

CLINICAL CASE CHALLENGES

Sinus Arrest and Cardiogenic Shock Precipitated by Immune Checkpoint Inhibitors



Kris Kumar, DO, MSc, Ryle Przybylowicz, MD, Babak Nazer, MD, Eric C. Stecker, MD, Charles A. Henrikson, MD, Ahmad Masri, MD, MS

A 60-year-old man presented with a chief complaint of lightheadedness and dizziness. Patient reported progressive fatigue throughout the prior 24 h causing him to lose consciousness and call emergency medical services. On initial evaluation, the patient was afebrile and saturating well on room air, bradycardic to 30 beats/min with a blood pressure of 84/42 mm Hg. Examination revealed bradycardia, no murmurs, rubs, or gallops, and a jugular venous pulsation that was elevated to 16 cm H₂O, along with 2+ lower extremity pitting edema.

His past medical history was significant for a history of metastatic renal clear cell carcinoma (RCC) status post-unilateral nephrectomy status post-nivolumab cycle 5, hypertension, diabetes mellitus, and chronic kidney disease. The RCC diagnosis was made 2 years before. The patient was started on pazopanib, which was discontinued following development of proteinuria, leading to initiation of nivolumab in the setting of worsening metastatic lung disease. Three months before presentation, the patient presented to the emergency department with abdominal pain in the setting of gross hematuria (hemoglobin 10.2 g/dl, reference range 13 to 17 g/dl), and was noted to have a non-ST-segment elevation myocardial infarction (NSTEMI) with normal ejection fraction and no wall motion abnormalities (WMAs). Angiography was not pursued at that hospitalization due to low-risk transthoracic echocardiogram (TTE) features, acute kidney injury, and acute blood loss was felt to be the cause of his type II myocardial infarction event.

Initial differential diagnosis of the index presentation included acute coronary syndrome, immune checkpoint inhibitor (ICI) myocarditis also affecting the conduction system, and idiopathic high-grade atrioventricular block. Electrocardiogram (ECG) on arrival at the emergency department revealed sinus arrest with a wide complex escape rhythm with a QRS morphology of right bundle branch block (RBBB) and left anterior fascicular block (LAFB) (Figure 1). Review of prior ECGs up to 10 years before showed a history of normal sinus rhythm with RBBB and LAFB. A bedside TTE revealed no pericardial effusion but a severely reduced left ventricular ejection fraction <20% without regional WMAs. Initial troponin I was 3.75 ng/ml (reference range <0.80 ng/ml), NT-proBNP was 176 pg/ml (reference range <125 pg/ml) and creatinine was elevated to 3.19 mg/dl (reference range 0.70 to 1.30 mg/dl) with a baseline of 2.2 mg/dl. While in the emergency department, atropine was given in consecutive escalating doses with no effect and epinephrine started in the setting of bradycardia and systemic hypotension. The patient was subsequently admitted to the cardiovascular intensive care unit for further management.

Acute coronary syndrome was considered as part of the differential diagnosis in the setting of previous NSTEMI and potential for myocardial infarction involving the proximal right coronary artery lesion that supplied the conduction system and sinus node. However, without active chest pain or ECG evidence of ischemia, and given acute kidney injury in the setting of RCC with unilateral kidney, coronary angiography was deferred. In addition, with no WMAs noted on TTE, alternative causes for symptoms were explored. Due to symptomatic

From the Knight Cardiovascular Institute, Oregon Health and Science University, Portland, Oregon, USA.

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bradycardia with sinus arrest and profound hypotension, a transvenous pacemaker was inserted via the right internal jugular vein, and the patient was paced at 70 beats/min. After 3 h, an attempt was made to lower the pacemaker backup rate; however, the patient once again became symptomatic, bradycardic, and hypotensive with sinus arrest and a slow escape rhythm.

Shortly thereafter, the thyroid-stimulating hormone (TSH) level returned at 105 mIU/l (reference range 0.46 to 5.56 mIU/l), with a serum free T4 (FT4) of 0.3 ng/dl (reference range 0.6 to 1.2 ng/dl). Review of records before initiation of ICI showed a TSH of 3.05 mIU/l and FT4 of 1.2 ng/dl with normal levels 6 weeks before presentation. There was no evidence of ICI toxicity to other organ systems because the patient was without respiratory distress or pneumonitis, the liver panel showed no abnormalities, and the patient had no symptoms of gastrointestinal toxicity or gross neurological deficits. With severe hypothyroidism confirmed, both by laboratory investigations and physical examination, a unifying explanation for sinus node dysfunction was established.

As the patient was being transvenously paced, cardiac magnetic resonance imaging was not obtained. Coronary angiography was deferred at this juncture because the NSTEMI was considered to be type II myocardial infarction precipitated by prolonged hypotension as a result of symptomatic bradycardia and not acute plaque rupture, along with the absence of any ECG evidence of ischemia or chest pain. An urgent formal TTE while paced revealed a left ventricular ejection fraction of 55%, moderate concentric left ventricular hypertrophy, and impaired relaxation.

The temporary transvenous pacemaker was subsequently replaced with a left internal jugular active fixation lead at 70 beats/min using ventricular demand pacing to ensure consistent and reliable pacing was achieved.

Before thyroid replacement, a cosyntropin stimulation test was performed and found to be negative, ruling out adrenal insufficiency and need for concurrent corticosteroid treatment. Hypophysitis was considered, but in the setting of slight volume overload, normal sodium of 138 mmol/l, and normal cortisol levels, this was considered less likely a cause of the patient's presentation, and therefore pituitary magnetic resonance imaging and gonadotropin hormone evaluation were not pursued. In consultation with endocrinology, intravenous (IV) levothyroxine was then administered due to a better absorption and pharmacokinetic and pharmacodynamic profile versus the oral formulation at 300 µg IV and 200 µg IV on consecutive days. FT4 improved to 0.7 ng/dl, and the patient was then continued on levothyroxine 200 mg orally per day with serial monitoring of both TSH and FT4 levels while assessing the need for permanent pacemaker implantation.

Electrophysiological response to thyroid replacement was concurrently assessed during the inpatient hospitalization. The patient remained paced initially for the first 2 days due to a lack of normal sinus node activity when the pacemaker was decreased from 70 beats/min. On day 3 of the hospitalization, the patient had an escape rhythm at 40 beats/min, and the backup rate was decreased to 35 beats/min. Seven days into the hospitalization, the patient demonstrated improvement in sinus node function with a heart rate in the mid-50s, without pauses and with stable hemodynamics. The patient also had a positive chronotropic response to 70 beats/min while ambulating. The active fixation lead was subsequently turned off and removed. The ECG following removal of the pacemaker revealed sinus bradycardia at 50 beats/min and a prolonged PR interval of 300 ms, along with known RBBB and LAFB.

The patient's symptoms throughout the hospital course dramatically improved. Facial and pre-tibial myxedema decreased, and the patient's affect changed to the point of the patient stating that he felt the best he had since before his diagnosis of RCC, and that a "cloud" had cleared in his head, which he did not realize was due to something beyond his cancer diagnosis. FT4 on discharge was noted to be 0.8 ng/dl with a TSH of 75.8 mIU/l and creatinine improved to baseline levels. Due to clinical improvement, a permanent pacemaker was not indicated, and the patient was discharged on levothyroxine 200 micrograms daily. Creatinine improved to 2.2 mg/dl before discharge and remained stable during follow-up.

At 1-month clinic follow-up, the patient was without symptoms related to sinus arrest and hypothyroidism. Thyroid function on follow-up lab work remained in the normal range, with a FT4 of 1.2 ng/dl and TSH of 15.8 mIU/l. A 30-day Holter monitor revealed an average heart rate of 60 beats/min with and without ectopy, pauses, and bradycardic or arrhythmic events, and the ECG during follow-up showed return of normal sinus rhythm, with known RBBB and LAFB.

ABBREVIATIONS AND ACRONYMS

ECG = electrocardiogram

FT4 = free T4

ICI = immune checkpoint inhibitor

irAE = immune-related adverse event

IV = intravenous

LAFB = left anterior fascicular block

NSTEMI = non-ST-segment elevation myocardial infarction

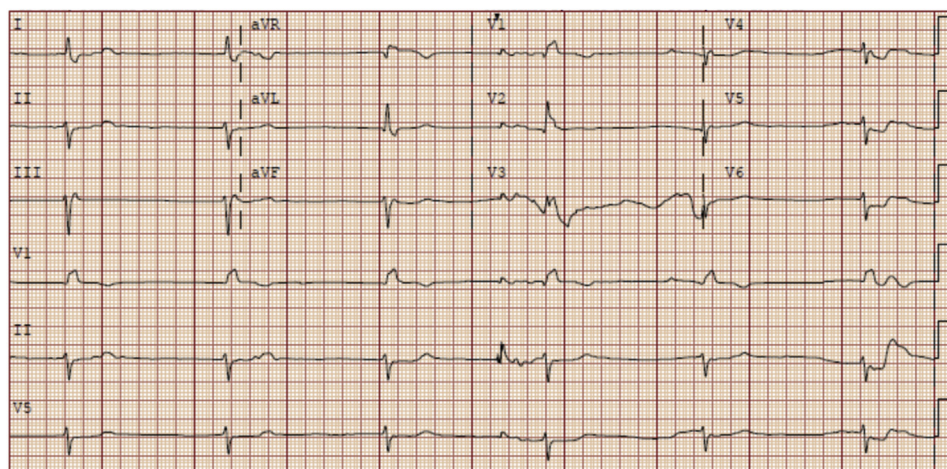
RBBB = right bundle branch block

RCC = renal cell carcinoma

TSH = thyroid-stimulating hormone

TTE = transthoracic echocardiogram

WMA = wall motion abnormality

FIGURE 1 Electrocardiogram on Presentation

Initial electrocardiogram on arrival to emergency department showing sinus arrest with a wide complex escape rhythm with a QRS morphology of right bundle branch and left anterior fascicular blocks.

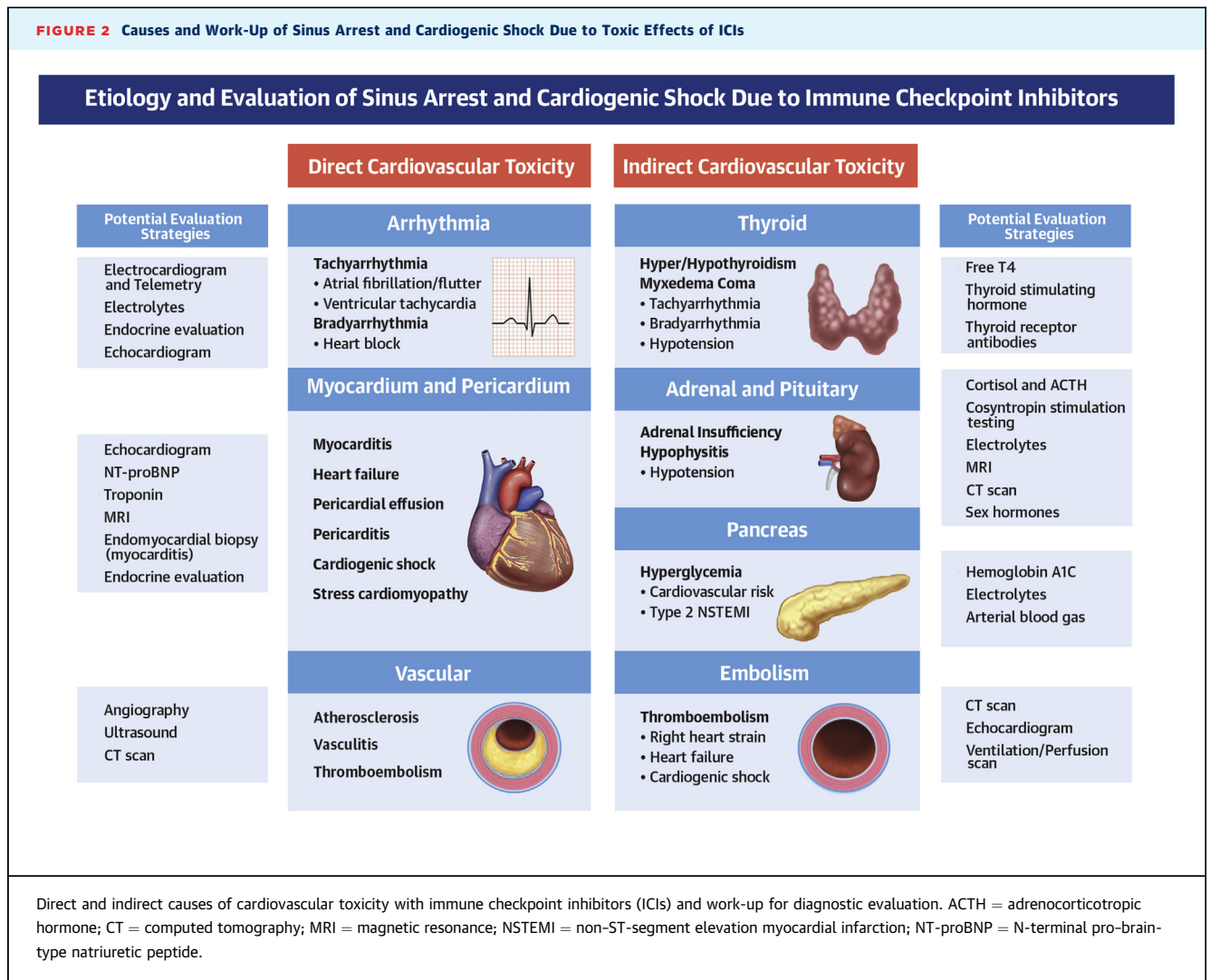
ICIs are a class of oncological therapeutic agents that act on inhibitory pathways by stimulation of the immune response system for antitumor effects through monoclonal antibodies that act upon programmed cell death protein-1 (PD-1) or programmed cell death-ligand 1 (PD-L1) or cytotoxic T lymphocyte associated protein 4 (CTLA-4) (1). This immunomodulation, although effective in the inhibition of tumor proliferation and killing of tumor cells, can also cause immune-related adverse events (irAEs) on a variety of organ systems throughout the body, including the cardiovascular, renal, and endocrine systems (2) (Figure 2). Myocarditis was first recognized (3), but subsequent studies have shown that the pericardium, vascular system, and the electrical conduction system can also be adversely affected, with 1 case of heart block noted in the IMpower133 trial (A Study of Carboplatin Plus Etoposide With or Without Atezolizumab in Participants With Untreated Extensive-Stage [ES] Small Cell Lung Cancer [SCLC]) of atezolizumab, a PD-L1 antibody used in the treatment of small cell lung cancer (4,5).

ICIs can also be a cause of indirect cardiovascular toxicity as a result of endocrinopathies. Endocrinopathy due to ICIs have been reported in up to 5% of patients, with hypothyroidism in up to 8% of patients through a mechanism that is thought to be autoimmune in nature due to increased immunogenicity driven by the therapeutics (6). IrAEs causing endocrinopathy, including both hyper- and hypothyroidism, have a wide range of effects on the cardiovascular system including effects on conduction, contraction, and rate. Current National Comprehensive Cancer Network and American Society of Clinical Oncology clinical practice guidelines recommend baseline and routine monitoring of TSH and FT4 every 4 to 6 weeks while on ICI therapy (7). IrAEs can also cause adrenal insufficiency which can result in profound hypotension. As a result, if endocrinopathy due to thyroid disorder is suspected, adrenal insufficiency and hypophysitis should be considered and excluded (7). In myxedema, the effect on the sinoatrial and atrioventricular nodes resulting in bradycardia is postulated to be due to edema, fibrosis, and mucin deposition compressing the conduction apparatus, with reversal of edema following normalization of circulating thyroid hormone levels (8). Treatment of the underlying thyroid imbalance has been shown to improve conduction in case reports (9,10).

Here, we report a case of ICI-induced severe hypothyroidism leading to sinus node dysfunction and cardiogenic shock presentation. This particular case required the exclusion of potential myocarditis and pericardial disease, and prompt attention to other irAEs that may have caused symptoms.

ICIs have a wide variety of cardiovascular side effects (Figure 2) and should be understood by clinicians due to the increased use of this class of medications. This case demonstrates a reported adverse effect of this class of medications, indirect cardiotoxicity induced via severe hypothyroidism leading to sinus arrest with subsequent cardiogenic shock requiring transvenous pacing, which completely resolved following administration

FIGURE 2 Causes and Work-Up of Sinus Arrest and Cardiogenic Shock Due to Toxic Effects of ICIs



of thyroid replacement. Awareness of both direct and indirect side effects of medical therapeutics is essential to providing comprehensive medical care for patients with complex, noncardiac primary diagnoses.

ADDRESS FOR CORRESPONDENCE: Dr. Ahmad Masri, Knight Cardiovascular Institute, Oregon Health & Science University, UHN-62, 3181 Southwest Sam Jackson Park Road, Portland, Oregon 97239. E-mail: masria@ohsu.edu. Twitter: [@MasriAhmadMD](https://twitter.com/MasriAhmadMD), [@B_Naz_MD](https://twitter.com/B_Naz_MD), [@OHSUCardFellow](https://twitter.com/OHSUCardFellow), [@OHSUCardio](https://twitter.com/OHSUCardio).

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