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.

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Renal Dysplasia Associated With Syndromes and Genetics

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<th>Associated Syndromes</th>
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<td>Meckel syndrome</td>
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<td>0.02–1.1 per 10 000 live births</td>
<td>Autosomal recessive trait; MKS3 mutation</td>
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<td>VATER association</td>
<td>Vertebral defect, anal atresia, tracheoesophageal fistula, and renal dysplasia</td>
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<td>Renal-colo-boma syndrome</td>
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<td>Prune belly syndrome</td>
<td>Deficient abdominal muscle, and genitourinary anomaly including dysplastic kidneys</td>
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<td>9 cases reported</td>
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<tr>
<td>Renal-hepatic-pancreatic</td>
<td>Cystic malformations of the kidneys, liver, and pancreas</td>
<td>Undetermined; fatal at birth</td>
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<td>Medullary thyroid carcinoma, pheochromocytomas, and parathyroid hyperplasia</td>
<td>One case reported</td>
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Abbreviations: EYA1, eyes absent homolog 1; MKS3, Meckel syndrome type 3; NPHP3, nephrocystin 3; PAX2, paired box gene 2; RET, rearranged during transfection.

Renal dysplasia is characterized principally by primitive ducts with a fibromuscular collar and lobar disorganization.³ 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 diagnostic areas. 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.³ Metaplastic cartilage is not essential for diagnosis of renal dysplasia; if present, metaplastic cartilage customarily appears within the cortex. Secondary to reflux or obstruction of the lower urinary tract, chronic pyelonephritis is occasionally detected in dysplastic kidneys.

**PATHOLOGIC FEATURES**

**Macroscopic Features**

Gross features of renal dysplasia are variable and depend on their dysplastic extents and cystic components.¹ 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 pelvicalcetal occlusion, partial or total absence of the ureter, and ureteral atresia.¹,³ 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.³ 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.³ Metaplastic cartilage is not essential...
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.\(^\text{21}\) 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\(^\text{22}\) 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,\(^\text{23}\) and heterozygous PAX2 mutant mice caused renal hypoplasia.\(^\text{24}\) 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.\(^\text{25-27}\) 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.\(^\text{25,26}\) Furthermore, p53-null mice showed the down-regulation of PAX2, leading to nephron deficit.\(^\text{27}\) 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.\(^\text{3}\) 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.\(^\text{1}\) 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.\(^\text{25,28}\) 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).\(^\text{22,25}\) 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

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**Figure 1.** Gross image: renal hypoplastic dysplasia in a 20-year-old woman with an ectopic ureter. The small kidney measures 5.5 × 3.5 × 1.5 cm and includes dysplastic (arrow) and hypoplastic (arrowhead) components.

**Figure 2.** Photomicrographs of renal dysplasia. a, Primitive ducts lined by cuboidal epithelium (arrow) and surrounded by a fibromuscular collar (★). b, Loss of normal renal structures showing lobar disorganization (hematoxylin-eosin, original magnifications ×200 [a] and ×20 [b]).
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 braches, 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.

Figure 3. Photomicrographs of Wilms tumor 1 (WT1) immunohistochemistry. a, Renal dysplasia showing WT1-positive immunoreactivity in fibromuscular collar, but negative in primitive ducts. b, Adult kidney showing WT1-positive immunoreactivity in endothelium and smooth muscle cells of vessels, as well as glomeruli (immunoperoxidase, original magnification ×200).

Figure 4. Photomicrographs of paired box gene 2 (PAX2) immunohistochemistry. a, Renal dysplasia showing nuclear immunoreactivity only in epithelial cells of primitive ducts. b, Adult kidney showing nuclear staining only at distal renal tubules and parietal epithelial cells of Bowman capsules (immunoperoxidase, original magnification ×200).

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


