Penpulimab-induced complete atrioventricular block in a patient with metastatic renal cancer

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Introduction

Immune checkpoint inhibitor (ICI) is a novel antitumor therapy that specifically enhances T-cell immune response by recognizing and inhibiting programmed cell death protein-1 (PD-1), PD-1 ligand, or cytotoxic T-lymphocyte–associated antigen 4, and has revolutionized the therapeutic landscape of various malignancies.[1,2] However, this robust antitumor immune response can also lead to a series of side effects, such as skin lesions, hepatitis, and colitis.[3–5] Penpulimab is a newly developed anti-PD-1 monoclonal antibody that eliminates Fc-mediated effector functions, and potentially poses a lower risk of immune-related side effects.[6] Here, we report the first case of atrioventricular (AV) block caused by penpulimab infusion and summarize the characteristics and prognosis of ICI-induced heart block.

KEY TEACHING POINTS

- Immune checkpoint inhibitor (ICI)-induced atrioventricular block is a rare, fatal, and refractory cardiovascular adverse event.
- It has a close association with ICI-related myocarditis, but can also be an isolated cardiotoxicity.
- The onset of this side effect ranges from 2 weeks to 12 weeks post ICI treatment; therefore close cardiac monitoring after ICI infusion is of great importance.
- Multidisciplinary cooperation including cardiology, oncology, and cardio-oncology will contribute to the adequate management of this rare side effect.

Case report

A 68-year-old woman was referred to our hospital owing to mild fatigue. She had a medical history of stage IV right renal pelvis transitional cell carcinoma metastatic to the right sacrum. Six weeks ago, she began to receive intravenous penpulimab infusion with the dosing protocol of 200 mg, 3 weeks apart. Her electrocardiogram (ECG, Figure 1) before penpulimab treatment revealed normal AV conduction and serum cardiac biomarkers showed no abnormalities. On examination, her vital signs were normal: blood pressure, 126/57 mm Hg; heart rate, 56 beats per minute (bpm); body temperature, 36.2°C. Neurological examination and cardiorespiratory auscultation were unremarkable.

Her ECG revealed complete AV block with a junctional escape rhythm of 57 bpm, sinus tachycardia with an atrial rate of 111 bpm, incomplete right bundle branch block, and symmetrical T-wave inversions (Figure 2). Serum tests reported elevated troponin I of 1.01 ng/mL (normal range: 0–0.11 ng/mL), creatine kinase of 474 U/L (normal range: 24–195 U/L), and creatine kinase MB of 35 U/L (normal range: 1.0–25.0 U/L). Her electrolytes and thyroid function were within normal limits. Transthoracic echocardiography revealed no structural heart disease. Computed tomographic angiography showed no stenosis in coronary arteries. Owing to claustrophobia, she refused cardiac magnetic resonance imaging examination.

Considering the new-onset conduction abnormality after ICI infusion and no evidence of coronary stenosis, the diagnosis of penpulimab-induced myocarditis and complete heart block was made. She was given immunosuppressive therapy with initial high-dose methylprednisolone at 500 mg daily for 3 days and then the dose gradually decreased. Since

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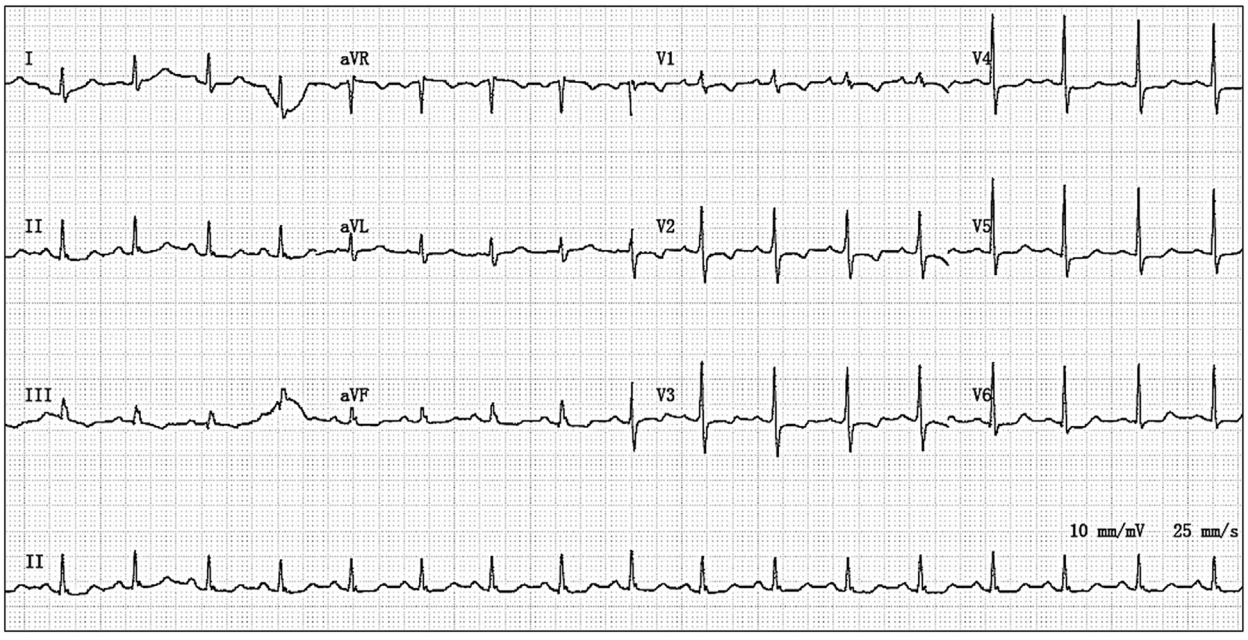

Figure 1 Twelve-lead electrocardiogram before immune checkpoint inhibitor infusion showed sinus tachycardia with normal atrioventricular conduction.

the Holter test showed a stable and fast junctional escape rhythm (average 50 bpm, maximal 60 bpm, and minimal 40 bpm), she had not implanted the temporary pacemaker during hospitalization. The cardiac biomarkers normalized within 1 week and the complaint of fatigue was completely relieved after 2 weeks' treatment. She was discharged home with no pacemaker. After 4-month follow-up, the T-wave inversion in the ECG partially recovered, while the complete AV block remained (Figure 3). Owing to financial considerations, she refused the suggestion of permanent pacemaker implantation.

We conducted an extensive search for studies of ICI-induced AV block indexed in Medline, Embase, and Cochrane Library. The keywords included "immune checkpoint inhibitor," "atezolizumab," "avelumab," "camrelizumab," "cemiplimab," "durvalumab," "ipilimumab," "nivolumab," "pembrolizumab," "penpulimab," "toripalimab," "atrioventricular block," and "heart block." Reference lists of relevant articles were also reviewed. According to our search, between 2010 and 2022, 16 case reports reported this side effect.[7–22]

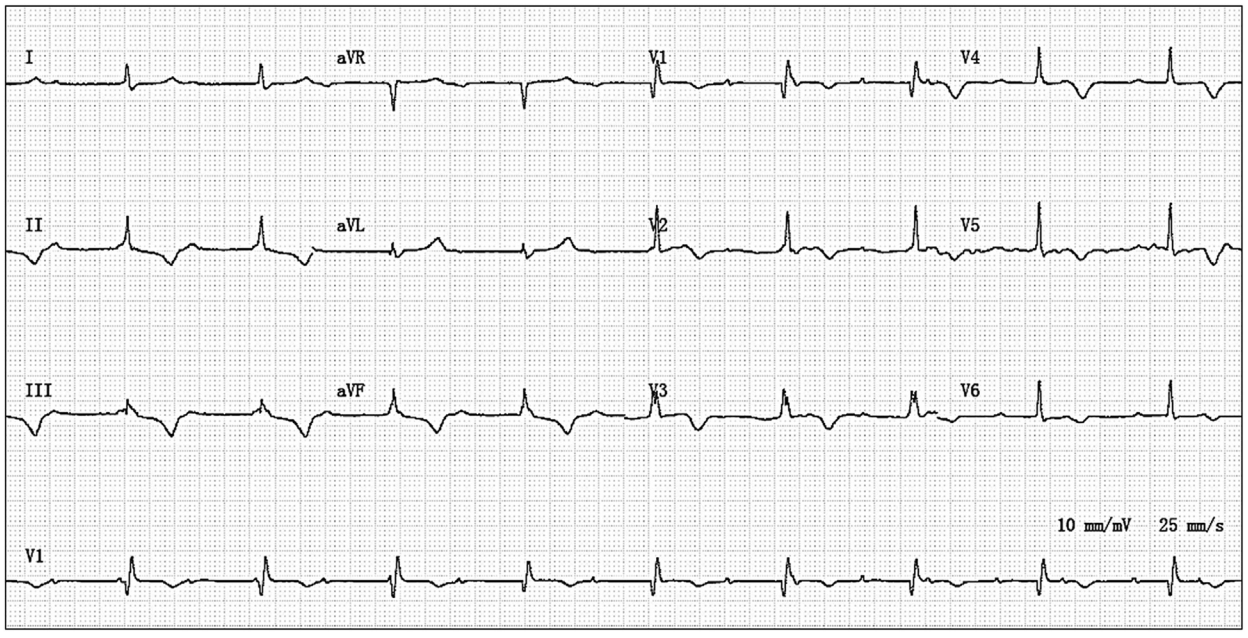

Figure 2 Twelve-lead electrocardiogram on admission showed sinus tachycardia, complete atrioventricular block, junctional escape rhythm, incomplete right bundle branch block, and T-wave inversion in lateral and inferior leads.

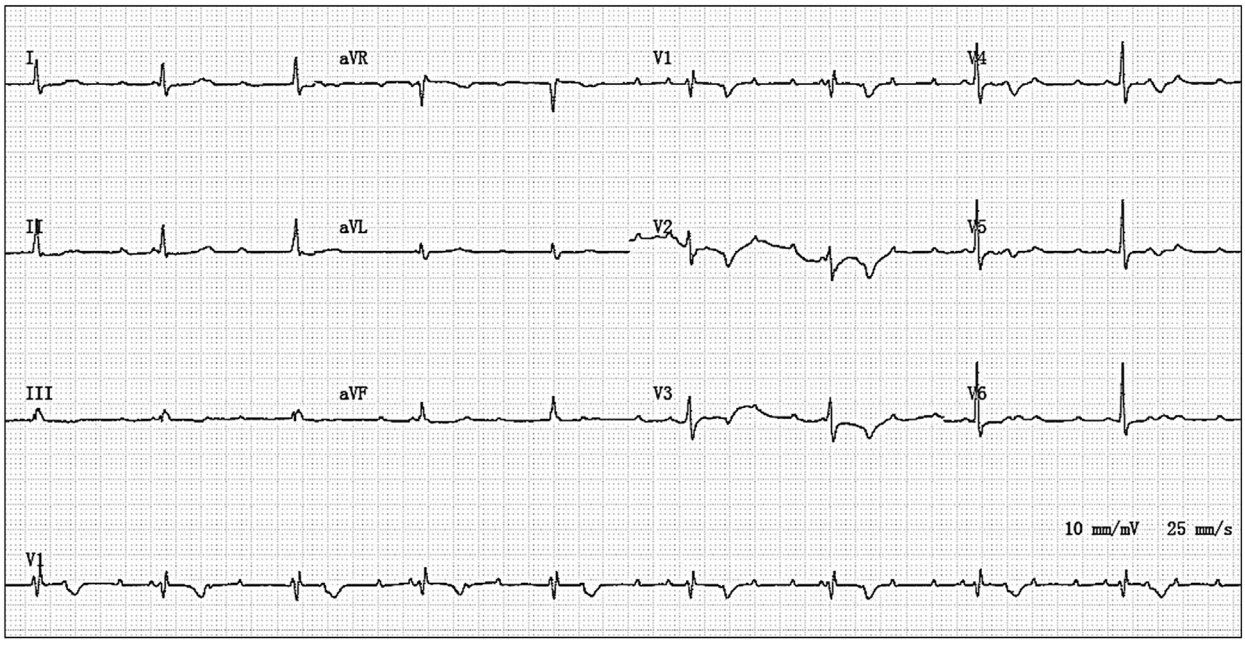

Figure 3 Twelve-lead electrocardiogram at 4-month follow-up showed complete atrioventricular block with new-onset atrial tachycardia.

Table 1 summarizes the case reports and our present case. Ages ranged from 47 to 88 years, with a median of 66.5 years old, and 61% of the patients were male. Five patients (28%) received nivolumab, 5 (28%) nivolumab plus ipilimumab, 5 (26%) pembrolizumab, 1 (6%) ipilimumab, 1 (6%) toripalimab, and 1 (6%) penpulimab. The clinical onset of AV block post-ICI treatment ranged from 13 to 90 days, with a median of 18.5 days. Sixteen patients (89%) had concomitant myocarditis and all received steroid treatment. Fifteen patients (83%) received cardiac pacing, of whom 7 implanted a permanent pacemaker, 1 inserted an implantable cardioverter-defibrillator owing to frequent ventricular tachycardia, and 1 received a cardiac resynchronization therapy because of reduced cardiac function (left ventricular ejection fraction: 31%). Eight patients (44%) died owing to immune-related complications. Among the 10 surviving patients, 3 restored the normal AV conduction, 3 maintained AV block, and the remaining 4 had not reported the conduction status. Compared with the surviving patients, those who died seemed to have the earlier presence of cardiac conduction abnormalities (median time 14.5 days vs 21.0 days).

Discussion

Penpulimab is a newly developed anti-PD-1 agent with the advantage of fewer side effects owing to its reduction of antibody-dependent cell-mediated cytotoxicity. To our knowledge, this is the first case report of penpulimab-induced myocarditis and complete AV block. Different from previous reports, our patients presented with significant conduction system abnormality with relatively slight myocardial injury. In addition, although this patient showed no improvement in complete heart block and refused pacemaker implantation, her prognosis was relatively good and she had no occurrence of cardiovascular discomforts during follow-up.

Over the past decade, ICIs have changed cancer therapy. Paralleled with its increased use, the recognition of its side effects has also improved.[23] Cardiac conduction system involvement is a very rare complication that is usually associated with immune-related myocarditis. According to our pooled data, 90% of such cases coexisted with myocarditis. A retrospective analysis from China revealed that immune-related myocarditis occurred in 1.06% of the study population, of whom one-third were complicated with heart block.[24] The mechanism for ICI-induced conduction disturbance remains unclear. It is thought to be a consequence of autoimmune-mediated inflammation in the cardiac conduction system.[25] In the report by Portolés Hernandez and colleagues,[17] endocardial biopsy demonstrated significant left ventricular lymphocytic infiltration after pembrolizumab infusion. Another multicenter study found that 40% of ICI-related myocarditis encroached upon the conduction system and affected the normal AV conduction.[26]

Interestingly, our patient presented with significant AV conduction abnormality while her cardiac biomarkers and systolic function showed slight changes, suggesting that conduction system disturbance may also be the direct cardiotoxicity of ICI treatment rather than a secondary manifestation of severe immune-related myocarditis. Similarly, in Oda and colleagues' case report,[16] a male patient who received nivolumab for malignant melanoma developed second-degree AV block with no evidence of myocarditis. It was unclear why these patients primarily exhibited conduction system abnormalities, but they seemed to have a better prognosis than those with significant myocarditis.

The median time from starting ICI infusion to exhibiting AV block was reported to be 18.5 days, and most cases

Table 1 Literature review of case reports and case series of immune checkpoint inhibitor–induced atrioventricular block

Reference	Age/sex	Tumor	Therapy	Onset day post ICI dose	ECG[†]	Myocarditis	Cardiac pacing	Outcome
Behling et al[7]	63/M	Melanoma	Nivolumab	20	3° AVB	Yes	TPM	Death
Berg et al[8]	66/M	Leukemia	Ipilimumab	14	3° AVB	Yes	TPM	Death
Bukamur et al[9]	88/F	Lung cancer	Nivolumab	14	3° AVB	Yes	TPM+PPM	Survival (remained AVB)
Jang et al[10]	60/M	Renal cancer	Pembrolizumab	21	3° AVB	Yes	PPM	Death
Jespersen et al[11]	57/M	Renal cancer	Nivolumab + ipilimumab	14	3° AVB	Yes	TPM+ICD	Survival
Johnson et al[12]	65/F	Melanoma	Nivolumab + ipilimumab	13	3° AVB	Yes	No	Death
Johnson et al[12]	63/M	Melanoma	Nivolumab + ipilimumab	15	3°AVB	Yes	TPM	Death
Katsume et al[13]	73/M	Lung cancer	Pembrolizumab	16	3° AVB	Yes	TPM+PPM	Survival (restored AVC)
Khan et al[14]	67/F	Lung cancer	Pembrolizumab	21	3° AVB	No	TPM+PPM	Survival
Luo et al[15]	47/M	Thymoma	Toripalimab	28	3° AVB	Yes	TPM	Survival (restored AVC)
Oda et al[16]	85/M	Melanoma	Nivolumab	90	2° AVB	No	PPM	Survival
Portolés et al[17]	48/F	Thymoma	Pembrolizumab	14	3° AVB	Yes	TPM+PPM	Death
Prevel et al[18]	80/M	Lung cancer	Nivolumab	48	3° AVB	Yes	TPM	Death
Szuchan et al[19]	70/F	Thymoma	Pembrolizumab	21	3° AVB	Yes	TPM+PPM	Survival
Tan et al[20]	74/M	Lung cancer	Nivolumab	17	3° AVB	Yes	TPM+CRT-P	Survival (remained AVB)
Velez et al[21]	69/F	Skin cancer	Nivolumab + ipilimumab	13	3° AVB	Yes	TPM	Death
Yanase et al[22]	59/M	Renal cancer	Nivolumab + ipilimumab	21	3° AVB	Yes	No	Survival (restored AVC)
Present case	68/F	Renal cancer	Penpulimab	42	3° AVB	Yes	No	Survival (remained AVB)

AVB = atrioventricular block; AVC = atrioventricular conduction; CRT-P = cardiac resynchronization therapy-pacing; ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; ICI = immune checkpoint inhibitor; MG = myasthenia gravis; PPM = permanent pacemaker; TPM = temporal pacemaker.
[†]Results indicate degree of AVB (2° = second-degree; 3° = third-degree).

occurred after the initial 2 infusions. Patients with early presence of conduction involvement (as early as 2 weeks) usually had significant immune-induced multiple organ dysfunctions.[8,10,21] These patients had worse prognoses and always required permanent cardiac pacing. Notably, late-onset AV block cases had also been reported in the clinic. In the report by Prevel and colleagues,[18] the patient was complicated with AV block 48 days post initial ICI administration. Thus, for patients receiving ICI treatment, close cardiac monitoring before, during, and after ICI infusion is of great importance to detect this lethal cardiovascular adverse event, especially in outpatient chemotherapy clinics.

Our pooled data showed that ICI-induced AV block was usually refractory and only 3 reported cases finally recovered normal conduction.[13,15,22] Current treatment suggestions for this side effect include the cessation of ICI infusion, the use of immunosuppression to alleviate the concomitant myocarditis, and the insertion of a pacemaker.[27] However, these strategies were empiric and absent of tests in any prospective study. In the present case, the patient was given early methylprednisolone intervention for her immune-related myocarditis and her abnormal cardiac biomarkers and T-wave changes in ECG had been well improved, while the conduction abnormality remained even after a 4-month follow-up. Benefiting from her stable escape rhythm and adequate heartbeat rate, the patient postponed implanting the pacemaker.

In some cases, the additional use of antithymocyte globulin, mycophenolate, or infliximab can be considered, which may improve the immune-related inflammation in the conduction system.[27] Nevertheless, permanent cardiac pacing was still needed in most of the surviving cases. Currently, the issue of whether these patients have the opportunity to resume ICI therapy remains unclear and it may require multidisciplinary evaluation among cardiology, oncology, and cardio-oncology, if possible.

Conclusion

ICI-induced AV block is a rare and refractory cardiovascular adverse event. With the expansion of ICI indications, this risk population will also increase. Extreme caution and close monitoring for the development of cardiac conduction injury are required after the initiation of ICI treatment. Multidisciplinary cooperation will contribute to the adequate management of this immune-related side effect.

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