


Incessant pericarditis following the second dose of SARS-CoV-2 mRNA vaccine successfully treated with anakinra: a case report

C. Conte^{1†}, G. Princi^{1†}, D. D’Amario ^{2*}, T. Sanna², D. Pedicino², and G. Liuzzo²

¹Department of Cardiovascular and Thoracic Sciences, Catholic University of Sacred Heart, Largo Francesco Vito 1, 00168, Rome, Italy; and ²Department of Cardiovascular and Thoracic Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Francesco Vito, 1–00168 Rome, Italy

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Background

The SARS-CoV-2 pandemic has led to the development of the first mRNA vaccines used in humans. These vaccines are well tolerated, safe, and highly effective; however, post-marketing surveillance is revealing potential rare adverse effects. We report a case of incessant pericarditis following administration of the second dose of mRNA-1273 SARS-CoV-2 vaccine, unresponsive to conventional therapy, and successfully treated with anakinra.

Case summary

A 30-year-old man presented to the Emergency Department for incessant pericarditis unresponsive to evacuative pericardiocentesis and conventional first-line anti-inflammatory therapy. Given the typical ‘inflammatory phenotype’ clinically characterized by fever, C-reactive protein (CRP) elevation, and leucocytosis, we decided, in agreement with the rheumatologist team, to avoid glucocorticoid and to administer anakinra. A sudden clinical and echocardiographic improvement was observed, with complete resolution of the symptoms and of the pericardial effusion; similarly, CRP values progressively decreased. The patient was discharged at home; no recurrences of pericarditis were described at clinical and instrumental follow-up made 3 months later.

Discussion

Several cases of pericarditis have been described in patients who received the COVID-19 vaccination, especially with the mRNA vaccine that can induce a non-adaptive immunity response against the viral spike protein, triggering cardiac damage for a molecular mimicry mechanism; however, defined pathogenesis of pericarditis associated with mRNA vaccine is still missing. The clinical scenario described is characterized by the typical ‘inflammatory phenotype’, triggered by a disproportionate and uncontrolled activation of the inflammasome based on an interleukin-1 (IL-1) overproduction. We administered anakinra, an IL-1 blocking drug, with a sharp clinical, echocardiographic and laboratoristic improvement. The complete response observed in this case suggests that vaccine-related pericarditis could be triggered by an auto-inflammatory pathway based on IL-1 overproduction. Further research is, therefore, warranted to determine the mechanisms by which the mRNA vaccine may cause pericarditis in order to choose the most targeted therapy.

* Corresponding author. Tel: +39 06 3551 0330, Email: domenico.damario@gmail.com

† Lead authors.

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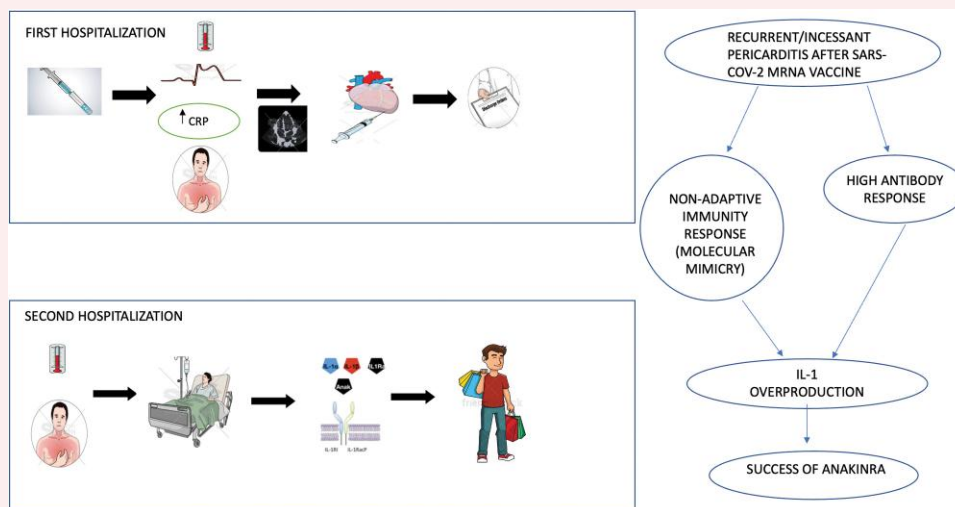
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Graphical Abstract



Keywords

Incessant pericarditis • COVID-19 mRNA vaccine • Inflammasome • Anakinra • Case report

ESC Curriculum

2.2 Echocardiography • 6.6 Pericardial disease

Learning points

- In the pandemic era, identifying the natural history of vaccine-related pericarditis is mandatory to understand whether these are similar or different entities compared with non-vaccine-associated forms, in order to decide the most appropriate therapy.
- Given the global clinical improvement obtained after anakinra administration, an auto-inflammatory pathway based on interleukin-1 overproduction might be hypothesized.

Primary specialities involved other than cardiology

Internal Medicine, Immunology, Radiology.

Introduction

Incessant pericarditis is defined as pericarditis with persistent symptoms and a symptom-free interval shorter than 4–6 weeks despite therapy,¹ with a higher risk of evolution towards constrictive pericarditis.

In 5–10% of patients with recurrent and incessant pericarditis, the conventional therapies (colchicine, non-steroidal, and steroidal anti-inflammatory agents) are unable to control the symptoms, and agents such as azathioprine, human immunoglobulin or interleukin 1 (IL-1) antagonists are recommended²

Several cases of pericarditis have been described in patients who received vaccination against COVID-19,^{3,4} but defined pathogenesis of the mechanism involved is still missing.

Further research is warranted to determine the mechanisms by which the mRNA vaccine may cause pericarditis in order to choose the most appropriate and targeted therapy; in this setting, the IL-1 blocking agents are probably useful for patients who display pericardial involvement.

Timeline

10 July 2021	Second dose of BNT162b2 mRNA vaccine against COVID-19
13 July 2021	Onset of fever and chest pain worsened by breathing, treated with paracetamol at home for some days
22 August 2021	First admission at the Emergency department (ED) for acute pericarditis with severe pericardial effusion, and haemodynamic impairment was treated with pericardiocentesis; oral therapy with ibuprofen and colchicine was started contextually.
9 September 2021	Second hospitalization for pericarditis during the tapering of anti-inflammatory therapy. Mild pericardial effusion at the echocardiogram. Oral anti-inflammatory therapy was potentiated with indomethacin.
11 September 2021	Worsening of the clinical conditions and of the

Continued

Continued

	pericardial effusion. First anakinra subcutaneous administration
14 September 2021	Resolution of the symptoms and of the pericardial effusion
10 December 2021	Anakinra withdrawal

Case presentation

On 22nd of August 2021, a 30-year-old smoker man without significant past medical history presented to the ED of Policlinico 'Gemelli' in Rome for interscapular chest pain that was worsened by breathing and lying in the left lateral position.

Few weeks before, he got vaccinated with BNT162b2 mRNA vaccine against COVID-19 (first dose on 5th of June 2021, second dose on 10th of July 2021); fever and chest pain, worsened by breathing, occurred on 13th of July, (3 days after the second dose), treated at home with paracetamol with the resolution of fever and persistence of mild chest pain in the following days. At the admission to the ED, body temperature was 37.7°C; electrocardiogram (ECG) showed sinus tachycardia with PR depression and diffuse concave-up ST segment elevation (Figure 1), and blood pressure was 130/70 mmHg. Physical examination including cardiovascular examination was normal. Troponin was negative, with a raise in inflammatory indices and leucocytosis; COVID-19 Polymerase Chain Reaction test was negative. The echocardiogram showed a severe

circumferential pericardial effusion of 3 cm and 2D and Doppler signs of cardiac tamponade. A chest computed tomography (CT) scan was then performed, confirming that the pericardial effusion resulted in a compressive effect on the right atrium and right ventricle and excluding an acute aortic syndrome (Figure 2); a diagnosis of acute pericarditis with signs of cardiac tamponade was made, and the patient underwent successfully pericardiocentesis with the aspiration of ~700 mL of pericardial serous fluid.

Table 1 Biochemical, microbiological, and cytological analysis made on pericardial fluid

Biochemical measurand	
Ph	8.0
LDH (UI/L) ^a	588
Glucose (mg/dL)	88
Total cholesterol (mg/dL)	128
Albumin (g/L)	32
Triglycerides (mg/dL)	47
Amilase (UI/L)	28
Lipase (UI/L)	28
LDH ratio ^b	3,30
Cholesterol ratio ^b	1
Albumin gradient ^c	0
Microbiological test	
Mycobacterium Spp (molecular research)	Negative
Aerobic bacterial culture	negative
Anaerobic bacterial culture	Negative
Fungal (miceti) culture	Negative
Yeasts research (mass spectrometry)	Negative
Molds research (mass spectrometry)	Negative
Enterovirus (RT-PCR)	Negative
Cytological evaluation	
Cytological research of malignant cells	Negative

LDH, lactate dehydrogenase.

^aValues > 200 suggest the presence of an exudate.

^bPericardial fluid value/serum value.

^cSerum albumin–pericardial fluid albumin.

Table 2 Microbiological, oncological, and autoimmunity examinations made on blood serum

Autoimmunity tests	
Antinuclear antibody (ANA)	Not detectable
Extractable nuclear antigen (ENA) SSB/La antibody	Lower than detectable limit
Extractable nuclear antigen (ENA) SSA/Ro antibody	Lower than detectable limit
Double-stranded (ds)-DNA antibody	Lower than detectable limit
Perinuclear anti-neutrophil cytoplasmic antibodies (pANCA)	Lower than detectable limit
Cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA)	Lower than detectable limit
Serum angiotensin-converting enzyme (SACE)	Negative
Microbiological analysis	
Hepatitis B virus (HBV) HbsAg	Negative
Hepatitis B virus (HBV) HbeAg	Negative
Hepatitis B virus (HBV) HbcAg	Negative
Hepatitis B virus (HBV) Antibody	Negative
Hepatitis C virus (HCV) Antibody	Negative
Human immunodeficiency virus (HIV)	Negative
Ebstein–Barr virus IgM anti-VCA	Negative
Ebstein–Barr virus IgG anti-VCA	Positive
Ebstein–Barr virus RT-PCR	Not detectable
Cytomegalovirus IgM	Negative
Cytomegalovirus IgG	Positive
Adenovirus IgM	Negative
Adenovirus IgG	Positive
Echovirus IgM	Negative
Echovirus IgG	Negative
Coxsackie virus IgA	Negative
Coxsackie virus IgM	Negative
Coxsackie virus IgG	Negative
Mycobacterium detection with interferon (IFN)–gamma dosage	Negative
Tumour markers research	
Carcinoembryonic antigen (CEA)	Negative
Alfafeto protein (AFP)	Negative
Carbohydrate antigen (CA) 125	Negative
Carbohydrate antigen (CA) 15–3	Negative
Carbohydrate antigen (CA) 19–9	Negative
Chromogranin A	Negative
S-100 protein	Negative
Enolase	Negative
Prostate-specific antigen (total PSA)	Negative

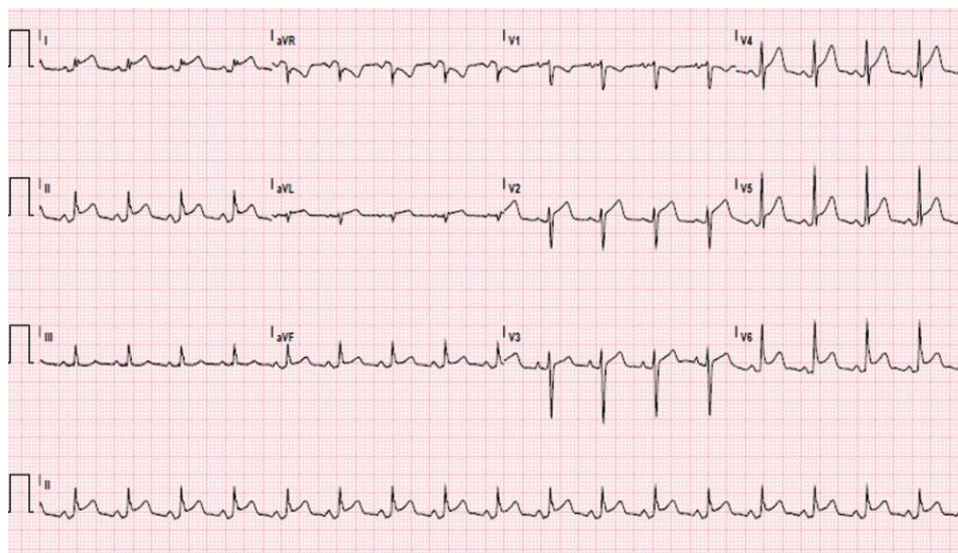


Figure 1 Admission electrocardiogram demonstrating sinus tachycardia, PR depression, diffuse concave-up ST segment elevation.

Chemical, microbiological and cytologic tests on pericardial samples were negative (Table 1); microbiological and autoimmunity examinations on blood serum were negative too (Table 2).

The patient was discharged at home in therapy with colchicine 0.5 mg bid and ibuprofen 600 mg 1 cp three times per day.

About 3 weeks later, on September 8th, due to exacerbation of persistent chest pain, the patient came back to the ED. Blood chemistry tests showed leucocytosis and raise of inflammatory markers, with stable negative troponin. Trans-thoracic echocardiogram showed mild circumferential pericardial effusion with initial signs of the fibrinous organization without 2D and Doppler signs of impaired ventricular filling.

The patient was hospitalized and anti-inflammatory therapy was potentiated with indomethacin 50 mg three times a day and colchicine 1 mg a day.

Given the gradual worsening of signs and symptoms of impaired left ventricular filling (tachycardia, hypotension, worsening dyspnoea), and the evidence of initial 2D sign of impaired ventricular filling at the echocardiogram, the patient was transferred to the intensive care unit for intensive monitoring.

After a multidisciplinary discussion with the team of rheumatologists, considering the criticality of the clinical picture and the results of recent studies^{5,6} that support the use of anti-IL-1 agents as a first-line treatment option in patients with recurrent pericarditis, not responsive to colchicine and other conventional anti-inflammatory therapies (including non-steroidal anti-inflammatory drugs and colchicine), and with the elevation of *c*-reactive protein (CRP),⁷ the same day therapy with anakinra was started with a sharp and sudden clinical and echocardiographic improvement with complete resolution of the symptoms and of the pericardial effusion in the following 3 days (Figure 3); similarly, CRP values progressively decreased, as reported in Table 3. The patient was discharged at home. A daily dose of anakinra (100 mg) was administered for 3 months; no replacements of chest pain were complained at the clinical evaluation three months after the discharge. He referred that his state of anxiety related to his clinical conditions progressively got better till ending.

Discussion

Acute pericarditis is one of the most common causes of all ED admissions for acute chest pain, especially in young people: although the exact incidence of acute pericarditis is difficult to determine due to a large

number of undiagnosed cases, pericarditis accounts for 5% of ED visits for chest pain in the absence of myocardial infarction.⁸

In about 15–30% of the patients, it is reported an early (<4–6 weeks) relapse or the persistence of symptoms after the acute episode, defined as ‘incessant’ pericarditis, a challenging clinical scenario in which patients often become unresponsive to conventional treatments with a higher risk of evolution towards constrictive pericarditis.¹

Several cases of pericarditis have been described in patients who received the COVID-19 vaccination, especially with the mRNA vaccine.²

In July 2021, the European Medicines Agency reported 138 cases of pericarditis of 177 million doses of the BNT162b2 vaccine performed, and 19 cases of pericarditis of 20 million doses of the mRNA-1273 vaccine administered.³

In November 2021, the Vaccine Adverse Event Reporting System received 1783 reports of cases of myocarditis or pericarditis among people who received COVID vaccines, in particular following mRNA vaccination (BNT162b2 and mRNA-1273 vaccine).⁹

A self-controlled case-series study of people vaccinated for COVID-19 in England between 1 December 2020 and 24 August 2021 showed that of the 38 615 491 vaccinated individuals included in the study, 1574 patients had pericarditis at any time in the study period, and 356 of these occurred in 1–28 days after any dose of vaccine.¹⁰

There is no certain evidence of a cause–effect relationship between vaccination and the development of pericarditis, even if a short time interval between the two events can suggest at least a concausal role.

Pericarditis seems to occur most frequently with mRNA vaccine and after the second dose of vaccine, during the first two weeks after the vaccination;³ however, it has been reported that it could appear between 5h and 92 days post-exposure to the vaccine.¹¹

Approximately 90% of pericarditis episodes are deemed idiopathic and presumed to be post-viral, but the underlying cause for the recurrences is not fully understood. In patients presenting with a typical ‘inflammatory phenotype’, clinically characterized by fever, CRP elevation, and leucocytosis, as in the case presented above, an auto-inflammatory response based on IL-1 overproduction might be hypothesized.¹²

Indeed, these inflammatory phenotypes share characteristics with some auto-inflammatory diseases clinically expressed with recurrent polyserositis, in which there is a disproportionate and uncontrolled activation of the inflammasome.

Table 3 Laboratory values during hospitalization across the anakinra administration

Laboratory testing (reference ranges)	Day of hospitalization							
	09/09 Access to ED	10/09 1st day of hospitalization	11/09 1st anakinra administration	12/09	13/09	14/09	15/09	16/09 Discharge at home
White blood cell count (4–10 × 10 ⁹ /L)	11.23	14.43	14.95	9.78	6.67	4.44	5.05	N/A
CRP values (< 5 mg/L)	12.7	219.8	305.9	287.4	178.9	104.3	58	34
Hs Troponin I (< 57 ng/L)	<2.5	4	N/A	N/A	N/A	3	N/A	N/A
Fibrinogen (200–400 mg/dL)	342	583	894	N/A	889	752	581	N/A

**Figure 2** Contrast-enhanced computed tomography thorax in arterial phase demonstrating the circumferential pericardial effusion (arrowed) in the axial plane (A) and sagittal plane (B) with a maximum diameter of 3 cm, in absence of signs of aortic dissection.

The IL-1 α precursor, already active inside healthy cells, is released during pericardial injury, activating adjacent cells bearing the IL-1 receptor. In contrast, IL-1 β , released by the inflammatory cells, needs to be activated by cleavage by caspase-1 after the assembly of the inflammasome during pericarditis; once activated, it is able to cause both local and systemic inflammation, promoting the secretion of other pro-inflammatory cytokines and bringing to hyperalgesia, vasodilation, and fever acting on the hypothalamic regulator.¹³

During the acute injury, pericardium cells release ‘danger signals’ or Damage-Associated Molecular Patterns, which are linked by pattern recognition receptors (PRRs), receptors able to identify potential harmful agents; four cytoplasmic PRRs, able to form an inflammasome complex, have been described in the literature, but NLR family pyrin domain containing 3 (NLRP3) has been the most extensively studied inflammasome activator.¹⁴ Caspase-1, recruited after NLRs activation, is involved in the proteolytic cleavage of many inflammatory mediators, such as IL-1 β and IL-18, finally amplifying the inflammatory process and driving tissue injury.

After the first episode of pericarditis, the reactivation of the inflammatory cascade can occur in predisposed patients, in which a chronic low-grade inflammation sustained by auto-reactive processes could be triggered by a broad spectrum of agents.

Several hypotheses have been postulated to explain the pericarditis related to COVID-19 mRNA vaccine, but defined pathogenesis is still missing.

One mechanism is that mRNA vaccine could induce a non-adaptive immunity response against the viral spike protein, triggering cardiac damage for a molecular mimicry mechanism between unknown proteins.¹⁵

It has also been proposed that the second dose of mRNA vaccines might induce a high antibody response, especially in young people, evoking a response similar to multisystem inflammatory syndrome in children (MIS-C) that is successfully treated with human immunoglobulins.¹⁶

In 5–10% of patients with recurrent and incessant pericarditis, conventional anti-inflammatory therapies (non-steroidal anti-inflammatory agents, colchicine, glucocorticoids) could be not able to control the disease and prevent relapses:¹⁷ in these cases, the use of azathioprine, human immunoglobulin or anti-IL-1 agents are recommended.⁷

Since IL-1 represents the final mediator of NLRP3 inflammasome activation, this cytokine has been widely investigated as a molecular target to prevent or dampen its detrimental effects in many cardiovascular diseases.^{18,19} In particular, IL-1 blocking drugs approved by Food and Drug Administration are as follows: anakinra, a recombinant human IL-1Ra, able to inhibit both IL-1 α and IL-1 β ; canakinumab, a specific monoclonal IL-1 β antibody that binds irreversibly to circulating human IL-1 β and prevents activation of the IL-1 receptor, without interfering with IL-1 α activity, and rilonacept, a recombinant fusion protein that acts as a soluble decoy receptor binding both soluble IL-1a or IL-1 b and preventing engagement with the cell-surface receptor for IL-1.

Currently, anakinra and rilonacept, both providing combined IL-1a and IL-1b antagonism, have been approved in the setting of recurrent pericarditis with corticosteroid dependence and colchicine resistance.²

During the COVID-19 pandemic era, recent evidence suggests that anti-IL-1 agents are safe in patients with pericarditis and these

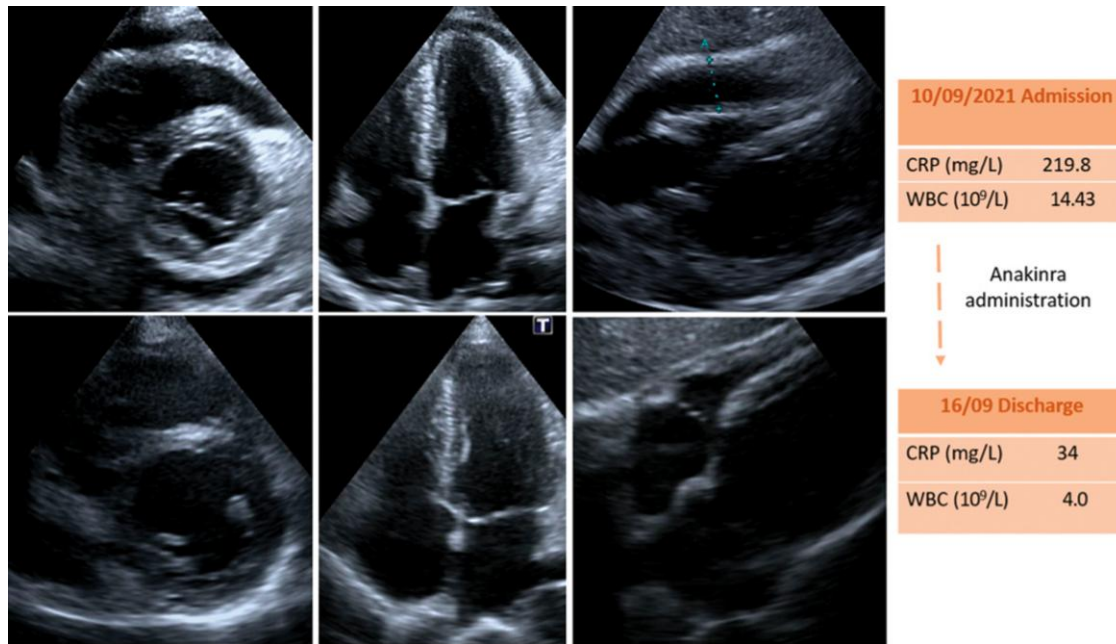


Figure 3 Trans-thoracic echocardiograms made during the hospitalization. The panel shows a significant decrease of pericardial effusion after the therapy with anakinra. On the 10th of September, admission to the sub intensive unit (the upper line): evidence of mild circumferential pericardial effusion with initial signs of the fibrinous organization without 2D and Doppler signs of impaired ventricular filling. Anakinra was started the next day. On the 16th of September, pre-discharge evaluation (the inferior line): evidence of complete resolution of the pericardial effusion, with a significant decrease of the inflammatory markers.

pharmacological tools are probably also useful for COVID-19 management in patients who display pericardial involvement.⁷

Conclusions

Further research is warranted to determine the mechanisms by which mRNA vaccine may cause pericarditis; however, the clinical response observed in the case described could suggest an auto-inflammatory pathway based on IL-1 overproduction; in this setting, anakinra, dampening the local inflammation, may be a valid therapeutic option in vaccine-related recurrent and incessant pericarditis unresponsive to conventional treatment.

Lead author biography



Cristina Conte obtained her medical degree in 2018 at the Catholic University of the Sacred Heart of Rome, Italy. Currently, she is completing the Cardiology residency at the Catholic University of the Sacred Heart of Rome, Italy.

Supplementary material

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

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We thank the patient for letting us present his case in this report.

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 image(s) and associated text has been obtained from the patient in line with COPE guidance.

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