Tohoku J. Exp. Med., 2022, **258**, 159-165

Cerebrospinal Fluid Interleukin-6 in Immune Checkpoint Inhibitor-Induced Autoimmune Meningoencephalitis

Takeshi Mizukami,[1,*] Teruaki Masuda,[1] Noriyuki Kimura,[1,*] Hirotatsu Uchida,[1] Mika Jikumaru,[1] Takuya Hanaoka[1] and Etsuro Matsubara[1]

[1]Department of Neurology, Faculty of Medicine, Oita University, Yufu, Oita, Japan

Immune checkpoint inhibitors (ICIs) have proven clinical benefits in various advanced cancers. However, despite their significant therapeutic efficacy, ICIs induce immune-related adverse events. Among these events, autoimmune meningoencephalitis often has severe effects on patients' outcomes, but its specific clinical features are still unclear. Here, we report two cases of ICI-associated meningoencephalitis with elevated interleukin-6 (IL-6) levels in the cerebrospinal fluid (CSF). A 47-year-old woman (Case 1) with renal cell carcinoma developed severe headache after a seventh nivolumab administration. A neurological examination revealed jolt accentuation signs and hyperreflexia in all extremities. CSF analysis revealed a high IL-6 value (6,620 pg/mL) with marked pleocytosis. A 70-year-old woman (Case 2) who received an initial administration of nivolumab plus ipilimumab for renal cell carcinoma developed alterations of consciousness. She presented with impaired consciousness, neck stiffness, and hyperreflexia in all extremities. CSF analysis demonstrated a high IL-6 value (49.3 pg/mL) with mild pleocytosis. Both patients were treated with steroid pulse therapy (methylprednisolone 1,000 mg/day, 3 days), followed by the administration of oral predonisolone. The symptoms and laboratory findings improved in both cases. CSF IL-6 values were proportional to the severity of meningoencephalitis and other clinical parameters. These findings may help elucidate the mechanisms of central nervous system complications that are caused by ICIs.

Keywords: autoimmune meningoencephalitis; cerebrospinal fluid; immune checkpoint inhibitor; immune-related adverse event; interleukin-6
Tohoku J. Exp. Med., 2022 October, **258** (2), 159-165.
doi: 10.1620/tjem.2022.J071

Introduction

Immune checkpoint inhibitors (ICIs) have become the standard therapy for many types of advanced cancer and have greatly improved the outcomes of patients with these cancers (Ribas and Wolchok 2018). To fight cancer, ICIs mainly target cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death ligand 1 (PD-1). However, they also trigger activation of the immune system and cause various immune-related side effects, which can affect any organ or system (Larkin et al. 2015; Postow et al. 2018; Johnson et al. 2022). Previous studies demonstrated the presence of neurological adverse events in 2-6% of patients with cancer who had been treated with ICIs (Xu et al. 2019; Bruna et al. 2020). The most common clinical presentations associated with neurological immune-related adverse events (irAEs) include peripheral neuropathies, myositis, and meningoencephalitis. Among these neurological irAEs, central nervous system (CNS) complications such as meningoencephalitis can be associated with significant morbidity and may affect the survival of patients (Velasco et al. 2021). ICI-induced meningoencephalitis is a rare but increasingly diagnosed complication. Because patients with ICI-induced meningoencephalitis often have poor outcomes, early diagnosis and therapeutic intervention are critical for improving both the quality of life of patients with irAEs and the patient's cancer-related prognosis (Vogrig et al. 2020). Moreover, accurate and reliable methods for determining the efficacy of treatment are needed. Several studies found that serum interleukin-6 (IL-6) values

Received May 11, 2022; revised and accepted August 15, 2022; J-STAGE Advance online publication September 1, 2022
*These two authors contributed equally to this work.
Correspondence: Teruaki Masuda, M.D., Ph.D., Department of Neurology, Faculty of Medicine, Oita University, 1-1 Idaigaoka, Hasama-machi, Yufu, Oita 879-5593, Japan.
e-mail: terumasu@oita-u.ac.jp

increased in patients with early-onset irAEs and that IL-6 values decreased after the administration of immunotherapy (Valpione et al. 2018; Husain et al. 2021), although the association of cerebrospinal fluid (CSF) IL-6 with irAEs has not been investigated in detail.

In this report, we describe two cases of renal cell carcinoma associated with ICI-induced autoimmune meningoencephalitis. In both cases, the level of IL-6 in the CSF reflected the clinical course of the irAE-related meningoencephalitis.

Case Presentation

Case 1

A 47-year-old woman presented to our hospital with headache and nausea. Three years earlier, she had undergone surgery for renal cell carcinoma; bone metastasis occurred 1 year later. She received nivolumab (a fully human monoclonal IgG4 antibody directed against PD-1) biweekly (240 mg/day). After the seventh nivolumab administration, she developed intractable diarrhea. She was diagnosed with nivolumab-associated colitis, and oral prednisolone therapy (30 mg/day) was initiated. Although the diarrhea gradually resolved, 5 weeks later the patient presented with headache and nausea and was admitted to our hospital. At the time of admission, she had severe headache [numerical rating scale (NRS): 10], and a slight fever (her body temperature was 37.1°C). A neurological examination revealed jolt accentuation signs and hyperreflexia in all extremities. We observed no abnormalities in the cranial nervous system, no paralysis, no ataxia, and no involuntary movements in all extremities. Laboratory examination showed increased serum C-reactive protein (CRP) levels (11.1 mg/dL; reference range 0-0.14) and a normal IL-6 level (6.2 pg/mL; reference range < 7). Values of anti-nuclear antibodies, anti-SS-A antibodies, anti-SS-B antibodies, paraneoplastic autoantibodies, and anti-N-methyl-D-aspartate receptor (NMDAR) antibodies were all normal. CSF analysis revealed pleocytosis (733 cells/μL, 98% neutrophils), an elevated lumbar puncture (LP) opening pressure (32 cm H_2O), an elevated protein level (120 mg/dL), a high IL-6 value (6,620 pg/mL) with a normal IgG index (0.5), a normal adenosine deaminase level, and negative CSF gram staining. The herpes simplex virus (HSV)-IgM test, HSV-IgG test, and real-time polymerase chain reaction (PCR) of HSV in the CSF all produced negative results. Brain magnetic resonance imaging (MRI)

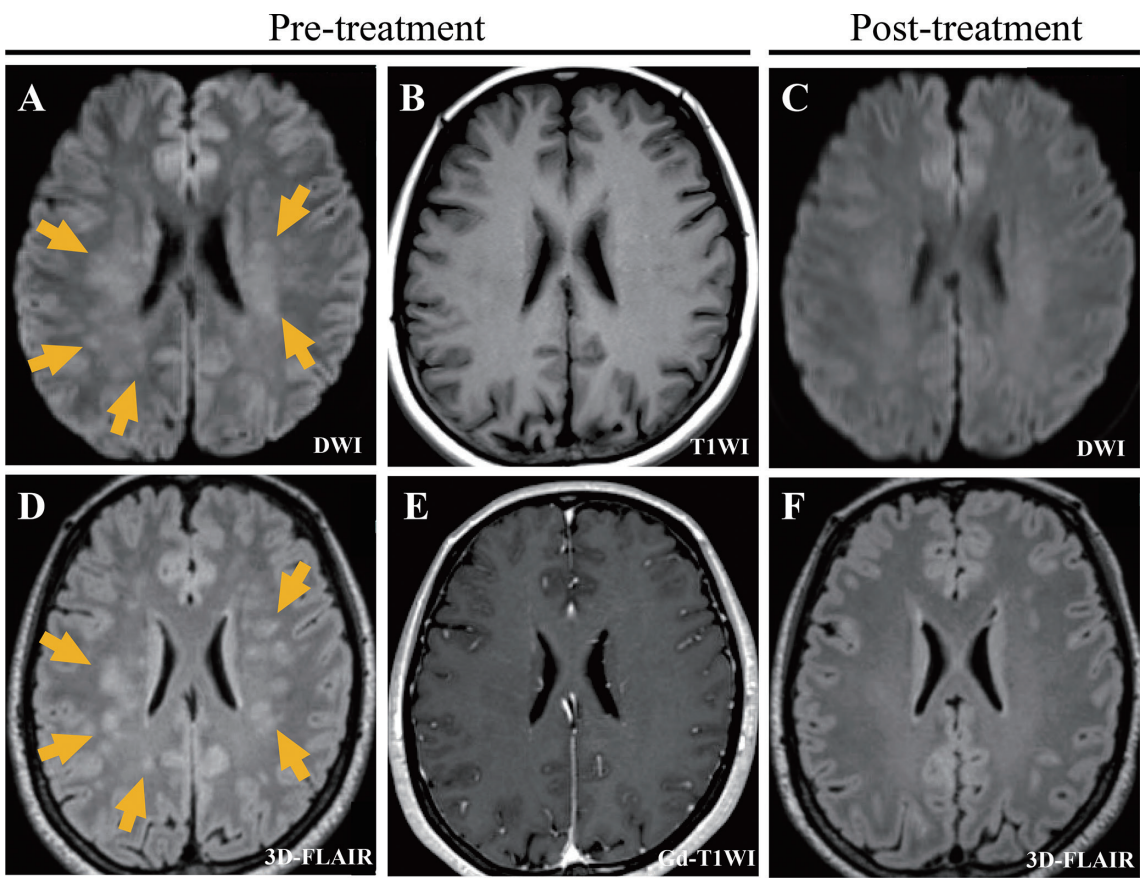

Fig. 1. Pre- and post-treatment brain magnetic resonance imaging (MRI) in Case 1.
Brain MRI at admission showed patchy high-intensity areas in the cerebral white matter on diffusion-weighted imaging (DWI) (A) and three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) (D) images, and unenhanced T1-weighted native images (B, E). Arrows point to the patchy high-intensity areas in the cerebral white matter. Brain MRI after corticosteroid administration showed reduced high-intensity lesions on DWI and 3D-FLAIR images (C, F).

demonstrated patchy high-intensity areas in the cerebral white matter on diffusion-weighted imaging (DWI) and three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) images and an unenhanced T1-weighted native image (Fig. 1A, B, D, E). Although the patient received empirical treatment with dexamethasone, vancomycin, and meropenem because of concerns about bacterial meningoencephalitis and autoimmune meningoencephalitis, she complained of a persistent headache (NRS 6-10) even after the initial therapy. CSF analysis on day 6 of therapy revealed pleocytosis (17 cells/μL; 98% mononuclear cells), however, she had a severe headache (NRS 8-10). After confirmation that the blood and CSF cultures were normal, vancomycin and meropenem were discontinued. These findings led us to assume that meningoencephalitis was associated with the use of nivolumab. Therefore, we began steroid pulse therapy (methylprednisolone, 1,000 mg/day for 3 days), and her headache improved (NRS 2-3). After the second course of steroid pulse therapy, oral prednisolone (50 mg/day) was initiated and gradually tapered. The patient's symptoms fully resolved, and we found no clinical evidence of meningoencephalitis by day 48 (Fig. 2). The serum CRP (0.01 mg/dL) and CSF IL-6 (0.72 pg/mL) values were normal. Brain MRI revealed significant reduction of the hyperintense areas on DWI and 3D-FLAIR MRI images (Fig. 1C, F).

Case 2

A 70-year-old woman with metastatic renal cell carcinoma involving the right adrenal gland and sixth thoracic vertebra received nivolumab (240 mg/day) and ipilimumab (a fully human IgG1 monoclonal antibody directed against CTLA-4) (46.8 mg/day). She reported fever and anterior cervical pain on day 5 after ICI administration. Laboratory examination revealed an increased level of free thyroxine (4.21 pg/mL), a reduced level of thyroid-stimulating hormone (0.3 μIU/mL), and increased levels of antithyroid peroxidase antibody (44.9 IU/ml; reference range 0-16) and antithyroglobulin antibody (53.1 IU/ml; reference range 0-28); the patient was diagnosed as having immune-related thyroiditis caused by ICIs. After 5 more days, the patient developed sudden alterations of consciousness and was transferred to our hospital. She presented with a fever (temperature up to 37.6℃) and headache; a neurological examination revealed impaired consciousness (drowsiness, disorientation in time and space, and hypoactivity), neck

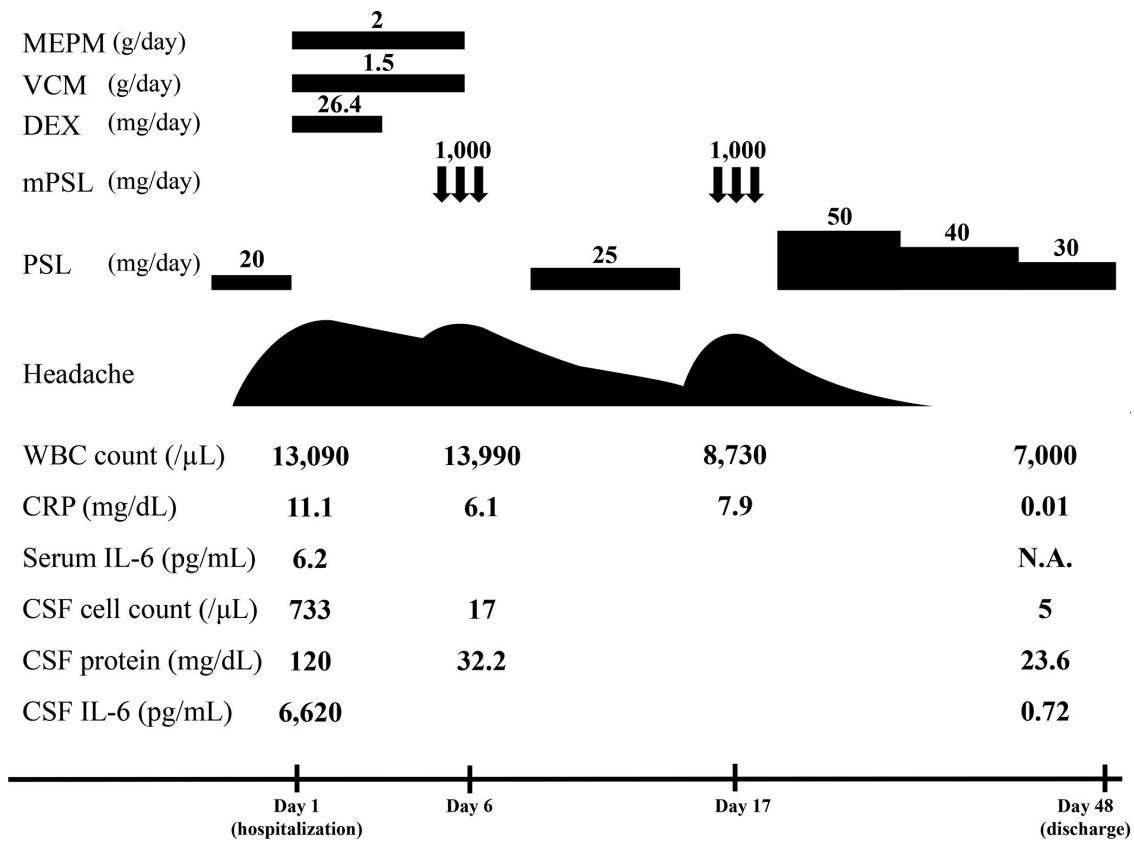

Fig. 2. Clinical course and treatment of Case 1.
After methylprednisolone pulse therapy, followed by oral prednisolone administration (50 mg/day), the patient's headache gradually improved. The levels of inflammatory markers in serum and CSF decreased after treatment.
CSF, cerebrospinal fluid; CRP, C-reactive protein; DEX, dexamethasone sodium phosphate; IL-6, interleukin-6; MEPM, meropenem hydrate; mPSL, methylprednisolone; N.A., not available; PSL, prednisolone; VCM, vancomycin hydrochloride; WBC, white blood cell.

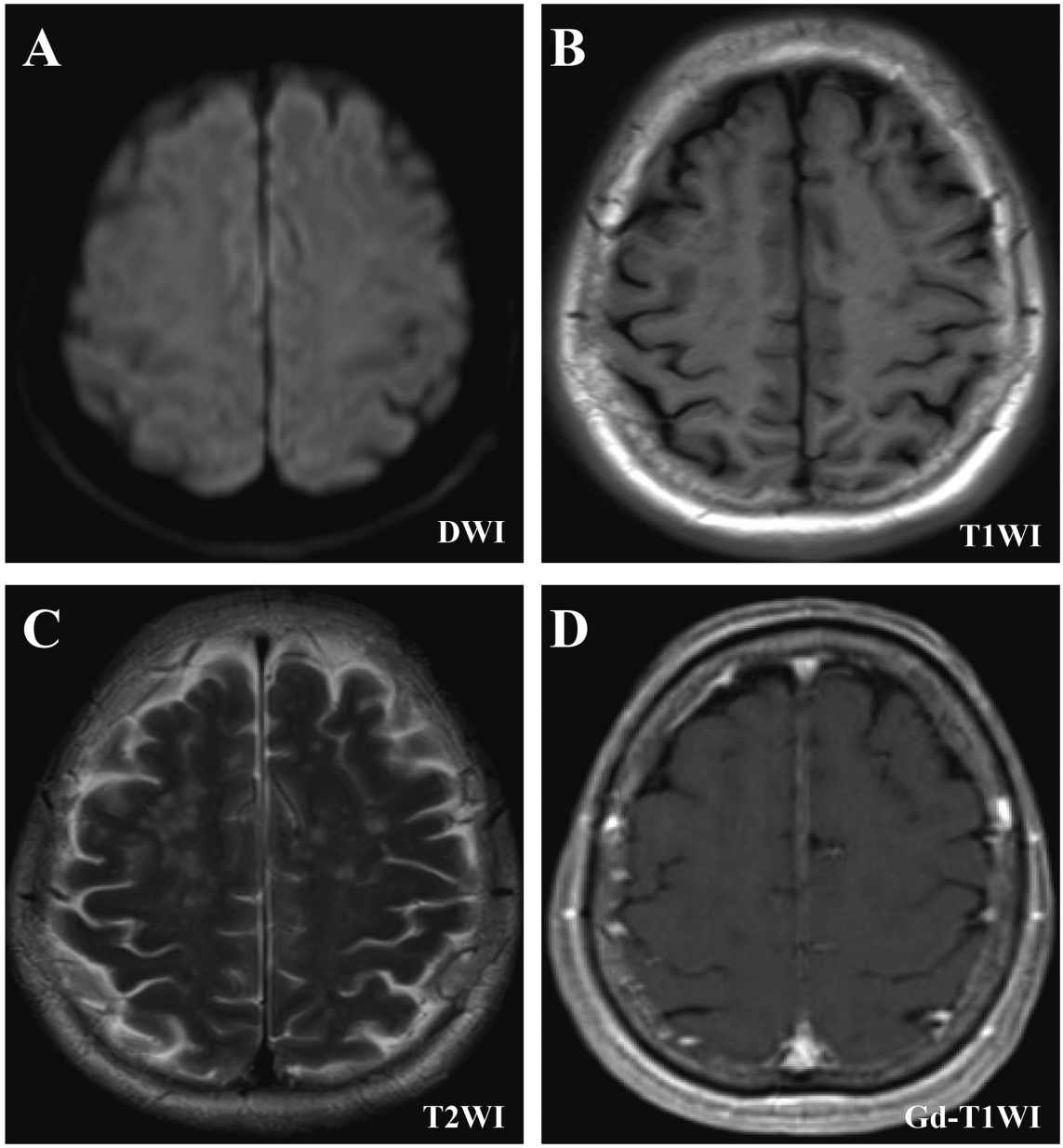

Fig. 3. Pre-treatment brain magnetic resonance imaging (MRI) in Case 2.
Brain MRI showed only nonspecific hyperintense lesions in the white matter on T2-weighted imaging (T2WI) (C). Diffusion-weighted imaging (DWI) showed no high-intensity lesions (A). T1-weighted imaging (T1WI) showed no abnormalities (B), and gadolinium (Gd)-enhanced T1WI showed no enhancement in white matter lesions (D).

stiffness, bilateral action tremor, hyperreflexia in all extremities, and bilateral positive Chaddock reflexes. Brain MRI showed only nonspecific T2-hyperintense lesions in the cerebral white matter (Fig. 3). Laboratory studies indicated elevated serum CRP (15.8 mg/dL) and IL-6 (79 pg/mL) levels. An analysis of the CSF demonstrated an increased protein value (72.1 mg/dL) with mild pleocytosis (16 cells/μL, 94% mononuclear cells), a mildly elevated LP opening pressure (18 cm H_2O), a high IL-6 value (49.3 pg/mL) with a normal IgG index (0.43), and a normal adenosine deaminase level. Other laboratory analyses of the CSF for HSV-IgM, HSV-IgG, and real-time PCR of HSV all produced negative results. Three oligoclonal bands were also observed. Additional analyses showed normal anti-nuclear antibodies, anti-SS-A antibodies, anti-SS-B antibodies, paraneoplastic autoantibodies, and anti-NMDAR antibodies. On the basis of these findings, the patient was diagnosed with meningoencephalitis associated with nivolumab and ipilimumab. Steroid pulse therapy (methylprednisolone 1,000 mg/day, 3 days) was started, and her state of consciousness improved. However, she had alterations of consciousness at 23 days and 35 days after admission. We therefore administered second and third courses of steroid pulse therapy, followed by the administration of oral prednisolone (45 mg/day) that was gradually tapered. Two months later, the patient's symptoms had fully resolved, and

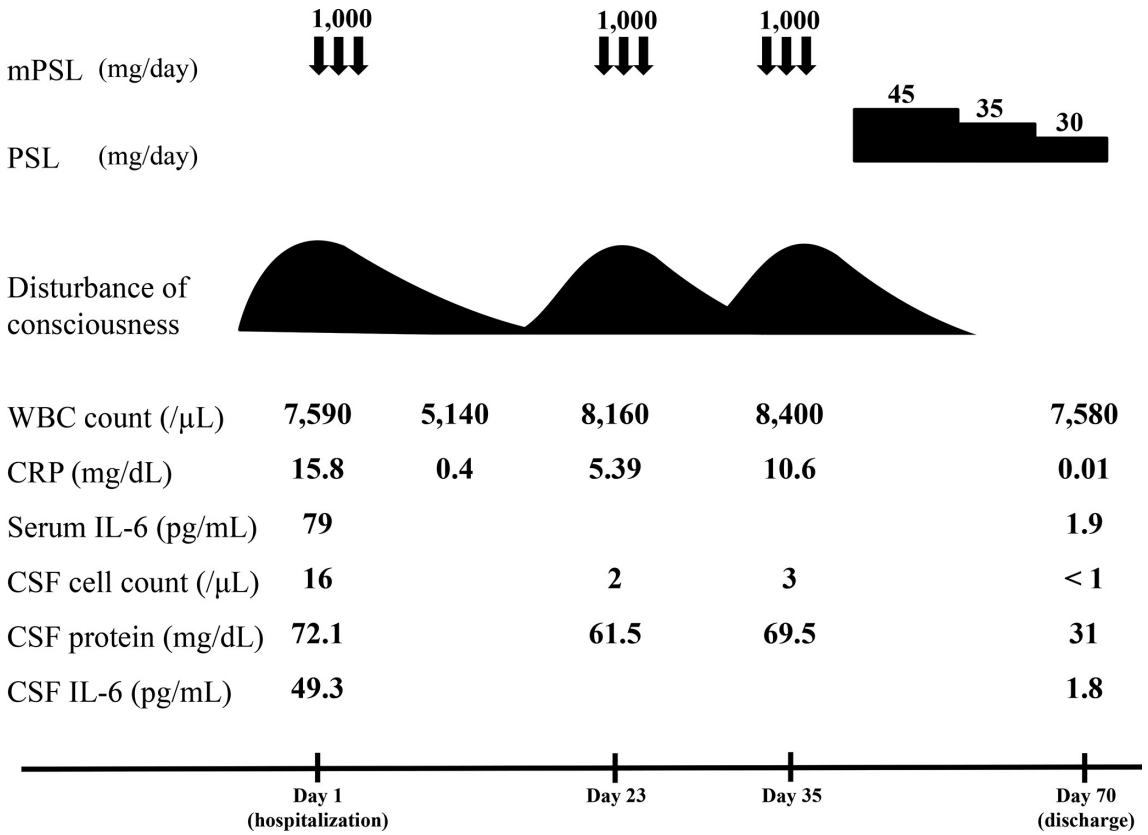

Fig. 4. Clinical course and treatment of Case 2.
After an examination, the patient received three cycles of pulse therapy with methylprednisolone, followed by oral prednisolone treatment (45 mg/day), after which prednisolone treatment was tapered. Her symptoms and laboratory abnormalities had improved at discharge.
CSF, cerebrospinal fluid; CRP, C-reactive protein; IL-6, interleukin-6; mPSL, methylprednisolone; PSL, prednisolone; WBC, white blood cell.

no abnormal neurological findings were seen (Fig. 4). Values of serum CRP (0.01 mg/dL), serum IL-6 (1.9 pg/mL), and CSF IL-6 (1.8 pg/mL) were normal (Table 1).

Discussion

Here, we describe two cases of meningoencephalitis associated with the use of ICIs. The CSF analysis and MRI evaluation demonstrated the therapeutic effects of corticosteroids. We found that the CSF IL-6 values were proportional to the severity of the meningoencephalitis caused by ICIs. These findings may provide insights into the early diagnosis and quantitative evaluation of ICI-associated meningoencephalitis.

irAEs affect nearly every organ and vary in their severity and time of onset (Eigentler et al. 2016). In a previous report that reviewed the Japanese Adverse Drug Event Report Database, the times to onset of ICI-induced meningitis (median 21 days) and encephalitis/myelitis (median 32.5 days) were shorter than those of other neurological AEs such as peripheral neuropathy (median 42 days) and hypophysitis (median 94 days) (Sato et al. 2019). Other reports also showed that most patients developed ICI-induced encephalitis and meningitis early, within 2 months after the start of therapy (Cuzzubbo et al. 2017). A few patients, however, developed ICI-induced encephalitis several months later (Fujiwara et al. 2019; Velasco et al. 2021). Therefore, careful consideration of ICI-induced encephalitis at any time during therapy is necessary. To diagnose ICI-induced encephalitis, physicians must first suspect this disease because of the clinical symptoms; differentiate it from other diseases such as herpes encephalitis, bacterial encephalitis, paraneoplastic syndrome, progressive multifocal leukoencephalopathy, and other autoimmune encephalitides, on the basis of supporting laboratory findings; and determine the final diagnosis. Case 2 developed meningoencephalitis after the first ICI administration, and combination therapy (nivolumab plus ipilimumab) may have accelerated the onset of the irAEs (Sznol et al. 2017). In addition, in our cases, colitis and thyroiditis preceded the occurrence of meningoencephalitis. Previous studies showed that patients frequently manifest co-occurring neurological and non-neurological irAEs (Dubey et al. 2020). Hence, the appearance of irAEs involving other organs should be carefully investigated.

In our present report, we indicated that CSF IL-6 values reflected the severity of the clinical presentations of

Table 1. Clinical and laboratory findings of the two study patients.

Variable	Case 1	Case 2
Age (years)/sex	47/F	70/F
Neoplasm type	Renal cell carcinoma	Renal cell carcinoma
ICI	Nivolumab	Nivolumab, ipilimumab
Encephalitis type	Meningoencephalitis	Meningoencephalitis
Treatment	Corticosteroids	Corticosteroids
IL-6, CSF (pg/mL)		
Pretreatment	6,620	49.3
Post-treatment	0.7	1.8
Cell count, CSF (/μL)		
Pretreatment	733	16
Post-treatment	5	< 1
Protein, CSF (mg/dL)		
Pretreatment	120	72.1
Post-treatment	23.6	31
LP opening pressure (cm H_2O)		
Pretreatment	32	18
Post-treatment	7	9
IL-6, serum (pg/mL)		
Pretreatment	6.2	79
Post-treatment	N.A.	1.9
WBC count (/μL)		
Pretreatment	13,090	7,590
Post-treatment	7,000	7,580
CRP, serum (pg/mL)		
Pretreatment	11.1	15.8
Post-treatment	0.01	0.01

CSF, cerebrospinal fluid; CRP, C-reactive protein; F, female; ICI, immune checkpoint inhibitors; IL-6, interleukin-6; LP, lumbar puncture; N.A., not available; WBC, white blood cell.

ICI-induced meningoencephalitis in the two patients. The CSF IL-6 values before and after treatment in patients with ICI-induced meningoencephalitis still have not been thoroughly investigated except for analyses published in two previous reports (Yamaguchi et al. 2020; Ohno et al. 2021). The mechanisms of irAEs depend on the type of ICI used. CTLA-4 blockade can induce primarily T cell activation and proliferation, reduced regulatory T cell (Treg)-mediated suppression, increased numbers of T helper cells, and autoantibody production. PD-1 blockade, in contrast, can enhance mainly T cell activation via suppression of Tregs and inhibitory signals through the PD-1 pathway. T cell activation, which increases production of inflammatory cytokines such as IL-6 by anti-PD-1 and anti-CTLA-4 antibodies, contributes to the development of irAEs (Ramos-Casals et al. 2020). IL-6 is a well-known pro-inflammatory cytokine that manifests increased levels in the CSF of patients with inflammatory CNS diseases, such as acute disseminated encephalomyelitis, neuromyelitis optica, neuro-Behçet's disease, and CNS infections (Akman-Demir et al. 2008; Wullschleger et al. 2013; Uzawa et al. 2017). Because IL-6 is produced locally in lesions, serum IL-6 may not reach the CSF. These data suggest that CSF IL-6 levels may help identify inflammatory CNS conditions. The CSF and serum IL-6 levels were markedly different in these two cases. The high IL-6 levels in the CSF in Case 1 may have reflected the severity of the CSF inflammation because both the increased cell count in the CSF and the MRI signal changes were significantly higher compared with those of Case 2. The difference in serum IL-6 levels may be explained by the use of oral predonisolone (20 mg/day) to treat colitis in Case 1, and by the occurrence of thyroiditis in the acute phase before the use of immunotherapy in Case 2. As an interesting finding, a significant reduction in CSF IL-6 levels was observed after corticosteroid administration, in parallel with the resolution of meningoencephalitis in both of our cases. These findings suggest that the clinical presentation of CNS complications associated with irAEs involves an increase in CSF IL-6 levels, and this cytokine may have potential for use in monitoring the treatment of irAEs. Additional studies are necessary to clarify our findings.

In conclusion, we describe here two cases of ICI-induced meningoencephalitis with increased IL-6 levels in

the CSF. CSF IL-6 values may be useful as a marker for early diagnosis that may aid in the quantitative evaluation of meningoencephalitis-associated irAEs, and therefore CSF IL-6 may be a target for therapeutic intervention in CNS involvement associated with ICIs.

Acknowledgments

We would like to thank all members of the Department of Neurology, Oita University Hospital, for helping with the collection of clinical data. We are indebted to Ms. Judith B. Gandy for providing professional English editing of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

References

Akman-Demir, G., Tuzun, E., Icoz, S., Yesilot, N., Yentur, S.P., Kurtuncu, M., Mutlu, M. & Saruhan-Direskeneli, G. (2008) Interleukin-6 in neuro-Behcet's disease: association with disease subsets and long-term outcome. *Cytokine*, **44**, 373-376.

Bruna, J., Argyriou, A.A., Anastopoulou, G.G., Alemany, M., Nadal, E., Kalofonou, F., Piulats, J.M., Simo, M., Velasco, R. & Kalofonos, H.P. (2020) Incidence and characteristics of neurotoxicity in immune checkpoint inhibitors with focus on neuromuscular events: experience beyond the clinical trials. *J. Peripher. Nerv. Syst.*, **25**, 171-177.

Cuzzubbo, S., Javeri, F., Tissier, M., Roumi, A., Barlog, C., Doridam, J., Lebbe, C., Belin, C., Ursu, R. & Carpentier, A.F. (2017) Neurological adverse events associated with immune checkpoint inhibitors: review of the literature. *Eur. J. Cancer*, **73**, 1-8.

Dubey, D., David, W.S., Reynolds, K.L., Chute, D.F., Clement, N.F., Cohen, J.V., Lawrence, D.P., Mooradian, M.J., Sullivan, R.J. & Guidon, A.C. (2020) Severe neurological toxicity of immune checkpoint inhibitors: growing spectrum. *Ann. Neurol.*, **87**, 659-669.

Eigentler, T.K., Hassel, J.C., Berking, C., Aberle, J., Bachmann, O., Grunwald, V., Kahler, K.C., Loquai, C., Reinmuth, N., Steins, M., Zimmer, L., Sendl, A. & Gutzmer, R. (2016) Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. *Cancer Treat. Rev.*, **45**, 7-18.

Fujiwara, S., Mimura, N., Yoshimura, H., Fujimoto, D., Ito, M., Mori, R., Ito, J., Tomii, K., Kawamoto, M. & Kohara, N. (2019) Elevated adenosine deaminase levels in the cerebrospinal fluid in immune checkpoint inhibitor-induced autoimmune encephalitis. *Intern. Med.*, **58**, 2871-2874.

Husain, B., Kirchberger, M.C., Erdmann, M., Schupferling, S., Abolhassani, A.R., Frohlich, W., Berking, C. & Heinzerling, L. (2021) Inflammatory markers in autoimmunity induced by checkpoint inhibitors. *J. Cancer Res. Clin. Oncol.*, **147**, 1623-1630.

Johnson, D.B., Nebhan, C.A., Moslehi, J.J. & Balko, J.M. (2022) Immune-checkpoint inhibitors: long-term implications of toxicity. *Nat. Rev. Clin. Oncol.*, **19**, 254-267.

Larkin, J., Chiarion-Sileni, V., Gonzalez, R., Grob, J.J., Cowey, C.L., Lao, C.D., Schadendorf, D., Dummer, R., Smylie, M., Rutkowski, P., Ferrucci, P.F., Hill, A., Wagstaff, J., Carlino, M.S., Haanen, J.B., et al. (2015) Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N. Engl. J. Med.*, **373**, 23-34.

Ohno, N., Sugimoto, T., Giga, M., Naito, H., Kono, T. & Nomura, E. (2021) A case of meningoencephalitis and polyradiculoneuropathy induced by combination therapy with ipilimumab and nivolumab. *Rinsho Shinkeigaku*, **61**, 658-662.

Postow, M.A., Sidlow, R. & Hellmann, M.D. (2018) Immune-related adverse events associated with immune checkpoint blockade. *N. Engl. J. Med.*, **378**, 158-168.

Ramos-Casals, M., Brahmer, J.R., Callahan, M.K., Flores-Chavez, A., Keegan, N., Khamashta, M.A., Lambotte, O., Mariette, X., Prat, A. & Suarez-Almazor, M.E. (2020) Immune-related adverse events of checkpoint inhibitors. *Nat. Rev. Dis. Primers*, **6**, 38.

Ribas, A. & Wolchok, J.D. (2018) Cancer immunotherapy using checkpoint blockade. *Science*, **359**, 1350-1355.

Sato, K., Mano, T., Iwata, A. & Toda, T. (2019) Neurological and related adverse events in immune checkpoint inhibitors: a pharmacovigilance study from the Japanese Adverse Drug Event Report database. *J. Neurooncol.*, **145**, 1-9.

Sznol, M., Ferrucci, P.F., Hogg, D., Atkins, M.B., Wolter, P., Guidoboni, M., Lebbe, C., Kirkwood, J.M., Schachter, J., Daniels, G.A., Hassel, J., Cebon, J., Gerritsen, W., Atkinson, V., Thomas, L., et al. (2017) Pooled analysis safety profile of nivolumab and ipilimumab combination therapy in patients with advanced melanoma. *J. Clin. Oncol.*, **35**, 3815-3822.

Uzawa, A., Mori, M., Masuda, H., Ohtani, R., Uchida, T., Sawai, S. & Kuwabara, S. (2017) Interleukin-6 analysis of 572 consecutive CSF samples from neurological disorders: a special focus on neuromyelitis optica. *Clin. Chim. Acta*, **469**, 144-149.

Valpione, S., Pasquali, S., Campana, L.G., Piccin, L., Mocellin, S., Pigozzo, J. & Chiarion-Sileni, V. (2018) Sex and interleukin-6 are prognostic factors for autoimmune toxicity following treatment with anti-CTLA4 blockade. *J. Transl. Med.*, **16**, 94.

Velasco, R., Villagran, M., Jove, M., Simo, M., Vilarino, N., Alemany, M., Palmero, R., Martinez-Villacampa, M.M., Nadal, E. & Bruna, J. (2021) Encephalitis induced by immune checkpoint inhibitors: a systematic review. *JAMA Neurol.*, **78**, 864-873.

Vogrig, A., Muñiz-Castrillo, S., Joubert, B., Picard, G., Rogemond, V., Marchal, C., Chiappa, A.M., Chanson, E., Skowron, F., Leblanc, A., Ducray, F. & Honnorat, J. (2020) Central nervous system complications associated with immune checkpoint inhibitors. *J. Neurol. Neurosurg. Psychiatry*, **91**, 772-778.

Wullschleger, A., Kapina, V., Molnarfi, N., Courvoisier, D.S., Seebach, J.D., Santiago-Raber, M.L., Hochstrasser, D.F. & Lalive, P.H. (2013) Cerebrospinal fluid interleukin-6 in central nervous system inflammatory diseases. *PLoS One*, **8**, e72399.

Xu, M., Nie, Y., Yang, Y., Lu, Y.T. & Su, Q. (2019) Risk of neurological toxicities following the use of different immune checkpoint inhibitor regimens in solid tumors: a systematic review and meta-analysis. *Neurologist*, **24**, 75-83.

Yamaguchi, Y., Nagasawa, H., Katagiri, Y. & Wada, M. (2020) Atezolizumab-associated encephalitis in metastatic lung adenocarcinoma: a case report. *J. Med. Case Rep.*, **14**, 88.