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【 CASE REPORT 】

Retrobulbar Optic Neuritis Induced by Pembrolizumab in a Patient with Lung Adenocarcinoma

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Abstract:
Pembrolizumab is a monoclonal antibody with anti-tumor effects. Only a few reports have previously described retrobulbar optic neuritis induced by pembrolizumab. We herein report the case of a 63-year-old man with advanced lung adenocarcinoma who received cisplatin, pemetrexed, and pembrolizumab combination therapy for six months. Following treatment, a visual field test showed a left central scotoma. Imaging studies showed left optic neuritis without brain metastasis. Blood tests showed an elevated serum creatinine level. He was diagnosed with retrobulbar optic neuritis and pembrolizumab-induced renal failure. After receiving corticosteroid treatment, his renal function rapidly improved. The optic neuritis improved somewhat, but it was not adequately resolved.

Key words: retrobulbar optic neuritis, pembrolizumab, non-small-cell lung cancer

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Introduction

Pembrolizumab, a programmed cell death-1 (PD-1) inhibitor, is the standard therapy for non-small cell lung carcinoma (NSCLC) (1). In the KEYNOTE-189 trial, the addition of pembrolizumab to standard chemotherapy, consisting of pemetrexed and a platinum-based drug, resulted in a significantly longer overall survival and progression free survival in patients with previously untreated metastatic non-squamous NSCLC (2). Immune-related adverse events (irAEs) may occur during PD-1 antibody administration. There have been few reports on optic neuritis as an irAE after pembrolizumab treatment. We herein report a case of pembrolizumab-induced retrobulbar optic neuritis.

Case Report

A 63-year-old Japanese man, with a relevant medical history including smoking 20 cigarettes a day, though the patient reported that he had stopped smoking one month previously, was admitted to our hospital due to an abnormal chest shadow. Computed tomography (CT) revealed a 32 mm mass in the right lower lung lobe. The right adrenal gland and mediastinal lymph nodes were also enlarged (Fig. 1). A bronchoscopic biopsy was performed, and the patient was diagnosed with lung adenocarcinoma with cT2aN2M1b cStageIVB. Additional genetic testing revealed that the patient was negative for epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) fluorescence *in situ hybridization*, c-ros oncogene 1 (ROS1), v-Raf murine sarcoma viral oncogene homolog B1 (BRAF), and PD-L1 22C3 immunohistochemical staining, with a tumor proportion score (TPS) of 5%. He was treated with cisplatin, pemetrexed, and pembrolizumab combination therapy every three weeks. After four cycles, the tumor had shrunk, so he was thereafter treated with pemetrexed and pembrolizumab maintenance therapy. After three cycles of maintenance therapy, a CT scan showed that mediastinal lymph node metastasis had increased in size. He complained of left central visual field disorder, and blood tests showed renal failure (Table 1).

We suspected that the renal failure had been induced by pemetrexed or pembrolizumab, while the irAE of optic neuritis had been induced by pembrolizumab. Magnetic resonance imaging (MRI) of the brain showed no metastasis.

Optical coherence tomography showed no uveitis or retinal disease.

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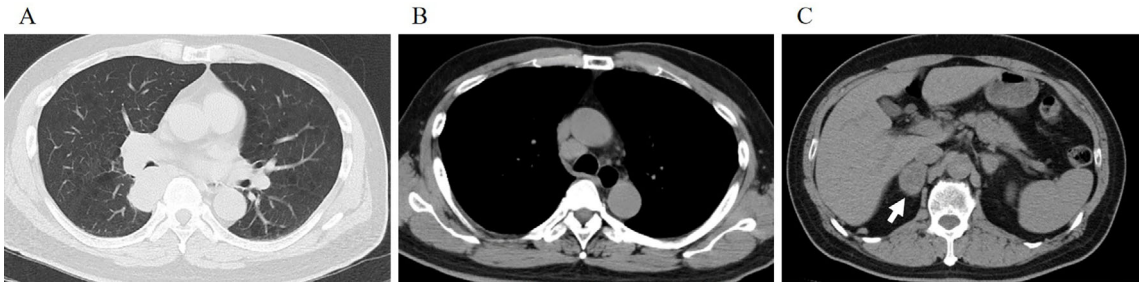

Figure 1. **(A) A computed tomography (CT) scan showing a 32 mm mass in the right lower lobe of the lung. (B) A CT scan showing enlarged mediastinal lymph nodes. (C) A CT scan showing an enlarged right adrenal gland.**

Table 1. **Laboratory Findings on Admission and at the First Visit.**

[Blood test]	At the first visit	On admission
White blood cell	9,300	7,600 /μL
Red blood cell	423	258 $\times 10^4$ /μL
Hemoglobin	12.8	8.9 g/dL
Platelet	22.9	23.7 $\times 10^4$ /μL
C-reactive protein	2.25	1.47 mg/dL
Total protein	6.7	6.7 g/dL
Albumin	3.4	3.5 g/dL
Total bilirubin	0.46	0.59 mg/dL
Aspartate aminotransferase	18	25 U/L
Alanine aminotransferase	22	10 U/L
Creatinine kinase	63	168 U/L
Sodium	138	136 mEq/L
Potassium	4.1	2.6 mEq/L
Chlorine	104	98 mEq/L
Blood urea nitrogen	7.2	19.7 mg/dL
Creatinine	0.67	1.94 mg/dL
Anti-Hu-antibody		<100 TITER
[Urine test]		
Urine qualitative		
Urine specific gravity	1.008	1.013
pH	7.5	7.5
Protein	(-)	(2+)
Sugar	(1+)	250 (2+)
Occult blood	(-)	(-)
Urine sediment		
hyaline casts	(1+)	(1+) high power field
epithelial casts	<1	<1 high power field
granular casts	(1+)	(1+) high power field
Red blood cell	<1	<1 high power field
β2-microglobulin		80,560 μg/L
N-acetyl-β-D-glucosaminidase		28.5 IU/L

Goldmann perimetry showed a left central dark spot (Fig. 2A, B). MRI of the orbit showed a slightly high intensity of the left optic nerve in short T1 weighted image inversion recovery (Fig. 3). Therefore, he was diagnosed with drug-induced renal failure and retrobulbar optic neuritis induced by pembrolizumab.

A renal biopsy showed minor glomerular abnormalities and mild tubular injury.

The patient was prescribed oral prednisolone (1 mg/kg/day) in order to treat the drug induced retrobulbar opitic neuritis and renal failure. The initial prednisolone dose was 60 mg, which was thereafter tapered every one or two weeks, and was changed to 1 mg dexamethasone after three months. After that, we continued to administer dexamethasone because of cachexia. His renal function improved to baseline, as determined by lab results indicating a creatinine level of 0.52 mg/dL. The progression of his visual field disorder improved, but the symptoms did resolve fully

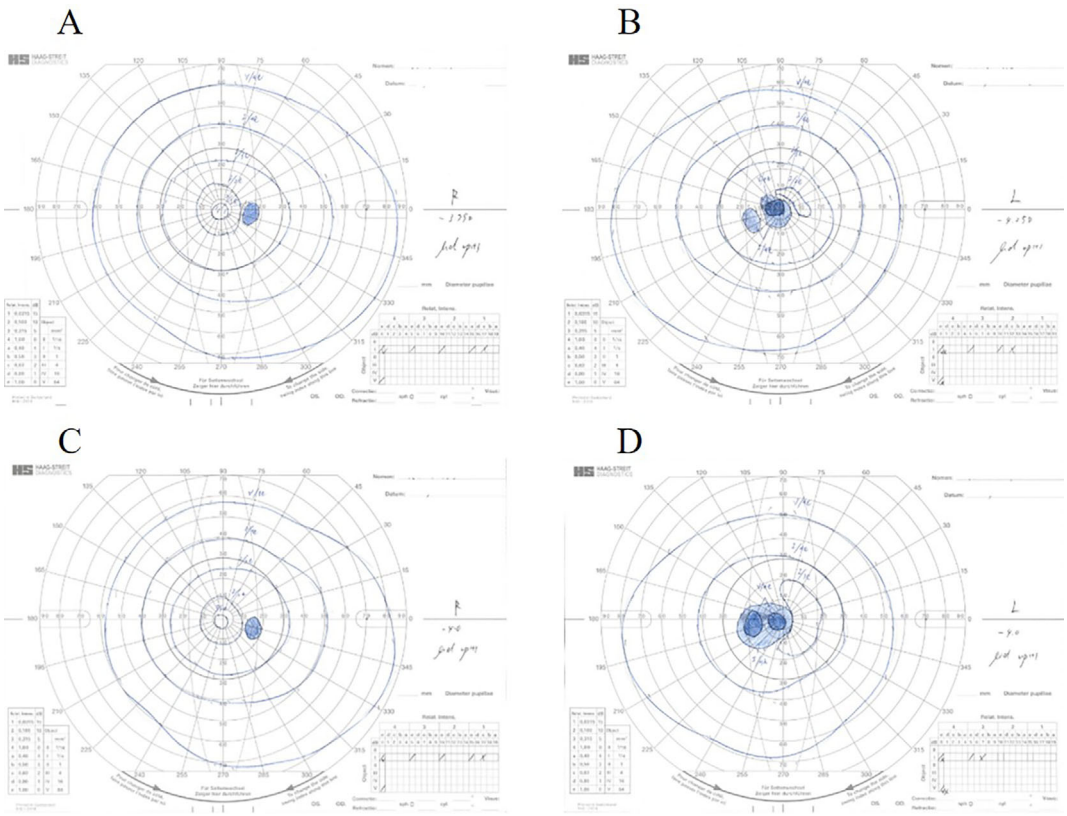

Figure 2. **Goldmann perimetry of the (A) Right eye at the time of diagnosis, (B) Left eye showing a central dark spot at the time of diagnosis, (C) Right eye after four months, and (D) Left eye after four months.**

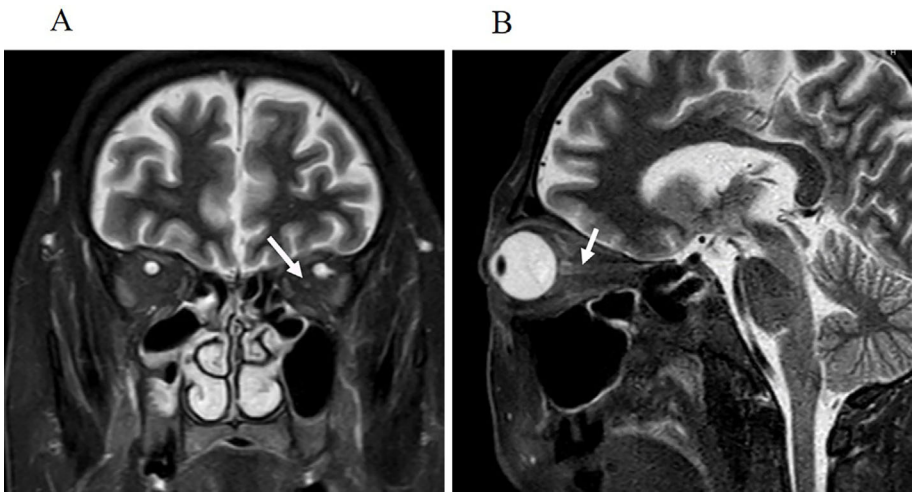

Figure 3. **Magnetic resonance imaging of the orbit showed a slightly high intensity of the left optic nerve in short TI inversion recovery. (A) Coronal view and (B) Sagittal view.**

(Fig. 2C, D).

Discussion

We herein report a case wherein corticosteroids suppressed an exacerbation of pembrolizumab-induced retrobulbar optic neuritis.

Uveitis is a commonly reported ocular symptom of irAE (2, 3), but there are very few reports on optic neuritis. We performed a search of the PubMed database using the following terms: "retrobulbar optic neuritis," and "immune checkpoint inhibitor." Our search yielded eighteen articles. After excluding both articles that were not available and those that did not specifically relate to retrobulbar optic neuritis and immune checkpoint inhibitors, we reviewed four articles (Table 2) (4-7). Three of five cases were unilateral

Table 2. A Literature Review of Reports on Retrobulbar Optic Neuritis Induced by Immune Checkpoint Inhibitors and Their Clinical Findings.

Reference	Age	Sex	Cancer type	Cycles	ICI Name	Side	Treatment	Outcome
4	9	Male	Glioblastoma multiforme	2 cycles	Nivolumab	Bilateral	Corticosteroids	Improved
5	76	Male	NSCLC	ND cycles 2months	Pembrolizumab	Left	Corticosteroids	Improved
6	64	Male	NSCLC	ND cycles 12months	Atezolizumab	Left	Steroid pulse and 30mg prednisolone administration	Improved
7	53	Male	Melanoma	3 cycles	Ipilimumab	Bilateral	Prednisolone, metchylprednisolone, mycophenolate mofetil with prednisolone, plasmapheresis	Improved
This case	63	Male	NSCLC	7 cycles	Pembrolizumab	Left	Prednisolone	Not progression

NSCLC: non-small cell lung carcinoma

ones. The patients were mainly treated with corticosteroids, but one patient required additional intervention, such as, plasmapheresis, and mycophenolate mofetil. In all cases, the symptoms were well controlled. In this case, as well, corticosteroid therapy could suppress progression, so retrobulbar optic neuritis was considered to be an irAE.

The leading causes of acute optic neuritis include brain tumors, cerebrovascular disorders, multiple sclerosis, neuromyelitis optica, paraneoplastic optic neuropathy, ischemic optic neuritis, and infection. The symptoms of optic neuritis include vision loss, central scotoma, and pain during eye movement or pressure. Useful diagnostic tests include pupil examination, fundus examination, critical fusion frequency, and blood tests for autoantibodies, such as anti-aquaporin-4 antibody for neuromyelitis optica, anti-Hu antibody, anti-Yo antibody, and anti-Ri antibody for paraneoplastic optic neuropathy. The inflammatory edema of the optic nerve manifests as a high-intensity lesion on orbit MRI with a short TI inversion recovery (4). Anti-Hu antibody is useful for diagnosing paraneoplastic neurological syndrome (specificity of 99% and sensitivity of 82%) (8). Paraneoplastic optic neuropathies are rarer than other retinopathies (9). In this case, paraneoplastic optic neuropathy cannot be excluded, but the anti-Hu antibody was negative.

After four cycles of cisplatin, pemetrexed, and pembrolizumab, and three cycles of pemetrexed and pembrolizumab maintenance therapy, renal failure and left central visual field disorder occurred. Cisplatin, pemetrexed, and pembrolizumab all have adverse events, including renal failure, so it is difficult to isolate the cause of in this case (10). However, the renal function improved after steroid therapy. As a result, we considered the cause of renal failure to be irAE. He was diagnosed with retrobulbar optic neuritis, induced by pembrolizumab, based on Goldmann perimetry and orbit MRI. A renal biopsy and blood tests supported the diagnosis of drug-induced renal failure. Retrobulbar optic neuritis was unilateral, had little effect on the patient's quality of life, and it did not shift to bilateral disease. Thus, no other immunosuppressants or immunoglobulin therapy were administered.

Conclusion

We herein described a case of unilateral central visual field disorder, diagnosed as retrobulbar optic neuritis, induced by pembrolizumab and treated with corticosteroids.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

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