Renal Dysplasia

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Renal dysplasia is an aberrant developmental disease usually diagnosed during the perinatal and childhood years. Prevalence is estimated at 0.1% of infants (via ultrasound screening) and 4% of fetuses and infants (via autopsy study). Occurrences may be combined with abnormalities in the collecting system or associated with complex syndromes. Histopathology shows primitive tubules surrounded by a fibromuscular collar. The differential diagnosis includes renal dysplasia, hypoplasia, and renal atrophy. Immunohistochemical expression of the paired box genes 2 and 8 (PAX2/8) and Wilms tumor 1 (WT1) is increased in the primitive ducts and fibromuscular collar, respectively. Renal dysplasia pathogenesis is not well understood, but may be caused by a nephron-inductive deficit due to ampullary inactivity or abnormal budding of the ureteric bud from the mesonephric duct. Either the PAX2 mutation only or cross-talk with the p53 pathway is involved in this deficit. Nephrectomy is the treatment of choice for symptomatic renal dysplasia.


Renal dysplasia is defined as abnormal metanephric differentiation diagnosed histopathologically, which can be diffuse, segmental, or focal. The diffuse type shows dysplastic area involving an entire kidney. The segmental type shows dysplastic area involving a portion of the kidney. The focal type is characterized by an admixture of normal and abnormally formed nephrons. Usually diagnosed around the time of birth or during childhood, renal dysplasia is rarely seen in adults. Ultrasound screening has indicated a 0.1% prevalence in infants, and an autopsy study estimated a 4% prevalence in fetuses and infants. However, data on the prevalence of renal dysplasia in adults are unclear. While investigating the etiology of benign nonfunctioning kidneys removed by nephrectomy, Gupta et al discovered that renal dysplasia was one of the etiologies, accounting for 3.7%.

Renal dysplasia with or without reflux is the most common cause of childhood end-stage renal disease and accounts for 34% of prevalent cases, with a male to female ratio of 2.0. Renal dysplasia is a developmental aberration characterized by cells undergoing active proliferation and programmed cell death in a deregulated manner, and this process has been reported to involve the paired box gene 2 (PAX2), paired box gene 8 (PAX8), Wilms tumor 1 (WT1), and B-cell lymphoma 2 (BCL2) genes.

We review the clinical features, pathologic features, pathogenesis, differential diagnosis, and treatments for renal dysplasia. Additionally, variable immunohistochemical expressions of PAX2, PAX8, WT1, and BCL2 are discussed for their roles in the differential diagnosis of renal dysplasia, hypoplasia, and fetal kidney.

CLINICAL FEATURES

Renal dysplasia can be combined with abnormalities of the collecting system, including obstruction of the ureteropelvic junction, ureteral atresia, urethral obstruction, and vesicoureteral reflux. Therefore, patients’ symptoms and signs depend upon the extent and severity of the renal dysplasia and the associated anomalies. In the prenatal period, renal dysplasia is always found by ultrasound screening and manifests as multicystic kidney, pelvic cyst, renal agenesis, or genital mass. The presentations of maternal oligohydramnios and fetal hydrenephrosis or hydrourteronephrosis are also reported. In the neonatal period, renal dysplasia with cysts is usually detected when a flank mass is palpable. In childhood and adulthood, conditions linked to renal dysplasia include voiding dysfunction, urinary incontinence, repeated urinary tract infections, flank or abdominal pain, vaginal discharge, genital masses, and chronic renal failure. Of these, urinary incontinence is more common in women than in men who have dysplastic kidneys with an ectopic ureter. Symptomatic renal dysplasia can be further investigated by renal ultrasound, magnetic resonance imaging, and magnetic resonance urography. Eventually, a definitive diagnosis of renal dysplasia can be made after the affected kidney is removed by nephrectomy or autopsy.

The renal dysplasia–associated syndromes include Meckel syndrome, VATER association, renal coloboma syndrome, Herlyn-Werner-Wunderlich syndrome, prune belly syndrome, branchio-oato-renal dysplasia, renal-hepatic-pancreatic dysplasia, and multiple endocrine neoplasia type 2A. The VATER association is defined as vertebral defect, anal atresia, tracheoesophageal fistula, and renal dysplasia. More cases of Meckel syndrome and VATER association than of the other syndromes have been reported. Most of these complex syndromes are derived from the developmental problems under genetic controls. Some syndromes are hereditary, including Meckel syndrome, renal-coloboma syndrome, branchio-oato-renal dysplasia,
renal-hepatic-pancreatic dysplasia, and multiple endocrine neoplasia type 2A. The anomalous structures and genetic alterations of these syndromes are listed in the Table.

**PATHOLOGIC FEATURES**

**Macroscopic Features**

Gross features of renal dysplasia are variable and depend on their dysplastic extents and cystic components. Their gross morphologies show large irregular cystic masses or small rudimentary structures. Multicystic renal dysplasia exhibits dysplastic kidney with multiple irregular cysts. Aplastic dysplasia is characterized by small, barely recognizable rudimentary structures. Both multicystic and aplastic renal dysplasias are associated with pelvicaliceal occlusion, partial or total absence of the ureter, and ureteral atresia. Hypoplastic dysplastic kidneys have patent ureters, often have a reniform shape with corticomedullary differentiation, and may be partially functional (Figure 1).

**Microscopic Features**

Renal dysplasia is characterized principally by primitive ducts with a fibromuscular collar and lobar disorganization. Primitive ducts, which may be cystic, are considered as altered collecting ducts lined by undifferentiated or columnar-to-cuboidal epithelium (Figure 2, a). The fibromuscular collar is comprised of spindle cells arranged circumferentially around the primitive ducts. Incomplete and abnormal corticomedullary relationships and rudimentary medullary development constitute lobar disorganization (Figure 2, b). The cysts derived from primitive ducts may be large or small and numerous or scarce, and eventually lead to divergent macroscopic features of multicystic, hypoplastic, or aplastic renal dysplasia. The other pathologic findings include metaplastic cartilage, bone, basement membrane thickening of the primitive ducts, nodular renal blastema, and proliferating nerves. Metaplastic cartilage is not essential for diagnosis of renal dysplasia; if present, metaplastic cartilage customarily appears within the cortex. Secondary to reflex or obstruction of the lower urinary tract, chronic pyelonephritis is occasionally detected in dysplastic kidneys.

**PATHOGENESIS**

In normal development, the kidney is derived from 2 components of the embryonic metanephros: the metanephric parenchyma, which undergoes an epithelial transformation to form nephrons, and the ureteric bud, an epithelium that branches to form collecting ducts. On a molecular basis, the conversion of metanephric parenchyma to neophron epithelia involves many transcriptional factors, including WT1; eyes absent homolog 1 (EYA1); forkhead box C1 (FOXC1); PAX2; PAX8; growth differentiation factor 11 (GDF11); sal-like 1 (SALL1); SIX homeobox 1 (SIX1); wingless-type MMTV integration site family, member 4 (WNT4); and GATA binding protein 3 (GATA3). These genes and their encoded proteins interact to form a network rather than a linear and hierarchic pathway. The reciprocal induction of WT1 and PAX2 expression has been demonstrated for the differentiation of metanephric mesenchyma; furthermore, WT1 can down-regulate the expression of PAX2. Expression of WT1 involves the early induction of the renal mesenchyma and the production of growth factors, which can stimulate growth of the ureteric buds. The expression of PAX2/8 involves the late induction that drives the conversion of the metanephric mesenchyma to neophron epithelia. Both WT1 and PAX2 are down-regulated when the kidney becomes mature. BCL2 is a survival factor and protects the differentiating cells from cell apoptosis. Expression of BCL-2 is also detected in the metanephric mesenchyma when it undergoes epithelial transition. Thus, the WT1, PAX2/8, and BCL2 gene expressions are the most important in normal nephrogenesis, including branching morphogenesis and nephron differentiation.
In comparison with normal nephrogenesis, dysplastic kidneys show abnormal differentiation of nephrons and renal tubules, and are comprised of abnormally developed metanephric elements with an abnormal structural organization. Jain et al. investigated the expression profile of human renal dysplasia in comparison with a normal kidney, and the results, as expected, showed that WT1 mRNA expression was decreased in renal dysplasia. Winyard and Feather demonstrated that PAX2 and BCL2 immunoreactivities were shown in the dysplastic epithelia. They proposed that cyst formation in dysplastic kidneys was caused by the persistent expression of PAX2 and BCL2, which provided a continuous proliferation and decreased apoptosis of immature epithelia.

In animal studies, homozygous PAX2-null mutant mice had no kidneys because the ureteric bud failed to branch from the mesonephric duct, and heterozygous PAX2 mutant mice caused renal hypoplasia. However, urinary tract abnormalities are often combined with renal dysplasia. Recently, some studies have provided evidence that PAX2 and p53 gene alterations involve their connection. Mice with p53 deletion showed development abnormalities of the kidney and urinary tracts such as duplex ureter formation, renal hypoplasia or dysplasia, and impaired terminal differentiation of renal epithelia because of excessive apoptosis and decreased proliferation of the ureteric epithelium. Furthermore, p53-null mice showed the down-regulation of PAX2, leading to nephron deficit. Collectively, PAX2 mutation only or combined with p53 deletion involves the pathogenesis of renal dysplasia.

**DIFFERENTIAL DIAGNOSIS**

Histopathologic examination is used to distinguish various etiologies among small kidneys, because this distinction is important for disease prognosis and genetic counseling. The diagnosis of renal dysplasia is not difficult; however, the diagnosis is sometimes confused with other conditions including polycystic kidney disease, fetal kidney, renal hypoplasia, and renal atrophy. The dysplastic kidney contains primitive ducts with or without dilated cysts. The kidney with concomitant multiple cysts and dysplasia is diagnosed as multicystic renal dysplasia, although it grossly resembles polycystic kidney disease. Additionally, these cysts in multicystic renal dysplasia are usually smaller than those in polycystic kidney disease. The fetal kidney contains poorly differentiated tissues that are compatible with gestational development. The hypoplastic kidney has fewer nephrons than the normal kidney, but no dysplastic elements. The atrophic kidney exhibits segmental loss of parenchyma due to renal scarring and compensatory hypertrophy in the remnant parenchyma.

**Immunophenotypic Features**

Based on a review of the literature, the protein expressions of PAX2, PAX8, WT1, and BCL-2 are variable in renal dysplasia, hypoplasia, the fetal kidney, and the adult kidney. These conditions are considered as differential diagnoses. Between 2010 and 2012, 2 cases of renal dysplasia were diagnosed in our hospital. Both patients were female; they were aged 20 and 4 years. They shared the same symptom: urinary incontinence due to an ectopic ureter in their right kidney.

In renal dysplasia, the WT1 immunoreactivity exhibits nuclear staining in the spindle cells of the fibromuscular collar, but negativity in the columnar-to-cuboidal epithelial cells of the primitive ducts (Figure 3, a). In the hypoplastic fetal and adult kidneys, WT1 immunoreactivity is exhibited in the smooth muscle cells of vascular walls, in the podocytes and parietal epithelial cells of Bowman capsules, and in the endothelial cells of the vessels and glomeruli (Figure 3, b). The intensity of WT1 expression in...
the glomeruli or vessels is not different among the hypoplastic, fetal, and adult kidneys. In renal dysplasia, PAX2 immunoreactivity, in contrast to WT1 immunoreactivity, exhibits strong nuclear staining in the columnar-to-cuboidal epithelial cells of primitive ducts, but negativity in the spindle cells of the fibromuscular collar (Figure 4, a). In hypoplastic fetal and adult kidneys, PAX2 immunoreactivity exhibits less strong nuclear staining in the distal convoluted tubules and parietal epithelial cells of Bowman capsules. Relatively weak cytoplasmic staining of PAX2 in the podocytes of glomeruli and epithelial cells of proximal convoluted tubules is also detected (Figure 4, b).22,28 The features of PAX8 immunohistochemistry are similar to those of PAX2.

Winyard and Feather22 found BCL2 immunoreactivity at mesenchymal condensates of fetal kidney, negative staining at ureteric bud branches, and ectopic staining at dysplastic primitive ducts, but negative staining at surrounding collar cells. In comparison with our cases, the immunostaining of BCL2, partially consistent with the findings of Winyard and Feather,22 exhibits cytoplasmic staining in the epithelial cells of primitive ducts and immature or mature renal tubules, in which the intensity and proportion of BCL2-positive cells are variable in these conditions. The mesenchymal condensates of the fetal kidney and fibromuscular collar surrounding dysplastic tubules also show no BCL2 staining.

According to the immunophenotypic features, PAX2, PAX8, WT1, and BCL-2 immunohistochemical expressions cannot be useful to differentiate renal dysplasia from renal hypoplasia and fetal kidney.

CURRENT TREATMENT AND PROGNOSIS

Although a nephrectomy of the dysplastic kidney is the routine treatment, there is a trend toward conservative management with careful follow-up.29 If the condition is limited to one kidney and the patient has no symptoms, the patient is usually monitored with periodic ultrasound to examine the affected kidney and the contralateral kidney to determine whether they continue to be normal. Removal of the kidney should be considered only if the kidney causes bothersome symptoms for the patient. A nephrectomy can cure the symptoms. Neild et al30 investigated the effect of angiotensin-converting enzyme inhibitor in patients who had chronic renal failure due to renal dysplasia with or without reflux. This study suggests that there is a watershed glomerular filtration rate of 40 to 50 mL/min, at which angiotensin-converting enzyme inhibitor treatment can be successful in improving renal function. Nonetheless, there is no evidence of malignant transformation in renal dysplasia.
References

Submissions Now Accepted for CAP ‘15 Abstract Program

Abstract and case study submissions are now being accepted for the College of American Pathologists (CAP) 2015 meeting, which will be held October 4th through the 7th in Nashville, Tennessee. Submissions for the CAP ‘15 Abstract Program will be accepted from:

Monday, February 9, 2015 through 6 p.m. CT Friday, April 10, 2015

Accepted submissions will be published as a Web-only supplement to the October 2015 issue of the Archives of Pathology & Laboratory Medicine and will be posted on the Archives Web site. Visit the CAP ‘15 Web site at www.cap.org/cap15 to access the abstract submission site and additional abstract program information as it becomes available.