New mutation in WT1 gene in a boy with an incomplete form of Denys-Drash syndrome
A CARE-compliant case report

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Abstract
Rationale: Pediatric patients with WT1-associated syndromes (including Wilms’ tumor-aniridia syndrome and Denys-Drash syndrome), Perlman syndrome, mosaic aneuploidy, and Fanconi anemia with a biallelic breast cancer type 2 susceptibility protein mutation have the highest risk of developing Wilms’ tumor.

Patient concerns and diagnosis: We describe a patient with bilateral metachronous Wilms’ tumor, ambiguous genitalia characterized by 46, XY disorder of sexual development (DSD) with scrotal hypospadias and bilateral abdominal cryptorchidism, but without nephropathy. At the age of 7 months, the child underwent left nephrectomy with left orchiopexy. At follow-up after 8 months, a second tumor with a diameter of 10 mm was detected in abdominal CT scans at the lower pole of the right kidney.

Intervention: Intra-operative macroscopic inspection of the right kidney revealed a tight attachment of the right proximal ureter to the tumor. Thus, retroperitoneoscopic resection of the lower pole of the right kidney had to be changed to an open surgical procedure with partial resection of the proximal ureter and high uretero-ureterostomy. We subsequently performed orchiopexy and two-stage correction of hypospadias using a free skin graft.

Outcomes: At the last follow-up at the age of 8 years, no pathology requiring treatment was noted. A pair-end-reading (2 × 125) DNA analysis with an average coverage of at least 70 to 100 × revealed a previously unknown heterozygous mutation in exon 7 of the Wilms’ tumor suppressor gene 1 (WT1) gene (chr11:32417947G>A), leading to the appearance of a site of premature translation termination in codon 369 (p.Arg369Ter, NM_024426.4). This mutation had not been registered previously in the control samples “1000 genomes,” Exome Sequencing Project 6500, and the Exome Aggregation Consortium. Thus, to the best of our knowledge this represents a newly identified mutation causing incomplete Denys-Drash syndrome.

Abbreviations: DDS = Denys-Drash syndrome, DSD = disorder of sexual development, WT = Wilms’ tumor, WT1 = Wilms’ tumor suppressor gene 1.

Keywords: children, Denys-Drash syndrome, disorder of sexual development 46, hypospadias, surgical treatment, Wilms’ tumor, WT1 gene mutation, XY

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This case report describes the diagnostic procedures and treatment applied in a patient suffering from DDS related to a mutation of exon 7 of the WT1 gene that had not previously been described. The affected child developed bilateral metachronous WT in early infancy but did not develop nephrotic syndrome or gonadoblastoma. 46, XY DSD characterized by scrotal hypospadias and bilateral cryptorchidism was evident. To the best of our knowledge, the mutation of the WT1 gene at exon 7 described here represents a new mutation encoding DDS and DSD. Our findings need to be confirmed by other authors and should therefore be generalized with caution.

We describe a “de novo” mutation at exon 7 of WT1 gene in a child suffering from DDS. To ensure optimal and individual care for patients with WT1 gene pathology, an international database collecting data on rare mutations is urgently required.

Written informed consent was obtained from the patient’s parents for publication of the case details and accompanying images.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Since the publication of the monograph “Mischgeschwülste der Niere” by Max Wilms in 1899, the most common solid neoplasm of the urinary tract described in children has been Wilms tumor (WT), with an incidence of 3.9 to 10.9 cases per 1 million children.[1,2] WT is the most frequently observed childhood tumor in Europe and North America.[3] The malignant tissue of WT is composed of embryonal tissue consisting of blastemic, epithelial, and stromal components.[4] Overall, 9% of WTs occur in children below the age of 1 year and rank 4th among pediatric tumors in this age group. In 6% to 10% of patients, bilateral disease is found.[5,6]

Overall, 75% of WTs occur in children below the age of 5 years.[7] Protocols for the comprehensive management of patients with WT (International Society of Pediatric Oncology, National Wilms’ Tumor Study Group) have been established successfully. If this type of pediatric cancer disease is detected at an early stage, oncologic treatment results are promising.[8,9] Overall survival of children suffering from WT is approximately 80% with a significantly lower survival of children with bilateral tumors.[10] Approximately 10% of WTs are associated with germ line mutations and congenital anomalies.[11]

In the etiology of this type of childhood cancer, a genetic disposition was identified for roughly 1 third of children affected by WT.[6,11,12] In affected children, a mutation of a gene located on the short arm of chromosome 11 at the 13th locus was identified initially.[13] Subsequently, other mutations were identified.[4,10,12,14] Over time, cases of a combination of WT and other diseases have been described, which together give rise to a more severe course of disease.[14,15] WT progression has been linked to impaired expression of genes other than Wilms’ tumor suppressor gene 1 (WT1), WTX, and CTNNB1, which were found in about 1/3 of WT patients.[11] Especially mutations in TP53 appear to be linked to unfavorable histology of WT.[16,17] All of them had similar genetic manifestations, that is, mutation of the WT1 gene (OMIM no. 607102). In 1967 and 1970, one of these syndromes, that is, Denys-Drash syndrome (DDS, OMIM no. 194080) named after its discoverers, was described for the first time. DDS is characterized by a triad of symptoms, that is, nephropathy, 46, XY disorder of sexual development (DSD), and ophthalmologic, neurologic, and psychiatric evaluations showed normal findings. The mass of the removed tumor and kidney weighed 520 g, accounting for about 10% of the body weight of the child. Histopathologic examination of the tumor revealed “mixed nephroblastoma,” and TNM classification was pT3 N0 M0. The postoperative course was uneventful, and the members of our pediatric oncologic tumor board decided not to conduct postoperative chemotherapy.

At follow-up after 8 months, a spherical lesion (diameter: 10 mm) at the lower pole of the right kidney was detected in abdominal CT scans (Fig. 2). In view of this new finding, the initial diagnosis was corrected to bilateral metachronic nephroblastoma pT4 NH M0.

We opted for retroperitoneoscopy to resect the lower pole of the right kidney, but because of macroscopic involvement of the proximal right ureter, we switched to open minilumbotomy for resection of the lower pole of the right kidney, partial resection of
proximal right ureter, and uretero-ureterostomy with insertion of a ureteral stent. Histopathologic investigation of the kidney tumor on the left side revealed mixed nephroblastoma (epithelial-blastemic) G2 with tumor-free resection margins (R0). Histopathologic examination of the tumor of the right lower pole showed cystic nephroma (G1). Resection margins were free of tumor tissue (R0). Histopathologic examination of the right proximal ureter confirmed that the ureteric wall was not invaded by the tumor.

After 2 months, we removed the ureteral stent by cystoscopy. At follow-up after 1 year, the child was free of pain and exhibited adequate body height and weight gain for age. CT scan confirmed the absence of recurrent nephroblastoma. We undertook orchiopexy to correct cryptorchidism on the right side when the child was 2.5 years old. After 8 months, we undertook Bracka-I urethroplasty, in which a free skin graft of the foreskin was used. There were no postoperative complications, and the graft healed uneventfully. We performed tubularizing urethroplasty 10 months after Bracka I procedure.²⁷

Figure 3 shows a CT scan obtained 3.5 years after resection of the lower pole of the right kidney. No residual tumor was noted and complete remission of nephroblastoma was confirmed. Every subsequent year, the child underwent follow-up examinations with clinical evaluation and ultrasound scans of the abdomen, retroperitoneum, and testes at our institution. At ultrasound examination of the right kidney 6 years after resection of the lower pole of the right kidney, we noted hypertrophy of the remaining right kidney (Fig. 4). No abdominal or retroperitoneal tumor residuals were discernable at ultrasonography. There was no evidence of proteinuria. Levels of urea and creatinine were within the physiologic ranges. The external genitalia appeared normal with a penis of normal size for age. The meatus was located at the tip of the glans, and voiding was described as uneventful with a single stream. Both gonads were residing in the scrotum. The left testicle showed normal size for age, and the right testicle was hypoplastic.

At the last follow-up of the boy at the age of 8.5 years, we recorded a stature-for-age percentile of 35 and a weight-for-age percentile of 3. Urine analysis revealed no proteinuria. The child and his family did not report any urologic complaints or health problems related to DDS or DSD.

After obtaining informed consent from the family, we searched for pathogenic mutations associated with hereditary kidney disease, as well as with other hereditary diseases with similar phenotypic manifestations. DNA analysis was performed by the pair-terminal reading method (2 × 125) with an average coverage of at least 70 to 100×. For sample preparation, we used the technique of selective capture of DNA regions belonging to the coding regions of genes with known clinical significance. Sequencing data were processed by an automated algorithm. This included alignment of reads to the reference sequence of the human genome (hg19), postprocessing alignments, identifying variants and filtered variants, and annotation of identified variants in all known transcripts of each gene from the RefSeq database using a number of methods for prediction of pathogenicity of substitutions (SIFT, PolyPhen2-HDIV, PolyPhen2 HVAR, MutationTaster, LRT), as well as methods of calculating evolutionary conservative positions (PhyloP, PhastCons). Samples of the 1000 genomes, Exome Sequencing Project 6500, and Exome Aggregation Consortium projects were used to estimate the population frequencies of the identified variants.

We found a previously undefined heterozygous mutation in exon 7 of the WT1 gene (chr11: 32417947G > A), leading to the appearance of a premature translation termination site in the 369
codon (p.Arg369Ter, NM_024426.4). Heterozygous mutations in the WT1 gene leading to impaired synthesis of the full-sized protein have previously been described, particularly in patients with DDS (OMIM: 194080) and WT type 1 (OMIM: 194070). The mutation was not registered in the control samples “1000 genomes,” Exome Sequencing Project 6300, and the Exome Aggregation Consortium. Since the mutation disrupts the synthesis of a full-size protein, it must be considered pathogenic.

3. Discussion

DDS is characterized by a variable combination of early onset steroid-resistant nephrotic syndrome, WT, DSD, and gonadoblastoma.[28] There is a paucity of publications of DDS cases, and the classical triad of clinical manifestations appears incomplete in many patients.

The WT1 gene encodes a zinc-finger protein crucial for regulations of many genes by DNA binding.[29] Normal development of gonads, kidneys, and development of the urogenital tract are regulated by WT1.[16,17] Although we noted a favorable outcome in our patient at long-term follow-up of WT, it must be kept in mind that Perlman et al.[30] warned that loss of heterozygosity (LOS) on 11p in children younger than 2 years suffering from small WT and allele loss on 11p puts these children at a greater risk for relapse when treated with minimal (chemonaive) therapy.[30] An investigation of 63 families with 2 or more family members suffering from WT revealed that WT1 mutations account for 6% of familial WT.[11] Cresswell et al. demonstrated evidence for 2 separate tumor sites in unilateral WT disease with divergent histology, and in bilateral WT.[15] We observed a bilateral macrotubular nephroblastoma formation in our patient characterized by an exon 7 mutation. Cresswell et al. showed that bilateral WT appear genetically distinct and probably arise independently.[15] Thus, multiple tumor biopsies are required to assess genetic heterozygosity of WT.[15]

The majority of WT1 mutations in DDS patients occurs sporadically and represents missense mutations in exons 8 and 9 of the zinc-finger DNA binding region.[25] In clinical manifestations of DDS, mutations in other initial exons of the 11p13 locus are less common.[20,31,32] We detected a new mutation in exon 7 encoding the first zinc-finger protein. Bruening et al. described a case of a mutation in exon 7 in a female patient with nephropathy, but without malignant tumor or DSD.[13] In another study published in 2003, Aubert et al. described several patients with mutations in the WT1 gene not located at the hot-spot mutation regions at exons 8 and 9 but at exons 3, 4, and 7.[13] In a patient with changes in exon 7, a point mutation was detected, which led to the replacement of arginine 301 with the formation of a stop codon in a patient with karyotype 46, XY. Clinically, DDS was characterized by bilateral inguinal cryptorchidism (testicular hypoplasia was observed at the age of 19 months and testicular insufficiency at the age of 16 years). External genitalia appeared female, with formation of a vagina. However, the uterus was absent. In this patient, bilateral WT was treated with unilateral nephrectomy and resection of the contralateral kidney tumor. In this patient, no nephrotic syndrome occurred.[13]

Takata et al. also described 2 patients with a mutation in exon 7.[34] A male patient (46, XY) suffered from nephrotic syndrome at the age of 2 years with rapid progression to renal failure but did not have either WT or DSD. The second patient exhibited a similar mutation (46, XY) with clinical manifestations of nephropathy, female genitalia, and DSD, but without WT.[14]

In the literature, there are other descriptions of mutations of the WT1 gene in uncharacteristic exons, but they have similar manifestation of DDS.[16,35–37] Various mutations of the WT1 gene with atypical clinical manifestations have been grouped into a category termed “non-complete DDS” as proposed by Bardeesy et al. in 1994.[38] The authors suggested using this term to describe patients with nephropathy, DSD, or WT.[34,38] The key manifestation of this disease is nephrotic syndrome resistant to pharmacologic treatment, which necessitates kidney transplantation in affected patients.[34,38]

Because 46, XY DSD can be associated with variable clinical findings, exome sequencing has been recommended to discover a genetic cause without preconceived phenotype suggestion.[39] Additional investigation of parental samples represents an effective test not only to test for a familiar inherited genetic disorder, but also to determine the pathogenicity of these mutations.[39]

In multicenter studies, cases of nephropathy with DSD and/or WT were analyzed.[16,33–35] In all patients, the leading symptom was nephrotic syndrome. Weaver et al. at the Washington Children’s Hospital introduced a classic DDS case.[40] Their patient with karyotype 46, XY was diagnosed with gonadal dysgenesis, end-stage renal disease, and bilateral WT. Because of the genetically confirmed DDS (mutation in exon 8 in zone 2 of the zinc finger of the WT1 gene), bilateral nephrectomy and bilateral gonadectomy were performed.[40] According to other authors, nephrotic syndrome may appear later or will not manifest itself at all. Nevertheless, this is possible only with mutations in noncharacteristic exons. For example, specialists from the Denver Children’s Hospital described a case of mutation in exon 6 of WT1 in a patient with karyotype 46, XY, incomplete androgen insensitivity syndrome, and bilateral WT without nephrotic syndrome.[41] A group of authors from Germany also noted the absence of nephropathy.[42] Among 53 patients included in their study, 3 did not suffer from proteinuria. Two patients with karyotype 46, XY had mutations in exon 1 and bilateral WT. One patient exhibited a mutation in exon 2, and this patient showed 46, XY DSD without nephroblastoma.[42]

Baxter et al. recommended early identification of the genetic cause of DDS in order to facilitate correct management of the patient by obtaining more focused endocrine and imaging studies. This approach also allows for correct surgical management of DSD patients.[39] Dattolo et al. described a patient with a mutation in exon 6 with untypical manifestations.[43] After detecting unilateral WT, nephrectomy was performed. Subsequently, an expansive lesion in the contralateral kidney was identified, but renal dysplasia was confirmed histopathologically. At the age of 15 years, the patient experienced symptoms of nephropathy that increased over time. Hemodialysis was required, and kidney transplantation was performed subsequently. This case represents a variant of untypical manifestation of DDS, even in its incomplete and cross-sectional forms. This underlines the need for a genetic study in patients with WT and nephropathy.[40] Testing for WT1 mutations or deletions is recommended also in 46, XY dysgenesis with structural renal alterations and/or proteinuria.[44] Many authors described unusual situations in patients with presumed pathology associated with the WT1 gene. Finnset et al.[45] proposed revising the hypothesis of Köhler et al.[46] and recommended to conduct genetic studies in all patients with
gonadal dysgenesis even if no kidney pathology is evident. Thus, not only patients with 46, XY gonadal dysgenesis with structural changes of the kidneys and/or proteinuria should undergo genetic studies.

Thus, mutations in exons 8 and 9 are always associated with nephropathy. Mutations in other WT1 sites, most often outside the “zinc fingers” zone, can occur without impaired renal function. The cases described above indicate that nephropathy can be absent or appear later in life. This raises the question whether there is a connection between unilateral nephrectomy and kidney resection for the manifestation of nephrotic syndrome. It is unlikely that nephropathy occurs later if it was not encoded by genetic mutation, but an influence of kidney resections on the timing of its manifestation may be responsible for the different time intervals until manifestation of nephrotic syndrome.

The clinical manifestations of DDS differ markedly and require variable treatment. Thus, it may be more reasonable to treat each of these mutations in a patient-specific manner. In DDS patients, proteinuria has been found to occur very early in life. Diffuse mesangial sclerosis or mesangial hyperplasia cause end-stage renal disease in patients suffering from missense point mutations at exons 8 and 9 encoding the 2nd and 3rd zinc-finger region of the protein.[16] In our patient, the point mutation at exon 7 did not result in nephrotic syndrome. This is in accordance with the findings of Auber et al.[13] However, Bruening et al reported on 1 patient with exon 7 mutation suffering from end-stage renal disease.[33]

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