

Genetic Testing Proves Crucial in Case of Ambiguous Genitalia and Renal Masses



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OBJECTIVE	The Denys-Drash syndrome consists of a triad of ambiguous genitalia, Wilm's tumor and nephrotic syndrome.
METHODS	We present a diagnostically challenging case of an XY patient with female appearance and Müllerian structures with a WT1 mutation.
RESULTS	These genetic findings resulted in gonadal dysgenesis, end-stage renal disease, and precursor changes to Wilm's tumor in both kidneys. Genetic testing proved critical in this case, helping to solidify a diagnosis and guiding our decision to proceed with bilateral nephrectomy and bilateral gonadectomy.
CONCLUSIONS	Denys-Drash syndrome can present quite dramatically. WT1 testing should be considered early in the workup for patients with differences of sexual development, particularly those with 46XY karyotype. UROLOGY 129: 194–196, 2019. © 2019 Elsevier Inc.

The Denys-Drash syndrome consists of a triad of ambiguous genitalia, Wilms tumor, and nephrotic syndrome. The classic presentation of Denys-Drash syndrome is in the newborn period as a child with ambiguous genitalia.¹⁻³ Renal involvement is classically 2 fold. Wilms tumor and mesangial sclerosis often present concurrently in a confounding manner.³ We present a diagnostically challenging case of an XY patient with female appearance and Müllerian structures with a *WT1* mutation resulting in gonadal dysgenesis, end-stage renal disease, and precursor changes to Wilms tumor in both kidneys.

CASE REPORT

We present a newborn who was found to have ambiguous genitalia after birth. Physical exam findings included an enlarged 1.5 cm clitorophallic structure, 2 perineal openings between labioscrotal folds likely corresponding to vagina and urethra, and nonpalpable gonads. There was no evidence of salt wasting, as she was normotensive without electrolyte derangements. Congenital adrenal hyperplasia screening with 17-hydroxyprogesterone testing was normal. Serum testosterone was 8 ng/dL (reference range

75-400 ng/dL), dihydrotestosterone (DHT) was 80 pg/mL (reference 5-60 pg/mL), androstenedione was 43 ng/dL (10-279 ng/dL), and anti-Müllerian hormone (AMH) was 7.3 ng/mL (male reference range 32-262 ng/mL, female reference range 0.5-7.8 ng/mL).

Abdominal ultrasound showed a normal-appearing, maternally stimulated, and newborn uterus. No gonads were identified. Karyotype was XY. No defects were noted in the *SRY* gene. After multidisciplinary discussion between endocrinology, genetics, psychology, urology and the family, parents planned to raise patient as female. To rule out complete or partial gonadal dysgenesis testing for gene variants in *CBX2*, *DHH*, *MAP3K1*, and *NR5A1* were sent. Patient was discharged uneventfully from the hospital.

Genetic studies were still pending when at 4 months age she presented to an outside hospital with a 3-day history of nonbilious, nonbloody emesis. She was transferred to our institution, and on exam, the abdomen was distended. She was found to be tachypneic, hypertensive, hyponatremic, hyperkalemic, hypochloremic, hyperphosphatemic, and acidotic. Her creatinine was 2.8 mg/dL. Despite negative prior congenital adrenal hyperplasia work-up, endocrinology recommended stress-dose hydrocortisone given concerns for adrenal crisis. Electrolyte abnormalities persisted. A renal ultrasound was ordered and showed enlarged, echogenic kidneys with small cysts bilaterally. The appearance suggested an infiltrating process as compared to a normal ultrasound 4 months prior (Figs. 1 and 2).

Given the history of XY DSD (difference of sexual development), there was concern over the possibility of a *WT1* mutation, and testing was sent. She became

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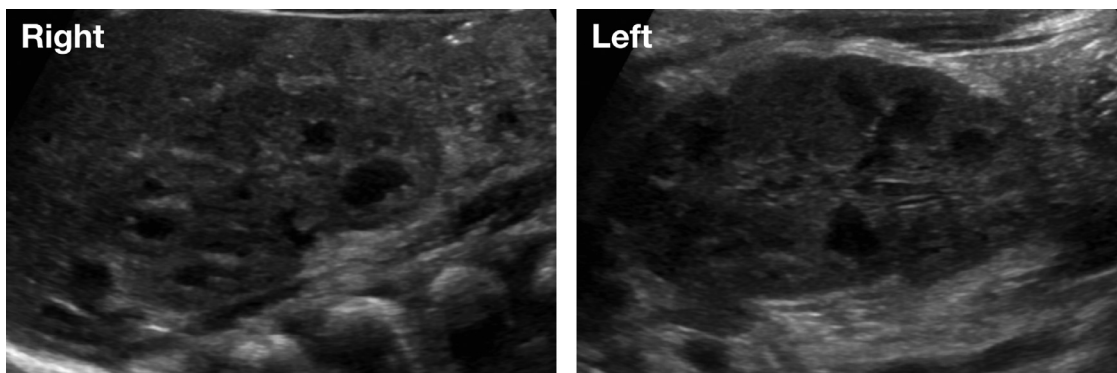


Figure 1. Ultrasound images of right and left kidneys on day of life 2.

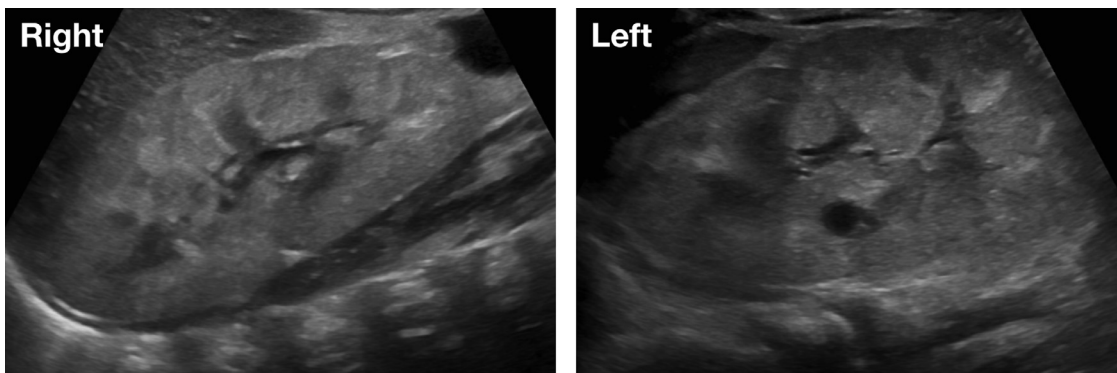


Figure 2. Ultrasound images of right and left kidneys at 4 months of age.

progressively oliguric and then anuric with worsening metabolic acidosis. She was started on hemodialysis. CT chest, abdomen and pelvis with oral and intravenous contrast demonstrated enlarged, bilateral kidneys with minimal cortex and bilateral renal masses within the medullary pyramids with small cystic components (Fig. 3 and Supplemental Figure 1). Testing ultimately returned positive for a *WT1* mutation. Patient was found to have a heterozygous missense variant, p.H445R (p.H377R) in exon 8 of *WT1*, encoding a portion of the *WT1* zinc finger 2 domains. This pathologic variant has been associated with Denys-Drash syndrome in 3 unrelated patients. The remainder of the genetic testing sent after birth returned normal. She was taken to the operating room for bilateral

laparoscopic adrenal-sparing radical nephrectomies, lymphadenectomy, and bilateral gonadectomies.

Pathology demonstrated bilateral intralobar cystic nephrogenic rests with diffuse mesangial sclerosis, and glomerulosclerosis. Bilateral gonads showed fallopian tube and dysgenetic testes. No gonadoblastoma was identified.

Her postoperative course was complicated by disseminated intravascular coagulation. Respiratory, urine, and blood cultures were negative. Hematological testing demonstrated elevated d-dimer, recurrently low fibrinogen, platelet and hemoglobin levels despite transfusions. No definitive etiology could be identified despite extensive workup. Her clinical picture improved with supportive treatment. She was transitioned to peritoneal dialysis 6 weeks after surgery and listed for kidney transplantation.

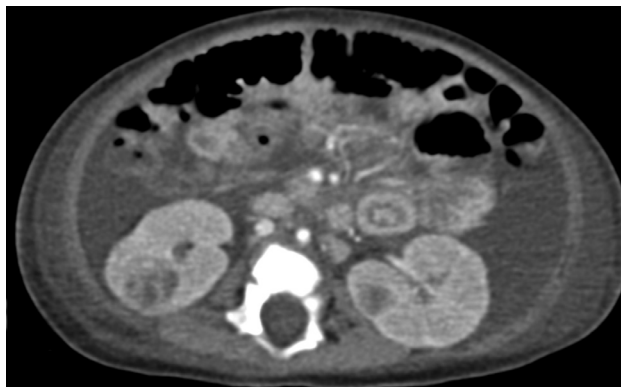


Figure 3. Axial CT image of kidneys at 4 months of age.

DISCUSSION

We present a case of an XY patient with female-appearing external genitalia and Müllerian structures with a *WT1* mutation resulting in gonadal dysgenesis, end-stage renal disease, and precursor changes to Wilms tumor in both kidneys. Her pathology featured findings classically described in cases of Denys-Drash syndrome.¹⁻³ This case was diagnostically challenging for several reasons. There was initially concern for adrenal crisis, hyperaldosteronism, pseudohyperaldosteronism or intrinsic renal disease. Following renal ultrasound, concern increased for a malignant process (nephrogenic rests vs Wilms tumor vs lymphoma). Lymphoma was felt to be less likely in her age group. Autosomal recessive polycystic kidney disease and glomerular cystic disease would have been present on her earlier studies. Additionally, renal vein thrombosis, and congenital nephrotic syndrome were less likely given her history. Genetic testing was key to substantiating the underlying diagnosis and facilitating management decisions for this patient.

The Denys-Drash syndrome usually occurs sporadically secondary to mutations in the *WT1* gene. The characteristic glomerular damage causing the nephrotic syndrome manifests as diffuse mesangial sclerosis.¹⁻³ Renal involvement can also include Wilms tumor and can present concurrently in a confounding manner.

The majority of patients have a normal male karyotype, although this is not universal. The relative paucity of cases of Denys-Drash with a female karyotype (XX sex chromosomes) may be secondary to under diagnosis of the syndrome in phenotypic females with nephropathy or as a result of under ascertainment secondary to previous poor survival of children with renal failure in infancy or early childhood.³⁻⁵

A similar nephropathy is seen in Frasier syndrome. However, in Frasier syndrome the nephropathy occurs later in life and there is no predisposition to Wilms tumor.^{3,6}

CONCLUSION

We have presented a diagnostically challenging case of an XY patient with female appearance and Müllerian structures with a *WT1* mutation resulting in gonadal dysgenesis, end-stage renal disease, and precursor changes to Wilms tumor in both kidneys. Genetic testing proved critical in this case and supports the push for earlier genetic screening for *WT1* mutations in newborns with ambiguous genitalia, particularly those with XY disorders of sexual development. Additionally, multi-institutional collaboration will be needed in the future to adequately study these rare syndromes in the hopes of gaining a better understanding of them and ultimately improving clinicians' recognition of them.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.urology.2019.03.011>.

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