Clinical Kidney Journal, 2019, vol. 12, no. 1, 81–88

doi: 10.1093/ckj/sfy100
Advance Access Publication Date: 9 November 2018
Original Article

ORIGINAL ARTICLE

Renal toxicities associated with pembrolizumab

Hassan Izzedine[1,2], Alexis Mathian[3], Stephane Champiat[4], Cécile Picard[5], Christine Mateus[6], Emilie Routier[7], Andrea Varga[4], David Malka[8], Alexandra Leary[9], Judith Michels[9], Jean-Marie Michot[4], Aurélien Marabelle[4], Olivier Lambotte[10], Zahir Amoura[3], Jean-Charles Soria[4], Sihem Kaaki[11], Nathalie Quellard[11], Jean-Michel Goujon[11] and Isabelle Brocheriou[5]

[1]Department of Nephrology, Peupliers Private Hospital, Ramsay Générale de Santé, Paris, France, [2]UPEC (Université Paris Est Créteil), INSERM U955, Institut Mondor de Recherche Biomédicale (IMRB), Equipe, Créteil, France, [3]Department of Internal Medicine, Pitie-Salpetriere Hospital, Paris, France, [4]Drug Development Department (DITEP), Gustave Roussy, Villejuif, France, [5]Department of Pathology, Pitie-Salpetriere Hospital, Paris, France, [6]Department of Supportive Care, Gustave Roussy, Villejuif, France, [7]Department of Medical Oncology, Dermatology Unit, Gustave Roussy, Villejuif, France, [8]Department of Medical Oncology, Gastrointestinal Cancer Group, Gustave Roussy, Villejuif, France, [9]Department of Medical Oncology, Gynecology Unit, Gustave Roussy, Villejuif, France, [10]Department of Internal Medicine and Clinical Immunology, Bicetre University Hospital, Le Kremlin Bicêtre, France and [11]Departement of Pathology, Electron Microscopy Unit, CHU Poitiers, Poitiers, France

Correspondence and offprint requests to: Hassan Izzedine; E-mail: h.izzedine@ramsaygds.fr

ABSTRACT

Objective. Expanded clinical experience with patients treated by pembrolizumab has accumulated. However, renal toxicities associated with this anti-programmed cell death 1 agent are poorly described because kidney histology is rarely sought. As a nephrology referral centre, we aimed to describe the clinic-biological and histopathological characteristics of pembrolizumab-related nephropathy and its response to treatment.

Methods. We conducted a monocentric large case series study, including all pembrolizumab-treated cancer patients presenting a renal toxicity addressed to our centre from 2015 to 2017.

Results. A total of 12 patients (7 men) out of 676 pembrolizumab-treated patients (incidence 1.77%) were included (median age 69.75 years). Patients were referred for acute kidney injury ($n = 10$) and/or proteinuria ($n = 2$). A kidney biopsy was performed in all patients, with a median duration of use of 9 months (range 1–24 months) after the beginning of treatment. Biopsy showed that four patients had acute interstitial nephritis (AIN), whereas five had acute tubular injury (ATI) alone, one had minimal change disease (MCD) and ATI, and one had MCD alone. Pembrolizumab withdrawal coupled with corticosteroid therapy was the most effective treatment for kidney function recovery. Drug reintroduction resulted in a more severe recurrence of AIN in one patient who required maintenance of pembrolizumab. Two patients died of cancer progression with one of them developing severe renal failure requiring dialysis.

Received: 20.6.2018; Editorial decision: 5.9.2018

Conclusion. In our series, ATI, AIN and MCD are the most frequent forms of kidney involvement under pembrolizumab therapy. Kidney dysfunction is usually isolated but can be severe. Use of corticosteroids in case of AIN improves the glomerular filtration rate.

Keywords: acute interstitial nephritis, acute kidney injury, acute tubular injury, minimal change nephropathy, pembrolizumab

INTRODUCTION

Agents that block the interaction between programmed cell death 1 (PD-1) receptor and programmed cell death ligand 1 (PD-L1) and which inhibit cytotoxic T lymphocyte antigen 4 (CTLA-4) are transforming the therapeutic landscape in oncology. These so-called immune checkpoint inhibitors (ICPIs) target these key immune regulatory pathways and thereby unleash a restrained T cell-mediated anti-tumour response [1]. The interest has grown recently in ICPIs as anti-cancer agents. Extensive research was conducted over the past few years evaluating their efficacy in the management of a variety of cancers [2–4]. Likewise, the safety profile of ICPIs has generated considerable research interest [5–9].

Pembrolizumab (KEYTRUDA®, Merck & Co., Inc., Kenilworth, NJ, USA) is a highly selective monoclonal IGg4-kappa (immunoglogulin G4-Kappa) isotype antibody that selectively binds to PD-1 blocking the receptor's negative impact on lymphocyte function [10]. Pembrolizumab has been explored in a series of trials in patients with advanced melanoma and in other cancers such as renal cell carcinoma (RCC), lymphoma and others. In a pooled analysis based on randomized controlled trials including 3953 patients, the overall incidence of any pembrolizumab-based therapies emergent adverse events was 74.3% [95% confidence interval (CI): 0.671–0.805] [11] including all-grade rash (14.8%, 95% CI: 0.102–0.204), pain (13.7%, 95% CI: 0.011–0.689), pruritus (17.7%, 95% CI: 0.128–0.240), vitiligo (11.0%, 95% CI: 0.089–0.169), arthralgia (11.3%, 95% CI: 0.082–0.154) and dry mouth (10.0%, 95% CI: 0.045–0.206) [11]. There is, however, no mention of kidney disorders.

In this study, we conducted a prospective analysis of 12 biopsy-proven pembrolizumab-related nephropathies. We describe here the clinical and biological presentation of pembrolizumab-associated kidney disease, the kidney pathology data and the response to treatment.

MATERIALS AND METHODS

Patients

This is a single-centre large case series study concerning an observational cohort of patients. We analysed patients who were referred for acute kidney failure and/or proteinuria following pembrolizumab therapy and all of them underwent kidney biopsy (KB).

All patients gave informed consent for the anonymous use of their personal health data. Each patient medical record was thoroughly reviewed with the collection of clinical, biological and pathologic data at onset, at diagnosis, and at last follow-up. This study was approved by the local ethics committee and was in accordance with the Helsinki Declaration of 1975.

The clinical and laboratory studies were assessed at the time of KB, and follow-up data were available for all patients (Table 1). Each patient was followed over time for the development of specific endpoints, including progression to severe kidney failure and death.

Histology

All biopsy specimens had a part for light microscopy (fixed and prepared using standard techniques) and a part for immunofluorescence-labelling studies [immuoglobulin (Ig) G, IgM, IgA, Kappa and Lambda Ig light chains, fibrin, C3 and C1q anti-sera tests on frozen biopsies]. Kidney light microscopy specimens and immunofluorescence results were systematically reviewed by a senior pathologist without access to the patients' files.

Statistical analyses

A two-sided chi-square test was used to compare all qualitative variables. Mann–Whitney rank testing was applied for all comparisons of quantitative variables. The results are expressed as mean values unless otherwise stated. A $P < 0.05$ was considered to be statistically significant.

RESULTS

Clinicopathologic characteristics

Twelve Caucasian patients (seven men) out of 676 pembrolizumab-treated patients in our centre were included in the study (incidence 1.77%). Median age was 69.75 years (range 46–84 years). The most common cancer was metastatic melanoma (nine patients, 75%). Other affected organs/cancers were Hodgkin's lymphoma, endometrium and ileal neuroendocrine tumour (NET). Pembrolizumab was used at standard dosage (2 mg/kg intravenously every 3 weeks).

Kidney involvement occurred at a median time of 9 months (range 1–24 months) after the beginning of treatment, characterized by acute renal failure defined by an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (11 patients, 91.5%), proteinuria (2 patients, 16.6%, with proteinuria > 3 g/day), microscopic haematuria (3 patients, 25%) and/or aseptic leucocyturia (4 patients, 33.3%). Mean serum creatinine (SCr) and aMDRD creatinine clearance were 96.4 μmol/L (range 70–147) and 62.5 mL/min/1.73 m^2 (range 43–80), respectively.

Kidney biopsies identified three distinct types of renal damage associated with pembrolizumab therapy: acute interstitial nephritis (AIN; four patients, 30%), acute tubular injury (ATI; five patients, 41.6%) and minimal change disease (MCD; two patients, 16.6%) (Figure 1). Patients with AIN also had tubulitis (four patients), flattening of the tubular epithelium (four patients) and interstitial fibrosis. No significant glomerular deposit was found by immunofluorescence analysis. Transmission electron microscopy analysis in nephrotic syndrome (NS) case (Patient 2) showed marked effacement of visceral epithelial cell foot processes in some areas (Figure 2). Histopathological findings are summarized in Table 2.

Clinical outcome

The median follow-up was 13 months (range 1–36 months).

Clinical Kidney Journal

Ten out of the 12 patients stopped pembrolizumab treatment. Of these 10 patients, 7 received steroids on top of pembrolizumab withdrawal and 1 patient was dialysed for 1 month and died because of melanoma evolution. The other six have a favourable renal evolution with a recovery of ∼50% (mean GFR 27.3 versus 44.5 mL/min/1.73 m^2) of their renal function (Table 3). For one patient, the reintroduction of pembrolizumab resulted in a more severe recurrence of AIN. Three of them are in complete remission, two patients remained tumour-active and one other patient died after 24 months due to the evolution of his illness. For the remaining three patients who did not receive corticosteroids, renal function remained stable (mean GFR 43.3 versus 42.6 mL/min/1.73 m^2) and one patient remained in complete remission.

Two tumour-active patients maintained pembrolizumab treatment with a variable improvement of their kidney function (patient on corticosteroids, GFR 26 versus 40 mL/min/1.73 m^2, patient without corticosteroids GFR 43 versus 48 mL/min/1.73 m^2).

Table 1. Characteristics of patients with biopsy-proven pembrolizumab-related renal involvement

Number of patients	12 patients
Demography	
Gender	7 M/5 F
Age, years, median (IQR)	69.75 (46–84)
Comorbidities	
HT	5
Diabetes	1
MGUS IgG	1
Horton disease	1
Cancer type	
Metastatic melanoma	9
Hodgkin lymphoma	1
Endometrial carcinoma	1
Ileal NET	1
Previous anti-cancer drugs	
Cisplatin/VP16	1
Carboplatin/taxol	1
Ipilimumab	1
Dabrafenib/trametinib	1
Renal involvement at presentation	
Time to KB, months (IQR)	9 (1–24)
Renal abnormalities	
AKI	11
NS	2
Proteinuria	1
Microscopic haematuria	3
Aseptic leucocyturia	4
Histological characteristics	
AIN	6
Plasma cell infiltration	6
+ Tubulitis/ATI	6
+ Interstitial fibrosis, % (IQR)	18.75 (0–50)
ATI	4
MCD	2
Crystal	1
Superimposed NAS	10

IQR: interquartile range; F, female; HT, hypertension; M, male; MGUS: monoclonal gammopathy of undetermined significance; NAS: nephroangiosclerosis.

DISCUSSION

This study, which is the largest series of biopsy-proven pembrolizumab-related nephropathies published so far, focused on the clinical, biological and pathological presentation of this complication. Kidney involvement related to pembrolizumab can lead to acute kidney injury (AKI) and/or NS associated with AIN, ATI and podocytopathy like MCD, respectively.

As previously reported, two different types of immune-related kidney injury have been reported under immune checkpoint inhibitors (ICPI) therapy: AIN and more rarely glomerular diseases [12, 13] (Table 4). Indeed, most of the ICPI-related AKI presented as acute tubulointerstitial nephritis (ATIN) pattern on kidney biopsies (88%), 25% of which were associated with granulomatous features [12–15]. The knowledge of the timing of

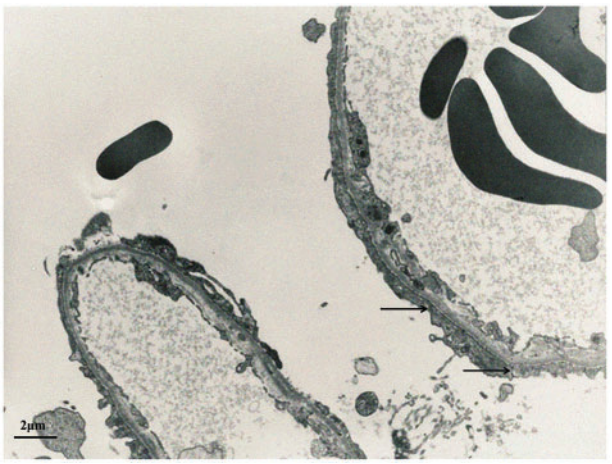

FIGURE 2: Diffuse foot process effacement (magnification ×6000)

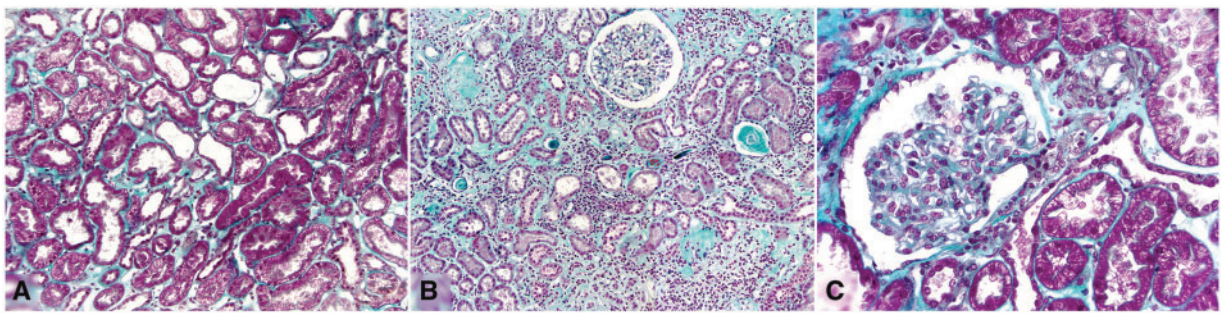

FIGURE 1: Pathological findings in pembrolizumab-related nephropathies (Masson's trichrome). (**A**) Nephron segments with flattened tubular epithelium and loss of brush border defining ATI. (**B**) AIN with interstitial oedema and lymphoplasmacytic infiltrate associated with tubulitis. (**C**) Preserved cortical area with normal-appearing glomerulus in this patient with NS.

Table 2. Pathological findings in 12 patients receiving pembrolizumab

Patients	ATI	Interstitial inflammation	Glomeruli	Interstitial scar (percentage of cortical area)	Vascular changes	Final diagnosis
Pt 1	+ (crystal)	0	Normal, ischaemic; area of cortical atrophy with numerous sclerotic glomeruli	60	cv3	ATI
Pt 2	++	0	Normal, ischaemic	15	cv2, myocyte cytoplasmic vacuolization	MCD, ATI
Pt 3	+	0	Normal	10–15	cv2, ah1	ATI
Pt 4	+	+++[a]	Normal	60 (fibro-edema)	cv1, ah2	AIN
Pt 5	0	+ focal	Normal, ischaemic	25	cv3, myocyte cytoplasmic vacuolization	ATI
Pt 6	+	0	Normal	15 (fibro-edema)	cv3	MCD
Pt 7	0	0	Normal	10	cv1	NC
Pt 8	++	+++[a]	Normal, ischaemic	100 (fibro-edema)	cv1	AIN
Pt 9	+ (with cytoplasmic clarification)	0	Normal	20	cv3, ah1	ATI
Pt 10	+	0	Normal	20 (fibro-edema)	cv1	ATI
Pt 11	+	+++[a]	Normal, sclerosis (25%)	50 (fibro-edema)	cv1	AIN
Pt 12	+	+++[a]	Normal, sclerosis (10%)	60 (fibro-edema)	cv3	AIN

[a]With tubulitis.
ah, arteriolar hyalinosis; cv, chronic vascular changes (fibrous intimal thickening); NC, nonspecific changes.

Table 3. Evolution of renal function during follow-up [range (SD)]

		Months	At KB	At the end of follow-up
Delay			1–24 months (9.0 ±7.4)	1–36 months (13.1 ± 14.1)
All patients, $n = 12$	SCr	70–147 (96.4 ± 24.1)	120–295 (184.5 ± 63.0)	90–190 (126.4 ± 28.2)
ICPIs stopped, $n = 10$				
With Cs $n = 7$	SCr	60–120 (87.4 ± 19.5)	144–295 (191.5 ± 56.1)	90–155 (119.6 ± 24.6)
Without Cs $n = 3$	SCr	80–123 (101 ± 21.5)	120–170 (141.6 ± 25.6)	104–190 (140.6 ± 44.3)
ICPI maintained, $n = 2$				
Pt 1 Cs+	SCr	95	172	118
Pt 2 Cs−	SCr	147	145	133

MDRD, Modification of Diet in Renal Disease (mL/min/1.73 m^2); Cs, corticosteroid.

Table 4. Summary of renal effects of immune checkpoint inhibition

	CTLA-4 antagonists	PD-1 inhibitors
AIN	Common: 6–12 weeks after initiation	Common: 3–12 months after initiation
Glomerular findings	Cases	Cases
Outcomes after kidney transplantation	No transplant rejection (2 patients)	Transplant rejection (7 out of 10 patients)

Source: Adapted from Jhaveri and Perazella [13].

onset of AKI may not be as helpful as in other immune-related adverse events (irAE). However, extrarenal irAE such as hypophysitis and colitis preceded AKI in half of the cases, the existence of which might have helped diagnose renal irAE.

ATI

About half of our patients had ATI. Those patients had more frequently cardiovascular risk factors and marked histological vascular lesions and are more frequently men than AIN patients. Two of them received platinum but at least 1 year before pembrolizumab was introduced. None of our patients was treated with non-steroidal anti-inflammatory drugs or BRAF (B-Raf proto-oncogène) inhibitors. Thus, the underlying vascular field may have favoured the occurrence of ATI without being the cause. In fact, decrease in kidney function occurred after pembrolizumab started. We believe that the ATI is due to pembrolizumab related to an unknown mechanism (Table 5).

This is an important point as many oncologists presume that AKI developing with ICPI therapy is due to AIN and treat with steroids without getting a biopsy. This would be the incorrect therapy for AKI in such patients. Hence, there is a requirement for more such studies of KB tissue to work out the pathomechanism of kidney injury by these drugs.

Table 5. Clinical characteristics of patients under pembrolizumab (ATI versus AIN)

	ATI ($n = 5$)	AIN ($n = 4$)
Age, years	59–84	62–86
Gender	3 M	3 F
SBP, mmHg	125–150	150
DBP, mmHg	70–90	70–80
Underlying AKI risk factors	HT (5) T2DM (1) IHD (1) Carcinoid HD (1) Stroke (1) ARA (4) and Diuretic (3)	HT (1) T2DM (1) MGUS (1) Horton disease (1) ARA (1)
Previous chemotherapy	Platin (2), ipilimumab (1)	Dabrafenib, trametinib (1)
Cancer	Melanoma (3) Ileal NET (1) Endometrial (1)	Melanoma (4)
Vascular changes on KB	Discrete to moderate	Normal to discrete

SBP, systolic blood pressure; DBP, diastolic blood pressure; HT, hypertension; T2DM, type 2 diabetes mellitus; IHD, ischaemic heart disease; ARA, angiotensin receptor antagonist; M, male; F, female; MGUS, monoclonal gammopathy of undetermined significance.

AIN

One-third of our patients had AIN. None of them was using other molecules that could give AIN, in particular non-steroidal antiinflammatory drugs (NSAIDs), antibiotics or pump proton inhibitor (PPI), nor had eosinophilia or rash.

Two clinical reports of ipilimumab-, nivolumab- and pembrolizumab-related adverse kidney effects have been reported [15, 16]. Based on a listing of 13 patients who reported ICPI-induced AKI, described by Cortazar *et al.* [15], the median time for AKI development was 3 months (21–245 days). AKI events (4.9%) were more commonly observed in patients on combined ICPI therapy, compared with those on ICPI monotherapy (ipilimumab 2.0%, nivolumab 1.9% and pembrolizumab 1.4%). ATIN was observed in 12 patients (3 with granuloma formation). Among the 12 patients with ATIN, glucocorticoid treatment of 10 patients resulted in a complete (2 patients) or partial (7 patients, as in our cases) recovery of kidney function. Four patients required haemodialysis despite treatment with glucocorticoids, of whom only two required chronic dialysis. No improvement in kidney function was seen in the remaining two patients with ATIN, who did not receive glucocorticoid treatment. The overall incidence of AKI was 2.2% among 3695 patients. The incidence of Grade III or IV AKI or the need for dialysis was 0.6% [15].

Shirali *et al.* [14] reported six cases of biopsy-proven ATIN developed between 3 and 18 months following therapy with nivolumab and pembrolizumab for lung cancer. Similar to the observations described by Cortazar *et al.* [15], renal function improved back to baseline level following discontinuation of the ICPIs and potential co-offending drugs, combined with the introduction of steroid treatment in five out of six patients. No patient required haemodialysis. One patient developed recurrent AKI following ICPI rechallenge [14].

Finally, a trial in melanoma patients treated with ICPIs identified that, based on autopsy results, 4 of the 12 treated patients developed interstitial nephritis, including one patient with granuloma [17].

These studies highlight the variable, and often prolonged, time course between drug exposure [2 weeks to 8 months; and, in some cases, extending beyond drug cessation (2 months)] and the development of kidney injury [14, 18–20].

Although initial studies showed a low incidence of AKI associated with ICPI, emerging data suggest an incidence ranging from 9.9% to 29.0% [21].

The mechanism of injury is assumed to involve cell-mediated immunity as other drug-induced AIN as T-cell-dominant infiltration of the kidney interstitium. ICPI therapy may promote a permissive environment for the migration of T-cell effector(s) into the kidneys, thus initiating an inflammatory response that could clinically lead to ATIN [22]. ICPIs may reactivate exhausted drug-specific T cells previously primed by nephritogenic drugs, and consequently, due to loss of tolerance, memory T cells are activated against the drug. It is noteworthy that 14 out of the 19 patients reported by Cortazar *et al.* [15] and Shirali *et al.* [14] were on culprit drugs associated with ATIN (proton pump inhibitors and non-steroidal anti-inflammatory drugs) [23]. Thereby, KB is needed as patients frequently have ATI/ATN, which is likely unrelated to the ICPI. This will allow the clinician to potentially continue the ICPI without exposing the patient to corticosteroids. Alternatively, ICPIs could synergistically potentiate antigen recognition and T-cell proliferation in lymph nodes and provoke untethered cytotoxic T-cell effects in the periphery, not only against the tumour, but also against normal tissues [20].

Glomerulonephritis

To our knowledge, only a few other cases of glomerulopathies, mainly podocytopathy-like minimal change nephropathy/focal segmental glomerulosclerosis (MCN/FSGS) ($n = 7$), immune complex glomerulonephritis (GN) ($n = 3$) or proteinase 3 anti-neutrophil cytoplasmic auto-antibodies (PR3-ANCA) vasculitis ($n = 1$) associated with cancer immunotherapy, have been described [24–31] (Table 6).

As shown in Table 5, glomerular disease occurred after 1–72 weeks of therapy with ipilimumab (three cases), nivolumab (three cases) and pembrolizumab (five cases including ours). These cases highlight the variable and often prolonged time course between drug exposure (1 week to 18 months) and clinical recognition of kidney injury. In these cases, ICPI therapy was prescribed for various cancers [metastatic melanoma (five), renal cell carcinoma (two), Hodgkin's lymphoma, lung squamous cell carcinoma (LSCC), mesothelioma and ileal NET (one each)]. In 10 patients, kidney histology was obtained with a diagnosis of podocytopathy-like MCD/FSGS (two, one and four cases for ipilimumab, nivolumab and pembrolizumab, respectively), lupus-like membranous nephropathy (MN) (ipilimumab, one case) or IgA nephropathy (nivolumab, two cases). One patient on ipilimumab had additional inflammatory interstitial infiltrate (associated with MCN) and three patients on pembrolizumab or nivolumab, ATI. One patient developed rapid granulomatosis with polyangiitis and vasculitis unleashed by pembrolizumab treatment. Oral cyclophosphamide (CYC), 150 mg once daily and pulse methyl prednisone induced rapid resolution of symptoms [31].

Treatment with glucocorticoids coupled with discontinuation of ICPIs resulted in complete improvement of proteinuria and/or kidney function. One patient (pembrolizumab) required transient haemodialysis and died because of melanoma evolution. Two patients (pembrolizumab and nivolumab, one patient each) required transient haemodialysis. In one case of MCD with ipilimumab, complete remission of NS was observed under drug withdrawal with steroid use. Two years later, ipilimumab was restarted as salvage therapy. Four months following reintroduction of ipilimumab therapy, the patient developed

Table 6. Clinicopathological features of cancer patients with glomerular diseases associated with ICPIs use

Drug [Ref]	Cancer type | Prior therapy and potential nephrotoxins	Timing of glomerular disorders	Renal findings and kidney function	Kidney pathological findings	Clinical course
Ipilimumab [24]	Melanoma | conventional chemotherapy	6 weeks	• NS: SAlb 2.45 g/dL, Pu 7.5 g/day • SCr 49 μmol/L	Lupus-like MN	12 months after diagnosis, only non-nephrotic proteinuria (1 g per day) persisted after discontinuation of ipilimumab therapy and a short course of steroid
Ipilimumab [26]	Melanoma | TMZ, sorafenib	18 months	• NS: SAlb 2.6 g/dL, Pu 9.5 g/day • SCr 49 μmol/L	MCD	Proteinuria largely remitted (0.39 g/day) following discontinuation of ipilimumab and treatment with corticosteroids (prednisone, 1 mg/kg) initiated and tapered over 4 months
	Ipilimumab restarted	4 months	Recurrence of NS		Ipilimumab therapy was again discontinued, with subsequent remission of proteinuria
Ipilimumab [25]	Melanoma | not reported	2 weeks	• NS: SAlb 2.2 g/dL, Pu 9 g/day • AKI: SCr 261 μmol/L	MCD and AIN	Renal function improved and NS resolved under high-dose steroids
Nivolumab [27]	Papillary RCC | not reported	8 weeks	• NS: SAlb 1.9 g/dL, Pu 17 g/day • AKI: SCr 261 μmol/L	FSGS	High-dose corticosteroids + mycophenolate mofetil resulted in remission of the NS and recovery of renal function. Proteinuria subsequently relapsed during corticosteroid tapering
Nivolumab [28]	LSCC | not reported	6 months	• Pu 3 g/day and micro-haematuria • AKI: SCr 119 μmol/L	IgA nephropathy	Improvement of proteinuria (0.24 g/day) and AKI (SCr, 132 μmol/L) 4 months following cessation of nivolumab therapy
Nivolumab [29]	RCC | pazopanib	10 months	• Pu 3 g/day and micro-haematuria • AKI: SCr 880 μmol/L	Crescentic IgA nephropathy + ATI	After 5 months of cessation of nivolumab, high dose of steroids and haemodialysis, the patient's kidney function improved to his baseline level (159 μmol/L)
Pembrolizumab [26]	Hodgkin lymphoma | not reported	4 weeks	• NS: SAlb 1.8 g/dL, Pu 10.3 g/day • AKI: SCr 346 μmol/L	MCD and ATI	Improvement of proteinuria (3.1 g/day) and AKI (SCr, 132 μmol/L) 6 months following cessation of pembrolizumab therapy with tapering corticosteroid treatment
Pembrolizumab [30]	Mesothelioma | CPV	8 weeks	• NS: SAlb 1.5 g/dL, Pu 19 g/day • AKI: SCr 346 μmol/L	MCD	Creatinine values normalized and proteinuria resolved within 5 days following cessation of pembrolizumab with initiation of prednisone and angiotensin II receptor blocker
Pembrolizumab [31]	Melanoma | ipilimumab, dacarbazine	1 week	• Proteinuria, haematuria • SCr not available • Purpura, positive PR3-ANCA	• KB not performed • Skin biopsy showed • Non-Ig-Cpt vasculitis	Diagnosis of granulomatosis with polyangiitis after sequential immune checkpoint inhibition with ipilimumab and pembrolizumab and improvement after 3 weeks of high-dose steroids and cyclophosphamide (CYP)
Pembrolizumab, our case	Melanoma | not reported	4 weeks	• NS: SAlb 1.7 g/dL, Pu 6 g/day • GFR from 90 to 28 mL/min	MCD and ATI	Improvement of proteinuria under steroid treatment. However, patient was dialysed for 1 month and died because of melanoma evolution
Pembrolizumab, our case	Ileal NET | cisplatin, VP16	18 months	• SAlb 4.2 g/dL, Pu 3.5 g/day • AKI: SCr 146 μmol/L	MCD	No change on renal parameters under maintenance of pembrolizumab without steroids

Cpt, complement; CPV, carboplatin pemetrexed vinorelbine; Pu, proteinuria; SAlb, serum albumin level; TMZ, temozolomide.

recurrence of proteinuria and NS. Ipilimumab therapy was again discontinued, with subsequent remission of proteinuria [26]. The remaining patient (our second patient) with NS who did not receive corticosteroids while maintaining pembrolizumab, had no improvement in kidney parameters.

We distinguish two glomerular disease type: podocytopathy-like MCD/FSG and immune complex GN.

(i) Among the podocytopathy-like MCD/FSG, cancers and in particular haemopathies (Hodgkin's lymphoma) and drugs are the most common causes [32–37].

Besides the proposed mechanism based on a remote production of a 'permeability factor' that may cause release of cytokines promoting podocyte foot-process effacement via candidate factors such as vascular endothelial growth factor, which is known to act on systemic capillaries and the glomerular permeability barrier [38, 39], the pathogenesis of NS/MCD can be explained otherwise. Indeed, the finding of *de novo* podocyte CD80 expression in NS may suggest a more direct link between the innate immune response and podocyte injury [26, 40]. Interestingly, both the PD-1 and CTLA-4 pathways modulate T-cell activation through signals involving antigen-presenting cell CD80 (B7-1) [41, 42]. As such, a direct effect by these agents on podocyte CD80 (B7-1) may also be possible [26]. However, there remains a doubt about the MCD mechanism (cancer or drug-related) since PD-1 was not performed on the kidney biopsies.

(ii) Three immune complex GN cases are reported [lupus-like MN ($n = 1$) and IgA nephropathy with ($n = 1$) or without ($n = 1$) crescentic GN].

PD-1 checkpoint knockout mice developed glomerulonephritis [43] suggesting that PD-1 signalling pathway is important for minimizing T-cell-mediated renal inflammation.

Although it may be difficult to prove a causal relationship between IgA nephropathy and ICPI therapy, recent studies have shown that galactose-deficient IgA molecules and anti-glycan antibodies play a role in immune complex formation in patients with IgA nephropathy [44], suggesting a possible role of nivolumab in the occurrence of IgA nephropathy cases [27–29]. However, there might be some association as IgA nephropathy is very common in the world and it is not certain whether ICI is triggering anything there.

(iii) Additionally, one case of positive PR3-ANCA granulomatosis polyangiitis (GPA) related to pembrolizumab treatment has been reported. Unfortunately, KB was not performed despite proteinuria and haematuria. Likewise, several forms of vasculitis, including large-vessel vasculitis have been reported after ipilimumab treatment [24, 45, 46]. Together, aberrant expression of PD-1 on Th cells in GPA [47] and polymorphisms in *PDCD1* (the gene encoding PD-1) and the cytotoxic T-lymphocyte-associated protein 4 (*CLTA4*) gene [48] are reported to play a role in the pathophysiology of GPA, highlighting the important role of PD-1 in the development of GPA [31].

Such pathophysiologic hypotheses merit further investigation to improve our understanding of the immunopathogenesis of these poorly understood glomerular diseases [26].

CONCLUSION

Given the increasing prevalence of ICPI therapies, the small incidence of kidney adverse events and the fact that glomerular disorders are atypical, physicians need to pay more attention to the possible renal side effects. Early biopsy and use of corticosteroids may be warranted in some cases.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Johnson DB, Sullivan RJ, Menzies AM. Immune checkpoint inhibitors in challenging populations. *Cancer* 2017; 123: 1904–1911
2. Lynch TJ, Bondarenko I, Luft A *et al*. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter Phase II study. *J Clin Oncol* 2012; 30: 2046–2054
3. Kwon ED, Drake CG, Scher HI *et al*. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (ca184–043): a multicentre, randomised, double-blind, Phase 3 trial. *Lancet Oncol* 2014; 15: 700–712
4. Eggermont AM, Chiarion-Sileni V, Grob JJ *et al*. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. *N Engl J Med* 2016; 375: 1845–1855
5. Horinouchi H, Yamamoto N, Fujiwara Y *et al*. Phase I study of ipilimumab in phased combination with paclitaxel and carboplatin in japanese patients with non-small-cell lung cancer. *Invest New Drugs* 2015; 33: 881–889
6. Margolin K, Ernstoff MS, Hamid O *et al*. Ipilimumab in patients with melanoma and brain metastases: an open-label, Phase 2 trial. *Lancet Oncol* 2012; 13: 459–465
7. Aglietta M, Barone C, Sawyer MB *et al*. A Phase I dose escalation trial of tremelimumab (cp-675, 206) in combination with gemcitabine in chemotherapy-naive patients with metastatic pancreatic cancer. *Ann Oncol* 2014; 25: 1750–1755
8. Mcdermott DF, Drake CG, Sznol M *et al*. Survival, durable response, and long-term safety in patients with previously treated advanced renal cell carcinoma receiving nivolumab. *J Clin Oncol* 2015; 33: 2013–2020
9. Mcneel DG, Smith HA, Eickhoff JC *et al*. Phase I trial of tremelimumab in combination with short-term androgen deprivation in patients with PSA-recurrent prostate cancer. *Cancer Immunol Immunother* 2012; 61: 1137–1147
10. Hamid O, Robert C, Daud A *et al*. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med* 2013; 369: 134–144
11. Wang M, Ma X, Guo L *et al*. Safety and efficacy profile of pembrolizumab in solid cancer: pooled reanalysis based on randomized controlled trials. *Drug Des Devel Ther* 2017; 11: 2851–2860
12. Izzedine H, Mateus C, Boutros C *et al*. Renal effects of immune checkpoint inhibitors. *Nephrol Dial Transplant* 2017; 32: 936–942.
13. Jhaveri KD, Perazella MA. Adverse events associated with immune checkpoint blockade. *N Engl J Med* 2018; 378: 1163
14. Shirali AC, Perazella MA, Gettinger S. Association of acute interstitial nephritis with programmed cell death 1 inhibitor therapy in lung cancer patients. *Am J Kidney Dis* 2016; 68: 287–291
15. Cortazar FB, Marrone KA, Troxell ML *et al*. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. *Kidney Int* 2016; 90: 638–647
16. Harmankaya K, Erasim C, Koelblinger C *et al*. Continuous systemic corticosteroids do not affect the ongoing regression of metastatic melanoma for more than two years following ipilimumab therapy. *Med Oncol* 2011; 28: 1140–1144
17. Bavi P, Kiehl R, Adeyi O. Immune-related adverse events (irAEs) following CTLA-4 and PD-1/PD-L1 blockade in

advanced melanoma: a comprehensive rapid autopsy study. *Mod Pathol* 2016; 29 (Suppl 2): 4A
18. Eigentler TK, Hassel JC, Berking C *et al*. Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. *Cancer Treat Rev* 2016; 45: 7–18
19. Izzedine H, Gueutin V, Gharbi C *et al*. Kidney injuries related to ipilimumab. *Invest New Drugs* 2014; 32: 769–773
20. 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: 411–417
21. Wanchoo R, Karam S, Uppal NN *et al*. Adverse renal effects of immune checkpoint inhibitors: a narrative review. *Am J Nephrol* 2017; 45: 160–169
22. Perazella MA. Checkmate: kidney injury associated with targeted cancer immunotherapy. *Kidney Int* 2016; 90: 474–476
23. Troxell ML, Higgins JP, Kambham N. Antineoplastic treatment and renal injury: an update on renal pathology due to cytotoxic and targeted therapies. *Adv Anat Pathol* 2016; 23: 310–329
24. Fadel F, El Karoui K, Knebelmann B. Anti-CTLA4 antibody induced lupus nephritis. *N Engl J Med* 2009; 361: 211–212
25. Kidd JM, Gizaw AB. Ipilimumab-associated minimal change disease. *Kidney Int* 2016; 89: 720
26. Kitchlu A, Fingrut W, Avila-Casado C *et al*. Nephrotic syndrome with cancer immunotherapies: a report of 2 cases. *Am J Kidney Dis* 2017; 70: 581–585
27. Daanen RA, Maas RJH, Koornstra RHT *et al*. Nivolumab-associated nephrotic syndrome in a patient with renal cell carcinoma: a case report. *J Immunother* 2017; 40: 345–348
28. Kishi S, Minato M, Saijo A *et al*. A case of IgA nephropathy after nivolumab therapy for postoperative recurrence of lung squamous cell carcinoma. *Intern Med* 2018; 57: 1259–1263
29. Jung K, Zeng X, Bilusic M. Nivolumab-associated acute glomerulonephritis: a case report and literature review. *BMC Nephrol* 2016; 17: 188
30. Bickel A, Koneth I, Enzler-Tschudy A *et al*. Pembrolizumab-associated minimal change disease in a patient with malignant pleural mesothelioma. *BMC Cancer* 2016; 16: 656
31. van den Brom RRH, Wayel H, Abdulahad WH *et al*. Rapid granulomatosis with polyangiitis induced by immune checkpoint inhibition. *Rheumatology* 2016; 55: 1145–1147
32. Alpers CE, Cotran RS. Neoplasia and glomerular injury. *Kidney Int* 1986; 30: 465–473
33. Dabbs DJ, Striker LM, Mignon F *et al*. Glomerular lesions in lymphomas and leukemias. *Am J Med* 1986; 80: 63–70
34. Glassock RJ. Secondary minimal change disease. *Nephrol Dial Transplant* 2003; 18 (Suppl 6): vi52–vi58
35. Auguet T, Lorenzo A, Colomer E *et al*. Recovery of minimal change nephrotic syndrome and acute renal failure in a patient with renal cell carcinoma. *Am J Nephrol* 1998; 18: 433–435
36. Martinez-Vea A, Panisello JM, Garcia C *et al*. Minimal change glomerulopathy and carcinoma. Report of two cases and review of the literature. *Am J Nephrol* 1993; 13: 69–72
37. Izzedine H, Escudier B, Lhomme C *et al*. Kidney diseases associated with anti-vascular endothelial growth factor (VEGF): an 8-year observational study at a single center. *Medicine (Baltimore)* 2014; 93: 333–339
38. Lagrue G, Xheneumont S, Branellec A *et al*. A vascular permeability factor elaborated from lymphocytes. I. Demonstration in patients with nephrotic syndrome. *Biomedicine* 1975; 23: 37–40
39. McCarthy ET, Sharma M, Savin VJ. Circulating permeability factors in idiopathic nephrotic syndrome and focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol* 2010; 5: 2115–2121
40. Reiser J, von Gersdorff G, Loos M *et al*. Induction of B7-1in podocytes is associated with nephrotic syndrome. *J Clin Invest* 2004; 113: 1390–1397
41. Yu CC, Fornoni A, Weins A *et al*. Abatacept in B7-1-positive proteinuric kidney disease. *N Engl J Med* 2013; 369: 2416–2423
42. Gagliardini E, Novelli R, Corna D *et al*. B7-1 is not induced in podocytes of human and experimental diabetic nephropathy. *J Am Soc Nephrol* 2016; 27: 999–1005
43. Nishimura H, Nose M, Hiai H *et al*. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity* 1999; 11: 141–151
44. Suzuki H, Kiryluk K, Novak J *et al*. The pathophysiology of IgA nephropathy. *J Am Soc Nephrol* 2011; 22: 1795–1803
45. Goldstein BL, Gedmintas L, Todd DJ. Drug-associated polymyalgia rheumatica/giant cell arteritis occurring in two patients after treatment with ipilimumab, an antagonist of CTLA-4. *Arthritis Rheumatol* 2014; 66: 768–769
46. Minor DR, Bunker SR, Doyle J. Lymphocytic vasculitis of the uterus in a patient with melanoma receiving ipilimumab. *J Clin Oncol* 2013; 13: e356
47. Wilde B, Hua F, Dolff S *et al*. Aberrant expression of the negative costimulator PD-1 on T cells in granulomatosis with polyangiitis. *Rheumatology* 2012; 51: 1188–1197
48. Slot MC, Sokolowska MG, Savelkouls KG *et al*. Immunoregulatory gene polymorphisms are associated with ANCA-related vasculitis. *Clin Immunol* 2008; 128: 39–45

Clinical Kidney Journal
ckj