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Bilateral Venous Access for Cardiac Resynchronization Therapy in a Hemodialysis Patient With Cabozantinib-associated Heart Failure

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Abstract

Background: Cabozantinib, a multi-targeted tyrosine kinase inhibitor, is widely used for the treatment of renal and hepatic cancers. While cabozantinib-associated cardiotoxicity is rare, it has been documented in several cases. In most instances, cancer therapeutics-related cardiac dysfunction (CTRCD) is managed by discontinuing cabozantinib and initiating cardioprotective agents. In this report, we present the case of a 63-year-old male with cabozantinib-induced heart failure (HF) with reduced ejection fraction (EF) and complete left bundle branch block (CLBBB).

Case Report: The patient, undergoing hemodialysis for chronic kidney disease, had limited therapeutic options due to prior treatment failures. Despite six months of standard HF therapy, symptoms persisted, prompting cardiac resynchronization therapy (CRT) implantation without interrupting cabozantinib. Due to the presence of a dialysis shunt in the patient's left arm, the right subclavian vein was selected for venous access to minimize the risk of lead-related complications. Using a tunneling tool, the left ventricular lead was placed *via* the contralateral vasculature to the ipsilateral generator. Six months post-CRT, echocardiography showed significant reverse remodeling with improved EF and reduced left ventricular end-diastolic diameter, alongside clinical symptom relief.

Conclusion: This case highlights the utility of bilateral venous access with a tunneling tool in cardiac resynchronization therapy, particularly for patients with hemodialysis shunts.

Keywords: Cancer therapeutics-related cardiac dysfunction, cardiac resynchronization therapy, cabozantinib, onco-cardiology.

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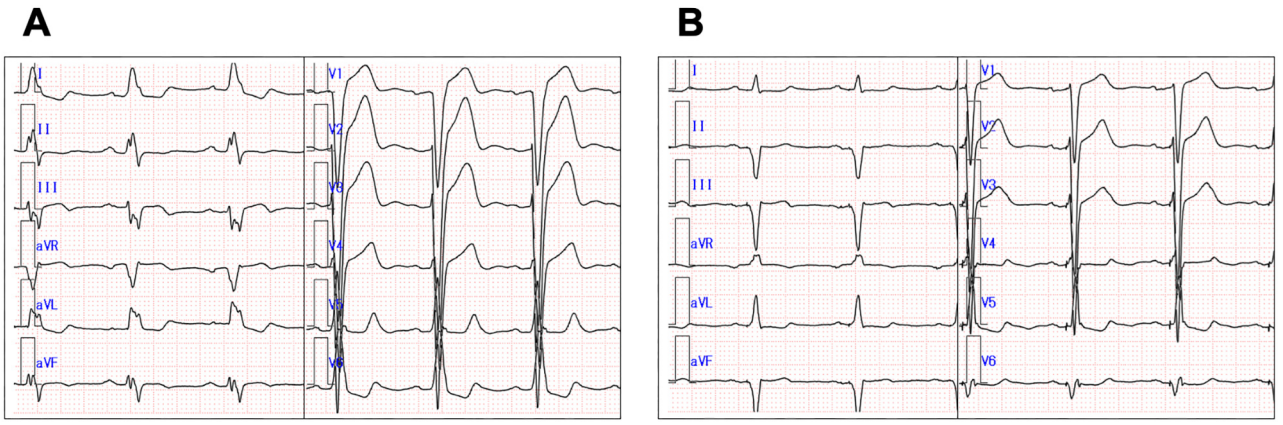

Figure 1. *Electrocardiogram (ECG) before and after cardiac resynchronization therapy (CRT). A) ECG showing complete left bundle branch block (CLBBB) with a QRS duration of 154 ms at the initial cardiology visit. B) ECG taken at the follow-up visit after CRT, showing a reduced QRS duration of 124 ms. Left ventricular pacing, rather than biventricular pacing, was employed based on echocardiography-guided optimization.*

Introduction

Cabozantinib is a multi-targeted tyrosine kinase inhibitor widely used to treat renal and hepatic cancers. Although rare, cabozantinib-associated cardiotoxicity has been documented in several cases (1-6). In most instances, cancer therapeutics-related cardiac dysfunction (CTRCD) has been managed by discontinuing cabozantinib and initiating cardioprotective agents. Here, we present a case of heart failure (HF) with reduced ejection fraction (EF) that developed complete left bundle branch block (CLBBB) during cabozantinib treatment. HF was successfully managed without interrupting anticancer therapy by implementing cardiac resynchronization therapy (CRT), albeit with necessary technical adjustments.

Case Report

A 63-year-old male patient was referred to the cardiovascular department for evaluation of dyspnea attributed to HF, which had developed one week prior. His medical history includes left-sided clear cell renal cell carcinoma (ccRCC), treated with radical nephrectomy 27 years ago. Due to metastatic recurrence of ccRCC, he underwent multiple chemotherapy regimens, including interferon-alpha, various tyrosine kinase inhibitors such as sorafenib and axitinib, and the immune checkpoint inhibitor nivolumab. However, all treatments were discontinued due to adverse events or disease progression. Three years ago, cabozantinib was initiated as fifth-line therapy, resulting in moderate tumor shrinkage. Hemodialysis was started two years ago due to worsening renal function.

During his visit, an electrocardiogram (ECG) revealed a complete left bundle branch block (CLBBB) (Figure 1A), although his QRS complex had been narrow prior to chemotherapy (four years ago). A chest X-ray showed cardiomegaly with a cardio-thoracic ratio of 57.7% (Figure 2A). Transthoracic echocardiography revealed a dilated left ventricle (left ventricular end-diastolic diameter: 61.9 mm) with a reduced EF of 34% (Figure 3A). Additional findings included apical shuffling, a septal flash, moderate aortic stenosis, and mild-to-moderate functional mitral regurgitation. Three months later, coronary angiography was performed to evaluate ischemic etiology, revealing no significant stenosis. Cardiac magnetic resonance imaging was contraindicated due to impaired renal function, and a myocardial biopsy was avoided to minimize procedural risk. While cabozantinib-induced CTRCD was suspected to be a potential cause of the reduced cardiac function, the urology department recommended continuing cabozantinib due to

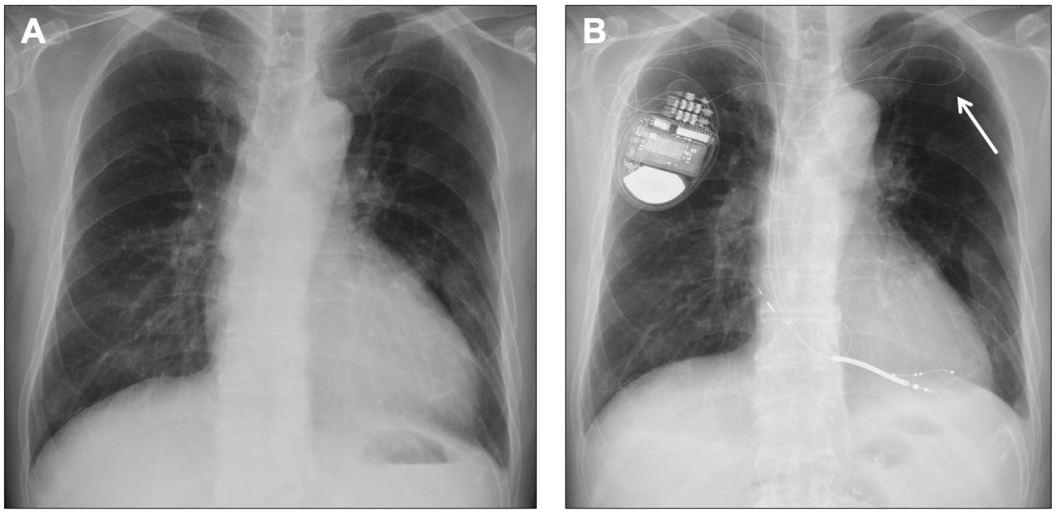

Figure 2. *Chest X-rays before and after cardiac resynchronization therapy (CRT). A) Chest radiograph from the initial cardiology visit, demonstrating cardiomegaly with a cardiothoracic ratio of 57.7%. B) Follow-up chest radiograph after CRT, showing a reduction in the cardiothoracic ratio to 54.6%. The CRT generator is implanted in the right chest, with the left ventricular lead positioned via the left subclavian vein (arrow).*

the limited availability of alternative anticancer treatments (a decision also supported by the patient). Subsequently, medical therapy with an angiotensin receptor-neprilysin inhibitor and carvedilol was initiated. Despite this, the patient's symptoms, classified as NYHA Class III, showed no improvement over six months of cardioprotective treatment. Approximately one year after the initial cardiology visit, the patient was admitted for implantation of a cardiac resynchronization therapy-defibrillator (CRT-D) device to manage wide QRS heart failure with reduced ejection fraction (HFrEF).

Upon admission, the patient's blood pressure was 103/51 mmHg, and his heart rate was 76 beats per minute. A physical examination revealed a Levine grade 2/6 systolic murmur. Laboratory findings indicated anemia, with a hemoglobin level of 9.4 g/dl, and impaired renal function, evidenced by a creatinine level of 5.9 mg/dl. Additionally, BNP was elevated at 398.7 pg/ml, and N-terminal pro b-type natriuretic peptide (NT pro-BNP) was markedly elevated at 12,468 pg/ml.

On the fifth day of hospitalization, a CRT-D implantation procedure was performed. Due to the presence of a dialysis shunt in the patient's left arm, the right subclavian vein was

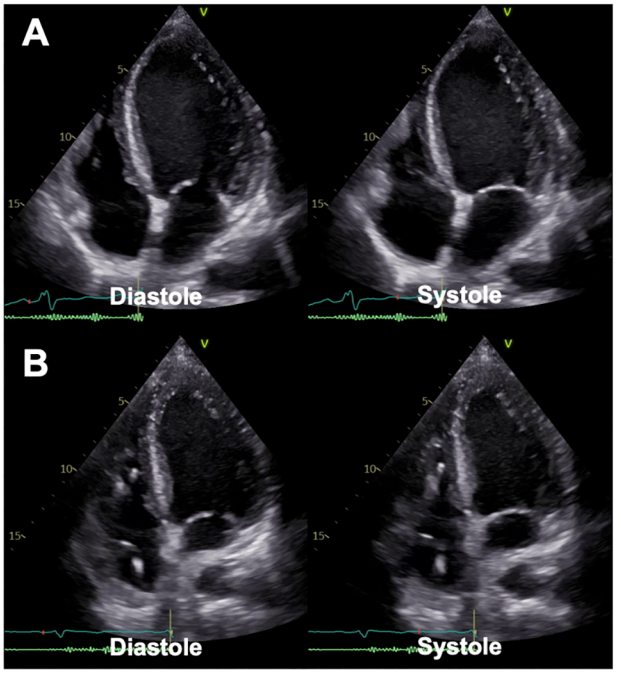

Figure 3. *Apical four chamber views of echocardiography before and after cardiac resynchronization therapy (CRT). A) Transthoracic echocardiography (TTE) at the initial cardiology visit, showing a dilated left ventricle (left ventricular end-diastolic diameter [LVEDD]: 61.9 mm) and a reduced ejection fraction (EF) of 34%, with apical shuffling and a septal flash. B) TTE at the follow-up visit after CRT, demonstrating reverse remodeling with an improved EF of 53% and a reduced LVEDD of 57.3 mm.*

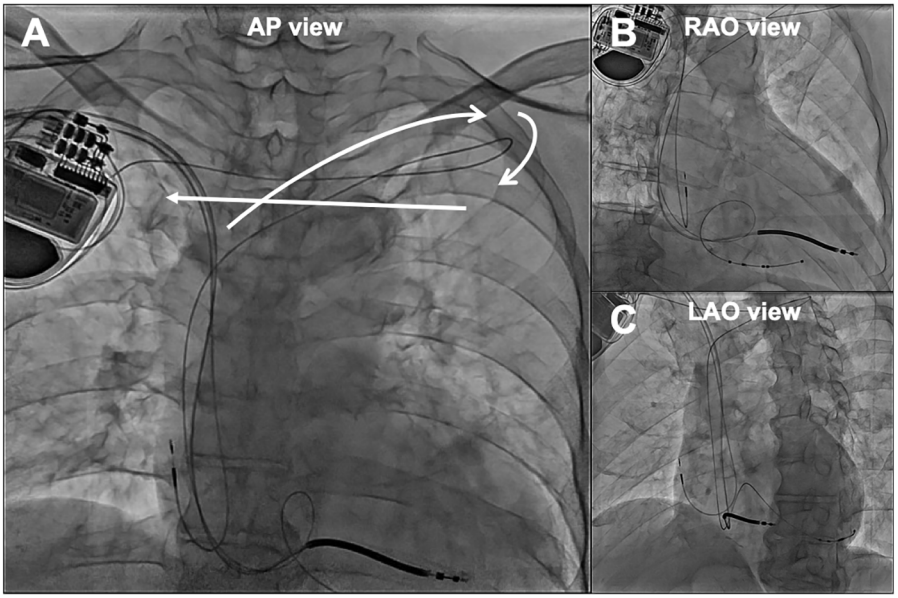

Figure 4. *Bilateral venous approach for cardiac resynchronization therapy (CRT). A) A tunneled lead from the contralateral vasculature to the ipsilateral pulse generator. B) Final view of CRT implantation in the right anterior oblique (RAO) projection. C) Left anterior oblique (LAO) view following CRT completion.*

chosen for venous access to minimize the risk of lead-related complications. The right ventricular and atrial leads were successfully placed *via* the right subclavian vein; however, placement of the left ventricular lead proved challenging due to insufficient backup support from the guiding catheter. After several unsuccessful attempts, the right-sided approach was abandoned. Subsequently, the left subclavian vein was punctured, and a sheath was inserted. This allowed for smooth catheter advancement and successful placement of the left ventricular lead into the postero-lateral branch of the coronary sinus. A tunneling tool was then used to route the left ventricular lead subcutaneously from the left anterior chest to the right-sided pocket, where it was connected to the device (Figure 4A). Using this bilateral approach, the CRT procedure was completed successfully (Figure 4B and C). Guided by echocardiographic optimization, left ventricular pacing was chosen over biventricular pacing.

Six months post-CRT-D implantation, echocardiography demonstrated reverse remodeling, with an improved EF of 53% and a reduced left ventricular end-diastolic diameter of 57.3 mm (Figure 3B). The QRS duration improved to 124 ms under left ventricular pacing (Figure 1B). A chest X-ray revealed no signs of pulmonary congestion, and the cardiothoracic ratio had decreased to 54.6% (Figure 2B).

Discussion

According to Iacovelli *et al.*, who examined 22 patients with renal cell carcinoma, the cardiotoxic risk of cabozantinib is modest and rarely results in systolic dysfunction (7). However, accumulating evidence suggests that cabozantinib can cause congestive heart failure (1-6). In most reported cases, the cardiac dysfunction was reversible following discontinuation of cabozantinib and initiation of cardioprotective agents (1, 2, 4). In our case, however, it was essential to continue cabozantinib, as it was considered the only viable treatment option. Additionally, the use of mineralocorticoid receptor antagonist or SGLT2 inhibitors was challenging due to end-stage renal failure, limiting the available options for conservative medical treatment. This necessitated finding

a way to manage heart failure symptoms effectively, leading us to explore CRT as a potential solution.

When performing cardiac implantable electrical device (CIED) therapy, it is known that an increased number of transvenous leads raises the risk of venous occlusion (8). Additionally, there have been reports of dialysis failure due to central venous stenosis when a pacemaker was implanted on the same side as the dialysis shunt in patients on hemodialysis (9). Therefore, it is considered desirable to place leads from the side opposite to the dialysis shunt when implanting a CIED in hemodialysis patients.

Since the patient was on hemodialysis, the implantation was attempted through the right subclavian vein, opposite the arteriovenous shunt. However, lead insertion from the right side is often technically challenging due to insufficient backup force. In such cases, we believe that our approach using a tunneling tool may be beneficial. Recently, Mekary *et al.* reported that tunneling the lead from the contralateral vasculature to the ipsilateral generator has proven to be an effective and safe solution for occluded ipsilateral subclavian veins (10). Therefore, we believe our case study supports this evidence.

In summary, we presented a case of cabozantinib-related heart failure that improved with CRT without discontinuing anticancer therapy, despite encountering technical challenges during the procedure.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in relation to this report.

Authors' Contributions

Conceptualization: AH. Writing original draft: AO. Writing review and editing: AH, NM, KK, KY, TN, RH, AA, YN, TF, SM, YA, TM, HK, HH, ST, KN, KI, SI and OY. All Authors have read and agreed to the published version of the article.

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