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Case Report

Brugada-like Arrhythmia and Suspected Myocarditis Following Immune Checkpoint Inhibitor Therapy in a Patient with Metastatic Renal Cell Carcinoma: A Case Report

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Abstract

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy, but their immune-activating properties can precipitate a diverse array of immune-related adverse events (irAEs) [2,3,8]. We present the case of a 41-year-old woman with metastatic renal cell carcinoma (mRCC) who, following treatment with ipilimumab and nivolumab, developed Brugada-like ventricular arrhythmias and suspected myocarditis, a rare but potentially fatal cardiovascular irAE [2,4,7]. Initially presenting with ventricular tachycardia (VT) and diabetic ketoacidosis after three cycles of ICI therapy, coronary angiography revealed a flow-limiting lesion necessitating percutaneous coronary intervention (PCI). Despite successful revascularization and optimal medical management, she experienced recurrent VT. Electrocardiographic (ECG) findings revealed a Brugada pattern [5], prompting initiation of quinidine and implantation of an implantable cardioverter-defibrillator (AICD) [12,13,14]. Suspecting ICI-induced myocarditis, she was treated with corticosteroids [10,11], which resulted in the resolution of VT. This case underscores the importance of heightened vigilance for cardiac irAEs, including Brugada-like arrhythmias, in patients receiving ICIs [2,4,15,16]. Early recognition, prompt diagnosis, and multidisciplinary management are crucial for mitigating the risk of these potentially life-threatening complications [3,6,18]. Further research is needed to delineate the underlying mechanisms and optimize treatment strategies for ICI-induced Brugada-like arrhythmia [2,4].

Introduction

ICIs have dramatically improved outcomes for patients with various cancers, including mRCC [1]. However, by activating the immune system, these agents can trigger irAEs affecting any organ[2,3]. Cardiovascular irAEs, although less common than those involving the skin, gastrointestinal tract, or endocrine system, can be life-threatening[2,4]. Brugada syndrome is a rare inherited cardiac channelopathy characterized by a distinct electrocardiographic (ECG) pattern and an increased risk of sudden cardiac death due to ventricular arrhythmias[5].

While myocarditis is a recognized irAE, the association between ICI therapy and Brugada-like arrhythmias is not well established[2,6]. This case report describes a patient with mRCC who developed Brugada ECG

features and ventricular tachycardia (VT) following ICI therapy, raising the possibility of ICI-induced Brugada phenocopy or myocarditis[7].

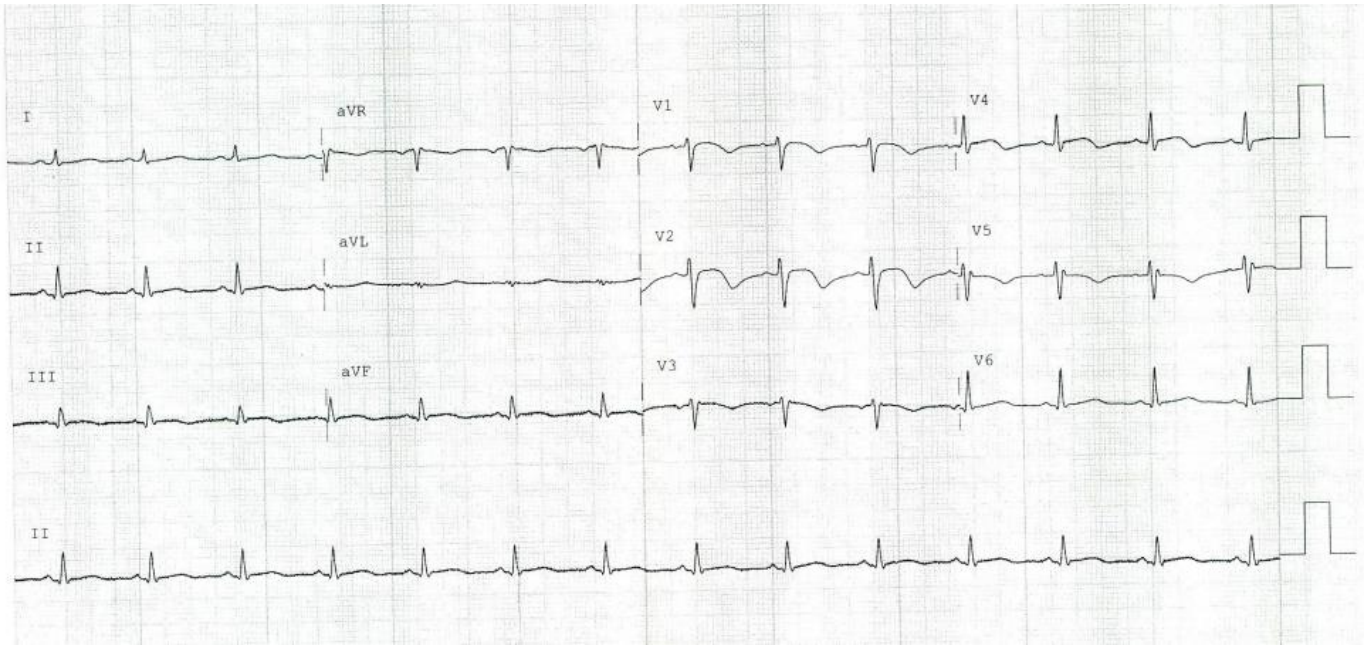


Figure 1: Brugada

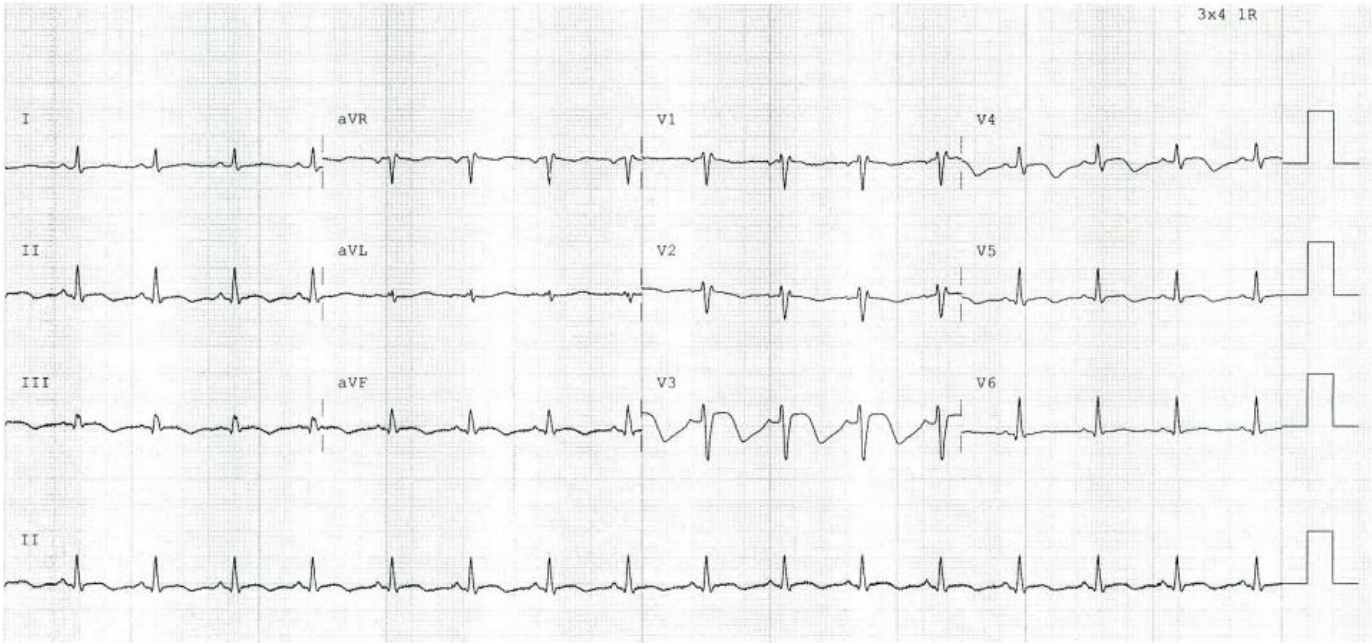


Figure 2 Brugada

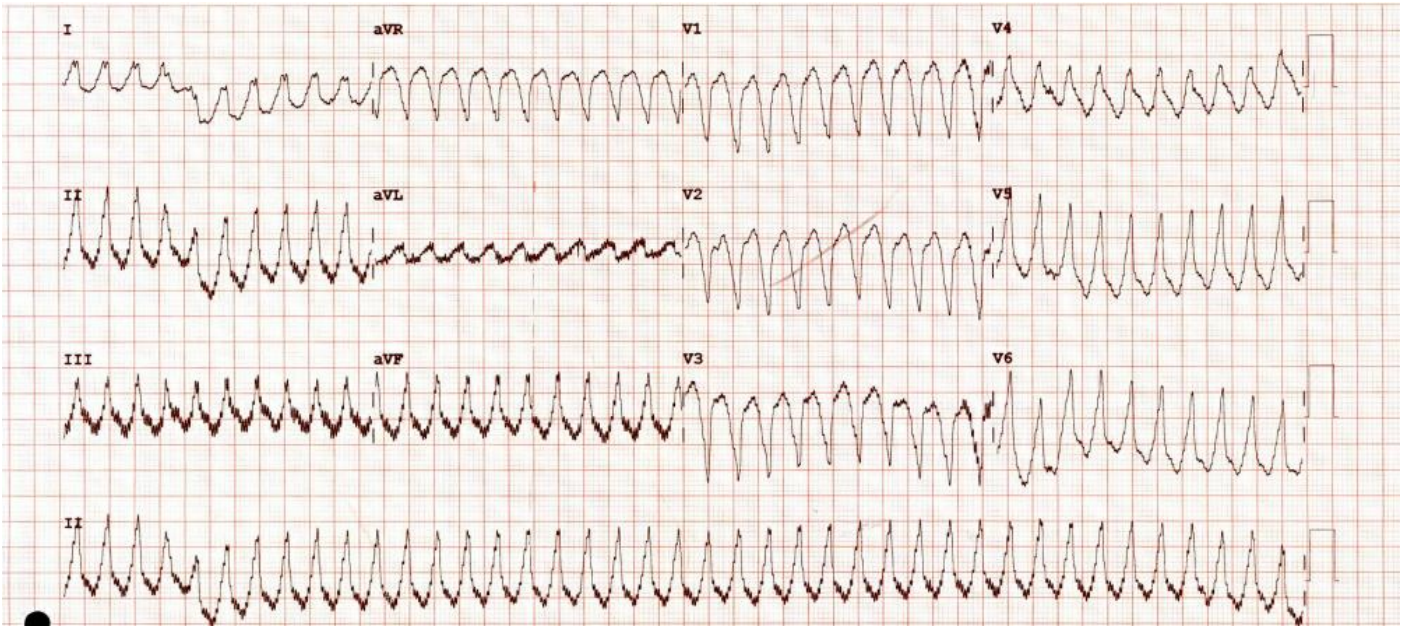
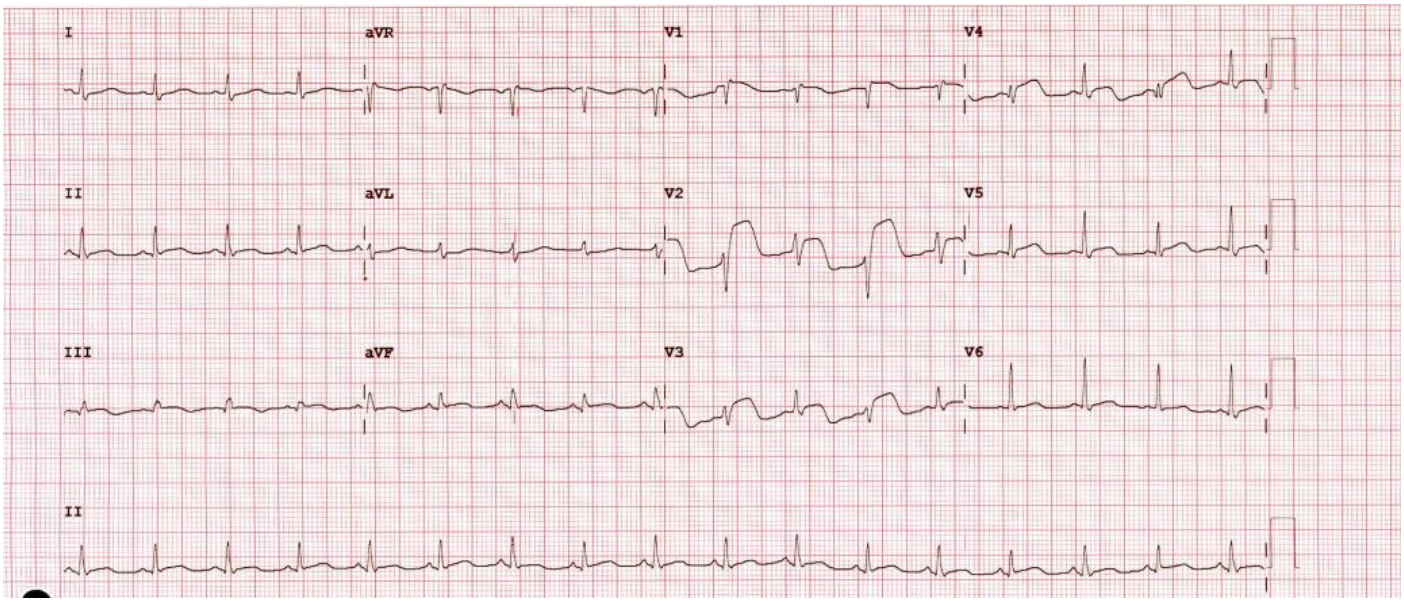


Figure 3: Ventricular tachycardia



Figute 4: St Elevation

Case Presentation

A 41-year-old woman presented in December 2021 with de novo metastatic clear cell renal cell carcinoma with extensive bony and hepatic metastases. She was commenced on ipilimumab and nivolumab. After three

cycles, she was admitted with diabetic ketoacidosis secondary to immunotherapy-induced type 1 diabetes mellitus. She subsequently developed ventricular tachycardia with a massive VT storm initially thought to be secondary to ischemic heart disease. Coronary angiography revealed a culprit lesion in the left anterior descending (LAD) artery, which was treated with percutaneous coronary intervention (PCI) and stent placement in February 2022. She was commenced on anginal medications, including dual antiplatelet therapy, a beta-blocker, a statin, and an angiotensin receptor blocker (ARB).

She was readmitted to the hospital with recurrent episodes of conscious VT. Following cardioversion for VT in the emergency department, her ECG demonstrated ST-elevation myocardial infarction (STEMI) features. Although she had a history of LAD stenosis with stent placement several weeks prior, repeat coronary angiography revealed a patent LAD stent and no new coronary occlusion. During her ICU admission, her ECG showed Brugada features, and she continued to experience recurrent VT. She was commenced on quinidine 200 mg three times daily and metoprolol 25 mg twice daily. An implantable cardioverter-defibrillator (AICD) was inserted. Radiofrequency ablation was considered but deemed challenging due to the tumor burden in her pelvis.

The constellation of arrhythmias, Brugada ECG pattern, and prior ICI exposure raised the suspicion for immunotherapy-related myocarditis. She was commenced on a 3-day course of intravenous methylprednisolone followed by oral prednisolone 1 mg/kg. No further episodes of VT occurred in the ICU. This raised the possibility of VT requiring an ICD with possible underlying Brugada syndrome exacerbated by conduction abnormalities related to immunotherapy.

Her admission was further complicated by DKA requiring insulin infusion. Immunotherapy was ceased, and she was commenced on sunitinib. In August 2023, she developed a new right atrial pericardial lesion, suspicious for metastasis, and new hypothyroidism, for which she was started on levothyroxine. Due to progressive disease, she was started on cabozantinib in mid-October 2023 following sunitinib and then lenvatinib in early March 2024. Her disease continued to progress, and she passed away in July 2024.

Discussion

This case highlights the complex interplay between immunotherapy, cardiac arrhythmias, and underlying structural heart disease. While a causal relationship between ICI therapy and the development of Brugada-like arrhythmia cannot be definitively established, the temporal association raises significant concern for a potential drug-induced phenomenon[2,4].

ICIs are known to induce a wide spectrum of immune-related adverse events (irAEs) by disrupting immune tolerance[8]. Cardiovascular irAEs, though less common than those affecting other organs, can be life-threatening [2]. Myocarditis, characterized by inflammation of the heart muscle, is a recognized irAE associated with ICI therapy [5]. Myocarditis can manifest with various arrhythmias, including ventricular tachycardia (VT), as seen in this patient [2]. However, the development of Brugada-like ECG features in the context of ICI-induced myocarditis is a rare and intriguing finding [9].Several mechanisms may explain the association between ICI therapy and Brugada-like arrhythmia:

1. Direct Cardiotoxicity: ICIs may directly affect cardiac myocytes, disrupting ion channel function and altering the electrophysiological properties of the heart. This could potentially unmask latent Brugada syndrome or create a Brugada-like electrophysiological substrate, predisposing to VT[2].
2. Immune-mediated Inflammation: ICIs can trigger an immune response against cardiac tissue, leading to myocarditis and subsequent electrical instability. Inflammation and fibrosis within the myocardium can disrupt the normal conduction system, creating pathways for re-entrant arrhythmias and potentially mimicking the ECG pattern of Brugada syndrome[2].
3. Unmasking of Underlying Channelopathies: It is possible that the patient had a subclinical predisposition to Brugada syndrome, which was unmasked by the inflammatory or direct cardiotoxic effects of ICI therapy [2].

The management of ICI-induced cardiac irAEs, particularly those involving arrhythmias, can be challenging [2,4]. Prompt recognition and initiation of appropriate therapy are crucial [3,6]. Corticosteroids, as used in this case, are the mainstay of treatment for ICI-induced myocarditis [10,11]. However, the optimal management of Brugada-like arrhythmias in this setting remains unclear. Quinidine, an antiarrhythmic drug with sodium channel blocking properties, is often used in Brugada syndrome and may be beneficial in preventing recurrent VT [5,12]. AICD implantation provides life-saving protection against sudden cardiac death [13,14].

This case underscores the importance of heightened vigilance for cardiac irAEs in patients receiving ICIs, even in the absence of prior cardiac history [15,16] . Any new-onset cardiac symptoms, including palpitations, chest pain, or syncope, should prompt a thorough cardiac evaluation, including ECG, echocardiography, and potentially cardiac MRI [2,17]. Early involvement of a cardiologist and electrophysiologist is essential for optimal management [18].Further research is needed to better understand the incidence, risk factors, and underlying mechanisms of ICI-induced Brugada-like arrhythmia[2,4]. This knowledge will help to identify

patients at risk and guide the development of effective prevention and treatment strategies.

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