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Case Report

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Multi-system Immune-related Adverse Effects after a Single Dose of Pembrolizumab Therapy in a patient with Metastatic Non-Small Cell Lung Carcinoma: A case report

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Abstract

Background: *Immune-checkpoint inhibitors are at the forefront of treatment for oncological pathologies. It is a promising new option for patients with metastatic non-small cell lung carcinoma. Case reports of immune-related adverse effects (irAEs) have been reported in literature in recent years. We report the first case of multisystem organ dysfunction resulting from irAEs after a single dose of pembrolizumab.*

Case presentation: *A 69-year-old male, diagnosed with metastatic non-small cell lung carcinoma, presented to our emergency department with worsening respiratory distress. He received his first dose of pembrolizumab twenty days prior his symptoms. The laboratory investigations showed evidence of myocarditis, myasthenia gravis and hepatitis. Intravenous steroids were initiated as well as intravenous immune globulin for myasthenia gravis.*
Conclusion: It is essential that physicians are aware of immunotherapy use and possible complications to facilitate early diagnosis, treatment, and improve patient outcomes.

Keywords: *Immune-checkpoint inhibitors, pembrolizumab, multisystem organ dysfunction.*

Background

Immune checkpoint inhibitors are at the forefront of the immuno-oncology field in the treatment of cancers [1]. By inhibiting immune-checkpoints, it allows the T-lymphocytes to attack cancer cells. This serves to enhance the body's immune response and to suppress tumor "resistance" toward the body. The main immune-checkpoints that have been targeted include programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte protein 4 (CTLA-4). Several monoclonal antibodies have been developed to inhibit these immune checkpoints. Pembrolizumab and nivolumab are examples of PD-1 inhibitors, while ipilimumab is an example of CTLA-4 inhibitor. These have been approved for a myriad of different cancers, including melanoma, non-small cell lung cancer among many others [2]. However, there have been case reports of immune-related adverse events (irAE) linked to the use of immune-checkpoint inhibitors [3]. Severe multisystem organ dysfunction is a rare complication of this treatment. With an increasing number of patients on immune checkpoint inhibitor therapy, a high index of suspicion of irAEs is required. Here, we report a case of fulminant myocarditis, myasthenia gravis and hepatitis in a patient who had received one cycle of Pembrolizumab.

Case Presentation

A 69-year-old male with a background of metastatic non-small cell lung carcinoma (Flourescence in situ hybridization [FISH] negative, Somatic Solid Tumour Panel [SSTP]: BRAFV600E mutation, programmed death ligand 1 [PDL1] 50%, Blood First Assay Screening Trial [BFAST] pre-screen negative for BRAF) initially presented to the emergency department with worsening dyspnea for three days associated with orthopnea and paroxysmal nocturnal dyspnea. He had a pre-morbid Eastern Cooperative Oncology Group (ECOG) status of 0. His other medical conditions include hypertension, hyperlipidemia, atrial fibrillation, Grave's disease, and Thymoma status post open thymectomy and post-operative radiotherapy. He did not have a history of

ischemic heart disease. He was given the first dose of pembrolizumab twenty days prior to symptom onset.

On examination, patient was noted to be tachycardic of 130/minute. There were decreased breath sounds over the right lower zone. His jugular venous pressure was not raised and he had no bilateral lower limb edema. Electrocardiogram (ECG) showed sinus tachycardia with a rate of 130/minute. With the initial findings of decreased breath sounds over the right lower zone of the lung with tachycardia and worsening tachypnea, initial differentials included malignant pleural effusion or a parapneumonic effusion with sepsis. However, a Chest X-ray (CXR) performed showed a raised right hemi-diaphragm with no consolidation, right sided pleural effusion or any signs of acute heart failure. The raised right hemi-diaphragm is likely contributed by a transection of his right phrenic nerve from a previous thymoma resection surgery.

His initial Troponin-T was 773 ng/L rising to 1223 ng/L. (Figure 1) His creatinine kinase and creatinine-kinase MB were elevated at 6364u/L and 283 U/L respectively. His alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were 255 and 771u/L respectively. He developed worsening tachypnea at rest in the emergency department, with respiratory rate rising to thirty per minute. He also developed a gradual desaturation and was started on supplemental oxygen with improvement in oxygen saturation. With the recent history of being started on pembrolizumab and the involvement of multisystem dysfunction, he was admitted for further work up of irAE and for further evaluation of differentials including acute coronary syndrome and pulmonary embolism. A computed tomography pulmonary angiogram (CTPA) was performed in the emergency department which showed no evidence of pulmonary embolism. Cardiac catheterization performed showed minor coronary artery disease. A bedside transthoracic echocardiogram showed mildly impaired left ventricular systolic function with an ejection fraction of 48% and no regional wall motion abnormalities or pericardial effusion. The likely cause was attributed to myocarditis. Epstein-Barr Virus (EBV), Cytomegalovirus (CMV) and Human immunodeficiency Virus (HIV) testing were also reported as negative.

During the hospitalization, this was complicated by recurrent atrial fibrillation episodes, ventricular standstill requiring insertion of transcutaneous pacing wire for four days. He also developed hemodynamically unstable ventricular tachycardia requiring electrical cardioversion and was subsequently started on four days of intravenous lignocaine infusion.

He also subsequently developed ptosis, proximal weakness and increasing respiratory distress. Nerve conduction studies and anti-acetylcholine receptor (AChR) antibody were suggestive of myasthenia gravis. There was a strong positive for Titin antibody which is associated with myasthenia gravis and thymoma. He developed worsening type-2 respiratory failure and was intubated and then subsequently re-intubated for decreasing Glasgow Coma Score (GCS). He developed cardiac arrest after the second intubation, and return of spontaneous circulation was achieved after three minutes of cardiopulmonary resuscitation. At time of writing, he has been weaned off mechanical ventilation, but still supported with non-invasive ventilation in view of persistent type-2 respiratory failure.

Hepatitis workup for hepatitis B, C and E were unremarkable. The patient's liver enzymes started to downtrend in the days after the initiation of high-dose systemic steroid therapy (Figure 2).

The patient also developed recurrent episodes of diarrhea during inpatient stay. A computed tomography of the abdomen and pelvis noted terminal ileitis. Differentials remain broad at time of writing. Infective or autoimmune inflammatory colitis unmasked by pembrolizumab are possible diagnoses. Colitis workup was not completed with endoscopic evaluation at time of writing as patient has been very unstable.

He was initially started on enoxaparin for potential acute coronary syndrome. He was also started on intravenous pulse methylprednisolone as well as oral prednisolone. Cardiac enzymes and liver enzymes down-trended after the initiation of steroid therapy for immune related toxicities. He was also initiated on intravenous immune globulin for myasthenia gravis presumptively based on high clinical suspicion.

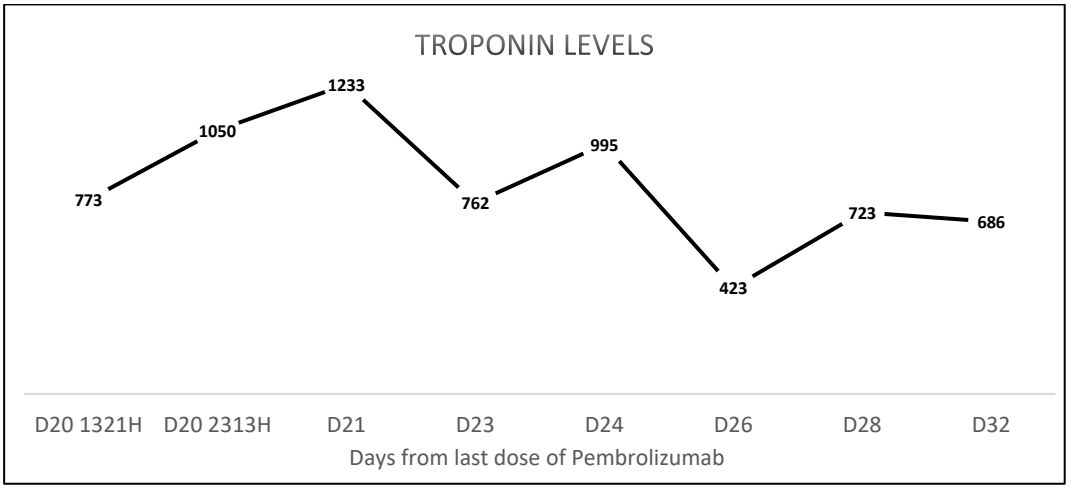

Figure 1: Graph Showing Troponin-T Levels Since Presentation at The Emergency Department on Day 20 Since Last Dose of Pembrolizumab. 60mg Of Oral Prednisolone Was Initiated on D21 And Iv Pulse Methylprednisolone Was Initiated on D22. The Graph Shows Good Initial Response to Immunosuppressant Therapy.

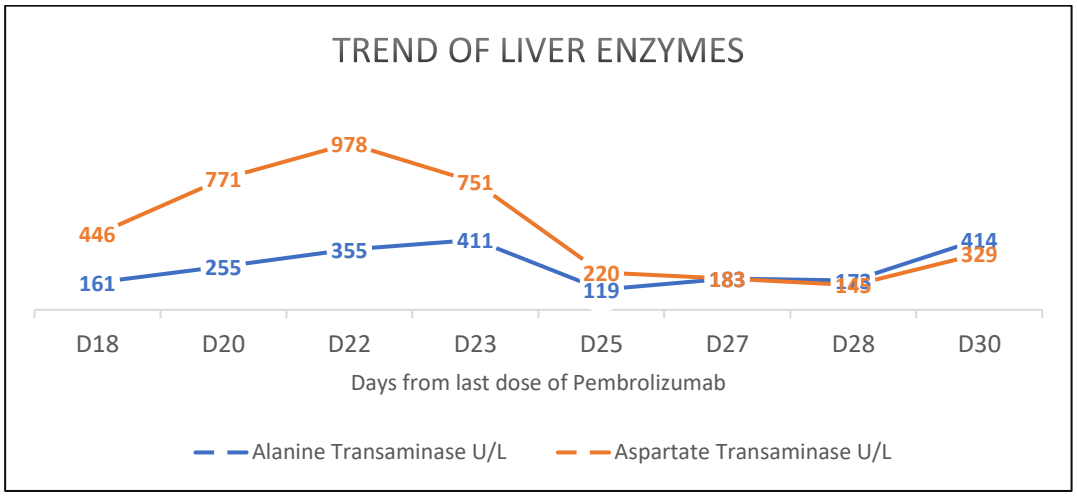

Figure 2: Graph Showing ALT and AST Levels Before Symptom Onset (D18) And beyond. Oral Prednisolone Was Initiated on D21 And Iv Pulse Methylprednisolone Was Initiated on D22 With Good Initial Response.

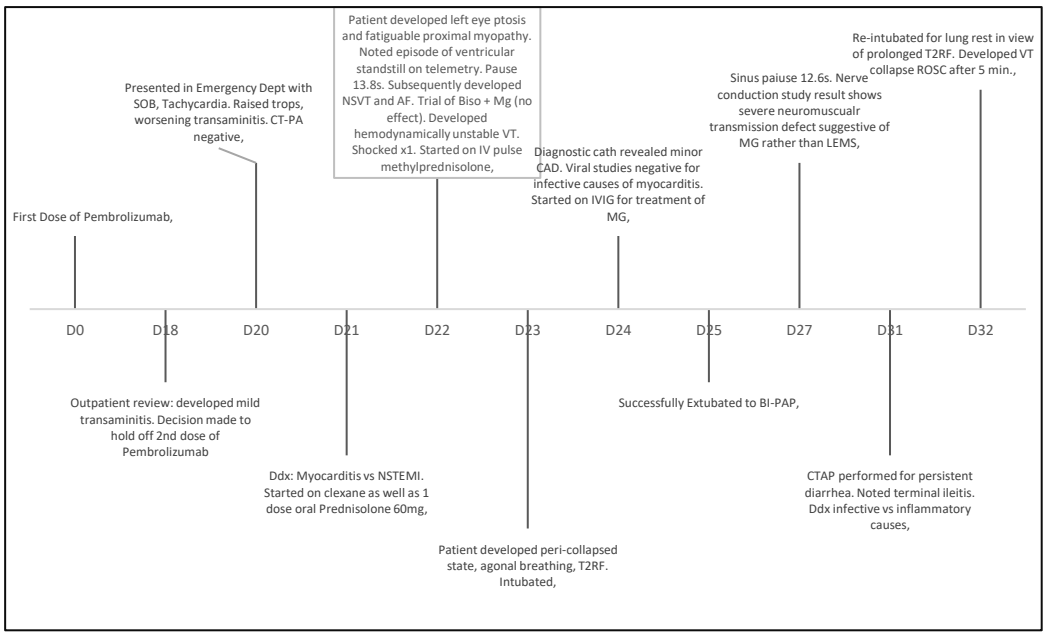

Figure 3: Brief Timeline of Events After 1st Dose of Pembrolizumab

Discussion/Conclusion

Discussion

Pembrolizumab is a IgG4 monoclonal antibody that works as a PD-1 immune-checkpoint inhibitor [4]. It has been proven to be efficacious in several advanced malignancies. As the number of patients using immune-checkpoint inhibitors increase, case reports of possible adverse effects have been increasing. As the population of such patients increase, it is vital that emergency physicians become well-versed with immune-related adverse events.

A literature review was conducted with key words such as "pembrolizumab", "adverse effects", "myocarditis", "myasthenia gravis", "hepatitis". In a study published by Garon et al 2 for NEJM, treatment-related adverse events were reported in up to 70.9% of patients. However, only 9.5% of patients reported more severe adverse events of grade 3 and above. Inayat et al [5] described a case of pembrolizumab induced myocarditis in a 74-year-old gentleman with non-small-cell lung carcinoma. He was initially treated with four cycles of carboplatin and pemetrexed followed by maintenance pemetrexed. However, he showed disease progression and was switched to pembrolizumab. He developed dyspnea on exertion nineteen days after completion of his second cycle of pembrolizumab therapy. He achieved good symptom resolution with initiation of 1mg/kg oral prednisolone therapy with a gradual tapering dose on discharge. The exact cause of myocarditis in PD-1 inhibition is not well known. However, PD-1 is known to protect against tissue inflammation and myocyte damage [6]. Inhibition of PD-1 may predispose patients to myocarditis.

Makarious *et al* [7] reviewed multiple cases of de novo presentations and exacerbations of pre-existing myasthenia gravis in patients receiving immune-checkpoint inhibitor therapy. Among these patients receiving pembrolizumab, 70% were de novo and 30% were exacerbations. It is postulated that the over-expression of PD-1 is associated with favorable outcomes in autoimmune diseases as it potentiates CD8 T-cell exhaustion. PD-1 inhibition with agents such as pembrolizumab may thus precipitate autoimmune conditions such as myasthenia gravis.

To our knowledge, this is the first case of myocarditis, myasthenia gravis and auto-immune hepatitis after 1 cycle of pembrolizumab therapy in the treatment of metastatic non-small cell lung carcinoma. This case is significant because it reveals the possibility of multi system immune-related adverse events. The patient could also present to the physician with a diagnostic challenge as they could present with undifferentiated symptoms. A high index of suspicion is warranted as an expeditious initiation of treatment will be of great benefit to patients.

Quick decision making is vital in the treatment and disposition of the patient in the emergency department. Multi-disciplinary discussions should be made early with oncologists and other specialties. Discontinuation of immune-checkpoint inhibitors as well as initiation of high-dose steroid therapy are the mainstay of treatment. As steroids are antagonistic to the mechanism of action of immune-checkpoint inhibitors, discussion with oncologists should be considered before initiation of treatment [8]. With prompt treatment of adverse events, patients could also potentially go back to receiving life-saving immunotherapy again in the future [9].

Moving forward, further reports and reviews of immune-related adverse events will be useful. A better understanding of pathogenesis, patterns of disease, it's relations with different types of immune-checkpoint inhibitors can help us to better risk stratify patients and identify and treat these conditions quickly. In this case, a liver panel was performed after eighteen days of pembrolizumab initiation. This aided in the decision by the oncologist to withhold the second cycle of pembrolizumab. Perhaps routine cardiovascular and neurological assessments such as ECG, troponin-T testing, and neurological examinations could assist physicians in following up and treating closely higher risk patients more aggressively to improve outcomes.

Immune-related adverse events have been reported mostly between three weeks to months after initiation of treatment. Patients with a history of autoimmune conditions are also at risk of developing flares of immune-related adverse events [10]. In this case, our patient had a history of thymoma with no known clinical signs of myasthenia previously. With his development of myasthenia gravis, this opens the possibility of having auto-immune linked diseases being manifested only after administration of immune-checkpoint inhibitors.

Conclusion

This case report is critical in raising the level of awareness amongst physicians of immunotherapy use and its potential complications, so that prompt recognition, relevant multisystem evaluation, multidisciplinary consultation and specific therapy can be started early with better outcomes for patients.

Conflict of Interest Disclosure

All authors declare that they have no conflict of interest.

Competing interest: The authors declare that they have no competing interest

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