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Non-neoplastic Kidney Diseases in Adult Tumor Nephrectomy and Nephroureterectomy Specimens in a Southeast Asian Tertiary Medical Center

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ABSTRACT

OBJECTIVE: Non-neoplastic kidney diseases are concurrently present in up to 15% of patients with renal and ureteral tumors, which have been most studied in the United States. This study was conducted to determine the prevalence and spectrum of renal parenchymal diseases in similar patients from a Southeast Asian academic institution.

METHODS: We searched the database of the Department of Anatomical Pathology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University (2012–2022) and found 194 adult nephrectomy and nephroureterectomy specimens with renal, renal pelvis, and ureteral tumors. Additional stains included periodic acid-Schiff, methenamine silver, and Masson trichrome. Direct immunofluorescence microscopy was performed on the paraffin tissue sections for immunoglobulin (Ig) G, IgA, IgM, and kappa and lambda light chains. Clinical information, including age, gender, and co-morbidities, was obtained from the electronic medical records.

RESULTS: Analysis of the 194 cases demonstrated the average age was 61 years (range: 17-89 years), with 126 males (65%) and 68 females (35%). After re-examination of the non-neoplastic renal parenchyma, 14 cases (7%) had diffused and/or nodular mesangial sclerosis. Diabetic nephropathy (12 cases) and idiopathic nodular glomerulosclerosis (2 cases) were diagnosed and associated with either stage 1 or 2 genitourinary cancers. Another case was diagnosed with atheroembolic renal disease. In all cases, the concurrent renal diseases were not identified during the initial evaluation.

CONCLUSION: Examination of the non-neoplastic renal parenchyma is important to identify non-neoplastic kidney diseases, such as diabetic nephropathy, so early treatment may result in improved clinical outcomes for kidney and urothelial cancer patients.

KEYWORDS: chronic kidney disease, diabetic nephropathy, nephrectomy, nephroureterectomy, non-neoplastic parenchyma, renal tumor

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INTRODUCTION

In 2020, there were an estimated 431,288 new cases of kidney cancer globally[1]. In Thailand, kidney cancer is the 20th most common malignant tumor, accounting for 2,170 (1.1 %) of new cancer diagnoses and 1,230 (1%) of cancer deaths according to GLOBOCAN 2020[2], radical nephrectomy, partial nephrectomy, and nephroureterectomy are the standard treatments for renal, renal pelvis, and ureteral cancers[3-10] but these procedures also remove large numbers of functional nephrons and increase the risk of chronic kidney disease (CKD)[4-5]. Long-term follow-up studies of patients undergoing nephrectomy and nephroureterectomy reveal a significant decline in renal function[11-12]. In addition, non-neoplastic kidney diseases are concurrently present in up to 15% of tumor nephrectomy and nephroureterectomy specimens, and can further accelerate CKD progression and decrease life expectancy[6-10].

The cancer synoptic reports developed by the College of American Pathologists (CAP) are widely used. These synoptic reports remind the pathologist to evaluate a variety of important pathologic parameters for every specimen. Prior to 2010, the evaluation of the non-tumor renal parenchyma was optional for both tumor nephrectomy and nephroureterectomy specimens[9]. Early-stage renal malignancies are increasingly detected, which have 5-year survival rates that approach 100% in the United States[13]. Therefore, the identification of a concurrent non-neoplastic kidney disease can result in early intervention and improve patient outcomes.

To our knowledge, the incidence of non-neoplastic kidney diseases in kidney cancer patients has not been well studied in Asia. This study was conducted to determine the spectrum and incidence of non-neoplastic renal diseases (NNRD) in kidney and urothelial cancer specimens in a Southeast Asian medical center.

METHODS

We searched the Department of Pathology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University database for adult tumor nephrectomy and nephroureterectomy specimens from January 2012 to August 2022. Basic clinical data, such as age, sex, and history of diabetes/hypertension, were obtained from electronic medical records. Exclusion criteria included renal allografts, specimens that were consistent with end-stage renal disease, and partial nephrectomies given that this procedure is rarely performed at this institution and they are no available slides or paraffin blocks for review. This research was approved by the institutional review board of the Faculty of Medicine Vajira Hospital (COA168/2565).

The hematoxylin and eosin-stained slides were reviewed by a pathologist. The slides were initially assessed for the presence or absence of non-neoplastic renal parenchyma. The pathologic evaluation was performed without prior knowledge of the patients' clinical histories or laboratory data. If glomerular alterations (e.g. diffuse or nodular mesangial sclerosis, segmental sclerosis, mesangial hypercellularity, endocapillary hypercellularity, or capillary wall thickening) were present, this triggered further evaluation by periodic acid–Schiff, Jones methenamine silver, Masson trichrome and Congo red stains with immunofluorescence (IF) microscopy of immunoglobulin (Ig) G, IgA, IgM, and kappa and lambda light chains on paraffin tissue sections. Global glomerulosclerosis, interstitial fibrosis, tubular atrophy, and arteriosclerosis were considered non-specific findings and we did not include arterionephrosclerosis as a specific diagnosis for this study.

RESULTS

One hundred and ninety-four cases were identified and the patient demographics, pathologic diagnoses, and clinical information are summarized in Table 1. We identified significant diffuse and/or nodular mesangial sclerosis in 14 (7%) cases and another one with atheroembolic disease.

The remaining 179 specimens did not demonstrate definite diagnostic parenchymal alterations. Review of the electronic medical record confirmed a clinical diagnosis of diabetes in 12 of 14 with diffuse and focally nodular mesangial sclerosis, and none of these 12 had a prior kidney biopsy or diagnosis of diabetic nephropathy (DN) (figure 1). Of these 12 DN cases, there were seven associated with stage 1 and two cases associated with stage 2 renal cell carcinoma (RCC). Two additional DN cases were present with stage 1 and stage 2 transitional cell carcinoma/urothelial carcinoma. The last case of DN was found with an angiomyolipoma. In the absence of a clinical history of diabetes, the remaining two cases with prominent mesangial sclerosis were considered to represent idiopathic nodular glomerulosclerosis, as both patients were hypertensive and heavy cigarette smokers, which are known associations with this entity. Of these, one of each was present in stage 1 and 2 RCC. The additional case of atheroembolic disease had a clinical diagnosis of hyperlipidemia and was associated with stage 3 RCC. In all 15 cases, the concurrent renal diseases were not identified during the initial evaluation.

Table 1 Demographics of the study population

Patient variable	Number (%) N = 194
Age	61 (17-89 years)
Gender	
Male	126 (65)
Female	68 (35)
Underlying Disease	
Hypertension (HTN)	16 (8)
Diabetes mellitus (DM)	11 (6)
Hyperlipemia	7 (4)
DM with HTN	3 (1)
DM with HTN and hyperlipidemia	4 (2)
None provided/unknown	153 (79)
Procedure	
Nephrectomy	155 (80)
Nephroureterectomy	39 (20)
Pathological Diagnosis	
Renal cell carcinoma, clear cell	80 (41)
Renal cell carcinoma, papillary	25 (13)
Renal cell carcinoma, chromophobe	9 (5)
Renal cell carcinoma, sarcomatoid	2 (1)
Renal cell carcinoma, unspecified	7 (4)
Oncocytoma	2 (1)
Angiomyolipoma	16 (8)
Transitional cell carcinoma/Urothelial carcinoma	31 (16)
Squamous cell carcinoma	4 (2)
Other*	18 (9)
AJCC Cancer Staging	Number (%) N = 174
Stage 1	103 (59)
Stage 2	38 (22)
Stage 3	13 (8)
Stage 4	20 (11)

Abbreviations: AJCC, The American Joint Committee on Cancer; DM, diabetes mellitus; HTN, hypertension; N, number
*Includes: Solitary fibrous tumor, neuroendocrine carcinoma, liposarcoma, malignant epithelial tumor, pleomorphic undifferentiated sarcoma, metastatic carcinoma

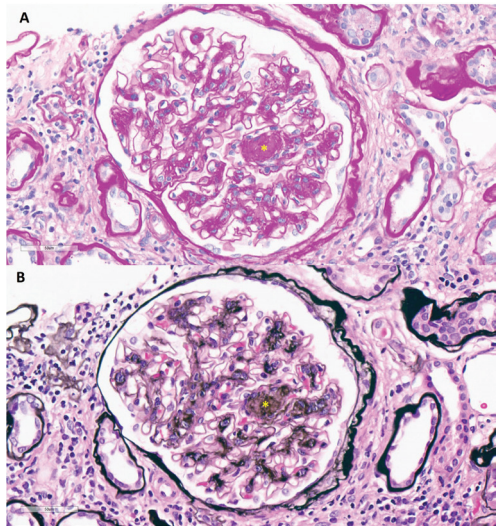

Figure 1 Diabetic glomerulopathy
Histopathological findings reveal mesangial expansion mainly due to increased mesangial matrix, with nodular formation (*) (Kimmelstiel-Wilson nodule). The nodule is round with a hypocellular matrix core surrounded by patent capillary loops. (A. x400, periodic acid-Schiff stain, B. x400, Jones methenamine silver stain)

Of the 15 patients with NNRDs, none were diagnosed with CKD or end-stage kidney disease before their surgeries. Additionally, at the 6-month follow-up, all patients had elevated blood urea nitrogen and creatinine levels and a decreased estimated glomerular filtration rate (eGFR) (table 2).

Direct IF microscopy performed on the paraffin tissue sections in these 15 cases for IgG, IgA, IgM, and kappa and lambda light chains showed no staining. Congo red studies in this subset also showed no evidence of amyloidosis.

The presence of non-neoplastic parenchymal renal alterations was associated with increased body mass index and underlying disease ($p < 0.001$, table 3).

Table 2 Summary of demographics, histology, and clinical features for the fifteen cases diagnosed with NNRDs

No.	Gender	Age	Pathological Diagnosis	Stage	NNRDs Diagnosis	BUN (mg/dL)		Cr (mg/dL)		eGFR (mL/min/ 1.73 m^2)	
						Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
1	Male	70	Renal cell carcinoma, papillary	I	DN	25	54	0.8	2.1	69	43
2	Male	55	Renal cell carcinoma, clear cell	II	ING	18	20	1.1	1.3	98	89
3	Male	60	Transitional cell carcinoma/ Urothelial carcinoma	II	DN	18	27	1.2	2.2	75	61
4	Male	59	Renal cell carcinoma, papillary	I	DN	21	30	1.3	1.9	82	54
5	Male	73	Renal cell carcinoma, unspecified	I	DN	28	32	1.1	1.8	64	39
6	Male	68	Renal cell carcinoma, clear cell	I	DN	25	31	1.3	1.7	71	51
7	Male	42	Renal cell carcinoma, clear cell	II	DN	19	26	1.5	2.2	76	64
8	Female	89	Renal cell carcinoma, clear cell	I	DN	18	20	1.3	1.7	65	55
9	Male	64	Renal cell carcinoma, papillary	III	AED	20	24	0.9	1.1	72	65
10	Female	78	Transitional cell carcinoma/ Urothelial carcinoma	I	DN	23	31	1	1.6	63	42
11	Male	66	Renal cell carcinoma, papillary	I	DN	24	41	0.9	2	92	54
12	Male	57	Renal cell carcinoma, clear cell	I	DN	26	38	1.1	1.9	80	64
13	Male	39	Angiomyolipoma	-	DN	15	20	0.8	1.4	115	90
14	Female	69	Renal cell carcinoma, clear cell	II	DN	14	25	0.9	1.5	83	69
15	Male	62	Renal cell carcinoma, papillary	I	ING	17	20	0.8	1.2	100	98

Abbreviations: AED, atheroembolic disease; BUN, blood urea nitrogen; Cr, creatinine; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; ING, idiopathic nodular glomerulosclerosis; m, meter; mg/dL, milligrams per decilitre; min, minute; NNRDs, non-neoplastic renal diseases; post-op, post-operation; pre-op, pre-operation

Table 3 Overall association among Sex, BMI, underlying disease, and non-neoplastic diagnosis

Parameter	Non-neoplastic Diagnosis, n (%)				P-value
	DN	ING	AED	No definite-diagnostic parenchymal alterations	
Sex					
Male	9 (5)	2 (1)	1 (< 1)	114	0.844
Female	3 (2)	-	-	65	
BMI*					
Underweight	-	-	-	16 (8)	< 0.001
Normal weight	1 (~ 1)	-	1 (< 1)	111 (57)	
Overweight	5 (3)	1 (< 1)	-	46 (24)	
Obesity	6 (3)	1 (< 1)	-	6 (3)	
Underlying disease					
Hypertension (HTN)	-	2 (1)	0	14 (7)	< 0.001
Diabetes mellitus (DM)	8 (4)	-	0	3 (2)	
Hyperlipemia	-	-	1 (< 1)	6 (3)	
DM with HTN	2 (1)	-	-	1 (< 1)	
DM with HTN and Hyperlipemia	2 (1)	-	-	2 (1)	
None provided/unknown	-	-	-	153 (79)	

Abbreviations: AED, atheroembolic disease; BMI, body mass index; DM, diabetes mellitus; DN, diabetic nephropathy; HTN, hypertension; ING, idiopathic nodular glomerulosclerosis; n, number
* Body mass index (BMI) Categories (kg/m^2): underweight ≤ 18.5, normal weight 18.5–24.9, overweight 25–29.9, obesity ≥ 30; Fisher exact test; P-value is indicating association between those factors. P < 0.05 considered as having significant association.

DISCUSSION

This is the first study from a Southeast tertiary care center to demonstrate that NNRDs occur at a rate of 8% in tumor nephrectomy/nephroureterectomy and interestingly the 7% rate of DN is similar to other larger studies[6,12]. NNRD can be found in 9 to 38% of kidney and ureteral cancer patients (table 4)[6,9,12,14-22]. Up to 90% of these diagnoses were not found at the initial pathologic evaluation, because pathologists focused on the renal neoplasm, and none of the patients in our cohort were initially diagnosed.

Table 4 Literature review

Study, Country	Year	Number of cases	Number of cases with non-neoplastic renal parenchyma disease (%)	Procedure
Bijol V et al,[14] USA	2006	110	42 (38)	partial and radical nephrectomy
Henriksen KJ et al,[6] USA	2007	246	24 (10)	partial and radical nephrectomy
Salvatore SP et al,[12] USA	2013	381	46 (12)	partial and radical nephrectomy
Bazzi WM et al,[15] USA	2015	800	72 (9)	partial nephrectomy
Wee JW et al,[16] Korea	2016	51	14 (27)	radical nephrectomy and nephroureterectomy
Tewari R et al,[17] India	2018	36	9 (25)	partial and radical nephrectomy
Shaw NM et al,[18] USA	2019	225	38 (17)	partial and radical nephrectomy and nephroureterectomy
Tjota MY et al,[9] USA	2020	63	7 (11)	total nephroureterectomy
Tripathy A et al,[19] India	2020	100	10 (10)	partial and radical nephrectomy
Dernell C et al,[20] USA	2021	59	15 (25)	radical nephrectomy
Kläger JP et al,[21] Austria	2021	206	39 (19)	partial and radical nephrectomy
Jia Y et al,[22] Canada	2022	156	14 (9)	partial and radical nephrectomy
Present study, Thailand	2022	194	15 (8)	radical nephrectomy and total nephroureterectomy

Almost 60% of the RCC and transitional cell carcinoma/ urothelial carcinoma in our cohort were stage 1 cancers, which have a five-year survival rate that is greater than 90%[23]. For the vast majority of patients with low-stage cancers, the oncologic outcomes should be excellent, but the NNRD has the potential to decrease their life expectancy through the detrimental effects of CKD and early intervention and management provides additional opportunities to improve outcomes. Thirteen of 15 patients with NNRD in our study had either stage 1 or 2 cancers, so early management of their NNRD could slow their CKD progression. One patient had an angiomyolipoma, which highlights the importance of evaluating the non-neoplastic parenchyma when benign neoplasms are present and synoptic reports may not be used. Preservation of renal function will be particularly important as 5-year actuarial cancer-specific survival for low-stage carcinoma has been estimated at ≥ 90%[9,23-24].

In our cohort, most patients who were identified to have diabetic nephropathy had mildly decreased eGFR pre-operatively. The diabetic patients in our study did not have a prior biopsy or clinical diagnosis of diabetic nephropathy, so the surgical pathologist often has the first opportunity to establish the diagnosis of diabetic nephropathy. Moreover, elderly patients (age ≥ 70 years) revealed pre-operative eGFR closer to 60 mL/min/1.73 m^2. The patients with a nephroureterectomy developed novel CKD or experienced progression of preexisting CKD or ESRD[25-28].

Synoptic reporting of cancer specimens is now common, and CAP developed one that is widely used. Prior to 2010, the evaluation of the non-neoplastic renal parenchyma in tumor nephrectomy and nephroureterectomy specimens was optional in the CAP protocol[29]. More than 25% of European genitourinary pathologists surveyed by the European Network of Uropathology in 2012 did not look at the non-tumor kidney parenchyma in tumor nephrectomy and nephroureterectomy specimens[30]. We suspect that this percentage is higher, especially beyond academic medical centers. There are many possible causes, but minimal exposure to nephropathology during residency training may be a significant contributor[6-7].

Investigating NNRD in kidneys removed for tumor event is a crucial method for determining the condition of the renal parenchyma in patients who will continue to have a single kidney. It is necessary to carefully examine appropriate sections of the nonneoplastic tissue, sectioned as far away from the tumor mass as feasible, utilizing standard special staining techniques used to evaluate renal pathologic changes including periodic acid-Schiff, methenamine silver, and Masson trichrome stains. It is necessary to obtain tissue samples from the renal cortex during the gross examination for potential immunofluorescence and electron microscopy examinations. Other stains, including Congo red for amyloid, should be conducted in specific situations such as patient who had history of a monoclonal protein, hereditary disorders. We have discovered that a systematic approach that includes a meticulous sequential examination of each kidney compartment (glomeruli, tubulointerstitium, and vasculature) yields the best results.

Strengths of this study: 1) Comprehensive data collection: The study collected data over a substantial period from a specific medical center, allowing for a focused analysis of NNRD in kidney and urothelial cancer specimens. 2) Clear methodology: The methodology section outlines the search criteria, inclusion/exclusion criteria, and the process of evaluation, providing clarity on how the study was conducted. 3) Clinical relevance: The study addresses a significant gap in research regarding the incidence and impact of NNRDs in kidney cancer patients, particularly in Southeast Asia, thereby contributing to the understanding of renal complications in this population. 4) Identification of NNRDs: The study identified various non-neoplastic renal diseases, including diabetic nephropathy, idiopathic nodular glomerulosclerosis, and atheroembolic disease, highlighting the importance of thorough pathological evaluation. 5) Emphasis on early intervention: The discussion section underscores the importance of early identification and management of NNRDs to improve patient outcomes, particularly in patients with low-stage cancers.

Weaknesses of this study: 1) Limited sample size: The study sample size of 194 cases may limit the generalizability of the findings, especially considering the diverse spectrum of renal diseases. 2) Single-Center Study: The study was conducted in a single medical center, which may not fully represent the broader population's demographics and disease prevalence. 3) Lack of longitudinal data: The study primarily focuses on the incidence of NNRDs at the time of surgery without longitudinal follow-up to assess the long-term impact on renal function and patient outcomes. 4) Potential bias in pathological evaluation: The retrospective nature of the study and the reliance on pathological evaluation.

Overall, while this study contributes valuable insights into NNRDs in kidney cancer patients, its limitations underscore the need for larger, multicenter studies with longitudinal follow-up to validate the findings and assess the long-term implications on patient outcomes.

CONCLUSION

In summary, our study found non-neoplastic kidney diseases involving nearly 8% of tumor nephrectomy and nephroureterectomy specimens from a Southeast tertiary care center. As oncologic outcomes continue to improve for kidney and urologic cancers, preservation of renal function and identification of non-neoplastic kidney diseases will provide opportunities for earlier interventions that may result in improved clinical outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

All data analyzed in this study are included in this published article.

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