—Case Reports—

Immune Checkpoint Inhibitor-Related Immunoglobulin A Nephropathy in a Patient with Advanced Head and Neck Cancer

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Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of many cancers, including cancers of the head and neck. Despite the promising therapeutic efficacy of ICIs, immune-related adverse events (irAEs) are a major concern. Acute tubular injury and interstitial nephritis are the most common irAEs involving the kidneys. The present patient was diagnosed as having advanced papillary squamous cell carcinoma of the head and neck. After failure of the initial treatments, including chemotherapy, nivolumab (programmed death-1 inhibitor) was introduced. Shortly after initial administration of nivolumab, the patient developed acute kidney injury with hematuria and proteinuria. A renal biopsy and his clinical course indicated a diagnosis of ICI-related IgA nephropathy. Although glomerular involvement in irAEs is rare and challenging to treatment, the present patient was successfully treated with steroids, which improved kidney function and led to complete remission, as confirmed by urinalysis. (J Nippon Med Sch 2025; 92: 420–425)

Key words: acute kidney injury, IgA nephropathy, immune-related adverse effects, nivolumab, head and neck cancer

Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment. Cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors, programmed death-1 (PD-1) inhibitors, and PD ligand 1 (PDL-1) inhibitors are currently approved for clinical use by the U.S. Food and Drug Administration[1]. Nivolumab is a fully human immunoglobulin (Ig) G4 anti-PD-1 monoclonal antibody that inhibits interaction between PD-1 and PDL-1, blocks cancer cell proliferation, and induces cancer cell apoptosis. Squamous cell head and neck cancer (HNC) is the sixth most common cancer worldwide, and its incidence is expected to increase by 30% by 2030[2]. Nivolumab improved overall survival in patients with recurrent squamous cell HNC in the global phase 3 CheckMate 141 study[3]. A recent multicenter cohort study demonstrated the effectiveness and safety of nivolumab in such patients in Japan[4]. Furthermore, in 2019, combination treatment with pembrolizumab (an anti-PD-1 inhibitor) and a cytotoxic anticancer drug was accepted as the first-line treatment for recurrent or metastatic squamous cell HNC.

ICIs have distinctive inflammatory adverse effects, known as immune-related adverse effects (irAEs). Common irAEs have been reported in the skin, bowel, liver, endocrine system, and lung. irAEs of the kidney can cause acute kidney injury (AKI). The most common pathological characteristic of AKI is acute tubulointerstitial nephritis (ATIN)[5]. In contrast, glomerular diseases such as thrombotic microangiopathy, focal segmental glomerulosclerosis, minimal change disease, membranous nephropathy, and IgA nephropathy are rare[1]. Therefore, the clinical course and optimal treatment for these conditions are unclear. Herein, we present a case in which nivolumab therapy for recurrent HNC led to develop-

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ment of AKI, which was subsequently diagnosed as IgA nephropathy.

Case Presentation

A 59-year-old Japanese man was referred to a nephrologist for evaluation of kidney injury with hematuria. The patient was diagnosed as having papillary squamous cell HNC at age 52 years. The initial treatment included tumor resection and postoperative radiotherapy. Over the next 7 years, three recurrences of HNC were treated with gamma-irradiation therapy, tumor re-resection, and combined anti-cancer drug therapy, in that order. The anti-cancer drug regimen consisting of cisplatin (CDDP), cetuximab, and 5-FU was administered in six courses but failed (**Fig. 1**). Then, nivolumab monotherapy was initiated as second-line therapy. After the initial administration of nivolumab, blood analysis showed a slight increase in creatinine (Cr) levels, from 1.02 to 1.21 mg/dL (**Fig. 2**). Importantly, urinalysis revealed microhematuria with red blood cell counts greater than 30-50 per high-power field. Hematuria had not been detected during the previous 5 months, and the patient was thus referred to a nephrologist for evaluation. The results of additional laboratory tests, such as anti-nuclear antibodies, myeloperoxidase and proteinase 3 anti-neutrophil cytoplasmic antibodies, and anti-glomerular basement membrane antibodies, were all negative (**Table 1**).

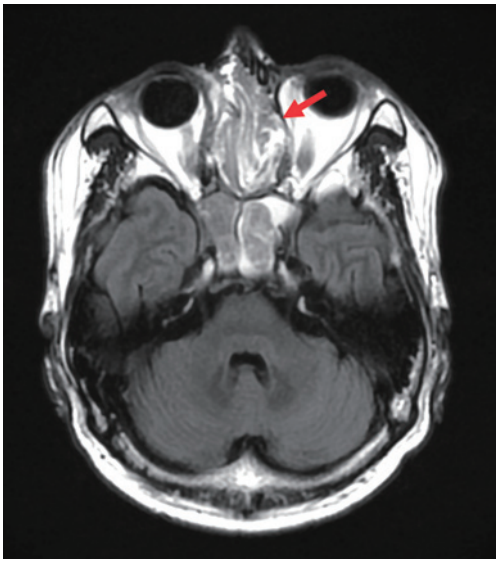

Fig. 1 Magnetic resonance imaging of head neck tumor recurrence

A renal biopsy was performed. Because of the rapid progression of HNC, the second cycle of nivolumab was administered before receiving the pathological results. Notably, just after the second nivolumab administration, the Cr level rapidly increased to 2.13 mg/dL, and hematuria and proteinuria worsened. Renal biopsy results were reported to the nephrologists (**Fig. 3**). On light mi-

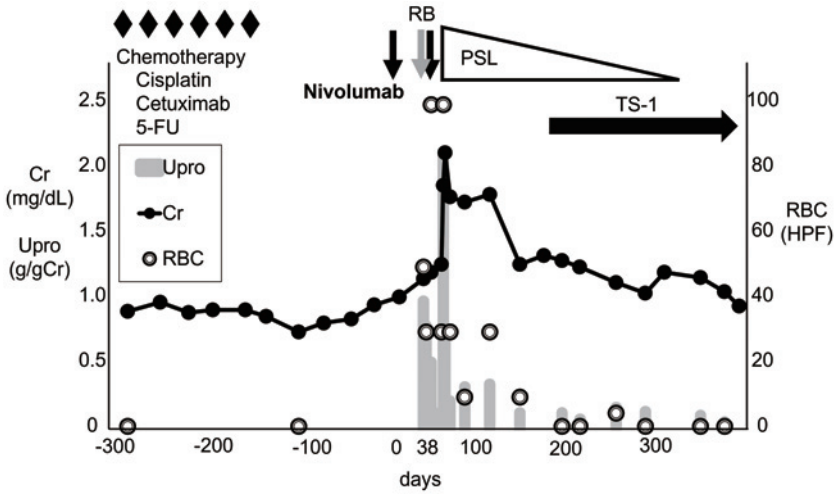

Fig. 2 Clinical course

The patient had received chemotherapy, which failed. Therefore, nivolumab was introduced as second-line therapy. After initial administration of nivolumab, creatinine levels increased to 1.21 mg/dL, with microscopic hematuria. After the second administration of nivolumab, Cr further increased and hematuria and proteinuria worsened. A renal biopsy confirmed the diagnosis of IgA nephropathy. Oral prednisolone was initiated after discontinuation of nivolumab. Subsequently, Cr decreased, with complete resolution of hematuria and proteinuria.

Cr, creatinine; PSL, Prednisolone; RB, Renal biopsy; RBC, Red blood cells; Upro, Urine protein.

Table 1 Patient laboratory data

Blood analysis				Urinalysis	
WBC	4,200 /μL	CRP	0.21 mg/dL	pH	8.5
RBC	348 /μL	UA	8.0 mg/dL	Sp. Gr	1.016
Hb	10.7 g/dL	Cr	1.21 mg/dL	Protein	2+
Plt	200,000 /μL	BUN	21.5	Glucose	-
PT	83.5 %	HbA1C	5.6 mg/dL	Occult blood	3+
APTT	28 Sec	ANA	<40 %	RBC	>100 /HPF
AST	17 IU/L	MPO-ANCA	1.1 IU/mL	WBC	1-4 /HPF
ALT	12 IU/L	PR-3 ANCA	0.8 IU/mL	Granular casts	10-19 /HPF
LDH	120 IU/L	anti GBM-Ab	1.3 IU/mL	Protein	46.0 mg/dL
Na	141 mEq/L	CH50	34 IU/mL	Cr	88.2 mg/dL
K	4.2 mEq/L	C3	57 U/mL	Na	102.9 mEq/L
Cl	107 mEq/L	C4	22 mg/dL	K	74.1 mEq/L
Ca	8.7 mg/dL	IgG	1,352 mg/dL	Cl	82.0 mEq/L
P	2.7 mg/dL	IgA	565 mg/dL	UN	555 mEq/L
Mg	2.6 mg/dL	IgM	82 mg/dL	NAG	19.1 U/L
TC	169 mg/dL	HBs Ag	Negative	B2MG	40,993 μg/L
TP	6.0 g/dL	HCV Ab	Negative		
Alb	3.3 g/dL	HIV Ab	Negative		

WBC, White blood cells; RBC, Red blood cells; Hb, Hemoglobin; Plt, Platelets; PT, Prothrombin time; APTT, Activated partial thromboplastin time; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; LDH, Lactate dehydrogenase; TC, Total cholesterol; TP, Total protein; Alb, Albumin; CRP, C-reactive protein; UA, Uric acid; Cr, Creatinine; BUN, Blood urea nitrogen; HbA1c, Hemoglobin A1c; ANA, Antinuclear antibody; MPO-ANCA, Myeloperoxidase anti-neutrophil cytoplasmic antibody; PR3-ANCA, Proteinase-3 anti-neutrophil cytoplasmic antibody; GBM-Ab, Glomerular basement membrane antibody; CH50, Serum complement level; C3, Complement factor 3; C4, Complement factor 4; IgG, Immunoglobulin G; IgA, immunoglobulin A; IgM, Immunoglobulin M; HBs Ag, Hepatitis B virus antigen; HCV Ab, Hepatitis C virus antibody; HIV Ab, Human immunodeficiency virus antibody; UN, Urea nitrogen; NAG, N-acetyl-β-D-glucosaminidase; and B2MG, Beta 2-Microgrobulin.

croscopic evaluation, most glomeruli had minor abnormalities. One glomerulus showed segmental mesangial proliferation. Interstitial nephritis or tubular injury, such as tubulitis, were not obvious. Interstitial fibrosis was limited and only observed around the glomerular sclerosis. Notably, immunofluorescence microscopy revealed positive staining for IgA and C3 and weakly positive staining for IgM, with a granular pattern, in the mesangial area. Pathological findings were consistent with IgA nephropathy (Oxford classification: M0, E0, S0, T0, C0; Japanese Histological-Grade II C).

Nivolumab therapy was discontinued and corticosteroid therapy (oral prednisolone [PSL] 40 mg/day) was started for IgA nephropathy. PSL was gradually tapered over 10 months (**Fig. 2**). Cr level decreased to baseline (1.17 mg/dL), with complete remission of hematuria and proteinuria. Although kidney function improved, the HNC progressed rapidly; thus, the third-line therapy, TS-1, was started.

This case study complied with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Nippon Medical School Hospital. Informed consent was obtained from the patient for the publication of the details of his medical care and accompanying images.

Discussion

In this report, we present a case of irAE of the kidney with IgA nephropathy that might have been caused by nivolumab therapy. Although it is challenging to manage irAEs of the kidney, particularly glomerular diseases, steroid therapy for IgA nephropathy in our case successfully improved renal function and resulted in complete resolution of hematuria and proteinuria.

IgA nephropathy is a much less common kidney irAE than ATIN[5]. Ten cases of possible ICI treatment-induced IgA nephropathy, including the present case, have been reported[6–13] (**Table 2**). Notably, five of these ten cases involved Japanese patients, which is consistent with the higher prevalence of IgA nephropathy in Asians. The pathogenesis of ICI-related IgA nephropathy is unclear, but possible causes include immune disturbance, un-

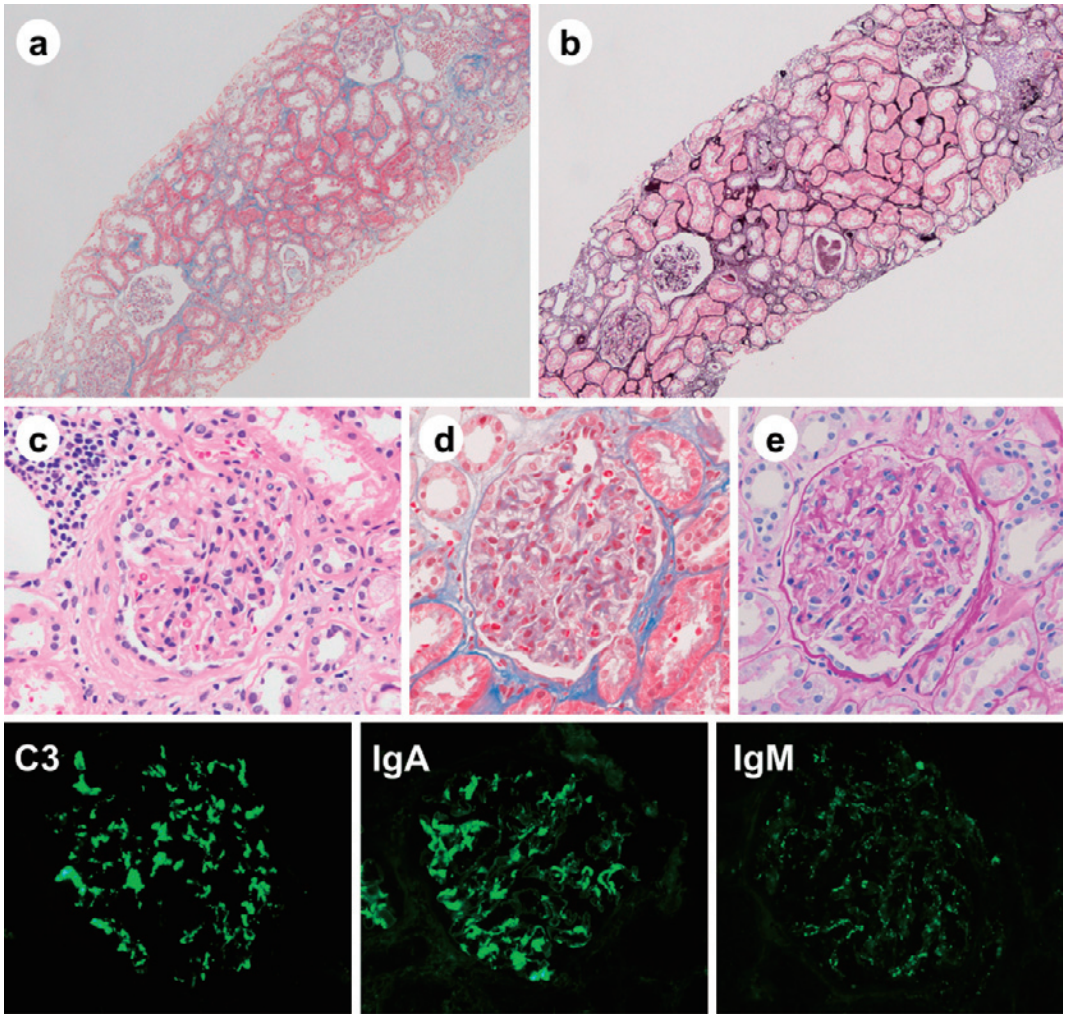

Fig. 3 Renal biopsy results
a: Masson-trichrome staining (×100); b: Periodic acid meth-enamine silver staining (×100); c: Hematoxylin-eosin staining (×400) showed segmental sclerosis with partial fibrosis of Bowmans capsule; d: Masson-trichrome staining (×400) and e: Periodic acid-Schiff staining showed an increase in mesangial matrix and segmental mesangial proliferation. Immunofluorescence showed positive staining for IgA and C3 and weakly positive staining for IgM, with a granular pattern, in the mesangial area.

masking of subclinical IgA nephropathy by enhancement of immune response, and alteration of gut microbiota after ICIs[6–13]. Regarding unmasked subclinical IgA nephropathy, a recent study described a patient who initially had a positive dipstick result for microscopic hematuria and developed IgA nephropathy after exposure to pembrolizumab[13]. Preexisting subclinical IgA nephropathy may have become symptomatic after exposure to ICIs because of disruption of peripheral tolerance. This report highlights the importance of monitoring urinalysis results before and after ICI use.

Although tubulointerstitial injury was not significant in the pathological evaluation of the present case, increases in urine β2MG, NAG, and granular casts indicated tubular injury. Granular casts were concomitant with hematuria after pembrolizumab administration and resolved with renal recovery, which suggests that pembrolizumab also induced tubular injury that was not as severe as IgA nephropathy.

ICI-related IgA nephropathy is challenging to treat. In most cases, culprit ICIs were discontinued (**Table 2**). In some cases, kidney function and urinary abnormalities improved immediately after discontinuation of ICIs. However, recovery from ICI-related IgA nephropathy can take several months because ICIs have a half-life ranging from 6.1 days (avelumab) to 27.3 days (pembrolizumab), and the effect of ICIs on the kidney persist for some time after their discontinuation[14]. Steroid therapy, which was used in six cases (**Table 2**), should not be selected solely on the basis of kidney function. Steroid use was associated with worse progression-free survival in patients with advanced non-small-cell lung carcinoma treated

Table 2 Ten cases of possible ICI treatment–induced IgA nephropathy.

Year	Author	Age	Sex	Population	ICIs	Cancer type	Previous treatments	Duration of ICIs	ICIs	Treatment	Renal outcome	Cancer outcome
2018	Kishi et al.[6]	72	M	Japanese	Nivolumab	NSCLC	-	17 cycles (1 year)	Discontinued	No	Stabilize with remission of proteinuria	No relapse
2019	Mamlouk et al.[7]	69	M	Whites	Ipilimumab + Nivolumab	Melanoma	-	2 cycles (6 weeks)	Discontinued	PSL 0.5 mg/kg	Complete recovery	19 months with no relapse
2019	Mamlouk et al.[7]	50	F	Whites	Pembrolizumab	Melanoma	-	5 cycles (16 weeks)	Discontinued	PSL 2 mg/kg + MMF 1 g/day + Infliximab (one dose)	Partial recovery	4 weeks progression of metastasis
2020	Tanabe et al.[8]	73	M	Japanese	Nivolumab	Gastric cancer	S-1 + Oxaliplatin Ramucirumab + Paclitaxel	2018/9-2019/2	Discontinued	PSL 0.6 mg/kg	Partial recovery with remission of proteinuria	-
2020	Oki et al.[9]	75	F	Japanese	Pembrolizumab	NSCLC	Cisplatin		Discontinued	No	Complete recovery with persisting hematuria	Relapse Carboplatin + Pemetrexed
2020	Wang et al.[10]	72	M	NA	Pembrolizumab	Mesothelioma	Cisplatin + Pemetrexed	2018/2-2018/6 2018/8-2019/11	Continued	No	No recovery	-
2024	Chabannes et al.[13]	65	M	NA	Pembrolizumab	NSCLC	-	2 cycles	Discontinued	PSL 1 mg/kg + Pulse of cyclophosphamide	Partial recovery	Progression
2024	Present case	59	M	Japanese	Nivolumab	HNC	Resection + radiation, Gamma-irradiation, Re-resection, Cisplatin + Cetuximab + 5-FU	2 cycles	Discontinued	PSL 0.5 mg/kg	Complete recovery with remission of hematuria and proteinuria	Relapse TS-1

HNC, Head and neck cancer; mPSL, methylprednisolone; NA, No assessment; NSCLC, Non-small cell lung carcinoma; and PSL, Prednisolone.

with pembrolizumab[15]. Thus, an in-depth discussion with oncologists and nephrologists is required.

ICI rechallenge after an episode of AKI remains controversial. A recent multicenter study reported that 31 of 138 patients diagnosed with ICI-related AKI were rechallenged with ICIs after a median interval of 1.8 months after the initial AKI episode [16]. When ICIs were reinitiated, the median serum Cr level was 1.3 mg/dL. Recurrent ICI-related AKI occurred in 23% of 31 patients after a median of 1.5 months of rechallenge, indicating a shorter latency period. Steroid therapy was concomitantly administered at a median dose of 10 mg/day; however, the frequency of steroid use did not significantly differ between patients who did and did not develop recurrent AKI. Failure to achieve kidney recovery after ICI-related AKI was reported to be an independent risk factor for mortality. In the present case, we discontinued nivolumab because the second administration significantly worsened hematuria and kidney function. Instead, we introduced TS-1 therapy to prevent tumor progression.

Cisplatin is a platinum compound that has been the mainstay of chemotherapy in many cancers; however, nephrotoxicity is a major adverse effect. Cisplatin is absorbed by basolaterally localized organic cation transporter 2, resulting in high cisplatin concentrations in the

renal cortex. Therefore, proximal tubular epithelial cells are the dominant sites of cisplatin nephrotoxicity. Clinically, cisplatin nephrotoxicity appears after 10 days of cisplatin administration and manifests as AKI, hypomagnesemia, and hypokalemia. In our evaluation of renal biopsy, tubular injury was not obvious, which suggests that cisplatin exposure was not an important contributor to kidney injury in the present case.

In conclusion, we described a case of ICI-related IgA nephropathy in a patient with advanced HNC. Although treatment is controversial, we successfully treated the present patient with steroids and achieved renal recovery with complete resolution of urinary abnormalities. Further study of therapeutic strategies for ICI-related IgA nephropathy is warranted.

Author Contributions: SA designed the study and wrote the initial draft of the manuscript. TM contributed to the analysis and interpretation of data, and assisted in the preparation of the manuscript. AS contributed to the analysis and interpretation of renal pathology. All other authors have contributed to data collection, interpretation, and critically reviewed the manuscript. The final version of the manuscript was approved by all authors.

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