Incidentally detected renal adenomatosis in a patient with urolithiasis: a case report

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ABSTRACT

A renal epithelial tumor with a papillary or tubulopapillary pattern and a low nuclear grade is defined as a renal adenoma if its diameter is 5 mm or less. Two important issues related to the renal adenoma are the lack of exact criteria for the histopathological differentiation from a papillary renal cell carcinoma and the lack of consensus as to whether it is a precancerous lesion. Renal adenomatosis is very rarely seen entity entity characterized by multiple and usually bilateral adenomas. Innumerable adenomas, adenomatous transformations within a single tubule and adenomas measuring 7 mm or less, were detected in a 47-year-old man who underwent simple nephrectomy due to nonfunctional hydronephrosis secondary to urolithiasis. In this paper, our diagnostic approach to this fairly rare entity is discussed along with a brief literature review.

Key words: AMACR; papillary renal cell carcinoma; renal adenomatosis; renal papillary adenoma.

Introduction

Benign tumors of the renal tubular epithelial origin are called renal adenomas. Based on their histomorphological characteristics they are classified as papillary or papillary adenoma, oncocytoma, and metanephric adenoma.^[1-3] In our article the term renal adenoma was used for papillary/tubulopapillary adenomas.

In the latest classification published by World Health Organization (WHO) in 2004, renal adenoma was defined as epithelial tumors smaller than 5 mm in diameter containing tubulopapillary structures with low-nuclear grade.^[1] As understood from this definition, the only discriminative criterion between low-nuclear grade papillary renal cell carcinoma (RCC), and adenoma is the diameter of the tumor.

In our case report, we have presented an incidentally detected case with renal adenomatosis without chronic renal failure, and history of hemodialysis who had undergone simple nephrectomy with the indication of urolithiasis. While presenting this rarely seen case, we planned to discuss two issues which came up to our minds: (1) How the lesions with a diameter of >5 mm should be reported? and

(2) Are micro-and/or macroadenomatous foci precancerous lesions for papillary RCC?

Case presentation

A 47-year-old male patient presented with complaints of left flank pain with a sudden onset starting two days ago, and inadequate urine output. From his medical history, it was learnt that he had passed a renal stone 10 years ago. His vital signs were not remarkable on physical examination. Tenderness on the region over the left costovertebral angle was detected on palpation, and percussion. Urinalysis revealed 1-2 WBCs, and 4-5 RBCs. On hematological examination his hemoglobin value was 10 g/dL, and WBC was 10.500/mm³. Serum creatinine level was 7.79 mg/dL idi. Urinary system US demonstrated grade IV hydronephrosis in the right kidney, a stone with a diameter of nearly 3 cm in the ureteropelvic junction, grade 1 hydronephrosis in the left kidney, and three stones with diameters ranging between 6, and 10 mm in the upper, and middle calyces of the left kidney. On multisliced upper, and lower abdominal computed tomograms, also a midureter stone with a diameter of 9 mm was detected. Renal parenchyma could not be evaluated optimally

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using non-contrasted CT, and a discrete lesion in both kidneys could not be identified. A DJ catheter was implanted in the left ureter. Following drop in the serum creatinine level down to 1.1 mg/dL, ureteroscopic lithotripsy was performed for the left midureteral stone. Renal nuclear scanning performed at that time revealed a nonfunctional right kidney. Then the right kidney was removed with simple nephrectomy. For stones in the upper, and middle calyces of the left kidney extracorporeal shock wave lithotripsy was planned.

He had passed stones previously, and he was still smoking 1 pack /day for 30 years. His family history was unremarkable.

Macroscopic examination: Nephrectomized right kidney specimen (14 x 8 x 3.5 cm) with a 6 cm-long ureteral segment with a diameter of 0.3-1 cm was opened, and stones, the largest one being 1.5 cm in diameter were seen both in the ureter, and pelvicaliceal region. Pelvicaliceal system was apparently enlarged at the risk of renal parenchyma, and parenchyma was partly thinned up to 2 mm. Numerous yellow-creamy colored solid nodules, the biggest one being 7 mm in diameter, struck our attention (Figure 1).

Histopathological examination: In addition to end-stage renal damage characterized by tubular atrophy, glomerulosclerosis, interstitial fibrosis, and inflammation, we detected greater number of adenomas than found in macroscopic examination. Adenomas consisted of cells with oval, and notched nuclei, and partially eosinophilic cytoplasm arranged in a papillary or tubulopapillary pattern (Figure 2). Some foci demonstrated adenomatous alterations involving only a single tubulus (Figure 2). Immunohistochemically, adenomatous foci positively stained with alpha-methyacyl-coenzyme A racemase (AMACR) (Clone 13H4, ThermoScientific, CA, USA), and cytokeratine 7 (Clone OV-TL12/30, Neomarkers, CA, USA) (Figure 3). Ki 67 (Clone SP6, Spring, CA, US) proliferation index was found to be decreased in the adenoma with the greatest diameter.

Discussion

Definition of renal adenoma which focused on criteria of diameter has been changed frequently over the years. Because of their lower risk of metastasis, for years tumors smaller than 3 cm have been accepted as adenomas, while after the second half of the 80's, nuclear grade I tumors smaller than 1 cm in diameter have been defined as adenomas.^[2-5]

In 1998, cut-off value for diameter criteria was lowered to 5 mm.^[2] Some authors recommended reporting of lesions with a diameter ranging between 5-20 mm as "papillary epithelial tumor with low malignant potential".^[1] Every tumor unavoidably is in a lower stage, before reaching its final size. Therefore, as seen in

Figure 1. (a) Marked thinning of renal parenchyma of the hydronephrotic kidney. (b) Solid intraparenchymal nodules which can be detected during macroscopic examination

our case, the following issue needs to be clarified " Is adenoma with a diameter greater than 5 mm detected in its early stage, a papillary renal cell microcarcinoma or can renal adenomas reach larger dimensions as oncocytomas? As literature reviews indicate, both possibilities appears to be valid assumptions.

Generally, it seems more appropriate to estimate demographic data of the patients with renal adenomas detected in speci-

Figure 2. (a) Adenomatous transformation in a single tubulus (it can be accepted as a hyperplastic lesion) (arrow) (x 400). (b) Two distinct adenomas with tubular and papillary pattern (arrows) (x 40). (c) renal papillary adenoma (x 100) (hematoxylin-eosin staining)

Figure 3. AMACR (+) tumor which infiltrated outside its capsule (x 40) (histochemical staining)

mens of nephrectomy performed for various reasons, based on autopsy series. Besides, if variations in the definition of adenomas within years are taken into consideration, use of data obtained in previous years can be misleading. Subcortical solitary renal adenoma is considered to be the most frequently encountered renal epithelial tumor. However its incidence varies in different series (0.26-22.4%).^[3,6] Though it can be observed in every age group, it can be detected in 10, and 40% of the patients younger than 40 or older than 70 years of age, respectively. In other words, its incidence increases with age.^[11] Presence of multiple adenomas (≥ 5) is termed 'renal adenomatosis' which is seen quite rarely.^[6] This term is firstly used by Syrjanen in 1979.^[7] Very scarce number of cases have

been reportedly associated with dialysis-related acquired renal cystic disease (ARCC) or chronic renal damage (Table 1).^[8-10] In our case adenomatosis developed on the ground of marked hydronephrosis, and chronic renal damage secondary to urolithiasis. Since functionality of the contralateral kidney was preserved, chronic renal failure did not develop, and thus the patient did not require dialysis therapy.

Histomorphologically, adenoma contains various amounts of tubuli, and papillary structures. These structures are lined with cuboid epithelium with scarce amounts of cytoplasm. They have oval nuclei with conspicuous notched contours. They don't contain nucleoli. These histomorphological findings resemble very closely to those of type 1 papillary RCC. In our case, all macro-, and microfoci we observed had the same morphology. The largest of these foci measured 7 mm in diameter, and nuclear atypia was not observed. Although occasional presence of mitosis attracted our attention, Ki67 proliferation index was very low. In the literature, because of absence of clear-cut histopathological criteria excluding diameter of the lesion, we confronted difficulties in the decision-making process for the pathological diagnosis between renal adenomatosis or papillary renal cell microcarcinoma on the ground of renal adenomatosis.

The potential role of immunohistochemical analysis in differential diagnosis has been also investigated, and common staining properties of papillary RCC, and renal adenomas have been revealed. AMACR is an enzyme found in mitochondria of normal tubular epithelial cells. Immunohistochemically, higher sensitivity, and specificity of AMACR positivity for papillary RCC has been indicated.^[11] Wang et al.^[3] stated that strong AMACR positivity was observed both in papillary RCC, and concomitant adenomas, while adenomas associated with ARCC were AMACR -negative which suggests that AMACR positivity might be an early sign representing carcinomatous transformation.

Table 1. Some cases with renal adenomatosis cited in the literature

Authors	Age Gender	Number of adenomas	Malignant tumor, and its diameter (cm)*		Concomitant tumor/ tumor-like lesions	Underlying pathology
Syrjanen	72 M	>100	-	-	-	-
Passegga et al.	25 M	Numerous	Papillary RCC (multifocal +bilateral)	1	-	Polycystic kidney
Ganzen et al.**	24?	>60	?	?	?	UPJ obstruction + Hydronephrosis
Spence et al.	33 M	Numerous	Papillary RCC microcarcinoma	0.7	-	UPJ obstruction + Hydronephrosis
Kizaki et al.	49 M	108	RCC	1.3	-	Invasive urothelial carcinoma of the ureter
Kiyoshima et al.	46 M	Numerous	Papillary RCC (multifocal +bilateral)	3.3	Clear cell RCC	-
Wang et al.	54 M	8	Papillary RCC	1.7	-	-
	66 M	7	Papillary RCC	2.0	-	-
	64 M	5	Papillary RCC	2.2	-	-
	34 M	10	Papillary RCC (multifocal +bilateral)	22	-	-
	64 M	9	Papillary RCC	2.6	-	-
Menendez et al.	76 F	Numerous	Papillary RCC microcarcinoma	1.0	Oncocytomatosis and oncocytoma	ARCD+CGN
Mazzucchelli et al.	74 M	Numerous	Papillary RCC microcarcinoma	<1	Oncocytomatosis and oncocytoma	ARCD +DN
Our case	47 M	Numerous	-	-	-	Urolithiasis + hydronephrosis

*If multiple the diameter of the biggest tumor, **Only abstract of the article was available. RCC: renal cell carcinoma; UPJ: ureteropelvic junction; ARCD: acquired renal cystic disease; CGN: crescentic glomerulonephritis; DN: diabetic nephropathy

Tickoo et al.^[12] also detected AMACR positivity in adenomas associated with carcinomas in the presence of end-stage renal damage. We detected AMACR positivity in almost all adenomatous foci. Therefore, we think that positivity of this molecule is not adequate *per se* to indicate the presence of carcinomatous transformation. Because of lack of some additional findings such as nuclear atypia, and solid areas defined by Kiyoshima et al.^[6] which might substantiate the diagnosis of carcinoma, we thought that the lesion with the greatest diameter might be accepted as a representative of adenoma. Therefore we spoke with the attending clinician, and expressed our opinion that it would be appropriate for us to accept the lesion with the greatest diameter as adenoma.

Etiology, and pathogenesis of renal adenomatosis are not known precisely. Even though its pathogenic mechanism is not known, end-stage renal disease carries a distinct, and increased risk of development of renal adenoma, and RCC when compared with the normal population.^[15] In a retrospective study where Tickoo et al.^[12] analyzed renal tumors associated with end-stage renal disease, and found papillary RCC, and adenoma as the most frequently associated tumors. In their series, tumors were small (mean diameter of 2.6 cm), multifocal (54.5%), and 26.9%

of them demonstrated bilateral development concurrently or within years. In a retrospective study, Wang et al.^[3] re-evaluated 542 nephrectomy specimens, and detected 38 (7%) papillary adenomas. These papillary adenomas were found in association with papillary RCC (n=18), ARCD (n=7), clear-cell RCC, chromophobe type RCC (n=3), end-stage renal disease (n=2), oncocytoma (n=1), angiomyolipoma (n=1), and renal schwannoma (n=1). In the abovementioned series, it is noteworthy that cases with papillary RCC were more frequently associated with adenomatosis rather than solitary adenomas, and also these cases with papillary RCC generally tended to be smaller, multifocal or even bilateral. Another important point is that without underlying renal damage, sporadic cases of adenomatosis associated with genetic anomalies can be seen. Otherwise, association between adenomatosis, and papillary RCC have been mentioned in case reports.^[4,6-10,13] In some of these reports, concomitancy of oncocytic lesions has been also indicated.^[9,10] Adenoma, and papillary RCC also share some common genetic anomalies.^[14] In carcinomas some mutations have been presumably added to these anomalies. However detection of much lesser number of mutations in some carcinomas contradicts this observation.^[11,15] Currently available genetic data fail to disclose the pathogenic mechanism of transformation from adenoma to carcinoma,

which will aid in differential diagnosis. Briefly, because of higher rates of concomitancy, multifocality, histological, and immunohistochemical similarities, and common genetic anomalies, some authors have indicated that adenomatosis, and papillary RCC might be an outcome of a common biological process, and adenomas can be considered as precancerous lesions.^[3-6]

In conclusion, rarely seen renal adenomatosis can develop on the ground of hydronephrosis secondary to urolithiasis. Clinical monitorization of the lesions larger than 5 mm in diameter just like low-grade papillary RCC seems to be appropriate for these tumors with variable reporting criteria. Though its pathogenesis has not been clarified up to now, whether it develops on the ground of chronic renal damage secondary to various etiological factors or not is not known. However, available literature tends to accept renal adenomatosis as a precancerous lesion of the papillary RCC.

Conflict of Interest: No conflict of interest was declared by the authors.

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