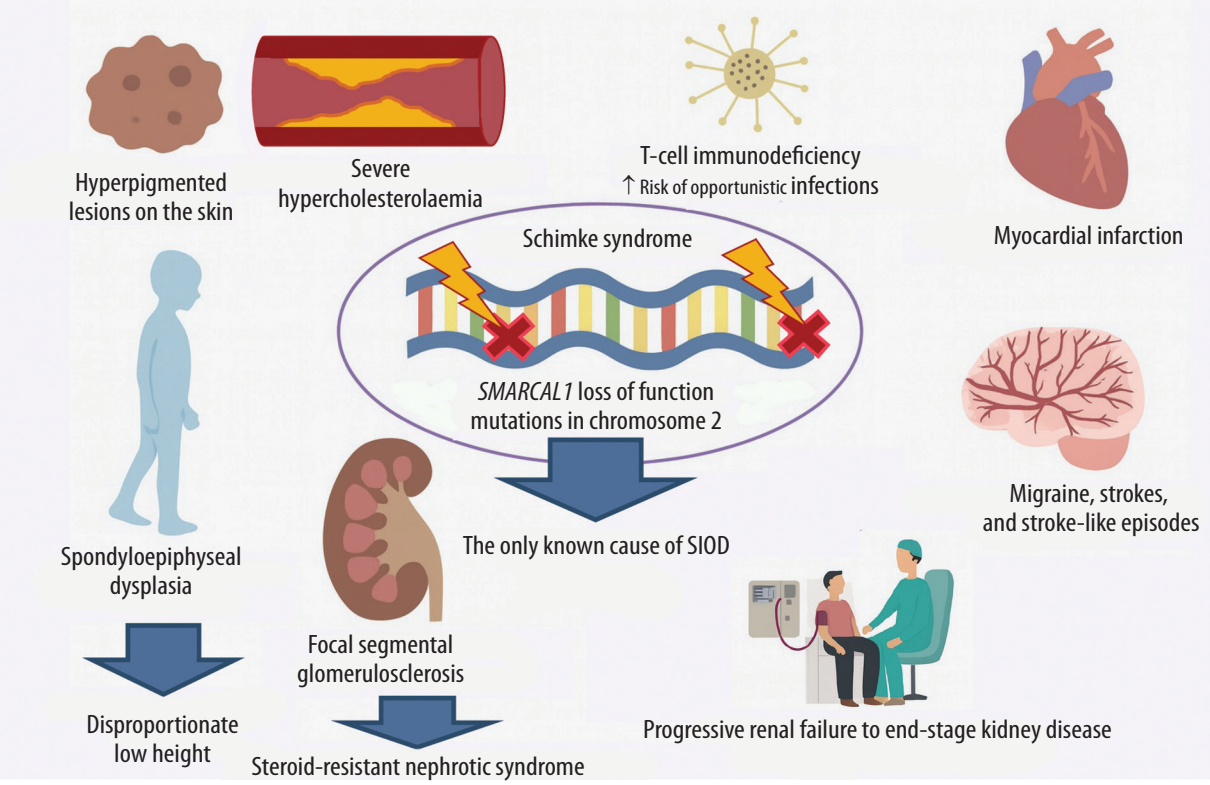

FIGURE 1. Typical clinical features of Schimke immuno-osseous dysplasia, including short stature, skeletal dysplasia, nephrotic syndrome, immune deficiency, hyperpigmentation, and vascular complications

SIOD – Schimke immuno-osseous dysplasia

and moderate T-cell immunodeficiency with preserved renal function. The present study provides a unique 15-year longitudinal follow-up of the same patient, offering rare insight into the natural progression of SIOD from early childhood through adolescence and culminating in the multisystemic deterioration typical of advanced disease [8].

Symptoms characteristic of SIOD are presented in Figure 1.

CASE REPORT

A 19-year-old male was admitted to the Nephrology Department of the University Hospital in Cracow for management of chronic renal failure in the course of SIOD. The patient was born by caesarean section after a pregnancy complicated by oligohydramnios at 6 months, with a birth weight of 1500 g and length of 44 cm (Apgar 8). His early development was normal, but from preschool age he experienced frequent respiratory infections and progressive growth failure.

At the age of 4.5 years, laboratory evaluation revealed isolated nephrotic-range proteinuria with a maximum of 9.1 g/day, accompanied by hypoalbuminaemia (31.5 g/l), total serum protein of 54.1 g/l, and hypercholesterolaemia (total cholesterol 7.45 mmol/l). Renal function was preserved with serum creatinine 41.3 µmol/l, urea 4.7 mmol/l, cystatin C 0.64 mg/l, and estimated glomerular filtration rate 90.7 ml/min/1.73 m^2 (Schwartz formula, 2009). Immunological evaluation demonstrated hypogammaglobulinaemia with reduced IgG levels and combined lymphopaenia affecting CD3+, CD4+, and CD8+ T-cells, as well as B-cells and NK-cells, with weak proliferative response to mitogens.

At the age of six years, hyperpigmented macules appeared in the groin area, progressively extending across the trunk and limbs. Over the years, pigmentation became generalised, consistent with chronic SIOD-associated skin changes. Immunological and orthopaedic evaluations led to a diagnosis of SIOD, confirmed by genetic testing, which revealed two heterozygous *SMARCAL1* mutations (each inherited from one parent):

- c.1859G>A; p.Trp620Stop (maternal allele),
- c.2542G>T; p.Glu848Stop (paternal allele).

Both truncating variants result in premature stop codons and loss of functional protein, consistent with the severe molecular phenotype of SIOD. Both variants have been previously reported in genetic databases, including ClinVar, and are classified as pathogenic loss-of-function variants causative for SIOD.

Renal manifestations appeared early: nephrotic syndrome was diagnosed in February 2007. A renal biopsy performed in October 2008 showed 65% glomerular hyalinisation, podocyte injury, mesangial expansion, and deposition of IgM and C1q findings characteristic of hilar-type focal segmental glomerulosclerosis (FSGS) associ-

ated with SIOD [7, 9, 10]. The nephrotic syndrome was steroid-resistant.

Progressive renal failure resulted in a two-stage bilateral nephrectomy performed in 2013, initially as unilateral nephrectomy and subsequently completed before kidney transplantation, followed by approximately 18 months of peritoneal dialysis and subsequent kidney transplantation. After transplantation, renal function initially stabilised with absence of proteinuria, although a gradual increase in serum creatinine of approximately 20% was later observed. Post-transplant course was complicated by thrombocytopaenia, diarrhoea and progressive deterioration of graft function, manifested by a gradual increase in serum creatinine. Chronic rejection of the transplanted kidney was suspected. In 2020, Evans syndrome was diagnosed, and the patient became the first minor in Poland to receive eltrombopag (Revolade) therapy for bone marrow failure related to SIOD [11, 12].

Over time, he underwent multiple procedures, including bilateral hip surgery due to spondyloepiphyseal dysplasia and coxarthrosis. The patient also experienced COVID-19 infection in 2021, requiring intensive care and oxygen therapy [13]. Despite significant growth retardation (height 116 cm, weight 34 kg), he remained ambulatory and engaged in regular rehabilitation.

A detailed comparison of the clinical and laboratory features observed in this patient with the typical manifestations of SIOD reported in the literature is presented in Table 1 [5, 6, 8]. This summary highlights both the characteristic findings, such as SRNS and skeletal dysplasia, and the unique aspects of this case, including prolonged survival and treatment with eltrombopag for bone marrow failure. Importantly, the table also provides a direct longitudinal comparison of key clinical and laboratory parameters observed in early childhood (age 4.5 years) and in late adolescence (age 19 years), illustrating the progression of disease over time.

In February 2024, a comprehensive medical interview and examination were conducted, with continuous communication maintained with the patient's mother. Then at the age of 19 years, laboratory evaluation demonstrated persistent leukopaenia (white blood cell 2.22 $\times 10^3$/µl), neutropaenia (1.43 $\times 10^3$/µl), and profound lymphopaenia (0.37 $\times 10^3$/µl), accompanied by elevated inflammatory markers (C-reactive protein 18.9 mg/l), reflecting ongoing immune dysregulation. Unfortunately, three months later, in May 2024, the patient was hospitalised due to severe infection and multi-organ deterioration, requiring pharmacological coma. Despite intensive treatment, he passed away shortly thereafter.

EVANS SYNDROME AND BONE MARROW INVOLVEMENT

Evans syndrome emerged in this patient in 2020, during mid-adolescence, and represented a pivotal shift toward profound immune dysregulation in the course of his SIOD. Although Evans syndrome is not considered a classical feature of Schimke immuno-osseous dysplasia, its development in this case is pathophysiologically coherent with the severe, progressive immunological impairment associated with biallelic truncating *SMARCAL1* variants.

In the earlier childhood phase, as documented in his prior case report [7], the patient displayed moderate T-cell lymphopaenia, reduced NK- and B-cells, and low IgG levels, yet he did not exhibit autoimmune cytopaenias or

TABLE 1. Longitudinal comparison of clinical and laboratory features in a patient with Schimke immuno-osseous dysplasia: typical manifestations, early childhood (age 4.5 years), and late adolescence (age 19 years)

Feature	Typical SIOD (literature)	Childhood (4.5 years)	Adolescence (19 years)
Proteinuria	Nephrotic	9.1 g/day	Absent
Renal function (eGFR)	Progressive decline over time	90.7 ml/min/1.73 m^2 (Schwartz 2009)	Post-transplant, ~20% ↑ creatinine
IgG [g/l]	Low (often < 5.0)	4.2 g/l (↓; ref. ~6.0–12.0)	IVIG-dependent hypogammaglobulinemia
CD3+ T-cells [cell/µl]	Decreased	~600/µl (↓; ref. ~1400–3700)	370/µl (ALC 0.37 $\times 10^3$/µl)
CD4+ T-cells [cell/µl]	Decreased	~320/µl (↓; ref. ~700–2200)	Markedly reduced
CD8+ T-cells [cell/µl]	Decreased	~210/µl (↓; ref. ~400–1200)	Markedly reduced
B-cells/NK-cells	Reduced	Decreased	Decreased
Platelets ($\times 10^9$/l)	Usually normal	220 (normal)	Evans syndrome (ITP + AIHA)
Bone marrow involvement	Variable dysfunction	No cytopenias	Marrow failure features
Main treatment	Supportive/immunosuppressive	Steroids, cyclosporine A	Eltrombopag, IVIG, immunosuppression

AIHA – autoimmune hemolytic anaemia, ALC – absolute lymphocyte count, eGFR – estimated glomerular filtration rate, ITP – immune thrombocytopaenia, IVIG – intravenous immunoglobulin, SIOD – Schimke immuno-osseous dysplasia

recurrent severe infections, and his immune system maintained partial functional stability. This immunological phenotype was consistent with the milder, early stage of SIOD.

Throughout childhood and adolescence, the patient received targeted immunoprophylaxis tailored to his evolving immunodeficiency. He was treated with prophylactic cotrimoxazole during episodes of recurrent respiratory infections and later as part of long-term protection in the context of progressing T-cell lymphopaenia. During periods of increased susceptibility to airway infections, seasonal azithromycin prophylaxis was introduced. Due to fluctuating IgG levels, he also received intermittent intravenous immunoglobulin (IVIG) substitution, administered particularly during episodes of significant hypogammaglobulinaemia and during the immune dysregulation associated with Evans syndrome. Following kidney transplantation, he was additionally placed on temporary antiviral prophylaxis with acyclovir according to post-transplant practice. Preventive vaccinations were carried out when possible, with live attenuated vaccines avoided because of cellular immunodeficiency.

By 2020, at the age of approximately 15 years, the patient developed full Evans syndrome consisting of autoimmune hemolytic anaemia and immune thrombocytopaenia, signalling a marked transition from immunodeficiency to combined immune dysregulation [14]. The timing of onset coincides with accelerated deterioration of both renal and immune function and reflects the cumulative impact of chronic replication stress, impaired T-cell proliferation, and deregulated lymphocyte selection inherent to *SMARCAL1* dysfunction. Emerging data suggest that SIOD, particularly its severe molecular forms, may exhibit dual features – immunodeficiency and autoimmunity stemming from defective regulatory T-cell function and loss of immune tolerance [11, 14, 15], making the late development of Evans syndrome biologically plausible.

Clinically, the disease course was severe. During disease flares, platelet counts dropped to critically low levels requiring repeated platelet transfusions, with an estimated cumulative exposure exceeding 400 units over the patient's lifetime. Therapeutic high-dose IVIG, administered for immune cytopaenias rather than substitution, were used with only transient or insufficient response. Due to refractoriness to corticosteroids and IVIG, eltrombopag therapy was initiated, resulting in partial haematological stabilisation and reduced transfusion requirements, although sustained normalisation of platelet counts was not achieved.

Platelet counts dropped to critically low levels with recurrent episodes of immune-mediated haemolysis, and disease flares frequently coincided with infections or physiological stress, while refractoriness to corticosteroids and progressive bone marrow failure further limited sustained haematological recovery.

Due to unresponsiveness to conventional treatment, the patient became the first minor in Poland to receive eltrombopag for SIOD-associated thrombocytopaenia and marrow dysfunction. His partial response aligns with emerging evidence supporting the utility of thrombopoietin receptor agonists in complex immune-mediated cytopaenias with underlying bone marrow failure [11].

In the context of SIOD, the onset of Evans syndrome in 2020 marked a critical turning point, reflecting advanced immune instability superimposed upon chronic T-cell immunodeficiency. This complication significantly contributed to the patient's vulnerability to severe infections, impaired haematological resilience, and ultimately to the multisystem deterioration that characterised the final years of his illness. As such, Evans syndrome in this patient should be viewed not as an isolated event, but as a manifestation of the broader immunopathological trajectory of SIOD.

DISCUSSION

Schimke immuno-osseous dysplasia is a rare multisystemic disorder characterised by marked phenotypic variability, spanning from attenuated forms compatible with prolonged survival to severe early-onset disease associated with rapid progression to renal failure, recurrent infections, cerebrovascular events, and early mortality [3–6]. The present case provides an exceptional longitudinal perspective by documenting 15 years of clinical evolution in the same patient, enabling direct comparison between early childhood and late adolescent manifestations – an opportunity rarely available in the SIOD literature.

In the earlier description of this patient at the age of 4.5 years, Zachwieja *et al.* [7] reported disproportionate short stature, spondyloepiphyseal dysplasia, hyperpigmentation, moderate T-cell lymphopaenia, and steroid-resistant nephrotic syndrome, but with preserved renal function and absence of severe infections or autoimmune cytopaenias. This childhood phenotype reflected the relatively stable phase of SIOD and aligned with the natural history of patients carrying biallelic truncating *SMARCAL1* variants, which are associated with severe molecular impairment but variable early clinical expression.

During adolescence, however, the patient transitioned into a markedly more severe phenotype, characterised by end-stage renal disease, transplant rejection, progressive marrow dysfunction, recurrent infections, and systemic complications. This clinical shift underscores the inherent trajectory of SIOD, in which initially moderate immunodeficiency and renal dysfunction give way to profound multisystem failure as cumulative DNA replication stress, impaired chromatin remodeling, and compromised immune regulation intensify over time [12].

A notable feature of this case was the development of Evans syndrome in 2020, a rare but pathophysiologically coherent complication in advanced SIOD. The emergence of autoimmune hemolytic anaemia and immune thrombocytopaenia at age 15 years reflects a critical transition from immunodeficiency to severe immune dysreg-

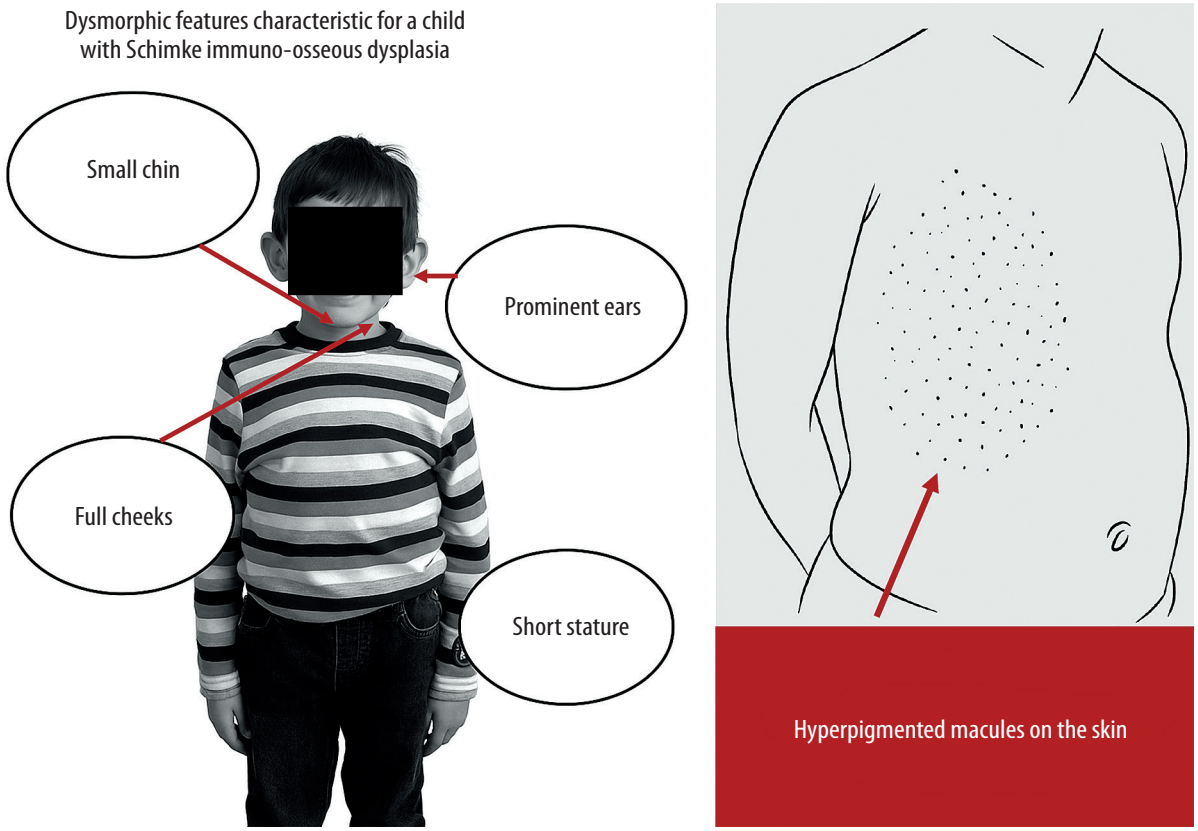

FIGURE 2. Dysmorphic features characteristic for Schimke immuno-osseous dysplasia

The figure illustrates the typical dysmorphic features observed in children with Schimke immuno-osseous dysplasia, including short stature, full cheeks, small chin, and prominent ears. On the right, a schematic drawing demonstrates the presence of diffuse hyperpigmented macules on the trunk, a hallmark cutaneous manifestation of the disorder. The photograph of the child represents the patient at 4.5 years of age [7]

ulation, probably driven by defective regulatory T-cell activity, impaired lymphocyte maturation, and chronic replication stress inherent to *SMARCAL1* deficiency. Evans syndrome significantly contributed to haematological instability, heightened vulnerability to infections, and the patient's overall clinical decline. The partial response to eltrombopag administered as the first use of this agent in a Polish minor with SIOD highlights the potential role of thrombopoietin receptor agonists in marrow failure associated with immune dysregulation [11].

The progression of renal disease in this patient mirrors established SIOD patterns: early steroid-resistant nephrotic syndrome, biopsy-proven FSGS with C1q deposition, progression to end-stage renal disease, and limited graft survival after transplantation. Approximately 60% of SIOD patients develop end-stage renal disease (ESRD), and renal transplant longevity is typically reduced due to persistent immune abnormalities and ongoing DNA repair defects [1, 9, 10]. The patient's decline in renal function and eventual graft rejection reflect these well-described challenges.

This case also highlights the musculoskeletal and dermatologic components of SIOD, which evolved from mild hyperpigmentation and early dysplasia in childhood [7] to marked growth failure (116 cm at age 19), chronic joint pain, and postoperative deformities. These findings align with the skeletal phenotype described in up to 90% of patients [2, 8]. Dysmorphic features characteristic for SIOD are presented in Figure 2.

Emerging therapeutic strategies may reshape future approaches to SIOD management. Recent reports describe the potential of sequential haematopoietic stem cell transplantation (HSCT) followed by kidney transplantation from the same donor, creating durable immunological tolerance and eliminating the need for long-term immunosuppression [15]. Such strategies may be particularly relevant for patients with combined immunodeficiency and ESRD, as in the present case.

Overall, this long-term observation reinforces the importance of early genetic diagnosis, structured multidisciplinary follow-up, and anticipatory monitoring of immune, renal, and skeletal complications. This case contributes significantly to the limited body of longitudinal SIOD data, representing one of the few detailed life-course descriptions of SIOD in the literature and the only such report from Poland. The most important events from the patient's treatment and course of illness are presented in Figure 3.

CONCLUSIONS

Schimke immuno-osseous dysplasia is a rare, multisystemic disorder that poses significant diagnostic and therapeutic challenges. This case, representing a unique

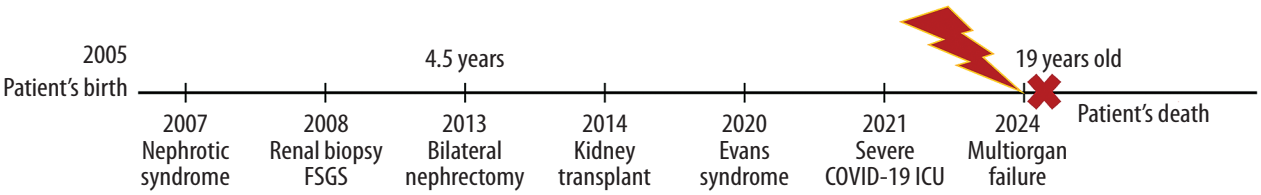

FIGURE 3. Timeline of major clinical events, complications, and therapeutic interventions observed in the patient from early childhood to late adolescence

ICU – Intensive Care Unit, FSGS – focal segmental glomerulosclerosis

Key milestones include the onset of steroid-resistant nephrotic syndrome, biopsy-proven focal segmental glomerulosclerosis, bilateral nephrectomy followed by kidney transplantation, and subsequent graft dysfunction. The figure also depicts the emergence of profound immune dysregulation with development of Evans syndrome, initiation of eltrombopag therapy for refractory immune-mediated cytopaenias and bone marrow failure, and a severe course of COVID-19 infection requiring intensive care and finally lead to multiorgan failure and the patient's death.

15-year longitudinal observation of the same patient from early childhood into late adolescence, provides rare insight into the natural history of SIOD and its progressive transition from renal and skeletal manifestations to profound immune dysregulation, Evans syndrome, and bone marrow failure. Such long-term, detailed clinical follow-up remains exceptional in the literature and highlights the heterogeneity and evolving complexity of SIOD.

The patient's clinical course demonstrates that early genetic confirmation of *SMARCAL1* mutations and consistent multidisciplinary monitoring are essential for optimal management. Importantly, this case illustrates the necessity of exploring innovative and individualised therapeutic strategies in rare disorders where conventional treatments often fail. The use of eltrombopag in this patient, who became the first minor in Poland to receive the drug for SIOD-associated marrow failure, underscores the potential value of carefully considered off-label or novel interventions when standard therapies are ineffective. Similarly, emerging concepts such as sequential HSCT followed by donor-matched kidney transplantation may offer future opportunities to improve outcomes and reduce the need for long-term immunosuppression.

Ultimately, this case emphasises that progress in managing ultra-rare diseases such as SIOD depends on clinicians' willingness to consider new therapeutic approaches, to individualise patient care, and to share detailed clinical experiences. Reports such as this not only broaden our understanding of the clinical spectrum of SIOD but also support the development of more effective and genotype-informed treatment strategies for future patients [5, 6, 13].

DISCLOSURES

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