Bilateral Wilms tumor with neonatal onset and the importance of prenatal diagnosis

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Wilms tumor (WT) occurs in 1:10,000 live births and affects mainly the unilateral kidney. The National Wilms Tumor Study Group registered 6832 patients with WT from 1969 to January 1993, out of whom only 11 patients (0.16%) were newborns. Since 1969, 14 cases of prenatal diagnosis of WT have been reported in literature, two of which were bilateral WT. Currently, the patients’ survival rate is greater than 90%, owing to a combination of surgery, chemotherapy, and radiotherapy for high-risk patients. We report a case of bilateral WT, undiagnosed during the prenatal period due to the incomplete evaluation of the abdomen with ultrasonography. The newborn was vaginally delivered at 40 weeks’ gestational age with a good perinatal adaptation. Suddenly, during the night the newborn showed respiratory distress, bradycardia and then respiratory arrest. For this reason, he was ventilated, intubated and subjected to conventional mechanical ventilation. Despite the normal cardiac ultrasonography, the health care providers suspected a cyanotic congenital heart disease with duct dependency. After a gradual resumption of the oximetry and blood pressure, the infant was transported by the neonatal emergency transport system to the Cardiac Pediatric Surgery Department of a level III hospital. There, the clinical condition became extremely serious and the infant died of asystole. During autopsy, two large tumoral masses were found in both kidneys, also the characterization of the tumors was done through histological exam, which confirmed the diagnosis of WT. A prenatal diagnosis of WT is very important because the families can take advantage of prenatal counseling to understand the risks of continuing the pregnancy and to evaluate the need for abortion, while health care providers can prepare to face a difficult delivery. The review of the literature suggests that prenatal diagnosis of bilateral WT is possible. During prenatal age, the complete assessment of the abdomen with ultrasonography and Eco-Color-Doppler can reveal kidney anomalies and raise suspicion of diseases with urinary malformations.
The National Wilms Tumor Study Group registered 6832 patients with WT from 1969 to January 1993, out of whom only 11 patients (0.16%) were newborns (3). Bilateral WT is most frequently diagnosed and recorded in patients aged between 30-33 months, with only 2 cases presenting during the prenatal period (2,4,5).

The cause of this disease is considered heritable in 10%-15% of individuals and may be associated with syndromic causes such as WAGR syndrome, Denys-Drash syndrome, Frasier syndrome, and genitourinary anomalies without renal failure. Among patients with WT, approximately 1%-2% have at least one parent with the same pathology. Families with many cases of WT have been studied in details, and the results indicate that this predisposition is due to an autosomal dominant pathogenic variant with incomplete penetrance (2).

In general, a higher frequency of bilateral tumors and an earlier age at diagnosis are observed in families with WT. Recently, the Children’s Oncology Group reviewed the five stages of WT defined by the National Wilms Tumor Study Group, as summarized in Table 1 (2).

Currently, the patient survival rate is greater than 90%, owing to a combination of surgery and chemotherapy, in addition to radiotherapy for high-risk patients (1,2). Prenatal diagnosis is fundamental to enable better management of the newborns with WT. We here report a rare case of WT that began dramatically and prematurely in the first hours of life. The disease was not evident upon prenatal tests, owing to the fact that the abdomen had not been carefully evaluated, and the health care providers were therefore unable to manage the newborn's critical condition, despite cardiac reanimation, his condition became irreversible and he subsequently died. Autopsy revealed two great masses in the bilateral kidneys, and histological examination detected WT stage V.

**Case Presentation**

A newborn male was vaginally delivered at 40 weeks’ gestational age. During the pregnancy, fetal ultrasound was performed, without assessment of the neonatal abdomen and renal conditions. Upon delivery, his airways were aspirated and he was ventilated (fraction of inspired oxygen = 0.70, peak inspiratory pressure = 20 cmH\(_2\)O, positive end-expiratory pressure = 5 cmH\(_2\)O, respiratory rate = 40 bpm) until respiratory arrest occurred. Consequently, he was ventilated, intubated, and started on conventional mechanical ventilation. Dopamine and dobutamine were administered at a dose of 5 \(\mu\)g/min and subsequently at 10 \(\mu\)g/min due to hypotension (40/20 mm Hg). Moreover, he was administered sodium bicarbonate due to metabolic acidosis (pH = 7.1, base excess = -18 and bicarbonate = 5.2 mmol/L), 10 mL/kg of fluid bolus of sodium chloride 0.9%, and a transfusion of 10 mL/kg of packed 0 Rh red blood cells, owing to a hematocrit level of 25%, along with antibiotic therapy. Despite the normal cardiac ultrasonography, the health care providers suspected a cyanotic congenital heart disease with duct dependency; accordingly, prostaglandin 0.1 g/kg/min was administered to the newborn. Hypotension of 45/40 mm Hg persisted despite adequate water and the administration of 0.45 g/kg/min of noradrenaline. After these procedures, the neonate showed a gradual resumption of the oximetry (\(\text{SpO}_2 = 88\%\)) and blood pressure (47/42 mm Hg) values. Signs of hyperkalemia were also found, and insulin was given to the infant at a dose of 0.1 UI/kg/h, along with 5% glucose. He was transported by the neonatal emergency transport system while on mechanical ventilation (fraction of inspired oxygen = 0.70, peak inspiratory pressure = 20 cmH\(_2\)O, positive end-expiratory pressure = 5 cmH\(_2\)O, respiratory rate = 40 bpm) to the Cardiac Pediatric Surgery Department of a level III hospital. There, his condition further worsened, since his blood pressure was undetectable but no cardiac complications were revealed. Thirty minutes after the arrival to the Cardiac Pediatric Surgery Department, as the infant was undergoing cardiac ultrasonography, which confirmed the absence of heart disease, his clinical condition became extremely serious and the infant died of asystole.

During autopsy, microscopic examination showed two large tumoral masses located in both kidneys. The

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**Table 1. Stages of Wilms tumor reviewed by Children’s Oncology Group**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>The tumor is limited to the kidney and can be completely excised. There is no penetration of the renal capsule or involvement of the renal sinus vessels</td>
</tr>
<tr>
<td>II</td>
<td>The tumor is extending beyond the kidney but can be completely excised. No residual tumor is apparent at or beyond the margins of excision</td>
</tr>
<tr>
<td>III</td>
<td>Gross or microscopic residual tumor, including inoperable tumors, positive surgical margins, diffuse tumor spillage or biopsy, regional lymph node metastases, and transacted tumor thrombus</td>
</tr>
<tr>
<td>IV</td>
<td>Hematogenous metastases (lung, liver, bone, brain) or lymph node metastases outside the abdominal and pelvic cavities</td>
</tr>
<tr>
<td>V</td>
<td>Bilateral renal tumors at diagnosis</td>
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tumoral masses in the right and left kidneys measured approximately 80×50 mm and 50×30 mm, respectively. The adrenal glands were affected by parenchymal hemorrhagic necrosis and the cause of death was ascribed to renal artery hemorrhage (Figure 1, A-C).

Characterization of the tumors was done through histological exam, which confirmed the diagnosis of WT with a blastemal pattern focally infiltrating the capsule and tubular structures [cluster of differentiation (CD)]56', chromogranin A*, S100, epithelial membrane antigen, pan-cytokeratin, CD99, transcription termination factor-1, Wilms tumor-1, vimentin, desmin, actin MS] (Figure 1, A-C).

Discussion
A prenatal diagnosis of WT is possible, while in most cases, it presents as an asymptomatic abdominal mass. On the other hand, in 20%-30% of cases, this disease presents signs and symptoms such as abdominal pain, malaise, microscopic or macroscopic hematuria, and hypertension. Hypertension is considered to develop due to increased renin activity or the presence of a renal mass, however, it resolves after nephrectomy. Tumor extension into the renal vein or inferior vena cava occurs in less than 4% of cases. In such cases, the symptoms include ascites, congestive cardiac failure, and hepatomegaly (1). To evaluate the presence of a tumor and its potential extension in the contralateral kidney, the initial exam is generally abdominal ultrasonography. However, it can also be identified by genitourinary anomalies, extension of the tumor into the inferior vena cava, and by assessment for liver metastasis (1). We searched all cases of bilateral WT diagnosed during the prenatal period reported on PubMed and compared these with our case. Since 1969, we found only 12 cases of unilateral WT (3,6-14) and 2 cases of bilateral WT (4,5) with a prenatal diagnosis (Table 2).

The mean age (±standard deviation) at the prenatal diagnosis was 32.3±4.1 gestational weeks (range, 24-37 weeks, excluding cases with unavailable data and gestational ages reported in months). Prenatal ultrasonography revealed the following; left renal mass (36% of cases), right renal mass (29% of cases), abdominal mass (21% of cases), and multiple renal cysts (14% of cases). Polyhydramnios and fetal hydrops were detected in three cases (11,12,14) and one case had bilateral clubfeet (9). Furthermore, nine infants were diagnosed as WT stage I (64%) (3,6,9-12,14), two as stage II (7,8), one as stage III (13) and two as stage V (4,5). A prenatal diagnosis of WT is very important because the families can take advantage of prenatal counseling to understand the risks of continuing the pregnancy and to evaluate the need for abortion, while health care providers can prepare to face a difficult delivery. In five of the previously reported cases, the surgical operation was performed as soon as possible to avoid rupture of the mass and/or to increase the chance of survival of the infants (5,6,11,12,14). In one case, intrauterine treatment was performed at 28+2 weeks to decompress the mass of the tumor, however, the surgery failed and the infant died 20 minutes after its preterm birth (12). Delayed surgical operations were performed in three cases; of these, two resulted in a good outcome (7,8) whereas one infant died (13). Elected surgical operations included nephrectomy and nephroureterectomy, which showed a survival rate of 42%, and, in five cases, the surgery was supported with chemotherapy (3,5,7,8,13). All patients treated with chemotherapy (vincristine and dactinomycin) survived, except one who did not tolerate the therapy and died due to tumor rupture (13). All infants who showed polyhydramnios and fetal hydrops along with an abdominal mass during the prenatal diagnosis died a few days after birth, despite surgical operation or prenatal intervention (11,12). In general management of WT are complex and required integrated approach (14-16). Molecular and innovative therapies are described in literature (17,18). No cases are displayed in literature.

**Figure 1.** (A, B, C) The bilateral kidneys and adrenal glands showed hemorrhagic parenchymal necrosis. (A) The tumor extended along the entire surface of the right kidney while (B) in the left kidney, there was still visible parenchyma.

**Figure 2.** (A) In the lower left figure, the adrenal cortex with hemorrhage can be seen, while in the upper right, proliferation of the Wilms tumor with a blastemal pattern can be observed. Hematoxylin and eosin staining, (light microscopy 10×) (B) Positive immunohistochemical staining for chromogranin A (light microscopy 20×). (C) Blastemal pattern of Wilms tumor with thin segmentations. Hematoxylin and eosin staining, (light microscopy 20×).
about cell based therapy Ca\(^{2+}\) toolkit targets mediated as described in neonatal and adult tumors including renal carcinoma (19-29). As mentioned above, in the literature, only two previous cases of prenatal bilateral WT diagnosed during the prenatal period have been reported (4,5). In the first case, the family chose to abort the fetus due to a de novo translocation t(7;19) (q11.2;q13.3) that suggested a syndromic disease, while in the second case, the newborn survived. In that case, during the prenatal period, a right renal mass was detected and the infant was delivered by cesarean section at 38 weeks to avoid rupture of the mass. The mass was removed by nephrectomy three days after the birth. Computed tomography and magnetic resonance imaging were performed to evaluate the left kidney which revealed a peri- and intralobar nephroblastoma. The infant was treated with vincristine and dactinomycin immediately after the birth. This case suggests that a correct prenatal diagnosis is crucial to better manage this disease, as cases of newborns with WT who have survived have been described. Complete assessment of the abdomen with ultrasonography and Ecocolor Doppler is needed to achieve a prenatal diagnosis of neonatal-onset WT. If a prenatal diagnosis had been made, the family would have received appropriate genetic counseling and would have been able to make a decision regarding whether to terminate the pregnancy. Moreover, this would have allowed the health care providers to be more prepared to manage the disease and its symptoms immediately after the birth.

## Conclusion
This case suggests that a correct prenatal diagnosis is crucial to better manage this disease, as cases of newborns with WT who have survived have been described. Complete assessment of the abdomen with ultrasonography and Ecocolor Doppler can reveal kidney anomalies and raise suspicion of diseases with urinary malformations.

## Authors’ contribution
All authors read and approved the final manuscript. AS, MG and SG contributed to references update and
manuscript final editing. DS and CB gave advise on the work and helped in the interpretation of the data. GDB, AL and GG planned the study design, supervised all the work and wrote the paper.

**Conflicts of interests**
The authors declare that they have no competing interests.

**Ethical considerations**
The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written consent was obtained by parents and a copy is available for the journal.

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**References**

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