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Simple renal cysts associated with ambiguous genitalia: Precursor to Wilms' tumor?

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ABSTRACT

Wilms' Tumor (WT) is the commonest renal tumor seen in children. WT frequently occurs in association with various urological malformations and genetic syndromes. We report a case of ambiguous genitalia with cryptorchidism and simple renal cysts, who went on to develop WT at the site of renal cysts. Management and follow up protocols are discussed along with relevant literature.

Key Words: Simple renal cyst, Wilms' tumor, genito-urinary malformations, child.

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Introduction

Wilms tumor (WT) is the most common pediatric renal tumor, with a peak incidence at 2–4 years of age. The prevalence of WT is 1:10,000 and 4–13 % of cases are bilateral. Various predisposing syndromes, genetic and clinical malformations are associated with WT. Extensive study of such rare syndromic patients which include clinical and genetic analyses has led to molecular clues which enhances our current understanding of the pathogenesis of this tumor. However many areas still remain an enigma [1-3].

Simple renal cysts are rare in the pediatric population, with an incidence of 0.22% and rarely have neoplastic potential [1]. There are very few published reports till date which show a possible association of simple renal cysts and WT.

We report a case of a child who presented with ambiguous genitalia, bilateral cryptorchidism with an incidentally detected simple renal cyst and eventually developed a WT at the site of the renal cysts.

Case report

A 6 months old infant presented with history of ambiguous genitalia. Examination revealed a small phallus with peno-scrotal hypospadias with bilateral impalpable undescended testis. Karyotyping showed 46XY. Magnetic resonance imaging, for localization of testis showed bilateral undescended testes with a small renal cyst in the lower pole of the right kidney. The cyst was classified as Bosnaic Type II and measured 5x3mm with fine septations (Fig. 1A and B).

Diagnostic laparoscopy showed both testes to be intra-peritoneal, and laparoscopic bilateral orchidopexy was done at the age of one year. Post operatively, initial 2 year follow up was uneventful. At the age of 3years, the patient, presented with fever for two months, abdominal lump noticed 15 days ago and a

single episode of hematuria. On clinical examination a mass was palpable in right lumbar region, which was ballotable (Fig. 2A). Ultrasonography showed 8x10 cm hypoechoic mass with multiple anechoic areas arising from right kidney suggestive of WT. Contrast enhanced computed tomography abdomen showed 10x10x12cm heterogeneous mass arising from the mid and lower pole of the right kidney (Fig. 2B).

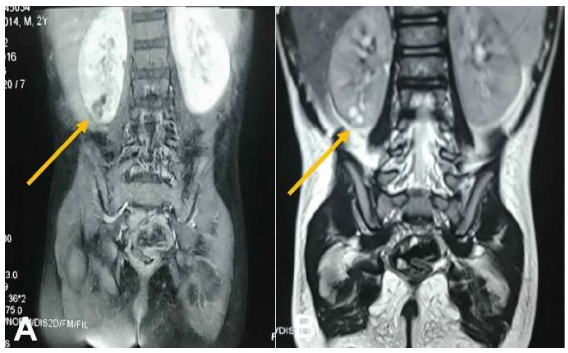

Fig. 1A, B. T1 diffusion weighted and T2 weighted images with renal cysts at the lower pole (marked with yellow arrow).

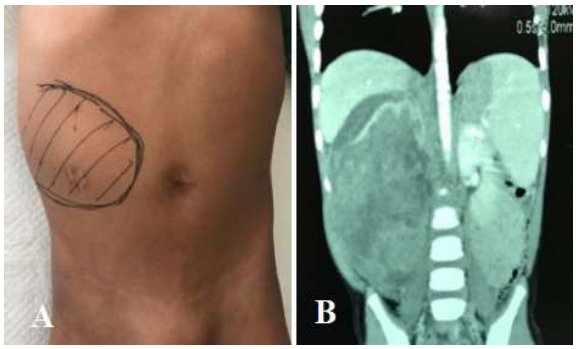

Fig. 2A, B. Clinical picture showing ambiguous genitalia and renal lump; CECT picture showing WT.

The infra-hepatic inferior vena cava was compressed by the mass but had color flow on doppler, ruling out an intra vascular thrombus. The patient was managed with modified International Society of Pediatric *Oncology* (*SIOP*) protocol. A pre chemotherapy fine needle aspiration cytology revealed extensive infarction necrosis of tumor with ghost cells, no viable tumor was seen for typing. A radical nephroureterectomy with lymph node dissection was performed after 4 cycles of chemotherapy (Vincristine and Actinomycin D).

Histopathology showed tri-phasic WT, comprising of epithelial (<10%), blastemal (<10%) and predominantly mesenchymal component (80-85%). Chemotherapy induced changes in form of hemorrhage and necrosis were noticed. Nephrogenic rests were not seen. Renal sinus was involved by the tumor. Ureteric and vascular resection margins were free of tumor. Para-caval, precaval and para-aortic lymph nodes were free of tumor. The tumor was staged as stage II (SIOP). WT-1 analysis done in the post -operative period was negative. The genetic work up included karyotyping and WT1 analysis. The patient is doing well at 24 months of follow up and is now planned for hypospadias repair. He had one episode of adhesive small bowel obstruction which was managed with laparotomy and resection anastomosis after 1 year of tumor excision.

Discussion

WT is present in >10 % of patients with various syndrome like WAGR syndrome, Beckwith-Wiedemann syndrome (BWS), Denys-Drash syndrome (DDS), Frasier syndrome, Perlman syndrome and genitourinary abnormalities like hypospadias, cryptorchidism and nephromegaly [4]. One-third of WT involve mutations in WT1.Our case does not fit specifically in any of the above genetic syndromes. Genitourinary (GU) malformations are also known to be risk factors for WT. These malformations may be a part of the syndromes or isolated and sporadic in nature. The GU malformations include

ectopic kidneys, renal cyst, hypospadias, ectopic or undescended testis etc.

WT1 has been localized to human chromosome 11p13. Initially thought to be the putative WT suppressor gene but the recent focus of research is on the holistic role of *WT1* in the development of the GU system and kidney rather than in WT tumorigenesis alone. Sakamoto et al reported a case of a 1 year old infant with ambiguous genitalia and WT with point mutation at intron 7. They reviewed nine cases in literature who presented with WT1 mutation associated with GU anomalies (Cryptorchidism, Hypospadias etc) wherein all the cases, genetic analysis was performed [5]. However none of these patients had any previous renal cyst. Our index case was associated with genitourinary abnormalities which included ambiguous genitalia with peno-scrotal hypospadias and bilateral undescended testis with presence of simple renal cyst.

Simanovsky et al, studied the association between renal cortical cyst and WT and they did not show any relationship in unilateral cases. However a strong association was noted in bilateral cases 7/8 (87%). In 25% cases of bilateral WT the location of cyst was consistent with the site of tumor origin, similarly in index case tumor site was noticed to be at the cyst site retrospectively [6]. Literature raises suspicion that cystic lesion leading to WT may represent some type of blastematous tissue which act as a precursor to the tumor. Hence, such patients are ideal candidate for genetic counselling for WT 1 gene mutation. Dumoucel et al. [4] proposed for genetic counselling in patients with clinical abnormalities which are strongly associated with WT, based on the following major and minor clinical criteria. The major criteria would include hemihypertrophy, mental retardation, aniridia and the presence of diffuse mesangial sclerosis in the histopathology. The minor clinical criteria include hernia, hypospadias, renal abnormalities and ectopic testis. If either one major or two minor criteria are fulfilled the patient must undergo genetic counselling [4]. They also found a significant difference regarding the age at diagnosis between patients with or without malformation. They also highlighted the importance of genetic consultation and counselling with further molecular genetic studies if required, which would improve the patient care. Our patient was having more than two minor clinical abnormalities with WT. Genetic consultation was sought and WT1 analysis was done. However, it was negative.

In recent study by Rediger et al. [7] the authors evaluated natural course of 87 patients of simple or minimal complex renal cyst in children, 22 of which were diagnosed either antenatally or in the first year of life, they found no malignant transformation in any of them with 4.1 years median follow up. They concluded that follow-up beyond the first 2-3 years after detection may not be justified. Whereas our index case of simple renal cyst with associated GU abnormalities was diagnosed at 3 years of age with Wilms', however follow up with regular ultrasonography may have helped us to diagnose the disease earlier.

Renal cystic lesions are commonly non-neoplastic, however may occasionally show neoplastic transformation. Family history, renal anatomy and MRI findings may give clues to the nature of the cystic lesion. If neoplastic, the lesion warrants to be excised whereas non-neoplastic cystic lesions conservative management and close follow up may suffice. There is paucity of literature regarding this subset of patients and

protocolized management may be difficult. Whether the coexistence of a renal cyst with genitourinary anomalies increases the possibility of developing WT is difficult to determine, given the rarity of such cases.

Conclusions

Renal simple cystic lesions with genitourinary abnormalities and ambiguous genitalia may be regarded with a high degree of suspicion. Such patients may be subjected to genetic counseling and testing for WT. Follow-up with clinical examination and ultrasound is recommended.

Compliance with ethical statements

Conflicts of Interest: None.

Financial disclosure: None.

Consent: Patient confidentiality has been maintained and written consent for the publication of patient details and clinical pictures have been obtained from the patient's father and can be furnished when required.

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