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CASE REPORT
Coronary heart disease

Proteasome inhibitor-induced coronary vasospasm in multiple myeloma: a case report

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Background Coronary vasospasm is an increasingly recognized cause of myocardial infarction or myocardial ischaemia in patients without obstructive coronary artery disease. A thorough medication review may identify drugs or toxins that could trigger coronary vasospasm. This case provides mechanistic insight into the off-target effect of proteasome inhibition leading to coronary vasospasm in a patient referred with chest pain consistent with typical angina.

Case summary A 72-year-old lady presented with anginal chest pain at rest with electrocardiogram evidence of myocardial ischaemia who was referred for invasive coronary angiography. This demonstrated minor coronary disease without an obstructive lesion. Vasoreactivity testing revealed diffuse coronary vasospasm of the left anterior descending artery. Carfilzomib was identified as the trigger for coronary vasospasm. Symptoms resolved without recurrence after appropriate treatment including cessation of the triggering agent.

Conclusion Coronary spasm is a rare but important adverse reaction to proteasome inhibitors. This case supports the clinical utility of invasive coronary vasoreactivity testing in patients with ischaemia with no obstructive coronary artery disease.

Keywords Case report • Carfilzomib • Coronary vasospasm • Vasospastic angina • INOCA

Learning points

- Carfilzomib is a proteasome inhibitor indicated for treatment of multiple myeloma that may increase propensity towards acute coronary syndromes via endothelial impairment and coronary spasm.
- Coronary vasospasm is a frequently overlooked but treatable cause of myocardial ischemia and/or infarction in patients without obstructive coronary disease (MINOCA)

Introduction

Coronary vasospasm is frequently overlooked but a treatable cause of myocardial ischaemia and/or infarction in patients without obstructive coronary disease. Recognition of non-atherosclerotic causes of myocardial ischaemia is important as it helps guide therapy. The prevalence of vasospasm in patients with symptoms and/or signs of myocardial ischaemia may be as high as 40%.[1] Invasive coronary vasoreactivity testing with acetylcholine is supported by consensus guidelines for chronic coronary syndromes.[2] Proteasome inhibitors such as carfilzomib have been shown to induce endothelial impairment and

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increase the risk of vasospasm and myocardial infarction.[3] We present a case detailing vasospastic angina secondary to carfilzomib use.

Timeline

3 months prior to the initial presentation	Intermittent chest pain
Initial presentation to hospital:	Chest pain during carfilzomib administration. Troponin within normal limits
1 week post-initial presentation	Seen by the cardiologist. Transthoracic echocardiogram demonstrated normal left ventricular function and size
2 weeks post-initial presentation	Coronary angiogram with vasoreactivity testing demonstrating coronary vasospasm. Commenced on statin and calcium channel blocker
4 weeks post-coronary angiography	Calcium channel blocker ceased due to intolerance
6 weeks post-coronary angiography	Routine outpatient electrocardiogram while pain free demonstrated resolution of changes previously noted
6 months post-coronary angiography	Well in the community without further chest pain. Electrocardiogram remains normal

Case presentation

A 72-year-old lady was referred to the emergency department with chest pain occurring during her twelfth cycle of carfilzomib infusions (56 mg/m^2 received on Days 1, 2, 8, 6, 15, and 16 of every 28-day cycle) as a treatment for her multiple myeloma. She had been receiving this therapy for the preceding 12 months but reported 3 months of similar intermittent chest pain. She described her pain as localized, central chest tightness with radiation to her right arm and the right side of her neck. The pain would typically last 5–10 min before spontaneously resolving. This could occur at rest or with exertion and did not have diurnal variation. She also described associated dyspnoea on exertion for the preceding 3 months without orthopnoea, paroxysmal nocturnal dyspnoea, or leg swelling. She had no traditional cardiac risk factors but was referred for cardiovascular assessment given the nature of her presentation. Clinical examination revealed a slim, normotensive woman with a normal cardiopulmonary exam.

Intercurrent medications included dexamethasone, thalidomide, and trimethoprim/sulfamethoxazole in addition to carfilzomib as part of her treatment for multiple myeloma. She was on no other regular medications.

The differential diagnosis at this time included obstructive coronary artery disease, disorders of coronary vasomotion including microvascular and/or vasospastic angina, congestive cardiac failure, and pulmonary emboli.

An electrocardiogram while pain free in the emergency department demonstrated sinus rhythm at a rate of 70 b.p.m. There was poor R wave progression and ischaemic T wave inversion through the anterior leads without conduction abnormalities (*Figure 1*). High sensitivity troponin T was 8 ng/L (reference range <16 ng/L). A transthoracic echocardiogram demonstrated normal left ventricular size and function with no regional wall motion abnormalities. There was no evidence of pulmonary hypertension or valvular disease. She was discharged from the emergency department and organized to see a cardiologist as an outpatient for further assessment.

Given the clinical presentation and electrocardiogram (ECG) abnormalities, her cardiologist organized for invasive coronary angiography. The angiogram demonstrated minor irregularities within the coronary vessels but no obstructive stenosis to account for the clinical presentation. Invasive physiological testing for disorders of coronary vasomotion was performed using incremental doses of 2, 20, and 100 µg of acetylcholine manually infused over a period of 3 min into the left coronary artery via the angiographic catheter. Vasoreactivity testing revealed diffuse epicardial coronary spasm with dynamic subtotal occlusion of the mid-distal left anterior descending artery (*Figure 2*). This was associated with >2 mm ST-segment depression on ECG monitoring with reproduction of the chest pain that triggered the initial presentation. Intra-coronary glyceryl trinitrate (GTN) was used to relieve the spasm. The diagnosis of vasospastic angina was made as per international guidelines and the proteasome inhibitor, carfilzomib, was implicated as a likely trigger given no alternative agent or lifestyle factor could be identified to account for the symptoms and findings.

The management of vasospastic angina typically requires the removal of any offending agents with the addition of anti-spasmodic agents as required. Carfilzomib was withheld and therapy to enhance endothelial function (Rosuvastatin 10 mg daily) and reduce vasospasm (Amlodipine 5 mg daily) was commenced. Cardiology and haematology teams made a joint plan to not re-challenge the patient with carfilzomib and alternative therapy with lenalidomide, ixazomib, and dexamethasone was used (as per haematological guidelines) to manage her progressive multiple myeloma. At 4-week follow-up post-angiography, she ceased the amlodipine due to intolerable facial flushing and ankle oedema.

Repeat ECG as an outpatient 6 weeks post-angiography demonstrated resolution of the anterior ECG changes. At 6-month post-angiography follow-up, she remains angina free in the community without taking regular anti-anginal therapy. Given the timing of symptom resolution and the demonstration of reversible epicardial spasm with carfilzomib, her presentation was most consistent with a proteasome inhibitor-induced coronary endothelial impairment and spasm. Her multiple myeloma is proving increasingly difficult to manage and next-line treatments are being considered.

Discussion

Carfilzomib is a novel proteasome inhibitor used to treat multiple myeloma. Proteasome inhibitors are known to induce endothelial impairment and increase the risk of myocardial infarction.[3] Mechanistic data from an animal model implicated increased vascular tone and exaggerated vascular spasmodic responses due to carfilzomib.[4] We performed a systematic literature review finding no previously reported case of carfilzomib-induced coronary spasm in humans

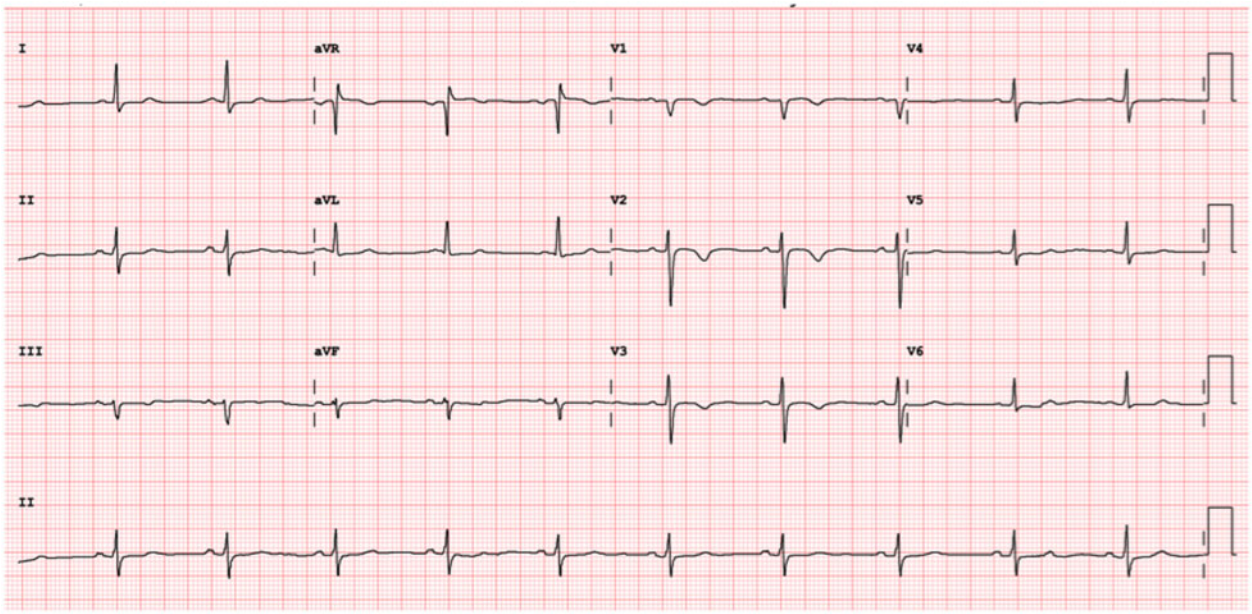

Figure 1 Electrocardiogram demonstrating widespread T wave inversion and poor R wave progression. Recorded when patient was pain free.

although we did note a case of coronary vasospasm associated with the proteasome inhibitor bortezomib.[5] Additionally, carfilzomib has also been shown to increase the risk of cardiovascular adverse events including atherosclerotic mediated acute coronary syndromes.[6] The mechanism for this remains poorly understood but disruption to the ubiquitin-proteasome system through off-target proteasome inhibition has been implicated.[7]

In general, the pathophysiology of coronary vasospasm relates to combinations of vascular smooth muscle hypercontractility, endothelial dysfunction, low-grade inflammation, and oxidative stress.[8] Carfilzomib-induced endothelial impairment may leave susceptible individuals prone to altered vascular tone and enhanced smooth muscle contractility resulting in downstream myocardial ischaemia.

Ischaemia and No Obstructive Coronary Artery disease (INOCA) is a heterogeneous clinical syndrome requiring careful stratified testing to reveal the underlying diagnosis. Invasive coronary vasoreactivity testing with acetylcholine is supported by consensus guidelines for chronic coronary syndromes but the recommendations are less clear after unstable angina.[2,9]

Meanwhile, the prevalence of vasospasm in patients with symptoms and/or signs of INOCA may be as high as 40%.[1] The true prevalence of vasospastic angina will depend on the population studied, timing and type of diagnostic testing as well as the definition used.

Vasospastic angina is a diagnosis requiring three considerations:[10]

(1) Nitrate responsive angina during a spontaneous episode with at least one of:
- Rest angina (especially in a nocturnal predominance)
- Marked diurnal variation in exercise tolerance (reduced in the morning)
- Precipitated by hyperventilation
- Reduction in number of events with the use of a calcium channel blocker

(2) Transient ECG changes during a spontaneous episode including any of the following in at least two contiguous leads
- ST-elevation ≥0.1 mV
- ST-depression ≥ 0.1 mV
- New negative U waves

(3) Coronary artery spasm is defined as transient total or sub-total (>90%) coronary artery occlusion with angina and ischaemic ECG changes either spontaneously or in response to a provocative stimulus.

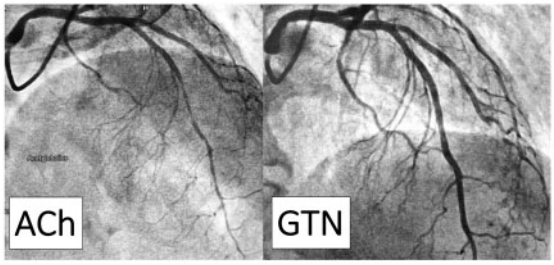

Figure 2 Coronary angiogram image demonstrating with sub-total occlusion of the left anterior descending artery after acetylcholine challenge (Ach) with resolution of artery after intra-coronary glyceryl trinitrate was administered. The patient experienced reproduction of angina with near occlusive diffuse distal coronary spasm (on angiography >90%) with 1–2 mm of dynamic ST depression. These three metrics fulfilled diagnostic criteria for vasospastic angina.

The diagnosis of vasospastic angina relies on having a high index of suspicion, particularly in patients with the non-cardiac disease, systemic treatments, and a compatible history (GTN responsive angina, diurnal variation, or exposure to potential triggering agents). The use of clear diagnostic criteria helps to establish the diagnosis and apply effective therapy to improve patient outcomes.[10]

Carfilzomib is a potentially important and reversible cause of coronary vasospasm. This case provides insight into the mechanism of proteasome inhibitors related to acute coronary syndrome. Coronary vasospasm is a frequently overlooked but treatable cause of myocardial ischaemia and/or infarction in patients without obstructive coronary disease.

Lead author biography

Dr Philopatir Mikhail is a Cardiology Advanced Trainee at Gosford Hospital in Australia with a special interest in coronary artery disease and coronary physiology. He hopes to pursue subspecialty training in Interventional Cardiology.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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