Case report: acute myocarditis in two patients with coronary artery disease presenting with chest pain; thinking outside the box

Nicola Amelotti †1,2*, Matteo Brusamolino †1,2*, Massimo Mapelli 1,2, Mauro Contini 1,
Andrea Baggio 1,2, Fabio Fazzari 1, Gianluca Pontone 1,3, Piergiuseppe Agostoni 1,2

† These authors share first authorship.
1 Centro Cardiologico Monzino, IRCCS, Milan, Italy
2 Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan, Milan, Italy.
3 Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy.

* Correspondence:
Corresponding Authors
matteo.brusamolino@unimi.it; nicola.amelotti@unimi.it

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Abstract
BACKGROUND:
In a subset of patients, acute myocarditis (AM) may mimic acute myocardial infarction, with a similar clinical presentation characterized by chest pain, electrocardiogram changes consistent with acute coronary syndromes (ACS), and serum markers increment.

CASE SUMMARY:
We present two cases of infarct-like myocarditis in patients with known coronary artery disease (CAD), in which the discrepancy between trans-thoracic echocardiogram findings, ECG and angiography prompted us to look beyond the simplest diagnosis. In these cases, making a prompt and correct diagnosis is pivotal to address adequate therapy and establish a correct prognosis.

DISCUSSION:
The right diagnosis can avoid unnecessary coronary revascularizations and subsequent antiplatelet therapy that may be associated with an increased hemorrhagic risk. Moreover, it
allows setting up guideline-directed therapy for myocarditis, proper follow-up, as well as recommending abstention from physical activity.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors’ contribution statement

The authors confirm contribution to the paper as follows: study conceptualization (NA, MB, MM, MC, AB, FF, GP, PGA), data collection and interpretation (NA, MB), manuscript and figure preparation, manuscript revision based on feedback from co-authors (NA, MB), supervision, manuscript critical revision (MM, MC, AB, FF, GP, PGA). All authors reviewed the results and approved the final version of the manuscript.

Author note

The lead authors (Dr. Amelotti, Dr. Brusamolino) contributed equally to the paper and share first authorship.
Learning points

- The diagnosis of AM poses a diagnostic challenge, especially in patients with a high pre-test probability of ACS, in which a myocarditis can be misdiagnosed as an ACS.

- The diagnosis of AM mimicking ACS is clinically relevant because it determines treatment and prognosis. A multidisciplinary approach and a high index of suspicion are needed.
Introduction

Acute myocarditis (AM) is an inflammatory disease of the heart that can present with a wide range of symptoms (1). In a subset of patients, AM may mimic acute myocardial infarction, with a similar clinical presentation characterized by chest pain, electrocardiographic changes consistent with acute coronary syndromes (ACS), and serum markers increment (2). The diagnosis of AM mimicking ACS is clinically relevant because it determines treatment and prognosis. Myocarditis is a frequent final diagnosis in patients who receive an initial diagnosis of acute myocardial infarction with nonobstructive coronary arteries (MINOCA) (3). However, differential diagnosis is particularly challenging in patients with known coronary artery disease, in whom coronary stenosis can represent only a bystander of an underlying inflammatory process. We present two cases of infarct-like myocarditis in patients with known coronary artery disease, in which the discrepancy between transthoracic echocardiogram findings, electrocardiogram and angiography prompted us to look beyond the simplest diagnosis.

Patient 1

A 68 years-old woman presented to the emergency department for retrosternal chest pain, not accentuated by movement or inspiration, lasting about 30 minutes, arose at rest, associated with sweating and nausea. She reported, while in pain, a sudden loss of consciousness, unwitnessed, due to which she fell to the ground reporting facial trauma. She did not present any preceding viral-like symptoms. In the emergency department, she was still symptomatic. She had a history of arterial hypertension and dyslipidemia. Six months before the presentation she underwent percutaneous coronary intervention (PCI) of mid-distal left anterior descending coronary artery for exertional angina. Her medication included acetylsalicylic acid 100 mg od, clopidogrel 75 mg
od, ramipril 5 mg bid, rosuvastatin 20 mg od, lansoprazol 30 mg od. The patient denied taking any other medication or illicit drug.

Physical and neurological examination was unremarkable. The presenting electrocardiogram showed sinus rhythm and subtle ST-segment elevation at the J-point in the inferior leads (1 mm) and V7-9 (0.5 mm), and a reciprocal ST segment depression in aVL (Figure 1 A-B). Blood tests showed negative C-reactive Protein (0.5 mg/L, normal value < 5 mg/L), slight neutrophilic leukocytosis (white blood cells count 10700/uL, normal values 3900-10500/uL; neutrophils 8650/uL, normal values 1800-7700/uL, 81%, normal values 37-73%; lymphocytes 1500/uL, normal values 1000-4800/uL, 14.2%, normal values 20-45%; monocytes 500/uL, normal values 0-800/uL, 4.2%, normal values 2.5-10%; eosinophils 0%, normal values < 5%, and basophils 0%, normal values 0-2%; hemoglobin 13.3 g/dl, normal values 13.5-17.2 g/dl; platelet count 191000/ul, normal values 140000-450000/ul) an elevation of high sensitivity Troponin I (hsTnI) up to 5891 ng/L (normal values < 53 ng/l). A transthoracic echocardiogram showed mid inferior, inferolateral and inferoseptal hypokinesia, preserved ejection fraction, mild-to-moderate mitral-aortic regurgitation, absence of pericardial effusion (supplementary video). A CT scan was performed, which excluded fractures or intracranial hemorrhage as result of the facial trauma. The coronary angiography showed a focal, eccentric, severe proximal left anterior descending coronary artery stenosis (80%), a focal, eccentric, severe mid left circumflex artery stenosis (80%) and a dominant right coronary artery free from stenosis (Figure 1 C-D-E; supplementary figures S1-2). The patient was hemodynamically stable. Therefore, the patient underwent primary PCI of the hypothesized culprit (mid left circumflex artery), and subsequent complete revascularization during the index procedure (Supplementary figure S3). In the following days the electrocardiogram showed negative T waves in inferolateral leads (Figure 1 F-G). Repetitive
ventricular ectopic beats were noted at continuous telemetry monitoring. Progressive reduction of
troponin values was observed (peak value 5992 ng/L on day one). C-reactive Protein remained
persistently within normal values for the entire duration of hospitalization, white blood cells
count underwent rapid normalization (day 2: WBC 8300/uL, N 560/uL, 67%). Given the
discrepancy between electrocardiogram findings, wall motion abnormalities and coronary
angiography we decided to perform a cardiac magnetic resonance (CMR). Indeed, the presence of
a large dominant right coronary artery free of stenosis, with a large posterolateral and posterior
descending artery free of disease was not entirely consistent with the segmental wall motion
abnormalities found at transthoracic echocardiography. The CMR (performed on the 7th day of
hospitalization) showed preserved biventricular size and ejection fraction with mid inferoseptal,
inferior and inferolateral hypokinesia; increase of myocardial signal intensity in T2-weighted
images, increase of T2 values (69 ± 4 ms) and late gadolinium enhancement with non-ischemic
subepicardial pattern at mid to apical septal and inferior walls (Figure 1 H-O). These findings
were in line with acute non-ischemic myocardial damage (myocarditis). The patient was
discharged on dual antiplatelet therapy (cardioaspirin 100 mg od, Ticagrelor 90 mg bid),
atorvastatin 80 mg od, bisoprolol 1.25 bid and ramipril 2.5 mg od. She was advised to avoid
strenuous physical activity for 6 months. Four months later the patient was asymptomatic. A
transthoracic echocardiogram showed mid-basal inferior hypokinesia, normokinesia of the
remaining segments. A 24 hours ambulatory ECG monitoring showed no sustained arrhythmias.
Blood exams, comprehensive of hsTnI and B-Type Natriuretic Peptide, were within normal
limits. A CMR performed 6 months later showed preserved biventricular size and ejection
fraction with normal tissue characterization (Figure 3).

Patient 2
A 57 years-old man presented to the emergency department reporting retrosternal chest pain following a quarrel, described as a stab wound, lasted 10 minutes. The patient reported low-grade fever and gastrointestinal malaise, with a few episodes of poorly formed stools, the week before the admission to our hospital. He was known for multiple cardiovascular risk factors (former smoker, hypertension, dyslipidemia, diabetes mellitus) and previous multiple NSTE-ACS (one 8 years before and one 1 year before, treated with percutaneous revascularization on left circumflex coronary artery and posterolateral branch of the left circumflex, respectively). His medication included olmesartan/amlodipin 40/5 mg od, acetylsalicylic acid 100 mg od, rosuvastatin/ezetimibe 20/10 mg od, metformin 1000 mg od, semaglutide 0.5 mg weekly subcutaneous injection. The patient denied taking any other medication or illicit drug. In the emergency department, physical examination was unremarkable, as were the presenting electrocardiogram, chest X-ray and transthoracic echocardiography. Blood exams were within normal limits (hemoglobin 13.5 g/dl, normal values 13.5-17.2 g/dl; platelet count 208000/uL, normal values 140000-450000/uL; white blood cells count 6700/uL, normal values 3900-10500/uL, neutrophils 2360/uL, normal values 1800-7700/uL, 35.2%, normal values 37-73%; lymphocytes 2500/uL, normal values 1000-4800/uL, 37%, normal values 20-45%; Monocytes 1700/uL, normal values 0-800/uL, 25%, normal values 2.5-10%; eosinophils 170/uL, normal values 0-450/uL, 2.5%, normal values <5%; basophils 0%, normal values 0-2%), except for elevated troponin (hsTn-I up to 4659 ng/L, normal values < 53 ng/l) and C-reactive protein (176 mg/L, normal values < 5.0 mg/l). A coronary angiography was performed, showing a right dominant coronary circulation with a moderate-grade focal eccentric stenosis of the mid-circumflex artery. Therefore, intravascular imaging (optical coherence tomography) was performed, showing severe eccentric atheromatous disease, thin-cap fibroatheroma, critical (minimal lumen area - MLA 4 mmq; planimetric stenosis of about 65%). The stenosis was treated...
with drug eluted stent implantation (Figure 2 A-B). The following days we observed progressive electrocardiographic evolution in precordial anterolateral leads (V3-V6) and peripheral inferior leads with isodiphasic T wave morphology (Figure 2 C-D). Given the discrepancy between postprocedural electrocardiographic alterations and coronary alterations observed at angiography, and considering the recent gastrointestinal syndrome, a CMR was requested and performed on the 4th day of hospitalization. It showed preserved biventricular size and function; mid to apical anteroseptal, anterior, and inferolateral increase in T1 and T2 values (T2 mapping value: 72 ± 6 ms, tissue equivalent of edema); apical anterior, lateral, and basal to mid inferolateral late gadolinium enhancement with non-ischemic pattern (intramyocardial and subepicardial). Those findings were in line with acute multifocal myocarditis (Figure 2 E-J). Blood tests showed progressive normalization of inflammatory indices (C-reactive protein at discharge 2.7 mg/L) and myocardial necrosis biomarkers (hsTnI at discharge 25.52 ng/L). A transthoracic echocardiogram, performed before discharge, showed preserved biventricular size and function. The patient was discharged on double antiplatelet therapy (cardioaspirin 100 mg od, ticagrelor 90 mg bid), rosuvastatin/ezetimibe 20/10 mg, and with cardioprotective therapy with bisoprolol 1.25 mg bid, ramipril 2.5 mg bid and eplerenone 25 mg od. He was also advised to avoid strenuous physical activity for 6 months. The patient reported no significant symptoms during follow-up. A CMR performed 6 months later showed preserved biventricular size and function, normal T1 and T2 values and basal inferolateral late gadolinium enhancement with non-ischemic pattern (Figure 4).

Discussion

AM is an inflammatory disease of the heart that may occur as a consequence of infections, exposure to toxic substances and drugs, and immune system activation (1) Some patients may
present with chest pain, electrocardiographic changes, and elevated serum levels of cardiac biomarkers. Therefore, differential diagnosis among AM and ACS may be difficult. Current guidelines advocate coronary angiography in patients with suspected myocarditis to rule out ACS, and myocarditis is a frequent final diagnosis in MINOCA patients, defined as the absence of obstructive disease on angiography (i.e. no coronary artery stenosis ≥50%) in any major epicardial vessel (4). Several authors described how myocarditis may mimic ACS (5–7). However, patients discussed in these papers are typically young, had a low prevalence of coronary risk factors, and coronary angiography showed no obstructive coronary artery disease. There are, to the best of our knowledge, only a few reports of episodes of acute myocarditis in patients already known for coronary artery disease. In our patients there was angiographic evidence of severe coronary artery stenosis, effectively excluding them from MINOCA classification; in these cases it can be very difficult to recognize that a significant coronary artery stenosis represent only a bystander of an underlying inflammatory myocardial disease. In both our cases, the decision to treat the lesions in the cath-lab was motivated by the belief that the patients had ACS.

In the first case, the patient underwent primary PCI of the hypothesized culprit infarct-related artery (mid circumflex artery) and subsequent complete revascularization during the index procedure, due to the evidence of a high-degree left anterior descending artery stenosis with high probability of functional relevance (e.g., >70% stenosis subtended by a relatively large area of myocardium), low complexity lesion and the low-to-moderate contrast volume load (8). Indeed, randomized trials have demonstrated that PCI of non-infarct-related artery lesions for complete revascularization in patients with STEMI improves clinical outcomes compared with infarct related artery-only PCI, and that fractional flow reserve-guided strategy did not have a significant
benefit over an angiography-guided strategy in guiding complete revascularization (9–11). It is well known that if a clear culprit is not detected, further invasive evaluation (using intravascular imaging) may be considered to identify the underlying cause (12). However, our patient showed a clinical presentation consistent with ST-segment elevation-ACS and a significant coronary artery stenosis in a plausible infarct related artery, and therefore no further investigation was undertaken in the cath lab. In the second case, the clinical presentation was different and suggestive for NSTE-ACS. In this case coronary intravascular imaging was performed. Even if no plaque rupture was detected on optical coherence tomography, the stenosis was judged to be amenable to PCI by the interventional cardiologist performing the procedure, given the very high-risk features of the plaque.

The decision to carry out further investigations and challenge the initial diagnosis of ACS is justified by the discrepancies between electrocardiography findings, echocardiography and the supposed culprit lesion found at coronary angiography. Indeed, in the first case, electrocardiography was suggestive for an inferior STEMI; culprit coronary could have been either circumflex artery (absence of reciprocal ST depression in lead I) or right coronary artery (ST elevation in lead III > lead II and reciprocal aVL depression). At echocardiography inferior, inferolateral and inferoseptal hypokinesia was documented. However, in the cath-lab we found a multivessel disease with a large dominant right coronary artery and its branches (posterolateral and posterior descending artery) free of stenosis (that collides with the inferior and inferoseptal hypokinesia) and a circumflex artery with severe stenosis but no evidence of obstruction. In the second case the discrepancy was observed between dynamic electrocardiographic changes (anterolateral and inferior T wave inversion) and coronary alterations observed at angiography.
(moderate mid-circumflex stenosis, absence of other epicardial stenosis in a right coronary artery-dominant circulation).

In our cases, CMR supported the diagnosis of acute myocarditis in both patients, according to the Updated Lake Louise Criteria (13), and ruled out ischemic etiology (non-ischemic LGE pattern). Indeed, the CRM performed in the acute phase showed in both patients at least one T2-based criterion with at least one T1-based criterion. The diagnosis of certainty, as well as the etiological diagnosis, is based only upon endomyocardial biopsy which, however, was not performed because of patients’ low risk profile (1). PCR testing and circulating antibodies of common cardiotropic viruses were not performed, due to their limited diagnostic usefulness (4).

In retrospect the history of recent gastrointestinal syndrome and the increase in C-reactive protein were further elements suggestive of AM in the second case. These features were absent in the first patient. However, up to 20% of acute myocarditis may have normal C-reactive protein values (1). We did not detect, with hindsight, any other features in the first patient that could have heralded the diagnosis earlier, beyond the aforementioned discrepancies.

The cases presented represent a real-life situation that highlights the difficulty in clinical practice of differentiating ACS from myocarditis-with-bystander-moderate-coronary artery disease. Indeed, the diagnosis of AM remains a challenge because of the lack of easily accessible diagnostic methods that are both sensitive and specific (4). Although the risk profiles and comorbidities of patients with AM and ACS differ substantially, significant overlap exists. CMR is not routinely performed after ACS and may be not available in the acute setting of a suspicious ACS, even if some authors have highlighted a possible role for this test in the assessment of chest pain in the ED (14). Moreover, the sensitivity of this test to detect edema and vascular permeability decreases over time, reducing its usefulness for the differential diagnosis between
ACS and AM if carried out late from the index event (15). Endomyocardial biopsy remains the reference standard, but it is not routinely performed owing to its associated risks (16).

Further studies are required to assess whether some of the cases of ACS in patients with high pre-test probability of CAD and evidence of ≥ 50% stenosis at coronary angiography constitute inflammatory processes. Indeed, we may suppose that in absence of the discrepancies seen in our patients, a diagnosis of AM would have been missed. Making a correct differential diagnosis between the two diseases is therapeutically and prognostically relevant: it could have allowed avoidance of unnecessary PCI, and subsequent antiplatelet therapy and associated increased hemorrhagic risk.

Eventually, as AM may lead to dilated cardiomyopathy in up to 20% of cases (17), patients should be offered long-term non-invasive cardiological follow-up. Uptitration of anti-remodelling drugs to maximal tolerated doses should be pursued, and serial echocardiograms and CMR should be performed over time. In the event of prolonged documented increase of cardiac enzymes or progressive reduction in ventricular function, an endomyocardial biopsy should be considered (4). In conclusion, the diagnosis of AM can be extremely challenging in these patients, and a high index of suspicion is needed to go beyond the simplest diagnosis.

Consent

The authors confirm that consent for submission and publication of this case report has been obtained from the patient in line with COPE guidance.

Data availability

The data underlying this article is available in the article and in its Supplementary material online.
References


Figure legends:

**Figure 1:**

Panels A and B: Presenting ECG: sinus rhythm and ST segment elevation in the inferolateral and posterior leads with specularity in aVL.

Panel C to E: invasive CAG showing a dominant RCA free from stenosis (Panel C), significant stenosis of proximal LAD (Panel D - arrow) and LCx (Panel E- arrow).
Panels F and G: dynamic ECG changes showing negative T waves in inferior leads, V6 and posterior leads (V7-9).

Panels H and I: mid (Panel H) and apical (Panel I) short axis view T2-weighted images showing increased signal intensity at mid to apical septal and inferior walls (arrows).

Panels J and K: mid (Panel J) and apical (Panel K) short axis view T2 mapping images showing increased in T2 values at mid to apical septal and inferior walls (arrows).

Panels L to O: mid (Panel L) and apical (Panel M) short axis view, 4ch long axis view (Panel N) and 2ch long axis view (Panel O) showing mild enhancement and subepicardial enhancement (both of non-ischemic pattern) at mid to apical septal and inferior walls (arrows).

**Figure 2:**

Panel A and B: invasive CAG showing RCA free from relevant stenosis (Panel A) and eccentric focal significant stenosis of mid LCx (Panel B - arrow).

Panel C and D: post-procedural ECG showing inferolateral ischemic evolution

Panel E: mid to apical short axis view T1 mapping image showing increase in native T1 values at septal and anterior level (arrows).

Panel F and G: mid to apical short axis view (Panel F) and 4ch long axis view (Panel G) T2 mapping images showing increase in T2 values at mid to apical septal and anterior wall, and basal lateral wall (arrows).

Panel H and J: basal short axis view (Panel H), mid to apical short axis view (Panel I) and 4ch long axis view (Panel J) LGE images showing subepicardial and intramyocardial enhancement (non-ischemic pattern) at basal anteroseptum, basal inferolateral wall, mid to apical septal and anterior walls (arrows).
Figure 3:

Panel A-D: follow up CMR. Apical 4 chamber (Panel A), mid-to-apical short axis (panel B) and apical short axis (panel C) showing absence of LGE. Mid short axis view T2 mapping image (panel D) showing normal T2 values.

Figure 4:

Panel A-D: follow up CMR. Apical 3 chamber (Panel A) and basal short axis (panel B) showing subepicardial LGE (non-ischemic pattern) at basal inferolateral segment (arrow). Basal (Panel C) short axis view T2-weighted image showing normal signal intensity at basal segments. Basal (Panel D) short axis view T2 mapping image showing normal T2 values at basal segments.
Figure 2
134x299 mm (x DPI)