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

Keita Kawakado, Tomoki Tamura, Masamoto Nakanishi, Go Makimoto and Shoichi Kuyama

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

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 nonsquamous 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.
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 optic 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 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.**

|                      | At the first visit | On admission |
|----------------------|-------------------|-------------|
| **[Blood test]**     |                   |             |
| White blood cell     | 9,300             | 7,600 /μL   |
| Red blood cell       | 423               | 258 ×10^4 /μL|
| Hemoglobin           | 12.8              | 8.9 g/dL    |
| Platelet             | 22.9              | 23.7 ×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 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 |             |
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...
and it did not shift to bilateral disease. Thus, no other unilateral, had little effect on the patient’s quality of life, of drug-induced renal failure. Retrobulbar optic neuritis was MRI. A renal biopsy and blood tests supported the diagnosis pembrolizumab, based on Goldmann perimetry and orbit was diagnosed with retrobulbar optic neuritis, induced by result, we considered the cause of renal failure to be irAE. He and blood tests for autoantibodies, such as anti-aquaporin-4 antibody, and anti-Ri antibody for paraneoplastic optic neuritis, anti-Hu antibody, and anti-Yo antibody was negative. paraneoplastic optic neuropathy cannot be excluded, but the pathies are rarer than other retinopathies (9). In this case, 99% and sensitivity of 82%) (8). Paraneoplastic optic neuro- 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 re- 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 adminis-

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

We thank the patient and Dr. K. Shibata for the opthalmic diagnosis.

References

1. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 375: 1823-1833, 2016.
2. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 378: 2078-2092, 2018.
3. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol 16: 908-918, 2015.
4. Kartal Ö, Ataç E. Bilateral optic neuritis secondary to nivolumab therapy: a case report. Medicina (Kaunas) 54: 82, 2018.
5. Makri OE, Dimitrakopoulos Fl, Tsapardoni F, et al. Isolated optic neuritis after pembrolizumab administration for non-small-cell lung carcinoma. Int J Neurosci 1-6, 2020.
6. Mori S, Kurimoto T, Ueda K, et al. Optic neuritis possibly induced by anti-PD-L1 antibody treatment in a patient with non-small cell lung carcinoma. Case Rep Ophthalmol 9: 348-356, 2018.
7. Wilson MA, Guild K, Galetta S, et al. Acute visual loss after ipilimumab treatment for metastatic melanoma. J Immunother Cancer 4: 66, 2016.
8. Sentries-Madrid H, Vega-Boada F. Paraneoplastic syndromes associated with anti-Hu antibodies. Isr Med Assoc J 3: 94-103, 2001.
9. Przeździecka-Doløy J, Brzecka A, Ejma M, et al. Ocular paraneo-

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, methyprednisolone, mycophenolate mofetil with prednisolone, plasmapheresis | Improved |
| This case | 63  | Male| NSCLC       | 7 cycles | Pembrolizumab | Left | Prednisolone Not progression |         |

NSCLC: non-small cell lung carcinoma
