Distal Tubular Hyperplasia

A Proposal for a Unique Form of Renal Tubular Proliferation Distinct From Papillary Adenoma

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Abstract: We identified an unusual pattern of renal tubular proliferation associated with chronic renal disease, found in 23 patients, diffusely (n = 12), or focally (n = 11). Incidence was 5% of end-stage renal disease kidneys from one institution (8/177) and 7/23 patients with acquired cystic kidney disease–associated renal cell carcinoma from another. Most (19 patients) had 1 or more neoplasms including papillary (n = 9), acquired cystic kidney disease (n = 8), clear cell (n = 4), or clear cell papillary (n = 3) renal cell carcinoma. All (20 men, 3 women) had end-stage renal disease. The predominant pattern (n = 18) was the indentation of chronic inflammation into renal tubules forming small polypoid structures; however, 5 had predominantly hyperplastic epithelium with less conspicuous inflammation. In 14 patients both patterns were appreciable, whereas the remainder had only the inflammatory pattern. Immunohistochemistry was positive for cytokeratin 7, high–molecular-weight cytokeratin, PAX8, and GATA3. Staining for alpha-methylacyl-CoA racemase was negative or weak, dramatically less intense than papillary neoplasms or proximal tubules. CD3 and CD20 showed a mixture of B and T lymphocytes in the inflammatory areas. Fluorescence in situ hybridization showed no trisomy 7 or 17 or loss of Y (n = 9). We describe a previously uncharacterized form of renal tubular proliferation that differs from papillary adenoma (with weak or negative alpha-methylacyl-CoA racemase, lack of trisomy 7 or 17, and sometimes diffuse distribution). On the basis of consistent staining for high–molecular-weight cytokeratin and GATA3, we propose the name distal tubular hyperplasia for this process. Future studies will be helpful to assess preneoplastic potential and etiology.

Key Words: distal tubular hyperplasia, papillary adenoma, immunohistochemistry, renal cell carcinoma, end-stage renal disease

(*Am J Surg Pathol* 2021;45:516–522)

Papillary adenoma is the only well-established precursor or preneoplastic lesion in the classification of renal cell carcinoma (RCC) at present.[1] However, we have occasionally encountered a proliferation in the setting of end-stage renal disease that appears different in morphology and distribution. We collected a multi-institutional series of kidney pathologic specimens with this process to attempt to characterize its phenotype, incidence, and distribution.

MATERIALS AND METHODS

After encountering an unusual renal tubular proliferation in select end-stage renal disease pathologic specimens, for which we propose the term distal tubular hyperplasia, we queried genitourinary and renal pathologists at multiple institutions for familiarity with this process. Specimens showing this finding were collected from the authors' archives. A series of 177 end-stage renal disease specimens from the Indiana University Health archives were re-reviewed by one of the authors (K.I.A.-O.) in search of this finding specifically. Available material from a previously published cohort of acquired cystic kidney disease–associated RCC[2] was also reexamined for this finding. Medical records were reviewed for the etiology of renal disease, presence of concurrent renal neoplasms, and tumor types. Immunohistochemical staining was performed with antibodies against high–molecular-weight cytokeratin (34βE12), cytokeratin 7, alpha-methylacyl-CoA racemase (AMACR), GATA3, PAX8, CD3, and CD20. Fluorescence in situ hybridization for a gain of chromosome 7 or 7 or loss of the Y chromosome was performed using methods previously described,[3–5] in 9 samples selected for the greatest abundance of the lesion for evaluation.

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S.R.W. and K.I.A.-O. contributed equally.

Conflicts of Interest and Source of Funding: Supported in part by Henry Ford Health System internal funding to S.R.W. (A20063). The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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RESULTS

We retrieved specimens from 23 patients, who ranged in age from 22 to 72 years (median: 55 y), including 20 men and 3 women (Table 1). All had end-stage renal disease, with distal tubular hyperplasia being found in the native kidneys of 22 patients and allograft kidney of 1. Bilateral kidneys were removed in 4 patients, and the remainder were left (n = 12) and right (n = 6). Causes of renal disease noted included hypertension (n = 13), diabetic nephropathy (n = 5), possible or definite focal segmental glomerulosclerosis (n = 3), unknown causes (n = 3), vasculitis (n = 1), hepatitis (n = 1), atrophic kidney (n = 1), nonsteroidal anti-inflammatory drug use (n = 1), and lupus nephritis (n = 1; numbers sum to > 23 due to multiple etiologies in some patients). Concurrent tumors were present in 19 patients, whereas 4 had no neoplasm. Tumor types included papillary (n = 9), acquired cystic kidney disease (n = 8), clear cell (n = 4), or clear cell papillary (n = 3) RCCs, ranging in size from 0.5 cm (an acquired cystic kidney disease RCC) to 6.8 cm (a clear cell RCC). Papillary adenomas were also present for 14 patients. Eight patients were found from the cohort of 177 end-stage renal disease specimens from Indiana University, yielding an approximate incidence of 5% within end-stage renal disease kidneys and 7 were found from 23 available specimens from a previously published cohort of acquired cystic kidney disease–associated RCC (30%).[2] Of the cases prospectively recognized by the pathologists as an unusual tubular proliferation, distal tubular hyperplasia was focal in 2 (defined as < 5 foci, not > 2

TABLE 1. Clinical and Pathologic Features of Distal Tubular Hyperplasia and Associated Tumors

Case No.	Sex	Age (y)	Laterality	Cohort	Radical/ Partial Nephrectomy	Associated Tumor	Tumor Size	Tumor Grade	Stage	Papillary Adenomas	Diffuse/ Focal	Pattern	Both Patterns Present
1	Male	72	Left	ACKD review	Radical	ACKD and papillary	1.5	3	pT1a	Yes	Focal	Hyperplastic	Yes
2	Male	55	Left	ACKD review	Radical	ACKD and papillary	Unknown	3	pT1a	Yes	Focal	Inflammatory	Yes
3	Male	45	Right	ACKD review	Radical	ACKD and clear cell papillary	0.8	3	pT1a	No	Focal	Inflammatory	No
4	Female	32	Left	ACKD review	Radical	ACKD	2.0	3	pT1a	Yes	Diffuse	Inflammatory	No
5	Male	64	Bilateral	ACKD review	Radical	ACKD and papillary	4.5	3	pT1b	Yes	Diffuse	Inflammatory	Yes
6	Male	24	Bilateral	ACKD review	Radical	ACKD	1.2	3	pT3a	Yes	Focal	Inflammatory	Yes
7	Male	44	Right	ACKD review	Radical	ACKD and clear cell papillary	3.0	3	pT3a	No	Diffuse	Inflammatory	Yes
8	Female	22	Left	ESRD review	Radical	None				No	Focal	Inflammatory	No
9	Male	49	Right	ESRD review	Radical	None				No	Diffuse	Hyperplastic	Yes
10	Male	54	Bilateral	ESRD review	Radical	None				No	Diffuse	Hyperplastic	Yes
11	Male	55	Right	ESRD review	Radical	Clear cell and multiple papillary	2.3	2	pT1a	Yes	Focal	Inflammatory	No
12	Male	58	Left	ESRD review	Radical	None				No	Focal	Inflammatory	No
13	Male	61	Left	ESRD review	Radical	Clear cell	1.8	2	pT1a	No	Diffuse	Hyperplastic	Yes
14	Male	62	Left	ESRD review	Radical	ACKD	0.5	3	pT1a	No	Focal	Inflammatory	No
15	Male	66	Left	ESRD review	Radical	Clear cell papillary	3.1	1	pT1a	Yes	Focal	Inflammatory	No
16	Male	27	Left	Prospective	Radical	Papillary	2.0	2	pT1a	Yes	Diffuse	Inflammatory	Yes
17	Male	46	Left	Prospective	Radical	Papillary	1.5	2	pT1a	Yes	Diffuse	Hyperplastic	Yes
18	Female	48	Allograft	Prospective	Radical	Clear cell	6.8	3	pT3a	No	Diffuse	Inflammatory	Yes
19	Male	54	Bilateral	Prospective	Radical	Papillary (left); none (right)	3.0	3	pT1a	Yes	Diffuse	Inflammatory	Yes
20	Male	55	Right	Prospective	Partial	Papillary	4.3	2	pT1b	Yes	Focal	Inflammatory	No
21	Male	62	Left	Prospective	Radical	Papillary	1.2	2	pT1a	Yes	Focal	Inflammatory	No
22	Male	65	Left	Prospective	Radical	Papillary	2.4	3	pT3a	Yes	Diffuse	Inflammatory	Yes
23	Male	66	Right	Prospective	Radical	Clear cell	3.8	2	pT1a	Yes	Diffuse	Inflammatory	Yes

ACKD indicates acquired cystic kidney disease; ESRD, end-stage renal disease.

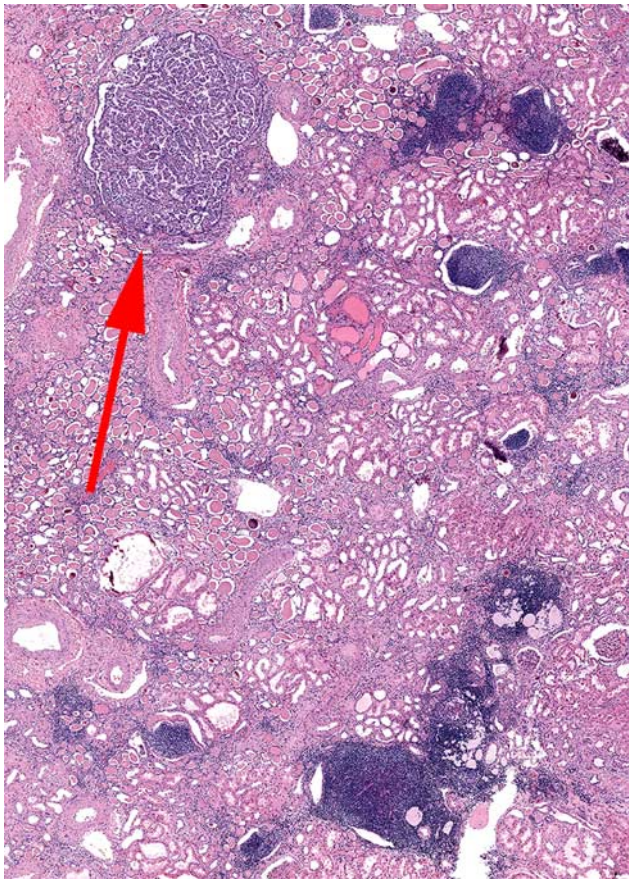

FIGURE 1. Distal tubular hyperplasia was often diffusely distributed, highlighted by the scattered inflammatory foci in this field. A conventional papillary adenoma is also present (red arrow).

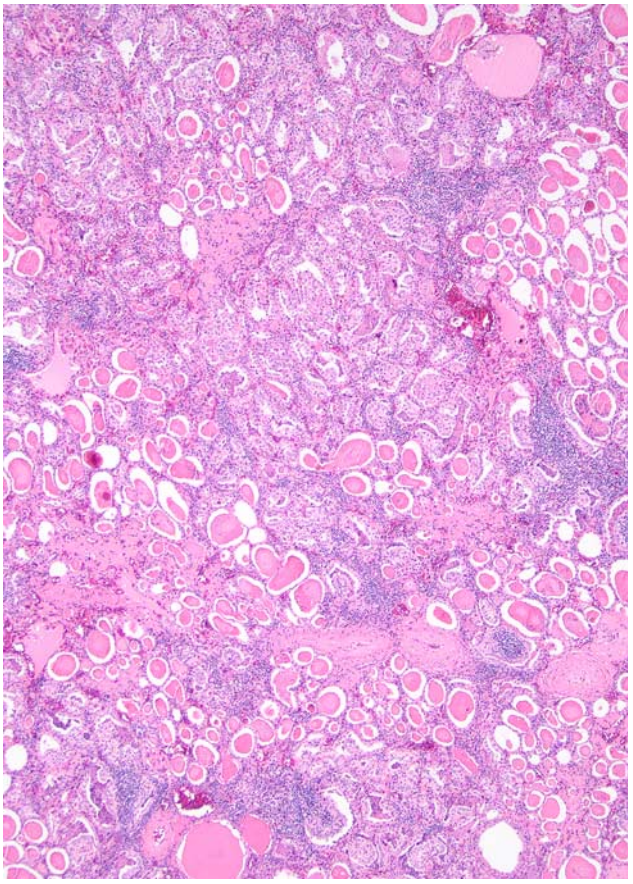

FIGURE 2. In this example of diffusely distributed distal tubular hyperplasia, the tufted epithelium is composed predominantly of increased cells with less conspicuous inflammation.

slides involved) (Figs. 1, 2) and diffuse in 6. In contrast, of the patients retrospectively identified from the end-stage renal disease and acquired cystic kidney disease cohorts, distal tubular hyperplasia was predominantly focal (n = 9) and less often diffuse (n = 6).

The predominant pattern was inflammatory in 18, with chronic inflammation indenting into the tubular epithelium forming small polypoid structures (Fig. 3A) and hyperplastic in 5, with tufts of lightly eosinophilic epithelial cells and inconspicuous inflammation (Fig. 3B). However, both patterns could be observed at least focally in 14 (Fig. 4). Those that had only one pattern showed only the inflammatory pattern, almost all of which were focal (8/9). Immunohistochemistry (Fig. 5) was consistently positive for high–molecular-weight cytokeratin (22/22, 10 weakly positive, excluding 1 which was negative but had no verifiable internal control staining), cytokeratin 7 (21/21), GATA3 (22/22, 4 weakly positive), and PAX8 (11/11, 1 weak). Staining was negative (12/22) or weak (10/22) for AMACR (Fig. 6), markedly less than the reaction of proximal tubules or papillary renal neoplasms in all patients. Staining for CD3 and CD20 revealed a mixture of B and T lymphocytes in the inflammatory pattern of all patients tested (13/13). Other stains done as part of the original diagnostic evaluation included CD10 (negative in 2 patients but labeled the luminal debris, 0/2), carbonic anhydrase IX (negative in 1 patient, 0/1), vimentin (negative in 1 patient, 0/1), KIT (negative in 1 patient, 0/1), and WT1 (negative in 1 patient, 0/1). One patient had additional lymphoma evaluation of the inflammatory lesions which revealed a normal germinal center pattern with BCL2, BCL6, and CD10, a normal pattern of CD5, and negative cyclin D1. Fluorescence in situ hybridization did not demonstrate trisomy 7 or 17 or loss of the Y chromosome in 9 samples studied (all male patients, Fig. 7).

DISCUSSION

We describe a previously unrecognized pattern of renal tubular proliferation in the setting of end-stage renal disease. The immunohistochemical pattern of this proliferation suggests a distal tubular phenotype (negative or minimal AMACR, contrasting to proximal tubules, and positive high–molecular-weight cytokeratin, cytokeratin 7, and GATA3, compatible with distal tubules).[6–8] Therefore, we propose the terminology "distal tubular hyperplasia" for this process.

It is difficult to be entirely certain of the incidence of this proliferation. From one of the participating institutions, it was found in 5% of end-stage renal disease

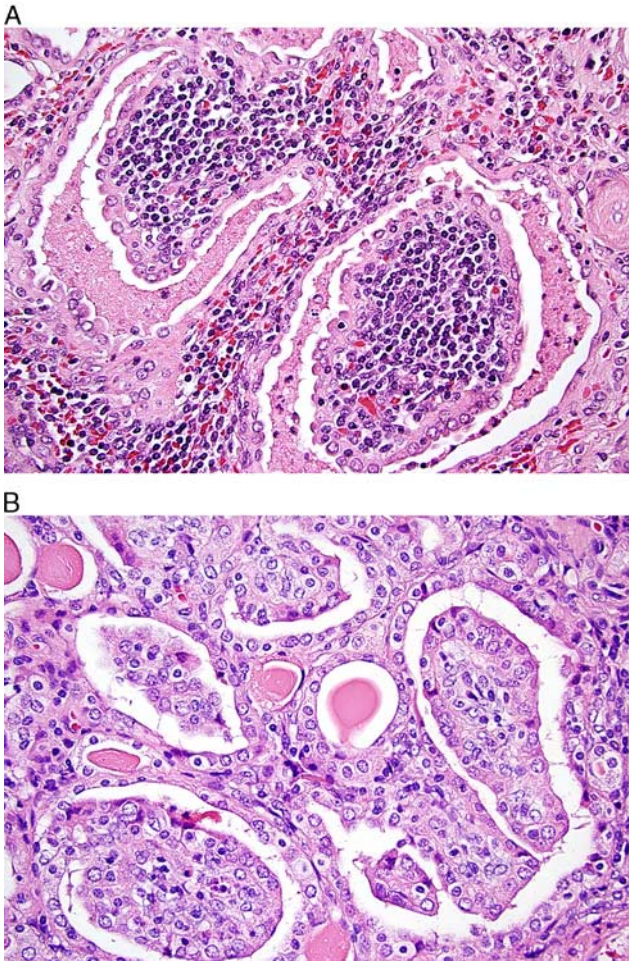

FIGURE 3. The 2 main patterns of distal tubular hyperplasia encountered included chronic inflammation indenting into tubules, forming small polyps (A), and hyperplastic tufts of the epithelium with less conspicuous inflammation (B).

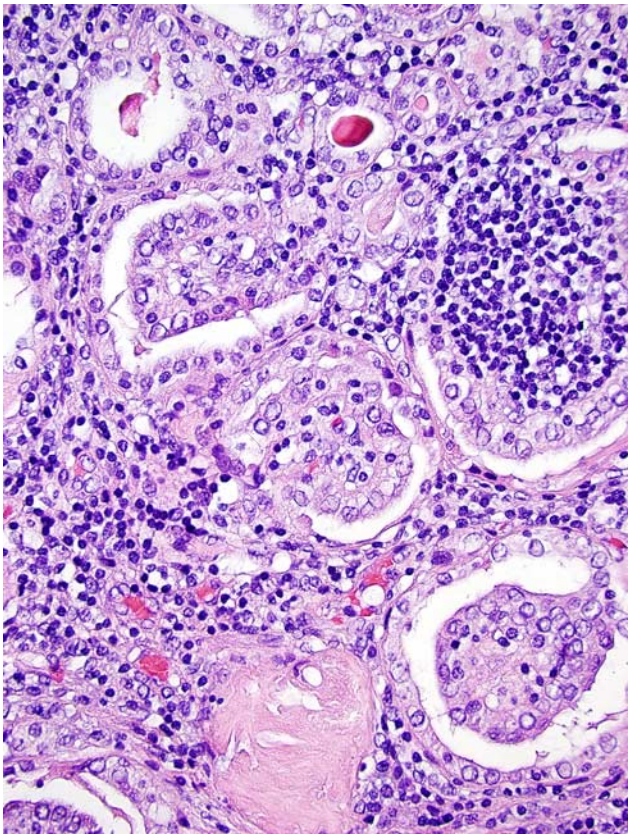

FIGURE 4. Although one pattern was typically predominant, both patterns could usually be found at least focally. This example shows predominantly hyperplastic epithelium with one tuft showing the inflammatory pattern.

kidney resection specimens. In contrast, it was found in 7 of 23 (30%) specimens upon reexamination of acquired cystic kidney disease–associated RCC kidneys. Distal tubular hyperplasia was more commonly diffuse in the cases that were prospectively recognized by the pathologists (6 vs. 2), whereas it was more often focal (9 vs. 6) in the retrospective review cohorts, reflecting that more florid cases were more prone to be recognized by the pathologist as an unusual finding and hence identified in the prospective practices of the contributors. However, focal changes can likely be identified after developing familiarity with this process and on a specific search. As a similar example, RCCs with very unusual features were initially recognized as "biphasic alveolosquamoid" RCC[9]; however, with increased awareness, it now appears that this is a pattern of papillary RCC[10,11] and subtle similar changes can likely be identified in papillary RCCs that would otherwise appear to be of the garden variety. The stronger association with acquired cystic kidney disease RCC cases is also interesting, as acquired cystic kidney disease RCC made up only 1 of the associated tumors excluding those gathered from a specific review of acquired cystic kidney disease RCC kidneys.

The differences between the 2 patterns of distal tubular hyperplasia (inflammatory and hyperplastic) may raise the question of whether both are correctly grouped as representing the same process. However, in our interpretation, the finding of both patterns at least focally in most cases (14/23, 61%, Fig. 4) and the identical immunohistochemical phenotype of both patterns would support these being a spectrum of the same process. Of note, what we describe as distal tubular hyperplasia bears substantial resemblance to what was described as "type B" papillary adenoma by Calio et al,[12] including a composition by broad papillae, sometimes containing lymphocytes in the cores.

It is currently unknown whether this should be considered a preneoplastic lesion. Likely, some of the extreme examples of this phenomenon have been interpreted as extensive involvement of the kidney by papillary adenomas in the past; however, since distal tubular hyperplasia lacks the strong AMACR staining and chromosomal abnormalities of papillary neoplasms, we hypothesize that this represents a different phenomenon. Although the immunohistochemical positivity for high–molecular-weight cytokeratin and GATA3 is similar

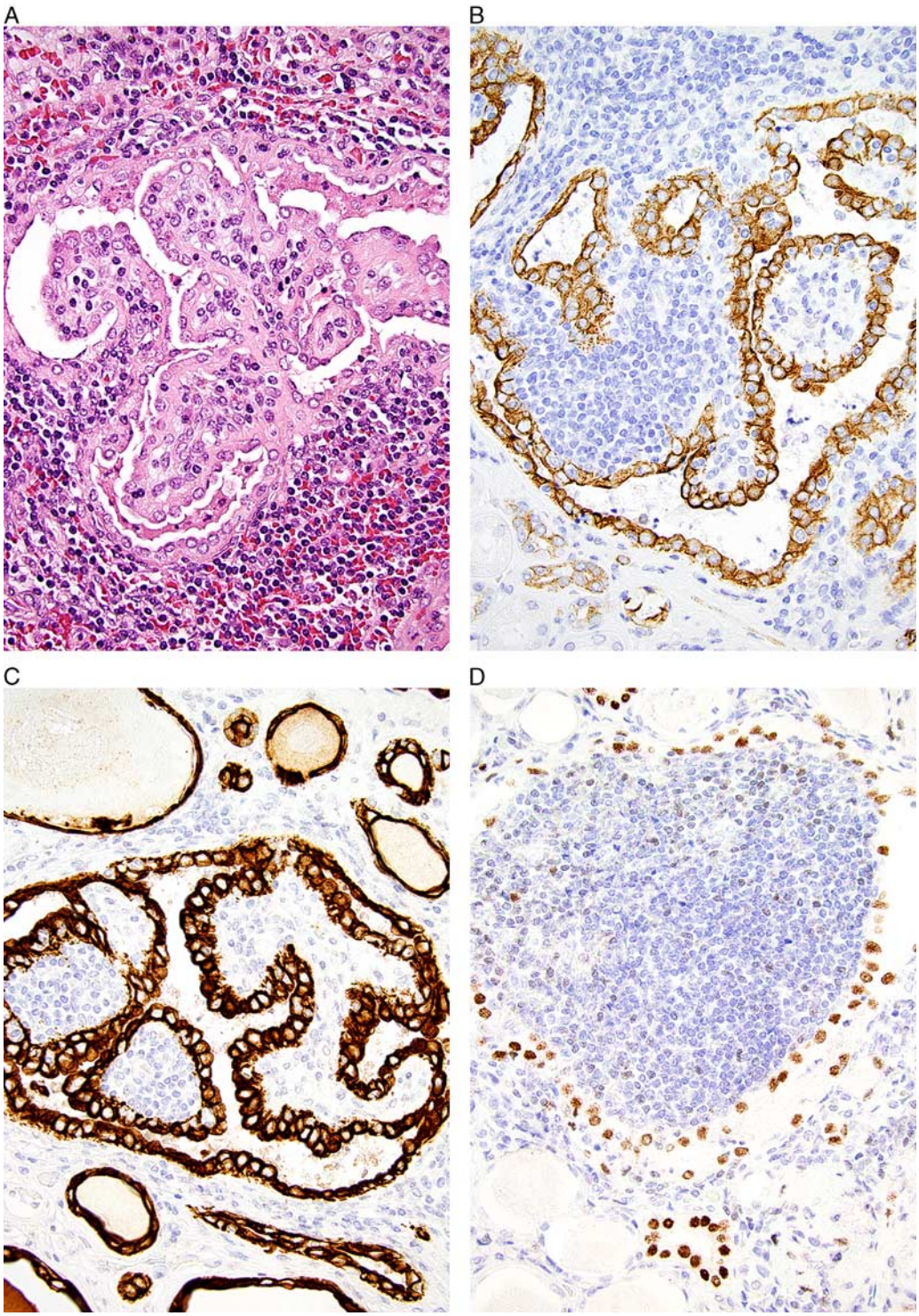

FIGURE 5. Immunohistochemistry of distal tubular hyperplasia (A) consistently showed positive staining for high–molecular-weight cytokeratin (B), cytokeratin 7 (C), and GATA3 (D).

to that of clear cell papillary RCC,[6] we otherwise see no morphologic similarity to this entity, and clear cell papillary RCC made up only 3 of the 19 histologic subtypes of RCC in these patients, arguing against this being a precursor to clear cell papillary RCC. Although this lesion was enriched in the acquired cystic kidney disease RCC cohort, we likewise doubt that this represents a precursor to acquired cystic kidney disease–associated RCC, because of its differing morphology

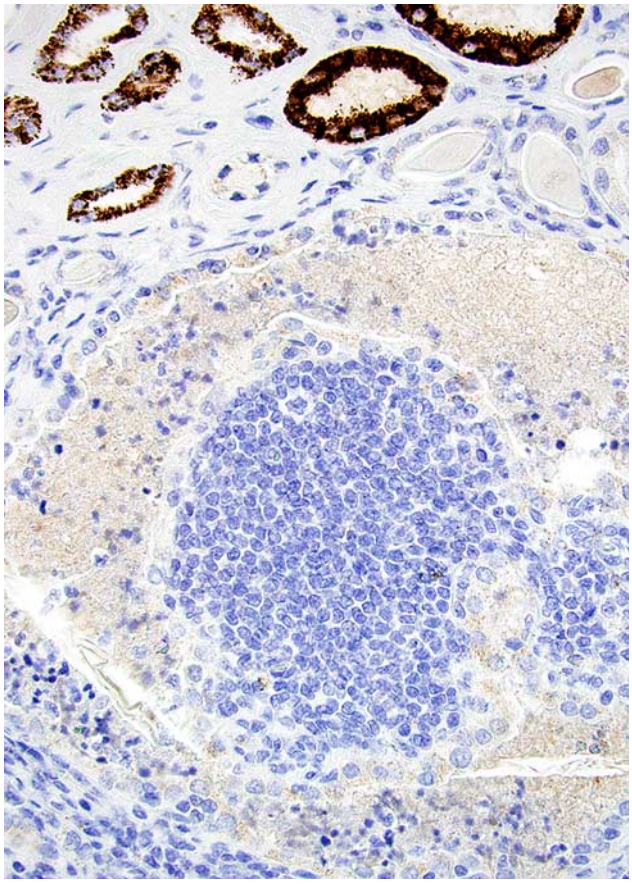

FIGURE 6. In contrast to papillary neoplasms and proximal tubules (top), distal tubular hyperplasia showed negative or weak staining for AMACR (center and bottom).

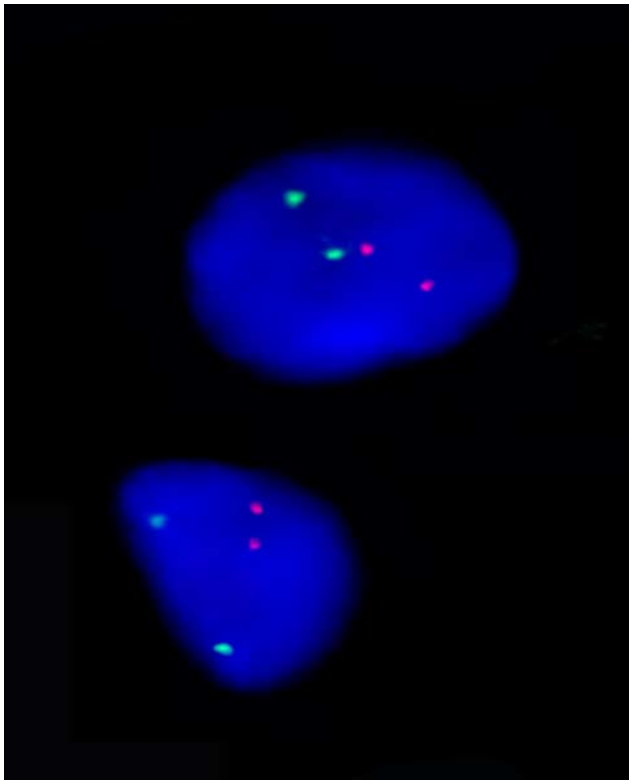

FIGURE 7. An example of fluorescence in situ hybridization shows 2 copies each of chromosomes 7 and 17, suggesting molecular distinction from usual papillary adenoma and papillary RCC.

and absence of AMACR labeling.[2] Although it would be natural to assume that this may be a precursor to papillary RCC, the study by Saleeb et al[13] found only the subset of papillary RCCs regarded as "oncocytic low-grade" papillary RCC to be GATA3 positive, analogous to those reported by Al-Obaidy and colleagues[3,14] as "papillary renal neoplasm with reverse polarity," and by others as "oncocytic papillary renal neoplasm with inverted nuclei."[15] Distal tubular hyperplasia seems to differ from this emerging entity by its typical association with end-stage renal disease and lack of predominant oncocytic morphology, although both share the findings of cytokeratin 7 and GATA3 reactivity with lesser AMACR labeling. At present, it is uncertain whether distal tubular hyperplasia represents a precursor to any RCC subtype or should be considered neoplastic or reactive.

Finally, the precise etiology of this process is not entirely clear. Although all patients had end-stage renal disease, definite commonality to the patients' renal disease was not discernible. Most patients had hypertension or diabetes; however, these are also among the most common causes of renal disease. In addition, hypertension is sometimes attributed presumptively for patients who have the end-stage renal disease of unknown etiology. Further recognition of this proliferation and additional study may determine whether it has any association with specific renal diseases.

In summary, we describe a previously unrecognized form of renal tubular proliferation in the setting of end-stage renal disease that may cause diagnostic difficulty to pathologists, especially when florid. Because of the often-diffuse distribution, lack of trisomy 7 or 17, and negative or weak AMACR staining, this appears different from papillary adenoma. We propose the designation distal tubular hyperplasia for this process, which warrants further study.

ACKNOWLEDGMENTS

The authors thank the genitourinary and renal pathologists who offered hypotheses regarding the potential nature of this process during our study design.

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