A Case Report of Complete Heart Block in a 58-Year-Old Woman with Multiple Myeloma Treated with Carfilzomib: Implications for Risk Stratification in High-Risk Populations

Mehrshad Ebrahimpour[1], Samin Ghorbani Moghadam[1], Hossein Rahimi[2], Amir Hooshang Mohammadpour[3], Omid Arasteh[3]*

[1]*School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.*

[2]*Department of Internal Medicine, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran.*

[3]*Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.*

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Abstract

Carfilzomib, a proteasome inhibitor used to treat relapsed multiple myeloma, is linked to rare cardiac complications. Complete heart block (CHB), though seldom reported, poses critical risks in patients with multiple comorbidities. This case report illustrates the development of CHB in a patient with multiple myeloma and high cardiovascular risk, underscoring the importance of risk-based monitoring rather than proposing a new mechanism. A 58-year-old Iranian woman with relapsed multiple myeloma, acute coronary syndrome, hypertension, dyslipidemia, type 2 diabetes, and hemodialysis-dependent chronic kidney disease (CKD) developed CHB 48 hours after carfilzomib initiation. The Naranjo Adverse Drug Reaction Probability Scale yielded a score of 3 (indicating a "possible" adverse drug reaction). Discontinuation of carfilzomib and temporary pacemaker implantation restored hemodynamic stability. Although the patient's hemodynamics improved following pacing, she ultimately died due to septic complications unrelated to the arrhythmia. This case demonstrates the complexity of attributing CHB to carfilzomib in a multimorbid patient. It highlights the necessity of comprehensive cardiac evaluation and risk stratification in patients receiving proteasome inhibitors, especially those with concurrent CKD, coronary artery disease (CAD), and polypharmacy.

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Introduction

Carfilzomib, a second-generation proteasome inhibitor, is a cornerstone of therapy for relapsed/refractory multiple myeloma due to its very active anti-plasma cell effect (1). However, cardiovascular toxicity in the form of hypertension, heart failure, and arrhythmias is a cause for concern. While hypertension and heart failure are more common, complete heart block (CHB) remains exceptionally rare (2,3). Only isolated reports, such as Shah et al.'s study (4), have described this phenomenon. The rarity of CHB suggests either an underrecognized, adverse event or a multifactorial complication that manifests in particularly vulnerable populations.

Established risk factors for developing heart block include older age, male sex, white population, overweight, combined diabetes or chronic kidney disease (CKD), impaired forced vital capacity (FVC), elevated inflammation biomarkers, left bundle branch block, and bifascicular block (5). The evolution of CHB in a patient with advanced cardiac and renal disease underscores the necessity of heightened clinical suspicion and careful causality assessment. This case also demonstrates the use of structured tools, such as the Naranjo scale (6), to assess drug-related adverse reactions in complex clinical settings.

Case Presentation

A 58-year-old Iranian woman was diagnosed with immunoglobulin G (IgG) kappa multiple myeloma through bone marrow biopsy and serum protein

*** Corresponding Author:** Omid Arasteh
Address: Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.
Email: ArastehO@mums.ac.ir

electrophoresis. Prior to the current admission, she had received six cycles of bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone [VRD], followed by six cycles of bortezomib (Velcade), cyclophosphamide, and dexamethasone [VCD], as well as one year of thalidomide maintenance therapy before developing progressive disease. The patient was admitted to the hospital presenting with profound fatigue, generalized weakness, and persistent lethargy. On admission, her vital signs included a blood pressure of 110/75 mmHg and a heart rate of 82 bpm. Pertinent baseline laboratory values were potassium 4.5 mEq/L, magnesium 2 mg/dL, and sodium 129 mEq/L. Her family history was negative for premature cardiac conduction disease or sudden cardiac death. Comorbidities included type 2 diabetes, hypertension, dyslipidemia, acute coronary syndrome with previous coronary stenting, and CKD stage 5D (requiring twice-weekly hemodialysis). Her home medications included prazosin, furosemide, carvedilol, lamotrigine, sertraline, thalidomide, aspirin, indapamide, hydralazine, atorvastatin, and insulin.

Due to progression of her multiple myeloma, she was started on carfilzomib (20 mg/m² on day 1, increased to 56 mg/m²) along with 16 mg of dexamethasone. Within 48 hours after the first cycle, she developed bradycardia and syncope; her electrocardiogram (ECG) revealed CHB.

Unfortunately, detailed cardiac data, such as serial ECGs, troponin levels, electrolyte trends, and echocardiographic findings, were not available in this case, limiting the ability to fully exclude alternative etiologies. CHB was controlled through pacing, achieving hemodynamic stability. However, 10 days after pacemaker implantation, the patient developed sepsis. Blood cultures were positive for Staphylococcus epidermidis and Klebsiella pneumoniae. Although the temporary pacing wire was a potential source of infection, definitive infective endocarditis could not be confirmed. Despite appropriate management, the patient expired five days later.

Discussion

Carfilzomib-induced cardiotoxicity is well established, with arrhythmias occurring in nearly 4% of patients (3). CHB, however, is an exceptionally rare condition. A critical question arises as to why this patient developed CHB with carfilzomib despite previously tolerating bortezomib, another proteasome inhibitor. This discrepancy likely stems from distinct pharmacological differences between the two agents. Bortezomib acts as a reversible boronate inhibitor, whereas carfilzomib acts as an irreversible epoxyketone inhibitor (7). The irreversible binding of carfilzomib leads to more sustained proteasome inhibition and accumulation of polyubiquitinated proteins in cardiomyocytes, potentially preventing the recovery of cellular function between doses (7,8).

Furthermore, unlike bortezomib, carfilzomib has been shown to induce profound endothelial dysfunction. Prospective studies have demonstrated that carfilzomib significantly impairs flow-mediated dilation and reduces nitric oxide bioavailability, which can precipitate coronary vasospasm and microvascular ischemia even in the absence of obstructive coronary artery disease (CAD). Mechanistically, carfilzomib has been linked to the inhibition of non-proteasomal targets, such as the adenosine monophosphate-activated protein kinase (AMPK) pathway and protein phosphatase 2A (PP2A). Disruption of these pathways impairs cardiac autophagy and exacerbates oxidative stress, leading to cardiomyocyte apoptosis (9).

In this patient, the combination of these potent molecular effects and her deteriorating clinical status likely created a "two-hit" phenomenon. Her progression to end-stage renal disease and worsening coronary atherosclerosis since her prior bortezomib therapy likely lowered her physiological reserve, rendering the conduction system uniquely vulnerable to the irreversible stress imposed by carfilzomib.

The multifactorial pathogenesis in this patient likely involved advanced CKD, pre-existing CAD, and concurrent use of medications with potential brady arrhythmic effects (carvedilol, indapamide, lamotrigine, and thalidomide) (10-13). While none of these drugs alone have a definitive causal association, their combined use likely increased the patient's vulnerability to conduction abnormalities.

The Naranjo Adverse Drug Reaction Probability Scale assigned the patient a score of 3, indicating that carfilzomib-associated CHB is a "possible" adverse event (Table 1). While the temporal relationship between carfilzomib initiation and CHB onset (within 48 hours) strongly suggests causality, competing risk factors, such as the patient's advanced CKD, prior acute coronary syndrome, and polypharmacy, reduce the certainty of a direct drug-related etiology. Carfilzomib's known cardiotoxicity and previous reports of arrhythmias indicate its possible role in CHB development; nonetheless, a score of 3 emphasizes the multifaceted nature of this issue in high-risk patients. This case exemplifies the difficulty of establishing definitive causality in patients with overlapping risk factors. It underscores the importance of comprehensive risk stratification, integrating cardiovascular, renal, and pharmacologic variables before initiating carfilzomib. Routine baseline ECG, echocardiography, and electrolyte monitoring, followed by early rhythm surveillance, are prudent in such populations.

This case illustrates that CHB can develop during

carfilzomib therapy, particularly in patients with overlapping risk factors, such as CKD, CAD, and polypharmacy. Although causality remains uncertain, this case underscores the necessity of pre-treatment cardiac evaluation, vigilant monitoring, and multidisciplinary management. It also reinforces that mortality in such cases may stem from the cumulative burden of comorbidities rather than cardiotoxicity alone.

Table 1. Naranjo adverse drug reaction probability scale for carfilzomib-associated complete heart block

Question		Yes	No	Do Not Know	Explanation
i.	Are there previous conclusive reports of this reaction?	+1			Yes – Carfilzomib has documented associations with arrhythmias (e.g., bradycardia, QT prolongation).
ii.	Did the adverse event appear after the drug was given?	+2			Yes – CHB occurred within 48 hours of carfilzomib initiation (strong temporal relationship).
iii.	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?			0	Unclear – CHB was managed with a pacemaker; discontinuation alone did not resolve the arrhythmia.
iv.	Did the adverse reaction reappear upon readministering the drug?			0	Not applicable – Carfilzomib was not rechallenged.
v.	Were there other possible causes for the reaction?	-1			Yes – CKD, ACS, infections, and concomitant medications (carvedilol, indapamide) are competing risks.
vi.	Did the adverse reaction reappear upon administration of placebo?			0	Not applicable – No placebo administered.
vii.	Was the drug detected in the blood or other fluids in toxic concentrations?			0	Not applicable – Drug levels were not measured.
viii.	Was the reaction worsened upon increasing the dose? Or was the reaction lessened upon decreasing the dose?			0	Not applicable – Dose was not adjusted during the first cycle.
ix.	Did the patient have a similar reaction to the drug or a related agent in the past?		0		No – prior bortezomib exposure without CHB.
x.	Was the adverse event confirmed by any other objective evidence?	+1			Yes – ECG confirmed CHB.
Final score: 3					

CHB: Complete Heart Block, CKD: Chronic Kidney Disease, ACS: Acute Coronary Syndrome, ECG: Electrocardiogram.

Conflict of Interest

Authors have nothing to declare.

Acknowledgments

Not applicable.

Ethics approval and consent to participate

Verbal informed consent was obtained from the patient for participation in this case report and publication of clinical details, with all personal and identifiable information anonymized to preserve confidentiality.

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