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CASE REPORT

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Successful mycophenolate mofetil treatment of a patient with severe steroid-refractory hepatitis evoked by nivolumab plus ipilimumab treatment for relapsed bladder cancer

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Abstract

Mycophenolate mofetil resulted in rapid improvement of steroid-refractory immune-related adverse event hepatitis, induced by nivolumab plus ipilimumab.

KEYWORDS

hepatitis, immune-related adverse events, ipilimumab, mycophenolate mofetil, nivolumab

1 | INTRODUCTION

A 78-year-old man with relapsed bladder cancer underwent combined nivolumab plus ipilimumab therapy but developed severe hepatitis after the third dose. Prednisolone (1 mg/kg/d) did not resolve the hepatitis. Liver function rapidly improved after treatment with mycophenolate mofetil (MMF; 2 g/d), highlighting the efficacy of MMF in steroid-refractory hepatitis.

Immune checkpoint inhibitors (ICI), represented by antiprogrammed cell death protein-1 (PD-1) antibody (eg, nivolumab) and anticytotoxic T-lymphocyte-associated antigen 4 (CTLA4) antibody (eg, ipilimumab), are standard therapeutic tools for patients with a variety of cancers.[1,2] A combination of nivolumab plus ipilimumab is a powerful therapy that can prolong overall survival (OS) for patients with advanced cancer, including urothelial cancers such as bladder cancer, compared to each monotherapy alone.[3,4] While ICI play an important role in cancer treatments, they can evoke various immune-related adverse events (irAE).[5] For example, the incidences of nivolumab- or ipilimumab-induced grade 3 to 4 hepatitis are 1% and 7%, respectively.[6] Of note, the incidence of grade 3 to 4 hepatitis has risen from 6.7% to 11% in response to combination therapy with nivolumab and ipilimumab.[3,7,8]

The recommended therapy for irAE hepatitis is the administration of steroids.[9] However, accumulating evidence suggests that a subset of patients with irAE hepatitis become refractory to steroid treatment.[10,11] In addition, strategies for steroid-refractory irAE hepatitis are not well established. We

herein describe the successful management of a patient with grade 4 hepatitis, induced by nivolumab plus ipilimumab treatment, using mycophenolate mofetil (MMF).

2 | CASE REPORT

In 1991, a 78-year-old man with gross hematuria was diagnosed with early bladder cancer and treated by the transurethral resection of a bladder tumor (TUR-BT). He subsequently underwent TUR-BT twice over 26 years. In August 2017, he underwent a total cystectomy and an ileal conduit construction as a radical treatment for advanced bladder cancer. However, in October 2018, 14 months after the radical resection, computed tomography (CT) imaging revealed multiple para-aortic lymph node metastases of bladder cancer. Therefore, combination therapy of nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) was initiated as part of a clinical trial in November 2018. Prior to 5 days of ICI administration, pyelonephritis developed and was accompanied by back pain and fever on the left side. After treatment with doripenem (DRPM), the patient consequently recovered from pyelonephritis. Subsequently, we started ICI combination therapy. Five days after a third dose of this double ICI regimen was administered and 71 days from when the first ICI was administered, laboratory tests revealed severe liver injury: grade 3 (defined by Common Terminology Criteria for Adverse Events v5.0) aspartate aminotransferase elevation (AST; 251 U/L); grade 3 alanine aminotransferase elevation (ALT; 266 U/L); grade 3 alkaline phosphatase elevation (ALP; 2867 U/L); and grade 3 gamma-glutamyl transpeptidase elevation (γGTP; 461 U/L), but without bilirubin elevation. Serological blood tests were negative for viral infections such as cytomegalovirus, Epstein-Barr virus, and hepatitis (B and C) viruses. Blood tests revealed levels of antinuclear antibody (×40) were weakly elevated, while moderate increases in IgG were observed (Table 1). The patient was negative for antimitochondrial (AMA) and AMA-M2 antibodies. Liver

TABLE 1 Patient's laboratory data

<Hematology>		**<Blood chemistry>**		**<Immunology>**	
WBC	$7.3 \times 10^3/\mu L$	T.P	5.7 g/dL	IgG	1152 mg/dL
Neut	62.7%	Alb	2.1 g/dL	IgA	509 mg/dL
Eos	26.6%	T-Bil	0.9 mg/dL	IgM	36 mg/dL
Baso	0.4%	AST	251 U/L	IgE	777 mg/dL
Mono	4.3%	ALT	266 U/L	ANA	×40
Lymph	6.0%	LDH	313 U/L	AMA	(−)
RBC	$2.96 \times 10^6/\mu L$	ALP	2867 U/L	AMA-M2	(−)
Hb	9.3 g/dL	γGTP	461 U/L	**<Viral marker>**	
MCV	93.6 fL	Na	142 mmol/L	HBs-Ag	(−)
MCH	31.4 pg	Cl	112 mmol/L	HBs-Ab	(−)
Ht	27.7%	K	3.5 mmol/L	HCV-Ab	(−)
Plt	$186 \times 10^3/\mu L$	Ca	8.2 mg/dL	CMV-IgG	×121.5
		BUN	22 mg/dL	CMV-IgM	(−)
<Coagulation>		Cr	1.68 mg/dL	EBV-VCA-IgG	×2.1
PT-INR	1.07	UA	6.0 mg/dL	EBV-VCA-IgM	(−)
PT%	86.0%	CRP	3.10 mg/dL	EBNA	×3.3

Abbreviations: <Hematology> Baso, basophils; Eos, eosinophils; Hb, hemoglobin; Ht, hematocrit; Lymph, Lymphocytes; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; Mono, monocytes; Neut, neutrophils; Plt, platelets; RBC, red blood cells; WBC, white blood cells. <Coagulation> INR, international normalized ratio; PT, prothrombin time. <Blood chemistry> Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; BUN, blood urea nitrogen; Ca, calcium; Cl, chloride; Cr, creatinine; CRP, C-reactive protein; K, potassium; LDH, lactate dehydrogenase; Na, sodium; T.P, total protein; T-Bil, total bilirubin; UA, uric acid; γGTP, γ-glutamyl transpeptidase. <Immunology> AMA, antimitochondrial antibody; ANA, antinuclear antibody; Ig, Immunoglobulin. <Viral marker> CMV, cytomegalovirus; EBNA, EBV nuclear antigen; EBV, Epstein-Barr virus; HBs-Ab, hepatitis B surface antibody; HBs-Ag, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; VCA, virus capsid antigen.

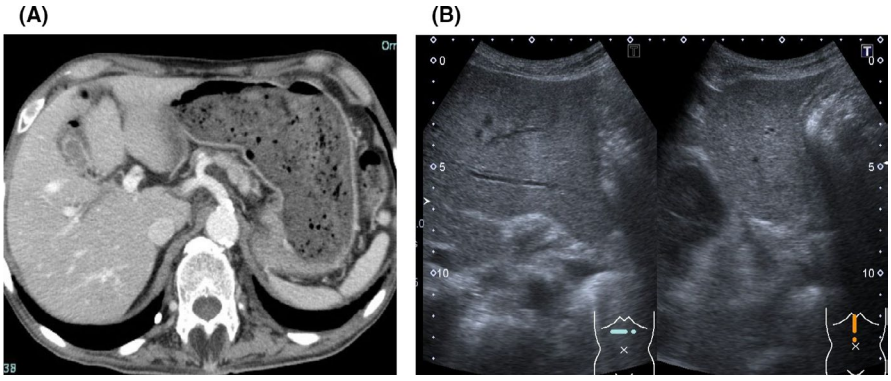

FIGURE 1 Abdominal computed tomography (A) and ultrasound image (B) findings when immune-related adverse event (irAE) hepatitis appeared

metastases and bile duct dilation were not detected by CT imaging and abdominal ultrasonography (Figure 1). Double ICI treatment achieved a partial response as revealed by CT (Figure 2). In view of his drug history, blood test results, and image findings, the patient was diagnosed with grade 3 irAE hepatitis. Subsequently, he was treated intravenously with 60 mg (1 mg/kg/d) prednisolone (PSL). On the same day, the infusion of DRPM was stopped. At this point, we could not completely rule out a DRPM-induced liver injury since the ALP level and eosinophil count increased after DRPM administration. To manage his liver injury, the patient was referred to our department. We did not carry out a liver biopsy since the patient's performance status (PS) worsened from 1 to 2, with the patient experiencing a general malaise due to liver injury. Despite treatment with an adequate amount of PSL, ALT, which at 1092 U/L was grade 4 and had reached its maximal level during this clinical course, and total bilirubin (2.2 mg/dL) levels worsened 5 days after PSL administration. The ALP level and eosinophil count decreased after the cessation of DRPM, unlike transaminase levels. According to the clinical course, the patient's irAE hepatitis was considered steroid-refractory. We, therefore, orally administered MMF at a dose of 2 g/d after approval by the institutional review board. The irAE hepatitis rapidly improved, ALT levels decreased to 179 U/L, and the total bilirubin level became normal 13 days after MMF administration. MMF treatment effectively continued to improve liver function, even when PSL was tapered to 10 mg/d (Figure 3). Subsequently, the administration of MMF continued to be tapered until it was eventually ceased after close monitoring with blood tests. No recurrence of irAE hepatitis was observed. Notably, at the time of writing, the patient's disease remains stable 14 months after the cessation of anticancer treatments.

3 | DISCUSSION

We describe the successful treatment, using MMF, of a patient with steroid-refractory hepatitis induced by ipilimumab plus nivolumab treatment for advanced bladder cancer. Treatment strategies for steroid-refractory irAE hepatitis have not been well established. Based on recent practice guidelines,[9,12,13] one of the recommended therapies is the additional use of MMF with steroid therapy for this disease. Generally, medical oncologists and/or hepatologists who treat patients with irAE hepatitis are unfamiliar with the use of MMF since this is approved for the prevention of organ transplant rejection and severe lupus nephritis in most countries, including Japan.[14,15] As a result, steroid-pulse therapies had been used for steroid-refractory irAE hepatitis, prior to the use of MMF,

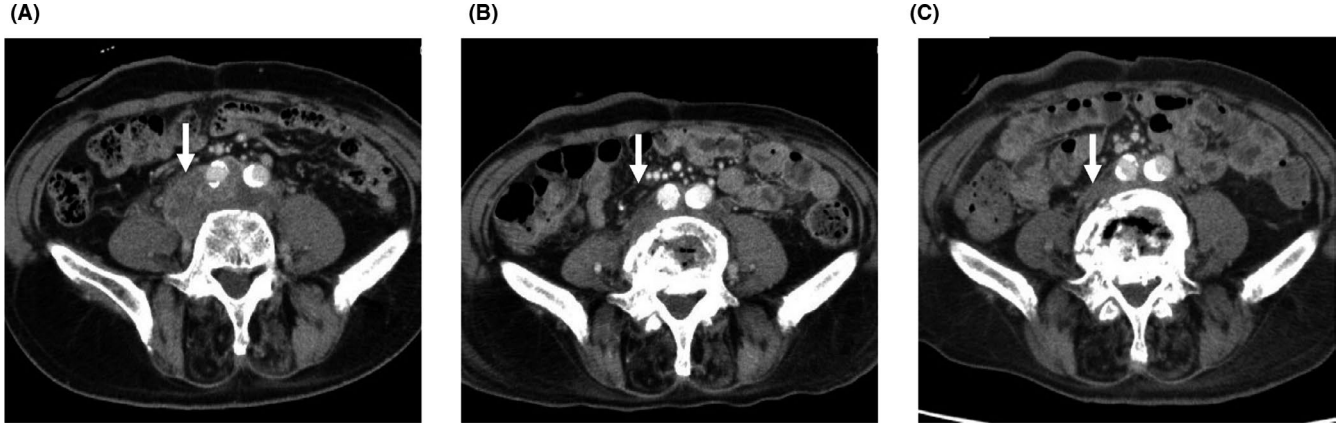

FIGURE 2 Computed tomography (CT) images. A, Pretreatment CT scan. B, CT scan after three doses of immune checkpoint inhibitors (ICI). C, CT scan 14 mo after stopping anticancer treatment

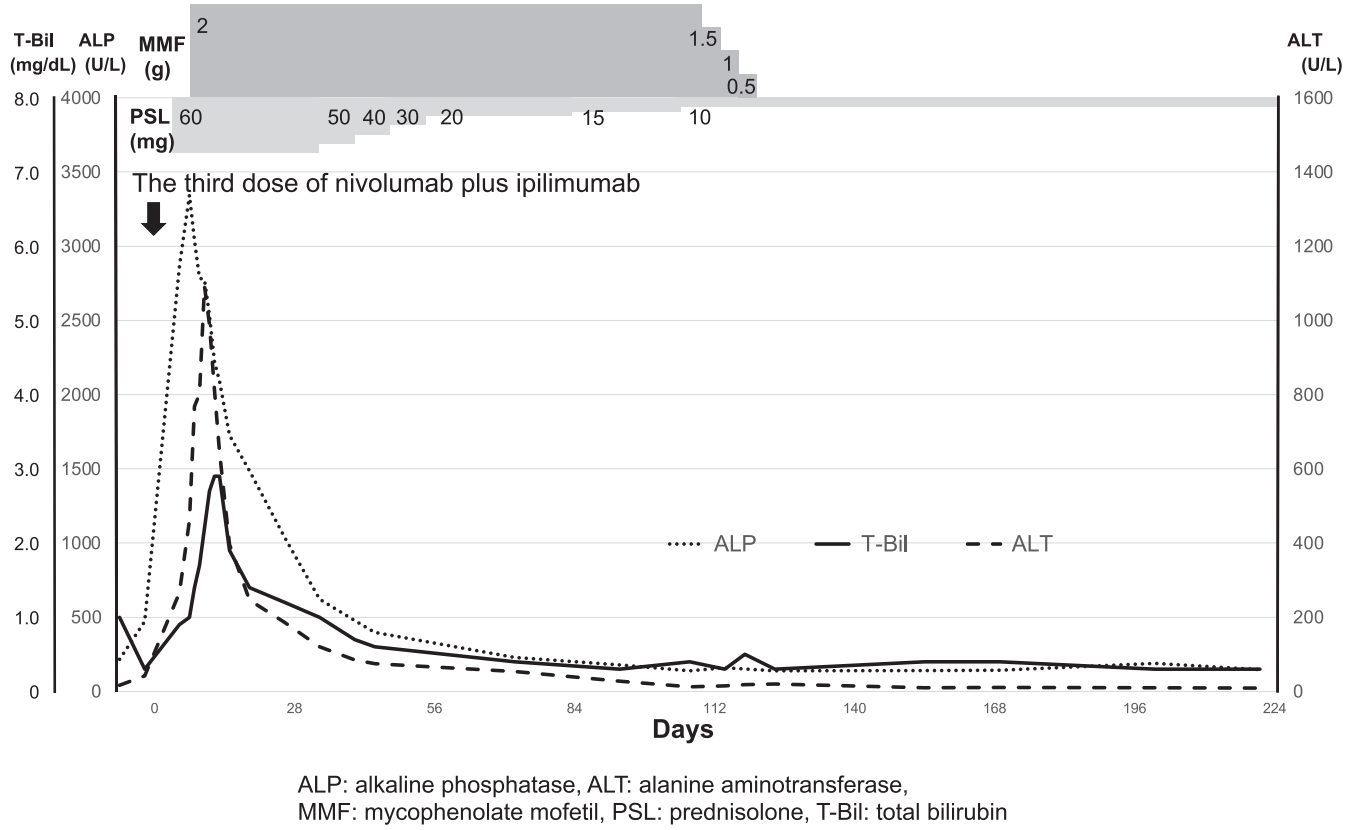

FIGURE 3 Clinical course. ALP, alkaline phosphatase; ALT, alanine aminotransferase; MMF, mycophenolate mofetil; PSL, prednisolone; T-Bil, total bilirubin

TABLE 2 Efficacies of mycophenolate mofetil for irAE hepatitis

Case	Age	Sex	Diagnosis	ICIs	Doses of MMF (g/d)	Prior treatment	Efficacy
1[11]	49	F	Melanoma	Pembrolizumab	2	PSL (1 mg/kg/d), UDCA	Ineffective
2[11]	76	M	Mesothelioma	Pembrolizumab	1	PSL (1 mg/kg/d), Cholestyramine, UDCA	Ineffective
3[10]	61	M	Melanoma	Ipilimumab	2	mPSL (500 mg/d)	Effective[a]
4[20]	59	M	Melanoma	Nivolumab → Ipilimumab	2	mPSL (1000 mg/d)	Effective
5[21]	50	F	Melanoma	Ipilimumab	2	mPSL (2 mg/kg/d), ATG	Effective
6[22]	38	F	Melanoma	Nivolumab	2	mPSL (2 mg/kg/d), UDCA	Ineffective[b]
7[23]	51	M	Laryngeal cancer	Nivolumab	2	mPSL (500 mg/d)	Effective
Our case	78	M	Bladder cancer	Ipilimumab + Nivolumab	2	PSL (1 mg/kg/d)	Effective

Note: Effective: improvement of liver function.

Abbreviations: ATG, antithymocyte globulin; F, female; ICI, immune checkpoint inhibitor; M, male; MMF, mycophenolate mofetil; mPSL, methylprednisolone; PSL, prednisolone; UDCA, ursodeoxycholic acid.

[a]Effective: improvement after ATG administered.

[b]Ineffective: discontinuation of MMF due to thrombocytopenia and neutropenia.

despite steroid-pulse therapy not being outlined in guidelines.[10,16] The efficacy of steroid-pulse therapy against irAE hepatitis has been limited as shown in Table 2. Specifically, Cheung et al have revealed that corticosteroid doses above 60 mg daily PSL were not successful in resolving liver damage. However, the early introduction of immunosuppressive

agents, including MMF, may have benefited patients who did not rapidly respond to steroids.[17]

Immune-related adverse events hepatitis is considered to be driven by a disruption of immune tolerances, which is mainly evoked by autoreactive T cells. Of note, pathological analyses revealed that most infiltrating lymphocytes in the parenchyma and portal tract of the liver expressed CD8, a T-cell marker.[6] To alleviate steroid-refractory irAE hepatitis, we should consider using a T-cell immunosuppressant such as MMF. MMF inhibits de novo purine synthesis, which is indispensable for the proliferation of lymphocytes, induces the apoptosis of activated T cells, suppresses the production of pro-inflammatory cytokines, and augments regulatory T cells.[18,19] Accordingly, the use of MMF is a reasonable strategy to treat steroid-refractory irAE hepatitis. Besides MMF, other drugs, such as azathioprine, antithymocyte globulin, and tacrolimus, are available for the management of irAE hepatitis.[9,12,13] However, priorities for these drugs have not been established in any guidelines. Further studies are needed to clarify the usefulness of these drugs and establish a treatment flow chart of steroid-refractory irAE hepatitis.

In our case study, a liver biopsy was, unfortunately, not undertaken because the patient did not consent to a liver biopsy and had already been treated with PSL. Such biopsies should be considered since these are helpful in the differential diagnosis of liver injury. However, according to a recent review, the significance of liver biopsies is unclear since irAE hepatitis does not show pathognomonic histologic findings.[13]

4 | CONCLUSION

Our case and those of previous reports suggest that MMF with steroids may be more effective than steroid-pulse therapy for patients with steroid-refractory irAE hepatitis. Therefore, we recommend that MMF be used for grade 3 or 4 steroid-refractory irAE hepatitis instead of steroid-pulse therapy.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

GO and KT: collected and analyzed data and wrote and edited the manuscript. KM, NH, HN, SI, HO, and KM: involved in the patient's care. FF and TT: were Urologists providing chemotherapy. NM and JK: supervised this study.

ETHICAL APPROVAL

This case report has been performed in accordance with the principles stated in the Declaration of Helsinki. Written informed consent was obtained from the patient for the publication.

DATA AVAILABILITY STATEMENT

Data available within the article.

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