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Cadherin 17 is a Sensitive and Specific Marker for Metanephric Adenoma

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Abstract

Metanephric adenoma (MA) is a rare benign renal neoplasm that shares morphologic and immunophenotypic overlap with epithelial predominant Wilms tumor (e-WT) and with the solid variant of papillary renal cell carcinoma (s-PRCC). Cadherin 17 (CDH17) is expressed primarily in the normal intestine and digestive tract tumors and has not been detected in tumors from other sites including the kidney. We investigated the diagnostic utility of CDH17 in differentiating between MA, e-WT, and s-PRCC. Immunohistochemistry for CDH17, CD57, AMACR, WT-1, and CDX2 was performed on 17 e-WTs, 15 s-PRCCs and 21 MAs and assessed based on a combined score of extent and intensity. Normal adult kidney parenchyma was negative for CDH17 staining. CDH17 was expressed in the late stages of fetal kidney development at the junction of the glomerular space and proximal nephron. The majority of MAs (81%) demonstrated membranous CDH17 immunoreactivity in all components (acinar, tubular, and papillary), while all cases of e-WTs and s-PRCCs were negative ($p<0.0001$). WT-1 was negative in s-PRCC and was positive in all cases of e-WT and MA. All MAs were strongly positive for CD57; however, this marker was also moderate to strongly positive in 6 (35%) e-WTs and 2 (13%) s-PRCCs. AMACR was strongly positive in all s-PRCCs, but moderate reactivity was seen in 3 (17%) e-WTs and 2 MA (10%). CDH17 is a sensitive (81%) and highly specific (100%) marker for MA, and should be considered in the IHC panel for distinguishing MA from its mimics.

Keywords

Metanephric adenoma; Wilms tumor; papillary renal cell carcinoma; cadherin 17; CDH17

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Introduction

Metanephric adenoma (MA) is a rare benign neoplasm of the kidney that is composed of tightly packed, highly cellular, small uniform epithelial cells forming acini, tubules, solid sheets, and papillary structures (1–3). MAs may contain glomeruloid bodies resembling abortive papillae, and often nuclear grooves and psammoma bodies. The morphologic features of MA often overlap with epithelial predominant Wilms tumor (e-WT), and with the solid variant of papillary renal cell carcinoma type 1 (s-PRCC) (4–8). It is important to differentiate MA from e-WT and s-PRCC, as the latter are malignant neoplasms that may require aggressive treatment.

Currently, immunohistochemistry is the most useful ancillary technique that helps to distinguish between MA and its mimics. MAs are usually diffusely positive for WT-1 and CD57, and typically negative for alpha-methylacyl CoA racemase (AMACR) (4,7,8). These markers are helpful in distinguishing MA from e-WT and s-PRCC, but in some cases the diagnosis may be challenging since there is overlap in the immunophenotype of these tumors.

The cadherin superfamily of transmembrane glycoproteins are calcium dependent cell adhesion molecules that demonstrate high tissue-specific expression (9). Expression of epithelial cadherin (E-CDH, CDH1), neural cadherin (N-CDH, CDH2), kidney specific cadherin (KSC, CDH16), cadherin 6 (CDH6), cadherin 8 (CDH8), and cadherin-11 (CDH11) has been described in normal and neoplastic kidney (10–18). Cadherin 17 (CDH17), also known as liver-intestine cadherin, is expressed in the normal small and large intestinal epithelium, normal pancreatic ducts, and in tumors originating from the digestive system, including colorectal, gastric, pancreatobiliary adenocarcinomas, and hepatocellular carcinoma (19–23). Although expression of CDH17 was demonstrated in the developing kidney of zebrafish (24), CDH17 was not found to be expressed in normal human kidney (20) or renal cell carcinoma (RCC), including clear cell, chromophobe, collecting duct and papillary RCC (20,21,23). Based on structural homology of CDH17 to kidney specific cadherin (CDH16) (13,14,25), we hypothesized that CDH17 may also be expressed in some histologic subtypes of kidney tumors.

Our goal in this study was to characterize the expression pattern of CDH17 in metanephric adenoma and to determine whether CDH17 expression may be useful in distinguishing MA from e-WT and s-PRCC.

Materials and Methods

Archival cases of MA (4 cases), e-WT (17 cases), and s-PRCC (15 cases) were collected between the years of 1998 and 2013 from the archives of the Departments of Pathology at the Rhode Island Hospital and The Miriam Hospital. In addition, 17 cases of MA were retrieved from the archives of the Department of Pathology at Cleveland Clinic, Cleveland, Ohio. Six cases of e-WT contained foci of nephrogenic rests. Human fetal kidney tissue from 10, 17, and 38 week fetuses, as well as 7 week and 8 month old infants were also examined. The original hematoxylin and eosin (H&E) sections were reviewed by 2

pathologists (E.Y. and S.M). Diagnoses were confirmed by histological re-review and supported by adjunctive immunohistochemistry for WT-1, CD57, and AMACR in all cases.

Tissue Microarray Construction

Tissue microarrays (TMAs) were constructed from 4 MAs, 17 e-WTs, and 15 s-PRCCs. Paraffin blocks containing representative tumor areas were identified based on review of the corresponding H&E stained sections. Areas of interest were identified and marked on the source block. The source block was cored, and a 1-mm core was transferred to the recipient "master block" using the Beecher Tissue Microarrayer (Beecher Instruments, Silver Spring, MD). Four representative cores of tumor and 2 cores of normal kidney tissue were arrayed per specimen.

Immunohistochemical Staining

Immunohistochemical staining of all MAs, e-WTs, and s-PRCCs for CDH17 was performed on whole tissue sections. Staining for other markers was done on TMAs. Consecutive sections from paraffin-embedded tissue blocks were cut at 4 μm, deparaffinized, and rehydrated with xylene and graded alcohols. Immunohistochemical staining for CDH17 was performed with the Ventana Discovery system using the DAB MAP detection kit (Ventana Medical Systems, Tucson, AZ). Epitope retrieval was performed in high pH buffer. A rabbit monoclonal antibody (Ab) SP183 against CDH17 from Cell Marque (Rocklin, CA) was used at a 1:100 dilution as the primary Ab. Sections of normal human colon and small intestine were used as positive controls. Immunohistochemical staining for WT-1, CD57, AMACR, and CDX2 was performed for all cases using the Dako Autostainer Link 48 (Dako, Carpinteria, CA) and EnVision Dual Link or EnVision Flex detection system (Dako) with DAB (Dako). Appropriate positive and negative controls were stained in parallel. Antibodies, their sources, antigen retrieval, and dilutions are presented in Table 1.

Staining results were assessed by two pathologists (EY and ZG) in a blinded manner (without knowing a diagnosis). Immunoreactivity was assessed based on a combined score of the extent and intensity of staining as described previously (26). Scores 0–3 were assigned according to the percentage of positive tumor cells (0=<5%, 1=5–25%; 2=25–50%; and 3=>50%). In positive cases, the staining intensity was scored as strong (3+) when immunoreactivity was easily detectable at low magnification (×40), as moderate (2+) when the staining was visible at ×100 magnification, or as weak (1+) when the staining was seen at higher-power magnifications (×200 and ×400) but not clearly observed at lower magnifications. The two scores were multiplied to give an overall score of 0–9, of which 0 was considered negative, 1–2 was considered weak, 3–6 moderate, and 9 strong staining. Any discordant scores were reviewed together by both scorers to obtain a consensus score.

Statistical Analysis

All statistical analyses were performed using the SAS software, JMP Base version 8.0.0 (SAS, Cary, NC, USA). Association between CDH17, WT-1, CD57, and AMACR expression and the histological subtypes of renal tumors was evaluated using Chi square test. P-values of less than 0.05 were considered as statistically significant.

Results

CDH17 expression in metanephric adenomas, epithelial predominant Wilms tumors and solid variant of papillary renal cell carcinomas

Microscopically, all metanephric adenomas were highly cellular tumors composed of small uniform epithelial cells arranged in tightly packed acini, tubules, solid sheets, and papillary structures (Figure 1A). Some MAs contained glomeruloid bodies resembling abortive papillae, and psammoma calcifications. Wilms tumors were of favorable histology and had a triphasic growth pattern with the epithelial predominant component (e-WT) composed of tightly packed cells arranged in tubular structures, occasional glomeruloid bodies, and psammomatous calcifications (Figure 1B). Solid papillary renal cell carcinomas contained tightly packed cells growing in solid sheets, ill-defined tubular patterns, and glomeruloid bodies, similar histologically to those of MAs and e-WT (Figure 1C).

The results of the immunohistochemical stains for CDH17 (whole tissue sections), CD57, AMACR, and WT-1 (TMAs) are summarized in Table 2 and Figures 2 and 3. Normal adult kidney parenchyma was negative for CDH17 staining. The majority of MAs (81%) demonstrated CDH17 immunoreactivity, while all cases of e-WTs and s-PRCCs were negative ($p<0.0001$, Table 2). The extent of CDH17 varied from patchy to diffuse, and even in cases with diffuse strong immunorteactivity the staining was not complete in all tumor cells (Figure 2A). Twelve of 17 (71%) positive MAs exhibited moderate to strong CDH17 expression. In five MA cases CDH17 showed overall weak staining based on a focal patchy distribution of staining (extent 1+) with moderate intensity (2+). CDH17 expression was seen in a membranous staining pattern with lateral intercellular border accentuation (Figure 2C) and immunoreactivity was observed in all components of MAs (acinar, papillary, and tubular; Figure 2D–F). In order to evaluate whether CDH17 expression is associated with CDX2, another marker of intestinal differentiation, immunohistochemistry for CDX2 was performed. All cases studied were negative for CDX2 immunoreactivity.

Positive nuclear staining with WT-1 was seen in the podocytes of normal renal glomeruli, all cases of e-WT and all MAs but absent in all s-PRCCs included in our study (Figure 3). CD57 was expressed in the proximal tubules in normal kidney. Strong positive staining for CD57 was seen in all MAs while moderate to strong positivity was observed in 6 (35%) e-WTs and 2 (13%) s-PRCCs (Figure 3 and Table 2). AMACR expression in the form of strong cytoplasmic positive staining was seen in the proximal tubules of normal kidneys and all s-PRCCs, but moderate immunoreactivity was seen in 3 (17%) e-WTs and 2 (10%) MA (Figure 3 and Table 2).

CDH17 expression in nephrogenic rests and fetal kidneys

One of six cases of nephrogenic rests expressed CDH17 (Figure 4A), four of six cases were immunoreactive for WT-1, focally for CD57, and all were negative for AMACR and CDX2 (Figure 4 B–D).

Fetal kidneys at 10 and 17 weeks gestational age were negative for CDH17 (Figure 5B); however, immunoreactivity was seen in the proximal tubule immediately adjacent to the glomeruli and focally extending to the parietal epithelium of Bowman’s capsule in the

kidney from a 38 week fetus (Figures 5C and 5D). A similar pattern, but with a patchy distribution, was noted in the kidney of a 7 week infant; however, staining in the kidney from an 8 month old infant was completely negative for CDH17 expression.

Discussion

This is the first study to investigate the utility of CDH17 in distinguishing metanephric adenoma from renal tumors with similar morphologic features.

Several immunohistochemical markers have been employed in order to assist in the histologic diagnosis of MA. A panel of immunostains including WT-1, CD57, and AMACR has been shown to be helpful in distinguishing MA from its mimics, namely, e-WT and s-PRCC (4,7,8). Our findings of high WT-1 sensitivity for e-WT and MA are in complete agreement with several previous reports (4,7,8). WT-1 positivity is of great utility in ruling out s-PRCC, but does not help in distinguishing MA from e-WT. CD57 is frequently expressed in MA (1,4,7), although in our study CD57 was moderate to strongly positive in 35% of e-WT and 13% of s-PRCC. Similar to our findings, CD57 positivity was reported in 12.5% of WT (8), in mature appearing tubules of WT (4), and in 70% of s-PRCC (7). Although AMACR is considered to be a helpful marker for s-PRCC (7,8) our results and previous studies have shown that AMACR is not entirely specific for s-PRCC and AMACR immunoreactivity can be seen in 5–10% of MAs (7,8). CDH17 appears to be a highly specific marker for MA, as in our series none of the cases of e-WT and s–PRCC was positive for CDH17.

CDH17, also known as liver-intestinal cadherin, is a member of the cadherin superfamily of calcium-dependent cell adhesion molecules. CDH17 is different from classic cadherins (such as E-cadherin) by its unique structural and functional features (19). CDH17 protein consists of an extracellular region, containing 7 cadherin domains, and a transmembrane region; however, is lacking the conserved cytoplasmic domain (27). Interestingly, CDH17 is structurally homologous to another member of the cadherin superfamily, cadherin 16, also known as kidney-specific cadherin (KSP-cadherin) (13,14,25). Due to this similarity CDH17 and KSP-cadherin were termed as “7D-cadherins” (28).

Expression of CDH17 appears to be tissue and species specific and is different between embryonal and adult tissues. CDH17 is mainly expressed in human fetal liver and gastrointestinal tract during embryogenesis (29). Its expression is lost in normal adult human liver, but maintained in normal adult human small and large intestine. CDH17 is not expressed in normal adult human renal tissue (20). Zebrafish embryonic model is a valid system for studying renal development and function, as well as identification of genes important to the physiology and pathophysiology of human kidney. Zebrafish cadherin 17 (*cdh*17) is closely related to human CDH17, possessing a 53% amino acid similarity (24). The expression pattern of *cdh*17 is strikingly different from that of mammalian CDH17. In zebrafish, *cdh*17 is expressed specifically in the posterior portion of pronephric ducts during embryonic development and knockdown of *cdh*17 disrupts the normal formation of the posterior portion of the pronephric ducts (24). The embryonic pattern of *cdh*17 kidney expression is retained into adulthood zebrafish. Our study is the first to demonstrate the

expression pattern of CDH17 during fetal development of human kidney. CDH17 appears to be differentially expressed during the late stages of fetal kidney development into early infancy, but is lost in later infancy through adulthood. It would be of interest to examine the role of CDH17 in human nephrogenesis in further studies.

The histogenetic relationship of MA with nephrogenic rests, Wilms tumor, and the developing proximal tubule of the fetal kidney remains controversial (1,4,30). Morphologically, MA is composed of cells that resemble nephrogenic rests, and this can explain many other terms that have been used to refer to MA, such as nephrogenic nephroma (31), and benign epithelial nephroblastoma (32). This resemblance of MA to nephrogenic rests and Wilms tumor as well as similar expression of WT1 and CD57 between MA, WT, and nephrogenic rests may explain why MA is considered by some authors as a hyperdifferentiated benign end of the Wilms tumor spectrum (4, 33). However, only one of six cases of nephrogenic rests was positive for CDH17 expression and all WTs were negative in contrast to MA positivity in our study. At the genetic level, MA appears to be distinct from WT, as chromosomal alterations frequently present in Wilms tumor have not been identified in MA, while *BRAF* V600E mutations have been described in approximately 90% of MAs (34, 35). Other investigators provided immunohistochemical and ultrastructural evidence of similarity between MA and developing proximal tubular epithelium. The tumor cells of MA express the proximal tubule marker URO-2 (30), and ultrastructurally, the tumor cells contain microvilli (1), a characteristic feature of proximal tubular epithelium.

Morphologic, immunohistochemical, and ultrastructural similarities have been described between MA and two rare entities. One is embryonal hyperplasia of Bowman's capsular epithelium (EHBCE), found typically in patients with end stage renal failure who are being maintained on dialysis (36). Another is designated as metanephric metaplasia of Bowman capsular epithelium and is associated with widespread malignant neoplasms of various types (37). De Silva *et al* described a case of MA associated with EHBCE (36). The lesions showed many similarities on a morphologic, immunohistochemical, and ultrastructural basis suggesting a possible relationship between these two entities. Bove *et al* (38) reported a case of EHBCE, which they called "diffuse metanephric adenoma", in a child who had been treated with dialysis since infancy for progressive renal failure. In this case, attempted suicide of the mother in the first trimester of pregnancy was thought to be responsible for the epithelial maturation defect present in this lesion. Persistent primitive epithelium at the junction of the glomerular space and proximal nephron was thought to be the most likely precursor of this proliferation, a hypothesis partly supported by electron microscopy (38). In the current study we found that MAs demonstrate a phenotype similar to the proximal tubules of the developing kidney in an area immediately adjacent to glomerulus and in the parietal epithelium of Bowman's capsule. Our findings are in complete agreement with Bove *et al* and support the histogenetic relationship of MA with the primitive epithelium at the junction of the glomerular space and proximal tubule.

In conclusion, CDH17 is a sensitive (81%) and highly specific (100%) marker for metanephric adenoma. CDH17 should be considered in the IHC panel for distinguishing MA from its mimics.

Acknowledgments

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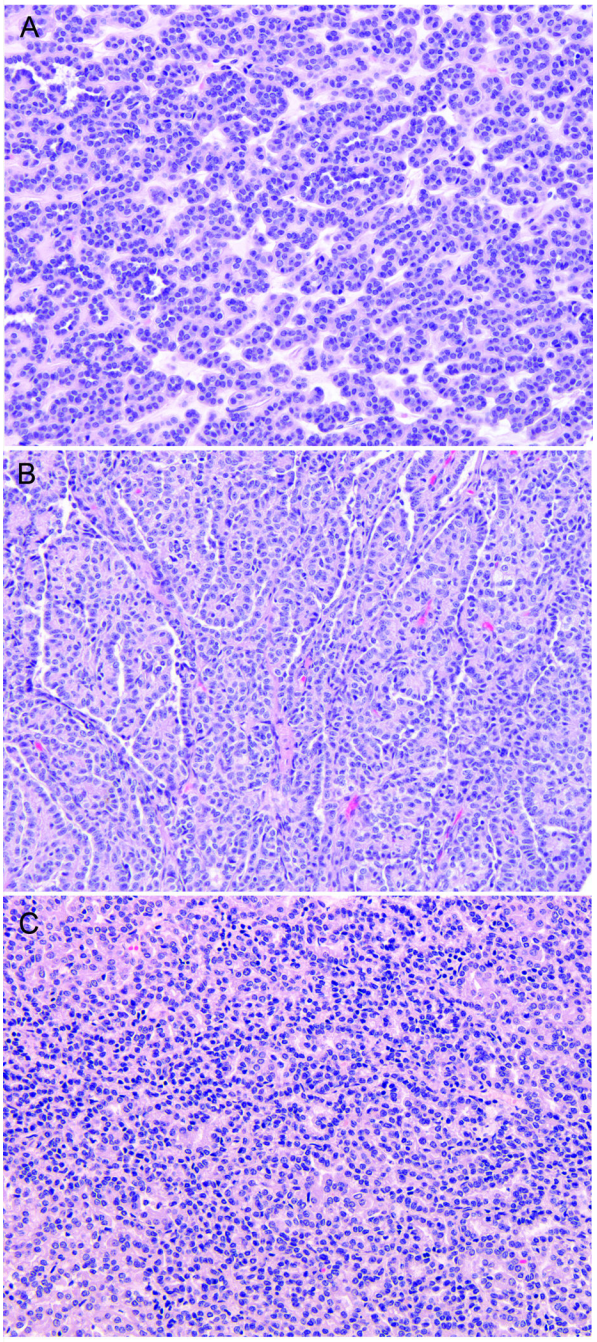

Figure 1.

A, Metanephric adenoma composed of small uniform cells arranged in closely packed tubules in acellular stroma. B, Epithelial predominant Wilms tumor with tightly packed cells arranged in tubular structures. C, Solid variant of papillary RCC containing tightly packed cells growing in solid sheets with ill-defined tubular pattern.

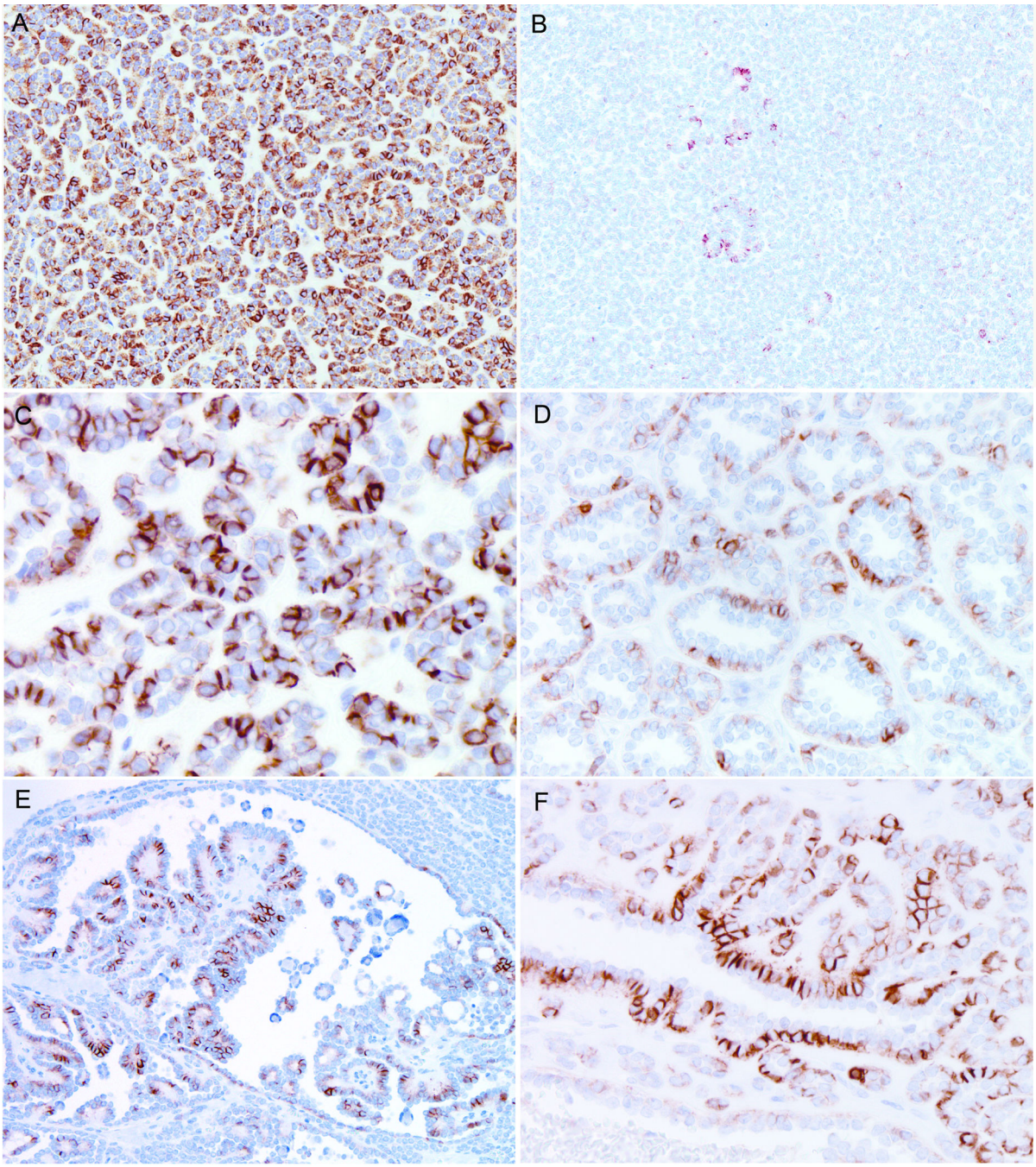

Figure 2.

Immunohistochemical staining of CDH17 in metanephric adenoma. A, Strong diffuse staining of 3+ intensity. B, Weak focal staining of moderate intensity. C, Membranous staining pattern with lateral intercellular border accentuation. Immunoreactivity of CDH17 in various components of metanephric adenoma: D, acinar component, E, papillary, and F, tubular.

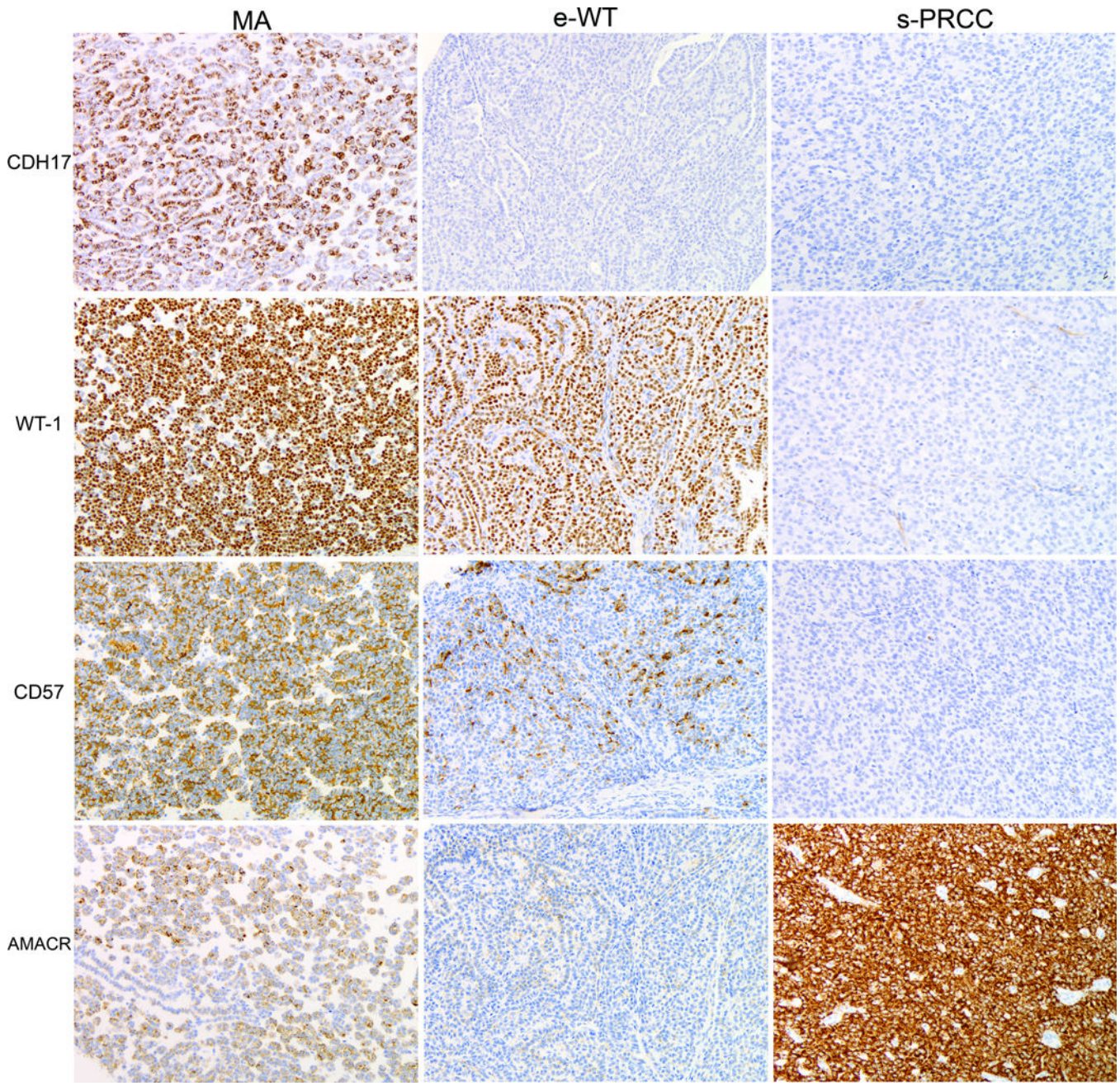

Figure 3.
Immunohistochemical staining of CDH17, WT-1, CD57, and AMACR in metanephric adenoma, epithelial predominant Wilms tumor, and solid variant of papillary RCC.

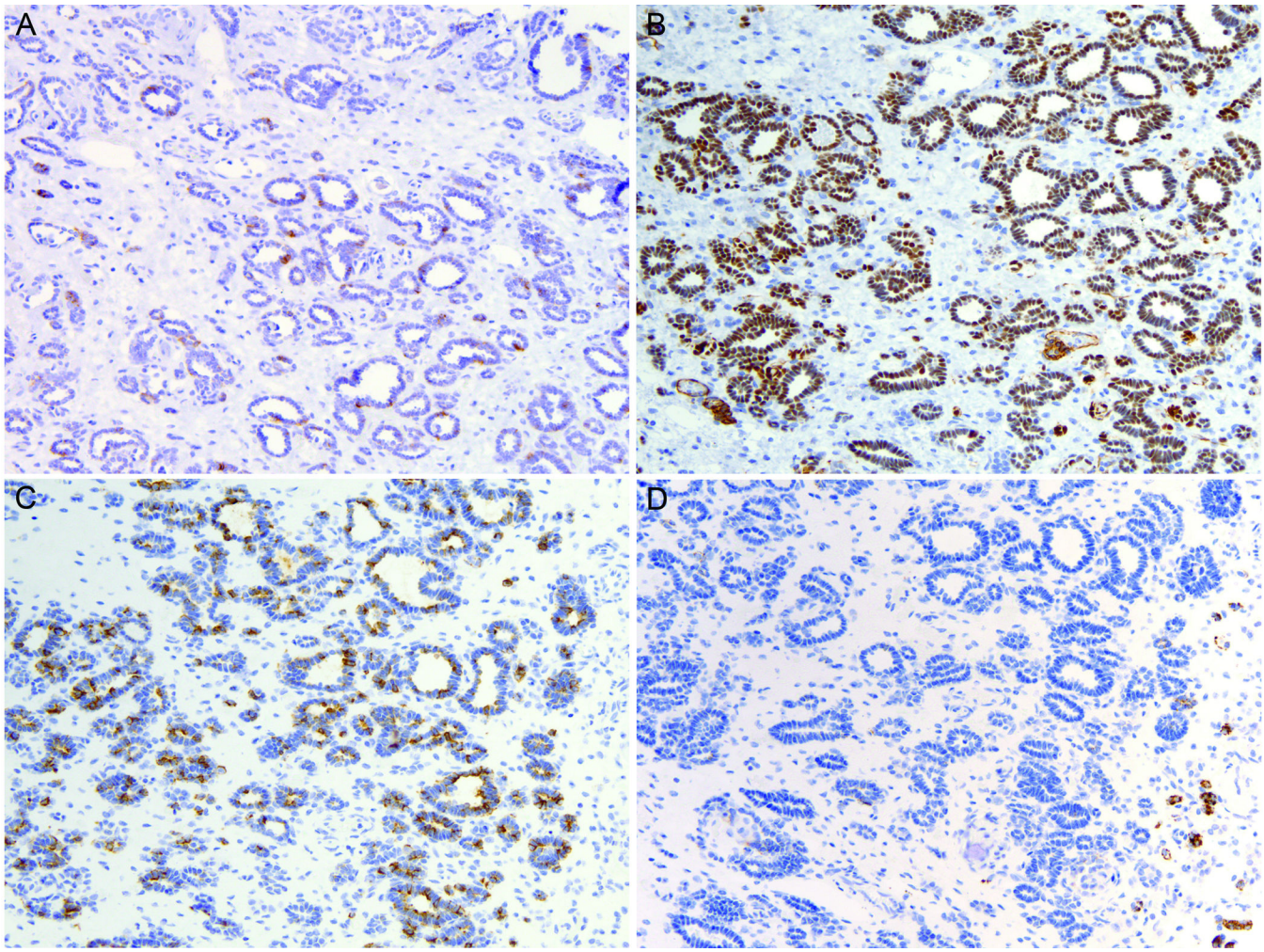

Figure 4.

Immunohistochemical staining of nephrogenic rests. A, Focal expression of CDH17, B, diffuse expression of WT-1, C, focal expression of CD57, D, negative AMACR staining (few normal tubules are positive on the right).

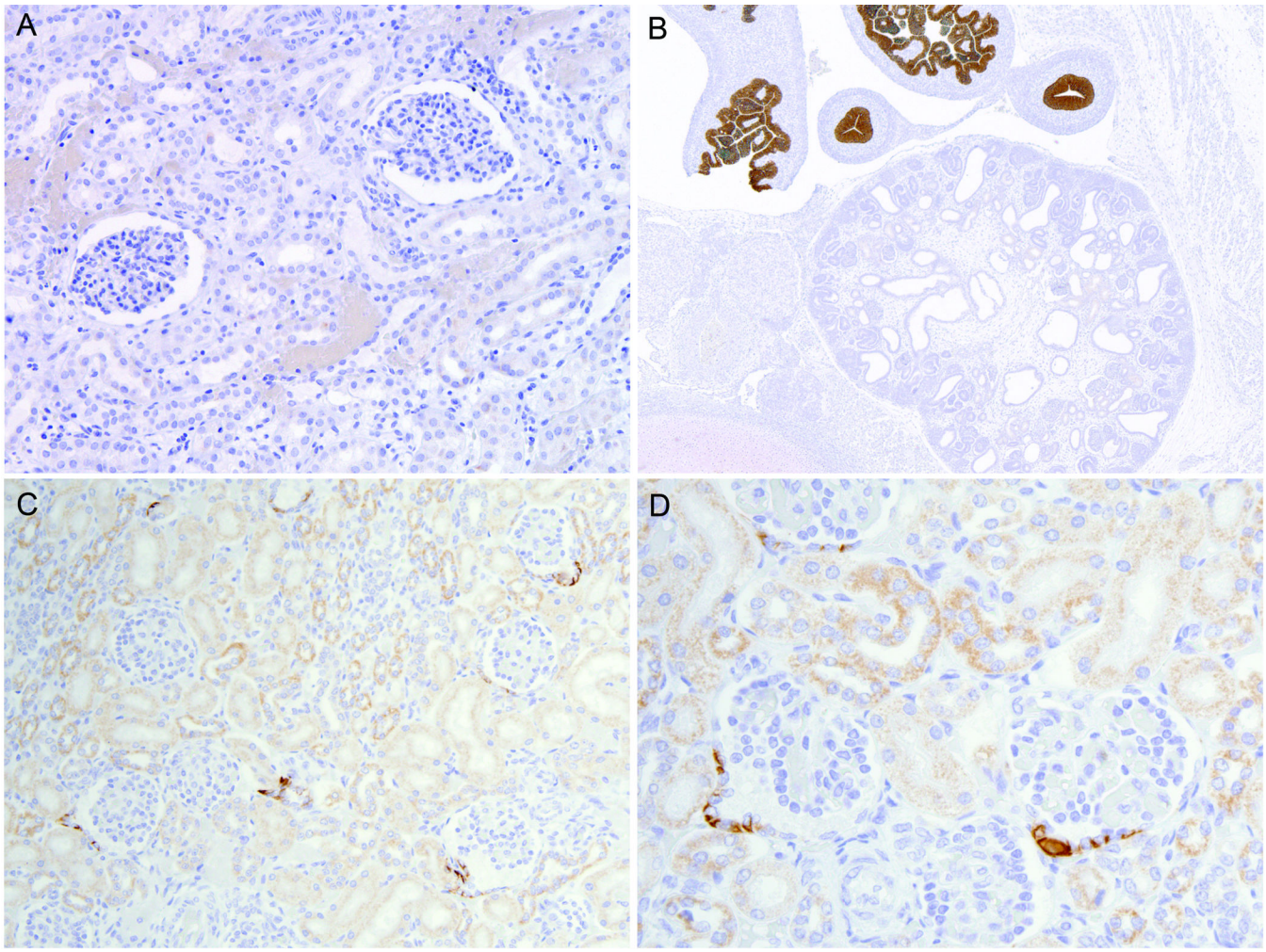

Figure 5.

Expression of CDH17 in fetal kidneys. A, Normal adult kidney tissue is negative for CDH17. B, Fetal kidney at 10 weeks gestational age is negative for CDH17. Fetal intestine (top) is strongly positive. C, Immunoreactivity in the proximal tubule immediately adjacent to the glomeruli and focally extending to the parietal epithelium of Bowman's capsule in the kidney from a 38 week fetus, low power view (×100). D, Details of (C) at higher magnification (×400).

Table 1

Antibodies used for immunohistochemistry

Antibody	Source	Clone	Pretreatment	Dilution	Platform
CDH17	Cell Marque	SP183	High pH target retrieval	1:100	Ventana
WT-1	Dako	6F-H2	Low pH target retrieval	1:50	Dako EDL
CD-57	Cell Marque	HNK-1	High pH target retrieval	1:50	Dako Flex
AMACR	Zeta Corp	P504S	High pH target retrieval	1:100	Dako Flex
CDX2	Biogenex	CDX2-88	Low pH target retrieval	1:50	Dako Flex

Table 2

Expression of CDH17 and other markers in renal tumors

Marker	Combined score	MA (n=21)	e-WT (n=17)	s-PRCC (n=15)	P value
CDH17	0	4	0	0	<0.0001
	Weak	5	0	0	
	Moderate	9	0	0	
	Strong	3	0	0	
WT-1	0	0	0	15	<0.0001
	Weak	2	3	0	
	Moderate	10	9	0	
	Strong	9	5	0	
CD57	0	0	7	12	<0.0001
	Weak	0	4	1	
	Moderate	0	6	1	
	Strong	21	0	1	
AMACR	0	18	11	0	<0.0001
	Weak	1	3	0	
	Moderate	2	3	0	
	Strong	0	0	15	

MA, metanephric adenoma, e-WT, epithelial predominant Wilms tumor, s-PRCC, solid variant of papillary RCC.