Pembrolizumab-induced aseptic meningitis in a patient with non-small cell lung cancer: A case report and literature review of aseptic meningitis as an immune-related adverse event

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Abstract. Aseptic meningitis is a rare immune-related adverse event (irAE), which occurs during treatment with immune checkpoint inhibitors (ICIs). This condition has non-specific symptoms and exhibits no clear signs on magnetic resonance imaging (MRI). There are only a few reports of aseptic meningitis caused by pembrolizumab treatment for non-small cell lung cancer (NSCLC). The present study includes a report of such a case and a review of the related literature. A 67-year-old Japanese man received first-line pembrolizumab treatment for NSCLC and subsequently developed severe nausea and vomiting. No significant findings were observed following a computed tomography (CT) scan, MRI of the brain and upper gastrointestinal tract, or upper gastrointestinal endoscopy. Cerebrospinal fluid analysis revealed lymphocyte infiltration and elevation of the IgG index, without indications of metastasis or infection, which suggested the presence of aseptic meningitis. The symptoms immediately improved following prednisolone treatment, and aseptic meningitis was diagnosed as an irAE related to pembrolizumab treatment. Given that aseptic meningitis can cause non-specific symptoms, including headache and nausea, the possibility of an irAE should be considered in patients with non-specific symptoms who are receiving ICIs, and a cerebrospinal fluid examination should be performed.

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Introduction

Immune checkpoint inhibitors (ICIs) are used to treat various malignant tumors, including lung cancer (1). However, the widespread use of ICIs has also led to reports regarding various immune-related adverse events (irAEs). Aseptic meningitis is a rare type of irAE (2) that typically responds well to steroid treatment. Thus, early diagnosis and treatment are important. Given the rarity of aseptic meningitis, our experience with a patient who developed this irAE during ICI treatment for non-small cell lung cancer (NSCLC) is reported herein and the related literature was reviewed.

Case report

In August 2018, a 67-year-old Japanese man with a history of asthma and chronic obstructive pulmonary disease was referred to our hospital due to chest pain. Chest radiography revealed linear opacity in the right middle lung field (Fig. 1A). A chest CT scan revealed a 27-mm tumor in the subcarinal space, pleural invasion in the right upper and middle lung segments (Fig. 1B) and a hilar mass shadow with contrast enhancement along the right main bronchus from below the tracheal bifurcation (Fig. 1C). A brain contrast-enhanced MRI revealed two small nodules in the cerebellum and cerebrum (Fig. 2A and B). Fluorodeoxyglucose (FDG) positron emission tomography with CT revealed intense FDG accumulation in the subcarinal space and pleural nodule. Histological examination of the tumor in the transbronchial lung biopsy specimens from the subcarinal space revealed adenocarcinoma, with a tumor proportion score of 100% for programmed death-ligand

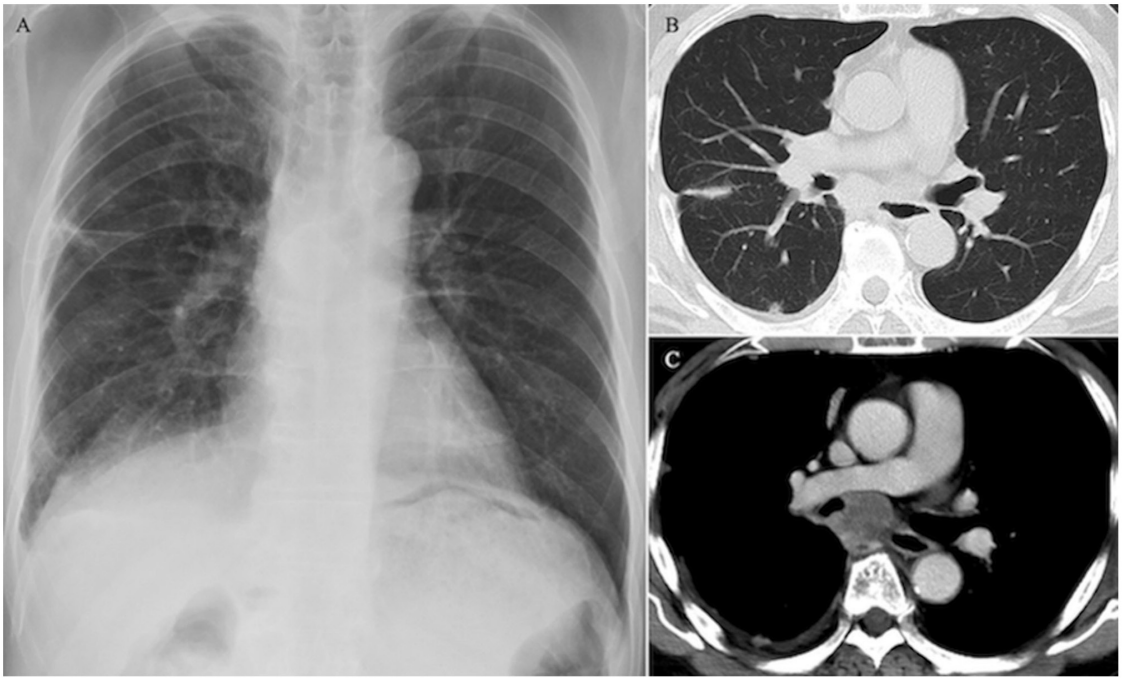

Figure 1. Radiography and CT findings. (A) Chest radiography revealed linear opacity in the right middle lung field. (B) Trunk CT revealed multiple thickenings in the right pleura and right pleural effusion. (C) Trunk contrast-enhanced CT revealed a hilar mass shadow with contrast enhancement along the right main bronchus from below the tracheal bifurcation. There were no findings to explain the nausea, despite the slight thickening and contrast enhancement on the stomach wall. CT, computed tomography.

(PD-L1) using a PD-L1 antibody (clone 22C3; Agilent Technologies, Inc.) and no expression of epidermal growth factor receptor (EGFR) mutation, anaplastic lymphoma kinase (ALK) fusion, ROS proto-oncogene 1, receptor tyrosine kinase (ROS1) fusion and B-Raf proto-oncogene, serine/threonine kinase (BRAF) mutation. Based on these findings, the patient was diagnosed with stage IVB lung adenocarcinoma (TxN2M1c, brain pleura).

Oxycodone hydrochloride hydrate tablet (10 mg/day) was administered for the chest pain that was caused by the pleural lesions, and γ-knife irradiation was performed for the two metastatic brain lesions. Six days later, the patient started treatment using pembrolizumab (200 mg, once every 3 weeks). However, on day 2 after starting pembrolizumab treatment, the patient developed persistent nausea and was admitted to our department on day 5 to identify the cause of the nausea. A physical examination showed no fever, Kernig's sign, Brudzinski's sign and a stiff neck, other than tachycardia, and no altered mental status. Blood tests revealed a slight increase in C-reactive protein (CRP) concentration (0.74 mg/dl), but no other abnormalities in electrolyte concentrations or endocrine function were observed. Contrast-enhanced abdominal CT showed only a slight thickening of the stomach wall and contrast effects, without other new findings, and upper gastrointestinal endoscopy showed no obstructive or bleeding lesions, only atrophic gastritis, which was insufficient to identify the cause of the nausea. The nausea was therefore attributed to the opioid treatment, and opioid rotation (from oxycodone hydrochloride hydrate tablet 30 mg/day to fentanyl continuous infusion 0.6 mg/day) was performed. The nausea appeared to improve by day 9 after starting pembrolizumab treatment, but subsequently worsened on day 15. Brain contrast-enhanced MRI revealed no tumor progression, no occurrence of new tumors and no subcranial enhancement, suggesting meningitis (Fig. 2C and D). Lumbar puncture was thus performed (Table I). Laboratory test results, including PCR findings, revealed a normal glucose concentration and negative results for the cerebrospinal fluid (CSF) smear, bacteria, fungi, mycobacteria and tuberculosis. However, the total cell count was slightly elevated, with an increased subset of lymphocytes. Pathological findings revealed lymphocytic inflammation and an elevated level of adenosine deaminase (ADA), which suggested the presence of lymphocyte proliferation and differentiation. Furthermore, at the same time as the nausea recurrence, the patient had an elevated IgG index and various symptoms that supported suspicion of an irAE, including a rash, liver enzyme elevation and destructive thyroiditis. Aseptic meningitis was therefore considered as an irAE for differential diagnosis. However, despite the negative brain MRI findings, meningeal carcinomatosis was also considered for differential diagnosis, due to the patient's history of metastatic brain tumors. Therefore, treatment was started using betamethasone (4 mg) to potentially manage meningitis as an irAE, and as a palliative treatment for meningeal carcinomatosis. The patient experienced immediate improvement of the nausea after starting steroid treatment (Fig. 3). The cytology findings were also negative for malignant cells, so the case was diagnosed as pembrolizumab-induced aseptic meningitis (grade 3). The betamethasone treatment was changed to prednisolone (80 mg at 1 mg/kg) for long-term treatment, with the dose tapering from 80 to 60 mg, then from 60 to 20 mg in 10-mg increments every 5 days, and finally from 20 to 10 mg in 5-mg increments every 2 weeks. The patient was discharged on day 75 of hospitalization, and steroid treatment was terminated on

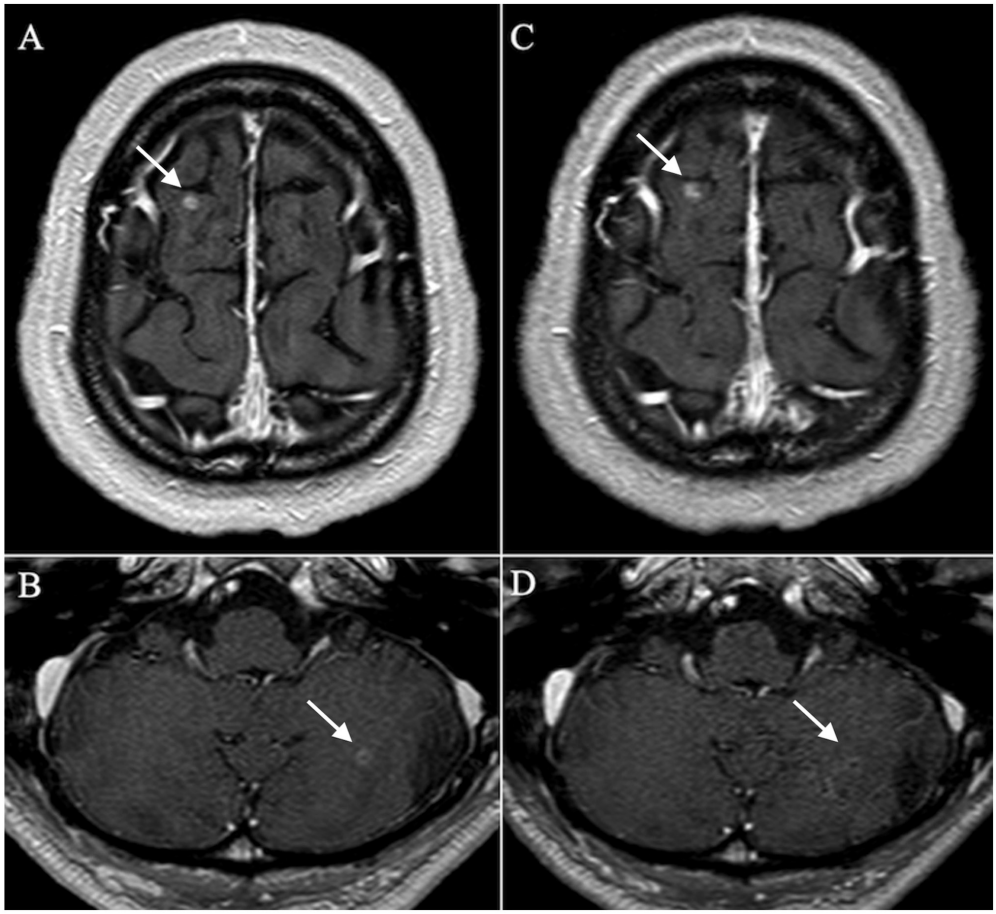

Figure 2. MRI findings. (A and B) Brain contrast-enhanced MRI at diagnosis revealed a metastatic brain tumor in the right frontal lobe and cerebellar hemisphere lesions (white arrows). (C and D) Brain-contrast MRI conducted after admission revealed no signs of encephalitis or meningitis, such as contrast enhancement at the brain and meninges. The existing lesions regressed after γ-knife irradiation, with no subsequent progression (white arrows). MRI, magnetic resonance imaging.

day 83 after steroid treatment initiation. The tumor response was judged to be a partial response (Fig. 4) at the patient's discharge, although ICI re-challenge was not attempted based on the potential risk of other irAEs. The patient experienced disease progression 4 months later, which presented as an enlargement of the tumor in the subcarinal space and was treated using second-line carboplatin plus pemetrexed.

Discussion

Treatment with immune checkpoint inhibitors (ICIs) can be used for various types of cancer, including renal cell carcinoma, melanoma, head and neck cancers, urothelial carcinoma and Hodgkin lymphoma (3). Furthermore, ICIs are an effective option for non-small cell lung cancer (NSCLC) treatment, along with chemotherapy and targeted therapy (1). Certain patients can experience long-term response to ICI treatment, which has less toxicity than chemotherapy (4). Recent studies have also combined ICIs with chemotherapy (5,6), utilized ICIs in maintenance therapy following chemoradiotherapy (7) or have used ICIs for small cell lung cancer treatment (8,9). However, while ICIs are effective, safe and increasingly used, they are also associated with a risk of immune-related adverse events (irAEs), which can cause treatment interruption and reduce the quality of life of these patients. The reported frequencies of irAEs grade ≥3 are 8% for nivolumab, 5-10% for pembrolizumab, 5-7% for atezolizumab, 2% for durvalumab and 15-42% for ipilimumab (3). Grade 3-4 neurological irAEs are uncommon (<1%), but include inflammatory myopathies, myasthenia gravis, neuropathies, multiple sclerosis, autoimmune encephalitis and aseptic meningitis.

Head jolt sign, Kernig's sign, Brudzinski's sign and stiff neck are well-known signs of meningitis, although only 29% of cases of aseptic meningitis involve these symptoms (10). Numerous other cases are associated with non-specific symptoms, such as headache, nausea, and vomiting (10). The frequency of aseptic meningitis as an irAE is thought to be 0.1-0.2% (2), although the underdiagnosis of this rare irAE may be associated with the manifestation of flu-like symptoms, headaches (11) or other mild symptoms. Head contrast-enhanced MRI rarely produces significant findings, and cerebrospinal fluid (CSF) examination is therefore necessary. Moreover, the diagnosis of irAE must exclude other diseases, such as bacterial, fungal, mycobacterial and viral infections, as well as cancerous meningitis. The pathophysiological development of irAEs is associated with the ICI-induced activation of CD8 T-cells (12), and an increased proportion of lymphocytes in the CSF is useful for diagnosing irAEs (2). Table II shows that an elevation in CSF lymphocytes was observed in 12 cases. In addition, adenosine deaminase

Table I. Cerebrospinal fluid analysis.

Test	Result	Test	Result	Test	Result
Color	Colorless	Total protein (mg/dl)	80	Bacteria	Negative
Turbidity	Clear	Albumin (mg/dl)	41	Fungi	Negative
Total cell count (/μl)	12	LDH (U/l)	22	Mycobacteria	Negative
Polynuclear (%)	8	Glucose (mg/dl)	61	Tb-PCR	Negative
Mononuclear (%)	92	CRP (μg/dl)	<1	MAC-PCR	Negative
Open pressure (cmH_2O)	10	CEA (ng/dl)	<0.8	Pathology	No malignant cells
		ADA	3.1		Lymphocyte infiltration
		IgG (mg/dl)	11.5		
		IgG index	0.64		

LDH, lactate dehydrogenase; CRP, C-reactive protein; CEA, carcinoembryonic antigen; ADA, adenosine deaminase; Tb-PCR, PCR assay for tuberculosis; MAC-PCR, PCR assay for the *Mycobacterium avium* complex.

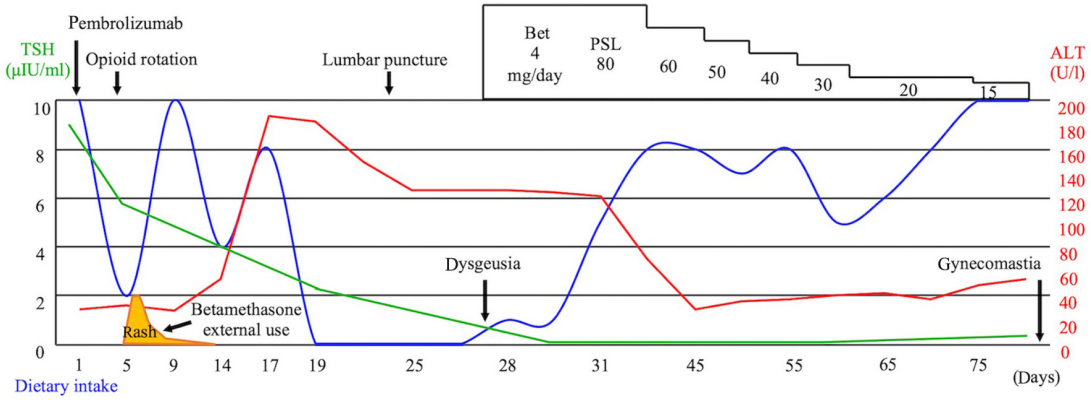

Figure 3. Clinical course. Following pembrolizumab treatment, red papules (CTCAE grade 1) appeared around the extremities. Abnormal laboratory findings included liver enzyme elevation (CTCAE grade 3), as well as decreased TSH and increased T4, which indicated the presence of destructive thyroiditis (CTCAE grade 2). These symptoms were improved after steroid treatment. Dysgeusia (CTCAE grade 1) and gynecomastia (CTCAE grade 1) were also observed during pembrolizumab treatment and persisted following steroid treatment. Bet, betamethasone; PSL, prednisolone; TSH, thyroid stimulating hormone; ALT, alanine aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events.

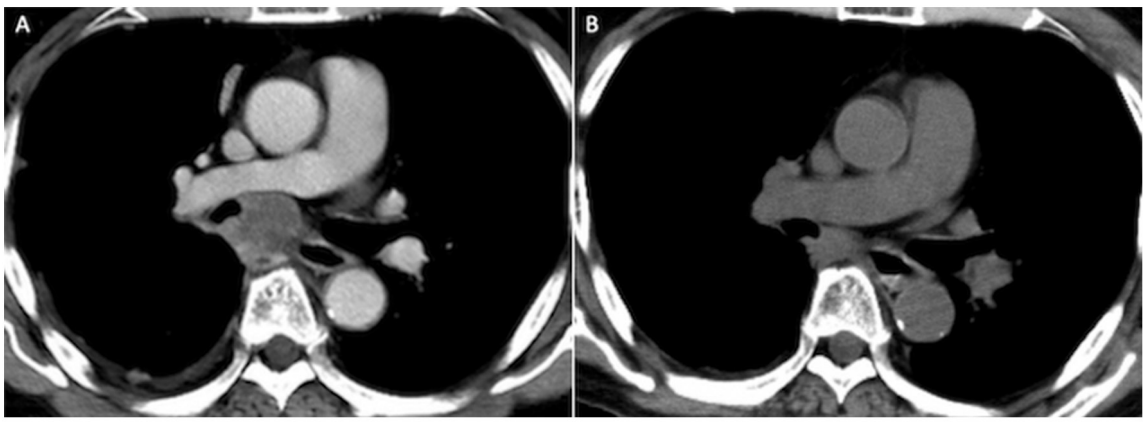

Figure 4. CT findings. (A) CT prior to pembrolizumab treatment. (B) CT 56 days after treatment showed tumor shrinking and partial response, based on the response evaluation criteria in solid tumors. CT, computed tomography.

(ADA) is a well-known marker for tuberculous meningitis (CSF ADA levels of >8 U/l provide a sensitivity of <59% and specificity of >96%) (13), as well as a marker of cellular immunity, based on its relationship with lymphocyte proliferation and differentiation (12). Therefore, elevated ADA levels may reflect a CD8 T-cell-related irAE, based on the elevated levels

Table II. Reported cases of meningitis as an immune-related adverse event after immune checkpoint inhibitor treatment.

Patient no./ Investigators (Refs.)	Age (years)	Sex	Cancer	ICIs	Cycle	Initial symptoms	CSF lymph ocytes	MRI abnormal	Other irAEs	Treatment	Time to resolution	Tumor Response	Re-challenge ICIs
#1/Spain *et al* (19)	N/A	N/A	Mela	I+N	1	Headache, nausea	+	-	Hepatitis	-	7 weeks	PR	After 4 weeks
#2/Spain *et al* (19)	N/A	N/A	Mela	I	2	Headache, drowsiness, nausea, vomiting	+	-	-	-	10 days	SD	-
#3/Spain *et al* (19)	N/A	N/A	Mela	I	2	Delirium	-	-	-	PSL p.o	8 weeks	PD	-
#4/Bot *et al* (20)	51	F	Mela	I	1	Headache, fever	+	-	N/A	Dex 8 mg p.o	2 days	N/A	N/A
#5/Voskens *et al* (21)	52	F	Mela	I	1	Nausea, vomiting, chills, rash	+	-	N/A	DEX	N/A	PD	-
#6/Bompaire *et al* (22)	56	M	Mela	I	4	Vertigo, dizziness, cervicalgia, headache	+	Brain-/ spinal+	Radiculo neuritis	mPSL 1g IV + IVIg	2 years	CR	-
#7/Yang *et al* (23)	N/A	N/A	Renal	I	4	Headache, photophobia, cranial nerve disorder	+	-	N/A	DEX	<1 month	N/A	N/A
#8/Takamatsu *et al* (24)	70	F	Renal	I+N	2	Headache, nausea, dizziness	+	-	Isolated ACTH deficiency	PSL 1 mg/kg IV	A few days	CR	50th day with PSL 10 mg/day
#9/Takamatsu *et al* (24)	70	F	Renal	I+N	3	Headache, anorexia	+	N/A	Liver dysfunction	PSL 1 mg/kg IV	N/A	CR	-
#10/Cordes *et al* (25)	58	M	UC	N	12	Fever, chills, malaise, dry cough, headache, bilateral eye pain, right ear pain	+	+	N/A	mPSL 1 mg/kg IV	<3 days	PR	-

Table II. Continued.

Patient no./ Investigators (Refs.)	Age (years)	Sex	Cancer	ICIs	Cycle	Initial symptoms	CSF lymphocytes	MRI abnormal	Other irAEs	Treat ment	Time to resolution	Tumor Response	Re-challenge ICIs
#11/Toyozawa *et al* (26)	71	F	NSCLC	A	1	Fever, consciousness disorder	-	-	N/A	mPSL 1 mg/kg IV	1 day	N/A	-
#12/Toyozawa *et al* (26)	55	M	NSCLC Ade	A	1	Fever, consciousness disorder	-	-	N/A	mPSL 1 mg/kg IV	4 days	N/A	-
#13/Toyozawa *et al* (26)	50	M	NSCLC Ade	A	1	Fever, neck and legs pain, consciousnesss disorder	+	+	N/A	mPSL 1 mg/kg IV	2 days	N/A	-
#14/Lima *et al* (27)	55	M	NSCLC Ade	P	11	Bilateral throbbing, frontal headache	+	-	Hepatitis	Dex 10 mg IV	1 day	CR	-
#15/Present case	67	M	NSCLC Ade	P	1	Nausea, vomiting	+	-	Hepatitis, dysgeusia, gynecomastia thyroid dysfunction	PSL 1 mg/kg IV	3 days	PR	-

ICIs, immune checkpoint inhibitors; CSF, cerebrospinal fluid; MRI abnormal means contrast effect of meninges or brain parenchyma; N/A, not available; M, male; F, female; Mela, melanoma; Renal, renal cell carcinoma; UC, urothelial carcinoma; NSCLC, non-small cell lung cancer; Ade, adenocarcinoma; I, ipilimumab; N, nivolumab; P, pembrolizumab; IV, intravenous; p.o, per os; PSL, prednisolone; DEX, dexamethasone; IVIg, intravenous immunoglobulin; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

being detected in patients who received ICIs and developed meningoencephalitis (14) and autoimmune encephalitis (12). Therefore, lymphocyte-related inflammatory findings (for example, elevated lymphocytes or ADA in the CSF) may be useful for diagnosing aseptic meningitis as an irAE. In the setting of elevated ADA, tuberculous cultures, PCR findings or CSF/serum glucose ratio (<0.5 in 95% of tuberculous meningitis cases) are useful for distinguishing aseptic meningitis from tuberculous meningitis (15). The present patient exhibited an elevated lymphocyte percentage and pathological findings suggestive of lymphocytic inflammation, but no marked increase in ADA level. This may be associated with the relatively mild clinical symptoms and the unremarkable increase in the CSF total cell count. In this setting, the IgG index [(CSF-IgG/CSF-albumin)/(serum-IgG/serum-albumin)] may reflect increased IgG synthesis in the central nervous system, which could indicate the presence of multiple sclerosis or central nervous system infections, such as encephalitis or meningitis (16). A previous report described an increased IgG index in nivolumab-induced encephalopathy, which might have been caused by nivolumab promoting IgG release as B cells were converted to plasma cells (17). Thus, ICI treatment may lead to an increased IgG index in cases involving central nervous system disorders.

To distinguish between cancerous and aseptic meningitis as an irAE is challenging. The sensitivity of CSF puncture for cancerous meningitis is 50-60% for a single dose and 80% for multiple doses (18); thus we cannot completely deny cancerous meningitis. Actually, the patient's general condition was not good, thus we judged that repeat lumbar puncture was risky. We should have examined after the recovery condition. In the present case, aseptic meningitis was diagnosed as an irAE based on the following findings: no atypical cells detected in the pathology and increased number of cells, high IgG index, low carcinoembryonic antigen (CEA) and other concurrent irAEs. Subsequent follow-up revealed no findings suggestive of meningeal carcinomatosis or brain metastasis recurrence. In addition, the symptoms may have appeared due to the effect after the γ-knife irradiation; we judged that the effect was small, because the head lesions were micronodules and no edema was observed on MRI following irradiation.

Table II summarizes the 15 reported cases of aseptic meningitis as an irAE following treatment with nivolumab, pembrolizumab, atezolizumab or ipilimumab (19-27). Nine cases were associated with ipilimumab treatment, which was administered for melanoma in 6 cases (19-22) and renal cell carcinoma in 3 cases (23,24). Three cases were treated with a combination of ipilimumab and nivolumab (19,24), and cases 8 and 9 involved the same patient, who experienced meningitis relapse following re-administration of an ICI (24). The majority of patients, except cases 7, 10 and 11, developed aseptic meningitis after 1-4 cycles of ICI treatment. Seven cases involved neurological symptoms (19,22,23,26,27). By contrast, most patients initially exhibited non-specific symptoms, such as headache or nausea. All patients underwent brain MRI and lumbar puncture, which revealed lymphocyte-dominated leukocyte elevation in 13 patients. However, the brain contrast-enhanced MRI failed to reveal abnormal findings in most cases; the only two findings were arachnoiditis during spinal MRI (22) and abnormal enhancements along the lines of the corpus callosum (26). A total of 13 patients received steroid treatment, while a follow-up observation was only performed in 2 patients (19). The steroid treatment was ineffective for case 6, and intravenous immunoglobulin (IVIg) was therefore administered in this case (22). All patients ultimately experienced an improvement in their symptoms. The tumor responses were progressive disease in 2 cases (19,21), stable disease in 1 case (19), partial response in 3 cases (19,23,25), and complete response in 3 cases (melanoma, renal cell carcinoma and NSCLC) (22,24,27). Two patients were treated again with ICIs (19,24) and 1 patient experienced relapse of meningitis (24).

Several reports have described ipilimumab-induced meningitis, which may be associated with the drug's affinity for the cranial nervous system. Indeed, ipilimumab frequently induces hypophysitis, which is thought to be caused by the expression of CTLA-4 in the anterior pituitary cells and a resulting type II hypersensitivity (28). There are only a few reports of pembrolizumab-induced meningitis (27) and meningoencephalitis (14), although the increasing use of this drug will presumably result in more cases being reported.

The main treatment for neurological irAEs involves immunosuppression, with prednisone or methylprednisolone being recommended for CTCAE grade 3 or higher meningitis (3). Aseptic meningitis as an irAE has a good neurological prognosis, as it typically responds well to steroid treatment (11). Furthermore, steroid use is not associated with reduced overall survival or time to ICI treatment failure (29). Steroid monotherapy is often effective in this setting, although select patients may require IVIg or plasma exchange (19). Natalizumab is a monoclonal antibody that targets α4 integrin (30) and might be effective in treating central nervous system symptoms of neurological irAEs, as it inhibits the transfer of lymphocytes to the central nervous system by inhibiting the binding of lymphocyte integrins and VCAM-1 in the blood-brain barrier (30). A previous report has indicated that, while steroid treatment was ineffective, natalizumab was effective in treating autoimmune encephalitis as an irAE, which was caused by the combination of ipilimumab and nivolumab (31).

A prospective cohort study of 43 patients with advanced NSCLC revealed that patients with irAEs after nivolumab treatment had a higher objective response rate (37 vs. 17%) and longer median progression-free survival (6.4 vs. 1.5 months) (32). Of note, autoimmune encephalitis as an irAE was also reportedly associated with an increased response to pembrolizumab in NSCLC cases (33). It was therefore suspected that a similar positive response may be observed in cases with central nervous system irAEs (for example, meningitis). In addition to the present case, 2 NSCLC cases had a good response rate to pembrolizumab.

While repeat treatment using ICIs may be an effective strategy for cases of aseptic meningitis as an irAE, it is associated with a risk of meningitis relapse (24). A previous study suggested that the risk-reward ratio for anti-PD or anti-PD-L1 re-challenge appeared to be acceptable, although there was no evidence of prolonged progression-free survival or overall survival outcomes (34). In the present case, platinum-based treatment was selected for the recurrence, based on the presence of other irAEs and the patient's opinion.

In conclusion, the present study reported a case of nausea and vomiting that was ultimately diagnosed as aseptic

meningitis, as an irAE related to pembrolizumab treatment. Although there are a few reports of meningitis as an irAE, this condition may be underdiagnosed due to its non-specific symptoms. The majority of patients will experience a good response to steroid treatment, and a good response rate for ICIs has been observed in patients with irAEs. A CSF examination is required to diagnose aseptic meningitis as an irAE, which may be supported based on lymphocytic inflammation findings, such as elevated lymphocyte or ADA values. Since there are few reports of aseptic meningitis after ICIs for lung cancer, an accumulation of further case reports is desired to discern whether re-administration of ICIs is acceptable.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

GI collected the data and wrote the paper. YF treated the patient and revised the article for important intellectual content as the corresponding author. HM and HT treated the patient and provided advice on the paper. KA, KK, YuukiH, RK, TN, KoheiY, YT, YS, TS and KosukeY collected, analyzed and interpreted the clinical data. SK collected, analysed and interpreted the neurological findings and provided advice on the paper. YU, YasushiH and KN analyzed and interpreted the pathological data and provided advice on the paper. MK and AY critically revised the manuscript for important intellectual content. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity (including the collected data) of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

This is to certify that the above case report was approved for publication by Tottori University Ethics Review Board (serial no. 22J002).

Patient consent for publication

As the patient was deceased, according to hospital policy, request to publish the case report was published online, and as no contest was made by any family member or other person, the hospital provided approval to proceed with publication of the case study.

Competing interests

The authors declare that they have no competing interests.

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