# Eosinophilic myocarditis during treatment of acute myeloid leukaemia: cardiac magnetic resonance in the very early phase mimicking triple-vessel coronary artery disease: a case report

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| **Background** | Chemotherapy of acute myeloid leukaemia (AML) can cause a broad spectrum of cardiotoxic effects. Cardiac magnetic resonance (CMR) is key for the diagnosis of eosinophilic myocarditis (EM) defined by the presence of sub-endocardial necrosis and fibrosis. This case report describes the picture of severe triple-vessel ischaemia due to infiltration of eosinophilia without atherosclerotic coronary artery disease (CAD). |
| **Case summary** | A 57-year-old woman was diagnosed with AML requiring chemotherapy. Three days after initiation of chemotherapy, the patient presented with chest pain and new left ventricular (LV) dysfunction and hyper-eosinophilia. A CMR examination initially was compatible with severe triple-vessel ischaemia. Tissue characterization by CMR was not done due to severe dyspnoea promoting the differential diagnosis of triple-vessel CAD or chemotherapy-induced triple-vessel coronary spasm. However, invasive coronary angiography excluded obstructive CAD. Severe LV dysfunction and troponin elevation persisted arguing against coronary vasospasm. Chemotherapy induced a massive increase in blood eosinophils, and EM was considered as most likely diagnosis. Immunosuppressive treatment improved the patient's status and a CMR later on confirmed the diagnosis of EM. |
| **Discussion** | Chemotherapy-induced massive eosinophilia can cause widespread coronary micro-vascular infiltration mimicking severe triple-vessel CAD. Early CMR did not evaluate tissue composition, and EM was not considered which delayed adequate treatment. A complete CMR assessment is key to establish the correct diagnosis. |
| **Keywords** | Eosinophilic myocarditis • Case report • Acute myeloid leukaemia • Cardiac MRI |
| **ESC Curriculum** | 2.1 Imaging modalities • 2.3 Cardiac magnetic resonance • 3.2 Acute coronary syndrome |

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> ### Learning points
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> - Global sub-endocardial hypoperfusion can be due to massive damage by hyper-eosinophilia but also triple-vessel atherosclerotic coronary artery disease (CAD), generalized vasospasms, a severe drop in perfusion pressure (e.g. in aortic insufficiency), or cardiac amyloidosis can cause extensive balanced sub-endocardial ischaemia.
> - Eosinophilic infiltration with massive damage of the coronary micro-circulation may mimic severe triple-vessel CAD.
> - In case of strong suspicion of eosinophilic myocarditis, late gadolinium enhancement by cardiac magnetic resonance is highly recommended to confirm/exclude the diagnosis and not delay treatment.

## Introduction

Cardiac manifestations of hyper-eosinophilia are the main causes of morbidity and mortality. An eosinophilic syndrome is a hyper-eosinophilia with organ involvement.[1] Up to 20% of patients with hyper-eosinophilic syndrome have cardiac involvement.[1–3] The aetiology of the eosinophilia must be determined and may be primary (myeloproliferative disease), secondary (parasite, medication, allergy), or idiopathic. The main clinical presentation is dyspnoea followed by chest pain and cough. The diagnosis of eosinophilic myocarditis (EM) is based on symptoms suggestive of acute coronary syndrome or heart failure associated with a peripheral blood hyper-eosinophilia of more than $1.5 \times 10^9$/L. Echocardiography and in particular cardiac magnetic resonance (CMR) are the next diagnostic steps, while endomyocardial biopsy (EMB) remains the gold standard to establish the diagnosis.[1–4] If no EMB is available, CMR is the non-invasive test of choice to support the diagnosis of EM.[1–3] In this case report, we will show the range of signs and symptoms and potential difficulties encountered in the diagnosis of EM in the setting of acute myeloid leukaemia (AML) chemotherapy.

## Timeline

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| 19 July 2021 | Diagnosis of myeloid leukaemia NPM1 |
| 21 July 2021 | Intra-thecal chemotherapy: hydrocortisone 30 mg, cytarabine 30 mg, methotrexate 15 mg 100% |
| 23 July 2021 | Chemotherapy (7 + 3): cytarabine 370 mg/dose d1–d7, daunorobucine 110 mg/dose d1–d3 |
| 25 July 2021 | Onset of chest pain with cardiovascular risk factors |
| 26 July 2021 | CMR: non-dilated LV with ejection fraction of 32% on global hypokinesia. Extensive sub-endocardial hypoperfusion during adenosine stress. Due to severe dyspnoea, the exam was stopped prematurely and no late gadolinium enhancement (LGE) imaging was performed. Differential diagnosis: severe myocardial ischaemia due to either to: triple-vessel coronary artery disease (CAD) or triple-vessel coronary vasospasm. $T_2$-mapping with high normal values indicating absence of myocardial oedema. Triple-vessel CAD was retained as working diagnosis |
| 26 July 2021 | Coronary angiography: no atherosclerotic coronary disease |

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| 11 August 2021 | Cardiorespiratory arrest due to ventricular fibrillation treated by external shock |
| 20 August 2021 | CMR: non-dilated left ventricular (LV) with persisting severely reduced Ejection fraction of 31% on global hypokinesia. LGE imaging was performed and shows extensive diffuse sub-endocardial fibrosis encompassing the entire LV typical for eosinophilic myocarditis (sub-endocardial, i.e. ischaemic fibrosis pattern due to inflammation of the micro-circulation). Wall thrombus lining the inferior wall at the middle and apical level. |

## Case presentation

A 57-year-old female patient with no relevant past medical history was admitted to our institution on 21 July 2021, following the incidental discovery of a peripheral blastosis two days earlier. Bone marrow biopsy was compatible with AML. The laboratory work-up revealed a leucocytosis of $31.9 \times 10^9$/L (normal range $4–10 \times 10^9$/L), with eosinophilia of $7.66 \times 10^9$/L (normal range: $0.05–0.03 \times 10^9$/L) and normocytic normochromic anaemia of 115 g/L (normal range: 120–165 g/L) without thrombocytopenia. Cardiovascular status showed no peripheral oedema or signs of hypoperfusion. An echocardiogram on arrival revealed preserved bi-ventricular function in the absence of valvular pathologies.

Intra-thecal chemotherapy was administered (hydrocortisone, cytarabine, methotrexate) followed by systemic chemotherapy with cytarabine and daunorubicin starting on 23 July 2021. Two days later, the patient developed chest pain without signs of volume overload. An ECG (*Figure 1A*) showed anterior and inferior segment depression. T troponin was elevated to 690 ng/L (normal: <14 ng/L) and eosinophilia of $33.32 \times 10^9$/L was present. The patient was known for cardiovascular risk factors (arterial hypertension and smoking). We opted to perform a CMR study first, in the absence of ST elevated myocardial infarction (STEMI), because the patient had a thrombocytopenia of 45 G/L which was considered as a relative contra-indication for catheterization. A CMR examination (Sola 1.5 T, Siemens Germany) on 26 July 2021 demonstrated a new severe left ventricular (LV) dysfunction with an ejection fraction of 32% due to global hypokinesia. First-pass perfusion CMR during adenosine stress revealed extensive sub-endocardial hypoperfusion (*Figure 2*) compatible with a generalized atherosclerotic triple-vessel coronary artery disease (CAD) or extensive triple-vessel vasospasm which can occur under cytarabine treatment. Due to severe dyspnoea requiring 3 L/min oxygen (adenosine effect, pulmonary infiltrates, and severe LV dysfunction), the CMR examination was stopped prematurely, thus preventing tissue characterization by late gadolinium enhancement (LGE). Pre-contrast myocardial $T_2$-mapping showed high normal values (*Figure 2*) not in
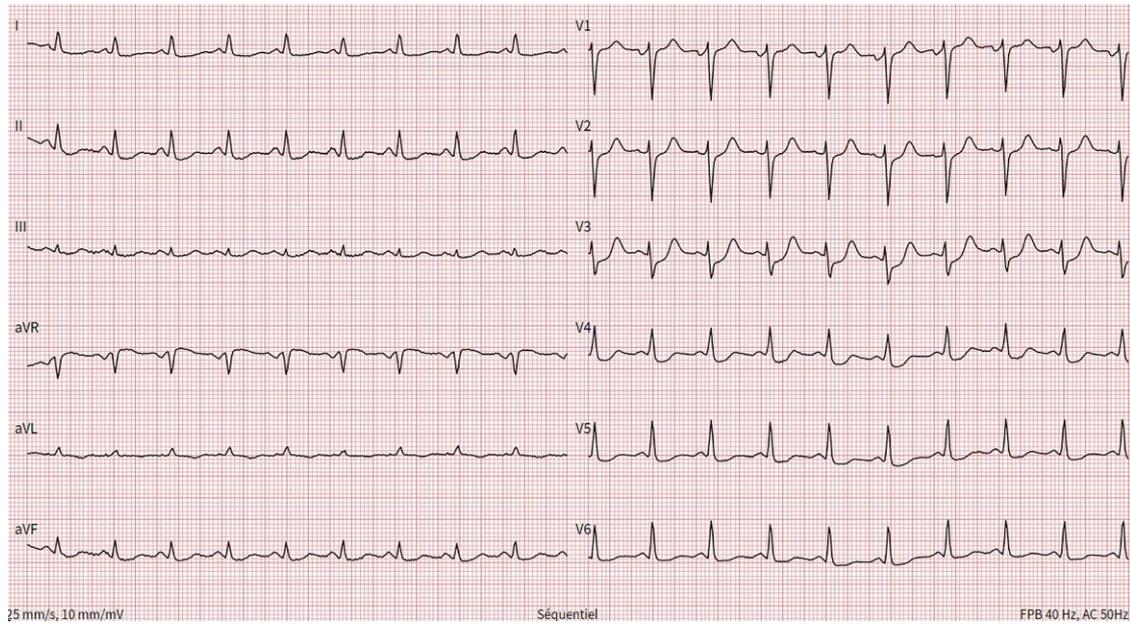
**Figure 1** ECG showing segment depression in V3–V5, II, and augmented vector foot (aVF).

favour of myocarditis. This incomplete CMR examination which yielded information on perfusion, but not on scar/necrosis (no LGE) did not allow us to establish a definitive diagnosis. Given the cardiovascular risk factors, CAD was considered as the most likely diagnosis at that time. A coronary angiogram, however, did not confirm atherosclerotic CAD. Since both, severe LV dysfunction and elevated troponin (between 600 and 1000 ng/L) persisted, the presence of generalized vasospasm was also deemed rather unlikely as being the underlying disease process. Due to signs of global cardiac decompensation, heart failure treatment was introduced with diuretics, angiotensin-converting enzyme inhibitors, and aldosterone receptor antagonists.

On 11 August 2021, the patient suffered a cardiorespiratory arrest due to ventricular fibrillation treated by an external electric shock (return of spontaneous circulation at 7 min, no flow 3 min, low flow 4 min). Due to this evolution and in light of the persisting hyper-eosinophilia, EM was the most likely diagnosis. We started high dose of corticosteroid treatment (methylprednisolone 250 mg for three days followed by prednisone 1 mg/kg). After a multidisciplinary evaluation, the risk of endomyocardial biopsy was considered too high in this clinical setting. After achieving haemodynamic stability and cessation of inotropic support, we performed a CMR examination under good haemodynamic condition (blood pressure 108/66 mmHg, heart rate 100/min, temperature 36.5°, 1 L/min of supplemental oxygen). On free-breathing high-resolution LGE-CMR images, extensive diffuse sub-endocardial fibrosis was detected involving the entire LV, a hallmark of EM (*Figure 3*). In addition, two mural thrombi lining the inferior and anterior wall at the middle and apical levels were demonstrated (*Figure 3*, arrows), also a typical finding of EM. Corticosteroid treatment was continued and we observed reduced congestion on clinical examination but with persistent cardiac dysfunction [Low ventricular ejection fraction (LVEF) 31%]. The eosinophil count was observed to decrease to an undetectable level ($0 \times 10^9$/L), which is believed to be attributed to the administration of glucocorticoids. A biological work-up [Antinuclear Antibodies (ANA), Antineutrophil Cytoplasmic Antibodies (ANCA), rheumatoid factor] was negative and reasonably excluded an immunological cause. Apart from mild pleural effusion, a CT scan showed no evidence of pulmonary eosinophilic

infiltration or infiltration of other organs and no tumour masses were found. Therefore, the hyper-eosinophilia was attributed to the AML treatment without an argument for another secondary reason such as drug hypersensitivity. Unfortunately, the evolution was fatal because of a massive haematemesis. A peptic ulcer in connection with recent steroid intake accentuated by anticoagulation was considered as potential cause, but the aetiology remained unknown. We performed no autopsy due to family wishes.

# Discussion

In this report, the patient had AML with NPM1 mutation associated with an ETV6-ACLS6 fusion transcript explaining the presence of eosinophilia of $7.66 \times 10^9$/L at arrival.[7] The abrupt increase in eosinophilia to $33.32 \times 10^9$/L secondary to chemotherapy is a well-known finding in this setting. This sudden rise in eosinophils with myocardial damage, severe LV dysfunction, and chemotherapy-induced hyper-hydration were the most relevant factors causing heart failure and decompensation.

The most prominent findings were the newly developed severe drop in LV function and the extensive global sub-endocardial hypoperfusion documented by CMR. Sub-endocardial hypoperfusion in all segments of the LV during stress test is compatible with triple-vessel atherosclerotic CAD. Other rare mechanisms of global sub-endocardial hypoperfusion are generalized vasospasm, a severe drop in perfusion pressure (e.g. in aortic insufficiency), cardiac amyloidosis, or endocardial fibrosis/necrosis. The hallmark of EM in CMR is extensive sub-endocardial necrosis in the acute phase that transforms into fibrosis in the chronic phase. The extensive sub-endocardial hypoperfusion revealed by the first CMR examination corresponded to sub-endocardial necrosis which is highlighted by the second CMR examination by LGE tissue characterization. Severe ongoing generalized vasospasm could explain global LV ischaemia but the persistence of severe LV dysfunction over weeks concurrently with persistent troponin elevations was not compatible with this diagnosis. The pattern of hypo-akinesia was not in favour of Takotsubo syndrome. Extracellular volume fraction on
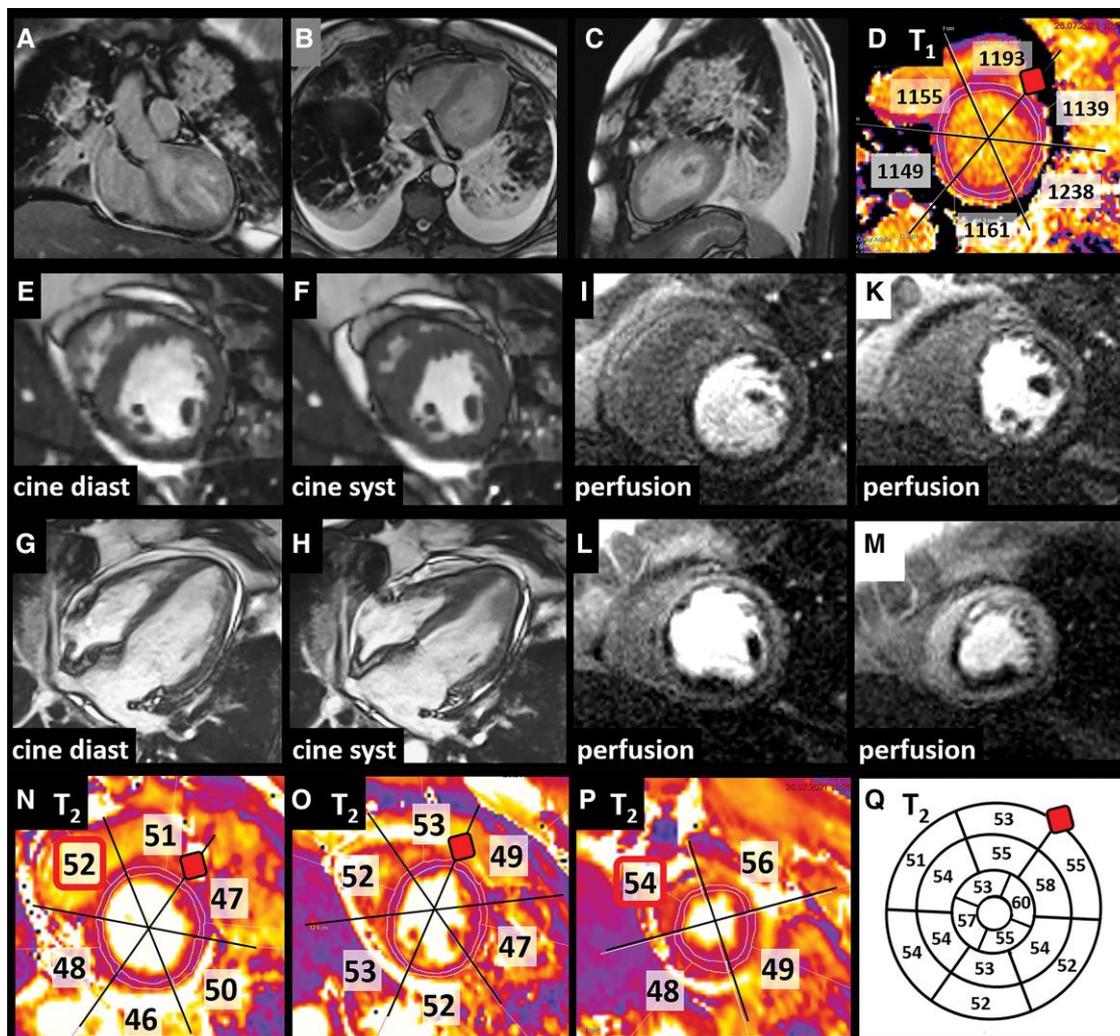
**Figure 2** Initial cardiac magnetic resonance examination (26 July 2021). Localized images in coronal (*A*), axial (*B*), and sagittal (*C*) orientation demonstrate severe pulmonary infiltrates and pleural effusion. This was associated with severe dyspnoea of the patient compromising a full cardiac magnetic resonance work-up with tissue characterization. Short-axis (*E, F*) and long-axis (*G, H*) cine images for functional assessment (end-diastolic (*E, G*) and end-systolic (*F, H*) phase) demonstrate a severely diminished left ventricular systolic function (with an ejection fraction of 32%). First-pass stress perfusion cardiac magnetic resonance images are given in *I–M*. Despite a real-time acquisition, we achieved a high image quality. On all short-axis images, a severe sub-endocardial perfusion deficit is found covering all coronary artery territories, while the sub-epicardial myocardium shows non-compromised perfusion. This finding is typical for extensive left ventricular ischaemia as seen in severe triple-vessel coronary artery disease. $T_2$-mapping (*N–P*, 1.9 × 1.9 × 8 mm$^3$, voxel 29 mm$^3$) shows values at the upper limit of normal with two segments with elevated values (*N, P*, with square). (*Q*) Normal $T_2$ values.[5] (*D*) $T_1$-map with unspecific $T_1$ elevation in all segments: upper limit of normal (= 95% confidence interval) in segments 7–12: in our laboratory: 1039, 1065, 1064, 1050, 1023, 1015 ms, respectively.[6]

CMR was only mildly elevated and the clinical presentation and cine images argues against cardiac amyloidosis. Direct chemotherapy (daunorubicin) induced cardiotoxicity was one of our suspicions as anthracycline cardiotoxicity can manifest as acute heart failure in rare case.[8,9] However, the severe and rapid evolution and the MRI findings made us consider the diagnosis of EM as most likely.

In case of haemodynamic deterioration with persisting troponin and hyper-eosinophilia, EM should be suspected. Clinical improvement under corticosteroid treatment and the typical findings on CMR (*Figure 3*) supported this diagnosis even in the absence of EMB.

EM is divided into three phases.[1–3] They may overlap or occur simultaneously. The first phase is associated with eosinophilic infiltration of the myocardium leading to myocardial necrosis. This causes the patient's chest pain and cardiac decompensation. LV dysfunction can be the result of necrosis due to eosinophilic inflammation or activation of coagulation leading to the formation of thrombi in the microcirculation.[10] The first CMR covers this phase with extensive sub-endocardial hypoperfusion (*Figure 2*). As this CMR examination was incomplete, it yielded no tissue characterization by LGE, and consequently, it was not possible based only on CMR to differentiate myocardial ischaemia (hypoperfusion of viable, LGE-negative myocardium) from myocardial necrosis or fibrosis (hypoperfusion of non-viable LGE-positive myocardium). Of note, myocardial ischaemia and necrosis can also coexist with residual ischaemia surrounding the necrosis. In
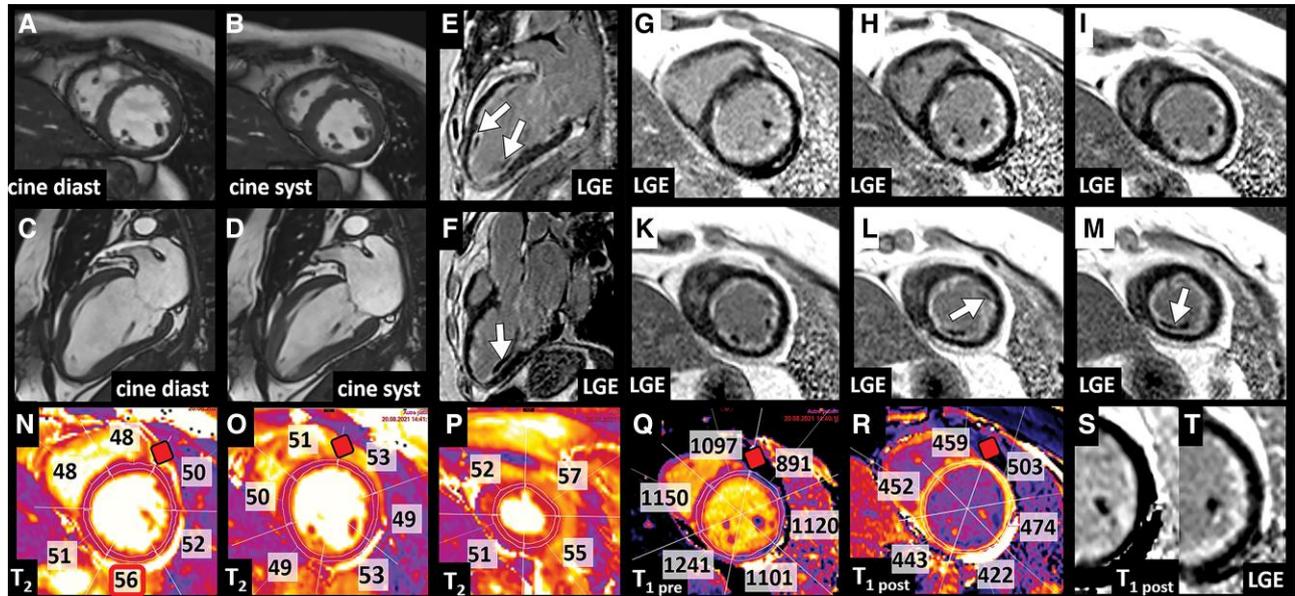
**Figure 3** The follow-up cardiac magnetic resonance examination (20 August 2021) to complete tissue characterization was not achieved during the initial due to prematurely interrupted first cardiac magnetic resonance. Short-axis (A, B) and long-axis (C, D) cine images for functional assessment; end-diastolic (A, C) and end-systolic (B, D) phase, LVEF 31%. E, F: two-chamber and three-chamber late gadolinium enhancement images. Thrombi are marked with arrows. (G–M) 6 short-axis LGE images out of a series of 14 short axis covering the entire LV demonstrating the fine endocardial layer of fibrosis as end-stage manifestation of eosinophilic myocarditis. Arrows: thrombi. (N–P) $T_2$-mapping with values at the upper limit of normal (1 segment with elevated value); for normal values see *Figure 2Q*. (Q) Native $T_1$-mapping with elevated values in three segments. The post-contrast $T_1$-mapping (R) is inverted as grey scale image (S) to correspond to the LGE image at that level (T). Mapping (S) provides inferior spatial resolution ($1.5 \times 1.5 \times 8$ mm$^3$, voxel 18 mm$^3$) compared with LGE (T, $1.3 \times 1.3 \times 6$ mm$^3$, voxel 10 mm$^3$), which demonstrates subtle sub-endocardial enhancement.

fact, the elevated troponin levels were compatible with this setting. However, the extent and localization of necrosis could not be determined given the lack of LGE images. Thus, perfusion assessment should always be combined with necrosis/fibrosis assessment (LGE imaging) for detection or exclusion of myocardial ischaemia.[9] Myocardial $T_2$-mapping showed high normal values, thus not excluding with certainty neither inflammation/necrosis nor (longstanding) ischaemia (*Figure 2*). Retrospectively, sub-endocardial inflammation/necrosis was present, but $T_2$-mapping (unlike high spatial resolution LGE) provided insufficient spatial resolution (specifically for the sub-endocardium) to demonstrate oedema in the sub-endocardium. The poor breath-hold capability of the patient may have further contributed to lower the spatial resolution of the $T_2$-mapping acquisition. Native $T_1$ values were elevated diffusely, thus indicating non-specific myocardial damage (*Figure 2*). The second phase is characterized by intra-cardiac thrombus formation caused by ventricular hypo-akinesia and damage of the endothelium with pro-coagulant activity of the endocardial surface. The second CMR examination completed the first CMR study by showing extensive sub-endocardial necrosis/fibrosis by LGE and by identifying a mural thrombus formation. The final phase of EM is characterized by this sub-endocardial fibrosis, which may lead to restrictive heart disease.[1–3]

Due to severe dyspnoea, the initial CMR examination was interrupted prematurely as even free-breathing LGE acquisition was not tolerated by the patient. This case illustrates the importance of a complete CMR examination which includes tissue characterization by LGE. It underlines the need to complete a prematurely interrupted CMR examination as soon as possible to initiate adequate treatment of EM. The

prognosis of EM is severe with in-hospital mortality ranging from 10 to 36.1%.[10,11] The treatment of EM depends on its underlying aetiology and is mainly based on symptomatic and immunosuppressive treatment such as glucocorticoids.[10–12] Glucocorticoid treatment appears important, particularly in severe cases; however, no clinical trials have systematically tested the efficacy of this treatment in EM.[11]

## Lead author biography



Adil Salihu graduated from the University of Lausanne in 2016 and completed his medical training in Switzerland. He has now started his training in the University Hospital in Lausanne, CHUV, in internal medicine and cardiology.

## Supplementary material

**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 informed consent for submission and publication of this case report including images and related text has been obtained from the patient's son due to the fatal issue of the patient and is in line with the COPE guidance.

**Conflict of interest:** None declared.

## Data availability
The data used to support the findings of this study are available from the corresponding author upon request.

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