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CASE REPORT

INTERMEDIATE

CLINICAL CASE

Checkpoint Immunotherapy-Induced Myocarditis and Encephalitis Complicated With Complete AV Block

Not All Hope Is Lost

Álvaro Lorente-Ros, MD,[a,b] Ez-Alddin Rajjoub-Al-Mahdi, MD,[a] Juan M. Monteagudo Ruiz, MD, PhD,[a] Sonia Rivas García, MD,[a] Rodrigo Ortega Pérez, MD,[a] Covadonga Fernández Golfín, MD, PhD,[a,b] Jesús Álvarez-García, MD, PhD,[a,b] José L. Zamorano Gómez, MD, PhD[a,b]

ABSTRACT

Immune checkpoint inhibitors are associated with a myriad of autoimmune adverse events. We present a 70-year-old patient with renal-cell carcinoma treated with nivolumab/ipilimumab complicated with myocarditis and encephalitis in which gradual impairment of the His-Purkinje system progressed to complete atrioventricular block. Full recovery was achieved after treatment with corticosteroids and immunoglobulins. (**Level of Difficulty: Intermediate.**)

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A 70-year-old man with a history of renal cell carcinoma receiving adjuvant treatment with nivolumab/ipilimumab was admitted because of 2 episodes in the previous 12 hours of severe dizziness, dyspnea, and profuse sweating. Upon arrival, he was asymptomatic, and his vital signs were normal: heart rate 88 beats/min, blood pressure 113/48 mm Hg, 98% oxygen saturation on room air, and afebrile. A baseline electrocardiogram (ECG) showed sinus rhythm with anterior and left septal fascicular block (**Figure 1A**). A previous ECG (30 days before initiation of chemotherapy) available in the electronic medical record showed no significant abnormalities (Supplemental Figure 1).

LEARNING OBJECTIVES

- To understand the case of a patient who presented with complete AV block, myocarditis, and encephalitis secondary to immune checkpoint inhibitor therapy.
- To understand and identify the potential adverse events of cancer immune therapy and its cardiac manifestations.
- To understand the importance of a timely diagnosis and the different treatments options available, inasmuch as even subtle ECG abnormalities may denote cardiac damage and precede serious complications.

MEDICAL HISTORY

The patient had a history of renal cell carcinoma initially treated with radical nephrectomy and laparoscopic lymphadenectomy. The anatomopathological results showed regional lymph node involvement (pT3aN1), and combination treatment with immune checkpoint inhibitors (ICIs)

From the [a]Cardiology Department, Hospital Universitario Ramon y Cajal, Madrid, Spain; and the [b]Centro de Investigación Biomédica en Red, CIBER Cardiovascular, Madrid, Spain.

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(nivolumab/ipilimumab) was initiated as adjuvant therapy 19 days before consultation.

DIFFERENTIAL DIAGNOSIS

On initial blood tests, high-sensitivity T troponin (7.2 ng/mL) and C-reactive protein (17.2 mg/L) were elevated. Renal and liver function test results were, normal and B-type natriuretic peptide levels were 88.3 pg/mL. A bedside echocardiogram showed normal left ventricular ejection fraction with mild inferior hypokinesis. The differential diagnoses included myocarditis, non-ST-segment elevation coronary syndrome, and type 2-myocardial infarction. The patient was consequently admitted to the coronary care unit.

FURTHER INVESTIGATIONS

Two hours after admission, he again described sweating and dizziness. A 12-lead ECG showed complete AV block with a ventricular escape rhythm at 36 beats/min originating from the right bundle, and over the next minutes progressive heart rhythm disturbances were registered on serial ECGs (Figure 1), including prolonged ventricular pauses for ≤15 seconds. A temporary pacemaker was inserted, and hemodynamic stability was achieved (Figure 2A). Immediately afterward, coronary angiography showed normal coronary arteries (Videos 1 and 2).

After the procedure the patient experienced hypoactive delirium and progressive deterioration in his level of consciousness, requiring endotracheal intubation. An urgent brain CT scan showed no significant findings. The results of extended autoimmunity laboratory tests, brain magnetic resonance imaging, lumbar puncture, and electroencephalogram were not diagnostic of any specific condition. Myasthenia gravis was considered, but the patient's test results were negative for anti-MuSK and antiacetylcholine-receptor antibodies and only mildly positive for antistriated muscle antibodies.

MANAGEMENT

The case was evaluated by a multidisciplinary team, and high-dose intravenous corticosteroids were initiated with the diagnosis of immune-mediated

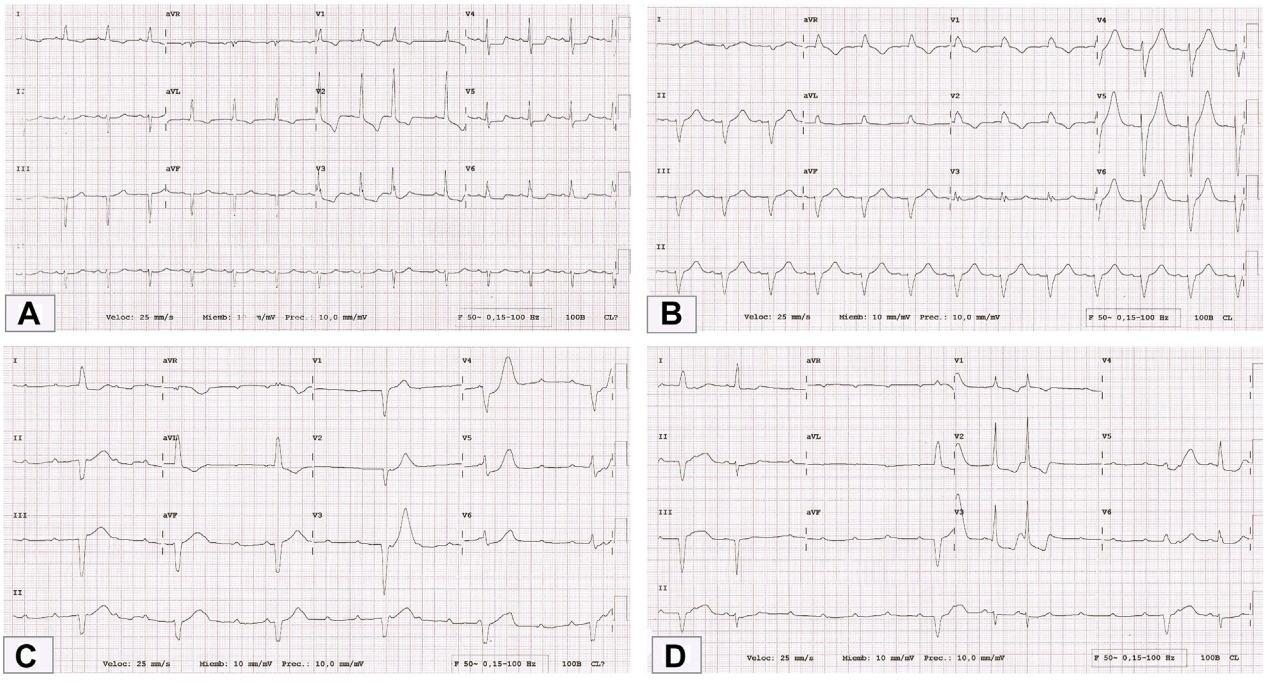
ABBREVIATIONS AND ACRONYMS

ECG = electrocardiogram

ICI = immune checkpoint inhibitor

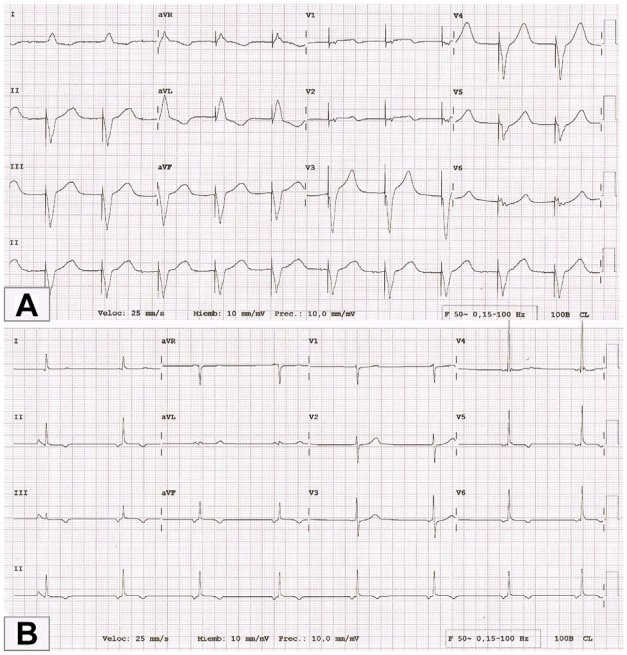
irAE = immune-related adverse events

FIGURE 1 Electrocardiograms Showing Progressive Injury to the His-Purkinje System



Normal sinus rhythm with normal PR interval and QRS duration of 100 ms that fulfill criteria of anterior and left septal fascicular block, an intraventricular conduction block that was not present previously **(A)**. Disturbances of the specific cardiac conduction system progressed to right bundle branch block and left anterior fascicle block **(B)**, complete atrioventricular (AV) block with a ventricular escape rhythm **(C)**, and high-degree AV block with an unstable escape rhythm and progressively longer ventricular pauses **(D)**.

FIGURE 2 Electrocardiograms After Pacemaker Implantation and at Discharge



(A) A temporary pacemaker was positioned in the right ventricular apex. **(B)** Ectopic atrial rhythm and resolution of conduction abnormalities after 48 hours of treatment.

myocarditis and encephalitis (1 g methylprednisolone daily for 3 days, which was afterwards de-escalated to 1 mg/kg/day). After 72 hours of treatment, the patient had recovered normal AV conduction and mental status and was extubated. However, <48 hours later, he experienced a relapse, with a low level of consciousness requiring reintubation, and intravenous immunoglobulins were initiated. Immunosuppressive treatment and respiratory support were maintained for another 3 days, afterward which the patient was extubated without further complications. No permanent pacemaker was required (**Figure 2B**). Cardiac magnetic resonance showed a small linear nonischemic late gadolinium enhancement in the inferolateral wall along with increased T2 values suggestive of diffuse myocardial edema and myocarditis (**Figure 3**). Left ventricular volumes and function were normal. He was discharged to receive corticosteroids, and treatment with nivolumab/ipilimumab was withdrawn.

DISCUSSION

ICIs block immune checkpoint target proteins to break the tolerance of T lymphocytes against cancer cells (Supplemental Table 1). Immune-related adverse events (irAEs), distinct from conventional chemotherapy, are present in ≤60% to 80% of patients taking ICIs.[1] Although cardiovascular events were thought to be rare, they are likely to be underrecognized, with 1 study reporting an incidence of ≤9.7%.[1,2] Moreover, recent evidence suggests that mild cases of myocarditis are common in patients treated with ICIs.[1] When myocarditis is associated with rhythm disturbances, mortality can be as high as 60%.[3] Although most cases are managed with permanent pacing, the present report shows that there is potential reversibility of the immune damage, and permanent pacing may not always be required. Thus, there is an imminent medical need for understanding the cardiovascular complications of ICIs treatment and their management.

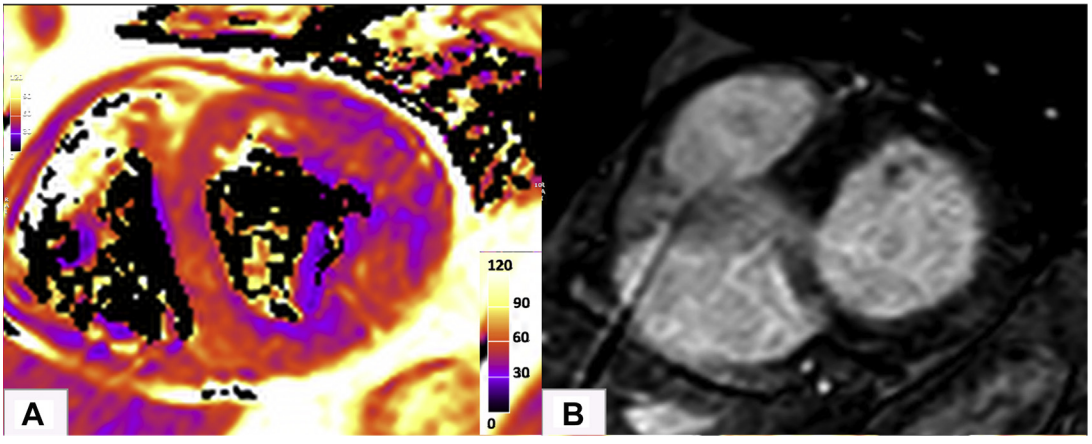
The median time to symptom onset after initiation of ICIs is 30 days for myocarditis and 55 days for vasculitis.[4] Neuromuscular irAEs are also common and may also be underdiagnosed. Myasthenia gravis is the most frequent neuromuscular irAE, with an incidence ranging between 0.12% and 0.2%. When ICIs are used in combination, there is an increased frequency of complications and multiorgan involvement.[5] In the present case, myocarditis coexisted with encephalitis, which has been rarely reported.

Conduction disturbances may be the initial presentation of ICI-induced myocarditis, present in ≤67% of cases, and 95% of patients with high-grade AV block received a definitive pacemaker in a multicenter registry.[6] Our case illustrates that even minor ECG abnormalities may precede more severe manifestations. Hence the importance of implementing close follow-up protocols and biomarker testing in these patients and the need for risk stratification strategies. There is exemplary preclinical evidence supporting a high risk of conduction disturbances,[7] showing leukocyte infiltration in the area of the Purkinje fibers in a myocarditis mouse model.[8]

Preclinical studies have confirmed the role of the interaction between CTLA-4 and PD-1 in a mouse model of ICI-associated myocarditis. It has been proposed that treatment with CTL4-immunoglobulin (abatacept) could attenuate myocarditis, providing preclinical and mechanistic support for future therapeutic clinical studies.[7]

Our patient presented with ECG abnormalities consistent with left septal fascicular block, which is most often caused by obstruction of the left anterior descending coronary artery.[9] After an ischemic cause was ruled out, myocarditis-related conduction abnormalities were considered. Indeed, the ECG changes, showing progression of the His-Purkinje system injury within hours and complete resolution after treatment, are noteworthy. These

FIGURE 3 Cardiac Magnetic Resonance 7 Days After Admission



(A) T2 mapping showing diffuse myocardial edema. **(B)** Midwall inferolateral late gadolinium enhancement.

considerations have clinical implications because early treatment with high-dose corticosteroids is crucial to prevent fatal outcomes. Other immunosuppressive strategies may be considered if the patient does not respond to corticosteroids; they include plasmapheresis or immunoglobulins, among others (Supplemental Table 2).[10]

FOLLOW-UP

Corticosteroids were successfully tapered down after discharge. The results of cardiac follow-up examinations have been unremarkable, and the tumor has remained under remission up to this day.

CONCLUSIONS

We present a case of ICI-induced myocarditis and neurologic involvement with 2 distinctive characteristics: rapidly progressive impairment of the conduction system, and complete restoration of normal conduction after treatment. A high degree of clinical suspicion is necessary to improve patient outcomes, inasmuch as conduction system disturbances may resolve with prompt and adequate treatment.

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The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Álvaro Lorente-Ros, Hospital Ramon y Cajal, Cardiology Department, Ctra. Colmenar Viejo Km 9,100, 28034 Madrid, Spain. E-mail: alvaro.lorente@salud.madrid.org.

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KEY WORDS complete AV block, encephalitis, immune checkpoint inhibitor, immune-related adverse events, myocarditis

APPENDIX For a supplemental figure, tables, and videos, please see the online version of this paper.