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CASE REPORT

Bilateral Wilms Tumor - Case Report of a Patient with Family History

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Abstract: Wilms' tumor (WT) is the most common renal neoplasm in children. Despite its rapid growth, it is often asymptomatic. It most commonly occurs between the ages of 3 and 5, more frequently in girls. Numerous studies report an association between the occurrence of Wilms' tumor and genetic background. Treatment of bilateral Wilms' tumor (BWT) presents several challenges. Recent studies raise the issue of the influence of genetics on the development of BWT. We believe that our case report is innovative as it provides information on a rare clinical presentation and comprehensively addresses the potential impact of genetic studies on favorable treatment outcomes, which are discussed only in limited detail in the literature. The case description concerns a 2-year-old and a 5-month-old patient who presented with his mother due to a change in abdominal contour. In the medical history, the boy's mother had been treated for WT. Imaging of the abdominal cavity revealed the presence of pathological tissue changes in both kidneys. Based on this, stage V Wilms' tumor was diagnosed. The boy underwent a right-sided tumor nephrectomy followed by a left-sided heminephrectomy. He also received pre- and post-operative chemotherapy. Genetic testing revealed a deletion fragment of exon 8 and exons 9–10 on one allele of the *WT1* gene. Despite optimistic data regarding overall survival in children with WT, a significant clinical issue remains with patients experiencing disease recurrence and bilateral BWT. Radical treatment is often required for such patients, which carries long-term consequences. Identifying patients at risk for familial WT or BWT allows for relatively early intervention and effective prevention. Furthermore, certain gene variants associated with WT can be considered prognostic biomarkers.

Keywords: nephroblastoma, Wilms' tumor, diagnostics, molecular diagnostics, treatment, children

Introduction

Wilms tumor accounts for approximately 7% of all childhood neoplasms and over 90% of malignant kidney tumors, making it the most common renal tumor in childhood.[1–3] It often presents asymptomatically, with abdominal distension becoming concerning. In 25–30% of the patients, abdominal pain, fever, anemia, hematuria, and hypertension may occur.[4,5] WT typically occurs between the ages of 3 and 5 years.[3,6] Nephroblastoma is one of the few childhood tumors that statistically occur more frequently in girls than boys.[7] WT often presents as a solitary lesion; however, approximately 7% present as multifocal lesions, and 5–9% of the patients have bilateral involvement.[6–8] Familial patterns are observed in approximately 1–2% of the cases.[3,8] Etiological factors have not yet been fully identified, but research suggests the involvement of certain tumor suppressor genes, such as WT1, WT2, as well as other genes including SIX1, SIX2, and DROSHA.[1,7] Furthermore, the presence of the genes WT1, NYNRIN, TRIM28, and the BRCA complex is associated with an increased susceptibility to the occurrence of BWT as pre-zygotic factors. Recent studies also indicate post-zygotic factors related to the occurrence of BWT associated with epigenetic changes, specifically highlighting hyper-methylation at the 11p15.5 h19/ICR1 locus.[9] Wilms tumor patients present with: cryptorchidism, hypospadias, facial

Received: 14 September 2024
Accepted: 29 November 2024
Published: 16 December 2024

dysmorphism, or developmental defect syndromes. Moreover, anomalies associated with the WT1 gene are: Wilms tumor, aniridia, genitourinary anomalies, and mental retardation (WAGR) which may occur separately or as a syndrome.[5,8,10] We report clinical and genetic findings of a child with BWT and family history. Written informed consent for publication of this case report was obtained from the patient and patient's parents.

Case Report

A two and a half year old boy of Romani descent, born at 25 weeks of gestation, was admitted to the Department of Pediatric Hematology, Oncology, and Transplantology on August 31, 2022, due to a tumor located in the abdominal cavity. Medical history was as following: the child's mother was treated for Wilms' tumor in childhood, however no genetic testing was performed at that time due to the lack of consent from her parents. The day before admission, the mother noticed a change in the contour of the child's abdomen. Physical examination revealed deviations from the norm: an abdomen with increased circumference, without palpable tenderness, on the right side, in the mid-abdominal and lower abdominal areas, a palpable mass was felt extending from the abdomen to the groin, and absence of testes in the scrotum. Laboratory tests showed slight abnormalities from the norm: elevated C-reactive protein (CRP) (3.57 mg/dL), D-dimers (6488 ng/mL), fibrinogen (699 mg/dL), and lactate dehydrogenase (LDH) (1093 U/L). Following admission, abdominal ultrasound revealed a pathological tissue change with polycyclic outlines in the right kidney displacing the liver upwards, absence of normal renal parenchyma, and a hyperechogenic heterogeneous lesion with fluid presence suggesting a proliferative change in the lower pole of the left kidney. CT scan confirmed the presence of a pathological tissue change measuring 94x85x167 mm in the right kidney and an oval tissue lesion measuring 32x23x37 mm in the lower pole of the left kidney [Figure 1, Figure 2], as well as a contrast defect in the lumen of the inferior vena cava hindering drainage from the left renal vein. Based on these findings, Wilms' tumor stage V was diagnosed. A decision was made to immediately initiate preoperative chemotherapy starting from September 6, 2022, according to the European Protocol UMBRELLA protocol. As a result of the applied chemotherapy vincristine (VCR) and actinomycin D (ACT)/VCR, the lesion in the right kidney regressed by approximately 50%, while the lesion in the left kidney enlarged to dimensions of 32x34x43 mm. A decision was made to change chemotherapy to carboplatin and etoposide, however, due to poor treatment tolerance and lack of further regression of the lesions, on December 15, 2022, a right-sided tumor nephrectomy was performed. Histopathological examination of the right kidney tumor revealed an intermediate-risk group nephroblastoma, predominantly stromal type without anaplasia, with partial regression, grade III. Subsequently, 4 cycles of chemotherapy (VCR+ACT) were administered. The patient underwent genetic test using Next-Generation Sequencing (NGS). The analysis indicates the presence of a deletion in exon 8 and exons 9–10 on one allele of the *WT1* gene. The analysis included the following genes: *ALX4, ASXL1, BLM, BRCA2, BUB1, BUB1B, CDC73, CDKN1C, CEP57, DHX37, DICER1, DIS3L2, EXT2, FIBP, GATA4, GPC3, GPC4, H19, H19-ICR, HDAC4, IGF2, KCNQ1, KCNQ1OT1, MAP3K1, NR0B1, NR5A1, NSD1, PALB2, PAX6, PHF21A, PIK3CA, POU6F2, PTCH1, REST, SETBP1,*

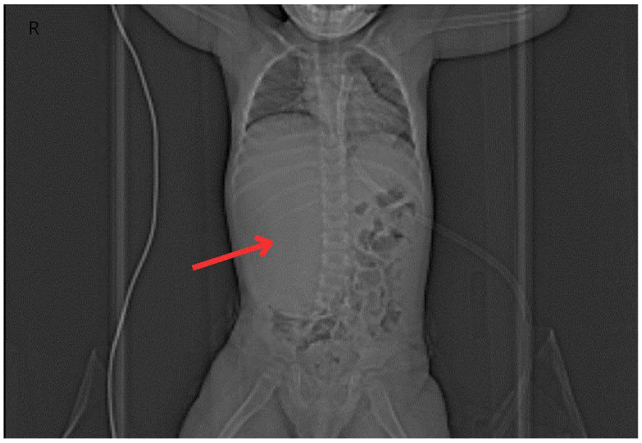

Figure 1 CT scan of chest, abdomen and pelvis. Frontal section. The arrow indicates the right kidney and a localized pathological tissue change.

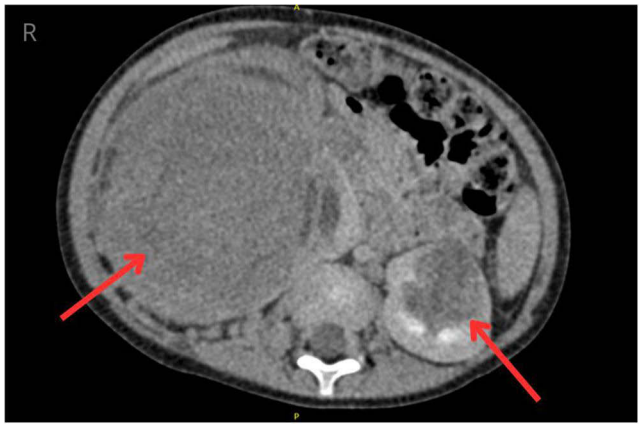

Figure 2 CT scan of abdomen. Transverse section. One arrow points to the right kidney with a heterogeneous pathological tissue change, with a multilobulated outline and maximum dimensions of approximately 94×85 x 167 mm. The second arrow points to an oval tissue change located at the lower pole of the left kidney, measuring approximately 32×23 x 37 mm.

SOX9, SPRED1, SRY, TP53, TRIM37, TRIP13, WT1, WWOX, ZFPM2, CTR9, TRIM28. Patient had variant in exon 7 causes a stop gained change in the tumor cells. The HGVS result is as follows: NM_024426.6(WT1): c.1153_1154delinsTA(p.Arg385Ter). The variant was absent in control chromosomes in the gnomAD project. On February 1, 2023, a left-sided heminephrectomy was performed. Histopathological examination revealed a partially differentiated, cystic nephroblastoma in a partially dysplastic kidney. Following the surgery, the boy continued chemotherapy, and abdominal radiotherapy on the right side was administered at a dose of 18.2 Gy.

Discussion

In our study, we report a rare case of a patient with bilateral Wilms Tumor with family history. We consider that our case report is valuable because it provides information on a rare clinical presentation that is described only in limited detail in the literature. Furthermore, it integrates this information with the potential impact of genetic studies on treatment outcomes.

Approximately 5% of the WT patients are present with bilateral involvement. Statistically increased occurrence of BWT is observed in patients with WAGR syndrome - approximately 17%, Beckwith-Wiedemann syndrome - 17.3%, Denys-Drash syndrome - 20%, Pearlman syndrome, as well as in familial WT - 16%.[10] Bilaterality remains a significant clinical issue despite satisfactory treatment outcomes for this tumor.

The overall survival rate for children diagnosed with Wilms' tumor in high-income countries is ~90% with the latest treatment protocols. Nevertheless, disease recurrence occurs in approximately 15% of all patients.[11] Surgical removal of tumor masses while preserving as much normal renal parenchyma as possible is part of WT treatment. The aim is to maintain renal function for as long as possible and avoid renal failure.[12] However, this method may have limitations in patients with BWT. One multicenter study reported a rate of bilateral kidney-sparing surgery of 35%. Most patients in this study underwent unilateral radical nephrectomy (RN) and nephron-sparing surgery (NSS) on the favorable side.[12] The risk of impaired kidney function and hypertension is higher in patients undergoing RN with NSS of the contralateral kidney compared to bilateral NSS.[13,14] Despite optimistic data regarding WT patient survival, it should be noted that a clinical challenge exists for a group of patients. These include patients who experience recurrence after surgical treatment and patients with BWT, who often, due to the lack of bilateral NSS possibility, are at increased risk of renal failure or arterial hypertension.

With a focus on patients with worse prognosis, alternative treatment methods are continuously being explored. Currently, under investigation are: inhibition of the insulin-like growth factor 2 (IGF2) pathway, particularly through the Insulin-like Growth Factor 1 Receptor (IGF1R); antiangiogenic therapy, with agents such as apatinib and bevacizumab; inhibition of the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway using agents like

buparlisib and temsirolimus; and immunotherapy, including chimeric antigen receptor T-cell (CAR-T) therapy and inhibition of cyclooxygenase-2 (COX-2).[15]

The etiology of WT is not fully understood, but there is growing scientific evidence confirming the association of specific gene mutations with WT predisposition. Among these genes, we distinguish *WT1, WTX, SIX1, SIX2, DROSHA, DGCR8, DICER1, H19-IGF2* locus (loss of *H19–IGF2* imprinting), and *CTNNB1*.[7] Furthermore, studies have shown that the most commonly known genes responsible for familial WT are *REST, TRIM28,* and *WT1*, each of which accounts for approximately 8% of familial WT. Additionally, other genes such as *NYNRIN, CTR9*, and *CDC73* also occur in familial WT.[8] Among families with confirmed variants in *CTR9, TRIM28,* and *REST*, pedigree analysis revealed an autosomal dominant mode of inheritance.[16] Despite scientific progress, further research is needed among patients with familial WT to confirm previous findings and detect other variants associated with WT. Genetic testing of WT patients and monitoring the patient's family members with a predisposing gene variant allow for earlier tumor detection and more effective treatment. Moreover, the presence of variants in certain genes indicates a correlation with disease severity. The *TRIM28* mutation is potentially associated with a better prognosis, while *MYCN, TP53*, gain of 1q, as well as *SIX1* and *SIX6* in combination with microRNA processing genes, indicate a more severe disease course.[1]

Conclusion

An early diagnosis significantly influences the effectiveness of treatment and the patient's long-term outcomes. Genetic testing is helpful in this regard, as it can identify mutations that are likely causes of WT, as well as highlight an increased risk of bilaterality and familial occurrence. This allows for the early monitoring of at-risk patients and their families and the application of less radical treatment methods, leading to improved health status and quality of life for the patient. Furthermore, some gene variants associated with WT can be considered biomarkers for predicting disease severity. Despite numerous discoveries regarding WT, further research is needed to confirm and expand current knowledge.

Abbreviations

WT, Wilms tumor; BWT, bilateral Wilms tumor; WAGR, Wilms tumor aniridia genitourinary anomalies and mental retardation; CRP, C-reactive protein; LDH, lactate dehydrogenase; VCR, vincristine; ACT, actinomycin D; RN, radical nephrectomy; NSS, nephron-sparing surgery.

Data Sharing Statement

All the used data are included in this article.

Consent for Publication and Ethics Approval

Written informed consent for publication of their details was obtained from the patient's parent. Institutional approval was not required to publish case details.

Acknowledgments

The authors would like to thank the patient and his mother for participating in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The author(s) report no conflicts of interest in this work.

References

1. Zheng H, Liu J, Pan X, Cui X. Biomarkers for patients with Wilms tumor: a review. *Front Oncol*. 2023;13:1137346. doi:10.3389/fonc.2023.1137346
2. de Sá Pereira BM, Azevedo RM, Aguirre Neto JC, et al. Intra-tumor genetic heterogeneity in Wilms tumor samples. *Rev Assoc Med Bras*. 2019;65(12):1496–1501. doi:10.1590/1806-9282.65.12.1496
3. Servaes SE, Hoffer FA, Smith EA, Khanna G. Imaging of Wilms tumor: an update. *Pediatr Radiol*. 2019;49(11):1441–1452. doi:10.1007/s00247-019-04423-3
4. Saltzman AF, Cost NG, Romao RLP. Wilms Tumor. *Urol Clin North Am*. 2023;50(3):455–464. doi:10.1016/j.ucl.2023.04.008
5. Turner JT, Brzezinski J, Dome JS. Wilms tumor predisposition. In: Mp A, Feldman J, Gm M, editors. *GeneReviews® [Internet]*. Seattle: University of Washington; 2022.
6. Deng C, Dai R, Li X, Liu F. Genetic variation frequencies in Wilms' tumor: a meta-analysis and systematic review. *Cancer Sci*. 2016;107(5):690–699. doi:10.1111/cas.12910
7. Spreafico F, Fernandez CV, Brok J, et al. Wilms tumour. *Nat Rev Dis Primers*. 2021;7(1):75. doi:10.1038/s41572-021-00308-8
8. Welter N, Brzezinski J, Treece A, et al. The pathophysiology of bilateral and multifocal Wilms tumors: what we can learn from the study of predisposition syndromes. *Pediatr Blood Cancer*. 2023;70: Suppl 2:e29984. doi:10.1002/pbc.29984
9. Murphy AJ, Cheng C, Williams J, et al. Genetic and epigenetic features of bilateral Wilms tumor predisposition in patients from the children's oncology group AREN18B5-Q. *Nat Commun*. 2023;14(1):8006. doi:10.1038/s41467-023-43730-0
10. Liu EK, Suson KD. Syndromic Wilms tumor: a review of predisposing conditions, surveillance and treatment. *Transl Androl Urol*. 2020;9(5):2370–2381. doi:10.21037/tau.2020.03.27
11. Groenendijk A, Spreafico F, de Krijger RR, et al. Prognostic factors for Wilms tumor recurrence: a review of the literature. *Cancers*. 2021;13(13):3142. doi:10.3390/cancers13133142
12. Murphy AJ, Davidoff AM. Nephron-sparing surgery for Wilms tumor. *Front Pediatr*. 2023;11:1122390. doi:10.3389/fped.2023.1122390
13. Khondker A, Jain A, Groff ML, Brzezinski J, Lorenzo AJ, Zappitelli M. Late kidney effects of nephron-sparing vs radical nephrectomy for Wilms tumor: a systematic review and meta-analysis. *J Urol*. 2022;207(3):513–523. doi:10.1097/JU.0000000000002387
14. Aldrink JH, Heaton TE, Dasgupta R, et al. Update on Wilms tumor. *J Pediatr Surg*. 2019;54(3):390–397. doi:10.1016/j.jpedsurg.2018.09.005
15. Hong B, Dong R. Research advances in the targeted therapy and immunotherapy of Wilms tumor: a narrative review. *Transl Cancer Res*. 2021;10(3):1559–1567. doi:10.21037/tcr-20-3302
16. Maciaszek JL, Oak N, Nichols KE. Recent advances in Wilms' tumor predisposition. *Hum Mol Genet*. 2020;29(R2):R138–R149. doi:10.1093/hmg/ddaa091