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CASE REPORT
Heart failure

Eosinophilic myocarditis complicated by permanent atrioventricular nodal block: a case report

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Background Eosinophilic myocarditis (EM) is a rare disease with different clinical pictures and disease courses. Little literature is available on the various courses of the disease.

Case summary A previously healthy 44-year-old male patient presented with acute heart failure and developed complete atrioventricular (AV) block requiring pacing. Acute heart failure was managed with inotropic support, non-invasive ventilation, and implantation of a permanent AV-sequential pacemaker. Cardiac magnetic resonance imaging was suggestive of myocarditis and endomyocardial biopsy diagnosed EM histologically. Endomyocardial biopsy was essential for definite aetiologic assignment, thus dispelling initial reservations about immunosuppressive therapy. Final treatment strategy consisted of steroids and Azathioprine.

Discussion Endomyocardial biopsy is essential to establish diagnosis and targeted treatment in EM, which can rapidly lead to life-threatening conditions. Left ventricular function recovered within 2 weeks in response to immunosuppression and the patient was consistently well during follow-up. Despite the otherwise good response to immunosuppression, complete AV block continued over time.

Keywords Eosinophilic myocarditis • Atrioventricular block • Immunosuppression • Endomyocardial biopsy • Case report

ESC Curriculum 2.3 Cardiac magnetic resonance • 2.2 Echocardiography • 7.1 Haemodynamic instability • 6.4 Acute heart failure

Learning points

- Eosinophilic myocarditis (EM) can progress rapidly and lead to a life-threatening condition.
- If EM is suspected, early diagnosis by endomyocardial biopsy and targeted treatment is critical to avoid adverse outcomes.
- Timely corticosteroid therapy usually leads to improvement in left ventricular function and clinical condition, although persistent impairment as in this patient (complete atrioventricular block) is possible.
- A normal peripheral eosinophil count does not exclude EM and should not lead to an incorrect diagnostic and therapeutic decision.

Introduction

Myocarditis encompasses a broad spectrum of different diseases that cause myocardial inflammation. Left ventricular (LV) dysfunction, heart failure and cardiogenic shock, as well as arrhythmias can substantially worsen prognosis.[1]

Early identification of underlying aetiology allows appropriate management.

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Although there is a lack of standardized medical treatment for various types of myocarditis, immunosuppressive therapy is the mainstay of medical treatment[2] in eosinophilic myocarditis (EM).

Herein, we present a patient with EM and normal peripheral blood count, in whom myocardial biopsy was essential for definitive diagnosis and therapy.

Timeline

	Events
1 week prior to admission	Onset of flu-like symptoms, started on macrolide antibiotics and non-steroidal anti-inflammatory drugs by family doctor.
Day of admission	Presented to hospital. Electrocardiogram showed first-degree atrioventricular block (AVB). Transthoracic echocardiogram showed normal left ventricular (LV) function and a small pericardial effusion.
Day 3	Due to increasing signs of congestion, non-invasive ventilation was started.
Day 4	Magnetic resonance imaging (cardiac magnetic resonance) showed typical signs of acute myocarditis (oedema and late gadolinium enhancement distribution) and a decrease in systolic LV function.
Day 8	Right heart catheterization was performed which showed a low cardiac output state (cardiac index 1.65 L/min/m^2). Electrocardiogram showed a complete AVB.
Day 11	A temporary pacemaker was placed and endomyocardial biopsies were taken. Corticosteroid therapy was started.
Day 14	Due to persistent pacing of the temporary system, a permanent pacemaker was implanted.
1-year follow-up	Follow-up showed continued improvement in LV function, but persitent complete AVB.

Case presentation

A 44-year-old, previously healthy male came to the emergency room with repeated chills since 3 days, as well as arthralgia mainly affecting knee and hip joints. These symptoms were preceded by several days of unproductive coughing and a headache. The patient's medical history was positive for smoking, but negative for alcohol or drug abuse. There was no family history of cardiovascular disease or cardiomyopathy. His last trip abroad was 2 months previously to Turkey and he did not take any long-term medication. Macrolide antibiotics and a non-steroidal anti-inflammatory drug (NSAID) were administered 1 week before presentation by the family doctor because of the symptoms mentioned.

At presentation, electrocardiogram showed sinus tachycardia, with a heart rate of 113 beats per minute and a first-degree atrioventricular (AV) block but was otherwise unremarkable (*Figure 1A*). Blood pressure was 126/64 mmHg, oxygen saturation 98% and body temperature 38.5°C. The physical examination showed a sensitivity to pressure during palpation in the epigastric region. Auscultation did not reveal any pericardial friction rubs or pulmonal crackles. Laboratory results showed a total white blood cell count of 13.4 × 103/µL (reference 4.0–10.0 × 103/µL), C-reactive protein of 16.9 mg/dL (reference 0.0–0.5), and a high-sensitive troponin T of 656.2 ng/L (reference 0.0–14.0). No eosinophilia or abnormal cells were found in the whole blood count. The erythrocyte sedimentation rate was 95 mm in 1 h. Serum electrolytes, as well as liver and kidney function parameters were within normal ranges. In blood cultures and serology, no specific pathogen could be identified. Neither in serodiagnosis nor specifically with the polymerase chain reaction (PCR) could any evidence of a microbial cause be found. Vasculitis associated autoantibodies were negative.

The first chest-X-ray showed only mild peribronchial cuffing (*Figure 2A*). Echocardiography revealed preserved LV function without wall motion abnormalities, but a circular pericardial effusion of 9 mm and slightly dilated inferior vena cava. Obstructive coronary artery disease was excluded by cardiac computed tomography. Based on the above and on clinical findings, pneumonia with pericarditis was suspected and antibiotic therapy was extended to levofloxacin and tazobactam/piperacillin. Within 2 days, however, the patient developed signs of congestion and became increasingly short of breath, requiring non-invasive-ventilation with nasal high-flow and forced diuresis using furosemide (*Figure 2B*). Pericardial tamponade and endocarditis were excluded by transoesophageal echocardiography. At this stage, LV ejection fraction was only 35% (*Video 1*).

Cardiac magnetic resonance imaging (CMR) performed on the 4th day of inpatient stay showed areas of late gadolinium enhancement, with both subepicardial involvement inferobasal (*Figure 2C*, arrow) and at the level of the midventricular to apical septum (*Figure 2D*, arrows), and subendocardial involvement at the basal anteroseptal level (*Figure 2E*, arrow). Native T1 map (*Figure 2H*) (T1 relaxation time septal 1211 ms) and T2 map (*Figure 2I*) (T2 relaxation time septal 65 ms) indicated areas of septal myocardial oedema. Accompanying pericarditis was diagnosed due to a circumferential

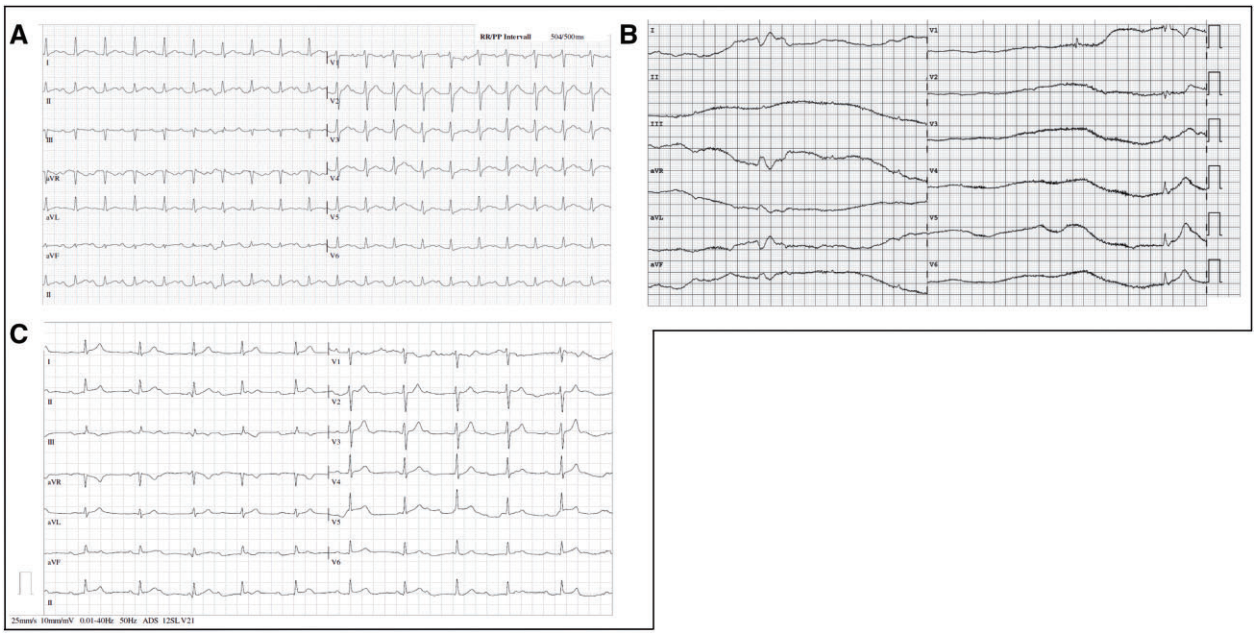


Figure 1 Electrocardiogram at presentation (*A*): sinus tachycardia 113/min, PQ time 210 ms (atrioventricular block I°). (*B*) Electrocardiogram shows complete heart block which caused syncopal asystole. A third-degree atrioventricular block (*C*) did not resolve even with continuous isoprenaline infusion.

pericardial effusion (*Figure 2C, I, and J*, asterisk) with accentuated contrast-enhancing (*Figure 2C*, arrowhead) and oedematous (*Figure 2J*, T2 TIRM, arrowhead) outer pericardial sheet. On Day 8, the course of the disease was further complicated by syncopal complete heart block (*Figure 1B*), which was managed by continuous isoprenaline infusion (*Figure 1C*). Despite short-term stabilization, the patient went into a low-output state within the next hours, with the need for inotropic support (continuous intravenous infusion of Dobutamine 250 mg/50 mL). In addition, a temporary pacemaker was implanted because of repeated episodes of non-sustained Stokes-Adams attacks. Right heart catheter showed a low cardiac index of only 1.65 L/min/m^2 and post-capillary pulmonary hypertension (pulmonary arterial pressure 56/31/41 mmHg, mean pulmonary capillary wedge pressure 34 mmHg). Left ventricular end-diastolic pressure was 29 mmHg. A total of eight endomyocardial biopsy (EMB) were taken from the left ventricle.

Antibiotics were switched to Doxycycline and Meropenem due to persistently high C-reactive protein values and to cover Lyme disease. The evaluation of the EMBs (*Figure 3*) showed moderate myocardial infiltration with inflammatory cell aggregates (red arrows). Additionally, multifocal eosinophilic granulocytes (blue arrows) were found with haematoxylin–eosin staining (HE, *Figure 3A*) and Giemsa staining (*Figure 3B*). Pathogen persistence in the myocardium was excluded by PCR.

Based on these findings, fulminant EM was diagnosed. High-dose steroid therapy (1 mg/kg/day) was initiated together with Azathioprine and subsequently tapered over the next 13 weeks (Prednisolone: 50 mg Weeks 1–2, 25 mg Week 3, 12.5 mg Week 4, 7.5 mg Weeks 5–12, 5 mg Weeks 12–20, 2.5 mg Weeks 20–21; Azathioprine 50 mg 2–0–1 Weeks 0–4 and 50 mg b.i.d. Weeks 5–13).

Pneumocystis carinii prophylaxis with Sulfametrole/Trimethoprim was administered and heart failure therapy with mineralocorticoid receptor-antagonist (Eplerenone 25 mg) and Sacubitril/Valsartan (24/26 mg) was started once the patient's blood pressure was sufficient to tolerate it and gradually uptitrated to 50 mg and 49/51 mg, respectively. Repeated attempts to deactivate the temporary pacemaker resulted in asystole. Consequently, a permanent AV-sequential pacemaker system was implanted.

Haemodynamic stabilization was achieved within a few days after pacemaker implantation (DDD-R) and initiation of immunosuppressive therapy. In addition to the mentioned medications, the discharge regime included a proton pump inhibitor (Pantoprazole 40 mg), a osteoporosis prophylaxis (calcium 1000 mg + vitamin d 880 IU) and a loop diuretic (Torasemide 10 mg, with dose adjustment according to body weight).

At 1-month follow-up, the patient had a New York Heart Association functional class of I. Transthoracic echocardiography showed full recovery of LV function and only minimal residual pericardial effusion. The excellent result was maintained (*Video 2*), while the complete AV block persisted over time.

Discussion

To the best of our knowledge, we report the first case of a persistent, therapy-refractory third-degree AV block after acute EM.

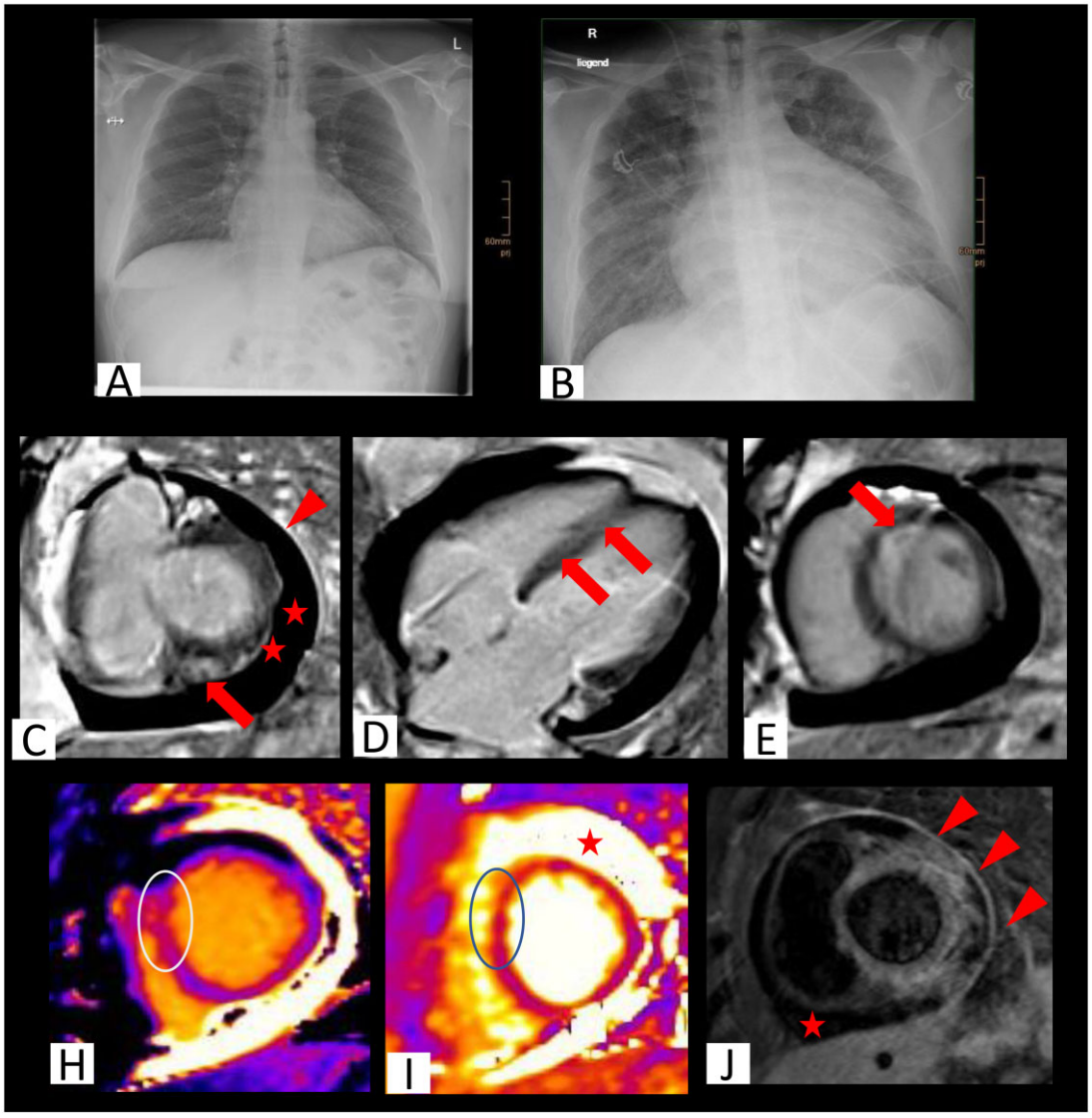


Figure 2 Imaging: initial chest-X-ray (*A*) reveals mild peribronchial cuffing. Follow-up after 2 days displays signs of congestion (*B*). Cardiac magnetic resonance imaging showed areas of late gadolinium enhancement with both subepicardial involvement inferobasal (*C*, arrow) and the midventricular to apical septum level (*D*, arrows) as well as subendocardial involvement at the anteroseptal basal level (*E*, arrow). Evidence for septal myocardial oedema is found in native T1 map (*H*) (T1 relaxation time septal 1211 ms) and T2 map (*I*) (T2 relaxation time septal 65 ms). Pericardialeffusion (*C*, *I* and *J* astersk) with accentuated contrast-enhancing (*C*, arrowhead) and edematous (*J*, T2 TIRM, arrowhead) outer pericardial sheet indicates concomitant pericarditis.

Myocarditis in general, and EM in particular, often initially shows unspecific signs and only mild symptoms similar to a common flu but can progress rapidly to severe heart failure and potentially fatal arrhythmias. Conduction abnormalities are known to occur in giant cell myocarditis or lymphocytic myocarditis but are very rarely observed in EM.[3] Cases of second-degree AV block were reported by Stempfl *et al.*[4] and Kaneda *et al.*[5] and a complete AV block in an infant by Bhogal *et al.*[6] In all cases, there was a rapid resolution of conduction disorders within days of onset, following corticosteroid therapy, while third-degree AV block persisted in our patient.

In everyday clinical practice, EMB is often omitted when myocarditis is suspected although it is the only method that allows definitive diagnosis and identification of the underlying aetiology. If no EMB is performed, therapy is usually empirically performed with steroids or intravenously administered immunoglobulins. In our patient, however, we were concerned about corticosteroid therapy because we initially suspected an underlying infectious aetiology. Blood analysis to screen for viral pathogenesis has shown to poorly correlate with EMB.[7] Similarly, EM cannot be excluded even in the absence of hypereosinophilia in peripheral blood. Even with imaging techniques such

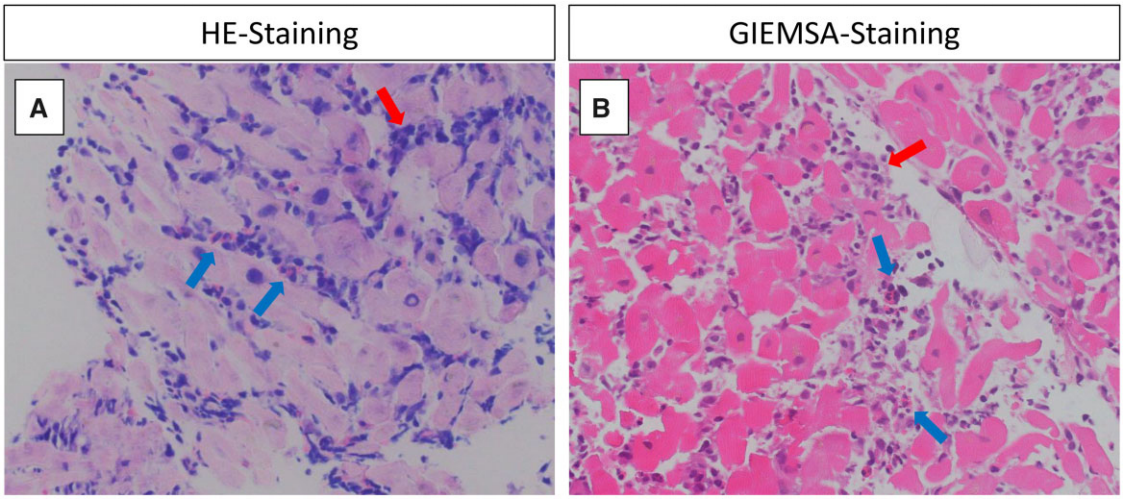
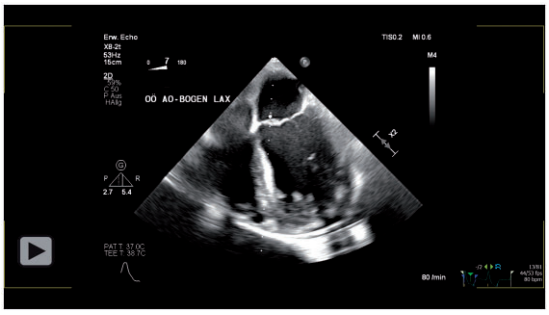
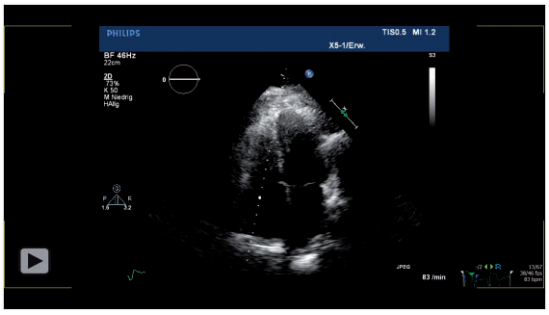


Figure 3 Endomyocardial biopsy stained with haematoxylin–eosin (*A*) and Giemsa (*B*). Immunohistochemistry revealed intermyocytic mixed inflammatory cell infiltrations (red arrows), rich in CD 45+ (leucocytes), CD 68+ (macrophages), and CD 11c (phagocytes). Detection of multifocal eosinophilic granulocytes (blue arrows) led to the diagnosis of a fulminant eosinophilic myocarditis.



Video 1 Transoesophageal four-chamber view before initiation of immunosuppressive therapy with markedly impaired systolic left ventricular function.



Video 2 Transthoracic echocardiography with four-chamber view and recovery of systolic left ventricular function after 5 months.

as CMR, the underlying cause of myocarditis cannot be determined. This is also one of the reasons why EMB is strongly recommended in the guidelines, especially for life-threatening clinical presentations.[8] The detection of multifocal infiltrates of eosinophilic granulocytes and the exclusion of pathogen persistence by means of PCR in EMB allowed us to make a final diagnosis in our patient and thus a clear therapeutic strategy.

As in this case of EM, the causative agent often remains unclear. Parasitic or helminthic infections are known to cause hypereosinophila.[9] Both of these aetiologies were definitely excluded in our patient. Also, no systemic eosinophilia was found in the differential blood count. Furthermore, a neoplastic aetiology[10] was excluded by unsuspicious distribution of lymphocytic subpopulation in fluorescence-activated cell sorting analysis and by whole body computed tomography. No evidence for autoimmune disease was found in vascular ultrasound and specific antibody screening. Persistent infectious disease was excluded by PCR. Nevertheless, a pre-existing viral infection was still a likely trigger of the disease, particularly since the patient reported preceding flu-like symptoms. Likewise, a hypersensitivity reaction to a NSAID as a putative cause must be considered even though signs of DRESS syndrome in form of a rash or hypereosinophilia were absent.

When eosinophilia is present in peripheral blood, increasing and decreasing values can be used to monitor the response to therapy.[11] If this is not the case, regular echocardiographic follow-up is helpful to detect a possible deterioration of cardiac function or, conversely, an improvement in response to therapy.

Fortunately, our patient showed a good response to immunosuppression and, despite an initially dramatic clinical course, he quickly recovered without the need for a mechanical circulatory support strategy such as extracorporeal membrane oxygenation. This is well in line with previously reported courses of EM.[5,12] This underlines

the pivotal role of early diagnosis and targeted treatment in avoiding adverse outcomes when EM is suspected. In our patient complete AV block and permanent pacemaker dependency remained the only long-term sequelae.

As a limitation, it must be mentioned that no control EMB after immunosuppression is available, therefore residual inflammatory activity in the conduction system as a cause of persistent AV block cannot be completely excluded.

Conclusion

EM can progress rapidly and result in a life-threatening condition. Endomyocardial biopsy to identify treatment options is valuable. Despite LV function and clinical condition recovered, the reported patient developed a complete AV block that persisted.

Lead author biography

Moritz Messner obtained his MD in 2013 and he has previously performed experimental murine studies dealing with cardiac regeneration after myocardial infarction as part of his PhD. He has a special interest in ageing processes of the cardiovascular system. He is currently working as Resident at the University of Innsbruck (Austria) at the Department for Cardiology and Angiology.

Supplementary material

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

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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.

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