Case Report

Pembrolizumab-induced fulminant triple M syndrome presenting with severe bradycardia

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Abstract

Immune checkpoint inhibitors have markedly transformed cancer treatment paradigms but are frequently associated with immune-related adverse events (irAEs) affecting multiple organ systems. Among the rare and severe complications is the "triple M syndrome", encompassing myositis, myocarditis, and myasthenic syndrome.

We present the case of an 83-year-old male with stage IIc melanoma who received pembrolizumab as adjuvant therapy following surgical excision of the primary tumor and regional lymph nodes, with no evidence of neoplastic invasion. Approximately one month post-infusion, the patient experienced episodes of syncope, leading to the diagnosis of a second-degree atrioventricular block. Despite normal findings on echocardiography, the patient subsequently developed profound proximal muscle weakness, dysphonia, and dysphagia. Pembrolizumab was promptly discontinued, and the patient was initiated on high-dose intravenous methylprednisolone; however, his clinical course rapidly deteriorated, culminating in the necessity for palliative care due to progressive respiratory failure.

This case underscores the potential for severe, life-threatening irAEs associated with pembrolizumab therapy, particularly in the form of triple M syndrome. Notably, the manifestations of myocarditis and myasthenia gravis (MG) within this context may occur in the absence of typical autoantibody markers, thereby complicating the diagnostic process and contributing to poor prognostic outcomes. This case highlights the imperative for heightened clinical vigilance and a proactive approach to monitoring for irAEs in patients receiving immune checkpoint inhibitors. Early recognition, coupled with the prompt initiation of therapeutic interventions, is paramount in mitigating morbidity and improving clinical outcomes in these critical scenarios.

Keywords: immune checkpoint inhibitors, myositis, myocarditis, myasthenia gravis

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Introduction

Immune checkpoint inhibitors have revolutionized cancer therapy by activating the body's immune system to target tumor cells [1]. However, this immune activation can lead to a distinct spectrum of adverse effects, which may involve multiple organ systems [2]. Among the rare but severe complications is the overlap syndrome involving myositis, myocarditis, and myasthenic syndrome, collectively termed "triple M syndrome," which is associated with significant morbidity and mortality [3].

This report presents a case of a patient who developed myositis, myocarditis, and myasthenic syndrome during treatment with pembrolizumab. We examine the clinical presentation, management, and outcomes associated with this adverse event.

Case Report

An 83-year-old male, recently diagnosed with stage IIc melanoma, underwent surgical excision of the primary tumor with no evidence of lymph node invasion, followed by adjuvant pembrolizumab therapy. He had a history of colonic neoplasm surgically treated four years before and hypertension, but no associated cardiac or neuromuscular disorders. One month after the first pembrolizumab infusion, the patient was admitted to the cardiology unit for evaluation following episodes of syncope. On physical examination, bradycardia was noted as the only significant finding. Electrocardiography revealed a second-degree atrioventricular block with a 3:1 conduction pattern, resulting in a ventricular rate of 30 beats per minute, as well as a minor right bundle branch block. Laboratory investigations showed elevated leukocyte and neutrophil counts, mildly elevated liver enzymes (ALT = 144 U/L, AST = 204 U/L), elevated serum creatine kinase (CK = 2166 U/L), and mildly increased levels of troponin (Tr = 1.64 mg/dL) and natriuretic peptide (NT-proBNP = 369.7 pg/mL).

Echocardiography revealed normal left ventricular ejection fraction, mild septal hypertrophy, and no evidence of wall motion abnormalities or pericardial effusion. Given the high-grade atrioventricular block, a cardiac pacemaker was implanted. Subsequently, the follow-up chest X-ray identified a hydropneumothorax, which necessitated the placement of a chest drain, leading to full resolution of the condition.

In the days following the pacemaker implantation, the patient experienced rapidly progressing proximal muscle weakness, dysphonia, and dysphagia. A repeat blood workup demonstrated an exponential rise in muscle enzymes, with creatine kinase levels reaching 8633 U/L, lactate dehydrogenase 757 U/L, and aspartate aminotransferase AST = 375 U/L. The patient's condition continued to deteriorate, with a marked reduction in muscle tone and strength, particularly in the proximal muscle groups affecting the neck, shoulders, and pelvic girdle. Additionally, he developed moderate dysphonia, bilateral ptosis, and severe dysphagia, necessitating the insertion of a nasogastric feeding tube. Comprehensive laboratory testing, including a myositis antibody panel, acetylcholine receptor antibodies, anti-striated muscle antibodies, and muscle-specific kinase antibodies, all yielded negative results. Due to the patient's poor clinical status, nerve conduction studies and electromyography could not be safely performed, and the patient declined a muscle biopsy. Furthermore, a therapeutic trial with the acetylcholinesterase inhibitor neostigmine did not result in any significant clinical improvement.

Pembrolizumab was discontinued, and the patient was initiated on high-dose intravenous methylprednisolone (1000 mg daily for three days), followed by oral glucocorticoid therapy. Despite these interventions, the patient's condition continued to deteriorate. The patient and his family opted against further therapeutic measures, such as immunoglobulins or immunosuppressive agents. Within ten days, the patient succumbed to respiratory muscle failure.

Discussion

Myocarditis is a potentially life-threatening complication associated with pembrolizumab treatment [3,6,9-14]. In some cases, complete atrioventricular block or Mobitz type 2 second-degree atrioventricular block may be the initial presentation of myocardial inflammation in these patients [11,12,14]. Pembrolizumab-induced myocarditis appears to occur more frequently in males and elderly individuals [12]. As observed in the present case, almost all reported cases of pembrolizumab-associated myocarditis exhibit elevated levels of cardiac biomarkers, such as troponin and creatine kinase [8,10,11,13]. Given the severity of this adverse event, Saad et al. have advocated for routine assessment of these biomarkers at baseline and before each cycle of pembrolizumab, especially in elderly patients at elevated risk [12]. The European Society for Medical Oncology (ESMO) guidelines for managing cardiotoxicity associated with immune checkpoint inhibitors recommend the use of corticosteroids as the first-line treatment, with immunosuppressive agents such as tocilizumab and mycophenolate mofetil as second-line options [2].

Pembrolizumab has been associated with the onset or exacerbation of myasthenia gravis (MG), a rare but potentially fatal immune-related adverse event [4–8]. The onset of MG symptoms typically occurs within the first eight weeks of pembrolizumab therapy [5,6,9], although cases of delayed onset have also been reported [5]. Importantly, patients with pembrolizumab-induced MG frequently test negative for acetylcholine receptor and muscle-specific kinase antibodies, as observed in the current case [7,8,15]. Moreover, only approximately half of these patients respond to acetylcholinesterase inhibitors, such as pyridostigmine, while corticosteroids alone provide improvement in another subset of cases [6,7]. Second-line therapies, including plasma exchange, intravenous immunoglobulins, ruxolitinib, and rituximab, may confer additional benefit, though their efficacy remains poorly established [5,10,15].

Furthermore, nearly half of MG cases associated with immune checkpoint inhibitors like pembrolizumab also manifest concurrent myocarditis or myositis [3,4,15]. Patients who develop this "triple M syndrome"—characterized by the co-occurrence of myasthenia gravis, myocarditis, and myositis—demonstrate significantly poorer prognoses [6,7]. Notably, outcomes in patients with generalized MG are less favorable than those with ocular MG, with only approximately one-third achieving resolution of symptoms [6].

In conclusion, we recommend close monitoring when dealing with patients receiving immune checkpoint inhibitors as well as a high index of suspicion for developing the triple M syndrome. Early recognition and initiation of appropriate treatment are crucial to improve outcomes in these life-threatening situations.

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