Chapter 7

Paraneoplastic Glomerulopathy Associated with Renal Cell Carcinoma

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Additional information is available at the end of the chapter

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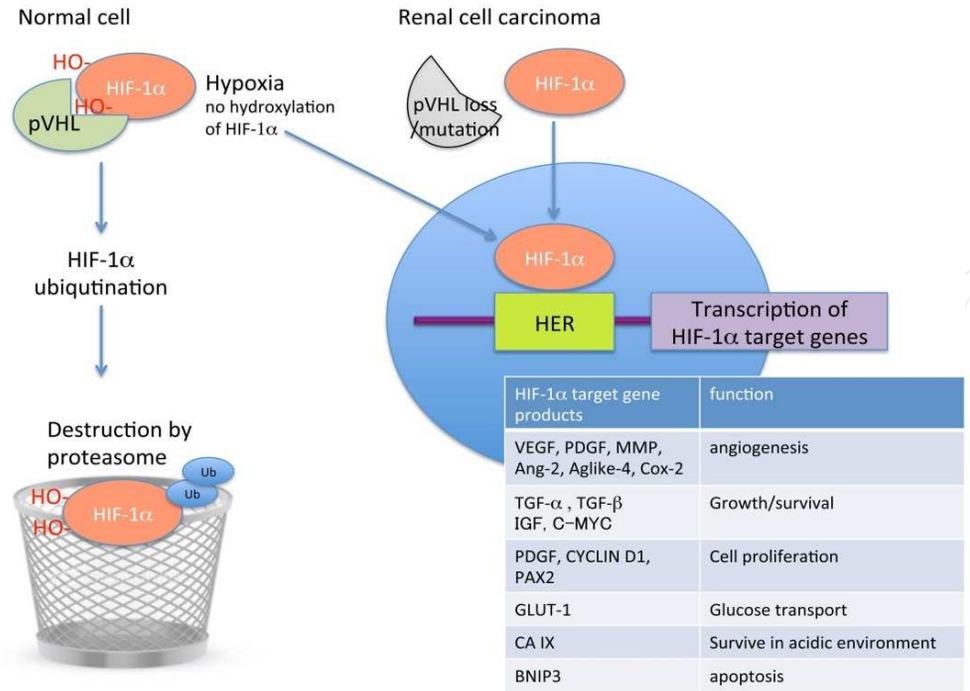
1. Introduction

Renal cell carcinoma is often associated with paraneoplastic syndromes caused by the secretion of tumor cell products such as hormones, cytokines, growth factors and tumor antigens, which show manifestations including impaired glucose metabolism, hypercalcemia, hypertension, Cushing syndrome, polycythemia, thrombosis, eosinophilia, leukemoid reactions and amyloidosis [1]. It has been reported that 10-40% of patients with renal cell carcinoma present paraneoplastic symptoms [1]. However, paraneoplastic glomerulonephritis associated with renal cell carcinoma has often been overlooked, for the urinary abnormalities including proteinuria and hematuria are often interpreted as clinical manifestations of the tumor itself, especially when the proteinuria is non-nephrotic.

The term of paraneoplastic glomerulopathy was first described by Galloway in 1922 in a case of nephrotic syndrome associated with Hodgkin's disease [2]. Hodgkin's lymphoma is associated with minimal change nephrotic syndrome, while solid carcinomas including lung cancer and carcinomas of the gastrointestinal tract frequently develop membranous nephropathy, which is the most common paraneoplastic glomerulopathy [3,4]. Although renal cell carcinoma is not a frequent cause of paraneoplastic glomerulopathy, recent advances in the study of the molecular mechanism of renal cell carcinoma as a cytokine producing tumor have promoted a better understanding of the mechanism of paraneoplastic nephropathy associated with renal cell carcinoma. In this chapter, I will discuss the mechanisms of paraneoplastic nephropathies associated with renal cell carcinoma.

1.1. Pathological types of renal cell carcinoma and molecular mechanisms of paraneoplastic syndrome

Renal cell carcinoma accounts for 85 % of renal neoplasms, and 25% of patients with renal cell carcinoma show advanced disease with local invasion or metastasis at the time of diagnosis [5]. Renal cell carcinoma is classified pathologically into five types: clear cell (75%), papillary (12%), chromophobe (4%), oncocytoma (4%), collecting duct carcinoma (<1%), and unclassified (3-5%) [5]. The most common type, clear cell renal cell carcinoma, shows hypervascularity. About 60% of sporadic clear cell renal cell carcinoma have mutations in the von Hippel-Lindau tumor suppressor gene (*VHL*) [6], which is a causative gene for von Hippel-Lindau disease, an autosomal dominant familial cancer syndrome consisting retinal angioma, hemangioblastoma of the central nervous system, pheochromocytomas, and clear cell renal cell carcinoma. VHL protein normally suppresses hypoxia-inducible genes by inhibiting HIF-1α [7] (Figure 1). However, when VHL protein is lost in clear cell renal cell carcinoma, various cytokines and growth factors induced by HIF-1α are enhanced; vascular endothelial growth factor (VEGF) which stimulates angiogenesis of carcinoma, platelet-derived growth factor (PDGF) and transforming growth factor alpha (TGF- α), which lead to tumor growth, glucose transporter (GLUT-1) and carbonic anhydrase IX (CA IX), which leads to tumor cell survival in an acidic environment [8-10]. NF-kB activity is also regulated by VHL protein, and cytokine-inducible transcription factors including NF-kB and STAT3 are activated in renal cell carcinoma [11-15]. Renal cell carcinoma tissue and cell lines of the tumor express mRNA of IL-6 and IL-6 receptor [16, 17], which may play a role in cancer cell growth in an autocrine or paracrine manner.



HIF-1α target gene products	function
VEGF, PDGF, MMP, Ang-2, Aglike-4, Cox-2	angiogenesis
TGF-α , TGF-β IGF, C−MYC	Growth/survival
PDGF, CYCLIN D1, PAX2	Cell proliferation
GLUT-1	Glucose transport
CA IX	Survive in acidic environment
BNIP3	apoptosis

Figure 1. Molecular mechanisms of renal cell carcinoma as a cytokine-producing tumor.

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The von Hippel-Lindau protein (pVHL) binds with hypoxia inducible factor 1α (HIF-1α) transcription factor and promotes the ubiqutination of HIF-1α, resulting in degradation by the proteasome under normoxic conditions. In renal cell carcinoma, the absence of wild type pVHL stimulates the accumulation of HIF-1α and activates transcription at hypoxia-response elements (HREs) in genes including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor α (TGF-α) and TGF-β, glucose transporter (GLUT-1) and carbonic anhydrase IX (CA IX).

MMP: matrix metalloproteinase; Ang-2: angiopoietin-2; Aglike-4: angiopoietin-like 4; COX-2: cyclooxygenase-2; BNIP3: BCL2/adenovirus E1B 19 kD interacting protein 3; PAX2: paired box gene 2.

The serum levels of VEGF and IL-6 are increased according to the stage of renal cell carcinoma, whereas TNF-α and IL-1β showed a slight increase as they are probably produced by infiltrating monocytes or macrophages (Figure 2) [18,19]. This indicates that clear cell renal cell carcinoma is a cytokine-producing tumor, whose functions are linked to the development of the various features of the paraneoplastic syndrome [9,20].

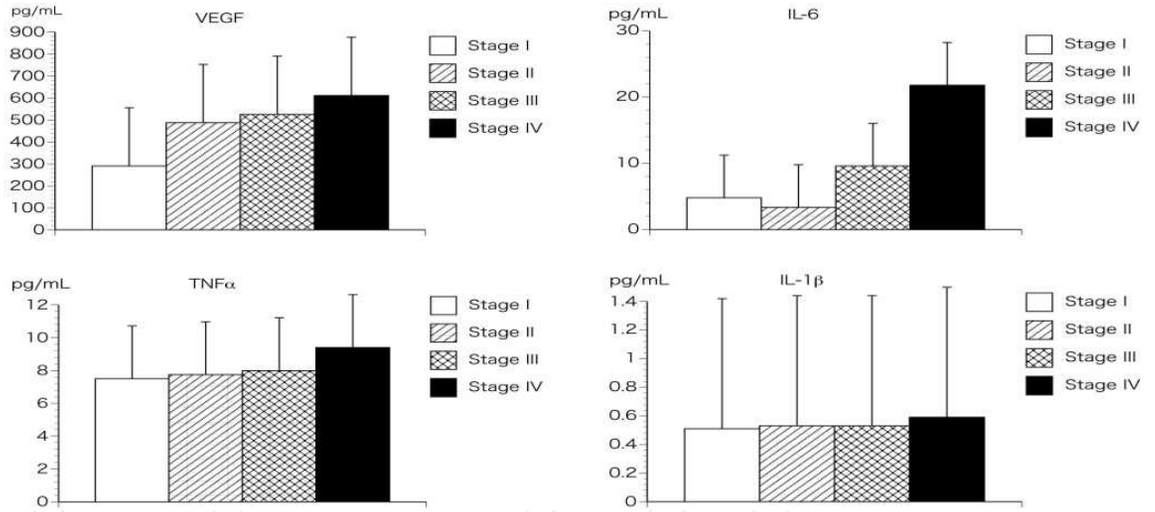

Figure 2. Serum vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α) and interleukin-1β (IL-1β) in various stages of renal cell carcinoma. Adapted from [18] and [19].

2. Incidence of paraneoplastic syndrome and glomerulopathy in renal cell carcinoma

The most frequent features of the paraneoplastic syndrome in renal cell carcinoma are hypercalcemia, hypertension and polycythemia. Their prevalence and their causative hormones and cytokines are listed in Table1 [1].

Phenomenon	Prevalence %	Hormones and cytokines
Hypercalcemia	13-20%	Non-bone metastatic disease 50%, PTH, PTHrP, TGF-α, β, OAF, IL-1, TNF
Hypertension	40%	Renin
Polycythemia	1-8%	Erythropoietin
Nonmetastatic hepatic dysfunction (Stauffer's syndrome)	3-20%	Hepatotoxines, lysosomal enzymes stimulating hepatic cathepsins or phosphatases, IL-6
Constitutional syndrome (fever, weight loss, fatigue)	20-30%	TNF-α, IL-6. IL-1, prostaglandins
	6%	β-HCG
Cushing's syndrome	2%	ACTH
Abnormal glucose metabolism		Insulin, glucagon
Galactorrhea		Prolactin
Amyloidosis	3-8%	SAA protein
Neuromyopathies	rare	unknown
Nephropathy		
Vasculopathy		
Coagulopathy		

PTHrP: parathyroid hormone-related peptide, OAF: osteoclast activating factor, TNF: tumor necrosis factor, HCG: human chorionic gonadotropin, ACTH: adrenocorticotropin, SAA: serum amyloid A.

Table 1. Prevalence and features of paraneoplastic syndromes in renal cell carcinoma.

Paraneoplastic glomerulopathy is believed to be a rare manifestation of the paraneoplastic syndrome. However, immunohistochemical analysis of resected kidneys from 60 patients of renal cell carcinoma revealed 27% of them had immune complex nephropathy including 11 patients (18%) with IgA nephropathy and 5 patients (8%) with focal segmental glomerulosclerosis [21]. Another immunofluorescence study revealed a positive staining for C3, IgM, or IgA in the mesangial deposits in 35% (14/40) of patients with renal cell carcinoma versus 5.4% in the control subjects [22] (Table 2). Thus, the occurrence of glomerular diseases is not so rare in renal cell carcinoma.

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	Prevalence %	Outcomes after resection of renal carcinoma	Reference
IgA nephropathy	11/60 (18%)	Remission 6, Azotemia 2	Magyarlaki [21]
FSGS	5/60 (8%)	Azotemia 3	
Diabetic nephropathy	3/60 (5%)	Nephrotic /Azotemia 2	
Nephrosclerosis	4/60 (7%)	Nephrotic /Azotemia 2	
Tubulointerstitial nephritis	16/60 (27)	-	
IgA/C3 deposition	1/40 (2.5%)	N.D.	Beaufils [22]
C3/IgM deposition	13/40 (33%)		
CEA deposition	2/9 (22%)		
HBs Ag/Ab deposition	6/29(21%)		

Table 2. Evaluation of glomerulopathy in resected kidneys of renal cell carcinoma patients.

3. Diagnosis and mechanism of paraneoplastic glomerulopathy associated with renal cell carcinoma

Recent development or worsening of diabetes mellitus, increased platelet or C-reactive protein (CRP), and hypercalcemia also suggests the existence of paraneoplastic syndrome. Glomerulonephritis is considered when urinalysis shows dysmorphic red blood cells and red blood cell casts, as hematuria caused by renal cell carcinoma usually shows isomorphic red blood cells. When proteinuria exceeds 1g per day, it is also better to speculate overlapping glomerulonephritis and examine serological tests including immunoglobulins (IgG, IgA, IgM), complements (CH50, C3, C4), anti-nuclear antibody, and anti-dsDNA antibody. A final diagnosis of glomerulonephritis can only be given by a renal biopsy. Renal cysts or masses identified by renal ultrasonography at the time of renal biopsy should be further investigated with CT and MRI. Renal cancer will progress rapidly after steroid therapy for glomerulonephritis.

The diagnosis of paraneoplastic glomerulopathy will be suggested following the criteria; 1) existence of a time relationship between the diagnosis of the glomerulopathy and cancer, 2) no obvious etiology for glomerular diseases, 3) clinical or histological remission of glomerulopathy after complete remission by surgical removal of carcinoma, 4) recurrence of the carcinoma associated with deterioration of glomerular diseases [3,23].

As mentioned above, inactivation of the *VHL* gene by frame-shift mutation is observed in about 60% of sporadic RCC [5]. Activated HIF-1α without VHL protein stimulates hypoxia-related proteins such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which lead to tumor growth and trigger angiogenesis (Figure 1) [8,10]. The increased VEGF accelerates glomerular permeability and causes proteinuria, and

PDGF and IL-6 stimulates mesangial cell proliferation, and TGF-β increases the mesangial matrix, contributing to the development of glomerulonephritis.

It is interesting that IgA nephropathy showed a higher prevalence than membranous nephropathy in renal cell carcinoma, whereas about 50% of glomerulopathies associated with gastrointestinal neoplasias and lung cancers were membranous nephropathy (Table 3). The mechanisms of paraneoplastic nephropathy may be different in renal cell carcinoma compared with gastrointestinal neoplasias and lung cancers. The paraneoplastic nephropathy of renal cell carcinoma may depend more upon overproduction of cytokines rather than cross-reaction with tumor antigen and production of autoantibodies.

	Renal cell carcinoma N=49	**Gastrointestinal neoplasia N=48**	**Lung cancer N=41**
Membranous nephropathy	10 (20%)	26 (54%)	20 (49%)
IgA nephropathy	15 (31%)	1 (2%)	2 (5%)
Minimal change disease	6 (12%)	9 (19%)	9 (22%)
Focal segmental glomerulonephritis	5 (10%)	2 (4%)	1 (2%)
Membranoproliferative glomerulonephritis	3 (6%)	2 (4%)	5 (12%)
Crescentic glomerulonephritis	10 (20%)	8 (17%)	4 (10%)

Table 3. Type of glomerulopathy in renal cell carcinoma compared with gastrointestinal neoplasia and lung cancer. Modified from [3].

4. Types of paraneoplastic nephropathy

4.1. IgA nephropathy and renal cell carcinoma

Although IgA nephropathy is more common in younger patients, when it occurs in patients older than 60 years, a high prevalence of malignancy (23%) is observed [24]. Solid tumors that invade mucosal tissue like the respiratory tract, the buccal cavity, and the nasopharynx increase circulating IgA levels and show deposition of IgA in the mesangium [24]. Several cases of IgA nephropathy associated with renal cell carcinoma have been reported previously [21,25-28]. In Figure 3, a 66 year-old male diagnosed IgA nephropathy with mesangial IgA deposition but weak C3 staining showed a rapid increase in renal cyst during steroid treatment, and a clear cell renal cell carcinoma was found in the resected kidney (Figure 3). The infiltrating plasma cells around the renal cell carcinoma produced IL-6 and IgA (Figure 3). Elevated levels of IL-6 have been reported in 18 (25%) of 71 patients with renal cell carcinoma [29], and IL-6 increased in more than 50% of patients with metastatic renal cell carcinoma, playing a role as a prognostic marker [19,20,30,31]. IL-6 stimulates IgA production

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[32], thus, the elevated IL-6 in renal cell carcinoma may increase circulating IgA, which deposits in the mesangial area causing IgA nephropathy.

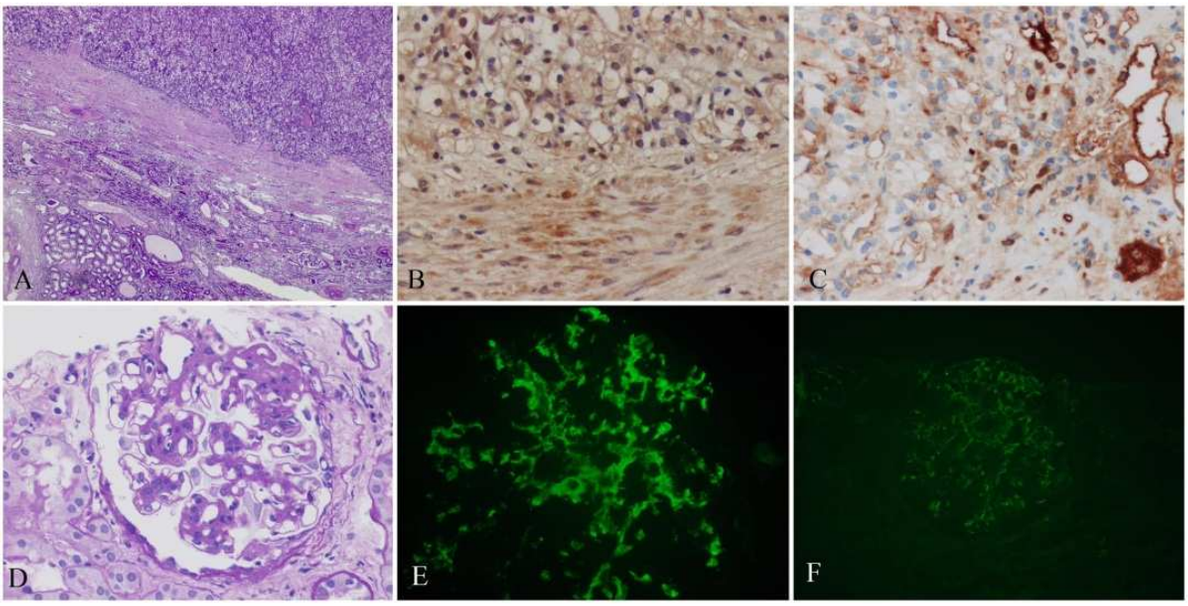

Figure 3. Clear cell renal cell carcinoma in association with IgA nephropathy. (A) PAS staining of clear cell carcinoma with a capsule. (B) immunostaining for IL-6 showing positive immunoreactivity in the infiltrating lymphocytes and plasma cells around the clear cell carcinoma and capsule. (C) IgA immunoreactivity positive in the plasma cells around renal cell carcinoma. (D) Renal biopsy sample showing segmental mesangial cell proliferation. (E) Immunofluorescence showed positive staining of IgA in the mesangial area, and weak staining of C3 (F).

4.2. Membranous nephropathy and renal cell carcinoma

The most frequent paraneoplastic glomerulopathy associated with solid tumors is membranous nephropathy and it is easy to detect because most of the cases manifest the nephrotic syndrome (paraneoplastic nephrotic syndrome) [3,23,33]. Since membranous nephropathy associated with malignancy has been attributed to tumor antigen-antibody immune complex formation, the cancer related antigens have been identified in immune complex in some cases including PSA in prostate cancer, CEA in gastrointestinal cancer [34]. Renal cell carcinoma has been reported to be associated with membranous nephropathy [35-43], but its prevalence is lower compared with gastrointestinal cancer and lung cancer (Table 3). As antibodies against phospholipase A2 receptor antibody have been identified in 70 % of patients with primary membranous nephropathy [44], a diagnosis of secondary membranous nephropathy should be considered when it is negative. IgG subclass immunofluorescence is useful to distinguish the primary membranous nephropathy in which IgG4 is stained predominately. In a case of secondary membranous nephropathy associated with renal cell carcinoma, showed predominantly IgG1 and IgG3 staining compared to IgG4 (Figure 4). The renal tubular epithelial antigen (RTE) has been identified in one case of renal cell carcinoma [45], but in most cases the tumor antigen-antibody complex were not identified in the serum

and elutes of glomeruli in patients with membranous nephropathy associated with renal cell carcinoma [35,40].

Even though tumor antigen-antibodies have not been identified yet, renal tumors may have some contribution to the pathogenesis of membranous nephropathy because nephrotic syndrome is transiently ameliorated after tumor excision [40-43].

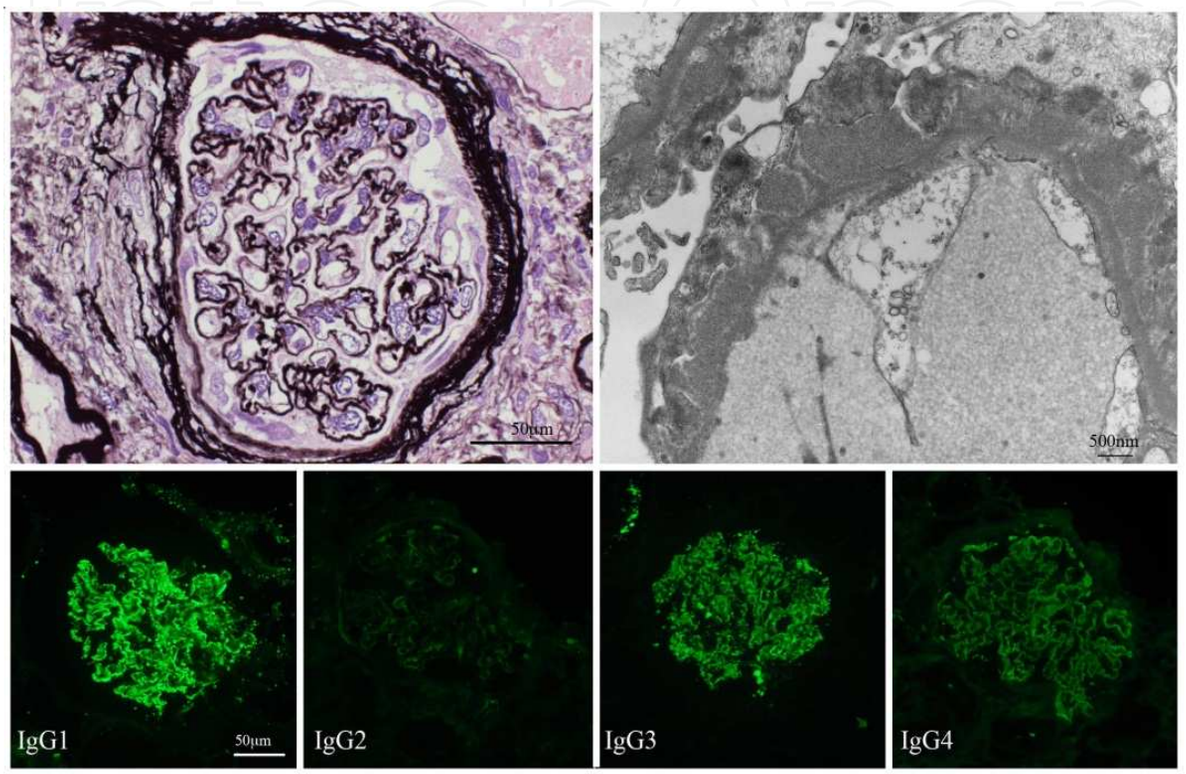

Figure 4. Secondary membranous nephropathy associated with clear cell renal cell carcinoma.

Light microscopy of PAM staining demonstrated thickening of the glomerular basement membrane, and electron microscopy revealed subepithelial electron dense deposits with spike formation. IgG1 and IgG3 were more strongly stained along the capillary wall than IgG4, suggesting secondary membranous nephropathy.

4.3. Minimal change disease and focal segmental glomerulosclerosis with renal cell carcinoma

In contrast to Hodgkin's disease, renal cell carcinoma associated with minimal change nephrotic syndrome is rare [46,47]. The onset of nephrotic syndrome is simultaneous [48,49] or precedes the diagnosis of renal tumor by 3-4 weeks [47,50], and there was a case in which complete remission was achieved after nephrectomy without steroids [49]. These lines of evidence suggest that occurrence of minimal change nephrotic syndrome may be a paraneoplastic syndrome associated with renal cell carcinoma. Renal oncocytoma, characterized by increased cytoplasmic volume containing abundant fine eosinophilic granules and mito-

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chondria, also show the paraneoplastic minimal change nephrotic syndrome [51]. The pathogenesis of minimal change nephrotic syndrome in not clear, but T cell-mediated immune response has been postulated. The increased secretion of VEGF from renal cell carcinoma may alter glomerular permeability and induce minimal change nephrotic syndrome.

Magyarlaki et al [21] reported 5 cases (8%) of focal segmental glomerulosclerosis in 60 autopsy cases of renal cell carcinoma, however, there are only a few reports of focal segmental glomerulosclerosis with renal cell carcinoma [52] and Wilms' tumor [53]. Glomerulosclerotic lesions are often observed in the renal parenchyma adjacent to a tumor, so parenchymal compression and urinary outflow obstruction by renal tumor may be involved in the development of focal segmental glomerulosclerosis.

4.4. Crescentic rapidly progressive glomerulonephritis and vasculitis with renal cell carcinoma

Crescentic glomerulonephritis with rapid progressive renal failure in conjunction with renal cell carcinoma has been reported previously [54-57]. The prevalence of renal cell carcinoma is significantly higher in patients with ANCA-positive Wegener's granulomatosis (7 in 477 patients) than in those with rheumatoid arthritis (1 in 479 patients) with an odds-ratio for development of renal cell carcinoma of 8.73 (p=0.0464, 95% CI 1.04-73.69) [58]. In most of the 7 cases, Wegener's granulomatosis was developed shortly after or simultaneously with the diagnosis of renal cell carcinoma [58]. There are many infiltrating cells around the clear cell renal cell carcinoma (Figure 5), and the chronic inflammation observed in renal cell carcinoma may induce anti-neutrophil cytoplasmic antibodies (ANCA) or the renal cancer cells may serve as an antigen source [59]. The renal prognosis in crescentic glomerulonephritis with renal cell carcinoma becomes poor when an anti-GBM antibody exists, and a rapid progression to end-stage renal failure with need of hemodialysis has been reported [54].

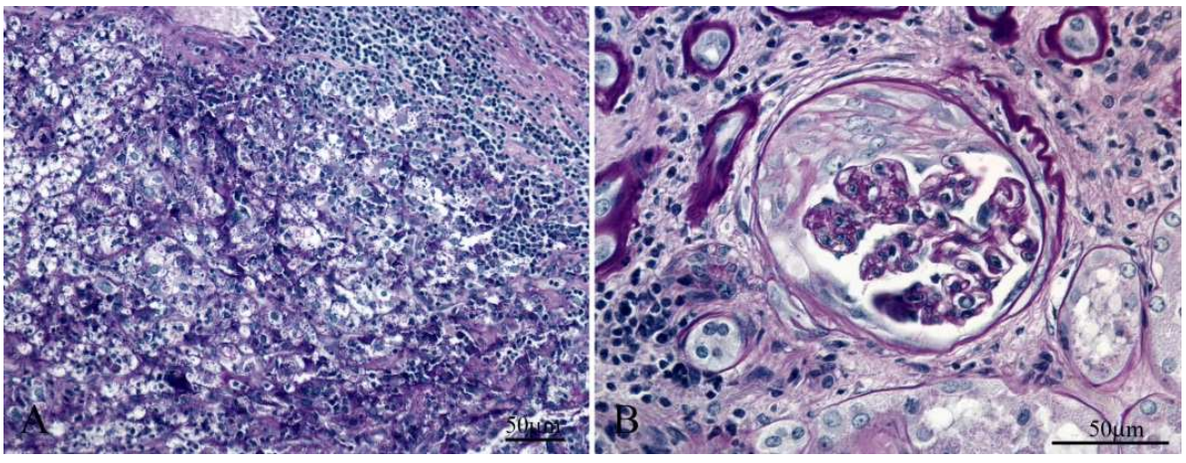

Figure 5. ANCA-related crescentic nephritis associated with renal cell carcinoma. A) The clear cell renal cell carcinoma was surrounded by many infiltrating inflammatory cells including lymphocytes, plasma cells and some neutrophils. B) Some glomeruli around the renal cell carcinoma demonstrated crescents, and the MPO-ANCA level was decreased from 217 EU to 99 EU after nephrectomy.

Membranoproliferative glomerulonephritis with crescents has been reported in patients with renal cell carcinoma, and elective nephrectomy improved both proteinuria and renal function after seven months [60]. Henoch-Schönlein purpura with leukocytoclastic vasculitis was also observed in a 25-year-old man with a small size (0.9x0.8cm) clear cell renal cell carcinoma [61]. Vasculitis associated with cancer is common in lymphoma and leukemia, but only 37 cases associated with solid tumor malignancies have been reported [62], including lung cancer, prostate cancer, colon cancer, renal cell carcinoma, breast cancer and squamous cell carcinoma [63]. Cytokine production by malignant cells, like renal cell carcinoma, may contribute to the development of vasculitis.

4.5. Scleroderma and lupus erythematosus with renal cell carcinoma

Renal cell carcinoma has an immunogenic feature. An interesting case was reported recently where clinical manifestations of scleroderma and proteinuria associated with renal cell carcinoma and membranous nephropathy in a 55-year-old man improved after heminephrectomy of the renal cell carcinoma [43]. Similarly, lupus nephritis developed in a 64 year-old male with clear cell renal carcinoma with para-aortic lymph node metastasis. After one year of partial nephrectomy, the renal cell carcinoma recurred with nephrotic syndrome and pericarditis, and laboratory examination showed an increase in IgG (3449 mg/dL), IgA (371 mg/dL), IgM (715 mg/dL), anti-nuclear antibody (x320) and anti-double strand DNA antibody (41 IU/mL) with low complement levels (CH50 10 U/mL, C3 60, C4 10 mg/dL). Immunohistochemical examination of the resected kidney and para-aortic lymph nodes revealed increased infiltration of plasma cells producing IgG, IgM and IgA around the tumor (Figure 6), suggesting that renal cell carcinoma may have some role in the development of lupus erythematosus.

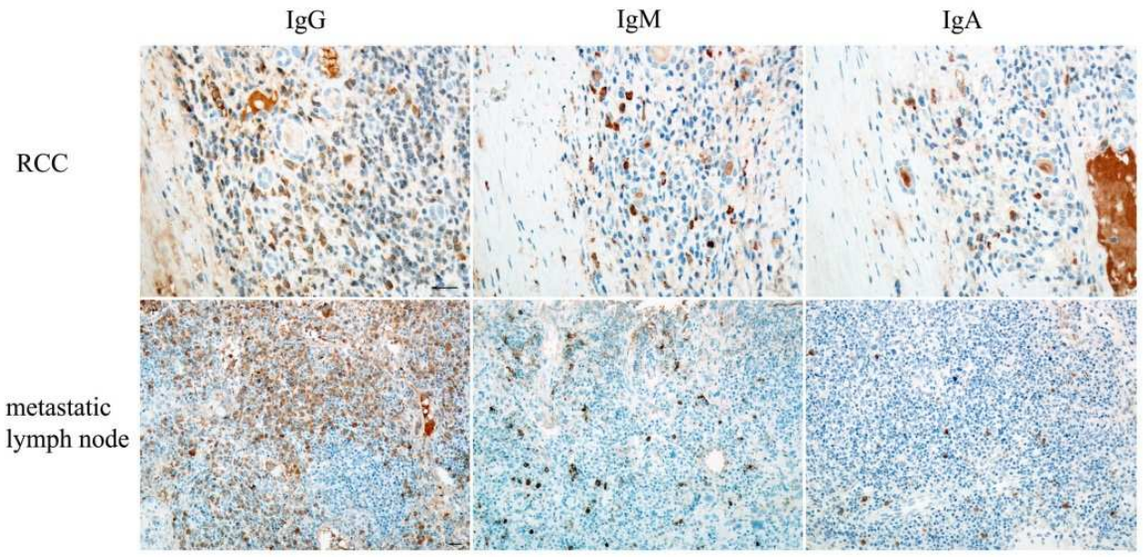

Figure 6. Immunohistochemistry for IgG, IgM, and IgA in the resected kidney of renal cell carcinoma and its para-aortic lymph node metastasis. The patient developed lupus erythematosus and nephrotic syndrome when renal cell carcinoma recurred and progressed.

4.6. Amyloidosis associated with renal cell carcinoma

About 3% of patients with renal cell carcinoma develop systemic amyloidosis [64], and the amyloid is composed of AA protein [65,66]. The renal cell carcinoma may be involved in the stimulation of hepatic production of acute phase reaction proteins including serum amyloid A protein, and the modification of amyloidogenic proteins by the monocyte-macrophage system in the chronic inflammatory lesion of renal cell carcinoma, causing the secondary amyloidosis. Remission of amyloidosis and nephrotic syndrome has been reported after nephrectomy [65,67,68].

4.7. Tubulointerstitial nephritis

Tubulointerstitial nephritis is often difficult to identify because it does not show obvious abnormalities in urine. However, 27% of patients with renal cell carcinoma showed tubulointerstitial nephritis in resected kidney (Table 2) [21]. Recently, as a mechanism of tubulointerstitial nephritis, the antibody against carbonic anhydrase II (CAII) was identified in Sjögren syndrome with renal tubular acidosis [69] and IgG4 related tubulointerstitial nephritis [70]. Carbonic anhydrase is a zinc metalloenzyme that catalyzes the hydration of carbon dioxide and the dehydration of bicarbonate in the proximal tubules and the distal nephron including the intercalated cells of the collecting duct. CA has 15 isoforms and CAII accounts for more than 95 % of CA activity in the kidney and exists in the cytosol, and the remaining 5% renal CA is membrane associated CAIV and CAXII [71]. CAIX is not expressed in the normal kidney, however, in renal cell carcinoma CAIX is induced by hypoxia as a tumor-associated antigen [72,73]. Inactivation of the VHL gene complex leads to the stabilization of hypoxia inducible factor-1α which activates CAIX gene expression [74]. CAIX may promote tumor growth and survival in hypoxic and acidic environments [73]. Serum levels of CAIX are higher in clear cell renal cell carcinoma than non-clear cell renal cell carcinoma and it is a useful marker for the differential diagnosis of renal cell carcinoma and also as a maker of tumor size [75]. It could be possible that an autoantibody against CAIX could be induced and cause tubulointerstitial nephritis in renal cell carcinoma.

5. Treatment of paraneoplastic glomerulopathy associated with renal cell carcinoma

The primary treatment for renal cell carcinoma is surgical excision including radical nephrectomy, nephron-sparing partial nephrectomy, laparoscopic nephrectomy and percutaneous ablation by radiofrequency heat or cryoablation [5]. Most cases of nephrotic syndrome associated with renal cell carcinoma showed remission or transient reduction of proteinuria just after nephrectomy as summarized in Table 4. It is interesting that only nephrectomy can achieve remission of nephropathy with amyloidosis [65,67,68], which is usually refractory to treatment. Some cases of IgA nephropathy, membranous nephropathy, crescentic glomerulonephritis and focal segmental nephrosclerosis associated with renal cell carcinoma progressed to end stage renal failure. In addition to nephrectomy, treatment with prednisolone

was attempted in some cases, especially in minimal change nephrotic syndrome, and showed reduction of proteinuria. However, it is noteworthy to recognize that the cyst at the time of biopsy rapidly enlarged after treatment with prednisolone for IgA nephropathy, and a diagnosis of renal cell carcinoma was made later [28]. Thus, the first line of treatment of paraneoplastic glomerulopathy associated with renal cell carcinoma is nephrectomy, and the use of steroids should be limited only to cases of controlled renal cell carcinoma.

Glomerulopathy	Age, sex	Treatment	Outcomes	References
IgAN	61 M	nephrectomy	Remission	Tanaka [26]
IgAN	8 cases	nephrectomy	Remission (6/8)	Magyarlaki [21]
IgAN	58 M 66 M 59 M	Steroid, nephrectomy Steroid 30mg, nephrectomy nephrectomy	Remission ESRD Remission	Mimura [28]
MN	76 F	nephrectomy	Died (33 days)	Stein [37]
MN	69 M	steroid 50mg	Died (6 months)	Nishihara [38]
MN	62 M	Partial nephrectomy	PR	Fujita [39]
MN	57 M	nephrectomy	TR/relapse	Togawa [40]
MN	72M	nephrectomy	TR/ESRD	Kapolas [41]
MN	77 F	nephrectomy	remission	Kuroda [42]
MN	55 M	nephrectomy	remission	Nunez [43]
MCNS	49 M	Nephrectomy, steroid	PR	Forland [51]
MCNS	70 M	nephrectomy	Remission after biopsy	Lee [49]
MCNS	69 M	Steroid 80mg, CPM150mg	Died of infection	Abouchacra [48]
MCNS	64 F	Nephrectomy, steroid 60mg	PR	Woodrow [50]
MCNS	78 M	nephrectomy, steroid 1mg/kg	Complete remission	Auguet [47]
FSGS	48 M	nephrectomy	Worsened sCr	Ejaz [52]
CresGN /GBM-Ab	74 M	nephrectomy	ESRD	Hatakeyama [54]
CresGN/MPO-ANCA	68 F	nephrectomy, steroid	Remission	Karim [56]
CresGN	35 F	HD	ESRD died on HD	Jain [57]
MPGN	26 F	nephrectomy	remission	Tydings [76]
MPGN	65 M	nephrectomy	remission	Ahmed [60]
amyloidosis	66 F	diuretics	NS, Died (respiratory failure)	Pras [66]
amyloidosis	58 F	Nephrectomy, splenectomy	Remission (7months)	Vanatta [65]
amyloidosis	62 M	nephrectomy	Remission (3years)	Karsenty [67]
amyloidosis	54 F	nephrectomy	Remission (5years) died of relapse	Tang [68]

IgAN: IgA nephropathy, MN: membranous nephropathy, MCNS: minimal change nephrotic syndrome, FSGS: focal segmental glomerulosclerosis, cresGN: crescentic glomerulonephritis, MPGN: Membranoproliferative glomerulonephritis, PR: partial remission, ESRD: end-stage renal disease, TR transient remission, CPM cyclophosphamide, HD: hemodialysis, NS: nephrotic syndrome.

Table 4. Treatment and outcomes of glomerulopathy with renal cell carcinoma

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6. Molecular-target therapy related nephropathy in renal cell carcinoma

About 30% patients will have distant metastasis at the time of diagnosis, and medical therapies including interleukin-2, interferons, and molecular-target therapy are generally offered for advanced renal cancer as listed in Table 5. Interleukin-2 showed transient proteinuria and renal dysfunction, but these changes are reversible and did not cause long-term intrinsic renal damage [77-79]. Interferons are well known to show proteinuria in 15-20% of patients [80]. The nephrotic syndrome and acute renal failure induced by interferon therapy are histologically due to minimal change disease and acute tubulointerstitial nephritis [80-82].

Bevacizumab, a humanized monoclonal anti-vascular endothelial growth factor antibody, is used for the treatment of metastatic renal cell carcinoma, but adverse effects such as hypertension, anorexia and proteinuria are increased with combination therapy of bevacizumab and interferon α compared with interferon α monotherapy [83,84]. High-dose bevacizumab therapy showed proteinuria of more than 1+ in 64% of patients with renal cell carcinoma and nephrotic range proteinuria of more than 3.5 g/day in 7.7% patients [85]. Renal biopsy revealed thrombotic microangiopathy in two patients treated with Bevacizumab and interferon-α [86]. As VEGF is expressed in the podocyte and its receptors are found in glomerular endothelial cells, blocking VEGF may disturb the function of VEGF to maintain the glomerular capillary permeability barrier, causing thrombotic microangiopathy [87,88].

Treatment of renal cell carcinoma with sunitinib or sorafenib, which inhibit the VEGF receptor and multi-tyrosine kinases, induced severe nephrotic syndrome with acute renal failure, and renal biopsy revealed minimal change disease and thrombotic microangiopathy with acute tubular necrosis [89,90]. Sunitinib also develops other pathological forms of renal diseases including acute interstitial nephritis [91], acute nephritic syndrome with subendothelial C3 deposition [92], FSGS [93], and sorafenib is also associated with IgA nephropathy [94], and interstitial nephritis [95]. Withdrawal of sunitinib or sorafenib with or without use of steroids ameliorated increased serum creatinine and proteinuria as well as hypertension and edema [91,93-95], but in some advanced cases hemodialysis was needed [89, 92] or proteinuria persisted [90]. Thus, early detection of renal adverse effects of these drugs is necessary.

Temsirolimus is a highly specific inhibitor of the mammalian target of rapamycin, which is a central regulator of intracellular signaling pathways and an inhibitor of angiogenesis. Temsirolimus has prolonged overall survival in patients with advanced renal cell carcinoma compared to interferon-α [96]. However, temsirolimus reduced synaptopodin and nephrin expression in podocytes and induced nephrotic syndrome caused by focal segmental glomerulosclerosis [97]. The amount of proteinuria decreased after withdrawal of temsirolimus, so it is necessary to notice the nephrotic adverse effects of this drug.

Medical therapy	Mechanism	Renal diseases	References
Interleukin-2	immunomodulatory cytokine	Proteinuria, transient increase in sCr	Belldegrun [77]
			Shalmi [78]
			Guleria [79]
Interferon α, γ	immunomodulatory cytokine	proteinuria, MCNS, IN, ARF	INF-α: Quesada [80]
			IFN-γ: Nair [81], Tashiro [82]
Bevacizumab	Humanized VEGF-neutralizing antibody	Proteinuria, TMA	Rini [83], Summers [84],
			Roncone [86]
Sunitinib	VEGF receptor and multiple tyrosine kinase inhibitor	MCNS, iATN	Chen [89]
		AIN	Winn [91]
		AGN	Rolleman [92]
		FSGS, TMA	Costero [93]
Sorafenib	VEGF receptor and multiple tyrosine kinase inhibitor	TMA, MCNS	Overkleeft [90]
		IgAN	Jonkers [94]
		AIN	Izzedine [95]
Temsirolimus	Inhibitor of the mammalian target of rapamycin	FSGS	Izzedine [97]

MCNS: minimal change nephrotic syndrome, IN: interstitial nephritis, ARF: acute renal failure, TMA: thrombotic microangiopathy, iATN: ischemic acute tubular necrosis, AGN:acute glomerulonephritis.

Table 5. Interleukin, interferon and molecular-target drugs related nephropathy in the renal cell carcinoma

7. Summary

Recent advances in the molecular understanding of renal cell carcinoma have shed light on the mechanism of paraneoplastic glomerulopathy. Clear cell renal cell carcinoma with a VHL gene mutation stimulates HIF-1α transcription, and produces various cytokines and growth factors including VEGF, PDGF, TGF−α/β, IL-6, CAIX and EPO. Renal cell carcinoma has a feature of cytokine disease or immunogenic disease, and enhanced cytokines and growth factors stimulate lymphocytes and plasma cells, and the latter works as a causative factor for various forms of paraneoplastic glomerulopathies. The precise mechanism of glomerulonephritis has not been completely elucidated, and further investigation of renal cell carcinoma related glomerulopathies will open a new perspective in the understanding of glomerular diseases.

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