—Review—

Current Trends in Anti-Cancer Molecular Targeted Therapies: Renal Complications and Their Histological Features

Akiko Tonooka[1,2] and Ryuji Ohashi[3]

[1]Division of Pathology, Cancer Institute, Japanese Foundation for Cancer Research, Tokyo, Japan
[2]Department of Pathology, Tokyo Metropolitan Cancer and Infectious Diseases Komagome Hospital, Tokyo, Japan
[3]Department of Integrated Diagnostic Pathology, Nippon Medical School, Tokyo, Japan

Among recent advances in cancer treatment, the emergence of novel drugs targeting specific molecules has considerably modulated therapeutic strategies. Despite the efficacy of these agents, renal complications that are distinct from those of conventional chemotherapeutic drugs have been reported. Targeted therapy drugs include monoclonal antibodies and small-molecule agents. Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor (VEGF) and blocks tumor angiogenesis. This anti-angiogenic effect causes endothelial injury, resulting in "thrombotic microangiopathy-like lesions" confined to the glomerulus. Segmental hyalinosis of the glomerular tuft is also observed. Small molecular agents, including tyrosine kinase inhibitors (TKIs) such as pazopanib, can cause endothelial injury and podocytopathy by blocking VEGF receptors and their downstream signaling. Minimal change nephrotic syndrome and focal segmental glomerulosclerosis are associated with TKI-induced renal complications. Immune checkpoint inhibitors (ICIs) such as PD-1, CTLA-4, and PD-L1 modulate immune checkpoints and are a novel form of immunotherapy against cancer. Owing to their unique function, ICIs cause inflammatory side effects referred to as immune-related adverse events (irAEs). irAEs in the kidney include acute tubulointerstitial nephritis and tubulitis, occasionally accompanied by granuloma formation. Vasculitis, thrombotic microangiopathy, and glomerulonephritis have also been reported. Renal toxicity associated with other molecular drugs, such as protease inhibitors and mammalian target of rapamycin inhibitors, has also been documented. In this article, we review the clinicohistopathological aspects of renal complications associated with molecular targeted therapies and focus on anti-VEGF agents and immune checkpoint inhibitors from a pathological perspective.
(J Nippon Med Sch 2022; 89: 128–138)

Key words: onconephrology, targeted therapy, anti-VEGF, immune checkpoint inhibitors, histopathology

Introduction

Cancer treatment includes surgery, anti-cancer drugs, and radiotherapy. For patients with advanced cancer, cytotoxic chemotherapy drugs, such as alkylating agents or antimetabolite, are commonly administered despite their severe side effects; cellular toxicity in cancer cells as well as non-cancer cells is a major issue to be resolved. On the basis of our understanding of cancer genomics and pathogenesis, molecular targeted therapies have recently emerged as potential cancer treatments[1]. Molecular targeted therapy involves identifying and destroying cancer cells by blocking specific molecules involved in tumor growth, such as receptor tyrosine kinase, or by activating immune cells programmed to target cancer cells. Because of tumor specificity, molecular targeted therapy is much less likely than traditional chemotherapy to have lethal side effects. However, distinct side effects affecting systemic organs have been reported, some of which are yet to be described, owing to the limited number of cases. In this article, we review and discuss the clinicohistopa-

Correspondence to Ryuji Ohashi, MD, PhD, Department of Integrated Diagnostic Pathology, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: r-ohashi@nms.ac.jp
https://doi.org/10.1272/jnms.JNMS.2022_89-221
Journal Website (https://www.nms.ac.jp/sh/jnms/)

Table 1 Common histological variations of drug-induced renal injury

		Tubules		Glomeruli			Others
		ATIN	ATI	Podocyto-pathy	TMA-like lesion	Immune complex-mediated glomerulo nephritis	
Broadspectrum Chemotherapy	Cisplatin		+++				Fanconi syndrome
	Ifosfamide		+++				Fanconi syndrome
	Gemcitabine	+			+++		
Targeted chemotherapy	Bevacizumab (anti-VEGF antibody)				+++		
	Ramucirumab (anti-VEGFR2 antibody)				+++		
	Tyrosine kinase inhibitors	+		++	++		
	Immune check point inhibitor	+++		+	+	+	
	EGFR inhibitors		+		+	+	
	mTOR inhibitors		+++	+	+		cast
	Proteosome inhibitors				++		

Abbreviations: ATIN, acute tubulointerstitial nephritis; ATI, acute tubular injury; TMA, thrombotic microangiopathy; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2; EGFR, epidermal growth factor receptor; mTOR, mechanistic target of rapamycin.

thological aspects of renal complications associated with molecular targeted therapy, including anti-vascular endothelial growth factor (VEGF) drugs and immune checkpoint inhibitors, to update knowledge for regular clinical practice while treating cancer patients.

Drug-Induced Renal Complications

Because of their role in excreting wastes from the body, the kidneys are highly susceptible to extrinsic insults. Renal complications can potentially be elicited by a variety of therapeutic agents, including antimicrobial agents, analgesics, immunosuppressive agents, and chemotherapeutic agents[2]. Clinically, drug-induced renal injury is classified as acute kidney injury (AKI), tubular dysfunction, glomerular disease, and nephrolithiasis[3]. From a histological perspective, AKI and glomerular injury are more likely to be associated with morphological changes. AKI is characterized by acute tubular necrosis and acute tubulointerstitial nephritis, and glomerular lesions include podocytopathy and glomerulonephritis. Although chemotherapy drugs and molecular targeted agents can both cause nephrotoxicity, the pattern of injury is different[4]. Chemotherapy drugs such as cisplatin and ifosfamide, an alkylating agent, commonly affect tubules, leading to acute tubular necrosis or injury[5]. In contrast, molecular targeted agents tend to cause glomerulopathy characterized by podocytopathy or thrombotic microangiopathy (TMA)[5–7] (**Table 1**). Below, we will address the histological characteristics of renal injury associated with each type of molecular targeted drug.

Renal Complications of Molecular Targeted Drugs (Table 2)

Targeted therapy drugs include monoclonal antibodies and small molecular agents[8]. Monoclonal antibodies are proteins that bind to specific targets on cancer cells. They include various antibodies, such as rituximab (anti-CD20 antibody), nivolumab (anti-programmed cell death-1(PD-1) antibody), and bevacizumab (anti-vascular endothelial growth factor (VEGF) antibody). Small molecular agents include low molecular weight compounds that enter cells to modify the cell signaling cascade. The currently used small molecular agents include the tyrosine kinase inhibitors (TKIs), such as anti-epidermal growth factor receptor (EGFR) (gefitinib) and anti-breakpoint cluster region-Abelson (BCR/ABL) (imatinib). A recent analysis of data from the Food and Drug Administration Adverse Event Reporting System found that small molecular protein kinase inhibitors such as entrectinib, sirolimus, and cobimetinib were strongly associated with AKI incidence[9]. In the following sections, we will discuss the histopathological features of renal injury induced by anti-VEGF drugs and other types of TKIs, as well as nephrotoxicity induced by immune checkpoint inhibitors.

Table 2 Targeted agents described in this review

	Target	Name of drug
Monoclonal antibody	CD20	Rituximab
	VEGF	Bevacizumab
	VEGFR2	Ramucirumab
	PD-1	Nivolumab, Pembrolizumab
	PD-L1	Durvalumab, Atezolizumab, Avelumab
	CTLA-4	Ipilimumab
Tyrosine kinase inhibitor	VEGF	Pazopanib
	EGFR	Gefitinib
	BCR/ABL	Imatinib
	ROS1/TRK	Entrectinib
	Bruton's TK	Ibrutinib
Other types of agents	Protease inhibitor	Bortezomib, Carfilzomib
	mTOR inhibitor	Everolimus, Sirolimus, Temsirolimus
	VEGF trap	Aflibercept
	MEK inhibitor	Cobimetinib

Abbreviations: VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte associated antigen 4; BCR/ABL, breakpoint cluster region-Abelson; ROS1/TRK, ROS proto-oncogene 1/tropomyosin receptor kinase; Bruton's TK, Bruton's tyrosine kinase; mTOR, mammalian target of rapamycin.

Anti-VEGF Drugs and Other Types of Tyrosine Kinase Inhibitors

1. Classification of Anti-VEGF Drugs

Anti-VEGF drugs include monoclonal antibodies, VEGF trap, and TKIs[10,11] (**Fig. 1**). Furthermore, monoclonal antibody drugs include anti-VEGF and anti-VEGF receptor (VEGFR) antibodies. VEGF trap, commercially recognized as aflibercept, is a recombinant fusion protein that comprises the VEGFR1 and VEGFR2 extracellular domains and acts as a soluble decoy receptor of VEGF[12,13].

2. Endothelial Injury Associated with Inhibition of VEGF and Its Receptors

VEGF and its receptors are the principal drivers of angiogenesis and lymphangiogenesis and are important for maintaining the vascular network[14]. VEGF induces endothelial cell proliferation and migration, and promotes permeability of vessel walls[15]. In the kidney, the integrity of glomerular capillaries is preserved by VEGF by promoting transmembrane communication between podocytes and endothelium[16]. VEGF, produced by podocytes, binds to VEGFRs on endothelial cells, thus exerting its effects while VEGF elicits an autocrine effect on podocytes. Anti-VEGF drugs can impair the function of glomerular capillary walls by blocking communication between endothelial cells and podocytes via VEGF[17].

Proteinuria and hypertension are the two major adverse effects associated with anti-VEGF drugs[18].

Although patients with acute TMA usually present with thrombocytopenia and fragmented erythrocytes, the typical bevacizumab-induced lesions are a renal-limited disease, histologically characterized by duplication of glomerular basement membrane, microaneurysm, and, rarely, thrombi formation[19] (**Fig. 2 A, B**). Once the endothelium is damaged, the subendothelial spaces are filled with proteinaceous fluid, causing microaneurysms. Over time, plasma insudations solidify to form segmental hyalinosis that can be described as "pseudo-thrombi" (**Fig. 2 C, D**). Because of these unique findings, the term glomerular microangiopathy was proposed for bevacizumab-induced lesions[19,20]. It remains uncertain why anti-VEGF drugs induce renal-limited TMA but not systemic acute TMA. We suspect that it may be due to the unique nature of glomerular endothelial cells, distinct from other vessels. The integrity of glomerular endothelial cells is maintained by communication between endothelial cells and podocytes over the glomerular basement membrane. Once this integrity is destroyed, glomerular endothelial cells suddenly become vulnerable, resulting in renal-limited TMA. Confirmation of this hypothesis will require further study. Electron microscopic observation revealed that this microaneurysmal space is filled by materials of differing intensity. By contrast, segmental hyalinosis has a structure consisting of homogeneous osmiophilic material[19]. In mass spectrometry, C4b-binding

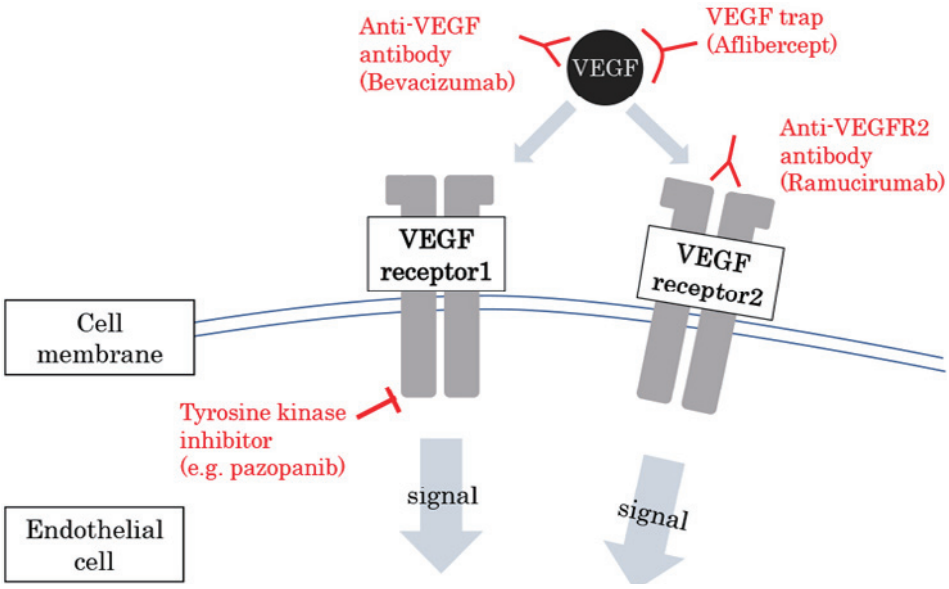

Fig. 1 Schematic diagram of anti-VEGF drugs

Vascular endothelial growth factor (VEGF) is released by podocytes and binds to VEGF receptors of endothelial cells, thus leading to the initiation of signal transduction pathways. Anti-VEGF drugs comprise anti-VEGF antibody, VEGF trap, anti-VEGFR2 antibody, and tyrosine kinase inhibitors. Anti-VEGF and anti-VEGFR2 antibodies block VEGF function at extracellular sites. VEGF trap is a recombinant fusion protein composed of the VEGFR1 and VEGFR2 extracellular domains and acts as a soluble decoy receptor of VEGF. Tyrosine kinase inhibitors are small molecules that enter endothelial cells to inhibit downstream signals.

protein alpha chain is the major protein occupying a bevacizumab-induced microaneurysm, whereas fibrin is a major constituent in other types of TMA-like lesions, such as transplant glomerulopathy[20].

A recent study reported that intravitreal injection of bevacizumab triggers TMA-like lesions in glomeruli, causing proteinuria[21–23]. These findings indicate that clinicians need to be aware that even local use of bevacizumab, such as by intravitreal injection, can lead to systemic side effects, although the possibility is likely negligible.

Ramucirumab is a monoclonal antibody against VEGFR 2, which causes renal-limited TMA-like lesions[24,25]. Some of our patients developed nephrotic syndrome soon after switching from bevacizumab to ramucirumab[24]. Renal biopsy revealed chronic TMA-like lesions, represented by duplicated glomerular basement membrane and segmental hyalinosis. The findings suggested that the chronicity of renal injury was not correlated with the rapid onset of nephrotic syndrome after the use of ramucirumab; however, bevacizumab use might have predisposed glomeruli to develop nephrotic syndrome, which was triggered by use of ramucirumab[25]. In addition to these chronic changes, infiltration of foamy macrophages was noted in some glomerular capillaries. It may be that these changes are associated with hyperlipidemia, as all patients had high cholesterol levels. A similar finding was reported in the setting of bevacizumab-induced glomerular microangiopathy, although the underlying cause is a matter of debate[19].

3. Podocytopathy in Anti-VEGF Drugs

Podocytopathy, characterized by minimal change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS), is another manifestation of renal complications with anti-VEGF-drugs (**Fig. 3A**). In particular, TKIs can preferentially cause podocytopathy by blocking several receptors, including VEGFR and its downstream signaling, resulting in suppression of endothelial proliferation and maintenance[15]. This process is hypothetically mediated by two intracellular proteins, c-mip and RelA, which regulate cell integrity, as suggested by the decrease in RelA expression and increase in c-mip expression in podocytes of patients treated with TKIs[13,26–28]. This finding was further confirmed in an *in vitro* study demonstrating that RelA blocking induced overexpression of c-mip, leading to podocyte injury[28,29]. In addition to podocytopathy, TMA-like lesions were reported in patients treated with TKIs[30,31] (**Fig. 3B**). In these patients, podocytopathy and TMA-like lesions developed simultaneously. These diverse histological changes are attributed to co-

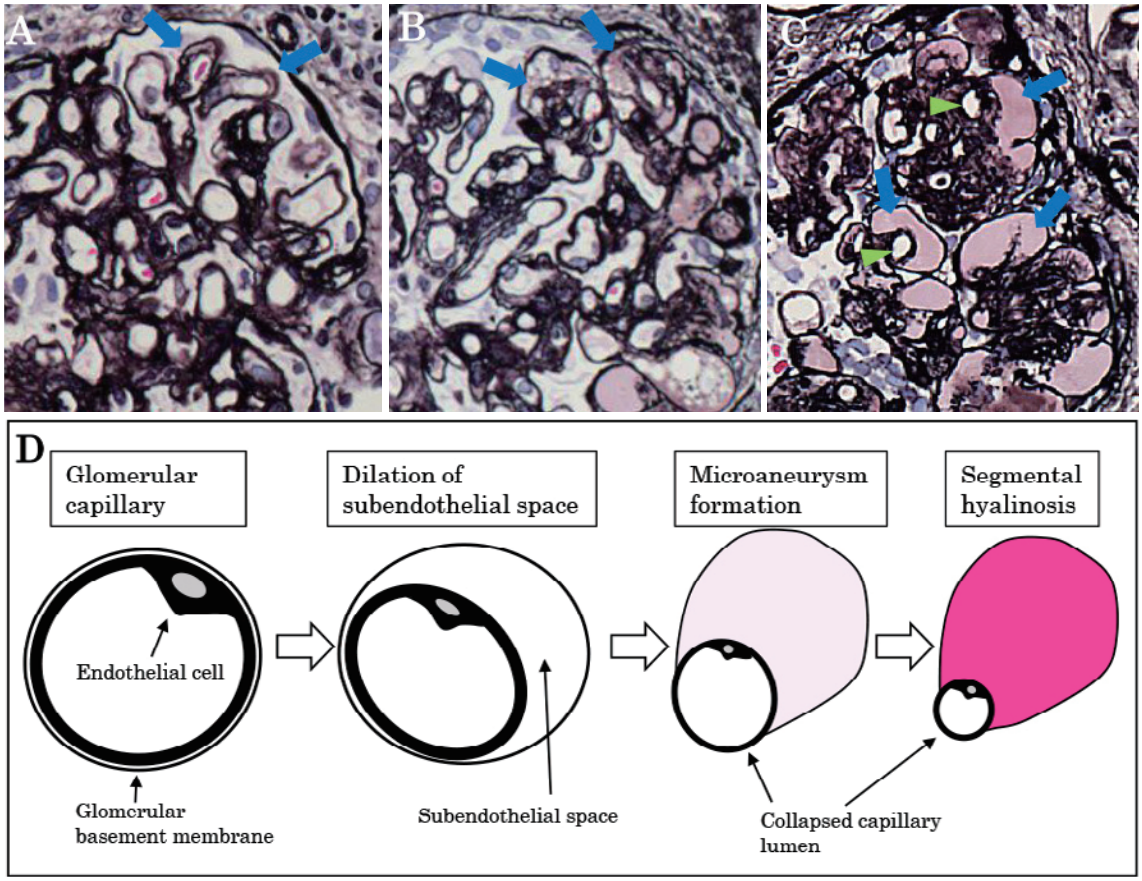

Fig. 2 Characteristic findings of anti-VEGF drug-induced thrombotic microangiopathy (TMA)
A-C. Bevacizumab-induced renal lesions (A-C. PAM stain). Within glomerular capillaries, the dilatation of subendothelial spaces is noted (A. arrows). Over time, the subendothelial spaces widen (B. arrows) and microaneurysms develop (C. arrows). Insudative materials within the dilated subendothelial space around narrowed capillary lumina (C. arrowheads) solidify to form segmental hyalinosis.
D. Schematic diagram of anti-VEGF drug-induced TMA in glomeruli. Endothelial injury causes dilation of the subendothelial space, whereas the original capillary lumen collapses, leading to development of a microaneurysm filled with proteinaceous fluid. Over time, plasma insudations solidify, forming segmental hyalinosis. Although these lesions are unique, it is sometimes difficult to distinguish between widened subendothelial spaces and the dilated capillary lumina when endothelial cells are severely damaged and are accompanied by insudative change.

incidence of podocytopathy, possibly by a mechanism involving c-mip and RelA, and endothelial cell injury by TKIs. We observed similar histological changes in a nephrectomy specimen resected after neoadjuvant therapy using TKIs for renal cell carcinoma. Although proteinuria was not severe in these patients, the rapid onset right after use of TKIs suggests that the glomerular injury might have been induced by drug administration (our unpublished data). This finding suggests that we should carefully monitor renal function during anti-VEGF drug therapy, regardless of clinical conditions.

4. Renal Injury Caused by Other Types of Tyrosine Kinase Inhibitors

Renal complications have been reported for other types of tyrosine kinase inhibitors[9,32]. An EGFR tyrosine kinase inhibitor, gefitinib, which was originally used for non-small cell carcinoma of the lung, was suggested to be a rare cause of renal disease. Recent reports, however, suggest that gefitinib can trigger diverse renal disease, MCNS, tubulointerstitial nephritis, membranous nephropathy, and IgA nephropathy, although the underlying mechanisms are unclear[33–35]. Conversely, an anti-EGFR antibody, such as cetuximab, was associated with hypomagnesaemia due to inhibition of EGFR-mediated Mg^{2+} reabsorption from urine in renal tubules[36].

Recently, renal toxicity due to the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib was reported[37,38]. BTK is important in regulating the immune system, including B-cell development, and in the production of inflammatory mediators and cytokines. Therefore, ibrutinib has been

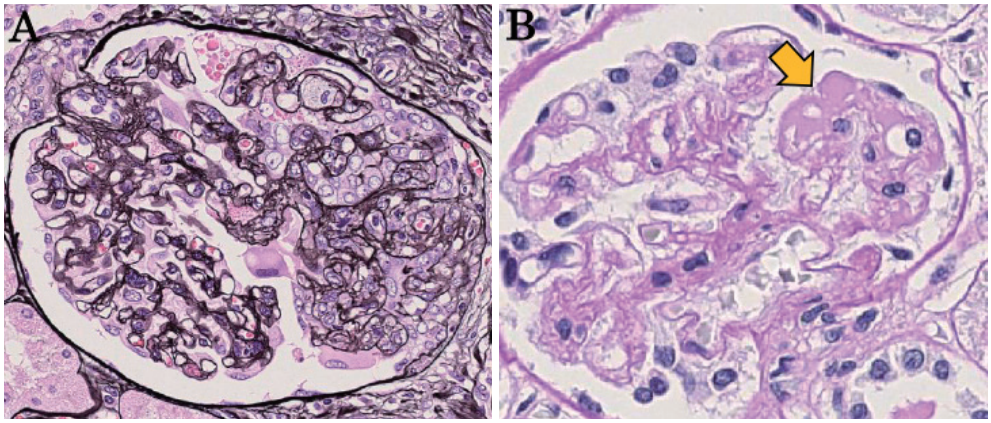

Fig. 3 Glomerular findings associated with pazopanib (tyrosine kinase inhibitor) (A, B).
Focal segmental glomerular sclerosis with hypertrophy of overlying epithelial cells (A. PAM stain).
Segmental hyalinosis (arrow) within the glomerular capillaries, referred to as a "TMA-like lesion" (B. PAS stain).

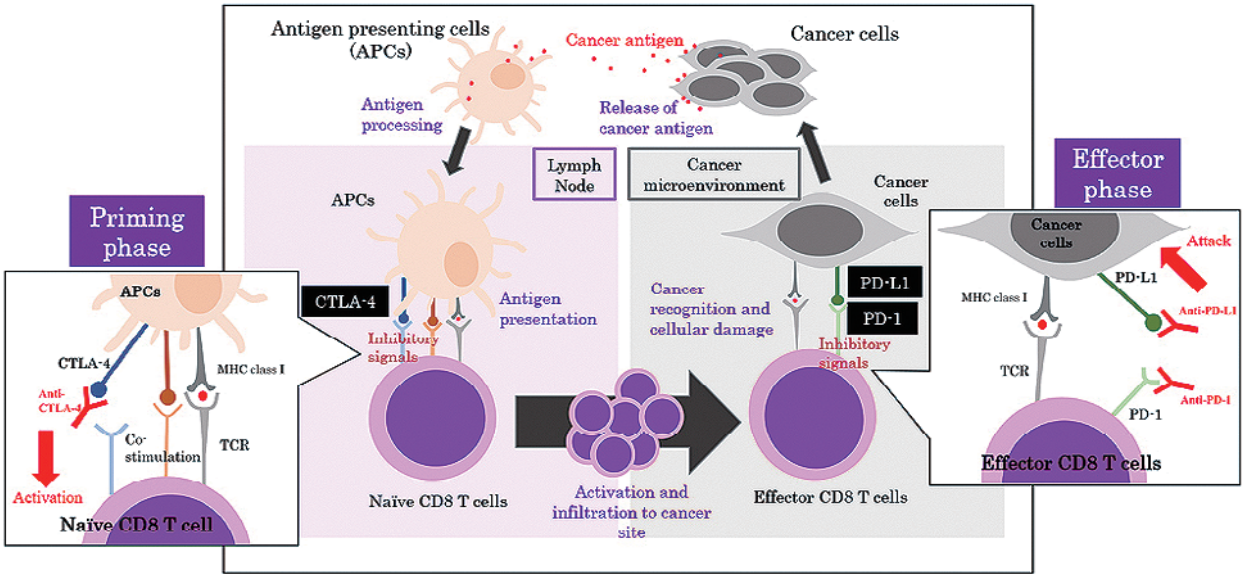

Fig. 4 Cancer immune cycle
Cancer antigens released by degenerated cancer cells are trapped and processed by antigen presenting cells and are presented on the surface of naïve CD8 T cells (priming phase). Then naïve T cells become activated T cells and infiltrate the cancer microenvironment to recognize and destroy cancer cells (effector phase). Some types of cancer can survive by escaping this immunity cycle via CTLA4 and/or PD-1/PD-L1-dependent mechanisms. CTLA4 and PD-1 / PD-L1 suppress T cells in the signal transduction of APCs or cancer cells and T cells, respectively. Anti-CTLA-4 / PD-1 / PD-L1 antibodies activate T cells by blocking their inhibitory signals and contribute to attacking cancer cells.

used to treat patients with chronic lymphocytic leukemia and mantle cell lymphoma[39]. A recent study reported several cases of ibrutinib-induced acute tubular injury and tubulointerstitial nephritis with elevated serum creatinine levels. Although the mechanisms for these lesions are unclear, an association with endothelial injury is suspected[37].

Immune Checkpoint Inhibitors (ICIs)

A novel treatment strategy against cancer using ICIs is a form of immunotherapy. This therapy involves modulation of immune checkpoints that are key regulators of the cancer immunity.

1. Cancer Immune Cycle

Figure 4 depicts a cancer immune cycle[40]. Currently approved ICIs target the immune checkpoint molecules, such as PD-1, cytotoxic T-lymphocyte associated antigen-4 (CTLA-4), and PD-L1[41,42]. In the cancer immune cycle, CD8+ T cells play a major role in recognizing and de-

stroying cancer cells. However, some cancer cells can evade this host immune system by taking advantage of peripheral tolerance mediated via CTLA-4-dependent or PD-1-dependent pathways[43]. In lymph nodes, antigens from degraded cancer cells are processed and presented to naïve CD8+ T cells by antigen presenting cells (APCs) (priming phase)[44]. Subsequently, activated CD8+ T cells are recruited as cytotoxic T cells to the cancer microenvironment to destroy the target cells (effector phase). To escape immunological attack, cancer cells mute T cells by limiting the binding of the ligand PD-L1, expressed on the cancer cell, to its receptor PD-1 on the T cells[45].

2. Characteristics and Associated Complications of ICIs

Anti-PD-1/PD-L1 antibody can disrupt the inhibitory effect of the immune checkpoint molecule and recover the cytotoxic effect of T cells. Anti-CTLA-4 antibody can also stimulate cytotoxic T cells by blocking the association between T cells and APCs via CTLA-4. Ipilimumab, an anti-CTLA-4 antibody, was the first ICI to be used, and was followed by anti-PD-1 antibodies, including nivolumab and pembrolizumab[41].

ICIs differ from other types of anti-cancer drugs in many ways. More specifically, they cause inflammatory side effects referred to as immune-related adverse events (irAEs)[46]. irAEs might occur because of overactivation of the immune system, which affects multiple organs, such as skin, gastrointestinal tract, and endocrine organs, among others. Common irAEs are hypophysitis, colitis, hepatitis, pneumonitis, and skin rash[46]. Some patients develop irAEs resembling those of autoimmune diseases such as arthritis, myositis, and polymyalgia-like syndromes[47]. Anti-CTLA-4 drugs are more likely than anti-PD-1 to be associated with irAEs[48]. Inhibition of CTLA-4 likely leads to diffuse and nonspecific T-cell activation during the priming phase, while blocking of PD-1/PD-L1 activates effector T cells that are already engaged in cancer immunity[42]. Renal irAEs were believed to be less common. However, the incidence of renal toxicity by irAEs increased from 2% to 16.5% during a recent 4-year period[49,50]. Combination therapy with anti-PD-1 and anti-CTLA-4 antibodies might cause more renal irAEs than monotherapy affecting both priming and effector phases involving dysregulation of Treg[45,49].

Another unique hallmark of ICI-related renal disease is that the interval from drug exposure to onset of renal irAEs ranges from a few weeks to 2 years[49,51]. The most common clinical feature of renal irAEs is AKI[52]. Upon nivolumab and pembrolizumab administration, AKI appears much later than for anti-CTLA-4 antibody after drug initiation[53]. For example, pembrolizumab-associated renal disease occurs after a median interval of 9 months, whereas AKI in anti-CTLA-4 antibody manifests within 3 months[51,53]. However, onset of ICI-related symptom is unpredictable, as there was one reported case of malignant melanoma treated with nivolumab in a patient who developed systemic vasculitis within 1 weak after the first drug infusion[54].

The difference in the interval between drug exposure and onset of AKI suggests a distinct mechanism for renal irAEs, and currently two theories have been proposed[55,56]. One implicates development of autoimmunity to renal self-antigens due to blockage of the CTLA-4 or PD-1 pathway. Immune checkpoint molecules are involved in regulating peripheral tolerance, which can be impaired by ICIs, leading to overactivation of T cells. The other theory is loss of tolerance to drug-specific effector T cells[53]. Interestingly, a significant proportion of patients with AKI due to administration of ICIs used nephrotoxic agents, such as proton pump inhibitors and nonsteroid anti-inflammatory drugs, long before initiation of ICIs. Inhibition of immune checkpoint signaling by ICIs can re-activate T cells that have been primed during a previous exposure to these nephritogenic drugs.

3. Histological Findings of Renal Injury by ICIs

Since the development of ICIs, the incidence of drug-related renal diseases has increased worldwide, illustrating various types of kidney injury. Common clinical features of renal irAEs include elevated serum creatinine levels with mild proteinuria, occasionally accompanied by sterile pyuria and microhematuria[52]. In these conditions, renal dysfunction is mostly due to acute tubulointerstitial nephritis (ATIN) alone or in combination with other kidney lesions, such as glomerular disease[53]. The histopathological features of ATIN induced by ICIs include massive infiltration of inflammatory cells, such as lymphocytes, and limited infiltration of eosinophils and neutrophils into the tubulointerstitium (**Fig. 5A, B**). Although T cells are predominant among the infiltrates, CD 4/CD8 ratios vary[57–60]. Granuloma is sometimes present[49,59] (**Fig. 5C**). Taken together, these observations indicate that the histological features of renal irAEs cannot be readily distinguished from those of conventional acute ATIN. Cassol et al. recently demonstrated focal staining of PD-L 1 along the cell membranes of tubular epithelial cells within the areas of interstitial inflammation in anti-PD-1 antibody-treated patients, suggesting that PD-L1 staining might be useful in differentiating renal irAEs from other

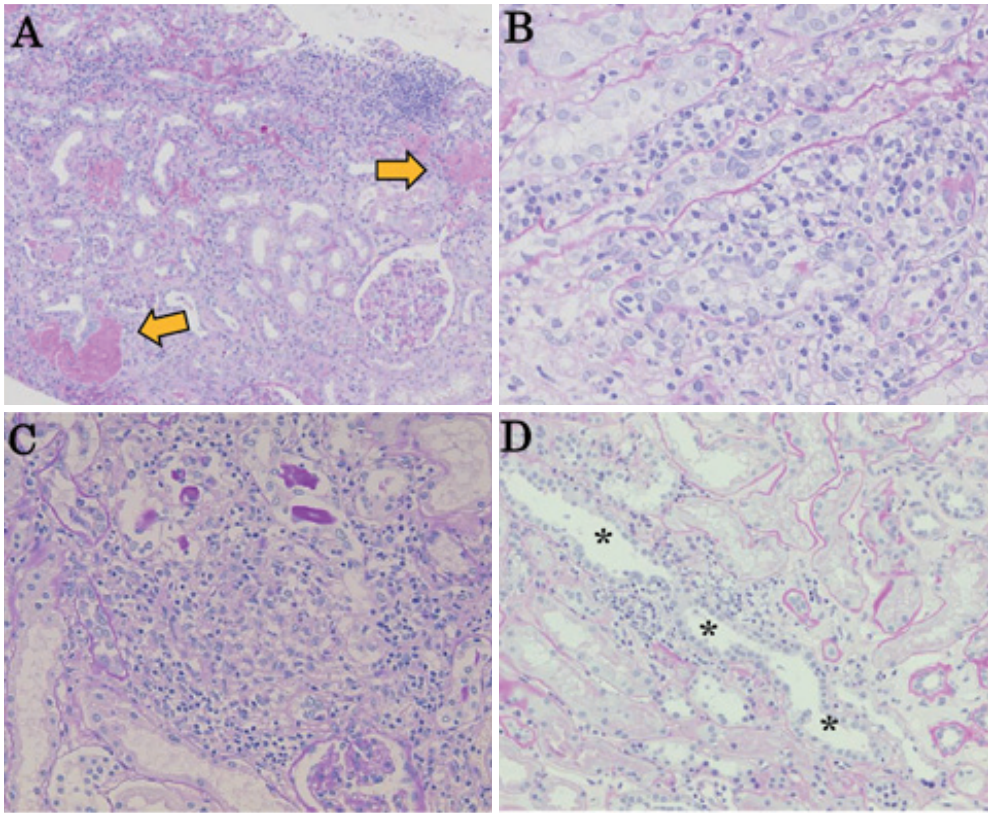

Fig. 5 Histological findings of immune checkpoint inhibitor-related renal disease (A-D. PAS stain).
Acute tubulointerstitial nephritis due to anti-PD-1 antibody (A, B. Pembrolizumab). The presence of extra-tubular deposition of cast (A. arrow) suggests significant tubular injury. Some tubules are infiltrated by inflammatory cells, exhibiting the features of tubulitis (B). Acute tubulointerstitial nephritis forming granuloma (C) due to combination therapy of anti-CTLA-4 antibody (ipilimumab) and anti-PD-L1 antibody (durvalumab). Anti-PD-1 therapy (nivolumab) can induce distal tubular acidosis, characterized by focal lymphocytic infiltration around distal tubules and collecting ducts (D. asterisks).

types of ATIN[61]. Additional studies are needed to confirm their findings.

Other histological features of renal irAEs include acute tubular injury[60], vasculitis[54], TMA[50], immune complex glomerulonephritis[62], and podocytopathy[63]. Mamlouk et al. described 16 patients with ICI-related nephrotoxicity, 14 of whom exhibited some form of glomerular lesion, such as pauci-immune glomerulonephritis and C3 glomerulonephritis[55]. Izzedine et al. reported 12 cases of pembrolizumab-related renal toxicity; AKI was the most common clinical manifestation, followed by nephrotic syndrome[51]. The histological characteristics involved ATIN, acute tubular necrosis, and MCNS. Distal tubular acidosis after several months of anti-PD-1 drug use has been reported[64]. Renal biopsy revealed interstitial edema-tofibrosis and mild lymphocytic infiltration around distal tubules and collecting ducts (**Fig. 5D**). irAEs associated with anti-PD-L1 antibody were reported in a small number of patients with ATIN, as was also seen in patients with anti-PD-1[65].

Renal Impairment Attributable to Other Molecular Targeted Agents

In addition to anti-VEGF drugs and ICIs, some molecular targeted agents were shown to exert nephrotoxic effects. The protease inhibitors (PIs) bortezomib and carfilzomib have been used to treat hematologic disorders such as multiple myeloma and mantle cell lymphoma but can sometimes trigger TMA[66,67]. Yui et al. reported PI-related renal TMA in 11 patients with clinical features of thrombocytopenia and microangiopathic hemolytic anemia[68]. In two of these patients, renal biopsy confirmed histological changes suggestive of TMA. Moore and Romeril postulated that autoantibodies against ADAMTS13, produced during the inflammatory process, might have triggered renal TMA in PI-treated patients[69]. As impairment of

ADAMTS13 was not found in all PI-related TMA, the presence of other mechanisms has been suggested[68].

Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase involved in many intracellular pathways responsible for cellular proliferation and tumor growth in some cancer types[70]. The mTOR inhibitors everolimus and temsirolimus were shown to decrease cancer cell growth by suppressing mTOR activity[70]. Renal impairment, including proteinuria and AKI, can sometimes occur in patients treated with mTOR inhibitors, although the incidence rate is low[71,72]. Histologically, renal dysfunction in mTOR inhibitors manifests as acute tubular necrosis, and FSGS was reported in some patients[72]. The underlying mechanism remains unclear, but disruption of the VEGF pathway is strongly suggested[73].

Conclusion

This article reviewed renal side effects associated with recent anti-cancer drugs, including molecular targeted agents and ICIs, and emphasized histopathological characteristics. As new drugs are developed, their side effects are reported. Some drugs are administered as part of multidrug therapy that combines conventional anti-cancer drugs and molecular targeted agents, thus complicating clinical manifestations of side effects. Renal biopsy is one of the most reliable methods to evaluate renal damage and clarify its cause. To correctly grasp a patient's condition and provide optimal treatment, clinicians and pathologists must understand the pathogenesis of nephrotoxicity for each anti-cancer agent. Close communication between pathologists and clinicians, including oncologists and nephrologists, is essential.

Acknowledgements: The authors are deeply grateful to Dr. Noriko Uesugi for providing histological images of the valuable case.

Conflict of Interest: The authors declare no conflicts of interests.

References

1. Sawyers C. Targeted cancer therapy. Nature. 2004 Nov 18; 432(7015):294–7.
2. Moeckel GW, Kashgarian M, Racusen LC. Ischemic and toxic acute tubular injury and other ischemic renal injuries. In: Jannette JC, D'Agati DV, Olson JL, Silva FG, editors. Heptinstall's pathology of the kidney: Wolters Kluwer Health; 2014.
3. Mehta RL, Awdishu L, Davenport A, et al. Phenotype standardization for drug-induced kidney disease. Kidney Int. 2015;88(2):226–34.
4. Capasso A, Benigni A, Capitanio U, et al. Summary of the international conference on onco-nephrology: an emerging field in medicine. Kidney Int. 2019;96(3):555–67.
5. Perazella MA. Onco-nephrology: Renal toxicities of chemotherapeutic agents. Clin J Am Soc Nephrol. 2012;7(10): 1713–21.
6. Perazella MA, Shirali AC. Nephrotoxicity of cancer immunotherapies: past, present and future. J Am Soc Nephrol. 2018;29(8):2039–52.
7. Perazella MA, Izzedine H. New drug toxicities in the onco-nephrology world. Kidney Int. 2015 May 26;87(5): 909–17.
8. Imai K, Takaoka A. Comparing antibody and small-molecule therapies for cancer. Nat Rev Cancer. 2006 Sep;6 (9):714–27.
9. Fan Q, Ma J, Zhang B, et al. Assessment of acute kidney injury related to small-molecule protein kinase inhibitors using the FDA adverse event reporting system. Cancer Chemother Pharmacol. 2020;86(5):655–62.
10. Stewart MW. Aflibercept (VEGF-TRAP): the next anti-VEGF drug. Inflamm Allergy Drug Targets. 2011 Dec;10 (6):497–508.
11. Zirlik K, Duyster J. Anti-Angiogenics: Current situation and future perspectives. Oncol Res Treat. 2018;41(4):166–71.
12. Ricci V, Ronzoni M, Fabozzi T. Aflibercept a new target therapy in cancer treatment: a review. Crit Rev Oncol Hematol. 2015 Dec;96(3):569–76.
13. Syed YY, McKeage K. Aflibercept: A review in metastatic colorectal cancer. Drugs. 2015 Aug;75(12):1435–45.
14. Karaman S, Leppänen VM, Alitalo K. Vascular endothelial growth factor signaling in development and disease. Dev. 2018;145(14):1–8.
15. Guan F, Villegas G, Teichman J, et al. Autocrine VEGF-A system in podocytes regulates podocin and its interaction with CD2AP. Am J Physiol Physiol. 2006;291(2):F422–8.
16. Eremina V, Jefferson JA, Kowalewska J, et al. VEGF Inhibition and renal thrombotic microangiopathy. N Engl J Med. 2008;359(2):205–7.
17. Ollero M, Sahali D. Inhibition of the VEGF signalling pathway and glomerular disorders. Nephrol Dial Transplant. 2015;30(9):1449–55.
18. Zhu X, Wu S, Dahut WL, et al. Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. Am J Kidney Dis. 2007 Feb;49(2):186–93.
19. Pfister F, Amann K, Daniel C, et al. Characteristic morphological changes in anti-VEGF therapy-induced glomerular microangiopathy. Histopathology. 2018;990–1001.
20. Person F, Rinschen MM, Brix SR, et al. Bevacizumab-associated glomerular microangiopathy. Mod Pathol. 2019;32(5):684–700.
21. Hanna RM, Barsoum M, Arman F, et al. Nephrotoxicity induced by intravitreal vascular endothelial growth factor inhibitors: emerging evidence. Kidney Int. 2019;96(3):572–80.
22. Touzani F, Geers C, Pozdzik A. Intravitreal injection of anti-VEGF antibody induces glomerular endothelial cells injury. Case Reports Nephrol. 2019;2019:1–4.
23. Hanna RM, Tran N-T, Patel SS, et al. Thrombotic microangiopathy and acute kidney injury induced after intravitreal injection of vascular endothelial growth factor inhibitors VEGF blockade-related TMA after intravitreal use. Front Med [Internet]. 2020;7:579603. Available from:

https://doi.org/10.3389/fmed.2020.579603
24. Fujii T, Kawasoe K, Tonooka A, et al. Nephrotic syndrome associated with ramucirumab therapy: A single-center case series and literature review. Medicine (Baltimore) [Internet]. 2019 Jul;98(27):e16236. Available from: ht tps://doi.org/10.1097/MD.0000000000016236
25. Yamada R, Okawa T, Matsuo K, et al. Renal-limited thrombotic microangiopathy after switching from bevacizumab to ramucirumab: a case report. BMC Nephrol. 2019 Jan 11;20(1):14.
26. Sendeyo K, Audard V, Zhang S, et al. Upregulation of c-mip is closely related to podocyte dysfunction in membranous nephropathy. Kidney Int. 2013 Mar;83(3):414–25.
27. Yu L, Lin Q, Feng J, et al. Inhibition of nephrin activation by c-mip through Csk-Cbp-Fyn axis plays a critical role in Angiotensin II-induced podocyte damage. Cell Signal. 2013 Mar;25(3):581–8.
28. Izzedine H, Mangier M, Ory V, et al. Expression patterns of RelA and c-mip are associated with different glomerular diseases following anti-VEGF therapy. Kidney Int. 2014;85(2):457–70.
29. Nowak DE, Tian B, Jamaluddin M, et al. RelA Ser276 Phosphorylation is required for activation of a subset of NF-κB-dependent genes by recruiting cyclin-dependent kinase 9/cyclin T1 complexes. Mol Cell Biol. 2008;28(11): 3623–38.
30. Maruyama K, Nakagawa N, Suzuki A, et al. Pazopanib-induced endothelial injury with podocyte changes. Intern Med. 2018;57(7):987–91.
31. Bollée G, Patey N, Cazajous G, et al. Thrombotic microangiopathy secondary to VEGF pathway inhibition by sunitinib. Nephrol Dial Transplant. 2009 Feb;24(2):682–5.
32. Ruebner RL, Copelovitch L, Evageliou NF, et al. Nephrotic syndrome associated with tyrosine kinase inhibitors for pediatric malignancy: case series and review of the literature. Pediatr Nephrol. 2014 May;29(5):863–9.
33. Maruyama K, Chinda J, Kuroshima T, et al. Minimal change nephrotic syndrome associated with gefitinib and a successful switch to erlotinib. Intern Med. 2015;54(7): 823–6.
34. Masutani K, Fujisaki K, Maeda H, et al. Tubulointerstitial nephritis and IgA nephropathy in a patient with advanced lung cancer treated with long-term gefitinib. Clin Exp Nephrol. 2008 Oct;12(5):398–402.
35. Kaneko T, Shimizu A, Aoki M, et al. A case of gefitinib-associated membranous nephropathy in treatment for pulmonary adenocarcinoma. CEN case reports. 2015 May; 4(1):31–7.
36. Tejpar S, Piessevaux H, Claes K, et al. Magnesium wasting associated with epidermal-growth-factor receptor-targeting antibodies in colorectal cancer: a prospective study. Lancet Oncol. 2007 May;8(5):387–94.
37. Manohar S, Bansal A, Wanchoo R, et al. Ibrutinib induced acute tubular injury: A case series and review of the literature. Am J Hematol. 2019;94(9):E223–5.
38. Markóth C, File I, Szász R, et al. Ibrutinib-induced acute kidney injury via interstitial nephritis. Ren Fail. 2021;43 (1):335–9.
39. Pal Singh S, Dammeijer F, Hendriks RW. Role of Bruton's tyrosine kinase in B cells and malignancies. Mol Cancer. 2018;17(1):1–23.
40. Chen DS, Mellman I. Oncology meets immunology: The cancer-immunity cycle. Immunity. 2013;39(1):1–10.
41. Darvin P, Toor SM, Sasidharan Nair V, et al. Immune checkpoint inhibitors: recent progress and potential biomarkers. Exp Mol Med. 2018;50(12):1–11.
42. Ott PA, Hodi FS, Robert C. CTLA-4 and PD-1/PD-L1 blockade: New immunotherapeutic modalities with durable clinical benefit in melanoma patients. Clin Cancer Res. 2013;19(19):5300–9.
43. Poschke I, Mougiakakos D, Kiessling R. Camouflage and sabotage: Tumor escape from the immune system. Cancer Immunol Immunother. 2011;60(8):1161–71.
44. Franciszkiewicz K, Boissonnas A, Boutet M, Combadière C, Mami-Chouaib F. Role of chemokines and chemokine receptors in shaping the effector phase of the antitumor immune response. Cancer Res. 2012 Dec 15;72(24):6325–32.
45. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways. Am J Clin Oncol. 2016;39(1):98–106.
46. Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: A systematic review of case reports. PLoS One [Internet]. 2016;11(7):e0160221. Available from: https://doi.org/10.1371/journal.pone.0160221
47. Jamal S, Hudson M, Fifi-Mah A, et al. Immune-related adverse events associated with cancer immunotherapy: A Review for the Practicing Rheumatologist. J Rheumatol. 2020;47(2):166–75.
48. Khoja L, Day D, Wei-Wu Chen T, et al. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: A systematic review. Ann Oncol. 2017;28(10):2377–85.
49. Cortazar FB, Marrone KA, Troxell ML, et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. Kidney Int. 2016;90(3):638–47.
50. Meraz-Muñoz A, Amir E, Ng P, et al. Acute kidney injury associated with immune checkpoint inhibitor therapy: Incidence, risk factors and outcomes. J Immunother Cancer. 2020;8(1):1–9.
51. Izzedine H, Mathian A, Champiat S, et al. Renal toxicities associated with pembrolizumab. Clin Kidney J. 2019;12(1): 81–8.
52. Shingarev R, Glezerman IG. Kidney complications of immune checkpoint inhibitors: A review. Am J Kidney Dis. 2019;74(4):529–37.
53. Wanchoo R, Karam S, Uppal NN, et al. Adverse renal effects of immune checkpoint inhibitors: A narrative review. Am J Nephrol. 2017;45(2):160–9.
54. Gallan AJ, Alexander E, Reid P, et al. Renal vasculitis and pauci-immune glomerulonephritis associated with immune checkpoint inhibitors. Am J Kidney Dis. 2019;74(6): 853–6.
55. Mamlouk O, Selamet U, Machado S, et al. Nephrotoxicity of immune checkpoint inhibitors beyond tubulointerstitial nephritis: single-center experience. J Immunother Cancer. 2019;7(1).
56. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev. 2010 Jul;236: 219–42.
57. Uchida A, Watanabe M, Nawata A, et al. Tubulointerstitial nephritis as adverse effect of programmed cell death 1 inhibitor, nivolumab, showed distinct histological findings. CEN Case Reports. 2017;6(2):169–74.
58. Murakami N, Borges TJ, Yamashita M, et al. Severe acute interstitial nephritis after combination immune-checkpoint inhibitor therapy for metastatic melanoma. Clin Kidney J. 2016;9(3):411–7.
59. Belliere J, Meyer N, Mazieres J, et al. Acute interstitial nephritis related to immune checkpoint inhibitors. Br J Cancer. 2016;115(12):1457–61.

60. Escandon J, Peacock S, Trabolsi A, et al. Interstitial nephritis in melanoma patients secondary to PD-1 checkpoint inhibitor. J Immunother Cancer. 2017;5(1):1−6.
61. Cassol C, Satoskar A, Lozanski G, et al. Anti–PD-1 Immunotherapy may induce interstitial nephritis with increased tubular epithelial expression of PD-L1. Kidney Int Reports. 2019;4(8):1152−60.
62. Jung K, Zeng X, Bilusic M. Nivolumab-associated acute glomerulonephritis: a case report and literature review. BMC Nephrol. 2016;17(1):1−6.
63. Kidd JM, Gizaw AB. Ipilimumab-associated minimal-change disease. Kidney Int. 2016;89(3):720.
64. Charmetant X, Teuma C, Lake J, et al. A new expression of immune checkpoint inhibitors' renal toxicity: When distal tubular acidosis precedes creatinine elevation. Clin Kidney J. 2019;13(1):42−5.
65. Xipell M, Victoria I, Hoffmann V, et al. Acute tubulointerstitial nephritis associated with atezolizumab, an anti-programmed death-ligand 1 (pd-l1) antibody therapy. Oncoimmunology. 2018;7(7):1−5.
66. Nunes AT, Annunziata CM. Proteasome inhibitors: structure and function. Semin Oncol. 2017 Dec;44(6):377−80.
67. Portuguese AJ, Gleber C, Passero FC, et al. A review of thrombotic microangiopathies in multiple myeloma. Leuk Res [Internet]. 2019 Oct;85:106195. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0145212619301407
68. Yui JC, Van Keer J, Weiss BM, et al. Proteasome inhibitor associated thrombotic microangiopathy. Am J Hematol. 2016;91(9):E348−52.
69. Moore H, Romeril K. Multiple myeloma presenting with a fever of unknown origin and development of thrombotic thrombocytopenic purpura post-bortezomib. Intern Med J. 2011 Apr;41(4):348−50.
70. Lameire N. Nephrotoxicity of recent anti-cancer agents. Clin Kidney J. 2014;7(1):11−22.
71. Abbas A, Mirza MM, Ganti AK, et al. Renal toxicities of targeted therapies. Target Oncol. 2015 Dec 30;10(4):487−99.
72. Izzedine H, Escudier B, Rouvier P, et al. Acute tubular necrosis associated with mTOR inhibitor therapy: A real entity biopsy-proven. Ann Oncol. 2013;24(9):2421−5.
73. Nicolaysen A. Nephrotoxic chemotherapy agents: old and new. Adv Chronic Kidney Dis. 2020;27(1):38−49.

(Received, May 8, 2021)
(Accepted, September 15, 2021)
(J-STAGE Advance Publication, November 26, 2021)