Incidentally detected nephrogenic rests in the setting of congenital obstructive uropathy

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Purpose: *Nephrogenic rests (NR) are clusters of cells similar to renal blastema. NR are frequently seen in kidneys with Wilms' tumor (WT) and are seen with higher frequency in nephrectomy specimens from obstructed and/or multicystic dysplastic kidneys (MCDK) compared to autopsy series of normal kidneys. The significance of NR and their role in tumorigenesis is largely unknown. We report the findings of two cases with NR associated with ureteral ectopy/obstruction and review the relevant literature.*

Materials and methods: *Two cases of upper pole heminephrectomy associated with ectopic upper pole ureter and resultant hydronephrosis were found to have nephrogenic rests present on pathologic examination. A literature search was done to review recent developments in the understanding of NR and their significance, primarily to guide patient recommendations regarding follow-up.*

Results: *Recent developments in the understanding of NR include the description of intralobar versus perilobar nephrogenic rests and prognostic considerations associated with each. However, the implications of finding nephrogenic rests in upper pole hemi-nephrectomy specimens associated with ureteral ectopy is not well delineated.*

Conclusions: *The role of NR in tumorigenesis is still poorly understood. Because of the still undefined relationship with WT we recommend patients with incidentally detected NR be followed with serial abdominal ultrasounds for the first 5 years of life.*

Key Words: nephroblastoma, kidney neoplasms, multicystic dysplastic kidney, Wilms' tumor

Introduction

Nephrogenic rests (NR) are clusters of cells that histologically appear similar to renal blastema. Renal blastema is seen normally in developing embryos and serves as the precursor from which glomeruli and tubules form. Blastemal cells are not normally persistent after 35 weeks gestation. The clinical significance of NR is based on its well-documented association with Wilms' tumor. Theories of Wilms' tumor formation incorporate NR as a precursor lesion that arises from either a first or second "hit" of a series of mutational events leading to a tumor.[1]

Clinicians and scientists have long struggled to define the exact role of NR in tumorigenesis. In kidneys with WT, NR are present in 25% to 40% of

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specimens.[2-4] Genitourinary anomalies other than obstruction are found in 4%-6% of WT, while aniridia (1%-2%) and hemihypertrophy (0.7%-3%) are less common.[5-8] Within the last few decades, obstruction secondary to congenital urinary tract anomalies has been found to be associated with the histological presence of NR and, therefore, the potential for Wilms' tumor (WT). While the incidence of NR ranges from 0.25%[2] to 0.9%[3] in autopsy series, case series of congenital renal anomalies with obstructive uropathy have found an incidence of 3.5% to 6.7%.[9] Despite this, no case of Wilms' tumor in the presence of obstructive uropathy has been reported.

Multicystic dysplastic kidneys (MCDK) are theorized to be the extreme side of the spectrum of congenital ureteric obstruction. The estimated incidence of NR in MCDK ranges from 2% to 6.7%.[10,11] In contrast to the lack of documented WT in the presence of obstructive uropathy, at least five Wilms' tumors have been reported in MCDK.[12-15]

We present two cases of incidentally detected NR associated with congenital obstructive uropathy and review the relevant English language literature. A Medline search using combinations of the following headings was performed; "nephrogenic rests", "nodular renal blastema", "multicystic dysplastic kidney", and "Wilms' tumor".

Case reports

Case one

Antenatal ultrasound demonstrated right hydronephrosis. A baby boy was delivered at term and subsequent postnatal ultrasound revealed bilateral duplex kidneys. The right upper pole moiety had a markedly dilated collecting system, associated hydroureter and thinned parenchyma. No ureterocele was apparent. A VCUG demonstrated no reflux and a MAG-3 renal scan documented a differential renal function of 60% on the left and 40% on the right with poor function of the right upper pole. At one year of age cystoscopy concurrent with open surgery confirmed he had no ureterocoele and thus a diagnosis of right upper pole ectopic ureter was substantiated. He underwent a right upper pole heminephrectomy under the same anesthetic. Postoperative recovery was uneventful. Pathology demonstrated the presence of nephrogenic rests within a background of dysplastic renal parenchyma from the right upper pole moiety. (Figure 1) He is currently well and being followed with periodic renal ultrasound to survey for the possibility of Wilms' tumor development.

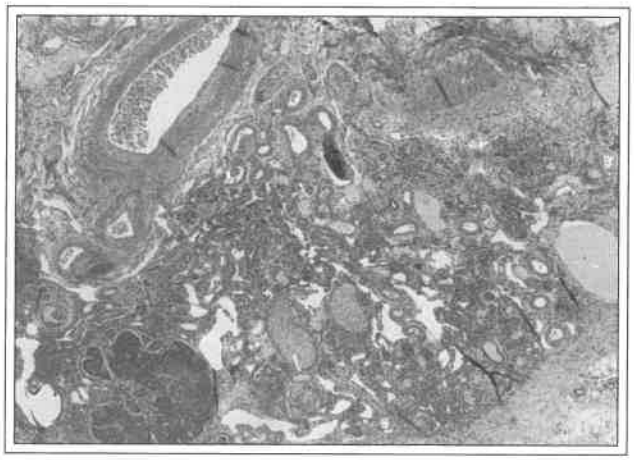

Figure 1. Section of kidney shows renal dysplasia including cartilage with an area of subcapsular perilobar nephrogenic rest (HPS x 70).

Case two

A 6-month old girl presented with a history of right hydronephrosis detected on antenatal ultrasound performed at 17 weeks gestation. Postnatal ultrasound confirmed a right duplex kidney with upper pole hydronephrosis and hydroureter extending behind the bladder. (Figure 2) VCUG demonstrated no vesicoureteric reflux and a MAG-3 renal scan showed differential function of 50% per side. At 6 months of age she underwent cystoscopy, which confirmed a right upper pole ectopic ureter at the distal urethra. She had a right upper pole heminephrectomy under the same anesthetic. Postoperative recovery was uneventful. Pathology demonstrated the presence of nephrogenic rests within a background of dysplastic

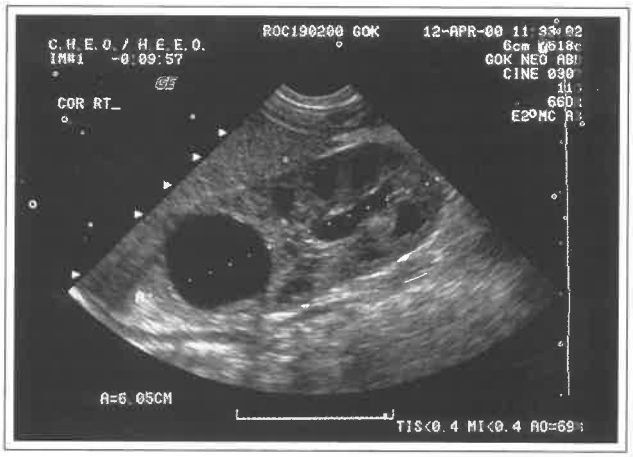

Figure 2. Ultrasound of right duplex kidney with marked upper pole hydronephrosis and thinned renal parenchyma.

renal parenchyma from the right upper pole moiety. (Figure 3) She is currently well and being followed with serial renal ultrasound to survey against the development of Wilms' tumor.

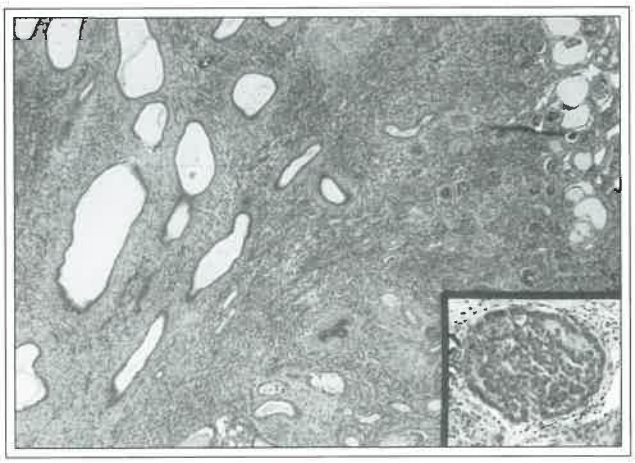

Figure 3. Section of kidney shows renal dysplasia (HPS x 70). Inset shows an area of subcapsular perilobar nephrogenic rest (HPS x 200).

Discussion

Nephrogenic rests have been found incidentally in surgical specimens of kidneys resected for a variety of obstructive lesions including ureteroceles, posterior urethral valves, ectopic ureters and ureteropelvic junction obstructions. These specimens are often accompanied by varying degrees of renal dysplasia. The incidence of NR observed with MCDK is 5%, approximately equal to that seen with obstruction.[9-11,16,17] This is consistent with the theory of MCDK representing the most extreme consequence of obstruction.[18] Although controversial, this concept is supported by the frequent clinical observation of concomitant ipsilateral ureteral atresia and a higher incidence of left sided involvement for both MCDK and obstructive urinary tract anomalies.[19,20] Lending further support, ovine animal models of early obstruction result in dysplastic changes in the kidney.[21,22] The type of obstruction and corresponding area of dysplasia in the kidney is theorized to be a result of an abnormal location of ureteral bud origin and/or development on the maturation of the metanephric blastema.[23]

In a retrospective review of 75 cases of obstructive uropathy, Craver et al found five cases of NR. Of these, three were secondary to ureteroceles and had no evidence of dysplasia, one had mild dysplasia and one severe. They postulated that high-grade obstruction resulted in severe dysplasia and a lower risk of NR formation as the majority of renal parenchyma was destroyed.[9] Subsequent to this, Noe and Dimmick reported in separate papers the presence of NR in 5% of MCDK suggesting that destruction of renal parenchyma is no protection against NR formation.[10,11]

The exact significance of NR as precursor lesions has remained elusive. In observations of the morphology of NR associated with WT, Beckwith has developed the concept of intralobar nephrogenic rests (ILNR) and perilobar nephrogenic rests (PLNR).[1] A renal lobe consists of a medullary pyramid and its overlying renal cortex. PLNR are situated in the periphery of the lobe while ILNR can be anywhere in the lobe or even in the renal sinus or wall of the collecting system. Their position is indicative of the relative timing of their development during embryogenesis. Each lobe develops as layers from the medullary pyramid to the periphery with 10 to 12 generations of nephrogenic blastemal cells. ILNR therefore arise early in development relative to PLNR.

Important epidemiological observations have highlighted the importance of identifying ILNR and PLNR in WT specimens. ILNR are more commonly found in metachronous bilateral WT whereas PLNR are typically associated with synchronous bilateral Wilms' tumor. The age of presentation is also significantly lower in ILNR with a mean of 16 months compared to PLNR with a mean age of 36 months. Those with both types presented at 12 months and those with no rests presented at 41 months.[1] To date, no series has addressed the issue of ILNR and PLNR detected incidentally in specimens resected with obstruction.

Beckwith has proposed that NR actually may represent the second mutational event or "hit" and that additional events are required for progression to WT. This is based on the observation that children with chromosomal disorders usually have only a few NR in an affected kidney yet the aberration is presumably present in every cell. In addition several other chromosomal abnormalities have been detected in these specimens.[1]

In the National Wilms' Tumor Study loss of heterozygosity (LOH) at both WT1 and WT2 was present in 27% of cases. This was associated with the presence of ILNR and a younger age of presentation.[24] In the two patients reported here, the NR were perilobar. We did not perform any genetic analyses of the specimens.

Conclusions

Regardless of position within a renal lobe, nephrogenic rests rarely progress to Wilms' tumors. More commonly NR regress and eventually become obsolescent. The majority of WT have no obstructive uropathy, dysplasia, or NR. Yet, the relatively high incidence of NR with both MCDK and obstructive uropathy and even higher incidence in WT results in a dilemma for the clinician when faced with NR as an incidental finding. There are few case reports of WT associated with MCDK but no reported cases in the upper pole of a duplex system. The rarity of WT in dysplastic renal tissue, coupled with the usual regression of NR argues against surgical management for dysplastic tissue in the absence of other indications. Perhaps with further understanding of the molecular basis for Wilms' tumor, the presence of NR will be put in context guiding management of this situation. Because the two patients described above are still young infants, and the occurrence of NR has been documented in their pathology specimens, we feel it is prudent to follow them with serial ultrasounds for the first 5 years of life. The length of follow-up is somewhat arbitrary but was chosen to reflect the mean age of presentation for Wilms' tumor of 3.5 years. Although it is unlikely that a Wilms' tumor will be detected given that the remnant renal tissue is likely histologically normal, such follow-up is innocuous and helps allay parental anxiety. □

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