Immunotherapy-associated complete heart block in a patient with NSCLC: A case report and literature review

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ABSTRACT

The role for PD-1/PD-L1 and CTLA-4 targeted immunotherapy is well outlined in the treatment of metastatic NSCLC. Increased survival benefit supports the use of these medications and the development of next-generation agents with improved efficacy and favorable side-effect profiles. The prevalence of immunotherapy-associated cardiotoxicity (IAC) has grown significantly over the past two years as awareness of this toxicity class has emerged. High-grade conduction disorders comprise a subset of cardiotoxicities with a high case fatality rate. We presented a case of suspected combination ipilimumab-nivolumab associated 3rd degree heart block. The onset of this event was 16 days after immunotherapy initiation. A literature review has suggested that over 75% of cases of cardiotoxicity are observed within the first 6 weeks. We present findings from an interrogation of the FDA Adverse Event Reporting System (FAERS) and provide clinical guidance for the early identification of high-risk patients.

1. Introduction

Immune checkpoint inhibitors (ICIs) are transformative agents in the field of immunotherapy. These medications have redefined treatment strategies for multiple indications, most notably for NSCLC. In 2015, Pembrolizumab was the first approved antibody targeting the programmed cell death protein 1 (PD-1) receptor in the treatment of NSCLC [1,2]. In subsequent years, atezolizumab, nivolumab, and ipilimumab were approved. Multiple studies have shown extended survival benefit with these new agents; most recently demonstrated with combination ipilimumab and nivolumab in CheckMate-227, independent of PD-L1 expression [3–5]. While effective therapeutically, a new toxicity class has emerged.

Immune-related adverse events (irAEs), notably pneumonitis, colitis, and endocrinopathies were first observed in clinical trials, but the recent recognition of immunotherapy-associated cardiotoxicity (IAC) is of growing concern [6,7]. Both myocarditis and supraventricular arrhythmia have been reported with increased prevalence in patients receiving immunotherapy, and infrequent reports of high-grade conduction disorders are associated with increased mortality [8–13]. Here, we present a rare case of complete heart block in a patient receiving combination ipilimumab and nivolumab.

2. Case presentation

A 78-year-old man with recently diagnosed metastatic ALK-negative, BRAF-positive NSCLC with histopathologic adenocarcinoma and 2% PD-L1 expression presented with subacute onset shortness of breath and feeling “shaky.” His medical comorbidities included, coronary artery disease (CAD), prior coronary artery bypass grafting (CABG), hypertension, diabetes mellitus (DM), chronic kidney disease (CKD), rheumatoid arthritis, and hypothyroidism. He underwent aortic valve replacement and CABG ten years prior. Home medications were valsartan, amiodarone, metoprolol tartrate, metformin, levothyroxine, aspirin, atorvastatin, and as-needed alprazolam. Although both metoprolol and amiodarone could affect atrioventricular (AV) node conduction, the patient was on these medications for over three years.

The patient was started on combination ipilimumab and nivolumab
15 days prior to admission and tolerated cycle one well. In addition, he reported worsening lower extremity swelling on presentation but denied lightheadedness, orthopnea, chest pain, or palpitations. The patient attributed these symptoms to underlying anxiety.

On examination, the patient was afebrile, normotensive, with a regular pulse of 63 bpm. He was anxious and tachypneic and was placed on 2 L supplemental oxygen. An EKG (Fig. 1A) showed sinus rhythm, left bundle branch block, and a gradually prolonging PR interval consistent with evolving heart block. There was no EKG for comparison. He had bilateral lower extremity edema and JVD with diminished breath sounds with evolving heart block. There was no EKG for comparison. He had bilateral lower extremity edema and JVD with diminished breath sounds in the left lower lung field. There were no skin changes or new lesions. Initial laboratory studies were notable for neutrophilic leukocytosis of 31.1 x10^9/L, stable normocytic anemia, potassium 5.9 mmol/L, BUN 52 mg/dL, and creatinine 1.8 mg/dL, at baseline. Initial troponin I was 1.36 (laboratory normal <0.30 ng/mL) and proBNP was 14,180 pg/mL. This was discussed with the cardiology service and attributed to type II NSTE MI complicated by known renal disease. A CT angiogram was negative for pulmonary embolism.

The troponin I remained elevated on the second day (range 1.10–2.18 ng/mL). He was asymptomatic but hyperkalemic to 6.0 mmol/L. Prior potassium levels during this hospitalization were serially between 5 and 6 mmol/L. At this point, an EKG was repeated (Fig. 1B) which revealed a new complete 3rd degree heart block and a junctional versus ventricular escape rhythm. A new right axis deviation was present. This was seen on two subsequent EKGs despite improvement of hyperkalemia. An echocardiogram performed the next day showed a left ventricular ejection fraction (LVEF) of 45% with hypokinesis of mid-anteroseptal and anterior wall segments. There was no valvulopathy or pericardial effusion.

The patient was deemed a poor surgical candidate due to his metastatic disease and comorbidities. He remained asymptomatic and, through shared decision-making, the patient and medical teams elected not to pursue emergent pacemaker placement. He was scheduled for an outpatient event monitor.

On hospital day three the patient was found in asystole. Despite several rounds of cardiopulmonary resuscitation, he unfortunately did not achieve return of spontaneous circulation. His family requested to stop further efforts and he expired.

3. Discussion

The exact prevalence of IACs remains unclear although compounding evidence suggests increased awareness of cardiotoxicity. A review of the WHO VigiBase found cardiac toxicities comprise 2,215 (2.09%) of 106,025 adverse drug reactions (ADRs) for six commonly used ICIs. Of these, nearly 7% were conduction disorders [13,14]. Our own interrogation of the FDA Adverse Event Reporting System (FAERS) is shown in Table 1. This demonstrates the high case fatality rate associated with high-grade heart block and myocarditis, which may present with conduction abnormalities as well.

The clinical significance is also in the time of onset of IAC from initiation of therapy. For immunotherapy associated myocarditis in particular, one study showed median onset of 17 days; another reported 34 days after starting ICI [10,15]. In a review of 101 cases reported to the VigiBase, 76% occurred in the first 6 weeks of therapy [16]. The onset of conduction disorders is less well defined but appears to follow a similar trend. Our case shows rapid onset of complete heart block on day 16 after starting combination ipilimumab-nivolumab. This therapeutic combination was recently found to have a 4.5-fold increase in cardiotoxicity compared with nivolumab alone [16]. A systematic literature review identified 99 cases of ICI-associated cardiotoxicity with mean age of 65 years. Of these, 45% were diagnosed with myocarditis and 12% with conduction disorders - this group carrying the highest case fatality rate, 55% in this series [17].

This case demonstrates the complexity of managing high-grade conduction disorders that develop in the setting of immune checkpoint inhibitor therapy. The nonspecific clinical manifestations of myocarditis make it difficult, in the absence of an endomyocardial biopsy, to rule out this inflammatory process as contributing to the heart block. The presence of several comorbid conditions should be considered. Hyperkalemia could have caused complete heart block. Our patient had low-grade hyperkalemia throughout the hospital course although this value did not reach greater than 6.0 mmol/L. In the absence of peaked T waves, sine waves, and normal P wave morphology on EKG it is less likely, though not impossible, that this mild hyperkalemia would cause a high-grade heart block particularly in a patient with CKD. The patient’s history of CAD requiring CABG supported the working diagnosis of type II NSTE MI as the etiology of the mild troponin elevation. Any direct cardiac tissue damage or inflammation was likely mild given the patient’s co-existent renal dysfunction with impaired renal clearance. It is possible that the patient had myocarditis-induced heart block, particularly given the propensity of myocarditis to affect the AV node. However, we hypothesize that the conduction disorder was a direct toxicity of the immunotherapeutic regimen given the time of onset relative to ICI therapy initiation. The low troponin elevation in the setting of CKD and CAD and the lack of characteristics hyperkalemic EKG changes making the other possible etiologies less likely.

In our patient’s case, emergent intervention with pacemaker placement was not absolutely indicated. His presenting symptoms of dyspnea and restlessness were non-specific and appeared incongruent with episodes of complete heart block. From a cardiac perspective, he was asymptomatic, and multiple advanced comorbidities precluded aggressive intervention during his hospitalization.

This case highlights three particular elements of surveillance and identification of IACs, specifically, conduction disorders. Complete atrioventricular dissociation, as with 3rd degree heart block, carries the highest morbidity and early identification of this sinister event is vital in management. This however remains a clinical challenge.

First, it is imperative to acquire a comprehensive history of cardiac risk-factors. The focus should be on ischemic injury, CAD or its equivalents (e.g. DM, CKD), arrhythmia, cardiomyopathy, pericardial disease, and, but not limited to, medication review with attention on nodal-blocking agents and duration of therapy. This further includes a history of primary, or drug-induced, infiltrative and autoimmune disorders contributing to pro-inflammatory states as was observed in our patient with mild rheumatoid arthritis [12,18]. Secondly, we advocate for consideration of serial biomarkers and EKG testing in the early weeks of therapy for high-risk patients. In one study, in cases reporting cardiac biomarkers, serum troponin I, creatine kinase (CK), and brain natriuretic peptide were elevated in 93%, 100%, and 100% of cases, respectively [17]. A second study identified elevated troponin in 94% of cases of myocarditis [15], at times in the absence of symptoms. Coupled with data regarding event onset and given increasing incidence and high case fatality rate of IACs, weekly troponin I, CK, and EKG may prove cost-effective and instrumental in early recognition of at-risk patients. Lastly, early evaluation with advanced diagnostic strategies may be helpful to identify early cardiotoxicity. This can be pursued if a positive biomarker or EKG evaluation is identified. An initial screen could be performed with a 2D-echocardiogram, a test that is sufficiently sensitive for the identification of wall-motion abnormalities and decreased systolic function, findings that may suggest asymptomatic myocarditis. If inconclusive, cardiac MRI may assist in the identification of tissue edema, hyperemia, or fibrosis albeit with variable sensitivity [19].

4. Conclusion

Immunotherapy-associated cardiac adverse events are more prevalent with the increased use of immunotherapeutic agents. Conduction disorders in particular often develop within 6 weeks of therapy initiation. Our case of an elderly gentleman with multiple cardiac risk factors developing complete heart block 16 days after starting ipilimumab-nivolumab combination therapy supports increased clinical vigilance
Fig. 1. EKG tracing captures evolving complete heart block
Sequential electrocardiogram (EKG) tracings in our patient with likely immunotherapy-associated cardiotoxicity as manifested by a complete heart block. The first tracing is from admission ($K = 5.9$ mmol/L) and captures atrioventricular dissociation (A), the second at the time of potassium level = 6.0 mmol/L with a 3rd degree heart block with an escape rhythm and new right axis deviation (B), and last on the following day showing persistence of the 3rd degree AV block despite lower potassium ($K = 5.6$ mmol/L)(C). Atrial impulses identified with thin black arrows, ventricular complex with thick black arrows, and new right axis deviation circled.
Regimens and combination ipilimumab/nivolumab. FDA AERS updated through 6/30/2020. Both complete heart block and myocarditis events carry a high case fatality rate particularly for pembrolizumab containing regimens and combination ipilimumab/nivolumab.

Future studies directed at the prospective identification of high-risk patients for IAC. Further studies are needed to determine the optimal timing, duration, and intensity of immunosuppressive therapy for IAC. 

Table 1: Overall cardiac adverse events by treatment regimen with complete heart block, and myocarditis events. Data secured from the FDA AERS database.

| Cardiac Adverse Event | Pembrolizumab | Iplimumab + Nivolumab | Atezolizumab | Durvalumab | Bevacizumab |
|-----------------------|---------------|------------------------|--------------|------------|------------|
| Cardiac Disorder, Total n | 2303 | 3217 | 586 | 198 | 4881 |
| Death a n (%) | 420 (35%) | 1121 (35%) | 163 (28%) | 76 (38%) | 1458 (30%) |
| Conduction Disorder b n | 56 | 105 | 15 | 5 | 30 |
| Death n (%) | 18 (32%) | 39 (37%) | 2 (13%) | 0 | 7 (18%) |
| Complete Heart Block n | 37 | 49 | 8 | 4 | 13 |
| Death n (%) | 13 (35%) | 18 (37%) | 1 (13%) | 0 | 3 (23%) |
| Myocarditis n | 234 | 506 | 74 | 23 | 32 |
| Death n (%) | 103 (44%) | 216 (43%) | 20 (27%) | 12 (52%) | 13 (41%) |

a Cases resulting in patient death without investigator assessment of association to immunotherapy.

Table 1 continued...

| Immunotherapeutic Agent/Regimen | Immunotherapeutic Agent/Regimen |
|--------------------------------|--------------------------------|
| Pembrolizumab | Iplimumab + Nivolumab |
| Atezolizumab | Durvalumab |
| Bevacizumab | Pembrolizumab Ipilimumab |
| Nivolumab Atezolizumab Durvalumab Bevacizumab | Pembrolizumab Ipilimumab |

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