LETTER TO THE EDITOR

To The Editor

Multiple Immune-Related Adverse Event Overlap in Two Patients Treated with Pembrolizumab

Keywords: Immune-related adverse events, Checkpoint inhibitors, Inflammatory myopathy, Myasthenia gravis, Myocarditis

The first checkpoint inhibitor (CPi) ipilimumab (Ipilimumab: Bristol Myers Squibb Canada. Montreal, Quebec, Canada) was approved by the FDA for the treatment of melanoma in 2011.[1] Since then, several CPis have been developed to treat a variety of malignancies[1] and can significantly prolong survival.[2] Immune-related adverse events (irAEs) are a known complication of CPis and are thought to be a consequence of altered immunologic homeostasis.[2] The inhibition of programmed cell death protein 1 (PD-1) by CPis increases T cell activity, reduces immune self-tolerance, dysregulates humoral immunity, and increases the production of inflammatory cytokines.[1,2] This results in immune-related injury to bystander organs. Multi-organ irAEs could place patients at risk for rapid deterioration or even death, requiring multidisciplinary management. We present two cases describing multiple systemic and neurological irAEs in patients treated with pembrolizumab (Pembrolizumab: Merck Canada Inc. Kirkland, Quebec, Canada).

A 71-year-old man with a history of metastatic melanoma treated with two cycles of pembrolizumab presented with a 5-day history of progressive dysphagia and 2 days of fluctuating dysarthria (case 1). He had no prior history of fluctuating weakness, bulbar symptoms, ptosis, or diplopia. Fatigable weakness was evidenced by left ptosis and diplopia that worsened with prolonged up gaze and improved with an ice pack. He had a positive curtain sign. His motor exam demonstrated 4/5 weakness of neck flexion, shoulder abduction, and hip flexion that worsened after sustained muscle contraction. His initial vital capacity was 3.55L, which dropped to 1.8L within 12 h with a worsening of the patient's bulbar symptoms. Laboratory investigations revealed an elevated creatine kinase (CK) at 1604 (0–195 unit/L), high-sensitivity troponin at 719ng/L (0–14ng/L), and abnormal liver enzymes in a hepatocellular pattern. Antinuclear antibodies were positive with a cytoplasmic pattern and titer of more than 1:640. In addition, a myositis antibody panel showed weak positive anti-Ro antibodies. Acetylcholine receptor antibodies (AChR) and Muscle-specific kinase (MUSK) antibodies were negative. His ECG demonstrated a transient left bundle branch block. His echocardiogram and cardiac MRI were normal; however, the MRI was done on day 3 of the presentation, which may have reduced its sensitivity. A CT chest demonstrated patchy, scattered variable-sized parenchymal and subpleural nodular opacification in keeping with acute pneumonitis (Figure 1A). An MRI of the brain with gadolinium was normal. Electromyography (EMG) revealed fibrillation potentials and positive sharp waves with normal recruitment and motor unit action potential morphology in keeping with acute inflammatory myopathy (IM); repetitive nerve stimulation was normal. A neostigmine 0.5 mg IV trial led to rapid improvement in his ptosis and bulbar symptoms. A biopsy of the left deltoid showed large clusters of inflammation with degenerative myofibers. Many of the small infiltrating inflammatory cells are marked as T lymphocytes (CD3) in keeping with a T lymphocyte-associated necrotizing myopathy (Figure 2). Fatigable weakness, a positive ice pack test, and a response to neostigmine led to a diagnosis of pembrolizumab-associated myasthenia gravis (MG) in addition to IM, myocarditis, hepatitis, and pneumonitis. The patient was treated with methylprednisolone 100mg IV daily, intravenous immunoglobulin (IVIG) 2g/kg divided over 5 days, and pyridostigmine 60mg t.i.d. His ptosis, diplopia, dysarthria, and neck flexor/proximal weakness improved rapidly and he was discharged after 6 days.

A 65-year-old woman with a recent diagnosis of metastatic squamous cell carcinoma treated with two cycles of pembrolizumab presented with 8 days of progressively worsening cough, dysphonia, dysphagia, dysarthria, myalgias, and proximal weakness (case 2). She had no history of similar symptoms. On exam, there was fatigable ptosis, orbicularis weakness, and proximal weakness (4−/5). Her vital capacity was low (1.68L). An EMG revealed fibrillations, positive sharp waves, and early recruitment showing instability of the neuromuscular junction. Repetitive stimulation was normal. AChR and MUSK antibodies were negative. Laboratory findings included elevated CK at 2993U/L (immune myositis panel was negative), high-sensitivity troponin at 926ng/L (with a normal echocardiogram and ECG, but her cardiac MRI showed T2 hyperintensity suggestive of myocarditis), alanine aminotransferase (ALT) of 194U/L (abdominal ultrasound and liver autoimmune and hepatitis panels were negative), a low TSH (0.02mIU/L), and elevated T4 (39.4pmol/ml). Her CT chest was in keeping with pneumonitis (Figure 1B). She was diagnosed with overlapping MG, IM, myocarditis, pneumonitis, hepatitis, and autoimmune thyroiditis presumed to be irAEs of pembrolizumab therapy. The patient was treated with methylprednisolone (1g daily for 3 days) and IVIG (400 mg/kg daily for 5 days). Within days, she had improved proximal muscle strength and resolution of dysarthria and dysphagia.

The incidence of neurological complications due to CPis has been cited from 2% to 4%.[3] A systematic review of irAEs found that MG and IM occurred in 14 out of 30 (46%) cases of new-onset MG.[4] Clinically, coexisting MG and IM can be difficult to differentiate. AChR antibodies were negative in 30% of cases, with no MUSK antibody-positive cases.[4] In addition, among 654 patients receiving CPis, 1.3% on pembrolizumab developed biopsy-proven myopathies.[3] A case series including 65 patients with CPi-induced MG, concurrent diagnosis of IM was noted in 24 patients (37%), and myocarditis in 5 (8%).[5] CPi-induced MG involves bulbar muscles and leads to respiratory failure more often than idiopathic MG.[5]

Immunotherapy is the mainstay of treatment of CPi-induced irAEs. Our patients responded well to IVIG and steroids. Other treatments cited in the literature include plasmapheresis, tumor necrosis factor-alpha antagonists, and azathioprine or mycophenolate mofetil.[4,6] Presently, recommendations for treatment of neurological irAEs due to CPis are based on case series, known treatment for autoimmune conditions and expert opinion.[4,6] Prognosis for patients with irAEs remains variable.

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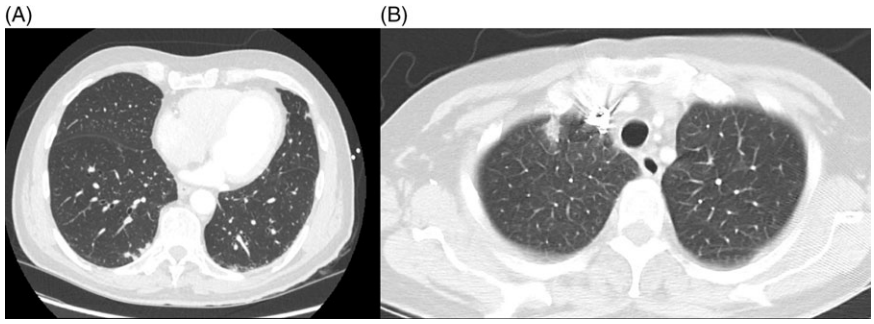

Figure 1: *CT chest scans showing pneumonitis. A, CT chest enhanced showing patchy, scattered variable size parenchymal and subpleural nodular opacification (case 1). B, CT chest enhanced showing new mild ground-glass in the anterior aspects of the upper lobes (case 2). Findings in both cases were in keeping with pneumonitis.*

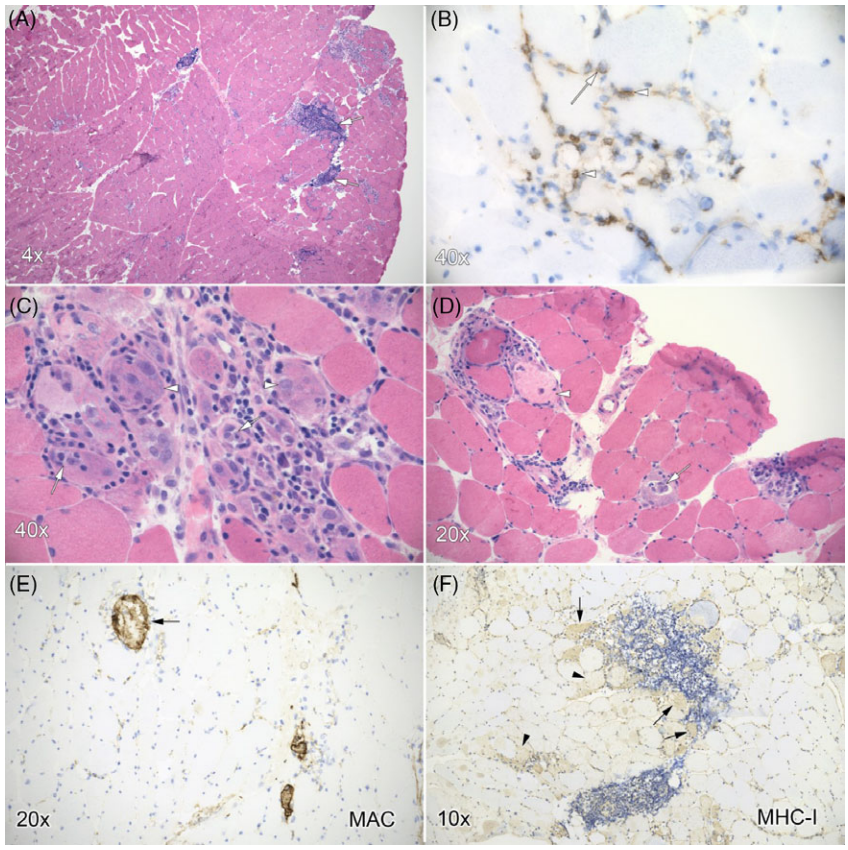

Figure 2: *Muscle pathology. Panel A shows several large clusters of inflammation (white arrows) that are separated by near normal muscle. In B, scattered small cells stain with the pan-T-lymphocyte marker CD3 (white arrowheads), including occasional cells "invading" myofibers (white arrow). Other areas (C) had clusters of necrotic fibers undergoing phagocytosis (white arrowheads) occur but with considerably less inflammation. Notice the two fibers having vacuoles filled with inflammatory cells (C, white arrows). D represents another area of muscle injury, including a recently necrotic myofiber (white arrowhead) and a vacuole filled with inflammatory cells (white arrow) in a basophilic regenerating myofiber. Staining for C5b-9 complement (E; membrane attack complex or MAC) only highlights necrotic or degenerating fibers (black arrow) but does not outline myofibers (as occurs in complement-antibody mediated myositides such as statin myositis) or capillaries (typical for dermatomyositis and certain collagen vascular diseases). Expression of the major histocompatibility complex 1 protein (F) is high in myofibers near the inflammatory hot spots (black arrows), then diminishes further away (black arrowheads) and is largely negative in most of the muscle biopsy. The findings are indicative of a T-lymphocyte-associated necrotizing myopathy.*

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When presenting with MG, mortality can reach 30-40%, and multi-systemic involvement may carry a worse prognosis.[5,7,8]

Multiple overlapping irAEs related to CPi use can lead to rapid clinical deterioration. Our cases illustrate the importance of recognition of these overlap syndromes to facilitate prompt interdisciplinary patient management, including appropriate cardiac and neurologic monitoring. Patients with MG and elevated troponins should be monitored closely for symptoms of respiratory failure (such as blood gases and forced vital capacity) and myocarditis (such as chest pain, arrhythmias, and symptoms of heart failure). Rapid initiation of immunotherapy is essential. The decision to restart CPi therapy after severe irAEs remains controversial and is an area in need of additional research.[2]

Conflict of Interest

The authors have no conflicts of interest to declare.

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