

Acute necrotizing eosinophilic myocarditis possibly triggered by an antimigraine drug as an uncommon cause of acute heart failure: a case report

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Background

Epigastric or chest pain with an abnormal electrocardiogram (ECG) in a young, otherwise healthy patient should trigger an investigation to rule out myocarditis. The myocarditis covers a wide spectrum of severity. The search for the aetiologic factor could be definitive for the success of therapy.

Case summary

A previously healthy 29-year-old woman presented to the Emergency Room with epigastric pain, eosinophilia, and an abnormal ECG. A thorough evaluation including cardiac magnetic resonance and endomyocardial biopsy was undertaken. A diagnosis of acute necrotizing eosinophilic myocarditis was made.

Discussion

The case is particularly unique for its suspected predisposing trigger: an antimigraine drug. A possible systemic hypersensitivity reaction, reflected by the occurrence of concomitant severe serum eosinophilia, acute myocarditis, and central nervous system vasculitis, was successfully treated with steroids, further supporting the diagnosis.

Keywords

Case report • Myocarditis • Acute heart failure • ANEM • Migraine

Learning points

- Epigastric pain may be the presenting symptom of a cardiac disorder.
- Prompt aetiologic diagnosis of myocarditis is of utmost importance.
- Serum eosinophilia may prompt a systemic investigation.
- After histological data, myocarditis may have specific and curative therapy.

Introduction

Epigastric or chest pain with an abnormal electrocardiogram (ECG) in a young healthy patient should trigger diagnostic suspicion and subsequent investigation to rule out myocarditis. Myocarditis, an inflammatory disease of the myocardium, has myriad possible causes and covers a wide spectrum of severity. Presentations can vary from a simple flu with mild myocardial involvement, resolving with no complications or sequelae, to life-threatening critical illness with heart

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failure and cardiogenic shock. A thorough search for the aetiology of myocarditis can be a decisive factor in determining the success of therapy and prognosis.

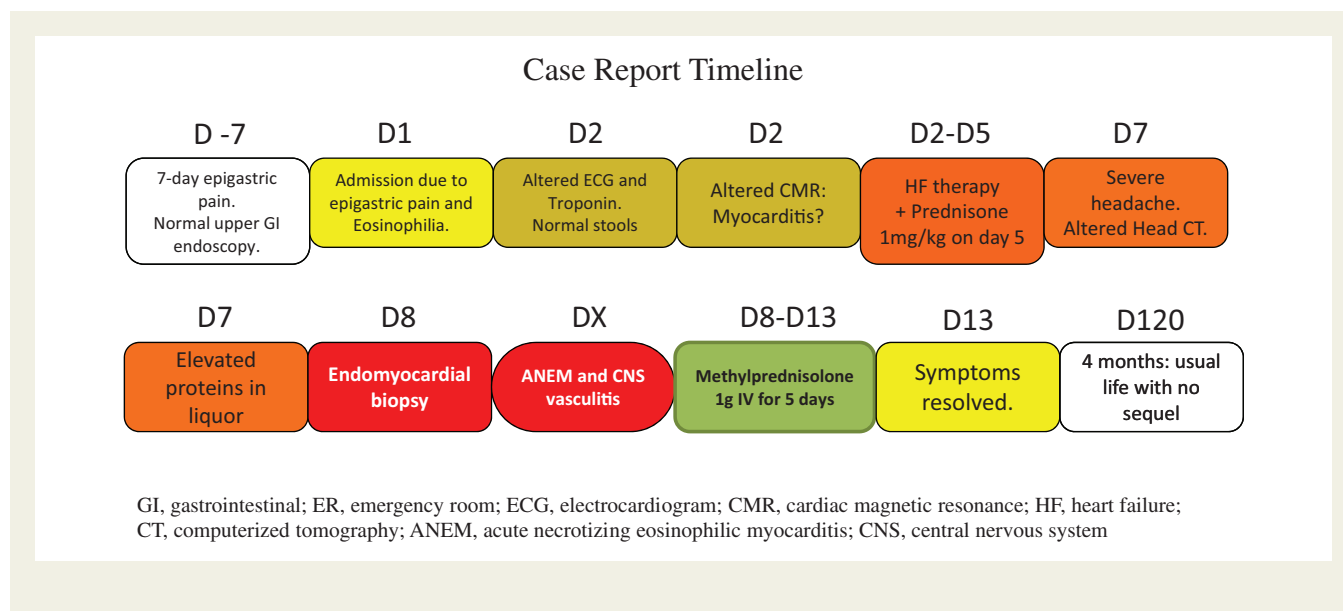
We report a case of acute necrotizing eosinophilic myocarditis possibly triggered by abuse of an over-the-counter combination anti-migraine drug (isometheptene mucate 30 mg, metamizole sodium 300 mg, and caffeine 30 mg; Neosaldina™). In this particular case, serum eosinophilia was prompted a more in-depth investigation.

repeat ECG showed progressive ST-segment depression on the anterior wall (Figure 3).

Additional laboratory tests, including blood cultures, Chagas disease serology, viral markers, and an autoimmune series provided no evidence of haematogenous infection or autoimmune diseases. Serum tryptase levels were normal, suggesting that eosinophilia was not due to an underlying monoclonal myeloproliferative disorder.

Cardiac magnetic resonance (CMR) imaging was suggestive of myocarditis, with oedema and mid-wall fibrosis on the lateral wall,

Timeline



Case presentation

A previously healthy 29-year-old woman presented to the Emergency Room with a 14-day history of significant epigastric pain, which had become retrosternal. An upper gastric endoscopy had been normal 5 days prior to admission. She did not smoke and had no history of illicit drug use. She was on no regular prescription medication but had repeatedly been taking an over-the-counter combination of isometheptene mucate 30 mg, metamizole 300 mg, and caffeine 30 mg (Neosaldina™) for recurrent migraines, up to six tablets a day for approximately 3 weeks.

The patient was initially admitted under the care of the Gastroenterology team due to her epigastric pain. However, an ECG performed while the patient was in pain showed a 1-mm ST-segment depression on the anterior wall (Figure 1).

The troponin level was significantly elevated at 13.0 ng/mL (reference range <0.16 ng/mL), as was the C-reactive protein (13.5 mg/L). Urgent echocardiography showed normal left ventricular function (Figure 2).

On the patient's first day in the hospital, a complete blood count was significant for marked eosinophilia (19%, 2810 cells/mm³). Stool examination was negative for ova and parasites. On the second day, a

basal, mid-, and apical segments of the septal wall, and apical segment of the anterior wall. Left ventricular global contractility was borderline abnormal (Figure 4).

Serum troponin plateaued from Days 3 to 4, when she was transferred to the intensive care unit due to overt signs of heart failure (HF), including orthopnoea, a third heart sound, dizziness, and chest pain. The B-type natriuretic peptide (BNP) level was >1200 pg/mL. Guideline-based medical treatment for HF was initiated. On Day 5, empirical therapy with prednisone (60 mg/day PO) was started, with some relief of HF symptoms and chest pain.

On Day 7, the patient reported a particularly severe headache, more intense than her usual migraines. Brain magnetic resonance imaging (MRI) revealed multiple, bilateral white-matter lesions with pitting and linear enhancement, associated with microbleeds. Combined with the patient's clinical picture and acute myocarditis, this suggested the possibility of systemic vasculitis with central nervous system (CNS) involvement. A lumbar puncture revealed abnormally high cerebrospinal fluid protein levels. A presumptive diagnosis of CNS vasculitis was made (Figure 4), but we could not rule out the possibility of a reaction to the vasoconstrictor effects of the isometheptene mucate contained in the patient's anti-migraine medication.

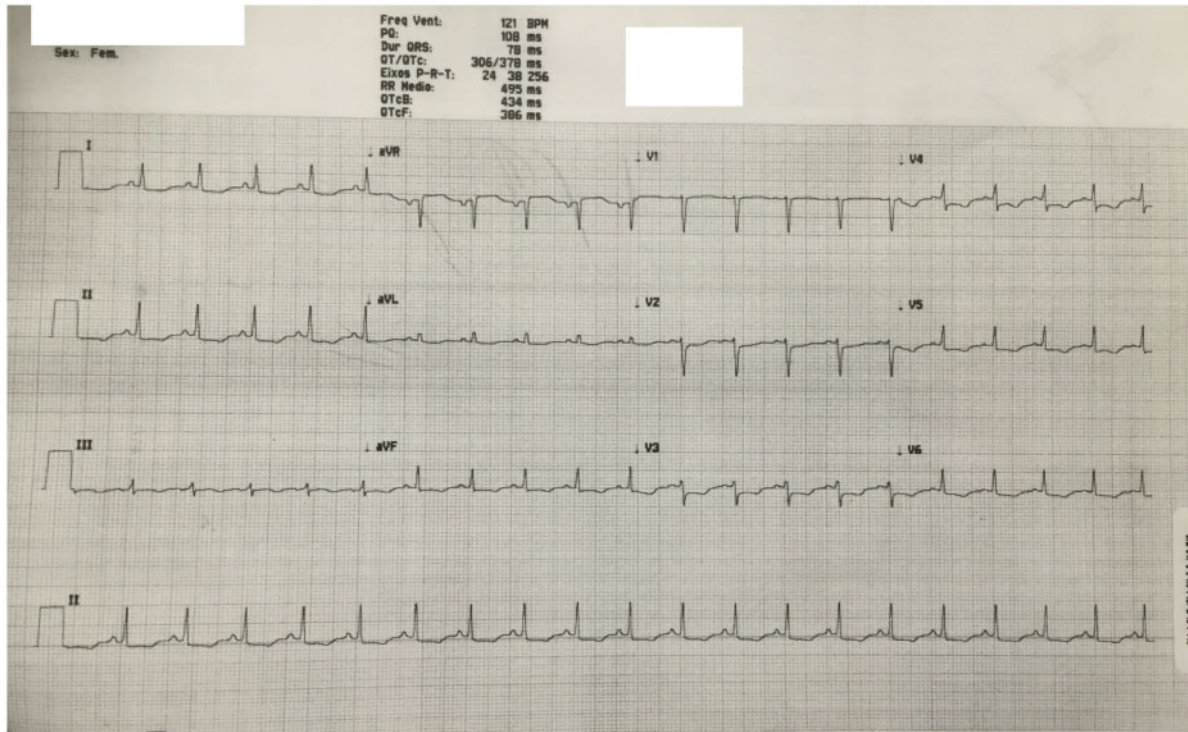


Figure 1 Electrocardiogram at hospital admission.

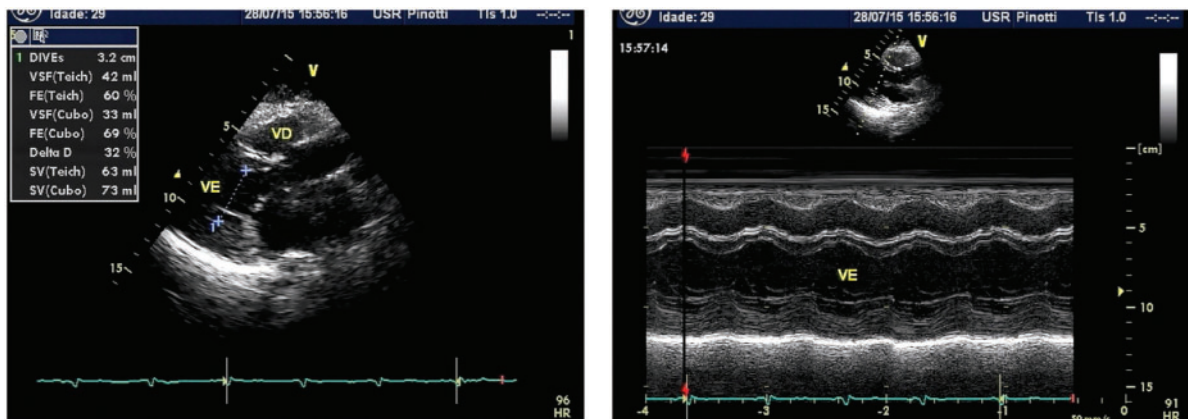


Figure 2 Doppler echocardiogram performed on Day 1.

On Day 8, a right ventricular endomyocardial biopsy was performed. Histopathological examination was consistent with acute necrotizing eosinophilic myocarditis (ANEM) (Figure 5).

Pulse therapy with methylprednisolone (1 g daily IV for 5 days) was started. On Day 1 of therapy, the patient exhibited improvement of overall clinical status. By the time of completion of the course of steroids, eosinophilia had resolved, troponin was normal, BNP was down to 400 pg/mL, and echocardiography showed normal left

ventricular (LV) function. Control CMR performed immediately after pulse therapy showed a significant reduction in myocardial oedema, preserved LV function, and few apical foci of fibrosis.

The patient was discharged with no signs of HF and normal LV function. At 4-month follow-up, repeat CMR showed preserved LV function and minimal apical foci of fibrosis (Figure 6). A follow-up brain MRI on Day 20 revealed the resolution of signs of vasculitis (Figure 7 and 8).

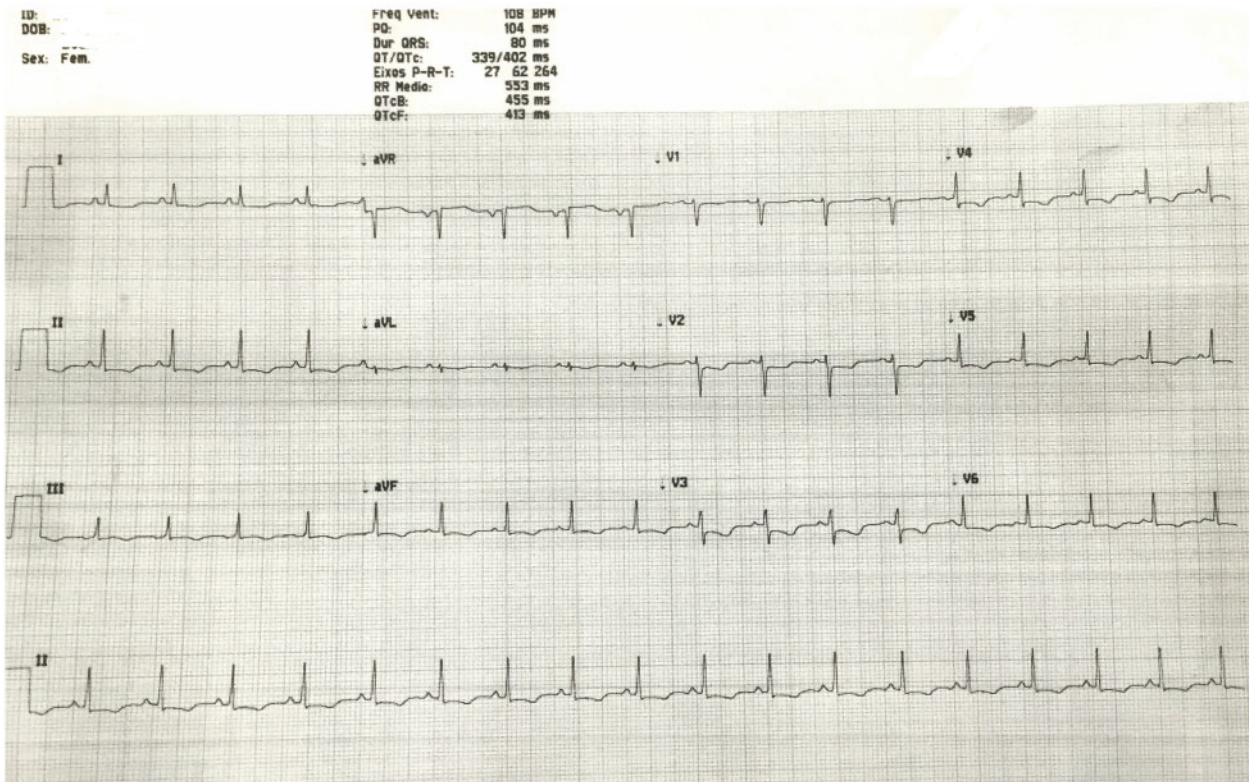


Figure 3 Electrocardiogram performed on Day 2 showing extensive anterior ST depression.

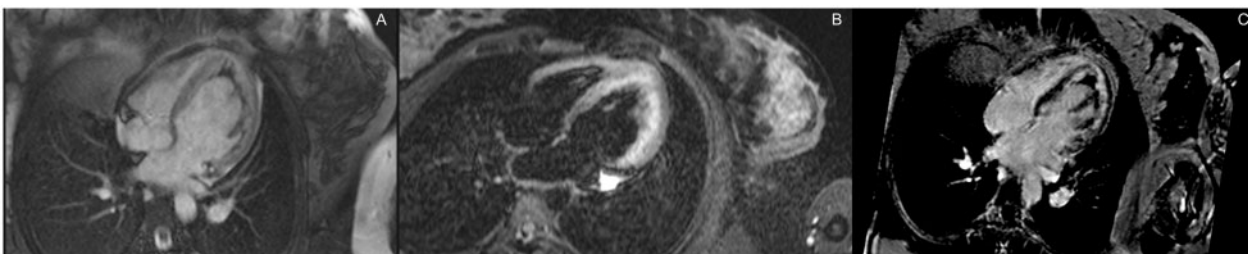


Figure 4 (A) True-Fast Imaging with Steady-State Precession (FISP) cine image in diastole with subendocardial hypointense signal. (B) High intensity signal in T2 weighted images. (C) Late gadolinium-enhancement as a subendocardial layer on the septum, apex, and lateral left ventricular wall.

Following pulse therapy, prednisone 1 mg/kg/day was continued for two months and tapered to zero during the third month after hospital discharge.

At 20 months, the patient returned for a scheduled follow-up appointment. She was completely asymptomatic, with no signs of HF; she had resumed her usual work and was planning her first pregnancy. The ECG was normal, and echocardiography showed preserved ejection fraction. Neurologic examination was normal. She no longer experienced migraine attacks.

At a 30-month follow-up, the patient remained asymptomatic. She had completed a healthy pregnancy and delivered a healthy boy at full term.

Discussion

We report a unique case of ANEM with no possible predisposing trigger other than an over-the-counter antimigraine drug, which the

patient had been taking at an inadvertently high dose. The possible systemic hypersensitivity reaction, reflected by the occurrence of severe serum eosinophilia, myocarditis, and CNS vasculitis with a marked response to corticosteroids, suggested an exogenous causal agent. We took great care to rule out the possibility of eosinophilic reaction due to a primary haematological malignancy. Hematology consultation concluded in favour of a hypersensitivity reaction, not a primary eosinophilia.

This previously healthy young woman presented initially with an apparently trivial complaint of epigastric pain, unexpectedly followed by sudden onset of HF requiring intensive care unit admission. Young patients with cardiac conditions not rarely present with gastrointestinal symptoms.¹ In this case, the progressively worsening clinical picture mandated a more in-depth diagnostic workup. The lumbar puncture prompted by evidence of CNS involvement and the urgent endomyocardial biopsy was crucial in understanding and establishing the final diagnosis.

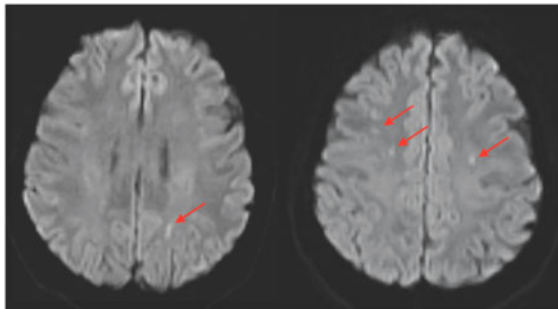


Figure 5 Brain magnetic resonance imaging performed on Day 7, showing multiple bilateral white-matter lesions consistent with central nervous system vasculitis.

Acute necrotizing eosinophilic myocarditis is a rare, potentially life-threatening condition that requires prompt recognition and treatment.² It is usually reported as a severe complication of drug rash with eosinophilia and systemic symptoms. The incidence is virtually unknown, but the reported mortality rate of >50% and an average survival of <4 days are remarkable.³ Cases reported in the literature have usually been of critically ill patients presenting with cardiac arrest,⁴ fulminant myocarditis requiring mechanical support⁴ or extracorporeal membrane oxygenation,⁵ or sudden death.

The potential causative drug in the present case was an over-the-counter, fixed-dose combination antimigraine drug (isometheptene mucate 30 mg, metamizole sodium 300 mg, and caffeine 30 mg). Of these, the component of interest is isometheptene mucate, a sympathomimetic drug with a mechanism of action based on vasoconstriction.⁶ Adverse effects include sedation, gastrointestinal disturbance, and worsening hypertension. Excessive use of isometheptene mucate has been discouraged in the literature, as it has been associated with medication-overuse headache, intracerebral haemorrhage,^{7,8} and vasospasm.⁹

The US Food and Drug Administration (FDA) considers isometheptene-containing drug products unapproved and thus banned from interstate commerce. As of 1 January 2018, all US companies agreed to cease the distribution of their isometheptene-containing drugs. In other countries, however, these compounds are freely available over the counter, as is the case in Brazil.

We emphasize the importance of accurate aetiological diagnosis in patients with HF, especially in cases where the most prevalent causes can be easily excluded, such as ischaemic, hypertensive, or alcoholic causes. The search for aetiology would generally include advanced imaging capabilities and possibly histopathological examination.

This is the first case ever reported of ANEM caused by excessive use of an isometheptene-containing drug product with associated CNS vasculitis (documented by MRI and high cerebrospinal fluid protein). The patient was successfully treated with a course of pulse-

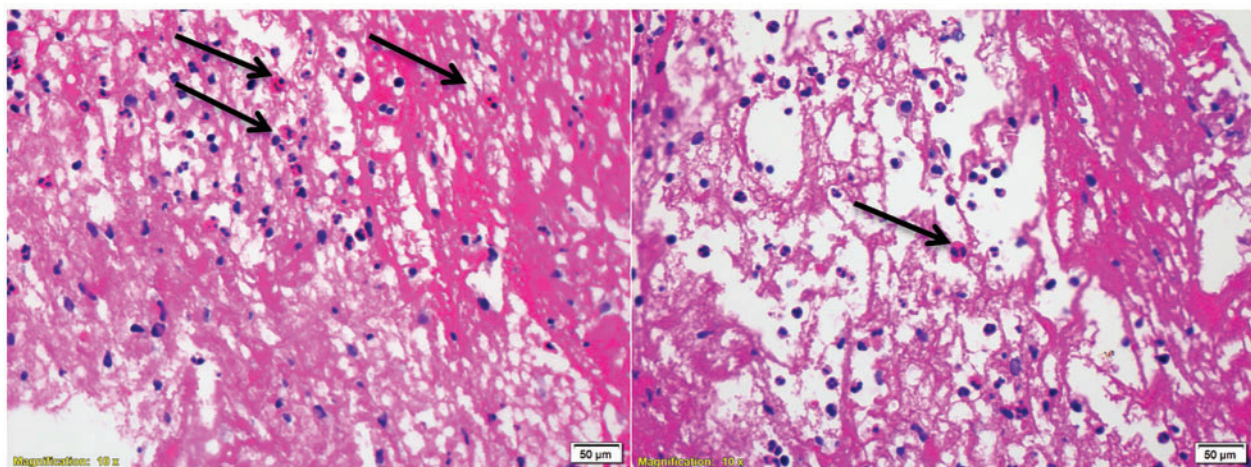


Figure 6 Haematoxylin and eosin-stained endomyocardial biopsy specimen, showing a patchy interstitial infiltrate with numerous eosinophils (black arrows).

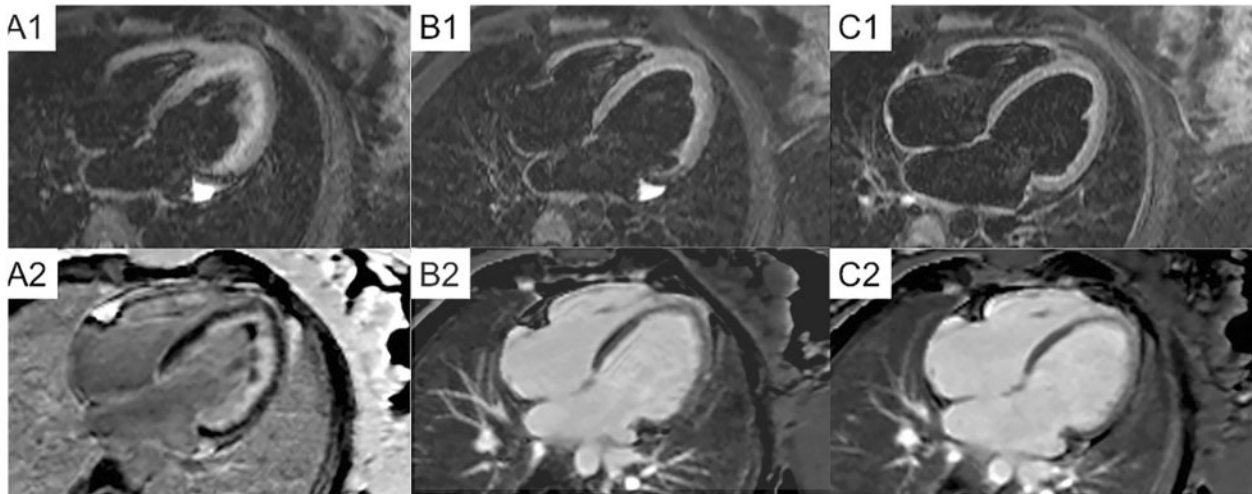


Figure 7 Follow-up cardiac magnetic resonance. (A) Initial scan showing evidence of myocarditis; (B) 30-day follow-up showing partial resolution; (C) 4-month follow-up showing complete resolution of myocarditis, normal ventricular function, and minimal apical foci of fibrosis.

dose methylprednisolone, with near-complete reversal of signs and symptoms of myocarditis and complete resolution of HF and CNS vasculitis.

Lead author biography



Graduated in Medicine at Federal University of Rio Grande do Sul (UFRGS) (1994), Master's and PhD in Cardiology at Federal University of Rio Grande do Sul (2000 and 2004), in Brazil. Heart Failure Research and Clinical Fellowship at University of Ottawa Heart Institute, Ottawa, ON, Canada. He has published 47 PubMed indexed papers and has 2186 citations in Google Scholar; H index of 22. He reviews manuscripts for *Journal of the*

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Supplementary material

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

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

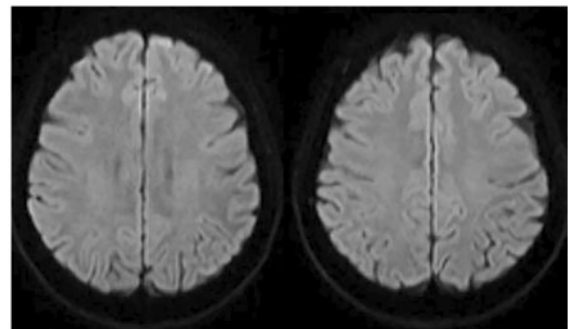


Figure 8 Brain magnetic resonance performed on Day 20 showing resolution of signs of vasculitis after pulse therapy.

Consent: The patient gave her consent for the material presented in this case report. It was explained to the patient that the material would have educational and scientific value, and that publication might help improve the care that others will receive in the future. She is aware that she will not receive any financial benefit or compensation. 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.

Conflict of interest: None declared.

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