Case Report

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Denys Drash Syndrome with Ambiguous Genitalia: A Case Report from Southern Philippines

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ABSTRACT

Worldwide, more than 200 cases of Denys-Drash syndrome have been published up to date. This patient from Southern Philippines presented with a left abdominal mass associated with signs of nephropathy such as periorbital, facial and bipedal edema. He also presented with ambiguous genitalia and undescended testis, left. The clinical triad of Nephrotic Syndrome, male pseudohermaphrodritism and Wilms tumor presenting as progressively enlarging abdominal mass were appreciated. Chromosomal analyses showed a 46, XY chromosomes and further diagnostic work up revealed a WT1c.1358G>C (p. Cys453Ser) heterozygous (Variant of Unknown Significance or VUS). In this patient, it resulted from mutations in the WT1 gene on chromosome band 11p13. The genital abnormalities in the Denys Drash Syndrome may result from pleiotropic effects of mutations in the WT1 gene itself. Despite the relatively good prognosis of our patient, he was not able to undergo these life sustaining measures because of health care associated infection.

Keywords: Denys Drash Syndrome; Wilms Tumor; Nephrotic Syndrome; Ambiguous genitalia; Claw sign

Abbreviations: DDS: Denys Drash Syndrome; DMS: Diffuse mesangial sclerosis; G6PD: Glucose-6-Phosphate Dehydrogenase; PTA: Prior to admission; ESRD: End-Stage Renal Disease; PCV: Pneumococcal conjugated vaccine; MMR: Measles, Mumps, Rubella; CAH: Congenital Adrenal Hyperplasia; WAGR: Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation; VUS: Variant of Unknown Significance; WT: Wilms Tumor

Introduction

Denys Drash Syndrome (DDS) is a rare genetic condition, characterized by a triad of progressive renal disease, male pseudohermaphoditism, and Wilms tumor. All patients were infants with severe proteinuria progressing rapidly to renal failure. Nephropathy is a constant feature and was identified as diffuse mesangial sclerosis (DMS) [1]. Management of patients with confirmed Denys-Drash Syndrome includes both medical such as maintaining fluid and electrolytes balance, treatment of complications like hypertension and renal replacement therapy in patients with End-Stage Renal Disease (ESRD); and surgical such as nephron-sparing surgery or radical bilateral nephrectomy. Kidney transplantation is the treatment of choice after bilateral nephrectomy.

Case Description

Patient I.J.P., a 14-month, male, Roman Catholic from South Cotabato, Philippines was admitted due to abdominal mass. He was born to a 33-year-old G1P1A0 mother, delivered full term via repeat cesarean section at a local government hospital with good cry and activity. He was small for gestational age with a birth weight of 2.3 kgs. Upon physical examination, the patient was noted to have ambiguous genitalia, thus a referral to a higher institution for further evaluation and management was advised. Newborn screening done revealed Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency; confirmatory test was not complied. Maternal and pregnancy history were unremarkable. The patient was apparently asymptomatic until 6 months prior to admission, when he was noted to have intermittent swelling around his eyes which spontaneously resolved.

There was no associated fever, abdominal distention, scrotal swelling or tea-colored urine. At this time, no medical consultation was done nor any medication taken. Twenty-eight (28) days prior to admission (PTA), patient was noted to have an abdominal mass, about the size of an adult fist located at left hemi-abdomen. It was associated with irritability when touched. This was accompanied with periorbital and scrotal swelling, cough, and undocumented and intermittent fever temporarily relieved by taking paracetamol drops. There was no consultation done. Twenty-four (24) days PTA, the patient was brought to a pediatrician because of a progressively enlarging abdominal mass and persistent cough. Assessment at that time was an abdominal mass probably malignant with concomitant respiratory tract infection. Patient was then given prednisone at 1mkd TID x 5days and an antibiotic but no relief of symptoms. An abdominal ultrasound was also done which showed a disparity in the size of the kidneys, the left being bigger than the right kidney. Measurements revealed the right kidney 7.7 x 3.7 cm while the left measures 9.9 x 9.3 cm. An echogenic solid mass further noted on the left kidney, measuring 8.6 x 7.9 cm with associated dilatation of the collecting system. The urinary bladder is partially distended.

Impression was to consider nephroblastoma with hydronephrosis on the left kidney, and minimal ascites. He was subsequently referred to pediatric nephrologist for further evaluation of the mass and requested an abdominal CT scan which revealed a huge expansile retroperitoneal heterogeneous solid mass occupying the left hemi-abdomen, demonstrating a claw-sign with a normal renal parenchyma. The lesion measured 10.96 cm x 10.20 cm x 10.79 cm (CCWAP) and slightly bulged into the right side and appears to extend into the renal pelvis. The primary consideration was Wilms Tumor. There was also calyceal dilatation noted in the inferior pole of the left kidney. No urinalysis was performed. At this time, patient's cough persisted. Patient was subsequently referred to our institution for further evaluation and management. Family history revealed, a maternal aunt died of probable chronic kidney disease at the age of 23 years old. His mother had bilateral breast tumors and subsequently underwent excision but biopsy was not performed. Patient's developmental milestones were at par with his age.

He was given was given BCG and Hepatitis B vaccines at birth. Moreover, he received pentavalent and oral polio vaccines on the 2nd, 7th, and 8th months. Pneumococcal conjugated vaccine (PCV) vaccines were also administered on the 2nd, 3rd and 5th months. At 12 months old, he was given Measles, Mumps, Rubella (MMR) vaccine. On physical examination, the patient was seen awake, irritable, afebrile, not in respiratory distress with stable vital signs: heart rate of 110 beats per minute, respiratory rate of 23 cycles per minute, temperature of 36.5C, blood pressure of 90/60 mmHg. Oxygen saturation was at 96% on room air. Patient weighed 14.1 kilograms, length of 75 cm, with a body surface area of 0.54 m^2. Upon admission, his chest circumference was 46.5 cm and head circumference of 40 cm. Patient was noted to have pale palpebral conjunctivae, anicteric sclerae, with note of periorbital and facial edema.

There was no aniridia with no abnormalities found on fundoscopic examination. Lips and buccal mucosae were moist, with no mouth ulcers noted. Macroglossia was not appreciated. There were no discharges in the eyes, ears and nose and no alar flaring. There was no ear crease or skin tag. Auscultation of the chest and lungs revealed crackles on both lung fields but no retractions on inspection. Examination of the cardiovascular system showed adynamic precordium with no heaves and thrills, cardiac rhythm was regular, and no murmur appreciated. Abdomen was distended with an abdominal girth of 57 cm and with visible superficial veins. There was no omphalocele observed. A hard, poorly circumscribed, non-tender mass was palpated at left hemi abdomen measuring 17 cm x 14 cm. (Figure 1). For the genitourinary system, patient was noted to have scrotal edema, with the presence of right testis upon palpated. Patient was likewise noted to have ambiguous genitalia (Figure 1B). A non-tender mass in the left inguinal area was noted. The patient had pitting bipedal edema with strong peripheral pulses. There were no rashes or any gross deformity on both extremities observed. Neurologic examination was unremarkable. The patient was initially admitted under the IDS service because COVID19 pneumonia was considered.

Baseline CBC showed anemia of 109, leukocytosis of 14.99, with predominance of lymphocytes (40) and thrombocytosis of 685. His chest radiograph showed bilateral pneumonia. Baseline urinalysis revealed clear, light-yellow appearance with a pH of 7.0, hyposthenuria with a specific gravity of 1.007, proteinuria of 2+. Urine nitrite and leukocyte esterase were both negative, with microscopic hematuria of 5 per high power fields. There was no pyuria, bacteriuria or crystalluria. Patient was started with antibiotics intravenously. His skeletal survey showed an unremarkable result. The findings of the whole abdominal CT scan with contrast are the presence of a large, well-defined, encapsulated, complex, heterogeneously enhancing mass measuring about 14.5 cm x 13.2 cm x 14.4 cm noted, arising from the anterior cortex of the left kidney. Within the mass are areas of non-enhancement suggestive of necrosis or cystic components.

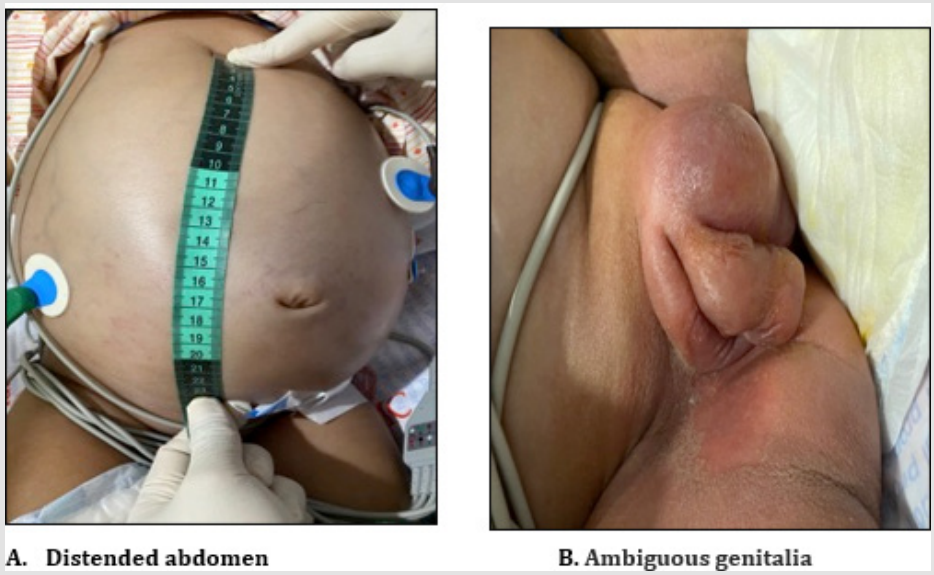

Figure 1: Pertinent physical examination findings:

A. Distended abdomen with an abdominal girth of 57 cm and with visible superficial veins. A hard, poorly circumscribed, non-tender mass was palpated at left hemi abdomen measuring 17 cm x 14 cm.

B. Ambiguous genitalia with noted scrotal edema and palpable right testes.

The mass crosses the midline and displaces the ipsilateral kidney posteromedially, as well as the midline structures to the right. The bowel loops are likewise compressed and displaced to the right. No vascular encasement appreciated. The pelvocalyceal system of the left kidney is dilated. The right kidney is normal in size with good excretion of the injected contrast. Renal arterial and parenchymal opacifications in both sides are symmetric and simultaneous. No evidence of lithiasis noted in both sides. The adrenal glands are unremarkable. Prominent and enlarged hypodense nodule densities are seen in the bilateral inguinal region and mesenteric areas with the largest measuring about 1.0 cm on its widest short axis diameter, seen in the mesenteric region. Vascular opacifications do not appear unusual.

The urinary bladder is adequately distended showing its regular contour and normal non thickened walls. No pathologic intraluminal densities were appreciated. There is herniation of a small intestinal segment through a peritoneal defect (lateral to the inferior epigastric artery) measuring 0.7 cm in the left inguinal region, extending inferiorly to the left scrotal region. The left testicle is not appreciated. However, a well-defined, ovoid, soft tissue density of about 1.5 x 1.1 x 0.7 cm is seen in the left inguinal region, medial to the external iliac artery. The right testicle is unremarkable. Free hypodense intraperitoneal fluid collection of about 114 cm is demonstrated in the rectovesical and suprapubic spaces.

The Impression of the study was a Huge renal mass, left with secondary pelvocaliectasia, Wilms tumor was considered; Axillary and mesenteric lymphadenopathies, may be metastatic; Ascites; Indirect inguinoscrotal hernia, left; Bilateral consolidative pneumonia with subsegmental atelectasis; Minimal pleural effusion, bilateral, more on the left. Patient was referred to nephrology service for co-management. Further laboratory work-ups were done which showed hyponatremia and hypocalcemia. Moreover, other baseline serum electrolytes showed unremarkable results, K: 4.72 mmol/L, Magnesium of 0.87 mmol/L and creatinine of 16.24 umol/L. In addition, patient presented with hypoalbuminemia of 7.26 g/L (35-50).

Repeat early morning urinalysis showed unremarkable result. A 24-hour urine albumin determination was done with a total protein spillage of 259 mg/m^2/hr, considered as nephrotic range proteinuria. Serum triglycerides and LDL were also elevated. Other diagnostic work-ups such as the liver function tests all showed unremarkable results. Clinically, the patient's pneumonia improved. Eventually, the oncology service started the Wilms tumor protocol for metastatic disease. He was given Vincristine, Actinomycin, and Doxorubicin as induction chemotherapy. His baseline echocardiogram showed a good ejection fraction of 81%, with minimal pericardial effusion of 0.3 cm. The plan was to complete 9 weeks neo-adjuvant chemotherapy then reevaluate for nephrectomy. Renal Doppler of both kidneys was planned to rule out thrombosis. The patient was also referred to Endocrine service for evaluation of ambiguous genitalia.

They assessed it as under-virilized male with testis, Congenital Adrenal Hyperplasia (CAH) unlikely. Since the patient manifested

with associated genitourinary features, he was referred to the Genetics section. The Invitae Wilms tumor panel was requested and buccal smear sample was taken and sent abroad which showed the result of WT1c.1358G>C (p.Cys453Ser) heterozygous (Variant of Unknown Significance or VUS). The service strongly recommended to do genetic testing of the parents and/or siblings. Importantly, pre-testing and post-testing genetic counseling sessions were done by a genetic counselor of the Newborn Screening Center Mindanao. Karyotyping result revealed a normal male karyotype with 46, XY.

The Palliative care service was likewise on board for the patient's improvement of quality of life and commitment to care. Level of understanding was discussed where the family is fully aware of the patient's diagnosis and current treatment plans. Family affirmed full commitment to care and amenable for current chemotherapy regimen. Other subspecialties also took part in the multidisciplinary care for the patient. He was referred to Pediatric surgery for his future surgical plans. The nutrition and diet of the patient was taken care of by the nutrition service of the department.

Discussion

The presence of left abdominal mass associated with signs of nephropathy lead to the following considerations:

1. Congenital Hydronephrosis is considered primarily because of the presence of a palpable mass at the left hemi-abdomen. Hydronephrosis usually presents with a unilateral abdominal mass and is frequently diagnosed in this age group. It can be secondary to ureteropelvic junction obstruction or ureterovesical junction obstruction. However, it was ruled out because of the presence of associated ambiguous genitalia and as well as the presence of nephrotic syndrome.

2. WAGR syndrome, this refers to the syndrome of Wilms' tumor, aniridia, genitourinary anomalies, and intellectual disability (mental retardation). Two features, particularly the Wilms' tumor and the pseudohermaphroditism are seen in our patient however absence of aniridia and intellectual disability cannot be totally established at this very young age. Moreover, nephrotic syndrome which our patient manifests is not a feature of patients with WAGR syndrome, thus it is unlikely to be the primary diagnosis.

3. Beckwith-Wiedemann syndrome (BWS) have a 5 – 10% chance of developing Wilms' tumors. Abdominal mass noted in our patient is more likely a Wilms' tumor thus considering this as one of the differential diagnoses. The major clinical features of BWS include macrosomia, macroglossia, omphalocele, prominent eyes, ear creases, and large kidneys. These features are not present in our patient, thus the unlikely disease condition.

4. Frasier Syndrome (FS) is one closest differential diagnosis. It is characterized by the association of male pseudohermaphroditism with female external genitalia and progressive glomerulopathy. Patients present with normal female external genitalia, streak gonads, and XY karyotype, and frequently develop gonadoblastoma. Glomerular symptoms consist of childhood proteinuria and nephrotic syndrome which is seen in our patient hence considering this disease condition. On the other hand, Wilms' tumor which is likely present in our patient, is not a usual feature.

5. Denys Drash Syndrome (DDS): It is a rare genetic cause of steroid-resistant nephrotic syndrome (SRNS) during the first year of life which is present in our patient. It consists of progressive renal disease with diffuse mesangial sclerosis, male pseudohermaphroditism, and Wilms' tumor. The patient was likewise noted with ambiguous genitalia since birth, likely to be an intersex disorder of male pseudohermaphoditism. Patients with DDD are high risk for early development of Wilms' tumor which is clinically observed in our patient.

An association between gross structural anomalies of the urinary tract and abnormalities of gonadal and/or external genital differentiation is well documented. Predisposing syndromes associated with an increased risk of Wilms Tumor (WT) are responsible for 9-17% of all cases of malignancy [2]. The most common syndromes associated with WT are WAGR (Wilms-Aniridia-Genitourinary-mental Retardation), Denys-Drash syndrome (DDS), Beckwith-Wiedemann syndrome (BWS), isolated hemihypertrophy, and Perlman syndrome. At least 100 other syndromes have been associated with WT [3], and that number seems likely to continue growing. Recent case reports persist in describing new syndromes associated with an increased incidence of WT [4,5]. The risk of developing malignancy varies by syndrome. Scott et al. assigned risk categories to various conditions. Syndromes with a high risk, or greater than 20%, of developing WT include: WAGR, DDS, familial Wilms, Perlman syndrome, mosaic variegated aneuploidy, Fanconi anemia/biallelic BRCA2. Those with a moderate risk, or 5–20%, include Frasier syndrome, BWS, and Simpson-Golabi-Behmel syndrome (SGBS).

Finally, syndromes where less than 5% develop WT, or low risk, include: isolated hemihypertrophy, Bloom syndrome, Li-Fraumeni, Hereditary hyperparathyroidism-jaw tumor syndrome, mulibrey nanism, Trisomy 18, and 2q37 microdeletion syndrome [3]. Denys Drash Syndrome (DDS) is a triad of progressive renal disease, male pseudohermaphoditism, and Wilms tumor. It is a rare genetic condition first reported by Denys and Drash, respectively [6,7]. All of the patients were infants with severe proteinuria progressing rapidly to renal failure. Nephropathy is a constant feature. Incomplete variants were described and the glomerulopathy was identified as diffuse mesangial sclerosis (DMS) [3]. DDS can be further classified into complete and incomplete variants. Complete DDS patients present with nephropathy, male pseudohermaphroditism, and Wilms tumor, whereas incomplete patients present with nephropathy with either Wilms' tumor or intersex disorders with the exception of 46 XX patients, whose gonads are usually normal. More than 90%

wherein affected individuals have a germline point mutation in the eighth or ninth exon of the WT1 gene, which results in an amino acid substitution, and almost all patients (90%) will develop Wilms tumor in any residual renal tissue.

Genetics

Denys-Drash syndrome is the result of mutations in the WT1 gene on chromosome band 11p13 [8-11]. The WT1 gene contains 10 exons that produce 4 different messenger RNAs (mRNAs) as a result of 2 alternative splicing sites in exons 5 and 9 that, in turn, encode 4 different isoforms of the WT1 protein. Splicing at the second alternative site (exon 9) is thought to have a great biological importance and results in the inclusion or exclusion of 3 amino acids, lysine, threonine, and serine (KTS), yielding the KTS-positive isoform when the amino acids are included and KTS-negative isoform when excluded. The precise ratio of the KTS-positive/negative isoforms seem to be crucial for the normal function of the WT1 gene. The WT1 protein is a transcription factor predominantly expressed in the embryonic kidneys and gonads. Exons 1-6 of the WT1 gene encode the regulatory domain, which regulates expression of target genes, and exons 7-10 encode the 4 zinc fingers of the DNA-binding region 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. The genital abnormalities in the Denys Drash Syndrome may result from pleiotropic effects of mutations in the WT1 gene itself. This hypothesis was first confirmed in a report which identified constitutional heterozygous mutations within the WT1 gene in some individuals with Denys Drash Syndrome [8]. Point mutations in the WT1 gene result in loss of its regulatory function, with the consequent abnormalities in glomerular formation and gonadal differentiation seen in Denys-Drash syndrome. Mutations that disrupt the second alternative splicing site of the WT1 gene alter the normal ratio of KTS-positive/negative isoforms from 2:1 to 1:2 and result in abnormalities in glomerular formation and gonadal differentiation seen in Frasier syndrome.

In striking contrast, complete deletions of band 11p13 result in the Wilms tumor, aniridia, genitourinary malformations, and mental retardation (WAGR) syndrome which is characterized by structural urinary tract abnormalities without nephropathy. For our patient, a buccal smear was sent to for Wilms Tumor Panel testing which subsequently revealed a WT1 mutation but with Variant of Unknown Significance (VUS). VUS pertains to detection of a significant change in the gene, however, depending on the current studies, are yet to be confirmed if pathogenic or not. The classification of variants may change over time as a result of new variant interpretation guidelines and/or new information. Genetic testing of the parents and/or siblings is recommended. There is a chance that this could be a novel mutation causing the disease. The frequency of Denys-Drash syndrome is unknown. Worldwide, more than 200 cases of Denys-Drash syndrome have been reported since 1967, when Denys et al originally described a child with nephropathy, ambiguous genitalia, and Wilms tumor [12-14]. New cases are being reported worldwide [15].

Denys-Drash syndrome has no race predilection. Although both sexes can be affected, the presence of intersex disorders makes the estimation of the male-to-female ratio misleading because individuals with Denys-Drash syndrome who are assigned the female gender may be genotypic males (XY gonadal dysgenesis with female phenotype). Ascertainment is also biased toward children with ambiguous genitalia (males), whereas diagnosis in females may be delayed or not established. Karyotyping was done in our patient which showed normal male karyotype [16].

Manifestations

Clinically, Denys-Drash Syndrome (DDS) presents signs and symptoms related to nephropathy, Wilms' tumor and intersex disorders. The renal manifestations of DDS are nephrotic syndrome and progressive nephropathy. Nephrotic syndrome in DDS usually manifests in infants aged 2 weeks to 18 months. In our patient, he presented with generalized edema around 10 months old however noted to resolved spontaneously without any treatment given [17]. His birth history did not reveal any enlarged placenta or any edema in the neonatal period. Prior to present illness, patient had several bouts of respiratory tract infections which were all managed medically by intake of antibiotics. On his current admission, he presented with anasarca along with hypoalbuminemia and nephrotic range proteinuria.

Furthermore, progressive nephropathy which leads to end-stage renal disease may occur as early as within few weeks to 2 years from the time of diagnosis or before the age of 3 years. This feature is not yet manifested by our patient since his renal function is still normal [18]. There was no note of oliguria, pallor or hypertension. However, the likelihood of him to reach ESRD in a younger age is high. Another significant component of DDS is the presence of Wilms tumor (WT). The median age at discovery of Wilms' tumor is 12.5 months in cases associated with Denys-Drash syndrome, as opposed to 36 months in patients with isolated Wilms tumor without Denys-Drash syndrome. The earliest tumor onset was in patients with truncation mutations (12 mo, 66 patients) compared with missense mutations (18 mo, 30 patients) [19].

Palpable abdominal mass is the most common manifesting symptom which is noted in our patient. Interestingly, hematuria and hypertension were absent in our patient instead he was noted to have a mass in the left inguinal area suggestive of an inguinal hernia. Lastly, signs related to intersex disorders were noted such as penoscrotal hypospadias with cryptorchidism in addition to the ambiguous genitalia observed since birth. These conditions usually manifest at birth. Altogether, these three major manifestations are in consonant with our patient who at time of diagnosis was 14 months of age.

Diagnosis

Essential to the diagnosis of Denys-Drash Syndrome apart from the clinical signs and symptoms are the diagnostic studies. Proteinuria is the hallmark of nephropathy in DDS; thus, a simple urinalysis may give us a clue. It is usually in the nephrotic range akin to our patient who has a total protein spillage of 259 mg/m^2/hr. In DDS, gross or microscopic hematuria can be seen although this feature is absent in our patient. Moreover, renal function tests such as BUN and serum creatinine must be done in all patients suspected with DDS to confirm any evidence of progressing renal dysfunction. As with other cases of Denys-Drash Syndrome, BUN and serum creatinine levels may be within reference ranges in the early stages but worsen with advancing nephropathy or development of bilateral Wilms tumor. End-stage renal disease (ESRD) development is accompanied by hyperkalemia and hyperphosphatemia [20].

These diagnostic attributes were not observed in our patient perhaps can be explained by the early course of the disease. Other equally important laboratory examinations to test out the presence of Wilms' tumor may be done such as the hyaluronic acid, hyaluronic acid-stimulating activity, erythropoietin, and renin prohormone for which elevated levels are associated with Wilms tumor. However, these tests were not done due to financial constraint. Chromosome analysis should be done. It is warranted to obtain karyotype determination in all patients with suspected Denys-Drash syndrome, even in the absence of ambiguous genitalia. Analysis of band 11p13 and determination of the WT1 mutation is important in all patients with the nephropathy of DDS, even in the absence of Wilms tumor or obvious intersex disorder.

These findings confirm the genetic diagnosis and alert the physician to the significantly increased risk of Wilms tumor development. A buccal smear sample was taken and sent to The Invitae for the Wilms tumor panel which subsequently showed the result of WT1c.1358G>C (p. Cys453Ser) heterozygous (Variant of Unknown Significance or VUS). Imaging Studies are likewise vital in the diagnosis of DDS. Abdominal and pelvic ultrasonography can be initially done in all patients who present with signs and symptoms that suggest Denys-Drash Syndrome to be able to visualize the presence of an abdominal mass or any gonadal tumor [21]. This can be readily done because its cost-effective and available even in resource-limited areas. Furthermore, it is but prudent to screen all individuals for the presence of abnormal internal genitalia (eg, undescended testes, undifferentiated and/or streak gonads) because of their risk of developing a gonadoblastoma (both in 46, XY and 46, XX individuals).

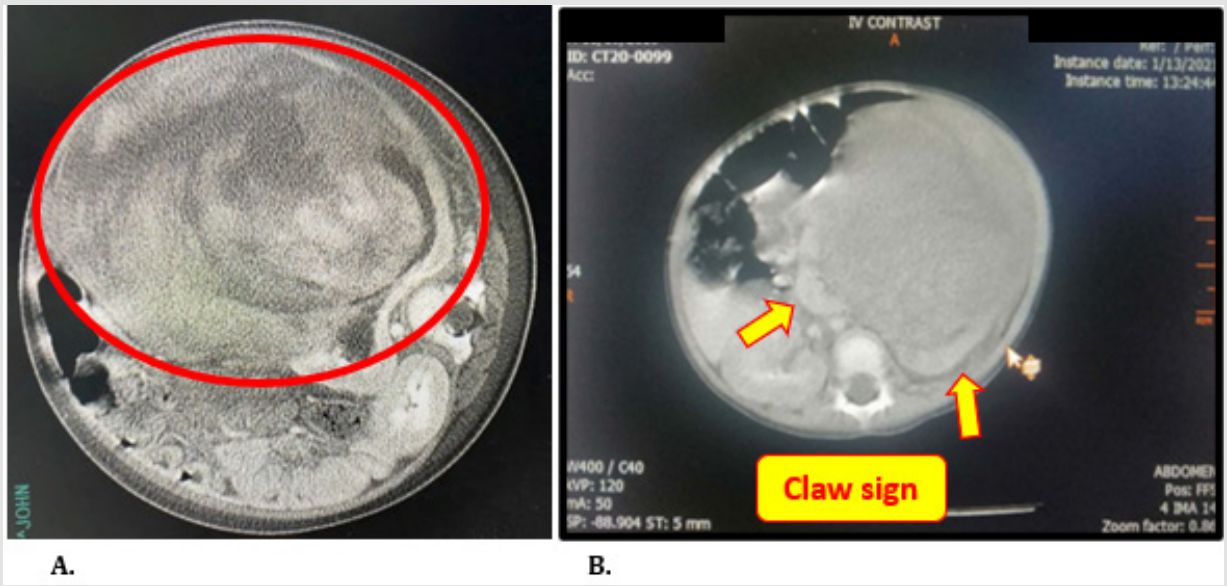

Figure 2: Computed Tomography Scan of the abdomen with contrast:

A. Showing a huge retroperitoneal mass in the left hemiabdomen measuring 14.5 cm x 13.2 cm x 14.4 cm. It arises from anterior cortex of the left kidney. The mass is large with well-defined, encapsulated, complex, heterogeneously enhancing suggestive of necrosis or cystic components. It crosses the midline and displaces the ipsilateral kidney posteromedially, as well as the midline structures to the right.

B. It demonstrates a claw sign suggestive of a Wilms tumor.

The patient's initial ultrasound revealed presence of an abdominal mass suggestive of a Wilms' tumor. Abdominal and pelvic CT scanning on the other hand, is considered a more sensitive test for revealing Wilms tumor, especially to reveal unsuspected contralateral tumor or metastases, to demonstrate invasion of contiguous structures, to predict surgical resectability, and to monitor response to chemotherapy and surgical resection. Initially, the presence of a huge expansile retroperitoneal heterogeneous solid mass occupying the left hemiabdomen, demonstrating a claw-sign with the normal renal parenchyma measuring 10.96 cm x 10.20 cm x 10.79 cm (CCWAP) and slightly bulged into the right side and appears to extend into the renal pelvis led to Wilms Tumor as the primary consideration (Figure 2). To rule out the presence of a pulmonary metastasis, a chest radiograph is of great value [22].

Biopsy is essential for the diagnosis of Denys-Drash syndrome because it confirms the presence of diffuse mesangial sclerosis. Obtain the kidney biopsy specimen by percutaneous biopsy in children without Wilms tumor at the time of presentation. In patients with Wilms tumor, obtain kidney tissue at the time of nephrectomy. Our patient already presented with an abdominal mass highly suggestive of a Wilms tumor even at the outset, thus a renal biopsy was not done [23]. The possibility of a nephrectomy after completion of chemotherapy is anticipated and a biopsy of the kidney should be performed.

The pathognomonic kidney lesion is diffuse mesangial sclerosis. Histologic features of the early phase include expansion of the glomerular mesangial matrix, obliteration of the capillary lumens, thickening of the glomerular basement membrane, and hypertrophy of the podocytes. Features of the late phase are mesangial matrix sclerosis, glomerular tuft contraction, prominent tubular atrophy, and interstitial fibrosis. Wilms tumor originates from pluripotential cells of the metanephric blastema and consists of blastemal, stromal, and epithelial cells. The presence of anaplasia suggests a poor prognosis. As for the patient, a biopsy was not done.

Treatment

Management of patients with confirmed Denys-Drash Syndrome includes both medical and surgical which may be influenced by the identification of a constitutional WT 1 mutation. The cornerstones of Denys-Drash syndrome (DDS) medical therapy include management of fluid and electrolyte balance, treatment of hypertension, renal replacement therapy for patients with end-stage renal disease (ESRD) or after bilateral nephrectomy, and chemotherapy for patients with Wilms tumor which must be tailored to the weight [24]. Patient I.J. had electrolytes imbalance which was corrected accordingly. There was no hypertensive episodes and patient did not present with renal failure which warrants renal replacement therapy. Wilms tumor was addressed with chemotherapy.

The management of Denys-Drash syndrome is challenging. Optimal management strategies have not been established. The plan must be guided by the typical early progression of diffuse mesangial sclerosis to end-stage renal disease (ESRD), high risk of Wilms tumor development, and highly variable clinical course. In patients without Wilms tumor at the time of diagnosis, two management strategies have been proposed: radical and conservative. The radical approach involves prophylactic bilateral nephrectomy prior to ESRD progression in order to avoid development of Wilms tumor and shortened total duration of renal replacement therapy prior to transplantation. The conservative approach involves close monitoring for Wilms tumor development using serial imaging studies [25]. In patients who develop Wilms tumor, radical bilateral nephrectomy is advocated over nephron-sparing surgery to preserve renal function as long as possible.

A 2018 survey of the international pediatric nephrology community described management of 21 confirmed cases of Denys-Drash syndrome. The authors concluded that, based on the known risks associated with ESRD, the variable course of Denys-Drash syndrome, and the relatively good prognosis associated with Wilms tumor, the guiding principle of renal function preservation is most logical. Most surveyed would advocate bilateral prophylactic nephrectomy after ESRD is reached owing to the high tumor risk, which is likely further heightened after transplantation. Surgical treatment of Wilms tumor should follow the guidelines of the National Wilms Tumor Study-4 and -5 Protocols.

Denys-Drash syndrome manifests as gonadal dysgenesis and increased risk of gonadal malignancy. According to the Chicago consensus and other published data, the incidence of gonadoblastoma in patients with 46-XY Denys-Drash is 40%. Gonadectomy versus close observation has been debated, although data supporting each approach are limited. In 2019, two patients who were managed conservatively experience delayed puberty owing to primary hypogonadism [26]. Hence, gonadal preservation does not provide endocrinological benefit while risking the development of gonadal malignancy. After bilateral nephrectomy, kidney transplantation is the treatment of choice. For patients with Wilms tumor, a 2-year period free of chemotherapy and tumor is recommended prior to renal transplantation.

Prognosis

Mortality and morbidity are high because of the natural history of the nephropathy and the high risk of malignancies. Patients with Denys-Drash syndrome develop early-onset nephrotic syndrome, have a high prevalence of severe hypertension, and experience rapid progression to end-stage renal disease (ESRD). Likewise, the vast majority of patients with Denys-Drash syndrome are destined to develop Wilms tumor in the native kidneys and are at significant risk for development of gonadoblastoma in the dysgenetic gonads. Our patient already presented with nephropathy. It would eventually lead to ESRD requiring renal replacement therapy [27].

Conclusion

Deny Drash Syndrome presents as advancing renal disease, male pseudohermaphoditism, and Wilms tumor. The condition will ultimately progress to End Stage Renal Disease with nephropathy as a consistent finding. Kidney transplantation is the prudent management for this case. Therefore, a multidisciplinary team is crucial to address the holistic care and management of the patient.

Declaration of Competing of Interest

The authors declare no conflicts of interest regarding this manuscript.

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References

1. Habib R, Loirat C, Gubler MC, Niaudet P, Bensman A, et al. (1985) The nephropathy associated with male pseudohermaphroditism and Wilms' tumor (Drash syndrome): a distinctive glomerular lesion--report of 10 cases. Clin Nephrol 24(6): 269-278.
2. (2006) Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers.
3. Segers H, Kersseboom R, Alders M, R Pieters, A Wagner, et al. (2012) Frequency of WT1 and 11p15 constitutional aberrations and phenotypic correlation in childhood Wilms tumour patients. Eur J Cancer 48(17): 3249-3256.
4. Scott RH, Stiller CA, Walker L (2006) Syndromes and constitutional chromosomal abnormalities associated with Wilms tumour. J Med Genet 43(9): 705-715.
5. Peterman CM, Fevurly RD, Alomari AI, Denise M Adams, Sophie Vadeboncoeur, et al. (2017) Sonographic screening for Wilms tumor in children with CLOVES syndrome. Pediatr Blood Cancer 64(12): e26684.
6. Drash A, Sherman F, Hartmann WH, Blizzard RM (1970) A syndrome of pseudohermaphroditism, Wilms' tumor, hypertension, and degenerative renal disease. J Pediat 76(4): 585-593.
7. Denys P, Malvaux P, van den Berghe H, Tanghe W, Proesmans W (1967) Association of an anatomo-pathological syndrome of male pseudohermaphroditism, Wilms' tumor, parenchymatous nephropathy and XX/XY mosaicism. Arch Fr Pediatr 24(7): 729-739.
8. Andrade JG, Guaragna MS, Soardi FC, Gil Guerra-Júnior, Maricilda Palandi de Mello, et al. (2008) Clinical and genetic findings of five patients with WT1-related disorders. Arq Bras Endocrinol Metabol 52(8): 1236-1243.
9. da Silva TE, Nishi MY, Costa EM, Regina Matsunaga Martin, Filomena Marino Carvalho, et al. (2011) A novel WT1 heterozygous nonsense mutation (p.K248X) causing a mild and slightly progressive nephropathy in a 46,XY patient with Denys-Drash syndrome. Pediatr Nephrol 26(8): 1311-1315.
10. Furtado LV, Pysher T, Opitz J, Randy Lamb, Jessica Comstock, et al. (2011) Denys-Drash syndrome with neonatal renal failure in monozygotic twins due to c.1097G>A mutation in the WT1 gene. Fetal Pediatr Pathol 30(4): 266-272.
11. Guaragna MS, Soardi FC, Assumpcao JG, Lílian de Jesus Girotto Zambaldi, Izilda Aparecida Cardinalli, et al. (2010) The novel WT1 gene mutation p.H377N associated to Denys-Drash syndrome. J Pediatr Hematol Oncol 32(6): 486-488.
12. Pelletier J, Bruening W, Li FP, D A Haber, T Glaser, et al. (1991) WT1 mutations contribute to abnormal genital system development and hereditary Wilms' tumor. Nature 353(6343): 431-434.
13. Schumacher V, Thumfart J, Drechsler M, Maximillian Essayie, Brigitte Royer-Pokora, et al. (2006) A novel WT1 missense mutation presenting with Denys-Drash syndrome and cortical atrophy. Nephrol Dial Transplant 21(2): 518-521.
14. Swiatecka-Urban A, Mokrzycki MH, Kaskel F (2001) Novel WT1 mutation (C388Y) in a female child with Denys-Drash syndrome. Pediatr Nephrol 16(8): 627-630.
15. Denys P, Malvaux P, Van Den Berghe H, Tanghe W, Proesmans W (1967) [Association of an anatomo-pathological syndrome of male pseudohermaphroditism, Wilms' tumor, parenchymatous nephropathy and XX/XY mosaicism]. Arch Fr Pediatr 24(7): 729-739.
16. Yue Z, Pei Y, Sun L, Huang W, Huang H, et al. (2011) Clinical pictures and novel mutations of WT1-associated Denys-Drash syndrome in two Chinese children. Ren Fail 33(9): 910-914.
17. Nishi K, Inoguchi T, Kamei K, Hamada R, Hataya H, et al. (2019) Detailed clinical manifestations at onset and prognosis of neonatal-onset Denys-Drash syndrome and congenital nephrotic syndrome of the Finnish type. Clin Exp Nephrol 23(8): 1058-1065.
18. Webb NJ, Lewis MA, Williamson K, van Heyningen V, Bruce J, et al. (1995) Do children with diffuse mesangial sclerosis in association with mutations of the Wilm's tumour suppressor gene (WT1) require bilateral nephrectomy?. Pediatr Nephrol 9(2): 252-253.
19. Schumacher V, Schärer K, Wühl E, Altrogge H, Bonzel KE, et al. (1998) Spectrum of early onset nephrotic syndrome associated with WT1 missense mutations. Kidney Int 53(6): 1594-1600.
20. Hodhod A, El-Sherbiny M (2018) 46-XY Denys-Drash Syndrome. Is There a Role for Nephron-sparing Modalities in Management of Renal Masses? A Report of 2 Cases. Urology 117: 153-155.
21. Auber F, Jeanpierre C, Denamur E, Jaubert F, Schleiermacher G, et al. (2009) Management of Wilms tumors in Drash and Frasier syndromes. Pediatr Blood Cancer 52(1): 55-59.
22. Gariépy-Assal L, Gilbert RD, Žiaugra A, Foster BJ (2018) Management of Denys-Drash syndrome: A case series based on an international survey. Clin Nephrol Case Stud 6: 36-44.
23. Breslow NE, Collins AJ, Ritchey ML, Yevgeny A Grigoriev, Susan M Peterson, et al. (2005) End stage renal disease in patients with Wilms tumor: results from the National Wilms Tumor Study Group and the United States Renal Data System. J Urol 174(5): 1972-1975.
24. Ehrlich PF, Ritchey ML, Hamilton TE, Haase GM, Ou S, et al. (2005) Quality assessment for Wilms' tumor: a report from the National Wilms' Tumor Study-5. J Pediatr Surg 40(1): 208-212.
25. Lee PA, Houk CP, Ahmed SF, Hughes IA (2006) International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Pediatrics 118(2): e488-e500.

26. Hodhod A, Noureldin YA, El-Sherbiny M (2019) Testicular Preservation in 46 XY Denys-Drash Syndrome: A Report of Two Cases. Urol Int 102(3): 367-369.

27. Cayrol J, Nightingale M, Challis J, Martin Campbell, Michael Sullivan, et al. (2019) Wilms Tumor associated with the 9q22.3 microdeletion syndrome: 2 new case reports and a review of the literature. J Pediatr Hematol Oncol 41(8): e517-e520.

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