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Papillary adenoma of the kidney with mucinous secretion

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Summary. Although infrequently, mucin secretion has previously been reported in papillary renal cell carcinoma. We here investigate the presence of mucin in a series of 93 renal papillary adenomas in 58 patients. Acid mucin was present in four cases (4.3% of the tumors; 6.9% of the patients), in which basophilic mucin secretion was evident with hematoxylin-eosin. To the best of our knowledge mucin secretion has not been reported in renal papillary adenoma. We describe two different types of mucin secretion: intracytoplasmic and luminal. The secretion was intracellular in numerous scattered tumor cells in two cases, focal luminal in one case, and mixed intracellular and luminal in another case. Mucin production, despite its low frequency, can be considered as an additional feature of renal papillary adenoma. Mucin production suggests that renal papillary adenoma and papillary renal cell carcinoma are actually not two independent biological processes, but a continuum of one biological process.

Key words: Papillary adenoma, Mucin, Mucinous metaplasia, Kidney

Introduction

The current development of imaging methods has resulted in an increase in the diagnostic yield for small renal cortical tumors. This has raised the problem concerning the appropriate management of the patients affected by these neoplasms and the suitable use of these kidneys harvested for transplantation. Due to the possibility of malignant progression of small renal cortical neoplasms, a strict definition of renal adenoma is imperative.

Data from autopsy and surgical pathology studies support the identification of a set of criteria within which the diagnosis of renal papillary adenoma is safe and justified. These criteria include: (a) papillary, tubular, or tubulopapillary architecture; (b) diameter less than or equal to 5 mm; and (c) lack of resemblance to clear cell, chromophobe, or collecting duct renal cell carcinomas (Delahunt and Eble, 1997a,b; Grignon and Eble, 1998). These aforementioned criteria were accepted at consensus conferences in Heidelberg (Kovacs et al., 1997) and Rochester (Störkel et al., 1997).

However, in the microscopic spectrum of renal papillary adenoma (RPA) so far reported, mucin production is not mentioned (Budin and McDonnell, 1984; Thoenes et al., 1986; Delahunt and Eble, 1997a,b; Kovacs et al., 1997; Störkel et al., 1997; Grignon and Eble, 1998). Mucin secretion has been reported in papillary renal cell carcinoma (Val-Bernal et al., 1999). In order to complete the histological spectrum of the benign counterpart of this type of tumor, we investigated the mucin production in a series of RPAs.

Material and methods

A study of 93 RPAs in 58 consecutive adult patients selected by the criteria proposed by Delahunt and Eble (1997a,b) and Grignon and Eble (1998) was accomplished at the Marqués de Valdecilla University Hospital. Foci of tubular hyperplasia were excluded. The tumors were collected from three distinct groups of patients. Group 1 consisted of 31 RPAs in 22 patients retrospectively retrieved from our files of 2,881 autopsies performed from 1988 to 1997. The kidneys were opened coronally by a single section from convex surface through the hilum. Occasionally, multiple coronal sections of the entire organs were made.

Group 2 consisted of 43 RPAs in 26 patients prospectively studied in 385 autopsies performed in the years 1998, 1999, and January 2000. The kidneys were sectioned serially at approximately 0.5 cm intervals.

Group 3 consisted of 19 RPAs in 10 kidneys obtained by nephrectomy from 10 patients in the period from 1993 to 1999. The kidneys were sectioned serially at approximately 1.0 cm intervals. These cases were retrospectively retrieved from our files.

All adenomas were found incidentally at autopsy or

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by examination of nephrectomies performed for diverse processes. All specimens had been fixed in 10% neutrally buffered formalin for at least 24 hours and embedded in paraffin. Representative sections from all the 93 adenomas were stained with hematoxylin-eosin, periodic acid-Schiff (PAS) with and without diastase digestion, Mayer's mucicarmine (MMC), Alcian blue (AB) at a pH of 2.5, high-iron diamine (HID), Mowry's colloidal iron (MCI), and Perl's method. One to four (mean 1.4) hematoxylin and eosin-stained sections were available from each case for evaluation. Positive reactivity was defined as intense staining of luminal or intracytoplasmic secretion. Staining restricted to the luminal surface of the cells or to the stalks of the papillae was not considered positive.

Nuclear grade was classified by a two-tiered system: type 1 (low grade) and type 2 (high grade) according to Delahunt and Eble (1997a,b).

The arteriolosclerotic renal vascular disease (ARVD) was graded in severity from 0 to 3 according to the criteria proposed by Budin and McDonnell (1984). Normal kidneys were assigned grade 0, those with small, shallow cortical scars were grade 1, those having broader, deeper, and more numerous scars were grade 2, and those with diffuse confluent cortical scarring were grade 3.

Results

Group 1

Thirty-one RPAs were found in 22 cases. Of the 22 patients 17 were male and five were female. Age ranged from 42 to 82 years (mean 64.2 years). Sixteen patients exhibited a solitary RPA, while 3 patients had two and 3 had multiple tumors. Seven cases involved the right kidney, 10 cases the left kidney, and five cases were bilateral. Tumor size varied from 0.5 mm to 5 mm with a mean of 2.4 mm in the largest diameter.

Group 2

Forty-three RPAs were found in 26 cases within a total of 385 autopsies. The incidence of RPAs was 11.2% of the autopsies and 5.7% of the autopsied

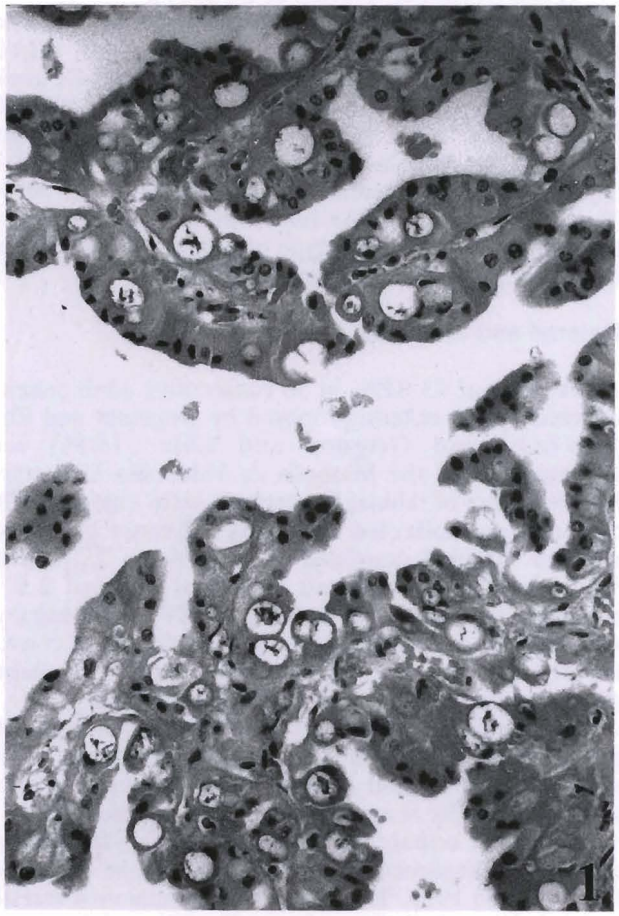

Fig. 1. Renal papillary adenoma showing intracellular secretion of mucin. Scattered tumor cells display large, basophilic, intracytoplasmic vacuoles occupied by mucin. From case 1. Hematoxylin and eosin, x 64

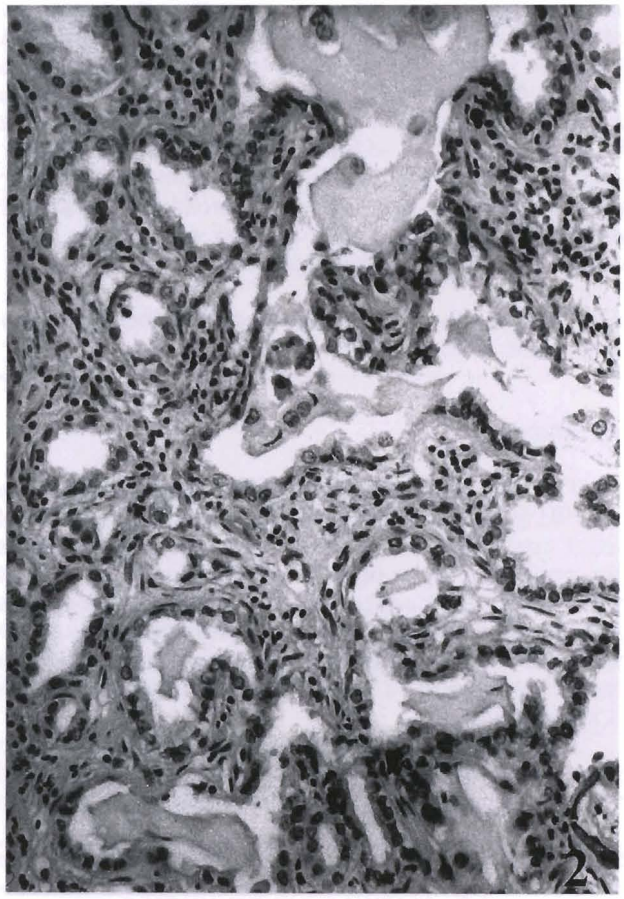

Fig. 2. Renal papillary adenoma showing focal, luminal basophilic mucin secretion. From case 3. Hematoxylin and eosin, x 64

patients. Of the 26 patients 21 were male and five were female. Age ranged from 48 to 92 years (mean 71.6 years). Eighteen patients exhibited a solitary RPA, while 2 patients had two and 6 had multiple tumors. These six cases showed bilateral tumors. Twelve cases involved the right kidney, eight cases the left kidney, and six cases were bilateral. Tumor size varied from 0.5 mm to 5 mm with a mean of 2.6 mm in the largest diameter.

Group 3

We observed 19 RPAs in 10 cases. Of the 10 patients nine were male and one was female. Age ranged from 39 to 80 years (mean 68.2 years). Six patients exhibited a solitary RPA, while one had two, one three, and two multiple (>3) tumors. Eleven cases involved the right kidney and eight cases the left kidney. Tumor size varied from 0.5 mm to 5 mm with a mean of 1.8 mm in the largest diameter. The indication for nephrectomy was the following: papillary renal cell carcinoma, 4 cases; conventional renal cell carcinoma, 2 cases; renal oncocytoma, 1 case; transitional cell carcinoma of ureter, 1 case; chronic pyelonephritis and lithiasis, 1 case; and kidney harvested of a cadaveric donor with advanced ARVD, 1 case.

Of the 58 cases, 15 (25.9%) showed ARVD grades 0-1, and 43 (74.1%) grades 2-3. All the 93 RPAs were located in the cortex and were predominantly well circumscribed. The structure of the adenoma was papillary in 52 (56%) tumors, tubular in six (6.4%) tumors, and tubulopapillary in 35 (37.6%) tumors. The RPA cells were eosinophilic in eight (8.6%) tumors, non-eosinophilic (basophilic or amphophilic) in 83 (89.2%) tumors, and mixed (eosinophilic and basophilic) in two (2.2%) tumors. As for nuclear grade, 90 (96.8%) RPAs were classified low-grade and three (3.2%) high-grade. Foam cells were present in 57 (61.3%) tumors. Microcalcification was observed in 32 (34.4%) tumors.

Table 1. Cases of mucin-secreting renal papillary adenoma: clinicopathological features.

CASE	AGE (years)/ GENDER	No. OF TUMORS/ LATERALITY	KIDNEY/SITE	SIZE (mm)	MUCIN PRODUCTION/ TYPE	COMMENT[a]
1	68/Female	1	Left/Upper pole	2	Intracellular/acid	Acute pancreatitis. Septic shock
2	80/Female	2, Unilateral	Left/Upper pole	5	Intracellular/acid	Adenocarcinoma of sigma. Multiple metastases
3	47/Male	1	Left/Upper pole	3	Luminal/acid and neutral	Adenocarcinoma of unknown origin. Multiple metastases. Massive PTEb
4	56/ Male	8, Bilateral	Right/Middle segment	1.3	Intracellular/acid	Large cell neuroendocrine carcinoma of lung. Metastases in dorsal(D2D3) vertebral bodies. Bronchopneumonia

[a]: all cases were incidental findings at autopsy; [b]: PTE, pulmonary thromboembolism.

Table 2. Cases of mucin-secreting renal papillary adenoma: histopathological features

CASE	CELL TYPE	ARCHITECTURE	NUCLEAR GRADE	FOAM CELLS	CALCIFI-CATIONS	HEMO-SIDERIN PIGMENT	LYMPHOCYTIC STROMAL INFILTRATE	FIBROUS PSEUDO-CAPSULE	OTHER FEATURES*
1	Columnar eosinophilic	Papillary	Type 1 (low)	no	no	no	no	no	no
2	Columnar eosinophilic	Papillary	Type 1 (low)	yes	no	no	no	yes incomplete	no
3	Cuboidal amphophilic	Tubulo-papillary	Type 1 (low)	yes	yes	no	yes	no	no
4	Cuboidal basophilic	Tubulo-papillary	Type 1 (low)	yes	no	no	no	no	no

*: sclerotic histology; edema of the papillary cores.

Table 3. Histochemical study of mucin.

CASE	MUCICARMINE	PERIODIC ACID SCHIFF	ALCIAN BLUE	COLLOIDAL IRON	HIGH-IRON DIAMINE
1	(+)	(-)	(+)	(+)	(-)
2	(+)	(-)	(+)	(+)	(-)
3	(+)	(+)	(+)	(+)	(-)
4	(+)	(-)	(+)	(+)	(-)

+: positive reaction; -: negative reaction.

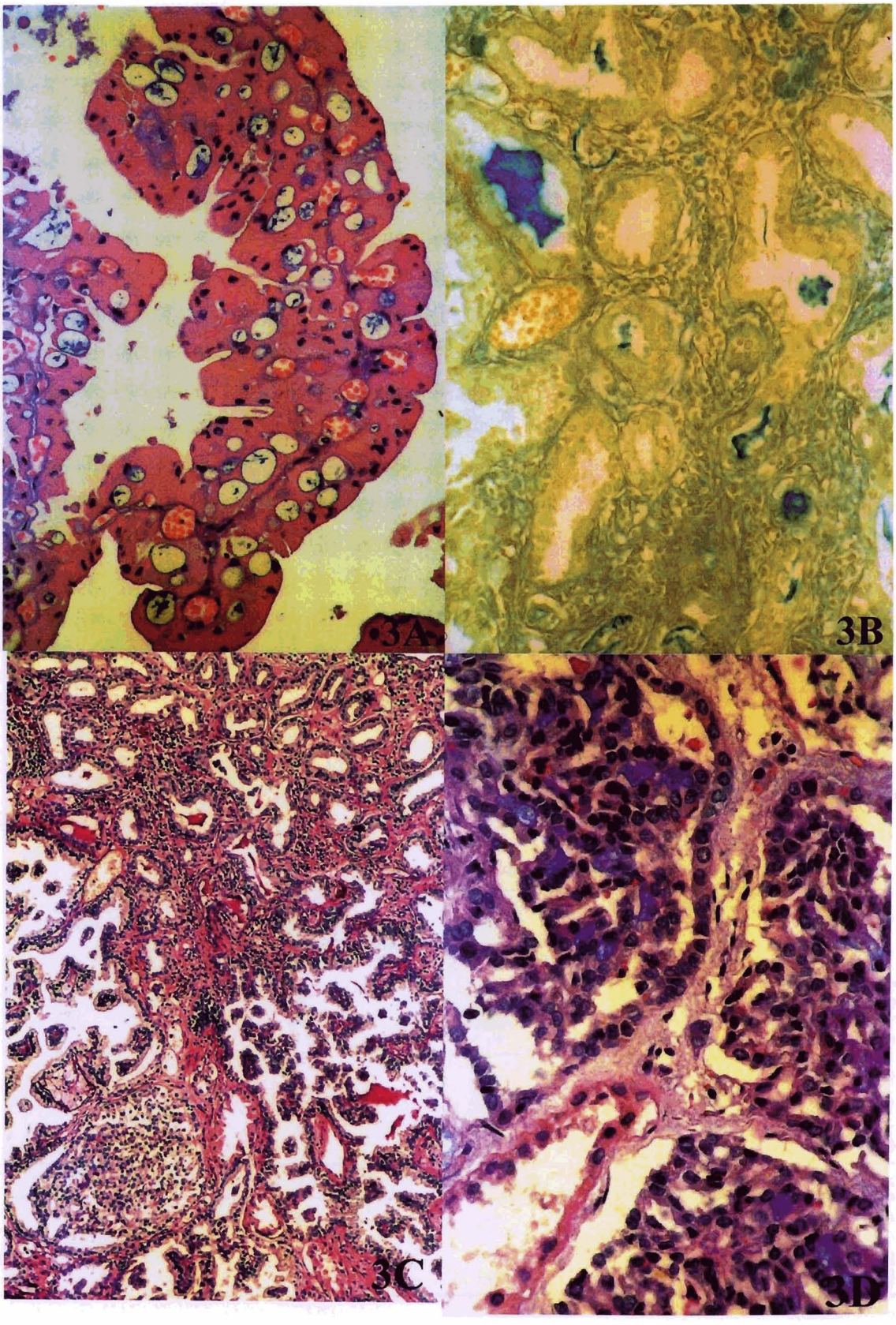

Fig. 3. A. Intracellular mucin in case 1. Alcian blue stain, x 64. **B.** Luminal mucin deposition in case 3. Mowry's colloidal iron stain, x 64. **C.** Luminal mucin in case 3. PAS stain, x 25. **D.** Intracellular mucin in case 4. Alcian blue stain, x 100

Other histological features were: lymphocytic stromal infiltration in 19 (20.4%) tumors, pseudocapsule in five (5.4%), intraneoplastic focal sclerosis in three (3.2%), hemosiderin pigmentation in five (5.4%), and intense edema of the papillary cores in one (1.1%).

In our series of 93 RPAs in 58 patients acid mucin was present in four tumors (4.3% of the tumors; 6.9% of the patients), in which the basophilic mucin secretion was evident with hematoxylin-eosin. All four cases with mucin secretion were observed in autopsy and were included in group 2. There were two different types of mucin secretion. In cases 1, 2 and 4 numerous scattered tumor cells showed large, well-delineated, solitary, round to oval, intracytoplasmic vacuoles containing stringy basophilic secretion (Fig. 1). Some of these cells displayed a signet-ring cell morphology. In case 3, the mucin secretion was focal and luminal (Fig. 2). In all cases the basophilic secretion reacted positively with MMC, AB, and MCI (Fig. 3). This secretion stained blue with HID indicating the absence of sulphomucins. Moreover, case 3 showed positive reaction for PAS (Fig. 3). This stain was negative in cases 1, 2, and 4. Table 1 summarizes the clinicopathological features of the four cases. The histopathological features are shown in Table 2. The histochemical study of mucin is shown in Table 3.

Discussion

Small well-differentiated neoplasms of the renal cortex are frequently found incidentally at autopsy as well as in surgically removed kidneys from adults. Their frequency in autopsy studies varies from 4% to 37%, depending on the patient population and study methods (Eble and Warfel, 1991; Grignon and Eble, 1998). These tumors occur more commonly in kidneys scarred from renal vascular disease (Budin and McDonnell, 1984) or in smokers (Xipell, 1971; Bennington, 1973). These lesions also frequently develop in patients on long-term dialysis and have been observed in up to 33% of patients with acquired renal cystic disease (Hughson et al., 1986). However, the classification of these tumors by size alone fails to predict metastatic potential. The current data support the definition of papillary adenoma in the set of three criteria mentioned in the introduction. However, Ligato et al. (1999) added to these criteria a new feature, namely, that these tumors must have morphology similar to low grade papillary renal cell carcinoma. However, not all authors are in agreement about the presence of this feature (Delahunt and Eble, 1997a,b; Grignon and Eble, 1998). Furthermore, Brooks et al. (1993) observed no difference in nuclear volume between small papillary neoplasms and large and more aggressive ones. Kovacs (1994), in an alternative approach, suggested that cytogenetic study could be used to classify renal epithelial tumors. In this scheme, papillary adenoma was defined by the finding of cytogenetic abnormalities limited to +7, +17, and -Y. The presence of additional trisomies may indicate malignant biological potential and, therefore, may characterize papillary renal cell carcinoma. However, this attractive hypothesis should be validated with a series of cases. In our series the incidence of RPAs was 11.2% of the autopsies and 5.7% of the autopsied patients. These tumors were more commonly observed in males and in kidneys with moderate and severe renal vascular disease. Thus, 74.1% of the RPAs were associated to grades 2-3 of ARVD. In our study we omitted oncocytoma, solid tumors, and papillary (chromophilic) tumors of more than 5 mm, which were included in other series. All RPAs were in the cortex.

RPA is considered a non-mucin producing tumor. However, in this study we have demonstrated that this neoplasm can produce cytoplasmic, luminal, or both mucin in location. The mucin was acid in type as indicated by MMC, AB, or MCI positivity. On the other hand, sulphomucin production was ruled out by negativity of the HID staining method in the tumors. In addition to acid mucin, case 3 also showed neutral mucin. Therefore, luminal or intracytoplasmic acid mucin, despite its low frequency, can be considered as one additional feature of RPA. We have also described mucin secretion in the papillary renal cell carcinoma (Val-Bernal et al., 1999). Thus, mucin production suggests that RPA and papillary renal cell carcinoma are actually not two independent biological processes, but a continuum of one biological process. An arbitrary dividing line has been chosen below which the diagnosis of carcinoma would not be rendered. Thus, the limit of 5 mm has been considered for the diagnosis of RPA because such small benign cortical nodules have never been reported to metastasize (Delahunt and Eble, 1997a,b; Grignon and Eble, 1998). This practical solution to a clinical problem should be in permanent revision in the case of donor acceptability. In contrast to individuals with normal immune systems, the small RPAs can be transmitted to organ transplant recipients due to their requisite immune suppression. In theory, tumors in this environment could show progression. In concordance with this idea, recently, the first case of a renal cell carcinoma of the papillary type arising from a donor kidney in a transplant patient has been reported (Niranjan et al., 1999). Therefore, careful examination of donor kidneys prior to transplantation should be a standard of care for transplant recipients.

Mucinous secretion in both papillary adenoma and carcinoma can be ascribed to modulation or direct metaplasia of the neoplastic epithelium (Val-Bernal et al., 1999). Aberrant gene activation may induce this mucin production by the tumors.

We support the viewpoint that papillary renal cell tumors form a continuum and that mucin production in these tumors is independent of macroscopic size. It is remarkable that mucin-secreting tumors are of low nuclear grade.

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