中文題目：Pembrolizumab 誘發之視神經炎、多發性神經病變、及修格蘭氏症候群

英文題目：Optic neuritis, polyneuropathy and Sjögren's syndrome induced by pembrolizumab

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Introduction

Immune checkpoint inhibitors (ICI) showed promising outcome for the treatment of several cancers. Primary targets included cytotoxic T-lymphocyte antigen 4 (CTLA4) (e.g. ipilimumab), programmed cell death 1 (PD-1) (e.g. pembrolizumab, nivolumab, dostarlimab) and programmed cell death ligand 1 (PD-L1) (e.g. atezolizumab, avelumab, durvalumab). However, an increasing number of studies discussing about their safety and immune-related adverse events (irAEs) had been published. In this report, we presented a case of optic neuritis, polyneuropathy and Sjögren's syndrome induced by pembrolizumab.

Case Presentation

A 51-year-old woman has a history of autoimmune thyroiditis with hypothyroidism and major depressive disorder. She received first course of chemotherapy and immune therapy with epirubicin(150mg) + cyclophosphamide (1002mg) and pembrolizumab(200mg) due to left breast invasive ductal carcinoma (cT2N0, triple negative). But unfortunately, she presented to our hospital due to high fever 10 days after 1st course of chemotherapy and immune therapy. Hence, she was admitted to surgical intensive care unit under the impression of neutropenic fever and septic shock with methicillin-resistant staphylococcus aureus bacteremia due to port/catheter related blood stream infection.

However, she complained of bilateral gradually blurred vision with both eye pain about one month after first course of chemotherapy and immune therapy. Acute onset of four limbs and whole trunk numbness and subjectively stiffness associated with dysphagia, nausea, vomiting, and easy hiccup happened about two months after first course of antineoplastic therapy. Laboratory examinatiomn showed anti-nuclear antibody (1:40), normal C3/C4, positive anti-Ro auto-antibody (>240 EliAU/ml) and negative AQP-4 autoantibody. Brain magnetic resonance imaging disclosed no central nervous system lesion. Nerve conduction velocity test confirmed severe polyneuropathy and L5-S1 radiculopathy. Brainstem auditory evoked potential test recorded left delay wave I latency. Somatosensory evoked potential test showed central conduction defect. Schirmer's test revealed positive result (right 3mm, left 5mm). Esophagogram disclosed tertiary peristalsis of the esophagus. Optic neuritis was diagnosed by ophthalmologist. These findings met ACR-EULAR Classification Criteria for Sjögren's syndrome.

Pulse steroid therapy with methylprednisolone 500mg every 12 hours for three days was prescribed, and shifted to oral steroid (0.5mg/kg) thereafter. Medication was then shifted back to intravenous methylprednisolone and added on azathioprine (50mg/daily)(but later hold due to leukopenia). Her impaired eye vision got partially improved. Methylprednisolone dose was titrated from 40mg daily to 40mg every 12 hours because immune checkpoint inhibitors related to diarrhea/colitis cannot be excluded.

Discussion

As to the incidence of ophthalmic irAE, one single-site case series reported incidence rate of 1.0% with 15 patients with ophthalmic irAEs from a total of 1474 patients treated with nivolumab with or without

ipilimumab [1]. Pharmacovigilance studies showed incidence of 9/2094 (0.43%) for ICI-associated optic neuritis [2]. The overall incidence of neuro-ophthalmic outcomes (e.q. optic neuritis, neuroretinitis, myasthenia gravis…) following ICI therapy was 0.46%. One systemic review reviewing 115 papers reported the median time to symptom onset was two cycles which ranged from 1 to 51 doses [2]. Bilateral optic neuritis was more common (9/12, 75.0%) in ICI-associated optic neuritis. Neuro-ophthalmic adverse drug reaction seemed to be more likely with pembrolizumab, while ocular side effects (e.q. uveitis) were more common with ipilimumab. Corticosteroids was the mainstay treatment with concurrent discontinuation of the offending agent, as well as additional interventions such as intravenous immunoglobulin, plasma exchange, and immune modulator. Little studies had shown correlation between irAEs and therapy efficacy or failure. Fortunately, most cases with ophthalmic irAE reported partial or reversible response to steroid treatment.

ICI-induced sicca syndrome accompanied by true Sjögren's syndrome was scarce, occurring at a rate of < 1% [3]. Moreover, there was different characteristic between 'primary Sjögren's syndrome' and 'Sjögren's syndrome triggered by ICIs' [4]. 'Sjögren's syndrome triggered by ICIs' had half cases being male (only 5% in primary), 20% cases had history of previous autoimmune disease, and older in age (mean 63-year-old).

Limitation among current studies was relatively small patient sample size, little understanding of timing to develop irAEs and unclear pathophysiology. No head-to-head comparison trials had been published, and therefore the interpretation and application of these studies should be taken with caution.

Conclusion

Herein, we described a 51-year-old woman with autoimmune thyroiditis encountered bilateral blurred vision and generalized numbness/stiffness about 1 month after receiving one dose of pembrolizumab. After a serial examination, optic neuritis, polyneuropathy and Sjögren's syndrome were impressed. Optic neuritis got partially improved after intravenous corticosteroid therapy.

References

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