A NOVEL WT1 GENE MUTATION IN A NEWBORN INFANT DIAGNOSED WITH DENYS-DRASH SYNDROME

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Summary: *A novel WT1 gene mutation in a newborn infant diagnosed with Denys-Drash syndrome:* Denys-Drash syndrome (DDS) is a rare disorder characterized by glomerulopathy, genital abnormalities and predisposition to Wilms' tumor. It is associated with constitutional *Wilms' tumor suppressor 1* (*WT1*) gene mutations, in which the majority being missense mutations in the zinc-finger region. Here, we present a newborn with DDS, associated with a novel heterozygous missense mutation, p.Asp396His, on exon 9 of *WT1*.

Key-words: Denys-Drash syndrome – *WT1* gene – Missense mutation – Wilms' tumor – Glomerulopathy – Genital abnormality.

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INTRODUCTION

Denys-Drash syndrome (DDS) is a rare disorder which consists of the triad of congenital glomerulopathy, Wilms' tumor and genital abnormalities resulting from mutations in the *Wilms' tumor suppressor 1* (*WT1*) gene (3, 5). Nephrotic syndrome (NS) associated with diffuse mesangial sclerosis (DMS) presents in the first months of life and progresses to end-stage kidney disease (ESKD) by the age of 4 years. Patients with XY karyotype may have a range of internal and external genital abnormalities, including ambiguous genitalia and male pseudohermaphroditism. Wilms' tumor is usually developed in children under 2 years (4, 8, 9, 12, 13). Over 90% of patients with DDS carry heterozygous mutations in *WT1*. *WT1* is located on chromosome 11p13, and encodes a zinc-finger transcription factor that is crucial to kidney, genital ridge and fetal gonadal development (10). The vast majority of *WT1* mutations in DDS patients are missense mutations in the zinc-finger DNA-binding region (6). These mutations occur especially in exons 8 and 9 (8, 9).

In the present study, we describe a newborn with typical DDS associated with a novel missense mutation, p.Asp 396 His, on the exon 9 of *WT1*.

CASE REPORT

A 20-day-old newborn was referred to our neonatal intensive care unit because of ambiguous genitalia, generalized edema and renal failure. He was born via cesarean section at 38 weeks of gestation, with a 2700 g birth weight, from a 17-year-old primipar woman. Parents were first degree cousins.

On admission, body weight was 3750 g. Arterial blood pressure was 110/70 mmHg (95th percentile value 90/60 mmHg), and generalized edema was noted (Fig. 1). Stretched penile length was 1.5 cm (<10th percentile) with penoscrotal hypospadias, bifid scrotum and nonpalpable gonads (Fig. 2). Laboratory investigations were as follows; urinary protein >1000 mg/dL with a spot urine protein/creatinine ratio of 33, blood urea nitrogen 55 (3-12) mg/dL, creatinine 3.5 (0.3-1) mg/dL, total protein 2.2 (4.6-7.4) g/dL, and albumin 1.2 (2.5-3.5) g/dL. The glomerular filtration rate was 6.2 ml/min/1.73m². Karyotype analysis showed a normal male karyotype, 46XY. The abdominal ultrasonography showed bilateral grade 2 increased renal parenchymal echogenity and a smooth contoured mass with a size of 25x27 mm in the lower pole of the right kidney (Fig. 3). Thus, the patient was diagnosed as DDS.

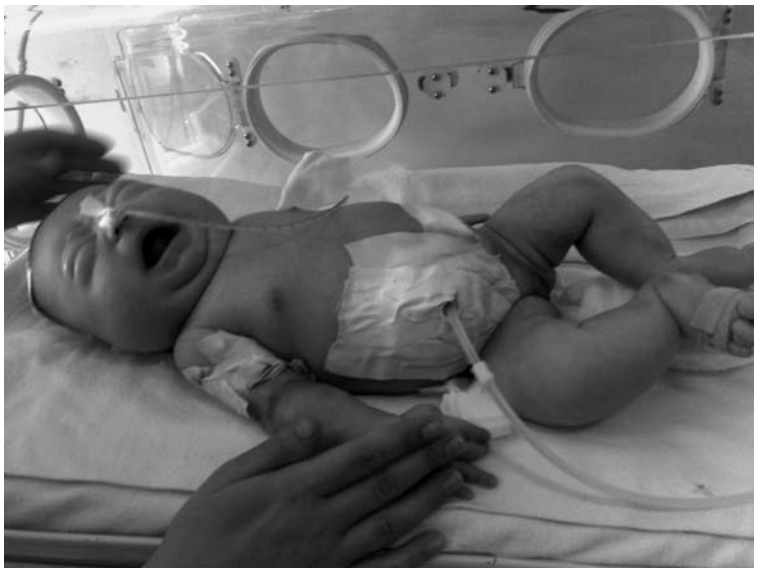

Figure 1: Note that the generalized edema.

On the 55th day, in addition to right nephroureterectomy, biopsies were obtained from two suspected gonadal tissues in the pelvic region and the left kidney. Pathological examination of the removed mass showed Stage-I neoplastic Wilms' tumor (Fig. 4), while histopathological as-

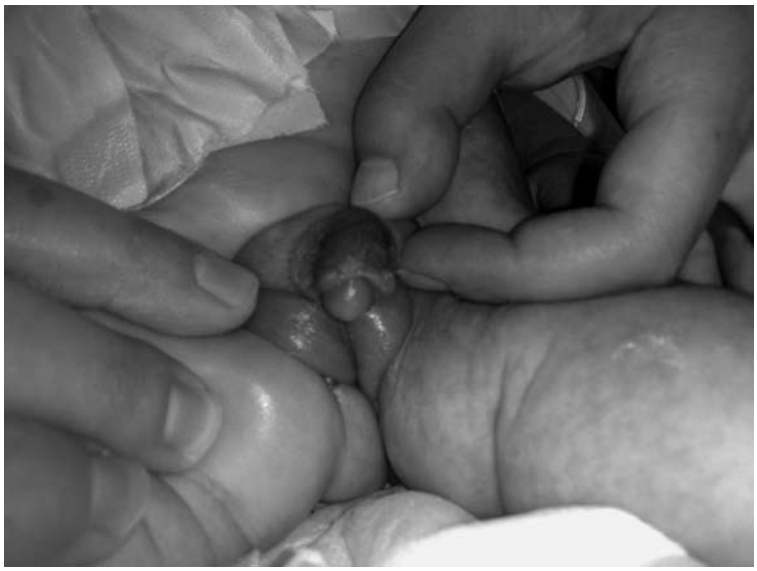

Figure 2: Ambiguous genitalia on urogenital examination.

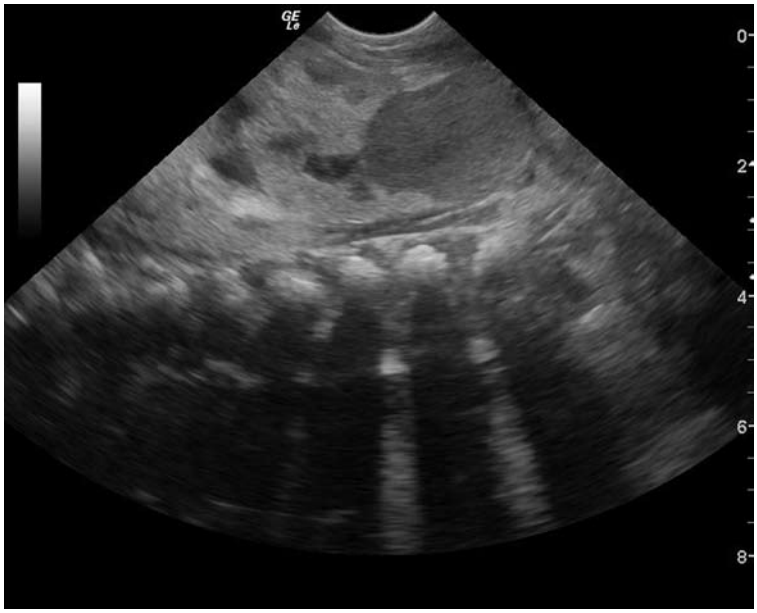

Figure 3: The abdominal ultrasonography scan demonstrating that grade 2 increased renal parenchymal echogenity and a smooth contoured mass in the lower pole of the right kidney.

sessment of the kidneys was compatible with DMS (Fig. 5). The biopsy specimens of the gonads showed normal testicular tissue. Direct sequencing analysis of exon 9 of *WT1* revealed a heterozygous missense mutation, c.1186G>C (p.Asp396His), confirming DDS diagnosis at the molecular level (Fig. 6). He **died** on the 95th day of life due to sepsis and ESKD despite intensive supportive care.

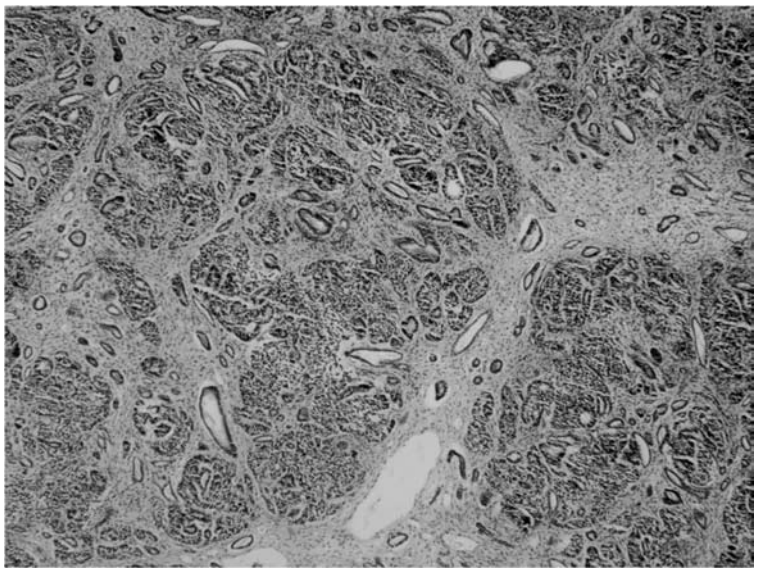

Figure 4: Pathological examination of the resected mass demonstrating Stage-I neoplastic Wilms' tumor.

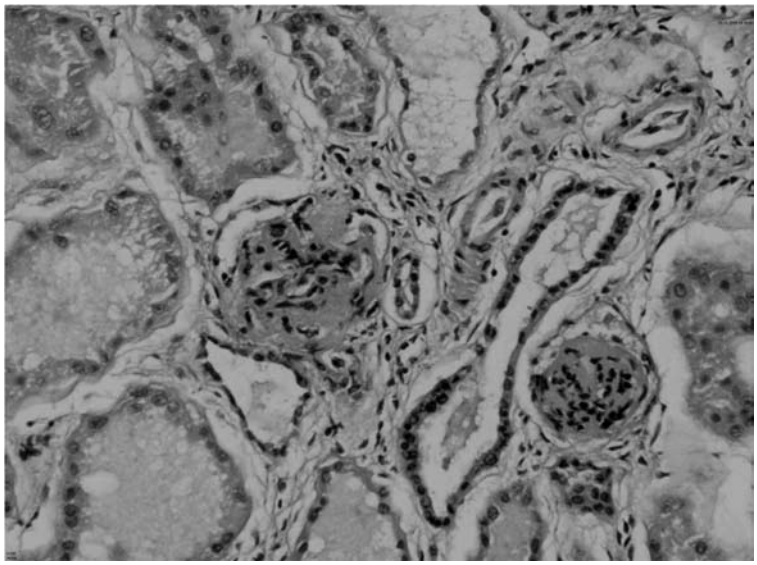

Figure 5: Pathological examination of the kidneys demonstrating DMS.

DISCUSSION

WT1 encodes different isoforms of the WT1 protein. The WT1 protein mediates the mesenchymal-epithelial transition and differentiation during morphogenesis of the kidney and gonad by repressing genes that encode cell proliferation factors and by activating genes that encode markers of epithelial cell differentiation (9, 10). Mutations in the

WT1 result in loss of its regulatory function. Mutations of *WT1* can also cause Frasier syndrome (FS) and WAGR syndrome (Wilms' tumor, aniridia, genital abnormality and mental retardation) in addition to DDS (1, 2, 7).

Most of the constitutional mutations reported so far in the DDS have been close to or within the zinc finger coding region of the *WT1* (6). c.384C>T mutation leading disruption of the third zinc finger of *WT1* has been reported in 17 of the 34 DDS patients (8). So far, an increasing number of mutations in other exons have been described. We found a previously unreported heterozygous missense mutation c.1186G>C (p.Asp396His) in exon 9 of *WT1* in our patient.

This range of clinical phenotypes demonstrates the difficulty in making phenotype-genotype correlations with type of *WT1* gene mutations. Pelletier *et al*. (9) reported a case of mutation c.1180C>T in exon 9 of *WT1* gene that is genotypically and fenotypically male. In contrast to our case, steroid resistant NS has started at 3.5 years old and renal biopsy has shown FSGS in their case. Similar to our case, it is reported that extrarenal anomalies such as hypospadias and cryptorchidism, and Wilms' tumor was present at the time of diagnosis. While NS and

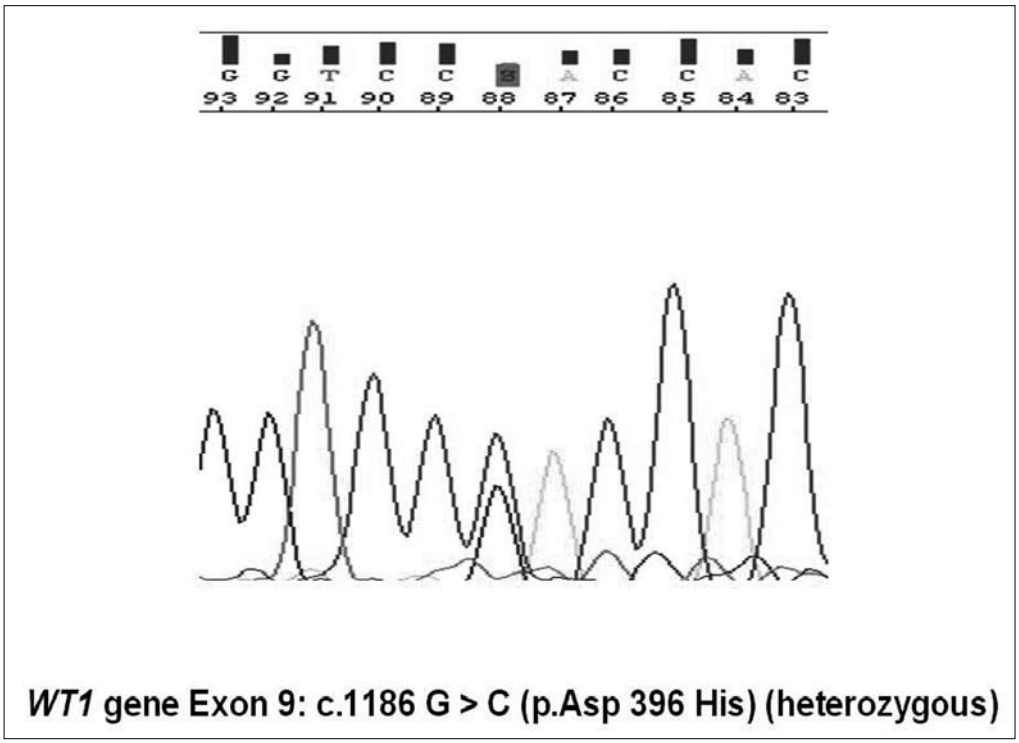

Figure 6: Sequence analysis of exon 9 of the *WT1* gene.

ESKD development were observed in our case within 1 month, they reported ESKD 6 months after diagnosis. In addition, Ruf *et al.* (11) reported a case with c.1162T>C mutation in exon 9 of *WT1* who was genotypically and fenotypically female and had no extrarenal anomalies. Similar to our case, it is reported that steroid resistant NS has started in the first month and renal biopsy has shown DMS. However, in contrast to our case, an ESKD and Wilms' tumor has developed 18 months after diagnosis.

As a conclusion, in case of NS associated with ambiguous genitalia DDS should be considered. Molecular analysis of *WT1* gene is helpful for confirming the diagnosis.

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