Rituximab in the treatment of Pembrolizumab induced Myasthenia Gravis

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Abstract:

Pembrolizumab is a monoclonal antibody programmed cell death 1 inhibitor that is an established treatment for melanoma and various lung cancers. Whilst an effective treatment option, it is known to have multiple immune related adverse events associated with its use, including neurological complications such as myasthenia gravis. Previous case reports on the treatment of Pembrolizumab induced myasthenia gravis have detailed the difficulty in managing the condition. There is increasing evidence that Rituximab, a monoclonal antibody directed at CD20 antigen B cells may be an effective treatment option for this condition. This case report outlines the successful treatment of a patient with Pembrolizumab induced myasthenia gravis who was managed with Rituximab.

Key words:

Rituximab

Myasthenia Gravis

Pembrolizumab

Immune-related adverse events

Introduction:

Pembrolizumab is a monoclonal antibody checkpoint inhibitor that is now an established line of therapy for melanoma and some subtypes of bronchogenic carcinoma (1,2). It generates an anti-neoplastic response by increasing the T cell mediated immune response. This occurs as a result of inhibiting binding of a programmed cell death 1 (PD1) receptor expressed on the surface of activated T cells (1–3).

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Despite the promising results of anti-PD-1 therapy, there has been an emergence of immune-related adverse events (irAEs) associated with their use. There are numerous reports of patients receiving anti-PD-1 therapy, who have developed irAEs including myocarditis and myasthenia gravis (MG) (1–10). Though comparatively rare, the occurrence of MG appears to be in a refractory form, unresponsive to conventional immunosuppressive therapy (2,4,9).

Previous case reports of Pembrolizumab-induced MG have included patients with metastatic melanoma and squamous cell lung cancer, with only two case reports to date of patients with thymic epithelial tumours (4,6). There are limited treatment options available for the management of thymic epithelial tumours (11,12) and up to 50% of patients develop paraneoplastic MG at some stage during their disease as a result of autoantibodies to nicotinic acetylcholine receptors (AChR) (13). Among patients with thymic tumours who developed MG associated with monoclonal antibody therapy, it has been difficult to conclude whether MG was the result of the malignancy or the anti-PD-1 therapy. However, authors have ultimately determined that MG was likely secondary to therapy (4,6), given the absence of a history of neuromuscular disorders.

Case Report:

We describe a patient who developed rhabdomyolysis, myocarditis, hepatitis and refractory myasthenia gravis following a single dose of Pembrolizumab for the treatment of recurrent metastatic thymoma.

A 68-year-old fit and well retired aviation engineer (Eastern Cooperative Oncology Group -performance status - ECOG = 0) Caucasian male presented to hospital with lethargy and malaise in April 2019 in the setting of receiving a single dose treatment with Pembrolizumab for recurrent thymoma (Stage III B2/ B3) 17 days prior. His TPS PD-L1 Thymic Cancer score was equal to 80 percent. His oncological history includes; incomplete resection of thymoma (5 years prior), followed by adjuvant radiotherapy, disease recurrence (3 years prior) with re-resection and eight cycles of Cisplatin, Doxorubicin and Cyclophosphamide. One year before his presentation he developed asymptomatic disease progression, with hilar, mediastinal and supraclavicular lymphadenopathy, and was managed with palliative Capecitabine and Gemcitabine which was ceased in January 2019.

On review in March 2019, computer tomography imaging of his chest revealed small volume right sided hilar and mediastinal lymphadenopathy. He was commenced on Pembrolizumab 200mg on March 21st 2019. Screening prior to Pembrolizumab treatment included liver function tests (LFTs) and Creatinine Kinase (CK) levels, which were within normal limits (CK = 112, reference range <201 U/L). Of note, there was no past history of any neuromuscular disease, and he was not screened for acetylcholine receptor antibodies. Upon presentation 17 days later, his CK level was elevated at 6809 U/L. This was associated with a troponin elevation (2.1ug/L, reference range <0.05 ug/L) and elevated liver enzymes (ALT 325 U/L, reference range <51 U/L, AST 476 U/L, reference range <41 U/L). He was diagnosed with rhabdomyolysis, myocarditis and hepatitis and commenced on pulse Methylprednisolone therapy.

The diagnosis of myasthenia gravis was made on the basis of the development of bilateral ptosis, periods of paradoxical breathing, and positive acetyl choline receptor antibodies (0.47, reference range <0.25nmol/L). He was commenced on Mycophenolate mofetil 1g twice daily, Pyridostigmine 30mg six-hourly and Methylprednisolone was changed to Prednisolone 60mg daily. He received intravenous immunoglobulin (IVIG) (total 180g spread over five doses), with his vital capacity monitored throughout. His symptoms improved, and he was finally discharged home 51 days after admission on Prednisolone 60mg daily and Pyridostigmine 30mg six-hourly (Mycophenolate ceased).

Unfortunately, he represented six days later with increasing lethargy and respiratory fatigue. He was admitted to the Intensive Care Unit, underwent urgent plasma exchange, received further IVIG and was continued on high-dose corticosteroid therapy. Within 2 days of admission, he required intubation for respiratory failure. He was managed with; nine rounds of plasma exchange, three cycles of 90g IVIG, and two doses of Rituximab 1g over 2 weeks. Failed extubation resulted in placement of a tracheostomy on day 9 of his admission, to allow for weaning from mechanical ventilation. His admission was also complicated by a right-sided phrenic nerve palsy secondary to mediastinal disease and unprovoked pulmonary embolism. He was eventually discharged to a rehabilitation centre after a 49-day admission.

Discussion:

This case highlights a number of key points regarding the use of anti-PD1 therapy. Firstly, this case illustrates the increasingly documented risk of serious irAEs including MG, even after single dose of Pembrolizumab. Often the outcome of serious adverse events in the setting of immune therapy is complete resolution (1,4–7,9), however there have been numerous reports of death as a direct result of therapy (2,8,9). Our case did not result in death but highlights the extensive associated morbidity and resource utilisation in this patient.

Secondly, the safety profile of anti-PD1 therapy in patients with thymic epithelial tumours, particularly thymoma, deserves attention given the known association between thymoma and MG. A review of current novel treatments for thymic epithelial tumours highlighted the trials currently underway for the use of Pembrolizumab for thymic epithelial tumours. The rationale for Pembrolizumab treatment being the high expression of PD-1/PD-L1 in these tumours. However, uncertainty remains regarding their efficacy given the high frequency of PD-1 and PD-L1 expression in the non-neoplastic thymus, and the fact that the presence of immature and mature T cells surrounding the tumours of the thymus is a part of the prototypic architecture and not a marker of actual anti-tumour response (14). A recent study by Weissfordt et al was una-

ble to demonstrate a significant correlation between the presence of PD-1/PD-L1 expression of thymic epithelial tumours and the burden of neoplastic disease. Whilst they demonstrated high rates of expression (PD-1 = 52% and PD-L1 = 61%) this was not correlated with tumour histology and grading, as has been the case in similar previous studies (15–17).

Thirdly, this case demonstrates the novel finding of the utility of Rituximab in refractory MG secondary to Pembrolizumab therapy. Rituximab is a monoclonal antibody directed at CD20 antigen B cells (18,19).The depletion of B cells via Rituximab is considered well tolerated and it is currently used based on evidence from systematic reviews and case studies rather than randomised-controlled trial data. Whilst the use of Rituximab has been documented in patients with refractory MG, this is only the second case report highlighting its use in immune-related MG (18,19) Our patient received multiple lines of treatment for MG, and it is difficult to conclude which interventions had a direct impact on the outcome. However, previous case reports of refractory MG secondary to anti-PD-1 therapy have documented very similar treatment regimens, including Pyridostigmine, Methylprednisolone and plasma exchange. Two such case reports had fatal outcomes, and the only difference in treatment between their patients and our patient, is the use of Rituximab (2,6).

This case adds to the literature about immune-related adverse events associated with the use of ati-PD-1 therapy. It describes the use of these therapies in patients with thymic epithelial tumours and the need for ongoing investigation into their safety and efficacy. It raises the question of the need for further screening prior to commencing therapy, such as screening for acetyl choline receptor antibodies. Finally, it highlights a new area of potential research into the use of Rituximab in refractory autoimmune complications of immunotherapy, including myasthenia gravis.

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