

Case Report

Bortezomib-Induced Perimyocarditis in a Multiple Myeloma Patient: A Case Report

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Keywords

Bortezomib · Perimyocarditis · Multiple myeloma

Abstract

Bortezomib (BTZ) is a proteasome inhibitor used in the treatment of multiple myeloma (MM) and other hematological malignancies. Although carfilzomib, a second-generation proteasome inhibitor, is most strongly associated with cardiotoxicity, BTZ has been associated with several cardiovascular complications including congestive heart failure, arrhythmias, and rarely myocarditis. Here, we report the first case of a BTZ-induced perimyocarditis. The patient was a 40-year-old woman with recently diagnosed MM who was admitted to the hospital with syncope at the start of her second cycle of induction therapy with BTZ, lenalidomide, and dexamethasone. She had a witnessed syncopal event in the emergency room with the telemetry showing sustained ventricular tachycardia. Laboratory workup showed elevated N-terminal pro B-type natriuretic peptide and normal troponin I. Transthoracic echocardiogram (TTE) showed a low ejection fraction of 40% with global hypokinesis of the left ventricle and trace pericardial effusion. Cardiac magnetic resonance imaging with gadolinium was consistent with acute myocarditis. The patient had recurrent pleuritic chest pain, and a repeat TTE showed worsening pericardial effusion consistent with pericarditis. Endomyocardial biopsy was done which showed nonspecific myocyte hypertrophy and foci of fibrosis, but was negative for giant cell myocarditis, hemochromatosis, and amyloidosis. Extensive infectious disease workup ruled out known infectious causes for perimyocarditis. Given the close timing between BTZ treatment (5 subcutaneous doses with a cumulative dose of 6.5 mg/m²), the absence of other iatrogenic or infectious causes, and probable or likely association with BTZ as assessed by the validated causality assessment scoring tools, it was concluded that the acute perimyocarditis was secondary to BTZ exposure. Here, we report the first case of BTZ-induced perimyocarditis and discuss the incidence and pathophysiology of BTZ-cardiovascular toxicity.

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Introduction

Bortezomib (BTZ) is a proteasome inhibitor that is currently used for the treatment of several hematologic malignancies including multiple myeloma (MM), mantle cell lymphoma, systemic light chain amyloidosis, T-cell lymphoma, Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma, and others [1]. Although rare, several cardiovascular complications including heart failure, ischemic heart disease, and arrhythmias have been reported in association with its use [2]. Here, we report the case of a patient who developed perimyocarditis and myocardial scarring after a brief exposure to subcutaneous BTZ in the context of treatment for newly diagnosed international staging system stage I standard risk multiple myeloma.

Case Report

In February 2020, a 40-year-old woman with no prior medical history presented at the emergency department with recurrent witnessed syncopal episodes. The patient was diagnosed with MM just few months before and was just starting her second cycle of anti-MM therapy with subcutaneous BTZ, lenalidomide, and dexamethasone in 21-day cycles. BTZ was delivered at 1.3 mg/m² on days 1, 4, 8, and 11. By the time of her presentation, she had received only 5 doses of BTZ (cumulative dose 6.5 mg/m²). Upon arrival at the emergency department, the patient's vital signs were stable, including heart rate, 91 beats/min; blood pressure, 138/104 mm Hg; respiratory rate, 23 breaths/min; temperature, 36.8°C; and oxygen saturation, 91% on room air. She reported 2-week history or gradually worsening exertional dyspnea and a 15-pound weight gain. She was evaluated as an outpatient with a computed tomography of the chest that showed evidence of bronchitis but no evidence of pulmonary emboli. While in the emergency room, the patient had another witnessed syncopal episode. Telemetry showed a 63-s episode of sustained ventricular tachycardia at a rate of 240 bpm. She was given a bolus of 150 mg of intravenous amiodarone. An electrocardiogram following this event was significant for sinus rhythm with frequent premature ventricular contractions and a prolonged QTc of 505 ms. On physical exam, there were bibasilar crackles on auscultation of the lungs, jugular venous distention with positive hepatojugular reflex, +1 pitting lower leg edema, and normal S1, S2 heart sounds with no extra sounds or pericardial rub. Initial cardiac troponin was elevated at 0.11 ng/mL (normal range 0.00–0.08 ng/mL), and her N-terminal pro B-type natriuretic peptide was elevated at 812 pg/mL (normal range 0–100 pg/mL). Additional lab work that was completed is outlined in Table 1 and included mild anemia and normal kidney and liver functions. A 2-dimensional transthoracic echocardiogram (TTE) showed depressed left ventricular (LV) systolic function (ejection fraction of 40%) with moderate global hypokinesis of the left ventricle, focal akinesis of mid inferior wall and mid septum, and trace pericardial effusion. Medical oncology, advanced heart failure, and cardiac electrophysiology services were consulted, and the patient was admitted to the cardiovascular progressive care unit. She was initiated on sotalol as treatment for ventricular arrhythmia in addition to spironolactone, captopril, and intravenous furosemide for LV dysfunction. Chemotherapy was held given concerns of medication toxicity as the culprit of the presenting clinical situation. A cardiac magnetic resonance imaging with gadolinium was significant for edema (elevated T2 values), hyperemia, regional wall motion abnormalities, and mid myocardial late gadolinium enhancement involving the mid to distal septal, mid to distal inferior, and mid to distal anterior segments consistent with acute myocarditis. Repeat electrocardiogram was conducted after the patient had

Table 1. Blood test results for the patient at the time of admission

Test, unit	Value (reference range)
White blood cells, $\times 10^3/\mu\text{L}$	8.4 (4.0–11.0)
Hemoglobin, g/dL	10.1 (11.0–15.1)
Platelet count, $\times 10^3/\mu\text{L}$	281 (150–400)
Magnesium, mg/dL	2.1 (1.8–2.5)
Procalcitonin, ng/mL	0.05 (<0.10)
Lactic acid, mmol/L	1.4 (0.5–2.0)
D-dimer, ng/mL	824 (<500)
Glucose, mg/dL	134 (70–139)
Creatinine, mg/dL	0.72 (0.44–1.03)
Blood urea nitrogen, mg/dL	12 (6–20)
Sodium, mmol/L	138 (136–145)
Potassium, mmol/L	3.4 (3.5–5.1)
Albumin, g/dL	3.4 (3.5–5.1)
Calcium, mg/dL	7.6 (8.6–10.4)
Total bilirubin, mg/dL	0.4 (0.3–1.0)
Alkaline phosphatase, U/L	51 (32–91)
Aspartate transaminase, U/L	17 (15–41)
Alanine transaminase, U/L	19 (7–52)

recurrent pleuritic chest pain and showed sinus rhythm without any ST segments or T wave changes. Repeat TTE demonstrated that the pericardial effusion had increased in size, without evidence of tamponade physiology. She was started on colchicine for acute pericarditis. A right heart catheterization with endomyocardial biopsy was conducted to rule out giant cell myocarditis. After the biopsy, the patient had recurrent pleuritic chest pain. Repeat TTE showed further worsening of pericardial effusion now measuring 8 mm in its widest dimension (posteriorly) without evidence of cardiac tamponade. Ibuprofen was added with improvement in her chest pain. Subsequent TTE showed stabilization of her pericardial effusion. While awaiting the results of the endomyocardial biopsy, the patient was started on high-dose pulse steroid therapy with 1 g of intravenous methylprednisolone. Endomyocardial biopsy was negative for giant cell myocarditis, amyloidosis, or hemochromatosis, and methylprednisolone was discontinued. The biopsy showed nonspecific nondifferentiating findings of myocyte hypertrophy with areas of fibrosis and foci of fat. Infectious disease was consulted to evaluate any infectious cause of her acute perimyocarditis (shown in Table 2), which were not identified. Cumulatively, all tests were negative except for a positive myocardial polymerase chain reaction (PCR) for parvovirus B19 which was however negative on immunohistochemistry staining. Additionally, serologic parvovirus B19 IgM was negative, IgG was positive, and serum qualitative PCR was negative, indicating latent rather than acute parvovirus B19 infection, and parvovirus B19 was therefore deemed unlikely as the cause of her perimyocarditis. The close timing between treatment initiation with BTZ and patient presentation with acute perimyocarditis, in the absence of other causes, led the involved teams to conclude that her perimyocarditis was most likely a complication of BTZ therapy. The patient was discharged with a wearable external defibrillator (life-vest) and on sotalol, spironolactone, captopril, furosemide, colchicine, and ibuprofen. One week later, a repeat TTE showed resolution of her

Table 2. Infectious workup

Test	Result
Antinuclear antibody	Negative
Double stranded DNA autoantibody	Negative
Cardiolipin antibodies (IgM and IgG)	Negative
Complements (C3 and C4)	Normal
Urine histoplasma antigen	Negative
Serum histoplasma antigen	Negative
<i>Bartonella henselae</i> antibody	Negative
Adenovirus quantitative PCR	Negative
<i>Coxiella burnetii</i> antibody (IgG)	Negative
<i>Trypanosoma cruzi</i> antibody (IgG)	Negative
Tuberculosis interferon antigen response	Negative
Epstein-Barr virus quantitative PCR, blood	Negative
Cytomegalovirus qualitative PCR, blood	Negative
Toxoplasma PCR, blood	Negative
Enterovirus (including coxsackievirus) RNA RT-PCR, blood	Negative
Varicella-zoster virus PCR, blood	Negative
Human-herpes-virus-6 PCR, blood	Negative
Parvovirus B19 IgG	Positive
Parvovirus B19 IgM	Negative
Parvovirus qualitative PCR, blood	Negative
Parvovirus B19 qualitative PCR on heart tissue	Positive
Enterovirus RT-PCR on heart biopsy	Not detected
Immunoperoxidase stain for adenovirus on heart biopsy	Negative
Immunoperoxidase stain for cytomegalovirus on heart biopsy	Negative
Immunoperoxidase stain for parvovirus on heart biopsy	Negative
In situ hybridization for Epstein-Barr virus on heart biopsy	Negative
Human-herpes-virus-6 PCR on heart biopsy	Negative

DNA, deoxyribonucleic acid; IgM, immunoglobulin M; IgG, immunoglobulin G; PCR, polymerase chain reaction.

pericardial effusion with persistent LV dysfunction. At 2-month follow-up, her wearable external defibrillator was discontinued as there was no evidence of recurrence of her arrhythmia on the loop recorder. At 6-month follow-up, a repeat cardiac MRI with late gadolinium enhancement showed scar formation in the distal inferior, distal septal, and mid anteroseptal segments but remained well controlled on goal-directed medical therapy and sotalol. She did not receive any additional doses of BTZ which was permanently discontinued. She eventually underwent autologous hematopoietic stem transplant for her MM, which was followed by uneventful lenalidomide-based maintenance therapy.

Discussion

The incidence of cardiotoxicity with the use of BTZ is reported between 0 and 17.9% [3]. Xiao et al. [4] reported the incidence of cardiotoxicity in a large meta-analysis at 3.8%, whereas Laubach et al. [5] reported the incidence of congestive heart failure to be 2.0–7.6%, the incidence of arrhythmias 1.3–5.9%, and the incidence of ischemic heart disease to be 1.2–2.9%. Both meta-analyses failed to show an association of BTZ with adverse cardiac events. However, there continues to be case reports describing several cardiovascular toxicities related to BTZ use. Complete heart block [3], ventricular tachycardia and myocardial scarring [6, 7], heart failure with reduced ejection fraction and moderate pericardial effusion [8], fulminant myocarditis [9], and cardiac tamponade [10] have been described in several case reports.

The ubiquitin-proteasome system, under normal conditions, “tags” altered or misfolded intracellular proteins for degradation [2]. Its substrates include signaling molecules, cell cycle regulators, transcription factors, and antiapoptotic proteins [8]. In MM, the 26S proteasome complex is hyperactive causing excessive intracellular removal of important proteins, such as tumor suppressor p53 and IκB (inhibitor of nuclear factor-κB). This results in the deregulation of cell cycle and apoptosis control leading to increased survival and proliferation of neoplastic clones [2]. Bortezomib, a dipeptidyl boronic acid, reversibly binds and inhibits the 20S proteasome which is the proteolytic core particle of the 26S proteasome [3], therefore blocking the oncogenic progression of neoplastic cells by interfering with proteasome activity. However, the exact mechanism by which bortezomib interacts with the cardiac tissue is unknown.

Proteasome is important in protein hemostasis in the heart [2]. It helps maintain the normal size and shape of the heart by maintaining the protein quality in the myocytes, preserving the cellular mass, and controlling the quality of the sarcomeres [8]. Inhibition of proteasome activity results in the abnormal accumulation of misfolded proteins that associate with one another to form a higher order protein that is toxic to the cell and ultimately leads to apoptosis and cell death with release of cytokines activating the immune system and consequent inflammation [8, 11, 12]. This might explain how BTZ can lead to acute perimyocarditis.

This case demonstrates rare adverse cardiovascular effects of BTZ. Our patient presented with ventricular tachycardia resulting in syncope and was later diagnosed with acute perimyocarditis. To our knowledge, this is the first case to report of acute perimyocarditis secondary to BZT.

Our patient met the European Society of Cardiology’s clinical diagnostic criteria for acute perimyocarditis (pleuritic chest pain, new pericardial effusion, syncope, ventricular tachycardia, elevated cardiac biomarkers, new left ventricular dysfunction on TTE, and cardiac MRI with late gadolinium enhancement) [12, 13]. The pericardial effusion was present prior to the EMB but worsened after the procedure. Pericardial effusion is a rare complication after EMB [14], and it might have contributed to worsening pericardial effusion in this case. Based on the proximity between initiating treatment with BTZ and clinical presentation with acute perimyocarditis, together with the absence of other causative agents (including infectious) upon extensive testing, we concluded that the acute perimyocarditis is likely secondary to BTZ exposure.

It is worth mentioning that in our patient, the parvovirus B19 IgG level and myocardial PCR testing were positive. However, IgM serology, serum qualitative PCR for deoxyribonucleic acid, and immunohistochemical staining on myocardial tissue for parvovirus B19 were all negative. Given the lack of viral prodrome in our patient and the lack of evidence supporting an acute parvovirus B19 infection, the positive IgG serology and myocardial PCR

for parvovirus B19 were thought to be indicative of latent persistence of the viral genome. Several studies in fact suggested that parvovirus DNA can persist in myocardial tissue after the prior primary infection, does not suggest a pathogenic role, and is not a proof of casual relationship between parvovirus infection and cardiac disease [15, 16].

To further evaluate the causality assessment of an adverse drug reaction to BTZ in our case, correlation was made using 2 separate causality assessment scoring tools: the World Health Organization – Uppsala Monitoring center (WHO-UMC) scale, which is a clinical judgment-based causality assessment tool [17], and the Naranjo algorithm [18]. Bortezomib association scored as “probable or likely” on the WHO-UMC and the Naranjo algorithm scored 6 points on a limited number of applicable questions, classifying association as “probable” (several algorithm questions could not be scored due to lack of applicability).

It is unclear whether lenalidomide might have potentiated this event as Fradley et al. [6] reported increased cardiovascular toxicity with combination of a proteasome inhibitor with immunomodulator drugs, but our patient was restarted on lenalidomide as a maintenance therapy after autologous hematopoietic stem transplant, with no recurrence or worsening in her cardiac function. Due to severity of the adverse drug reaction, BTZ was discontinued indefinitely. It is unclear if any patient-specific factors (genetic or otherwise) contributed to the likelihood of this event.

Conclusion

We describe a unique and – to our knowledge – the first case of acute perimyocarditis after BTZ therapy, as a rare and serious cardiac adverse event. This case illustrates that it can present with syncope and ventricular tachycardia, which further carry risks of patient morbidity and mortality. We recommend close clinical vigilance in patients receiving BTZ therapy and initiation of appropriate diagnostic and clinical cardiac monitoring for patients who may report cardiovascular symptoms. Last, all further BTZ use should be discontinued in such patients, and close monitoring employed, should the oncologic require further consideration of proteasome inhibitor-based therapy, as is usually the case in long-term management of MM and other hematologic malignancies.

Statement of Ethics

The article describes a case report. Therefore, no additional permission from our ethics committee was required. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Yaman Alali searched the literature and wrote the manuscript. Muhamed Baljevic supervised the patient treatment, critically revised, and edited the manuscript. All authors have made significant contributions to the manuscript and have reviewed it before submission. All authors have confirmed that the manuscript is not under consideration for review at any other journal. All authors have read and approved the final manuscript.

Data Availability Statement

All data underlying the results are available as part of the article, and no additional source data are required.

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