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CASE REPORT
Heart failure

Fulminant Influenza A myocarditis in a patient presenting with cardiogenic shock and biventricular thrombi: a case report

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Background Acute myocarditis is a common condition, with viral infections being the most common aetiology in North America and Europe. Influenza A myocarditis is however rare. As clinical manifestation may be fulminant, early recognition and management are paramount and may impact overall prognosis by hindering complications such as thromboembolism. A brief review of the literature, diagnostic modalities, work-up and treatment are discussed.

Case summary We present the case of a 42-year-old, previously healthy woman with recent flu-like symptoms, developing decompensated heart failure (HF) and cardiogenic shock within a week, due to Influenza A myocarditis. Biventricular thrombi were identified. Pharmacological haemodynamic support, followed by HF therapy, allowed full recuperation of heart function. Intracavitary thrombi disappeared under unfractionated heparin with bridging to rivaroxaban.

Discussion Fulminant myocarditis due to Influenza A is rare and, to the best of our knowledge, has not been associated with intracardiac thrombi formation. Echocardiography is the essential first-line imaging modality. Cardiac magnetic resonance plays a major role in the diagnosis of myocarditis and may preclude the need for an endomyocardial biopsy in selected cases. Coronary angiography may be required to rule out ischaemic aetiology. First-line therapy in fulminant disease is pharmacological and, if required, mechanical haemodynamic support. Standard HF therapy complete the therapeutic options and should be introduced as soon as possible. Complications such as intracardiac thrombi formation, require targeted treatment. Specific drug therapies targeting Influenza A have no proven benefit in myocarditis.

Keywords Acute myocarditis • Cardiogenic shock • Case report • Influenza A • Intracardiac thrombus

ESC Curriculum 6.4 Acute heart failure • 2.3 Cardiac magnetic resonance

Learning points

- Although rare, fulminant myocarditis due to Influenza A may lead to serious complications, such as intracavitary thrombi and thromboemboli, in the setting of ventricular dysfunction and hypercoagulable state.
- Cardiac magnetic resonance plays a major role by offering functional and morphological evaluation, as well as allowing myocardial characterization, and may preclude the need for endomyocardial biopsy, which should be reserved for selected severe cases.
- Specific drug therapies targeting Influenza A exist, although benefits in myocarditis are not proven.

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Introduction

Acute myocarditis is a common condition of various aetiologies. Clinical manifestations range from completely silent to fulminant disease. Early recognition and management are paramount in severe cases and may impact overall prognosis. Although viral infections are the most common aetiology in North America and Europe, Influenza A myocarditis is very uncommon, and to the best of our knowledge has not been associated with intracardiac thrombi formation.[1,2]

Timeline

Time	Events
Admission (Day 0)	Presentation at the emergency department with asthenia, fever, dyspnoea, and myalgia. The patient was febrile and in cardiogenic shock. Electrocardiogram and lab results were suggestive of myocardial injury.
Admission + 2 h	Positive naso-pharyngeal swab for Influenza A. Contrast chest computed tomography showing bilateral pleural effusion and hyperdensities in both left ventricular (LV) and right ventricular (RV) apex.
Admission + 3 h	Transthoracic echocardiography (TTE): • LV ejection fraction 25%. • 22 × 15 mm pedunculated intracavitary mass, indicating a thrombus, in the LV apex. • Severe RV systolic dysfunction. • Severe right cardiac chamber dilatation with massive functional tricuspid regurgitation and end-diastolic interventricular septal flattening.
Day 1	Endomyocardial biopsy confirming acute myocarditis.
Day 5	Cardiac magnetic resonance imaging: • Improvement of the biventricular systolic function. • Persistence of biventricular thrombi. • Late gadolinium enhancement of subepicardial and infero-lateral wall from base to apex.
Day 8	Recovery of cardiac function and absence of intracavitary thrombi on TTE.
Day 10	Patient discharged under oral anticoagulant, beta-blocker, and angiotensin-converting enzyme inhibitor therapy.
At 6 months	Patient symptom-free with normalization of cardiac function and absence of intracardiac thrombi.

Case presentation

A 42-year-old woman with no significant past medical history or known cardiovascular risk factors, presented to the emergency department with asthenia, myalgia, fever, worsening dyspnoea and orthopnoea for the past week. No chest pain was reported. She was under no medication. No substance abuse was reported. Vital parameters: tympanic temperature 38.6°C, pulse 104 b.p.m., symmetrical blood pressure of 86/62 mmHg, respiratory rate 28/min, and peripheral oxygen saturation 94%. Physical examination: patient appearing in severe distress, peripheral skin mottling, and bi-basilar hypoventilation on lung auscultation. Arterial blood gas analysis revealed a PaO_2 of 7.8 kPa (normal value: 10.5–13.5 kPa) and a lactate level of 3.5 mmol/L (normal value: <2.3 mmol/L). Laboratory workup was relevant for: haemoglobin 112 g/L (normal value: 120–150 g/L), white cell count 17.2 G/L (normal value: 4–10 G/L), C-reactive protein 49 mg/L (normal value: <5 mg/L), creatinine 99 µmol/L (normal value: 52–92 µmol/L), aspartate transaminase 578 U/L (normal value: <30 U/L), alanine transaminase 1287 U/L (normal value: <30 U/L), total bilirubin 14 µmol/L (normal value: <20 µmol/L), NT-proBNP 39 997 ng/L (normal value: <300 ng/L), creatine kinase 500 U/L (normal value: <200 U/L), and high-sensitive cardiac Troponin T (cTnT) 2339 ng/L (normal value: <14 ng/L) without substantial increase on repeat measurement at 1 h. Two sets of blood cultures remained sterile. A nasopharyngeal swab with real-time reverse transcriptase–polymerase chain reaction was positive for Influenza type A. The 12-lead electrocardiogram (ECG) showed sinus tachycardia with low QRS voltage, subtle ST-segment elevation in the inferior (II, III, aVF) and first precordial leads (V1, V2), as well as ST-segment depression in the lateral leads (I, aVL) (Supplementary material online, *Figure 1*). A contrast chest computed tomography revealed bilateral pleural effusions and the presence of a bulky oval-shaped hyperdensity in the left ventricular (LV) apex, as well as in the right ventricular (RV) apex (*Figure 1*). Transthoracic echocardiography (TTE) confirmed the presence of a 22 × 15 mm pedunculated intracavitary mass, suspect of a thrombus, in the LV apex (*Figure 2*), and additionally showed severe biventricular systolic dysfunction with an LV ejection fraction (EF) of 25%, severe right cardiac chamber dilatation with end-diastolic interventricular septal flattening and massive functional tricuspid regurgitation (*Videos 1–3*, Supplementary material online, *Videos S1–S4*). Haemodynamic support with dobutamine and

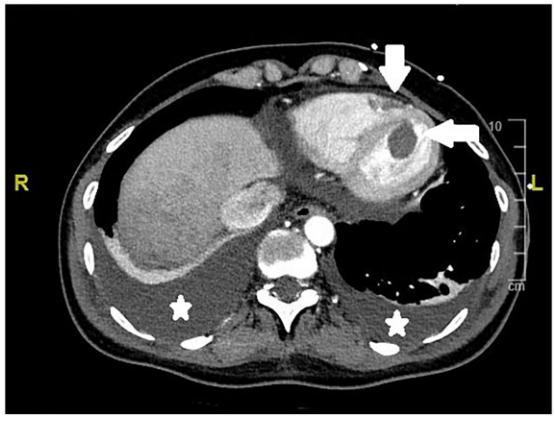


Figure 1 Sagittal view of the contrast chest computed tomography revealing bilateral pleural effusion (white stars) and the presence of a left ventricular thrombus (horizontal white arrow), as well as a right ventricular one (vertical white arrow).

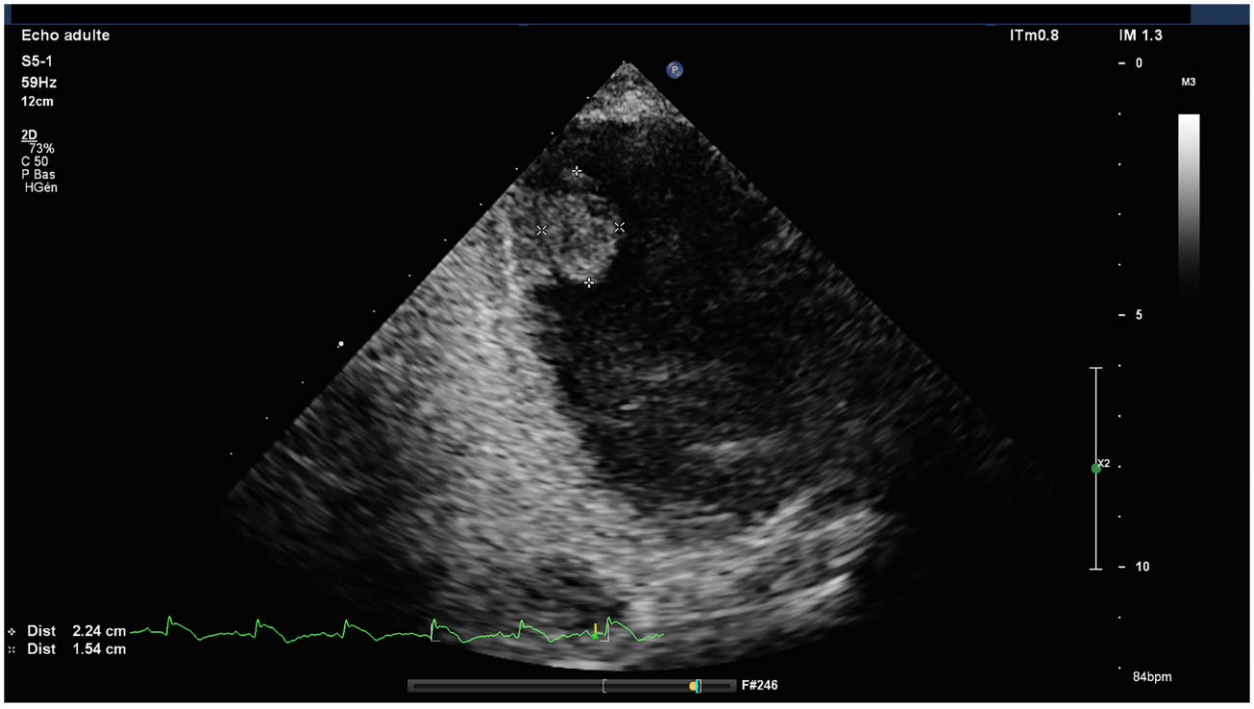
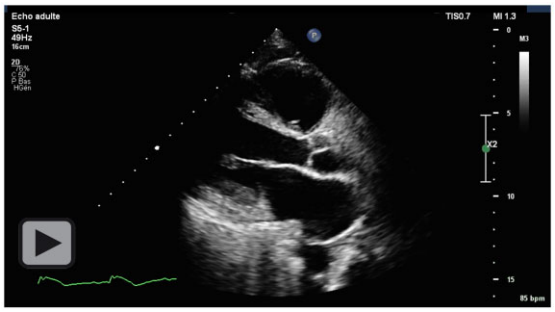
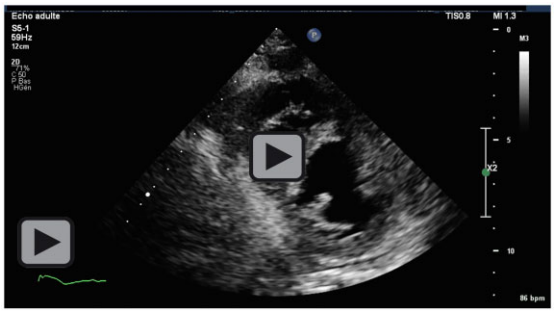


Figure 2 Modified two-chamber view showing a 22 × 15 mm pedunculated thrombus in the inferior apical segment of the left ventricle.



Video 1 Transthoracic echocardiography on admission: parasternal long-axis view showing severe left ventricular systolic dysfunction and right ventricular dilatation.



Video 2 Transthoracic echocardiography on admission: parasternal short-axis view at the mitral valve level showing severe left ventricular systolic dysfunction, right ventricular dilatation, and end-diastolic left ventricular D-shaping.

noradrenaline was initiated. Therapeutic anticoagulation with continuous intravenous Heparin was started and Oseltamivir 75 mg bi-daily given for 5 days. Diuretics were introduced once the perfusion status had improved.

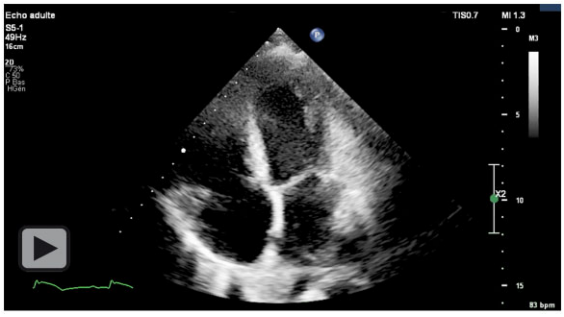
On Day 1, three myocardial biopsies were taken from the RV septum via right femoral venous access. Histological examination confirmed areas of acute and subacute myocardial necrosis, with perinecrotic lymphocytic inflammation. Giant-cell and necrotizing eosinophilic myocarditis could be excluded.

On Day 5, cardiac magnetic resonance (CMR) revealed substantial improvement in biventricular systolic function (LV-EF 46%, RV-EF 46%) with persisting biventricular thrombi [7 mm (LV), 3 mm (RV)] (*Figure 3A–C*; Supplementary material online, *Figure 2'A* and *B*). T2-weighted sequences [T2 map, short-tau inversion recovery (STIR)] showed a diffuse increase in LV wall T2 myocardial relaxation time and inflammation/oedema prominent in the inferolateral wall (STIR). Native T1 mapping also revealed increased relaxation times of the LV myocardium, with increased myocardial extracellular volume (ECV). Late gadolinium enhancement (LGE) imaging showed subepicardial enhancement of the infero-lateral wall from base to apex.

After weaning from vasoactive drugs, angiotensin-converting enzyme inhibitor, and beta-blocker were introduced. Heparin was switched to Rivaroxaban 20 mg once daily (OD). On Day 8, pre-discharge TTE showed complete normalization of the biventricular systolic function and absence of intracavitary thrombi (Supplementary material online, *Videos S5–S9*). The patient was discharged 10 days following admission under Rivaroxaban 20 mg OD, Lisinopril 7.5 mg OD, and Metoprolol 50 mg OD. Restriction of physical activity for 6 months was advised. At 6 months follow-up, the patient remained symptom-free with normal cardiac function.

Discussion

Acute myocarditis due to Influenza A was suspected in the settings of a positive naso-pharyngeal swab. The most common extrapulmonary manifestation of Influenza is indeed myocardial involvement, but acute myocarditis remains rare and concerns 0.4–13% of hospitalized adult patients with documented Influenza infection.[2] Fulminant myocarditis is defined by rapid onset heart failure (HF) and cardiogenic shock within 4 weeks of a prodromal phase. In-hospital mortality reaches 12%, and combined rates of in-hospital death or heart transplantation of 25.5% have been reported.[3] A review of 44 patients with Influenza-related myocarditis, described congestive HF in 84% of them (37/44), with about 60% (23/37) requiring advanced cardiac support modalities.[2] Mortality rate was 23% (10/44).



Video 3 Transthoracic echocardiography on admission: apical four-chamber view showing severe left ventricular systolic dysfunction and dilatation of the right cardiac chambers.

Initial management of acute myocarditis presenting with acute HF should follow current HF guidelines.[4] Our patient profile was 'wet and cold', and pharmacological haemodynamic support was begun. In the presence of concomitant right-heart dysfunction, diuretics and positive-pressure ventilation should be used with caution, respectively to avoid deleterious decrease in RV pre-load and increase in after-load. Evaluation of RV function is of utmost importance when mechanical haemodynamic support is being considered.

Elevated cTnT confirmed the myocardial injury. Although not completely excluded, myocardial infarction seemed very unlikely in the absence of chest pain, ECG criteria for ST-segment elevation acute coronary syndrome, and evidence of global dysfunction on initial TTE.

Based on the above, given the high suspicion for fulminant myocarditis, coronary angiography was avoided. An endomyocardial biopsy (EMB) was cautiously performed on the RV septum given the small RV apical thrombus. EMB is recommended in case of rapidly progressive HF or life-threatening presentation, to permit diagnosis of diseases necessitating prompt and targeted treatment such as giant cells myocarditis, eosinophilic myocarditis, or cardiac sarcoidosis.[1] Histologically, myocarditis is defined by the *Dallas* criteria, as evidence of myocardial inflammatory infiltrate, commonly lymphocytic in viral aetiologies, associated with myocyte degeneration and necrosis.[5] The biopsies of our patient showed a specific myocardial inflammation

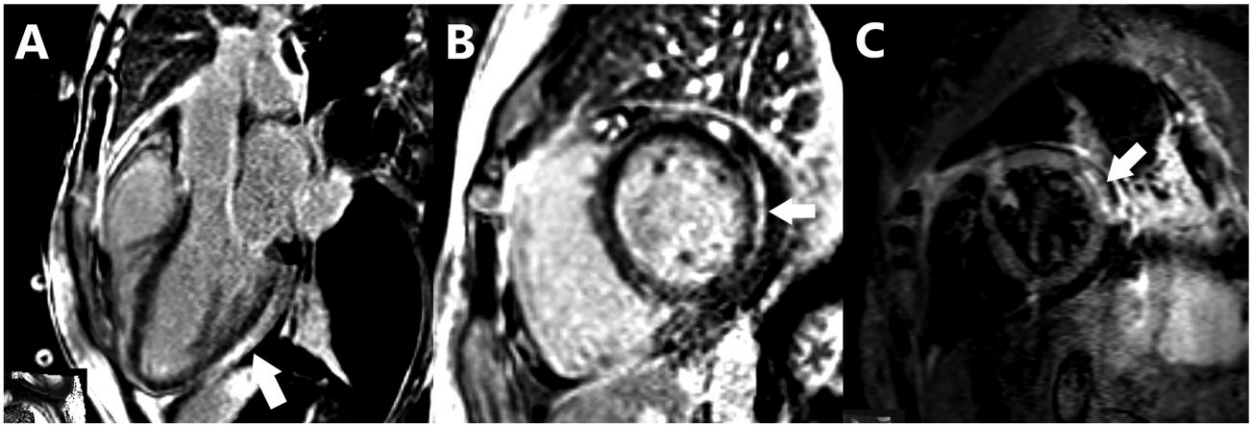


Figure 3 Cardiac magnetic resonance images. (*A*) Three-chamber late gadolinium enhancement view showing infero-lateral subepicardial enhancement (white arrow); (*B*) short-axis late gadolinium enhancement mid-cavity view showing the same area of infero-lateral subepicardial enhancement (white arrow); (*C*) T2-weighted short-tau inversion recovery sequence showing a short-axis mid-cavity view with enhanced signal (oedema) of the subepicardial infero-lateral wall (white arrow).

and necrosis, suggesting viral myocarditis due to Influenza A infection.[1,5]

CMR is the non-invasive gold standard diagnostic test for suspected myocarditis and may preclude the need for an EMB in haemodynamically stable patients. Diagnostic criteria have been published and refined to improve CMR accuracy and specificity in the diagnosis of myocarditis (*Lake Louise* criteria, updated in 2018[6]). In addition to quantify biventricular volumes, mass, ejection fraction and regional function, CMR allows myocardial characterization (T1 and T2 relaxation times, ECV), oedema-inflammation (early gadolinium enhancement, T2 sequences), and scar recognition (LGE). Typical findings include regional or diffuse myocardial oedema, elevated T1 and T2 relaxation times, elevated ECV and subepicardial LGE, preferentially affecting the LV inferior-lateral wall.[6]

The definite diagnosis of Influenza A myocarditis requires a molecular diagnosis on the EMB specimen, which is limited by a variable sensitivity.[1] This was not deemed necessary in our patient, as it would not have modified the overall management. The anti-viral treatment Oseltamivir, a neuraminidase enzyme inhibitor, prevents viral multiplication by inhibiting new virions from being released and is ideally administered <48 h after symptom onset.[2] We agreed on a pragmatic off-label use, as there is no evidence in the specific setting of Influenza myocarditis.[7] Glucocorticoid therapy may be considered in infection-negative lymphocytic myocarditis refractory to standard treatment.[7]

Among the causes of HF, acute myocarditis is more commonly associated with thrombus formation due to the co-existence of ventricular dysfunction and of hypercoagulability in the setting of active inflammation.[8] Current guidelines recommend initial treatment with unfractionated Heparin or low-molecular weight Heparin and bridging with vitamin K antagonists.[9] A minimum of 3 months is advised, with discontinuation after imaging evidence of thrombus resorption and recovery of cardiac function. Direct oral anticoagulants (DOACs) have not been widely studied in this setting, even though one retrospective study has shown non-inferiority of DOACs when compared with vitamin K antagonists.[10] Currently, no statement concerning preventive anticoagulation in myocarditis is available. In the absence of alternate indication for anticoagulation such as atrial fibrillation, treatment should be tailored individually considering features predicting thrombus formation, such as intracavitary smoke.

Conclusion

Fulminant myocarditis due to Influenza A is rare but may lead to serious, multiorgan and fatal complications. Intracavitary thrombus in the presence of ventricular dysfunction and hypercoagulable state should be looked for and appropriately treated. CMR plays a major role in the diagnosis of myocarditis, offering non-invasive, functional and morphological evaluation, and uniquely allowing myocardial characterization. EMB may be required in selected severe cases for rapid diagnosis and targeted therapeutic orientation. Pharmacological HF therapy and mechanical support are the standard therapeutic options. Specific drug therapies targeting Influenza A exist, although benefits in the setting of myocarditis are not proven.

Lead author biography

Dr Mylène Cottet has achieved her medical studies at the University of Lausanne, Switzerland, in 2014. She has particular interest in the field of cardiology, in which she performed a rotation during her 2-year residency in internal medicine at the University and Hospital of Fribourg, Switzerland. She intends to become a general physician.

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.

Conflict of interest: None declared.

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