Evolution of a Complete Heart Block: Insight into a Rare Side Effect of Immunotherapy

Alexander Vartanov MD1, Aditi Kalotra MD1, Jasmine Varughese DO1, Shovendra Gautam MD2, Wylie Hosmer MD3, Sean Kandel DO1,2

1 Department of Medicine, University of Connecticut School of Medicine 2 Department of Medicine, Hospital of Central Connecticut 3 Department of Medical Oncology, Hartford Healthcare

Introduction

Immune checkpoint inhibitors (ICIs) have redefined treatment strategies for multiple indications: melanoma, RCC, and most notably NSCLC. Pembrolizumab was the first approved antibody targeting the programmed cell death protein (PD-1) receptor in treatment of NSCLC (2015) [1]. Later, atezolizumab, nivolumab, and ipilimumab (anti-CTLA-4) were approved.

Studies have shown extended survival benefit with combination ipilimumab and nivolumab vs chemotherapy in CheckMate-227 (17.1 vs 14.9 months, p=0.007), independent of PD-L1 expression [2,3].

Immune-related adverse effects (irAEs), notably pneumonitis, colitis, dermatitis, and hepatotoxicity noted in clinical trials. A new class has emerged: immunotherapy-associated cardiotoxicity (IAC).

Myocarditis and supraventricular arrhythmias have been reported with increasing prevalence, with infrequent reports of high-grade conduction disorders [4-6]. Here, we present a rare case of rapid-onset complete heart block in a patient receiving combination ipilimumab and nivolumab.

Case Presentation

78-year-old male with recently diagnosed metastatic NSCLC presented with shortness of breath and feeling “shaky.” He denied lightheadedness, orthopnea, chest pain, or palpitations.

Medical history: CAD, HTN, DM, CKD stage 3, RA, hypothyroidism, aceric valve replacement and CABG 10 years ago.

Home medications: amiodopine, metoprolol tartrate, metformin, levothyroxine, aspirin, atorvastatin, alprazolam, ipilimumab and nivolumab (started 15 days prior, tolerated cycle 1 well). CCB and BB unchanged for 3 years.

Physical exam: afebrile, normotensive, heart rate regular at 63 beats/min, tachypneic and placed on 2L supplemental oxygen. JVD, lower lung field. No rash, neurologically intact.

Labs/testing: WBC 31.1 with 82% neutrophils, Hgb 9.0 (at baseline), potassium 5.9, BUN 52, creatinine 1.8 (at baseline), Mg 1.8, troponin I 1.36 (normal <0.30 ng/mL, trend in figure 1), proBNP 14,180 pg/mL. An EKG showed sinus rhythm, LBBB, gradually prolonging PR interval consistent with evolving heart block (Figure 2A, arrows). No prior EKG for comparison. CTA negative for PE.

Cardiomyopathy was considered for elevated troponin, attributed to type II NSTEMI. Troponin I remained elevated the following day (range 1.10-2.18 ng/mL). Potassium serially 5-6 mmol/L, Cr stable. Repeat EKG showed new complete heart block and a junctional vs ventricular escape rhythm with a new right axis deviation (Figure 2B-C). An echocardiogram showed a decreased LVEF of 45% with hypokinesis of the mid-antenorectal and anterior wall segments. No prior.

Symptomatically improved, no chest pain. Deemed a poor surgical candidate due to metastatic disease and comorbidities. Through shared decision making, elected not to pursue emergent pacemaker placement. Planned was for outpatient event monitor and consideration of non-emergent pacemaker.

On hospital day three, patient was found in asystole. Did not achieve ROSC after 10 minutes CPR. Emergency median sternotomy, pericardial laceration found and closed. Ablated IACs and revascularized right coronary artery. The patient died. Multidisciplinary collaboration: oncology, cardiology, and internal medicine.

Discussion

IACs are a growing concern in treatment of multiple malignancies. Internists and primary care providers must be aware of this toxicity class.

Our query of the FDA Adverse Event Reporting System (FAERS) is shown below. Myocarditis and conduction disorders carry highest case fatality rate.

Onset is typically early after initiation of immunotherapy: in one study 17 days, in another 34 days [5,7]. Our case: day 16. Of 101 cases reported to VigilBase, 76% occurred in first 6 weeks [8].

Equally important: maintaining a differential of causes of high-grade heart block. We considered ACS, PE, hyperkalemia in setting of CKD, myocarditis, and medication induced.

Early identification of at-risk patients. Consider risk factors (e.g. CAD, DM, arrhythmias), low threshold to monitor with biomarkers/serial EKGs.

Multidisciplinary collaboration: oncology, cardiology, and internal medicine.

Figures

Figure 1 (above). Persistent troponin elevation during 3-day hospital course. Echocardiogram consistent type II NSTEMI with impaired clearance due to CKD vs immunotherapy associated myocarditis.

Figure 2 (right). 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 new right axis deviation circled in red. The second tracing is from admission (K=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). a waves identified with black arrow, new right axis deviation circled in yellow.

References