

Eosinophilic perimyocarditis associated with eosinophilic granulomatosis with polyangiitis: a case report

Ludovica Blumetti *,¹, Maria Luisa De Perna¹, Michael Reinehr ^{1,2}, and Giovanni Pedrazzini ¹

¹Cardiocentro Ticino Institute, Ente Ospedaliero Cantonale, Via Tesserete 48, CH-6900 Lugano, Switzerland; and ²Institut für Pathologie und Molekularpathologie, Universitätsspital Zürich, Rämistrasse 100 8091 Zürich, Switzerland

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Background

Eosinophilic myocarditis (EM) is a rare and potentially life-threatening form of myocarditis, frequently (but not always) associated with eosinophilia, and presents with acute chest pain, or signs and symptoms of acute or chronic heart failure. Eosinophilic myocarditis has various aetiologies, including eosinophilic granulomatosis with polyangiitis (EGPA).

Case summary

A 52-year-old female with a long-standing history of asthma, acral paraesthesia, subcutaneous nodules, and recurrent chest pain treated with anti-inflammatory drugs was admitted to our hospital with chest pain, repolarization disturbances, eosinophilia, and increased troponin levels. After an initial evaluation by coronary angiography, echocardiography and cardiac magnetic resonance, a definitive diagnosis of EM was made with the help of an endomyocardial biopsy. The aetiological diagnosis of EM as a manifestation of tissue involvement in EGPA was concluded after ruling out other possible causes of eosinophilia and with the help of other diagnostic criteria for EGPA (asthma, eosinophilia, and neuropathy). Therefore, we started with a high dosage of glucocorticoids, and attained relief of symptoms and normalization of eosinophilic count after a few days.

Discussion

In cases of myocarditis (particularly if associated with eosinophilia), EM is a manifestation of EGPA and should be considered for a prompt differential diagnosis. Endomyocardial biopsy represents the gold standard for the diagnosis of EM. The mainstay of therapy for EM is immunosuppressive drugs to help prevent its evolution to a fulminant form and chronic progression towards restrictive cardiomyopathy.

Keywords

Eosinophilic myocarditis • Eosinophilic granulomatosis with polyangiitis • Eosinophilia • Endomyocardial biopsy • Acute chest pain • Case report

Learning points

- Eosinophilic myocarditis (EM) is a heterogeneous disease for its clinical presentation and its causes.
- Cardiac magnetic resonance imaging may be negative despite biopsy-proven EM.
- A prompt diagnosis and immunosuppressive therapy can improve prognosis which otherwise would be poor.

* Corresponding author. Tel: +41 078 911 22 25, Email: ludovica.blumetti@gmail.com

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Introduction

Eosinophilic myocarditis (EM) is a rare type of myocardial inflammation characterized by eosinophilic infiltration of the myocardium and is often associated with eosinophilia.¹

Eosinophilic myocarditis has been reported to be associated with immune-mediated conditions, such as Churg–Strauss syndrome [recently renamed as eosinophilic granulomatosis with polyangiitis (EGPA)], hypersensitivity reactions, parasitic infections, and haematological and solid neoplasia. However, the exact relationship with these diseases as well as their underlying mechanisms are not entirely defined.²

From a clinical standpoint, EM may present with chest pain mimicking acute coronary syndrome, heart failure, conduction disturbances, or occasionally with severe left ventricular dysfunction leading to cardiogenic shock. A working diagnosis of EM is usually based on transthoracic echocardiography and cardiac magnetic resonance (CMR), however, endomyocardial biopsy is mandatory for a definitive diagnosis.

Timeline

Since childhood	Asthma
24 months prior	Fever, fatigue, and arthralgias
14 months prior	Diagnosis of pericarditis associated with eosinophilia ($1.8 \times 10^9/L$)
12 months prior	Angioedema, recurrent subcutaneous nodules, numbness, and paraesthesia on toes and hands
2 weeks prior	Chest pain improved by sitting up and leaning forward, malaise, nausea, and sweating
Day of presentation	Admitted to emergency room for worsening chest pain 12 leads electrocardiogram: sinus rhythm, no alteration of PR and QRS, non-diagnostic repolarizations disturbances Laboratory exams: high-sensitive troponin T (193 ng/L), N-terminal prohormone of brain natriuretic peptide (1153 ng/L), C-reactive protein (101 mg/L), D-dimer (4.23 mg/L), white cell count $10.5 \times 10^9/L$, eosinophils $2.140 \times 10^9/L$ Transthoracic echocardiogram: ejection fraction (EF) 47%, pericardial effusion without tamponade and severe mitral regurgitation
During the hospitalization	Cardiac magnetic resonance: absence of late gadolinium enhancement, and normal T1 and T2 values Endomyocardial biopsy: diffuse infiltration of eosinophils
10 days later	Initiation of corticosteroids, disappearance of chest pain, normalization of eosinophilic count
9 months later	While tapering of corticosteroids, maintenance of clinical remission, at echo EF 54%, absence of pericardial effusion with stability of mitral regurgitation

Case presentation

A 52-year-old female was admitted to our hospital after suffering from chest pain in the previous weeks. She reported that the pain, which was associated with fatigue and malaise, became worse when breathing and lying down. Her clinical history was positive for asthma and for recurrent fever, arthralgia, and fatigue in the last 2 years. Twelve months before, she was diagnosed with idiopathic pericarditis, and was treated with non-steroidal anti-inflammatory drugs and experienced a rapid remission of symptoms. Since then, she also reported episodes of angioedema treated with glucocorticoids. The patient also had the appearance of painful subcutaneous nodules in the arms and legs, and numbness and tingling sensations in her toes and hands.

Physical examination revealed normal vital parameters with a holosystolic regurgitant murmur at cardiac apex, absence of cutaneous manifestations and neurological signs and her electrocardiogram (ECG) showed a diffuse flattening of T waves in inferior, lateral, and precordial leads (Figure 1). Serum biochemistry showed an inflammatory state with hypereosinophilia (C-reactive protein 101 mg/L, upper limit for a 50-year-old woman 16 mg/L, eosinophils at $2.14 \times 10^9/L$ upper limit at $0.5 \times 10^9/L$), myocardial injury (high-sensitive troponin T 193 ng/L, normal <52 ng/L), and an increase in the N-terminal prohormone of brain natriuretic peptide (1153 ng/L, normal in acute setting <300 ng/L). Transthoracic echocardiography showed mild left ventricular dysfunction [left ventricular ejection fraction (LVEF), 47%], severe mitral regurgitation due to prolapse of the posterior mitral leaflet (confirmed at transoesophageal echocardiography), grade I diastolic dysfunction (E/A 0.8 and E/e' 9.7), and pericardial effusion of 2.5 mm without haemodynamic impact (Figure 2) (Video 1, 2, 3). Given the clinical presentation, elevation of cardiac troponin, and left ventricular dysfunction, we excluded coronary artery disease through angiography. We performed CMR, which showed left ventricular dysfunction (EF 47%) and dilatation (left ventricle end-diastolic volume index 106 mL/m^2), the absence of late gadolinium enhancement (LGE), and normal T1 and T2 values; thus, excluding fibrosis, inflammation, and oedema (Figure 3) (supplementary videos).

Despite a non-conclusive CMR, but given the high clinical suspicion, we proceeded with an endomyocardial biopsy that revealed diffuse infiltration of eosinophils in the connective tissue of the myocardium, with evidence of endocardial thrombi and interstitial fibrosis without myocyte necrosis. These findings established a final diagnosis of eosinophilic perimyocarditis (Figure 4).

A multidisciplinary discussion was undertaken involving cardiology, rheumatology, and infectious diseases specialists to evaluate the causes of the eosinophilia and potential treatments. No history of drugs could explain the hypersensitivity syndrome, and a thorax and abdominal computed tomography scan excluded solid neoplasia (cause of paraneoplastic eosinophilia). A bone marrow biopsy, and a molecular and cytogenetics study excluded a lymphoid and myeloid neoplasm based on mutation analyses of PDGFRA, FGFR1, PDGFRB, and JAK2. A rheumatological work-up [antineutrophil cytoplasmic antibody (ANCA), antinuclear antibodies, extractable nuclear antigens] was also inconclusive. To exclude parasitic infections, a serological work-up was undertaken, which showed a positive ELISA test for *Strongyloides stercoralis*, which was interpreted as chronic infection

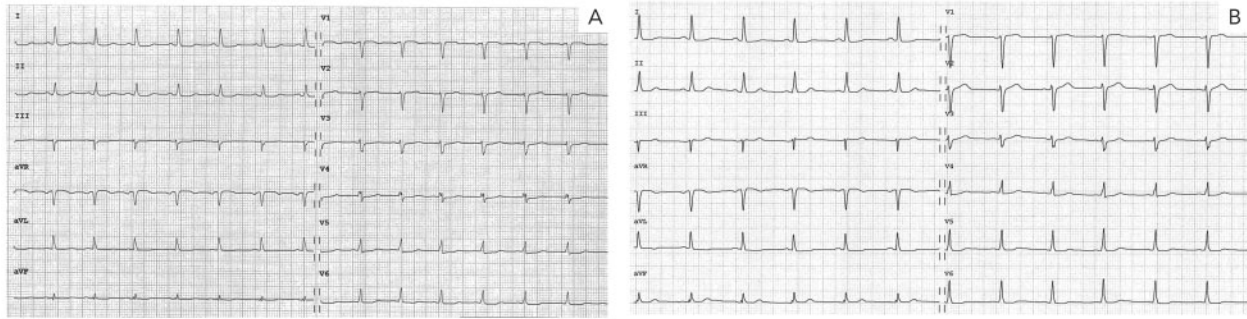


Figure 1 (A) Electrocardiogram at admission. (B) Electrocardiogram at discharge.

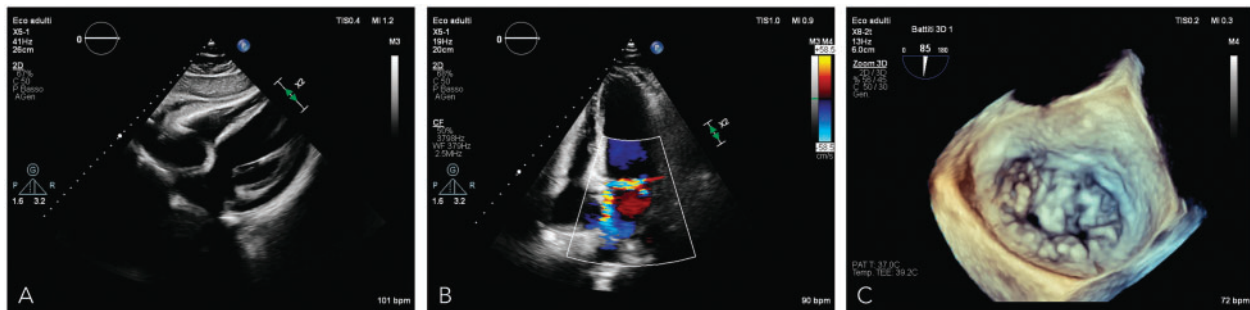


Figure 2 (A) Subxiphoid view of pericardial effusion. (B) Apical four-chamber view with colour-flow Doppler focused on severe mitral regurgitation. (C) Transoesophageal surgical view showing prolapse of posterior mitral leaflet.

based on the clinical presentation. In view of the likely onset of prednisone therapy, a two-dose regime with ivermectin was administered. Due to the patient's neurological symptoms, an electromyography was performed, which documented a mononeuritis multiplex, typical of EGPA.

After comprehensive evaluation, the patient received the diagnosis of EM secondary to EGPA based on the presence of four out of six criteria according to the diagnostic criteria defined by the American College of Rheumatology (ACR), namely asthma, eosinophilia, neuropathy, and extravascular eosinophils (in our case in the myocardium)³ (Table 1). In addition, pericardial effusion, history of angioedema, subcutaneous nodules, and the absence of ANCA (more frequently associated with cardiac involvement) gave support to this conclusion.

Although the patient was at high risk of poor prognosis (Five-Factor Score or FFS 2 for cardiac involvement and the absence of ear–nose–throat manifestations), we decided to introduce prednisone at 1 mg/kg/day without an additional immunosuppressant for the possible risk of strongyloidiasis hyperinfection.⁴ The initiation of therapy led to a normalization of the eosinophilic count within 3 days ($0.39 \times 10^9/L$), and improvement of symptoms and pericardial effusion (from 2.5 to 1.2 mm) after 14 days. At 9 months follow-up, while tapering the dosage of prednisone and

with the initiation of maintenance therapy with methotrexate, the patient did not experience relapse of the disease. Improvement of LVEF (EF, 54%) and the disappearance of pericardial effusion were also observed, while the mitral regurgitation remained unchanged (Figure 5).

Discussion

We have described a case of EM, which allowed us to obtain the diagnosis of EGPA. Eosinophilic granulomatosis with polyangiitis, an eosinophilic granulomatous vasculitis affecting small and medium vessels, can involve several organs (lung, heart, peripheral and central nervous system, skin, and kidney).⁵

Cardiac involvement is common, especially if ANCA is negative, and it is an FFS prognostic item being the major cause of death. FFS is a score used at diagnosis of systemic vasculitis to evaluate prognosis and to guide treatment: every risk factor in the FFS score is associated with a mortality rate of 21% within 5 years.⁴ The spectrum of cardiac manifestations includes pericarditis, myocarditis, valvular disease, acute coronary syndrome, arrhythmias, and rarely acute heart failure and sudden death. It is pathophysiologically derived from coronary vasculitis,

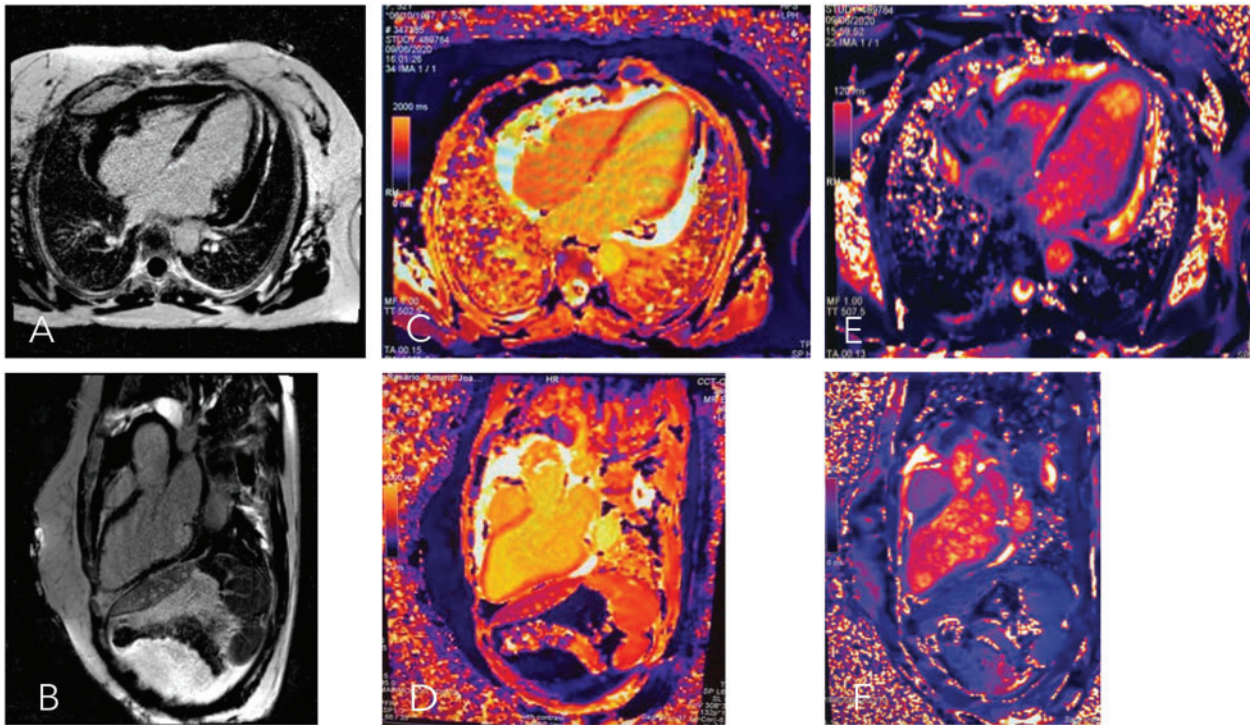


Figure 3 (A) Cardiac magnetic resonance four-chamber view with inversion recovery sequence after gadolinium administration showing absence of late gadolinium enhancement. (B) Cardiac magnetic resonance three-chamber view with inversion recovery sequence after gadolinium administration showing absence of late gadolinium enhancement. (C) Cardiac magnetic resonance T1 mapping four-chamber view showing normal T1 values (<1200 ms) and normal percentage of extracellular volume (13%). (D) Cardiac magnetic resonance T1 mapping three-chamber view showing normal T1 values and normal percentage of extracellular volume. (E) Cardiac magnetic resonance T2 mapping four-chamber view showing normal T2 values (<45 ms). (F) Cardiac magnetic resonance T2 mapping three-chamber view showing normal T2 values.

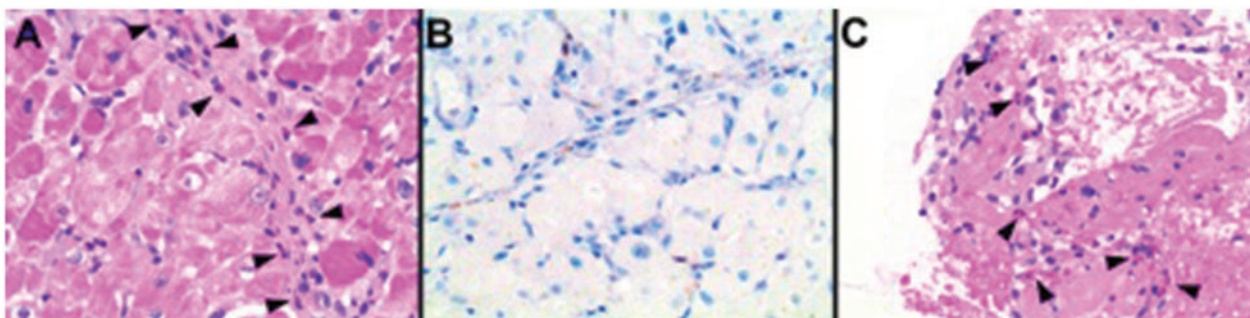


Figure 4 (A) Numerous eosinophilic granulocytes located in the interstitial connective tissue in interventricular septum (black arrowheads, haematoxylin and eosin stain). (B) Congo red stain of the same biopsy sample. (C) Fibrin thrombus material, attached to the endocardium, shows many eosinophilic granulocytes (black arrowheads, haematoxylin and eosin stain).

extravascular granuloma, and eosinophilic interstitial infiltrates.⁶ Eosinophilic infiltration can result in fibrosis and lead to chronic left ventricular dysfunction, due to dilated or restrictive cardiomyopathy (endomyocardial disease or Löffler endocarditis), which is

the most severe form of cardiac involvement, regardless of the underlying cause of eosinophilia. The development of restrictive cardiomyopathy depends on the duration and magnitude of eosinophilia, this could explain why EGPA patients show lower rate

of evolution into this form of cardiac involvement, compared to patients with other eosinophilia-associated diseases.⁷

In our patient, the presence of chest pain, ECG abnormalities, and systolic dysfunction required us first to exclude acute coronary syndrome through coronary angiography. In case of haemodynamic stability, a CMR is useful to identify myocardial inflammation and fibrosis, and to guide endomyocardial biopsy; however, the absence of LGE (usually subepicardial, but also reported as subendocardial or mid-wall, in focal or band-like pattern) and normal T2 values (indicating absence of oedema) do not exclude this diagnosis, especially in the early stages.^{8,9} In our case, despite a negative CMR, clinical suspicion remained high due to the presence of some typical manifestation of the disease: asthma is the most common clinical manifestation of EGPA in its prodromal phase, eosinophilia is typical of the second phase, and subcutaneous nodules together with arthralgia are characteristic manifestations of the late stage.¹⁰ We therefore performed an endomyocardial biopsy, the gold standard for the diagnosis, which was suggestive of EM. This led us to make the diagnosis of EGPA and secondary EM, together with the presence of other diagnostic criteria.

We interpreted the finding of *Strongyloides* as accidental, given the absence of respiratory, gastrointestinal, and cutaneous symptoms, which are characteristic of hyperinfection syndrome. In addition, cardiac involvement is extremely rare, and rarely results in increased eosinophil count and a fulminant course if it is not treated.

With respect to mitral regurgitation, after a review of the literature in which the association between EGPA and multivalvular

involvement (characterized by eosinophil infiltration resulting in valvular thickening) is described in rare cases, we believe that the echocardiographic finding of mitral prolapse is an incidental and independent finding.¹¹

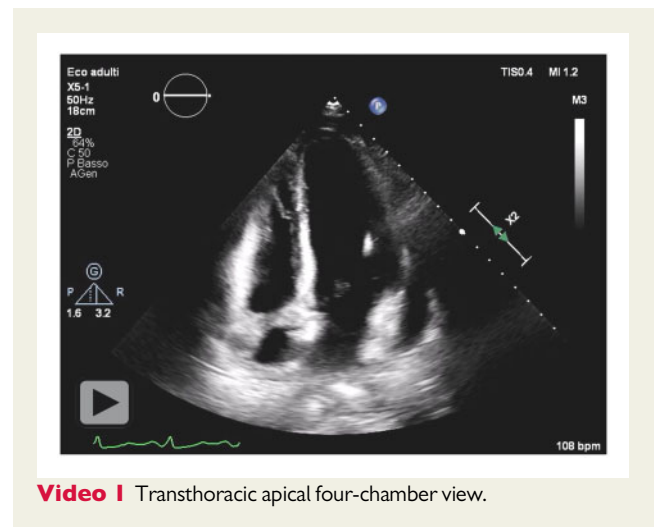
Conclusions

In cases of acute perimyocarditis, EM as a cardiac manifestation of EGPA should be considered as a differential diagnosis, particularly if eosinophilia is prominent, ANCA are absent, and there is a history of asthma. Echocardiography, CMR, and endomyocardial biopsy must be evaluated to reach a diagnosis. CMR has become a useful diagnostic tool in the work-up of EGPA and can help to guide the endomyocardial biopsy (EMB) in case of patchy cardiac involvement, but EMB still remains a mainstay (CoR IIa LoE C), especially in case of high clinical suspicion and negative CMR, as in our patient.¹²

A rapid diagnosis and timely a treatment are crucial for EM patients, as such factors can massively improve prognosis, which is generally poor in EGPA-associated myocarditis.

Table 1 1990 American College of Rheumatology criteria for classification of Churg–Strauss syndrome

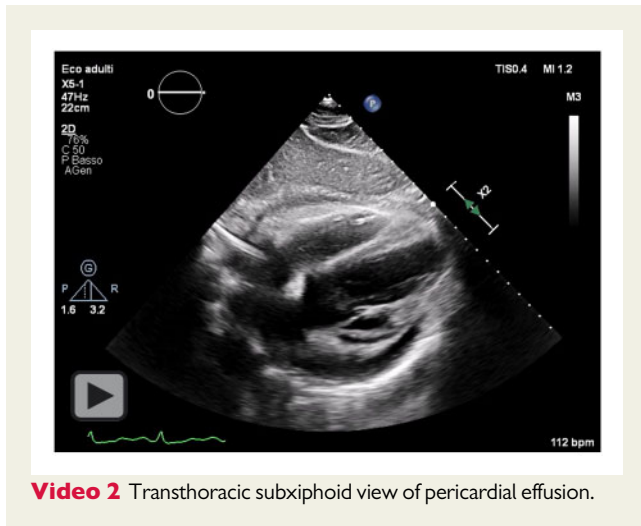
Asthma
Eosinophilia
Neuropathy
Pulmonary infiltrates
Paranasal sinus abnormality
Extravascular eosinophils



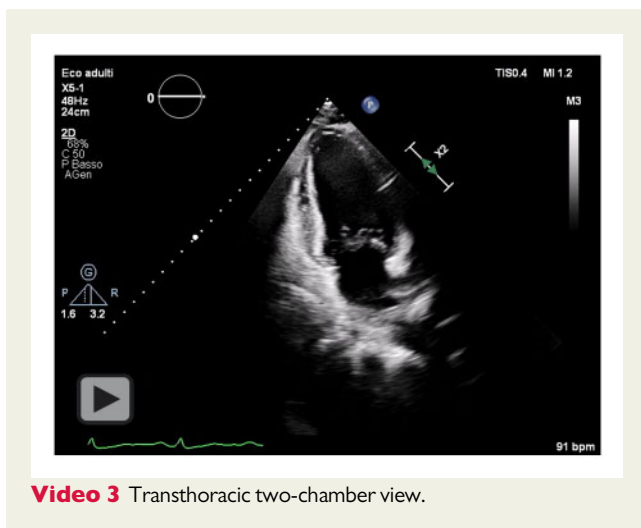
Video 1 Transthoracic apical four-chamber view.



Figure 5 (A) Follow-up echocardiography at subxiphoid view demonstrating resolution of pericardial effusion. (B) Follow-up echocardiography at apical four-chamber view with normalization of ejection fraction. (C) Follow-up echocardiography at apical four-chamber view with colour-flow Doppler focused on persistence of moderate–severe mitral regurgitation.



Video 2 Transthoracic subxiphoid view of pericardial effusion.



Video 3 Transthoracic two-chamber view.

Lead author biography



Dr Ludovica Blumetti is a second-year cardiology resident at Institute Cardiocentro Ticino in Lugano. She is interested in heart failure and acute cardiovascular care.

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 author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

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