CASE REPORT

Nivolumab-induced Diaphragm Dysfunction: A Case Report

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Abstract

Nivolumab is increasingly used in the treatment of melanoma. However, its use is associated with potentially severe side effects and every organ system can be affected. A case is presented where nivolumab therapy resulted in severe diaphragm dysfunction. With nivolumab's increased use, these types of complications may become more common and every clinician should be alerted to its potential presence when a patient on nivolumab treatment presents with dyspnea. Ultrasound is a readily available method to assess for diaphragm dysfunction.

Keywords: Diaphragm ultrasound, Myositis, Nivolumab.

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Highlights

Severe diaphragm dysfunction; a rare complication of nivolumab therapy.

Introduction

Nivolumab, an immune checkpoint inhibitor, has led to substantial clinical benefit in the treatment of melanoma.[1] However, the use of this drug is associated with immune-related adverse events (irAEs) and every organ system can be affected.[2]

Myositis is an uncommon side effect with variable presentation ranging from isolated oculomotor involvement to generalized weakness.[2] Diagnosis can be confirmed by muscle biopsy showing infiltration by CD4+ and CD8+ T cells.[3]

Current treatment consists of discontinuing the offending agent and initiating corticosteroid therapy. Response to the treatment is usually prompt; however, in over half of patients, symptoms do not fully resolve.[4] Due to potentially life-threatening consequences, timely recognition is warranted.

We presented a case of nivolumab-induced myositis with concurrent myocarditis, thyroiditis, and hepatitis. Although therapeutic intervention was initiated mere days after symptom onset, with quick resolution of myalgia and normalization of laboratory parameters, there was severe, progressing diaphragm dysfunction that did not resolve, eventually warranting noninvasive ventilation at nighttime when the patient was discharged.

We used ultrasound to assess diaphragm function, which is readily available in the emergency department and intensive care units (ICUs) and, with proper training, allows for quick identification and follow-up of diaphragm dysfunction.[5–7]

Case Description

A 74-year-old man presented at the emergency department with worsening dyspnea and bilateral pain in his legs over the past days.

Patient history mentions chronic obstructive pulmonary disease (COPD) and treatment for stage IIIb melanoma for which therapy with nivolumab was initiated 2 weeks before presentation. There was no fever and no leukocytosis; C-reactive protein (CRP) was 18 mg/L (<8 mg/L); and chest computed tomography (CT) was unremarkable. Electrocardiogram (ECG) showed new-onset atrial fibrillation with rapid ventricular response (136/minute) and new right bundle branch block without signs of ischemia. High-sensitive troponin T levels were 747 ng/L (<14 ng/L) and NT-pro-BNP levels 194 ng/L (<376 ng/L). Quick-look ultrasound was performed and showed slightly reduced left ventricular performance, but image quality was poor in part due to the patient's rapid ventricular response.

Initial admission diagnosis was decompensated heart failure due to slightly reduced left ventricular function caused by nivolumab-induced myocarditis exacerbated by new-onset atrial fibrillation with rapid ventricular response. However, the patient's low NT-pro-BNP levels did not exactly fit the diagnosis. In addition, multiple organ systems appeared to be affected. There were signs of myositis, the most probable cause of the patient's leg pain [creatin kinase (CK) 8.230 U/L (<171 U/L), signs of thyroiditis thyroid stimulating hormone (TSH) <0.01 (0.3–4.5 mU/L); free thyroxine (T4) 51.5 pmol/L (12–22 pmol/L)], and hepatitis [alanine transaminase (ASAT) 416 U/L (<35 U/L); aspartate aminotransferase (ALAT) 362 U/L (<45 U/L); alkaline phosphatase (AF) 87 U/L (<115 U/L); gamma-glutamyl transpeptidase (GGT) 22 U/L (<55 U/L)]. Nivolumab was discontinued and prednisone 1 mg/kg/day initiated. In addition, treatment with thiamazol was started to treat the patient's hyperthyroidism and treatment with metoprolol to combat his atrial fibrillation. Echocardiography in sinus rhythm 2 days later showed near-normal left ventricular function and was otherwise unremarkable.

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However, the patient's condition deteriorated over the following 2 days. He became increasingly tachypneic and hypoxic and had trouble clearing secretions. Chest X-ray showed elevation of the right hemidiaphragm, not seen on admission. All laboratory parameters mentioned above were improving.

Four days after his initial admission, the patient was admitted to the ICU and intubated due to hypoxic respiratory failure. Over the next 5 days, he was treated successfully for pneumonia caused by *Staphylococcus aureus* and *Haemophilus influenzae* treated respectively with flucloxacillin and ciprofloxacin. His hypoxia resolved quickly due to frequent suctioning of secretions during the first day of antibiotic treatment.

Because of persistent hypercapnia, diaphragm ultrasound was performed, which showed paralysis of the right hemidiaphragm and severe paresis of the left hemidiaphragm, in addition to severe atrophy on both sides. Maximum inspiratory pressure was severely affected, while maximum expiratory pressure was normal.

Extensive neurology consultation, including electromyography, showed no evidence of neuromuscular disease other than mild ICU-acquired weakness and reduced conduction velocity of the left phrenic nerve.

The rapid deterioration of diaphragm function in this patient was most likely caused by nivolumab-induced myositis. Discontinuation of nivolumab and initiation of corticosteroid therapy resulted in resolution of his myocarditis, myositis, thyroiditis, and hepatitis. However, over the following weeks, despite recovery of extremity strength, there was no recovery of diaphragm function and patient was successfully set on nightly bilevel positive airway pressure (BiPAP) and discharged for rehabilitation.

A muscle biopsy was not performed because there was a clear temporal relationship between initiation of nivolumab therapy and symptom onset in addition to lack of an alternative diagnosis after extensive neurology consultation and corticosteroid therapy. Acquiring a diaphragm biopsy would not have altered our patient's treatment and may have posed a substantial risk.

Conclusion

Our case shows a severe, uncommon complication of nivolumab therapy. Due to its increased use, practitioners should be mindful of these potential complications and maintain a high degree of suspicion when patients on nivolumab treatment present with respiratory symptoms. Ultrasound of the diaphragm is a readily available, noninvasive test to diagnose diaphragm dysfunction and atrophy and, with proper training, can easily be performed on arrival in the emergency department and when a patient is admitted to an ICU.

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