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Case Report

Primary renal glomus tumor with concurrent papillary renal cell carcinoma and multiple papillary adenomas in a patient with end stage renal disease: a case report and clinicopathologic analysis

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Abstract: Glomus tumors are mesenchymal tumors commonly seen in the extremities, and rarely seen in deep visceral organs. This is due to the lack of glomus bodies in visceral organs. Here, we describe an unusual association between glomus tumor and co-existing papillary renal cell carcinoma, multiple papillary adenomas, and end stage renal disease. We discuss our diagnostic approach and differential diagnoses, along with an extensive review of all reported benign and malignant primary glomus tumors. A 63-year-old male with a known history of a kidney transplant, end-stage renal disease, and previous nephrectomy of his right kidney due to a renal mass (papillary renal cell carcinoma) presented with a renal mass. Microscopic examination showed papillary carcinoma, multiple papillary adenomas, and a small nodule with uniform, round to oval cells. Immunohistochemical work-up revealed the small nodule to be a glomus tumor. Only 28 cases of primary renal glomus tumors have been reported in the literature. Most were discovered incidentally. None of the reported cases have occurred along with other renal tumors. This is the first case of the unusual combination of primary renal glomus tumor arising in the native kidney of a renal transplant patient with concurrent papillary renal cell carcinoma and multiple papillary adenomas (renal adenomatosis). We also explore the possible genetic basis behind this association.

Keywords: Primary renal glomus tumor, renal adenomatosis, papillary renal cell carcinoma, case report

Introduction

Glomus tumor is a mesenchymal neoplasm that arises from a modified smooth muscle cell that is located in the walls of the Sucquet-Hoyer canal involved in temperature regulation in the extremities [1]. Glomus tumors are rare, accounting for <2% of soft tissue tumors, with most cases occurring in young adults. Considering the cell of origin, the most common site of these tumors is the extremities, particularly the hands, where they occur as digital and subungual lesions. They are rarely seen in deep seated organs, such as stomach [2], trachea, female genital tract, lungs, and kidney [1, 3]. Consequently, while there are defined criteria for ascertaining benign or malignant nature of these tumors in the extremities, there is a need for further study of glomus tumor in deep visceral organs. Even among visceral organs, the kidney is an unusual site of occurrence, with only 28 cases of primary renal glomus tumors been described in the literature. We encountered a unique case of a primary renal glomus cell tumor that posed significant diagnostic difficulty because of glomus tumor being an uncommon tumor at this site. While we arrived at the diagnosis with the help of adjunctive immunostains, we were curious whether glomus tumors of the kidney, in particular, have any unique or characteristic features. This prompted us to conduct a thorough review of literature of all reported benign and malignant glomus tumors arising in the kidney, with respect to their clinical and histologic findings and follow-up data, wherever available. No cases, however, have been reported with coexisting renal carcinoma and papillary adenomas,

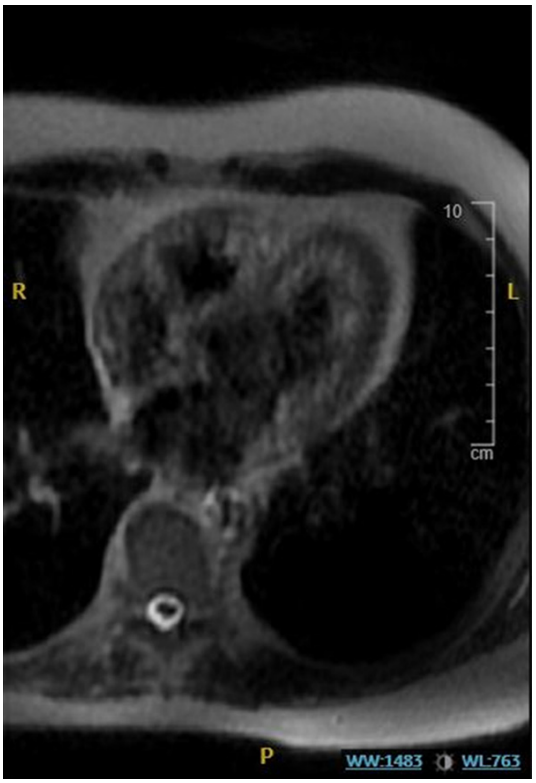

Figure 1. MRI abdomen showing a 2.4 cm left renal exophytic lesion, with the radiological impression, concerning for renal cell carcinoma.

as seen in this case. Papillary adenomas are unencapsulated tumors with a papillary, tubular, or tubulopapillary configurations of low histologic grade and a diameter of ≤15 mm. They can be seen in kidneys with RCCs, being common in kidneys of patients with hereditary papillary RCC. Papillary RCCs are the second most commonly encountered renal cell carcinoma, accounting for 18% of RCCs [4]. The incidence of RCC is 3-24 times higher in patients with end stage renal disease (ESRD), with papillary carcinomas, in particular, being more common in ESRD versus non-ESRD patients [5]. This case is unique as the glomus tumor occurred concurrently with papillary renal cell carcinoma with papillary adenomatosis in end stage kidney disease. We also found interesting aspects of glomus tumors occurring in the kidney as against their soft tissue counterparts as described in the following sections.

Case presentation

A 63-year-old male with a known history of a kidney transplant, end-stage renal disease, and previous nephrectomy of his right kidney due to a renal mass (papillary renal cell carcinoma, 7 years ago) presented with an enhancing and enlarging renal mass in the left kidney. The patient also had a past medical history of papillary thyroid carcinoma and follicular adenoma, necessitating a thyroidectomy 3 years prior. MRI abdomen showed a slowly growing, now 2.4 cm left renal exophytic lesion (2.1 cm, 3 months ago) worrisome for renal cell carcinoma (**Figure 1**). The patient underwent a left laparoscopic radical nephrectomy. Grossly, the kidney measured 23.4×10.7×9.2 cm and revealed a well-circumscribed tan-white soft mass measuring 2.8×2.5×2.4 cm located at the midpolar region of the kidney. Additionally, multiple tan-white well-circumscribed soft nodules were also noted in the cortex and renal sinus fat ranging from 0.1-1.2 cm in greatest dimension.

Microscopic examination of the mass showed type 1 papillary renal cell carcinoma, WHO/ISUP nuclear grade 2 (**Figure 5B**). Many papillary adenomas were also seen varying in size from 0.1-1.2 cm (**Figures 4** and **5A**). Another, well circumscribed cellular nodule, measuring 0.7 cm was observed that was distinct from the papillary adenomas. The lesion comprised small, uniform round to oval cells arranged in lobules and clusters. The tumor cells showed well defined cell borders, moderate amount of pale eosinophilic to clear cytoplasm with small, round nuclei with indistinct nucleoli, without atypia (**Figures 2** and **4A**). The tumor cells in the smaller nodule were positive for SMA, vimentin (focal), and negative for AE1/AE3, CAM5.2, PAX8, CD10, CAIX, CK7, p504s, desmin, S-100, CD34, CD31, HMB45, Melan A, inhibin, calretinin, and WT-1 (**Figure 3**). Ki67 stain was low (<1%). The morphology and immunostaining suggested glomus tumor.

A final diagnosis of papillary renal cell carcinoma with papillary adenomas and glomus tumor was rendered. The patient is alive and free from disease 12 months after the surgery.

Discussion

Glomus tumors are part of the spectrum of pericytic tumors of the kidney. In the largest study conducted on renal pericytic tumors [3], 11 out of 17 pericytic tumors were diagnosed as glomus tumor, and one as an atypical glomus tumor. In this study, necrosis, moderate

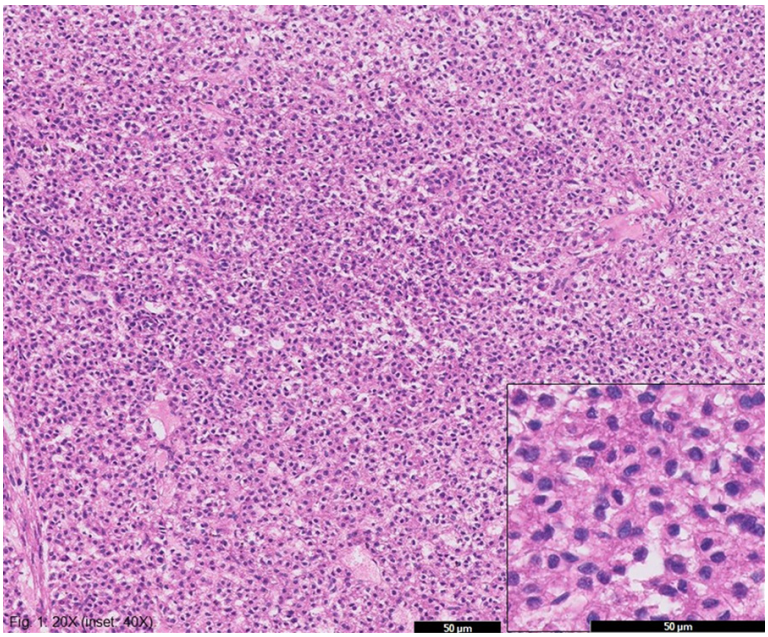

Figure 2. Uniform, round to oval cells arranged in lobules and clusters. Inset shows tumor cells with well-defined cell borders, moderate amount of pale eosinophilic to clear cytoplasm with small, round nuclei with indistinct nucleoli, without atypia. (H&E, 20X, inset: 40X).

cellular atypia and perinephric extension were considered as atypical features. In soft tissues, a diagnosis of malignant glomus tumor requires the presence of marked nuclear atypia or atypical mitosis. Even though the WHO classification of soft tissues [6] considers tumors >2 cm and in a deep location as having "uncertain malignant potential", the applicability of these criteria to renal glomus tumors is uncertain, as noted by Sirohi et al [3]. In our case, the tumor was small (less than 1 cm) and the tumor cells lacked any atypia or necrosis, consistent with a benign diagnosis. The patient had hypertension, as observed in the majority of tumors of pericytic origin [3].

With the morphologic finding of a tumor composed of uniform, small round to oval cells, we considered a differential diagnosis of metanephric adenoma, juxtaglomerular cell tumor, solitary fibrous tumor, or epithelioid angiomyolipoma. Metanephric adenomas are cellular tumors composed of cells with scant cytoplasm, arranged in tightly packed tubules, with abortive glomeruli. The cytologic features of this tumor were reminiscent of metanephric adenoma cells, but we did not see a tubular or glomerular arrangement of cells. Additionally, the tumor cells were negative for WT1, thus ruling out the possibility of a metanephric adenoma. A possibility of a juxtaglomerular cell tumor (JGCT) was also considered. The patient had a history of longstanding hypertension. However, there was no history of hypokalemia and the hypertension did not subside post-surgery. Additionally, the tumor cells were negative for CD34. Thus, a JGCT was ruled out. The absence of staining for CD34 also ruled out the possibility of a solitary fibrous tumor. Lack of staining for HMB45 and Melan A ruled out an angiomyolipoma.

We conducted a thorough search of the literature and identified a total of 28 cases of primary glomus tumors of the kidney (**Table 1**). Of these, 16 were primary benign glomus cell tumors [7-21], 5 were glomangiomas [11, 20, 22, 23], and one was symplastic glomus tumor [20]. There were 3 cases of glomus tumors of uncertain malignant potential [24-26], of which one was classified as an infiltrating glomus tumor of uncertain malignant potential [24]. Three cases of malignant glomus tumors were identified [25, 27, 28]. Glomangioma is a variant of glomus tumor that features dilated vascular spaces. One tumor with marked nuclear atypia but with no mitoses was classified as a symplastic tumor, similar to the criteria used in soft tissue. Of the three tumors classified as glomus tumors of uncertain malignant potential, two were classified as such on the basis of their deep location, infiltrative margins, and increased mitotic activity. One tumor focally invaded into the capsule and showed extension into the renal vein [25], but due to the lack of definitive metastasis, was designated as a glomus tumor with uncertain malignant potential. There are no established criteria for defining malignancy in glomus tumors of the kidney. But, from our review of the cases described in literature, metastasis is considered the only true defining feature of malignancy. All

Table 1. Summary of clinicopathologic characteristics of glomus tumors reported in the literature

Case No.	Author (Year)	Age/Sex	Site	Presentation	Size (cm)	Clinical history	Diagnosis	Other renal tumors/condition	IHC stains (+)	Procedure	Follow-up
1	Schwarz [7] (1957)	34/F	-	Flank pain	-	Pregnant	Glomus tumor, benign	None	-	-	-
2	Billard [8] (1991)	-	-	-	-	-	Glomus tumor, benign	-	-	-	-
3	Herawi [9] (2005)	53/F	R ureteropelvic junction	Flank discomfort, microscopic hematuria	2.5	-	Glomus tumor, benign	Hydronephrosis, non-functioning kidney with atrophy of parenchyma	SMA, Calp, Col IV	RN	Alive with no recurrence/ metastasis (6 months)
4	Siddiqui [10] (2005)	55/F	Lower pole	Incidental	2	GERD	Glomus tumor, benign	None	SMA, Vim	PN	-
5	Al-Ahmadie [11] (2007)	36/M	Interpolar region	Abdominal tenderness	3.3	None	Glomus tumor, benign	None	SMA, Lam,CD31, CD34	PN	Alive with no recurrence/ metastasis (62 months)
6		81/M	Lower pole	Renal mass	4	Prostate Carcinoma	Glomangioma, benign	None		TN	Alive with no recurrence/ metastasis (24 months)
7		48/M	Midpole	Renal mass	7.3	C/L renal cyst	Glomangioma, benign	None		TN	Alive with no recurrence/ metastasis (33 months)
8	Gill [24] (2010)	46/M	Lower pole	Hematuria	8.7	Hypertension, α-Thalassemia	Infiltrating glomus tumor of uncertain malignant potential	None	SMA, MSA, Vim, Ki67=10%	RN	Alive with no recurrence/ metastasis (15 months)
9	Nuwayhid [12] (2010)	17/M	Upper pole	Incidental	2.1	Hypertension, UC	Glomus tumor, benign	None	SMA, WT-1, h-Cald	PN	Alive with no recurrence/ metastasis (unknown follow-up)
10	Sugimoto [13] (2010)	41/M	-	Incidental	1.1	Leukoderma	Glomus tumor, benign	None	SMA, Vim, CD34	PN	-
11	Lamba [27] (2010)	44/M	Upper pole	Low back pain, due to osseus metastasis	-	Hypertension, gout, DM, dyslipidemia	Malignant glomus tumor	None	SMA, Vim, CD34, Col IV	CT, RT	Died within 6 months of diagnosis
12	Onishi [14] (2010)	36/F	Upper pole	Incidental	1.7	Proteinuria	Glomus tumor, benign	Hypoplastic kidney	SMA, Vim	RN	Alive with no recurrence/ metastasis (8 months)
13	Sasaki [15] (2011)	62/M	Lower pole	Incidental	1.8	Unexplained weight loss, anorexia	Glomus tumor, benign	None	SMA, Vim, CD 57, Col IV, weak synapto, desmin	PN	Alive with no recurrence/ metastasis (2 months)
14	Venyo [22] (2012)	32/M	Lower pole	Epigastric pain	3.5	None	Glomangioma, benign	-	Vim, SMA, Calret, h-Cald, patchy CD56, CD34, Col IV	PN	Alive with no recurrence/ metastasis (20 months)
15	Gravet [16] (2015)	60/M	Upper pole	Incidental	2.5	-	Glomus tumor, benign	-	SMA, Vim	-	Alive with no recurrence/ metastasis (8 months)
16	Lazor [17] (2016)	68/M	Interpolar region	Incidental	1.7	High grade T1 bladder cancer s/p BCG	Glomus tumor, benign	-	SMA, CD34 in capillaries	PN	Alive with no recurrence/ metastasis (7 months)
17	Lu [28], Chen [30] (2017)	46/M	Upper pole	Incidental	43.7	Nasopharyngeal carcinoma, s/p chemo	Malignant glomus tumor	-	-	RN	Alive with no recurrence (6 months)

18	Novis[18] (2018)	66/M	Upper pole	Incidental	5	Asthma, urticaria	Glomus tumor, benign	-	SMA, GATA 3	RN	-
19	Li [25] (2018)	31/F	-	Gross hematuria, flank pain	16	-	Malignant glomus tumor	-	Col IV, Vim	RN	Metastasis-C/L kidney at 7 years; Metastasis-L kidney remnant, Spleen, R gluteal muscle, brain at 9 years; Death from metastatic disease at 13 years
20		33/F	Extending into IVC, involving TV	Incidental during evaluation of heart murmur	9.5	Heart murmur	Glomus tumor of uncertain malignant potential	-	SMA, focal Vim	TN	-
21		55/M	-	Microscopic hematuria	1.5	-	Glomangioma	-	SMA, h-Cald in peripheral cells, Col IV	NSN	-
22	Dee [19] (2018)	49/F	-	Abdominal discomfort	4	-	Glomus tumor, benign	-	SMA, Vim, CD34	TN	Alive with no recurrence/ metastasis (6 months)
23-26	Zhao [20] (2018)	Ages 37-66: M=2, F=2	-	-	3-4	Hypertension (3/4 cases)	Glomus tumor, benign Glomus tumor, benign Glomangioma, benign Symplastic glomus tumor	-	SMA, h-Cald, MSA, Calp, Col IV (3/4 cases), CD34	-	Alive with no recurrence/ metastasis (6-64 months)
27	Almaghrabi [21] (2018)	57/M	Upper pole	Abdominal discomfort	2	-	Glomus tumor, benign	-	SMA, Vim, Col IV	PN	Alive with no recurrence/ metastasis (12 months)
28	Zhao [26] (2019)	8/F	Upper pole	Incidental	5	Tuberous sclerosis (hypermelanotic macules, cardiac rhabdomyoma, subependymal nodules, B/L renal cysts, epileptic seizures	Glomus tumor of uncertain malignant potential	-	SMA, Vim, Col IV	PN	Alive with no recurrence/ metastasis (16 months)
29	This case (2022)	63/M	Interpolar region	Incidental	0.7		Glomus tumor, benign	ESRD, Kidney transplant, history of RCC, Type 1 papillary RCC in remaining native kidney, papillary adenomas (multiple)	SMA, Vim (focal)	RN	Alive with no recurrence/ metastasis (15 months)

Abbreviations: SMA: smooth muscle actin, Calp: Calponin, Col IV: Collagen type IV, RN: radical nephrectomy, GERD: gastroesophageal reflux disease, Vim: vimentin, PN: partial nephrectomy, Lam: Laminin, TN: total nephrectomy, C/L: contralateral, MSA: muscle specific actin, UC: ulcerative colitis, WT-1: Wilms tumor antigen-1, h-Cald: h-caldesmon, DM: diabetes mellitus, CT: chemotherapy, RT: radiotherapy, Synapto: Synaptophysin, Calret: calretinin, s/p: status post, IVC: inferior vena cava, TV: tricuspid valve, NSN: nerve sparing nephrectomy, B/L: bilateral, ESRD: end stage renal disease, RCC: renal cell carcinoma.

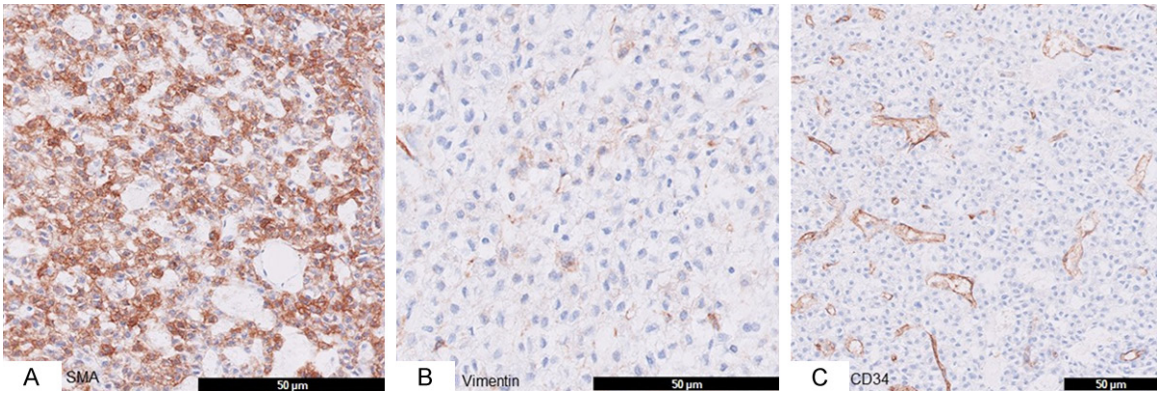

Figure 3. Immunohistochemical panel showing tumor cells staining positively with SMA (A), patchy Vimentin (B). CD34 is negative (C), staining only the interspersed blood vessels.

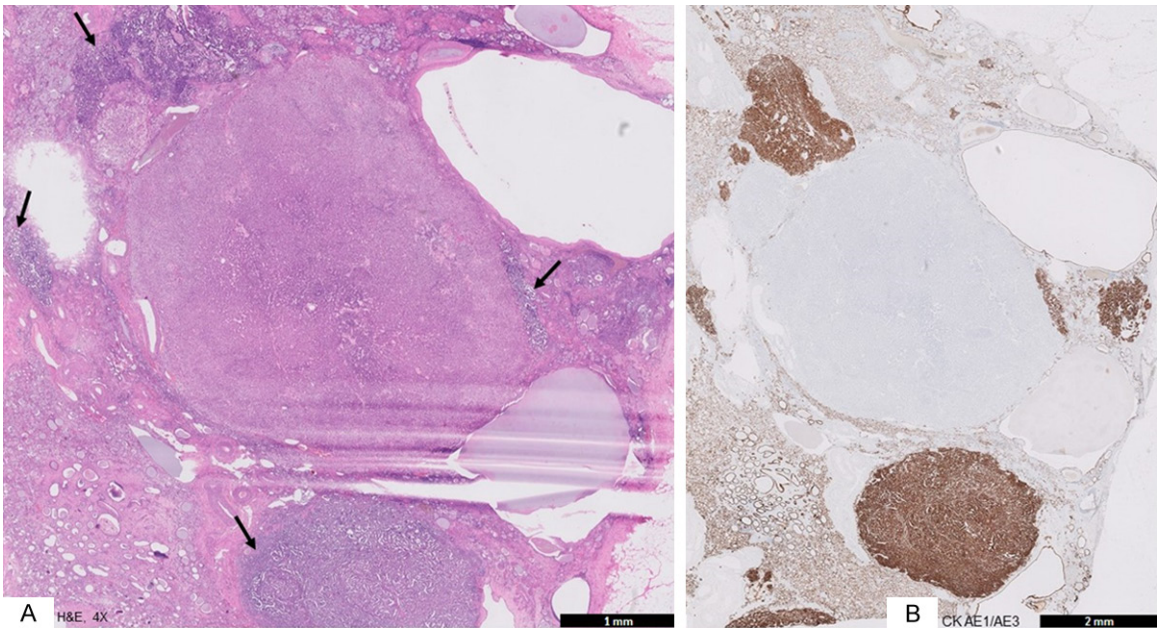

Figure 4. Morphological findings in glomus tumor. A: H&E image showing central glomus tumor with adjacent multiple, smaller papillary adenomas (black solid arrows) (4X). B: IHC image showing papillary adenomas staining positive for CKAE1/AE3 with CK-negative glomus tumor in the center (2X).

three malignant cases had the presence of metastasis.

Out of the 16 primary benign glomus tumors, 11 patients were men and 5 were women. Two of the three cases of tumors with uncertain malignant potential were seen in women, while all three malignant glomus tumors were seen in men. 5 cases of benign glomus tumor occurred in the upper pole of kidney, 2 in the lower pole, 2 in the interpolar/mid pole region, and one at the ureteropelvic junction. There was no significant difference in the clinical presentation of benign glomus tumors, glomangiomas, glomus tumors of uncertain malignant potential, or malignant glomus tumors. 9 cases of benign glomus tumors were incidentally detected, and 5 presented with abdominal discomfort, of which one also had microscopic hematuria that may also be attributable to the underlying chronic kidney disease in this patient. 2 cases of glomangioma presented with an abdominal mass, and one had abdominal discomfort. One case of glomangiomyoma presented with microscopic hematuria without underlying kidney disease. Of the three tumors of uncertain malignant potential, two were incidentally detected, and one presented with hematuria.

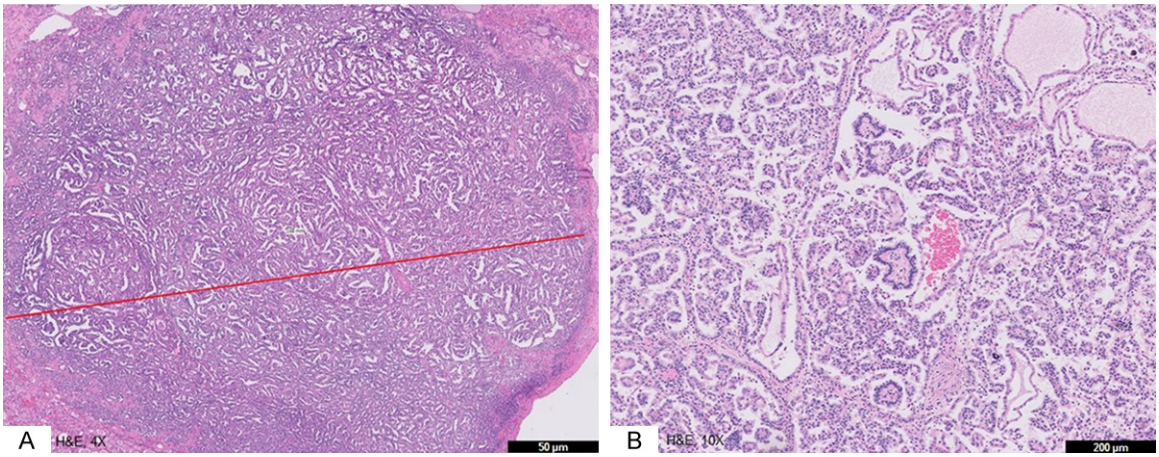

Figure 5. Concomitant papillary adenomas and papillary carcinoma. A: H&E image showing low power view of one of the papillary adenomas (red measurement line tool shows maximum dimension of 3.6 mm) (4X). B: H&E image showing papillary arrangement of tumor cells with ISUP grade 2 nuclei (10X) in papillary renal cell carcinoma.

With malignant glomus tumors as well, a similar clinical presentation was observed, with one tumor being detected incidentally, one presenting with back pain, and one with gross hematuria. Thus, no specific clinical presentation was associated with malignancy or uncertain malignant potential.

The size of benign glomus tumors ranged from 0.7 cm (our case) to 5 cm. Three tumors with uncertain malignant potential had sizes of 5 cm, 8.7 cm, and 9.5 cm. Malignant tumors were larger with sizes of 16 cm and 43.5 cm (largest dimension). 22 out of 25 cases in which information about immunostains was available, showed positive staining for SMA, with no difference in staining pattern for glomus tumors with malignant potential and malignant glomus tumors. Seven cases reported positive staining for type IV collagen. This lower number could be attributable to the lack of wide availability of this marker.

The surrounding kidney was unremarkable in all but 3 cases. Two cases (including our case) showed existing chronic kidney disease [9] while was one was seen in a hypoplastic kidney [14]. Additionally, in our case, the patient had a papillary renal cell carcinomas and multiple papillary adenomas, which makes our case unique.

All benign glomus tumors, and tumors of uncertain malignant potential, showed a good outcome with no recurrence (with a variable follow-up period ranging from 2 months to 64 months). However, two of the three patients with malignant glomus tumors succumbed to the disease at 6 months and 9 years after diagnosis.

Conclusion

This case is unique, as glomus tumor of the kidney has not been reported in the setting of end stage renal disease with concurrent papillary renal carcinoma and papillary adenomas. Of note, papillary tumor of the kidney show loss of chromosome 1p among other such genetic changes. Familial forms of glomus tumors also inactivating mutations of the G*lomulin* (*GLMN*) gene, located on chromosome 1p21-22 [29]. Conjecturally, there may be a common genetic defect leading to the multiple tumors seen in this kidney.

Disclosure of conflict of interest

None.

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