

## Wilms' Tumor in the Very Young: A Case Report

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Presented is a rare case of Wilms' Tumor (WT) in a 3-month old female with a palpable nontender left flank mass. In the early infancy period (<6 months), there is a low incidence of malignancy in renal masses, and congenital benign renal lesions (like congenital mesoblastic nephroma) predominate in this age group. We did nephroureterectomy and lymph node sampling. Histopathology revealed localized non-metastatic COG Stage I WT with favorable histologic features. The patient underwent adjuvant chemotherapy with dactinomycin and vincristine using an institution based protocol, which offers upfront surgery followed by chemotherapy. This approach is similar to the Children's Oncology Group (COG) protocol.

**Keywords:** Wilms tumor, nephrectomy, National Wilms Tumor Study

Pediatric malignancies are interesting because most of them are rare, difficult to diagnose, and are one of the leading causes of burden in the present healthcare system. Wilms' Tumor (WT) is the second most common solid tumor malignancy in children after neuroblastoma. It remains the most common malignant renal tumor in the pediatric age group.<sup>1,2</sup> WT commonly presents as a palpable abdominal mass in an asymptomatic, healthy infant. It may be associated with hematuria (due extension to the urinary system), abdominal pain (from intratumor bleed) or hypertension (due to excessive renin release). Although WT is the most frequent renal tumor in pediatric patients, less than 2% of these cases are diagnosed in the first 3 months of life.<sup>3</sup> Benign congenital mesoblastic nephroma is the most common etiology of renal mass in

the first 6 months of life (60-70%). Other considerations are benign nephrogenic rests of the kidney and congenital complex renal cysts.<sup>3,4</sup>

Epidemiologic features of patients included in the National Wilms' Tumor Study (NWTS) show preponderance of females (52.6% of cases), and among 1 to 4 year olds.<sup>4</sup> Approximately 10% of children with WT have congenital anomalies<sup>1</sup> and syndromes, and with the latter being categorized into overgrowth and non-overgrowth. Some examples of overgrowth syndromes include hemihypertrophy, Beckwith-Weidenman and Perlman syndrome. These syndromes may be associated with nephromegaly which increases the risk of WT. On the other hand, well-known examples of non-overgrowth syndromes are WAGR (Wilms Tumor, Aniridia, Genital anomalies, mental Retardation) and Denys-Drash syndrome. Germline mutations in the WT1 gene are being correlated in these syndromes;<sup>1,4</sup> hence the ongoing research is looking into the association.

There has been a continuing debate regarding the approach to WT. The approach of the NWTS, now incorporated into the Children's Oncology Group, is being followed by North American surgeons. Their protocol consists of upfront surgery followed by adjuvant chemotherapy. Meanwhile, the International Society of Pediatric Oncology (SIOP) from Europe, believes that pre-operative chemotherapy followed by surgery is the optimal treatment to WT. Disadvantages of the SIOP protocol are as follows: 1) administration of chemotherapy to a patient with a benign disease (as high as 20%<sup>2</sup>), 2) administration of chemotherapy with a different malignant histology other than WT, 3) modification of tumor histology during chemotherapy, and 4) loss of

staging information. On the other hand, the greatest disadvantage of NWTS approach is the risk of tumor spillage intra-operatively, which can increase relapse rates and tumor stage.<sup>5</sup>

At the PCMC, there is an institution-based protocol that adapts the NWTS protocol. In all cases of renal masses in children, upfront surgery then postoperative chemotherapy is offered. However, in cases where resection is not feasible because of: the huge size of the mass, extensive infiltration of thrombus up to the level of the hepatic veins, extensive contiguous local infiltration to surrounding structures, hematogenous metastasis and an emaciated child, pre-operative chemotherapy is offered after obtaining biopsy.

This is a report on a rare case of a 3-month old female with unilateral WT with favorable histology. This highlights the fact that although benign renal tumors predominate in this age group, malignancy can still be possible. The protocol on the management of WT is applicable to all pediatric age groups and has been safe. Currently, the authors are evaluating it in terms of overall survival as compared to international standards.

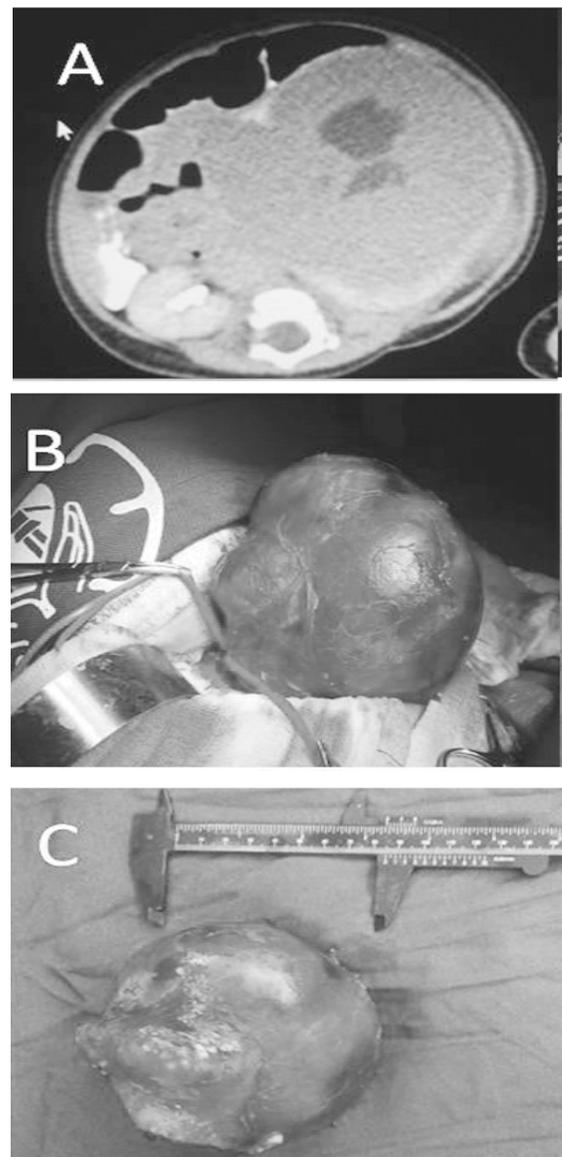
### The Case

This is a case of a 3-month old female who came in with a palpable, non-tender left flank mass with no history of hematuria or trauma. Antenatal history was unremarkable with an ultrasonogram done at 20 weeks of gestation showing no abnormalities.

The patient was born term to a G1P1 mother via normal spontaneous delivery at a tertiary medical center. At 2 months of age, the parents noted her to have left flank mass. The patient was brought to a primary physician and ultrasound revealed a retroperitoneal mass. She was then referred to PCMC for further evaluation and management. On physical examination, an ill-defined non-tender, fixed mass was palpated on the left hemi abdomen.

Abdominal ultrasonography with Doppler studies was done showing the left kidney has been converted to a mass 12cm x 15cm in size. There was no thrombus formation of the vena cava and the renal vein. The liver and the right kidney were normal. Tumor markers such as, Alpha fetoprotein,  $\beta$ -Human Chorionic Gonadotropin

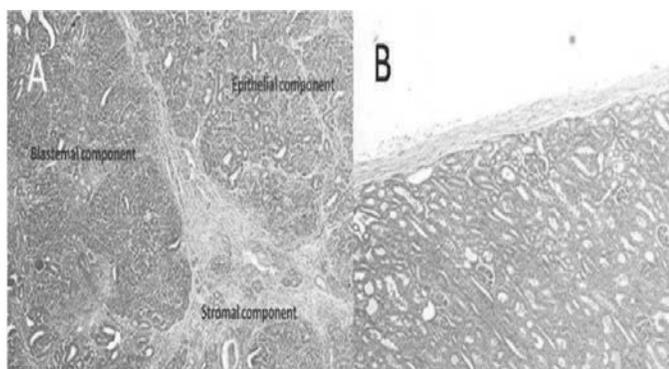
and urine. Vanillylmandelic acid was within normal level. A chest CT with IV showed no lung lesions suggestive of metastasis. A triple contrast CT scan of the abdomen revealed a solid retroperitoneal well-circumscribed tumor arising from the left kidney with no evidence of liver metastasis and lymph node enlargements. (Figure 1A).



**Figure 1.** A. Solid mass arising from the left kidney, well circumscribed with areas of central necrosis. B. Left solid renal mass, well delineated and with capsule intact. C. Specimen picture of the left renal mass.

The patient was then scheduled for laparotomy after pediatric clearance; no biopsy was done and no chemotherapy was given. Intra-operatively an 8cm x 10cm x 8cm solid mass arising from the left kidney with no involvement of the adjacent structures and no thrombus of the renal vein and vena cava were noted. (Figure 1B). There was no peritoneal seeding noted. The authors did nephroureterectomy and lymph node sampling of the perihilar and paracaval nodes. The capsule remained intact during the procedure. (Figure 1C). All pictures taken were with informed consent from the parents with proper documentation.

The specimen weighed 440grams. Histologically, the mass was of favorable histology, without anaplasia and with a classical tri-phasic component WT (blastemal, epithelial and stromal). (Figure 2) There was no lymph node involvement and no invasion to the capsule. The patient was diagnosed as COG stage I with favorable histology and no nephrogenic rests were seen.



**Figure 2.** A. Histology of the mass under low power view with classical WT with tri-phasic blastemal, epithelial and stromal component. B. No capsular invasion under low power field.

The patient underwent 18 weeks of adjuvant chemotherapy consisting of vincristine and dactinomycin following the institution's protocol for Wilms' Tumor chemotherapy of Stage I patients who are less than 2 years of age, with favorable histology and tumors weighing less than 550grams. The postoperative chemotherapy course was unremarkable. The patient is still on routine surveillance with no recurrence and metastasis at the last follow up when she was 1 year old.

## Discussion

In a report from patients who were enrolled in NWTS, with renal neoplasm in the neonatal and up to the early neonatal period, 27 out of 3340 patients (0.8%) were in the neonatal group. Four of the 27 had WT with favorable histology.<sup>6</sup>

The authors have yet to encounter a case of a neonate (<30days old) with WT. In their 4 year review of renal neoplasms they have handled at PMC, 2 out of the 54 cases were on children under 3 months old (3.7%). One of these is the case in this report and the other is a 2-month old female with a WT of favorable histology who refused chemotherapy and was eventually lost to follow-up.

The last NWTS-5 trial<sup>7</sup>, defined a cohort of children under 24 months of age with Stage I favorable histology WT, a specimen weighing less than 550 as the Very Low Risk Wilms Tumor (VLRWT) group. In VLRWT children, adjuvant chemotherapy does not offer benefit and thus, assigned to surgery only.

The patient in this report may belong to this VLRWT cohort. In that trial, VLRWT patients were assigned to either the surgery only arm or to the standard: surgery plus chemotherapy arm. That trial was closed early because there was relapse-free survival rate of less than 90% (expected calculated survival rate of 95%). Shamberger, et al.<sup>7</sup>, analyzed long term outcomes on those patients from the NWTS-5 in the surgery only arm. In the surgery only group Event Free Survival (EFS) was 84% at 5 years compared to the 97% EFS of the surgery and chemotherapy group. The difference was statistically significant. But when salvage therapy was done to those who relapsed in the surgery only group, the 5 year Overall Survival (OS) in the surgery group improved to 98% compared to 99% to the surgery plus chemotherapy group. The report showed that OS was not significantly different in VLRWT children whether surgery alone was done compared to surgery plus chemotherapy. This suggests that in VLRWT, surgery alone and salvage therapy for those who relapse may be an option as it lessens the hazardous effects of chemotherapy. A follow-up study is underway to confirm these findings.

To this date, PCMC still recommends giving adjuvant dactinomycin and vincristine to VLRWT patients even in

those less than 6 months old. These younger patients often need special attention because this is the group in which side effects of chemotherapy are amplified compared to older children. Chemotherapy is given on an out-patient basis. There is a low threshold to manage these patients as in-patient once side effects are observed.

Collectively, WT can achieve long term survival rates greater than 85%.<sup>8</sup> The success in the management is largely due to the efforts of two large cooperative groups, COG and SIOP. The two have different philosophies in the approach to WT but have reported same 2 year and 4 year OS rates stage for stage when their results were compared.<sup>12</sup> This leads to the question: which is better to use in the local setting, COG or SIOP?

PCMC has been using an approach similar to COG, but the risk of tumor spillage is ever present. Thus, radiotherapy is utilized more whenever this problem is encountered. Admittedly, access to radiotherapy in the Philippines is a real limitation, In fact, patients needing radiotherapy are referred to other centers as PCMC does not have its own radiotherapy unit. The authors are presently reviewing their results and compare them to those of other local institutions with SIOP-based protocol.

Other countries with resource limitations have also compared COG or SIOP. Bathnagar<sup>2</sup> concluded that in resource limited areas, SIOP offered a suitable protocol in which pre-operative chemotherapy lessened chances of tumor spillage or rupture. In the COG approach, an extensive work-up is needed prior to starting treatment, such as pre-operative biopsy which necessitates considerable time and resources to accomplish. This complicates matters in a child with delayed presentation of WT (such as patients who are malnourished or those with large tumors). A SIOP-based approach hastens management in this type of patients.

The disadvantage of upfront surgery is that most of these patients from developing countries were nutritionally depleted thus requiring build-up prior to the operation.<sup>9</sup> It would be unwise to operate in the nutritionally debilitated without adequate preoperative preparation. The time required to bring the child nutrition to an acceptable level delays surgical management.

What has been reported in literature is a reality for Filipino children, the majority of whom present with chronic malnutrition, delayed presentation and limited access to pediatric centers which can manage these cases. For patients who are not good candidates for surgery, a pre-operative percutaneous image guided biopsy is done and chemotherapy is started as soon as the histology is out. Having patients started on chemotherapy on the same admission can lessen delays. This report describes the authors' rare experience of WT in a very young patient. There has been constant change in the management of WT, and there is much more to understand in this enigmatic disease. With high expected survival rates of WT patients, the present thrust in research is to maintain excellent survival rates with minimizing the effect of chemotherapy. Thus, the results of the studies in the elimination of chemotherapy in VLWRT are eagerly awaited.

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