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Bortezomib: treating the cancer, killing the heart

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Authors' contributions
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Abstract
Multiple myeloma (MM), a malignancy of the plasma cells, accounts for an estimated 14% of all newly diagnosed hematologic malignancies. Advances in chemotherapy and stem cell transplantation have improved survival rates, but MM remains incurable. Bortezomib, a first-in-class proteasome inhibitor, has been approved for patients with MM who have received at least two prior treatments and have demonstrated disease progression on the most recent one. During clinical trials, most side effects were manageable with standard interventions. The most common toxicities were asthenic conditions (fatigue, malaise, and weakness), gastrointestinal disturbances (nausea, vomiting, diarrhea, and constipation), thrombocytopenia, peripheral neuropathy, pyrexia, and anemia. Most rare complication of cardiac toxicities include first degree and complete heart block eventually leading to decompensated heart failure.

Case report

A 57 year old female, post menopausal status, known case of hyperthyroidism since a year, TSH well controlled on tablet neormercazole 10mg once a day. After seeking medical help for generalized weakness and three months previously, the patient was first identified as having multiple myeloma. No complaints of fever, chest pain, loss of consciousness, breathlessness or bleeding PV or PR. She consumed a non vegetarian diet and did not suffer from any other co morbidities. No relevant family history. However, she had pallor and gave history of multiple blood transfusions in the last 1 year. Her vitals were normal and general examination of the patient showed no significant abnormalities. No signs or symptoms of hemolysis or history of trauma.

Bone marrow aspiration and biopsy study was done which showed hypercellular marrow particles. Normal haematopoietic cells of the marrow were replaced by plasma cells. Few cells are binucleated and few are showing flaming cytoplasm. Cells of myeloid and erythroid series are markedly diminished. Few megakaryocytes seen. No parasites seen. Iron stores 3+. Plasma cells 65%. Features suggestive of plasma cell myeloma. Normal LDH levels.

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Serum total proteins value was reduced to 6.0mg/dl and albumin concentration 3.4mg/dl. A/G ratio was 1.6. Serum protein electrophoresis showed presence of M band 9.4% and 0.59g/dl, seen in beta region. Low IgA and IgG values and serum beta 2 microglobulin. Serum calcium levels were normal. No metastasis found on radiological scans. She was diagnosed stage 1 plasma cell IgA myeloma and started on weekly cycles of injection dexamethasone 40mg IV and injection Bortezomib 2mg IV. Before starting treatment, her ECG showed normal sinus rhythm, and echocardiography of the heart showed an ejection fraction of 60% and no regional wall motion abnormality detected. 3 weeks post starting treatment, 3 doses of injection bortezomib later, patient came for the fourth cycle. Before starting the therapy, patient complained of palpitations. A routine ECG was taken which showed an increase in PR interval. No tachycardia, or rise or fall in blood pressure noted. She was hemodynamically stable. Echocardiography was normal, cardiac enzymes were in the normal range. Oncologist opinion was taken who suggested change in the course of management and with hold bortezomib.

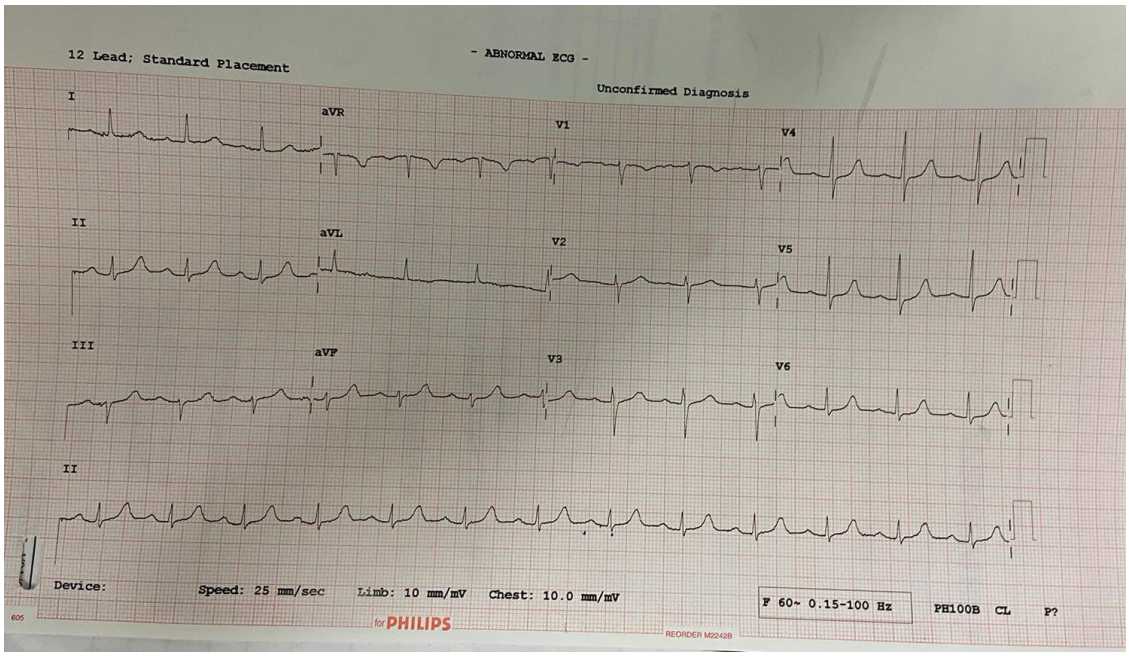

Figure 1: shows an electrocardiogram with a PR interval of 0.24s, first degree heart block.

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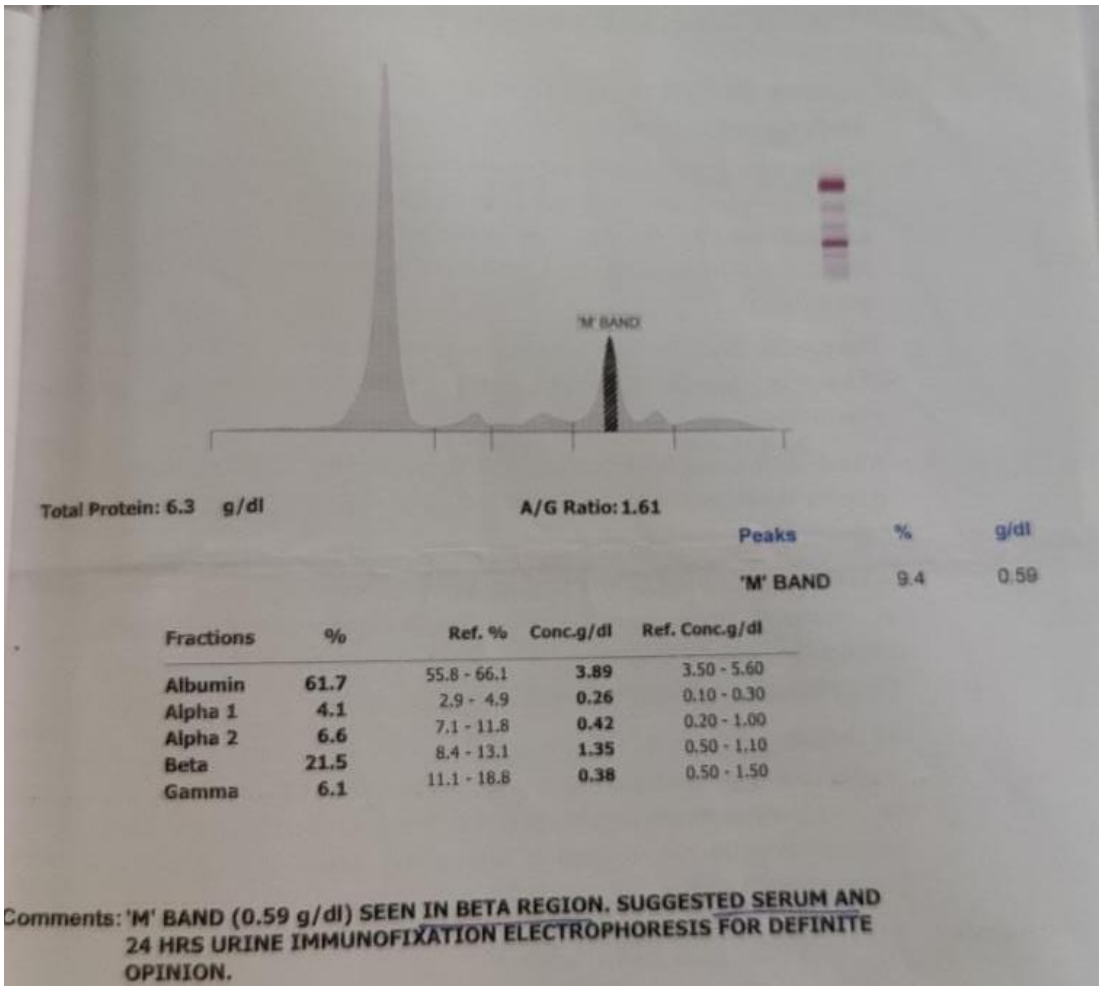

Figure 2: serum protein electrophoresis report.

Patient is now on regular follow up for new course of management.

Discussion

This patient reveals bortezomib's infrequently occurring severe cardiovascular effects and highlights the potential value of biomarkers in predicting cardiac dysfunction in individuals receiving this medication.

By upsetting protein homeostasis and inhibiting transcription factors like nuclear factor kappa-B, the ubiquitin-proteasome system is essential for controlling the cell cycle, death, and angiogenesis.[1] Therefore, it makes sense to target the ubiquitin proteasome pathway as part of cancer therapy.[2] A novel anti-cancer drug called bortezomib, a dipeptide boronate proteasome inhibitor, has been given the green light by the US Food and Drug Administration for the treatment of non-Hodgkin lymphoma and multiple myeloma (MM).[3]

The pathogenesis of bortezomib related cardiotoxicity is currently unknown.

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Reduced proteasome activity is linked to a higher incidence of death in smooth muscle cells, which leads to atherosclerotic plaque instability because the fibrous cap becomes weaker and the necrotic core becomes larger.[4] This increases the atherosclerotic plaque's propensity to rupture, which can lead to ischemic problems. According to cell culture studies, bortezomib significantly alters the structure of the cardiomyocytes' mitochondria, which reduces the production of adenosine triphosphate (ATP) and the contractility of the heart muscle.[5] Therefore, taking bortezomib can cause a serious left ventricular contractile dysfunction. This view is supported further by the fact that heart failure can be reversed after quitting bortezomib and by negative angiography results.

Pro-brain natriuretic peptide (pro-BNP) concentrations have been demonstrated to be higher in various case reports of individuals with congestive heart failure, but cardiac enzymes such creatinine phosphokinase and troponin I do not significantly rise.[6] Therefore, it is currently unclear if pro-BNP or cardiac enzymes could be employed to track the cardiotoxicity brought on by bortezomib. To overcome this issue, more research is still required.[7] The meta-analysis in this study by Xiao et al, demonstrated that bortezomib usage does not significantly increase the risk of all-grade and high grade cardiotoxicity. Clinicians should be aware of this risk and provide close monitoring in patients receiving these therapies.[8] The reported findings are most likely the result of cardiotoxicity brought on by chemotherapy. To rule out common cardiac disorders including atherosclerotic heart disease and myocarditis, which can result in the observed findings, the patient underwent a complete cardiac assessment. Additionally, there is no evidence to support cardiac amyloid or other infiltrative illnesses as the reason of his cardiac dysfunction based on the results of the echocardiography and cardiac MRI.

Cardiovascular actions of thyroid hormones are presented via different mechanisms in the body, including complex and multisystemic interactions.[9] Treatment of hyperthyroidism is important to prevent arrhythmic complications and even a subclinical hyperthyroid state should be treated, especially in high-risk patients.[10]

The non-lysosomal degradation of intracellular proteins, such as transcription factors that control essential mechanisms of plaque formation and rupture and important regulators of cell cycle, angiogenesis, and apoptosis, is carried out via the ubiquitin-proteasome system. Additionally, there is a correlation between reduced proteasome activity and a higher incidence of death in smooth muscle cells, which results in the instability of atherosclerotic plaques by weakening the fibrous cap and enlarging the necrotic core.[11] Additionally, NF-B activation is

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crucial for the second window of protection of delayed ischemic preconditioning in the myocardium, which results in myocardial cytoprotection.[12] There is ample experimental evidence that demonstrates the critical role that a deficiency in proteasome activity plays in reducing cardiac function through a number of mechanisms, the most significant of which is posited to be the accumulation of unfolded, damaged, and undegraded proteins inside myocytes.[13] Because the myocardium is made up of cells with a limited capacity for regeneration, chemotherapeutic drugs may have long-lasting or temporary negative effects on the heart. These illnesses range from generally benign arrhythmias to potentially fatal problems like cardiac ischemia/infarction and cardiomyopathy within the umbrella of this toxicity.[14] Because the myocardium is made up of cells with a limited capacity for regeneration, chemotherapeutic drugs may have long-lasting or temporary negative effects on the heart. These illnesses range from generally benign arrhythmias to potentially fatal problems like cardiac ischemia/infarction and cardiomyopathy within the umbrella of this toxicity.[15] A similar case reported of a 60 year old woman with multiple myeloma on bortezomib therapy developed heart failure, which was detected on gadolinium contrast enhanced MRI.[16] However our patient had not developed heart failure yet.

In an elderly population with numerous concomitant cardiovascular risk factors, MM arises. Heart problems are also a result of the main illness process. Additionally, a lot of MM patients have previously received cardiotoxic chemotherapy, namely anthracyclines. Identification, prevention, and management of cardiovascular problems are becoming more and more challenging as a result of these events. All three of the Proteasome Inhibitors that are now approved—bortezomib, carfilzomib, and ixazomib—have been linked to cardiotoxicity in numerous clinical studies and case reports. There is mixed information about the contribution of bortezomib to the development of cardiotoxicity, whereas carfilzomib has demonstrated the highest rates of cardiotoxicity. But numerous case studies have confirmed the existence of negative cardiac consequences.[17] The unfolded protein response, which results in cardiac myocyte death, is assumed to be the mechanism through which Proteasome Inhibitors produce cardiotoxicity. In an animal model, apremilast and rutin have been used to counteract this signalling. There are currently no standardised standards for identifying patients who are most at risk for problems or managing them. It has been effective to withhold medicine, use slower infusion rates, restrict fluid intake, and administer supportive care. The efficacy of screening echocardiograms has not been established.[17]

The pursuit of curing cancer and enhancing survivors' prognoses has propelled the development of novel antineoplastic medicines and produced notable advances in research. These developments, when coupled with quick screening and early identification, have greatly increased patients' chances of surviving various cancers. Consequently, one of the main causes of morbidity and mortality in cancer survivors is chemotherapy-related toxicity in various organ systems, particularly the cardiovascular system. Recent research places secondary malignant malignancies and chemotherapy-induced cardiotoxicity as the second and third main causes of morbidity and mortality, respectively.[18] A crucial component of modern anti-myeloma therapy, bortezomib has a strong clinical efficacy and tolerable side effects. Although fatigue and gastrointestinal problems are the most frequent side effects, peripheral neuropathy and thrombocytopenia are the main toxicities that limit the dose of bortezomib-based combination regimens. Since these combinations are more efficient, disease-related symptoms vanish more quickly, and the anti-inflammatory benefits of bortezomib were not found to be amplified, toxicity.[19] Contrary to intravenous bortezomib, subcutaneous bortezomib had a decreased incidence of peripheral neuropathy while not significantly reducing therapeutic efficacy. Subcutaneous bortezomib may lessen the frequency of thrombocytopenia and renal and urinary problems when compared to intravenous bortezomib, although additional clinical trials are required to validate this.[20]

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