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Original Article

Glomerular sparing pattern in primary kidney neoplasms: clinical, morphological and immunohistochemical study

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Abstract: Glomerular sparing (GS) is defined as a unique growth pattern in which tumor cells replace the majority of renal tubes and overrun intact glomeruli. This phenomenon has been well recognized by pathologists as a typical infiltrative pattern and some studies suggested it was an independent risk factor. Here, we study the clinical, pathological, and immunohistochemical features of primary kidney neoplasms with glomerular sparing pattern. We searched the archives of our pathology department for nephrectomy specimens and reviewed all pathology reports from 2009-2013. We selected cases with tumor and collected clinicopathological information, focusing on re-evaluation of cases with glomerular sparing pattern. To facilitate our study we performed immunohistochemical stains of PAX-8, p63, and Inl-1 on selected cases. We selected a total of 204 nephrectomy cases in this study, including 163 cases of renal cell carcinoma; 37 cases of urothelial carcinoma; 4 cases from other categories (Wilms tumor, primary diffuse large B-cell lymphoma, angiolipoma, rhabdoid tumor). Finally, we identified 7 cases of primary kidney tumors with glomerular sparing pattern: 2 cases of clear cell renal cell carcinomas (ccRCC), 1 case of collecting duct carcinoma, 2 cases of urothelial carcinoma (UC), 1 case of diffuse large B-cell lymphoma and 1 case of malignant rhabdoid tumor. The primary kidney tumors with glomerular sparing pattern are rare and incidence in our study is <4% (7/204). There is no specificity for any tumor type, but more commonly seen in high grade UC rather than RCC. It can also be seen in rare neoplasms such as collecting duct carcinoma, lymphoma and malignant rhabdoid tumor. These GS cases need to be recognized as they are often associated with high grade, high stage, large tumor size, and worse prognosis.

Keywords: Glomerular sparing pattern, primary kidney neoplasms, clinical, morphological, immunohistochemical study

Introduction

One of the unique histopathological features of kidney neoplasms is glomerular sparing (GS) pattern. GS is defined as a characteristic growth pattern in which tumor cells replace the majority of renal tubes and overrun intact glomeruli. This pattern is well recognized by practicing pathologists and images have been documented in the literature [1, 2]. It has been reported that growth pattern can be a predictive parameter for ccRCC and infiltrative growth pattern was an independent risk factor [1]. Although GS is a typical infiltrative growth pattern, there has been no systemic study on this entity. Therefore the aim of this study was to analyze glomerular sparing pattern of the kidney neoplasms by light microscopy, histochemistry, and immunohistochemistry to elucidate their clinicopathological significance.

Materials and methods

Material

After Institutional Review Board approval (IRB#WMC, L-10,884), electronic surgical pathology records were retrospectively searched for all cases of (total and partial) nephrectomy with tumor diagnosis, from 2009 to 2012 at the Department of Pathology, Westchester Medical Center, Valhalla, NY. 204 cases were identified and all pathological reports and H & E slides were re-reviewed with special focus on glomer-

Table 1. Clinical information of cases with glomerular sparing pattern

Case #	Type	Age	Size (cm)	Sex	Laterality	Pathological stage	Grade
1	ccRCC	88 Y	8.5	Male	Right	pT3aN1Mx	G4
2	ccRCC	61 Y	4.5	Female	Left	pT3aNxMx	G3
3	collecting duct carcinoma	69 Y	5.4	Male	Right	pT3a N1Mx	G4
4	UCa with glandualr differentiation	55 Y	6.8	Female	Right	pT3NxMx	High
5	UCa with extensive osteosarcomatous differentiation	69 Y	10.2	Male	Left	pT4NxMx	High
6	Diffuse large B-cell lymphoma (DLBCL)	77 Y	21	Male	Right	N/A	High
7	Malignant rhabdoid tumor	3 Month	7.5	Female	Left	pT4N1M1	High

ccRCC: clear cell type renal cell carcinoma; UCa: urothelial carcinoma.

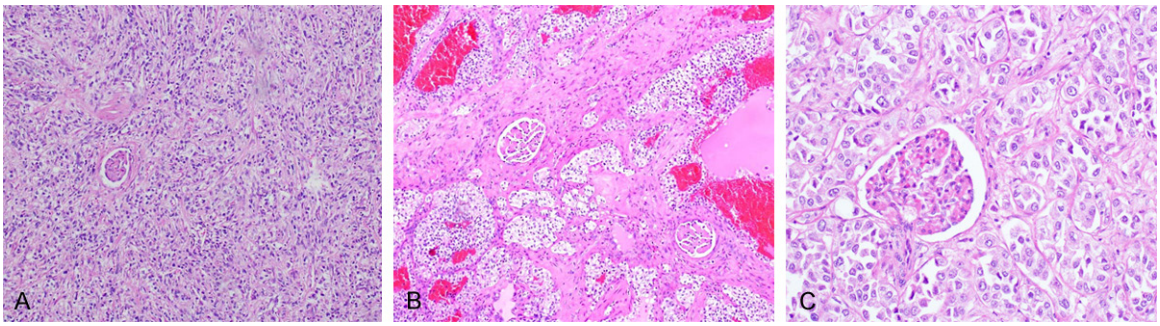

Figure 1. Renal cell carcinoma (RCC) with glomerular sparing (GS) pattern. A: Case #1, ccRCC; B: Case #2, ccRCC; C: Case #3, collecting duct carcinoma.

ular sparing pattern. Clinicopathologic information including sex, age, tumor laterality, focality, size, histological grade, pathologic stage, surgical margins, and lymphovascular invasion were evaluated. In all cases, tissues were fixed in neutral-buffered formalin and embedded in a paraffin block as part of a routine surgical pathology procedure.

Immunohistochemical stains

Immunohistochemical stains were performed on 5 micron (μm)-thick sections using the BenchMark ULTRA IHC/ISH stainer (Ventana Medical Systems, Oro Valley, AZ). The sections are deparaffinized and subjected to heat-induced antigen retrieval using EDTA buffer at pH 7.9. Prediluted primary antibodies (Pax8, P63, GATA3, CK5/6 and InI-1) were applied for 32-45 minutes at 37 to 42 degree Celsius. Ventana *Ultra view* universal DAB detection kit with brown chromogen was used to visualize the reaction. For double stain of P63 and PAX8, the section was first stain P63 with DAB and subsequently incubated with prediluted rabbit polyclonal anti PAX 8 (Cell Marque, MRQ-50) for 40 minutes at 42 degree Celsius. Ventana *Ultra view* universal DAB detection kit with red chromogen was used to visualize the reaction. For negative controls, the primary antibodies are replaced with phosphate-buffered saline.

Results

We have identified 7 cases of glomerular sparing pattern in 204 consecutive primary kidney neoplasms. These cases belonged to different malignant entities. However, most of the cases were high grade, high stage with large tumor size. The detailed clinical information is in **Table 1**. There were 3 cases of renal cell carcinoma with glomerular sparing pattern. Two cases (**Figure 1A** & **1B**) were clear cell type. The other case (**Figure 1C**) was collecting duct carcinoma.

We also identified 2 distinct cases of urothelial carcinoma (UCa) with glomerular sparing pattern: one with glandular differentiation (**Figure 2A**) mimicking collecting duct carcinoma (**Figure 1C**); the other one with extensive osteosarcomatous differentiation (**Figure 2C**). We employed double stains of Pax8 (red) and P63 (brown) to study UCa with glandular differentia-

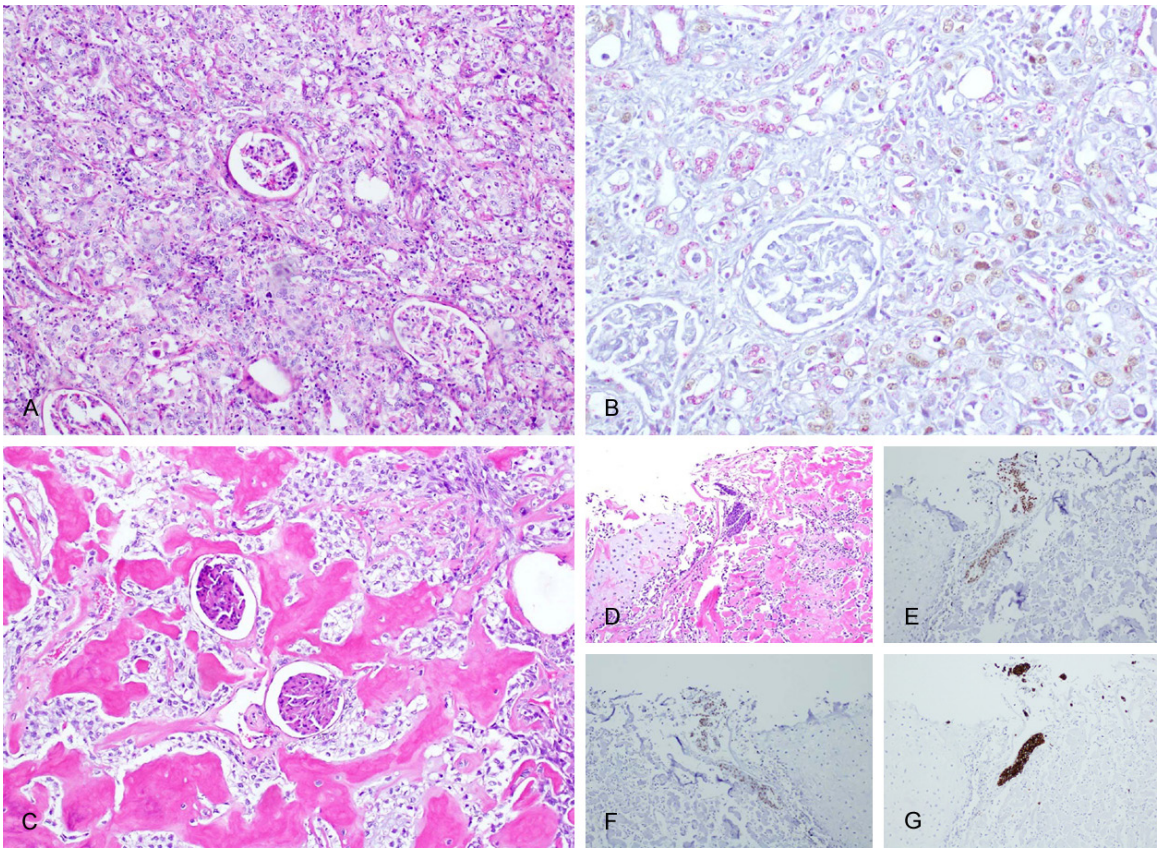

Figure 2. Urothelial carcinoma (UCa) with glomerular sparing (GS) pattern. A: Case #4 UCa with glandular differentiation; B: Double IHC stains of Pax8 (red) and P63 (brown); C: Case #5, UCa with extensive osteosarcomatous differentiation; D: The focal area with epithelioid features; E: IHC stain of GATA3; F: IHC stain of P63; G: IHC stain of CK5/6.

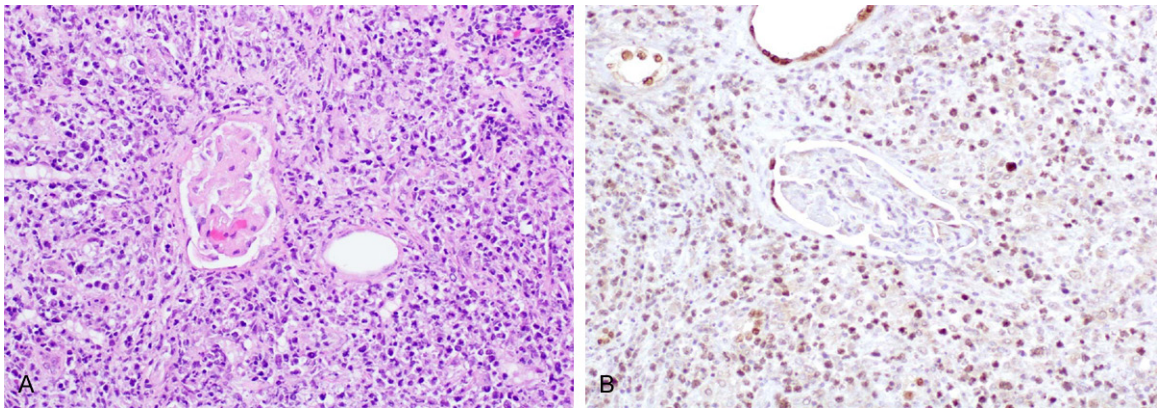

Figure 3. Diffuse large B cell lymphoma (DLBCL) with glomerular sparing (GS) pattern, case #6. A: H & E, section showed diffuse sheet growth pattern; B: IHC stain of Pax8 showed positive staining in entrapped renal tubule cells and DLBCL cells due to cross reaction of Pax5.

tion [3]. The double stains (**Figure 2B**) nicely distinguished reactive, entrapped renal tubule cells which were Pax8 (red) positive and high grade UCa cells which were P63 positive (brown). Non-invasive UCas were also seen in other areas. The case of UCa with extensive osteosarcomatous differentiation was much more difficult [4-7]. No obvious classical UCa could be identified. A small group of high grade, epithelioid tumor cells (**Figure 2C**) were identi-

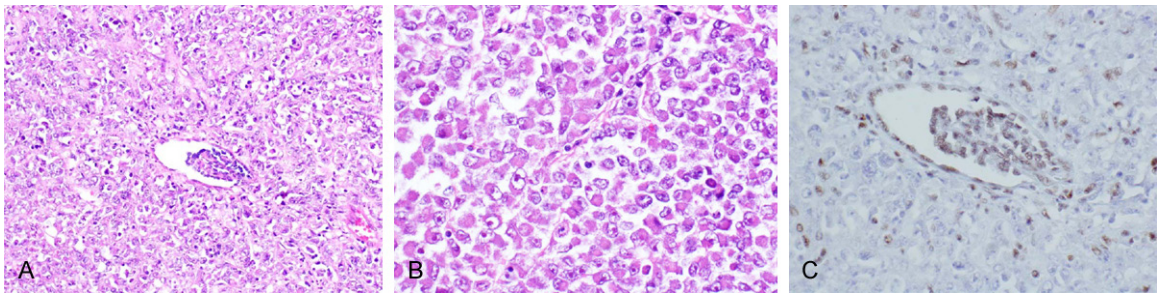

Figure 4. Malignant rhabdoid tumor (MRT) with glomerular sparing (GS) pattern, case #7. A: H & E, section showed similar diffuse sheet growth pattern of DLBCL in **Figure 3A**; B: Higher power view showed typical "rhabdoid" cytology; C: IHC stain of InI-1 showed loss of expression in MRT cells and retain expression in cells of glomerulus, vessel and stroma.

fied after extensive sectioning. These cells were positive for GATA3 (**Figure 2E**), P63 (**Figure 2F**), CK5/6 (**Figure 2G**) and were negative for Pax8 (data not shown) [8, 9]. In addition, TERT promoter mutation [10] was identified in this case (unpublished data).

Among other rare primary kidney neoplasms, one case of diffuse large B cell lymphoma (DLBCL) (**Figure 3A**) and one case of malignant rhabdoid tumor (MRT) (**Figure 4A**) have been found with glomerular sparing pattern. Both cases had similar diffuse sheet growth pattern. DLBCL appeared to be epithelioid and Pax8 positive [11] (**Figure 3B**). This might cause confusion with high grade RCC. In the MRT case, typical rhabdoid cytology (**Figure 4B**) was observed. The loss of INI-1 expression (**Figure 4C**) confirmed the diagnosis of MRT [9, 12].

Discussion

In order to investigate glomerular sparing pattern, we have re-visited 204 consecutive cases of (partial) nephrectomy with neoplasms. We have found that this unique morphology is not common or specific for any kidney neoplasms. In our collected cases, the incidence of GS is low, less than 4% (7/204). These include: 3 cases of renal cell carcinoma (2 cases of clear cell type and 1 case of collecting duct carcinoma); 2 cases of urothelial carcinoma (one with glandular differentiation and the other with extensive osteosarcomatous differentiation), 1 case of diffuse large B cell lymphoma (DLBCL) and 1 case of malignant rhabdoid tumor (MRT). Even though the incidence of GS was low, the frequency of GS in RCC and UCa, the two most common tumors in kidney, were significantly different: RCC was less than 2% (3/163) and UCa was 8% (2/37). The accurate incidence of GS in other rare kidney neoplasms, such as lymphoma and MRT, could not be established in this current study, due to limited case numbers. However, we predict that GS incidence in these neoplasms probably is higher than those in RCC or UCa. Due to the association of heterogeneous tumor entities, it is not surprising that age of patients spanned from 3 months to 88 years old (**Table 1**). The ratios of male to female and right to left kidney were roughly equal. The tumor size ranged from 4.5 to 21 cm. Most of the tumors were high stage and half of cases were with lymph node involvement (**Table 1**). Most areas with GS pattern were usually found at the junction of neoplasm and kidney parenchyma.

It is not clear what the exact mechanism of glomerular sparing pattern in kidney neoplasms is. One reasonable hypothesis is that glomerulus is more tolerable for neoplastic stress (physical or biological) due to enrichment of blood supply. On the other hand, renal tubules which lack blood supply are more vulnerable for neoplastic stress. This hypothesis is supported by the facts that most GS pattern is associated with high grade/fast growing neoplasm and is found at the edge of neoplasm.

There was significant morphological overlapping between different neoplasms with GS pattern. For example, collecting duct carcinoma and urothelial carcinoma with glandular differentiation were very similar, if not identical [3]. Both cases showed that high grade epithelioid cell forming solid tumor nests replaced mostly benign renal tubules and spare intact glomerulus. The other sections from the case with glandular differentiation showed classical non-inva-

sive, high grade, papillary UCa. Therefore, it is suggestive of association of high grade urothelial carcinoma with glandular differentiation and glomerular sparing pattern. In addition, double stains of P63 and Pax8 [3] confirmed the morphological impression: P63 labeled with brown color is positive in high grade UCa cells; Pax8 labeled with red color was positive in reactive renal tubule cells. In contrast, the collecting duct carcinoma case showed more uniform morphology: high grade epithelioid cell forming nests, tubules/ducts in which the tumor cells were positive for Pax8 and negative for P63 (data not shown). The diagnosis of collecting duct was rendered [3].

Another example of overlapping morphology is between diffuse large B cell lymphoma (DLBCL) and malignant rhabdoid tumor (MRT). At low power, both cases showed high grade, poorly differentiated tumor cells with diffuse sheet growth pattern. In MRT case, the tumor cytology at other areas showed typical rhabdoid features [13]: large cytoplasmic, round eosinophilic inclusions that pushed the nucleus to the side of the cell. InI-1 stain showed loss of expression in tumor cells and retained expression in cells of glomerulus, vessel and stroma. Thus, both morphology and IHC stain supported the diagnosis of malignant rhabdoid tumor [9, 12, 13]. It is well known that DLBCL can be epithelioid and may mimic high grade carcinoma. In addition, Pax8, a popular renal marker, is cross reactive with B cell marker, Pax5. The pitfall of both morphology and IHC stain can lead to misdiagnosis of DLBCL as high grade RCC.

The other interesting case was a kidney neoplasm with extensive osteosarcomatous differentiation. H & E stained section showed distinct morphology: typical osteosarcoma surrounding intact glomerulus. The differential diagnosis included: primary extra skeletal osteosarcoma [6], high grade renal cell carcinoma or high grade urothelial carcinoma with extensive osteosarcomatous differentiation [4, 5, 7, 14, 15]. After extensive sampling and IHC stains, we found a group of poorly differentiated, epithelioid cells which were positive for P63, GATA3 and CK5/6; negative for Pax8 [8, 9, 16, 17]. In addition, this tumor contained a TERT promoter mutation which occurs in 70% of the UCa but not in osteosarcoma or RCC [10]. Along these lines, we made the diagnosis: UCa with extensive osteosarcomatous differentiation.

In summary, we systemically studied the GS pattern in primary kidney neoplasms. We demonstrated that GS is an uncommon morphology associated with heterogenous malignant entities, including renal cell carcinoma, urothelial carcinoma, collecting duct carcinoma, lymphoma and malignant rhabdoid tumor. This study also clearly demonstrated that there was significant morphological overlapping. Careful morphological examination and appropriate immunohistochemistry stains are necessary for accurate diagnosis. Nevertheless, GS pattern is associated with high grade, high stage, large tumor size, and presumably bad prognosis.

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Disclosure of conflict of interest

None.

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