Combined lenalidomide/bortezomib for multiple myeloma complicated by fulminant myocarditis: a rare case report of widely used chemotherapy

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Background
Drug-induced myocarditis is a rare complication of certain cancer treatments, characterized by the development of myocardial inflammation shortly after initiation of treatment, potentially leading to heart failure and/or malignant arrhythmias. The development of eosinophilic myocarditis after administration of lenalidomide has been described and bortezomib has been associated with the development of cardiomyopathies and atherosclerosis.

Case summary
A 69-year-old woman, recently diagnosed with multiple myeloma underwent local radiotherapy for a pathological fracture of the 4th lumbar vertebra and was treated with bortezomib–lenalidomide–dexamethasone. Within 19 days after therapy initiation, she presented with gastrointestinal symptoms, an erythematous pruritic rash, and general fatigue. Surprisingly, routine electrocardiogram (ECG) showed upwardly concave ST-elevation in I and aVL and ST-depressions in II, III, and aVF. Troponin levels were markedly elevated to 5470 ng/L. Complete blood count revealed eosinophilia. Based on further cardiac work-up, including echocardiography, coronary angiography, and cardiac magnetic resonance imaging (MRI) showing positive T2 imaging and patchy subepicardial late gadolinium enhancement, she was diagnosed with hypersensitivity myocarditis. Additional endomyocardial heart biopsy did not reveal any abnormalities, probably due to sampling error. After discontinuation of chemotherapy and prompt treatment with high doses of corticosteroids, the patient recovered.

Discussion
Diagnosis of drug-induced myocarditis can be challenging and even long known widely used (chemo)therapy should be considered a potential trigger. Early diagnosis and treatment are crucial, warranting alertness for suggestive symptoms. Cardiac biomarkers, ECG monitoring, and cardiac MRI are key to confirm the diagnosis. In patients with preserved left ventricular systolic function, two-dimensional speckle tracking echocardiography can provide additional diagnostic information. Every patient presenting with eosinophilia and/or acute onset of auto-immune symptoms after initiation of therapy with lenalidomide/bortezomib deserves prompt cardiac screening. The gold standard remains an endomyocardial biopsy, although sampling error may occur.

Keywords
Case report • Cardiotoxicity • Myocarditis • Lenalidomide

ESC Curriculum
2.1 Imaging modalities • 6.9 Cardiac dysfunction in oncology patients

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Learning points

- Hypersensitivity myocarditis can be part of a generalized hypersensitivity syndrome. Its presentation can be insidious and diagnosis can be challenging.
- Transthoracic ultrasound with strain imaging can provide additional diagnostic information in the diagnostic work up of myocarditis.
- Every patient presenting with eosinophilia and/or acute onset of auto-immune symptoms after initiation of lenalidomide/bortezomib therapy deserves prompt cardiac screening.

Introduction

A number of drugs are associated with reactive hypersensitivity myocarditis.\(^1,2\) Lenalidomide is a second-generation immunomodulatory drug, widely used for treatment of multiple myeloma (MM), myelodysplastic syndrome, and non-Hodgkin lymphoma (follicular lymphoma, marginal zone lymphoma, and mantle cell lymphoma).\(^3\) Common side effects include fatigue, diarrhoea, muscle cramps, and skin rash. Cardiotoxicity has also been described.\(^4,5\) Bortezomib, a proteasome inhibitor, has very rarely been linked to the development of cardiomyopathies and atherosclerosis.\(^6\) Lenalidomide and bortezomib are both known to be radiosensitizers, and myocarditis has been described after the use of lenalidomide.\(^1,4,7,8\)

We report a case of therapy-induced myocarditis in a patient treated with the combination of radiotherapy and bortezomib–lenalidomide–dexamethasone (VRd) for MM. To our knowledge, this is the first case presenting with myocarditis as part of a reactive hypersensitivity syndrome without cardiac symptoms, highlighting (or underlining) the importance of screening for this rare but potentially fatal complication even in the absence of cardiac symptoms.

Hypersensitivity myocarditis is known to be a cardiac manifestation of delayed type hypersensitivity, mostly caused by drug exposure.\(^9\) The clinical presentation can be variable, ranging from paucisymptomatic to acute fulminant myocarditis or chronic restrictive cardiomyopathy.\(^1\) Eosinophils infiltrate the myocardium and release reactive substances directly damaging cardiac myocytes and endothelial cells. Increased peripheral eosinophilia can be detected in 63.5% but can also occur later during presentation.\(^2\)

Timeline

| Time      | Event                                                                                                                                                                                                 |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Day 1     | Start of bortezomib–lenalidomide–dexamethasone (VRd) treatment [bortezomib (1.3 mg/m\(^2\))–lenalidomide (25 mg/day)–dexamethasone (20 mg)] in a 28 day cycle, with concomitant local radiotherapy of lumbar vertebra L4 for newly diagnosed multiple myeloma. |
| Day 19    | Hospital admission with gastrointestinal complaints (nausea, vomiting, diarrhoea, and abdominal pain), general fatigue, and an erythematous pruritic rash. Electrocardiogram showed convex ST-elevation in I and aVL and reciprocal ST-depression in II, III, and aVF. Serum troponin were markedly elevated at 5470 ng/L, but serial follow-up values were non-progressive. Echocardiography showed a localized, posterolateral pericardial effusion without regional wall motion abnormalities. |
| Day 20    | Cardiac magnetic resonance imaging (MRI) showed a pseudo myocardial infarction pattern with myocardial oedema and inflammation, most pronounced in the anterior wall and localized severe dyskinesia. Initiation of pulse dose corticosteroids treatment in combination with low-dose angiotensin-converting enzyme inhibitors and betablockers. |
| Day 23    | Ventricular tachycardia. Return to sinus rhythm after administration of amiodarone.                                                                                                                  |
| Day 61    | Follow-up MRI showed thinning of the anterior left ventricular wall with a persistent, albeit less intense, contrast enhancement, suggesting regression of myocardial inflammation. |

Case presentation

A 69-year-old woman was diagnosed with MM, complicated with a pathological fracture of the fourth lumbar vertebra. She was known to have arterial hypertension, hypercholesterolaemia, and obesity (body mass index 32 kg/m\(^2\)). No other cardiovascular risk factors were identified. The patient underwent antalgic radiotherapy and was started on systemic therapy with lenalidomide 25 mg (Days 1–
21), bortezomib 1.3 mg/m² (Days 1, 4, 8, 11), and dexamethasone 20 mg (Days 1, 2, 8, 9, 15, 16, 22, 23) in a 28-day cycle regime (VRd). As per protocol in our hospital, enoxaparin 40 mg once daily subcutaneously was started as thromboprophylaxis together with the start of VRd treatment. Nineteen days after initiation of chemotherapy treatment, she presented at the emergency department with acute onset of abdominal pain in the last 12 h associated with nausea, vomiting, and diarrhea. She denied chest pain, shortness of breath, muscle pain, or fever. She mentioned increasing fatigue and pruritus since the third administration of bortezomib (on Day 8) and development of a rash on her chest, abdomen, and back over the last week.

At physical examination, her blood pressure was 114/54 mmHg, heart rate 76bpm, saturation 100% at room air, and temperature 36.8°C. Abdominal palpation revealed a tender right hypochondrium with muscle resistance on deep palpation. There was an extensive erythematous rash (Figure 1). Cardiorespiratory examination remained normal without clinical signs of cardiac decompensation (no rales, no edema, and normal jugular venous pressure).

In the presence of muscle resistance on deep palpation of the abdomen, a computed tomography scan of the abdomen was performed. It did not reveal any acute abdominal abnormalities and excluded mesenteric ischaemia and angio-oedema. Laboratory analyses showed elevated C-reactive protein (47.4 mg/L, normal value < 5.0 mg/L), elevated liver enzymes, lactate dehydrogenases (718 U/L), and creatine kinase (2122 U/L). Surprisingly, serum high-sensitive Troponin T (HS-TnT) were markedly elevated up to 5.47 mg/L (normal value <0.013 mg/L) without any complaints of chest pain. Furthermore, there was a significant increase in N-terminal pro-natriuretic peptide type B (1440 ng/L) without any complaints of chest pain. Electrocardiogram (ECG) showed a sinus rhythm with convex ST elevation in the lateral leads and reciprocal ST depression in the inferior leads (Figure 2). Bed-side echocardiography showed mild concentric hypertrophy of the left ventricle with normal systolic function and unremarkable regional wall motion. There was a localized, posterolateral pericardial effusion measuring 8 mm without haemodynamic repercussion (Figure 3). Bull’s eye plot showed subtle reduction of global longitudinal strain (GLS) in the anterolateral regions.

Differential diagnosis included acute coronary syndrome, myocarditis, and rhabdomyolysis. Since the patient had clinical signs of lenalidomide toxicity, in the absence of chest pain with non-progressive troponins and echocardiographic absence of any regional wall motion abnormalities, lenalidomide-induced myocarditis was most likely. The patient was admitted to the cardiac intensive care unit for monitoring. An immediate coronary angiography was decided not to be indicated. She was started on pulse dose with methylprednisolone 1 g for the first 3 days, followed by oral methylprednisone 64 mg (1 mg/kg) with gradual tapering every 2 weeks. High-sensitive Troponin T levels started to drop shortly after treatment initiation. Further diagnostic work-up with coronary angiography during admission did not reveal any significant coronary lesions, after which a right-sided endomyocardial biopsy was taken. Magnetic resonance imaging (MRI) of the heart confirmed the diagnosis of (mainly) left-sided myocarditis, revealing a pseudo myocardial infarction pattern with myocardial oedema and inflammation, most pronounced in the mid anterior wall with localized severe dyskinesia, but also in the inferior and lateral wall (Figure 4). As the patient was receiving enoxaparin 40 mg OD and cardiac ultrasound/cardiac MRI did not show intracardiac thrombi, myocardial infarction with non-obstructive coronary arteries was very unlikely. Both the abdominal discomfort and the rash disappeared after the initiation of methylprednisolone.

On Day 4, the patient developed sustained ventricular tachycardia. She experienced palpitations but remained haemodynamically stable. Sinus rhythm was restored 30 min after administration of loading dose amiodarone (300 mg). Maintenance therapy with amiodarone orally was continued, including after discharge, but ventricular tachycardia did not recur.

The patient was discharged from the cardiac intensive care unit on Day 10 with methylprednisolone 64 mg OD, in combination with a low-dose angiotensin-converting enzyme inhibitor (ramipril 2.5 mg) and betablocker (bisoprolol 2.5 mg). Troponin levels had decreased till 0.165 mg/L. After 12 days of hospitalization she was discharged home with a follow-up visit in our outpatient clinic after 5 days.

Figure 1 Erythematous pruritic rash over abdomen, chest, and back.
Gradual tapering of prednisolone was planned with dose reduction every 2 weeks (64 mg, 48 mg, 36 mg, 24 mg, 16 mg, 12 mg) and up titration of the heart failure therapy. Follow-up MRI scan was performed 6 weeks after initiation of treatment and showed thinning of the anterior left ventricular (LV) wall with persistent, albeit less intense, contrast enhancement, suggesting regression of myocardial inflammation and allowing further tapering of corticosteroids. Lenalidomide and bortezomib were withheld after this event. The patient was switched to second line treatment with Daratumumab, which was tolerated well. At the moment (January 2022), she is still being treated by our colleagues of haematology for her MM with currently a very good partial response, without signs or symptoms of heart failure.

**Discussion**

With the ever-expanding field of anti-cancer treatments and the growing number of cancer patients, therapy-induced cardiotoxicity has become increasingly important in clinical practice. However, many aspects of both radiation-induced and cancer drug-induced cardiovascular disease remain to be fully elucidated. The clinical
presentation of hypersensitivity myocarditis can be variable, and a high level of suspicion is warranted. Important differential diagnosis included acute coronary syndrome, which was ruled out during admission by coronary angiography as described above, and infective myocarditis. Differential diagnosis is particularly difficult due to similar clinical symptoms, ECG patterns and increased cardiac enzymes.
which are common findings in myocarditis and acute coronary syndrome.11 Diagnosing myocarditis in patients with preserved ejection fraction is especially difficult as conventional transthoracic echocardiography has several limitations in detecting subtle changes in ventricular function. In addition to functional assessment, strain imaging is more promising and seems to be a more sensitive measure of LV contractility.12 Cardiac MRI appears to be the most accurate non-invasive diagnostic modality, but its immediate availability remains limited.13 According to the Lake Louisa criteria, positive T2 imaging and invasive diagnostic modality, but its immediate availability remains limited. Interestingly, all patients were women and presented within 30 days after treatment initiation. To our knowledge, our case is the first patient presenting with hypersensitivity syndrome but without classical signs and symptoms of cardiac disease (no thoracic pain, no dyspnoea, and no signs of cardiac decompensation). Nevertheless, the patient developed a malignant arrhythmia during hospitalization underlining the importance of screening for this rare yet potentially fatal complication. In their paper published in 2020, Jacob et al.7 already recommend routine cardiac screening (cardiac enzymes, cardiac MRI, coronary angiography, and endomyocardial biopsy) when patients present with eosinophilia, skin reactions, or acute onset of auto-immune illness (e.g. colitis or thyroiditis) in the context of treatment with lenalidomide (Figure 5). We would suggest to include transthoracic ultrasound with strain imaging in the diagnostic work up, based on our case and the recent paper from Meindl et al.15 in which the diagnostic value of two-dimensional speckle tracking echocardiography was compared to late gadolinium enhancement by cardiac MRI in patients with acute myocarditis and normal global LV ejection fraction.

For logistical reasons, we performed right heart catheterization with endomyocardial heart biopsy before the cardiac MRI. Surprisingly, pathology results showed no significant abnormalities according to Dallas Criteria in our patient, while other cases have reported lymphocytic eosinophilic infiltration of the myocardium.14-7 In hindsight, this is most probably ascribable to sampling error as the biopsy was taken on the right side of the heart, while the typical myocarditis features were most pronounced on the anterior wall. Therefore, in order to reduce the risk of sampling errors, imaging-guided endomyocardial biopsy should be considered when feasible, as both diffuse and localized myocarditis have been described. Based on autopsy series of hypersensitivity myocarditis, it has been reported that half of the cases have infiltrates with focal lesions that could potentially be missed on biopsy.7 As the degree of eosinophilic infiltration in the heart is thought to depend on the degree and duration of eosinophilic exposure,2 the localized involvement can be thought of as an earlier stage in the process of eosinophilic infiltration. Besides this our patient was also treated with dexamethasone as part of her cancer treatment, which could potentially have tempered the inflammatory reaction.

**Conclusion**

Diagnosis of medication-induced myocarditis can be challenging and even long known widely used chemotherapy should be considered a potential trigger. Early diagnosis and treatment are essential, warranting alertness for suggestive symptoms. Every patient presenting with eosinophilia and/or acute onset of auto-immune symptoms after initiation of lenalidomide/bortezomib therapy deserves prompt cardiac screening. Cardiac biomarkers, ECG monitoring, and cardiac MRI are necessary to make the diagnosis. In patients with preserved LV systolic function, two-dimensional speckle tracking echocardiography can provide additional diagnostic information. Gold standard for diagnosis remains an endomyocardial biopsy and imaging-guided techniques should be considered in order to reduce the risk of sampling errors. Treatment consists of interruption of the culprit drug in combination with high-dose corticosteroids and heart failure therapy.

**Lead author biography**

Matthias Verbesselt graduated as MD at KU Leuven in 2018 and first spent 3 years in clinical training as a resident of Internal Medicine. His interests quickly veered towards cardiology, infectious disease, and intensive care. He is now a resident in Cardiology focusing mainly on heart failure and cardiac intensive care. He considers cardiovascular disease, cancer, and the effects of new cancer treatment on cardiac function as one of the main challenges of modern medicine.

**Supplementary material**

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

**Slide sets:** A fully edited slide set detailing this case 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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