

## CASE REPORT

## ADVANCED

## CLINICAL CASE

# Repetitive Immune-Mediated Noninfectious Endocarditis Necessitating 5 Mitral Valve Replacements



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## ABSTRACT

We present a young patient who had to undergo 5 mitral valve replacements (MVR) because of a repetitive immune-mediated noninfectious endocarditis. The patient was treated with multiple anti-inflammatory drugs and high-dose prednisone. After the fifth MVR, the patient remained in stable condition using Anakinra after 22 months of follow-up. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2021;3:1483-1488) © 2021 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## HISTORY OF PRESENTATION

A 27-year-old man was referred to our tertiary cardiac center for diagnosis and treatment of repetitive

endocarditis. The patient had already undergone 2 mechanical mitral valve replacements (MVR) within 2.5 months because of repetitive culture-negative endocarditis treated with antibiotics, and severe mitral valve (MV) insufficiency. The first and second MVR were performed, respectively, 2.5 months and 1 month before transfer. He was referred to our hospital during his third endocarditis episode. At referral, the patient presented with fatigue, dyspnea, and palpitations. On examination, a heart murmur at the apex was present. Furthermore, vital functions were normal, and no lymphadenopathy or joint abnormalities were objectified. His face and back showed scars from acne, and his axilla and groin area showed scars from previous hidradenitis. A positron emission tomography scan before referral revealed no abnormal fluorodeoxyglucose uptake.

## LEARNING OBJECTIVES

- To report a rare case of an unexplained repetitive immune-mediated noninfectious endocarditis
- To discuss the management options of an unexplained repetitive immune-mediated noninfectious endocarditis
- To illustrate that despite extensive diagnostic efforts, even today it is sometimes impossible to establish a fitting diagnosis
- To emphasize the importance of continuous and multidisciplinary collaboration in diagnostic and therapeutic efforts

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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## ABBREVIATIONS AND ACRONYMS

**CTD** = connective tissue disease

**Dacron** = polyethylene terephthalate

**IVIG** = intravenous immunoglobulin

**MV** = mitral valve

**MVR** = mitral valve replacement

**TEE** = transesophageal echocardiography

**TIA** = transient ischemic attack

## MEDICAL HISTORY

His cardiac history before the first MVR consisted of severe primary MV insufficiency resulting from MV prolapse, with subsequent atrial fibrillation. An MV repair and minimaze procedure were performed 18 months before the first MVR. After 6 months, the patient presented with thoracic pain, diagnosed as Dressler syndrome or serositis. Two months later he was readmitted for recurrent serositis. His further medical history consisted of a nasal septum correction, testicular torsion, hidradenitis suppurativa, acne vulgaris, and a tooth extraction. He did not have a history of connective tissue disease (CTD) or thrombotic events. His family history was positive for cardiac disease. His father had an arrhythmia of unknown origin at 30 years of age. The family history for CTD was negative.

## DIFFERENTIAL DIAGNOSIS

The first 2 episodes of endocarditis were, according to the modified Duke criteria, “rejected” for infectious origin because there was no pathologic evidence for infectious endocarditis at surgery, with antibiotic therapy  $\leq 4$  days (1). Therefore, noninfectious causes, such as antiphospholipid syndrome or inflammatory reaction to implanted material, were included in the differential diagnosis (Figure 1).

## INVESTIGATIONS

In the Appendix, all diagnostic tests are shown that were performed before every MVR (Supplemental Table 1).

Cytoplasmatic antibodies were detected at the referring center; however, proteinase-3 specificity could not be confirmed. Test results for anti-neutrophil cytoplasmatic antibodies at our center were negative. Rheumatoid factor immunoglobulin M was weakly positive. The results of polymerase chain reactions and blood and valve cultures were persistently negative. Inflammatory parameters, specifically neutrophil count, were consistently elevated. Flow cytometry of neutrophils established elevated progenitor cells, which can point to the presence of chronic neutrophilic leukemia or a reactive process. Subsequently, cytomorphologic analysis of bone marrow aspirate ruled out chronic neutrophilic leukemia or any other myeloproliferative disease. Owing to a suspicion of heritable (auto-)inflammatory disease, next-generation sequencing for primary immunodeficiency was performed, and the result proved negative. The result of (non-)criteria

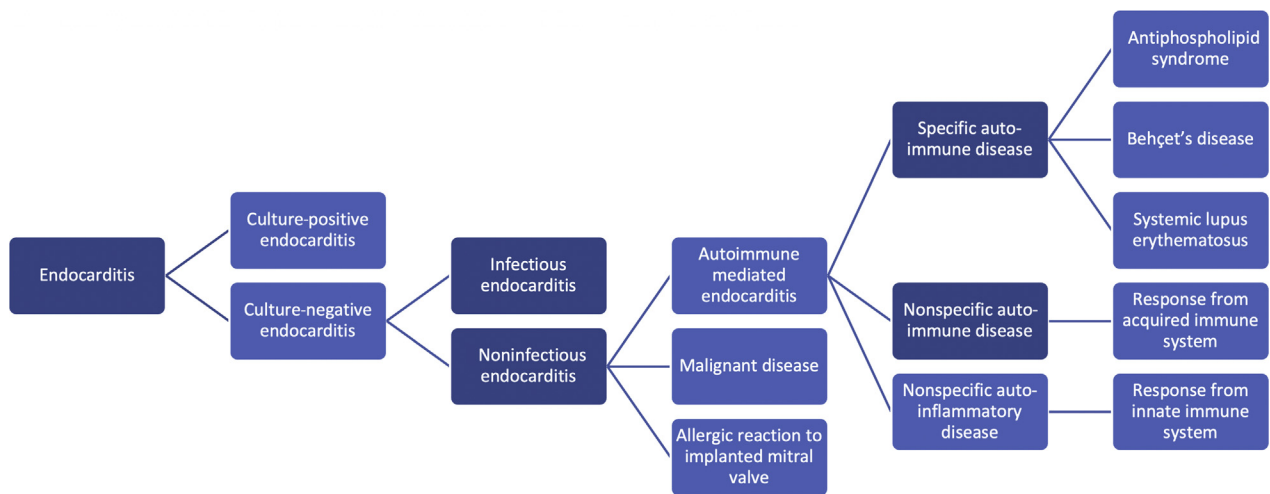
antiphospholipid antibody assays were negative. Table 1 shows the laboratory and echocardiography parameters at hospitalization before each MVR. Importantly, the results of patch tests, although performed under high-dose prednisone, investigating hypersensitivity to polyethylene terephthalate (Dacron) and polypropylene from sutures and/or sewing cuffs from the implanted MVs, were negative (2).

## MANAGEMENT

Given that the first 2 episodes of endocarditis were “rejected” for infectious origin, an infectious origin was thought to be unlikely. Therefore, an autoimmune cause was thought to be causative for the recurrent vegetations. Nevertheless, while awaiting blood cultures, the patient was extensively treated with broad-spectrum antibiotics and antimycotics. He did not experience symptoms or show signs indicative of underlying CTD or vasculitis (3,4). Figure 2 shows the prescribed medication and transesophageal echocardiography (TEE) parameters over time.

Two days after transfer, TEE showed a partially disconnected MV with massive paravalvular leakage (Video 1) and multiple vegetations, the largest being 18 mm on the MV ring (Figure 3A; Video 2). An emergency MVR was performed, a 33-mm Carbo-medics with a bovine pericardial patch was implanted. This reinforced the sewing cuff for enhanced fixation to the annulus, preventing a second disconnected MV. Pulse intravenous methylprednisolone was prescribed, followed by oral prednisolone, to suppress the hypothesized autoimmune response. Cyclosporin was added because a previous case of unexplained recurrent autoimmune-mediated endocarditis had been successfully treated with cyclosporin. However, 3 months after cyclosporin had been started and a prednisone taper had begun, a minor stroke occurred caused by a relapse of the endocarditis. Prednisone was increased again, and cyclosporin was replaced by adalimumab to treat a possible innate inflammatory cause, considering his previous hidradenitis. Unfortunately, after 4 months and 2 attempts to taper the prednisone dose, asymptomatic vegetations as large as 14 mm on the MV ring were visualized by echocardiography. Owing to pronounced neutrophilia with the presence of progenitor cells in the blood, a myeloproliferative disease such as chronic neutrophilic leukemia was considered, and adalimumab was switched to hydroxycarbamide to specifically target the neutrophils with increased dosing of prednisone. Although chronic neutrophilic

**FIGURE 1** Differential Diagnosis



The differential diagnosis of the case.

leukemia was ruled out soon after hydroxycarbamide was started, the hydroxycarbamide was continued because a neutrophil maturation problem was thought to be causative of the repetitive immune-mediated noninfectious endocarditis. Despite the treatment with hydroxycarbamide, the patient had, over the course of 11 months, multiple transient ischemic attacks (TIAs) caused by multiple vegetations on the MV ring when the prednisone dose was tapered, the largest vegetation being 18 mm. Therefore, myeloproliferative disease was rejected, and seronegative antiphospholipid syndrome was considered, allowing, apart from increasing prednisone dosing, a therapeutic switch to high-dose intravenous immunoglobulin (IVIG) and Rituxan. After 7 months the patient again experienced several TIAs caused by progression of vegetations on the MV ring (Figure 3B, Video 3), necessitating a fourth MVR. A bioprosthetic 33-mm Carpentier-Edwards Perimount was placed, with IVIG before and after the MVR. Despite these measures, 2 months after the fourth MVR, the patient had on routine examination TEE vegetations on multiple valve leaflets, the largest being 31 mm (Figure 3C, Video 4). A fifth MVR was performed, and a mechanical 33-mm (St. Jude Medical) was implanted with a bovine pericardial patch reinforcing the sewing cuff for enhanced fixation to the annulus. Because of the recurrent vegetations, IVIG and rituxan were changed to subcutaneous anakinra 100 mg once daily, to suppress the presumed underlying autoimmune disease differently.

Fortunately, after a 32-month disease process from the first MVR to the fifth MVR, this finally resulted in sustained absence of vegetations on the MVR and successful taper of prednisone.

## DISCUSSION

We describe a case of noninfectious endocarditis resulting in 5 MVRs. The diagnostic workup was done according to the guidelines, excluding infection, malignancy, rheumatic disease, and an allergic reaction (5,6).

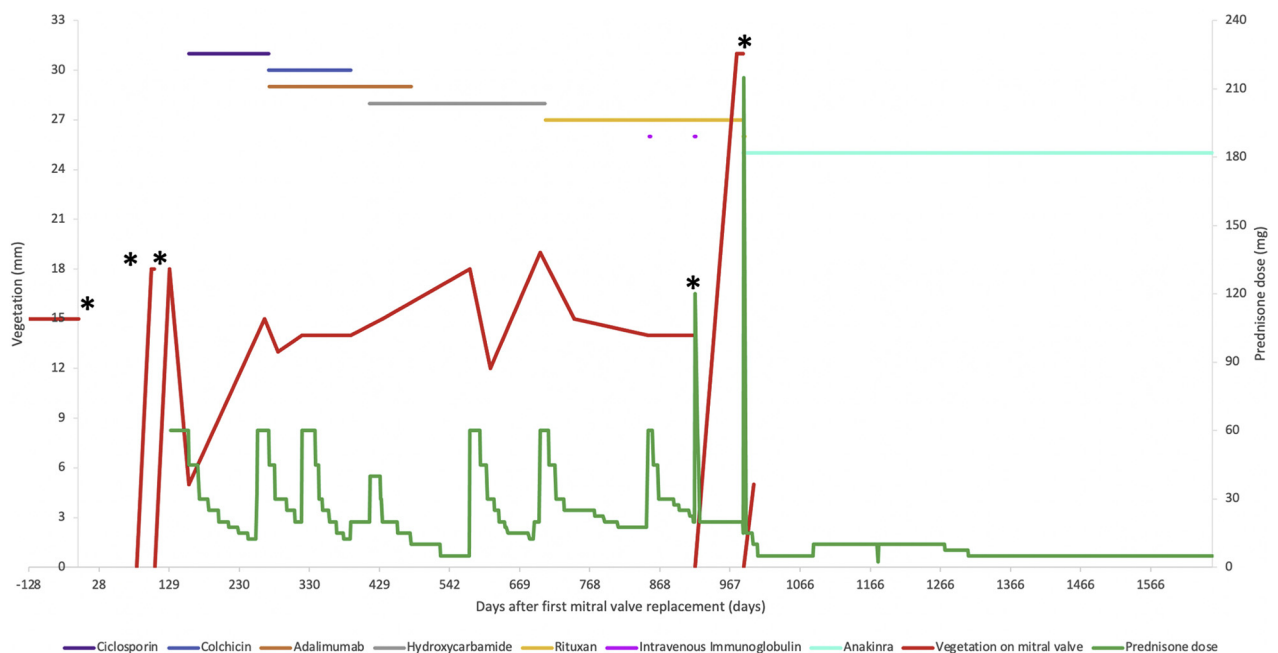
Extraordinarily, all vegetations on the implanted mechanical valves were sterile and on the MV ring (Supplemental Figures 1 and 2), potentially indicating an inflammatory response to components of the MV ring. Although the valves implanted were from 4 different manufacturers, making a specific inflammatory response less likely, all manufacturers use, in different arrangements, Dacron in the sewing cuff. However, a negative patch test result excluded Dacron as a trigger for the inflammatory response. A systemic disease was thought to be likely because of the presence of extracardiac manifestations, such as severe acne and hidradenitis.

Notably, the vegetations on the bioprosthetic valve were very large and presented just 2 months after the MVR. Fournier et al (7) described a case of endocarditis attributed to an allergic reaction to a porcine bioprosthetic valve. Although a bovine, not a porcine, valve was implanted in our patient, a hypersensitivity

**TABLE 1 Patient Characteristics Before Every Mitral Valve Replacement**

	Reference Values	First Mitral Valve Replacement	Second Mitral Valve Replacement	Third Mitral Valve Replacement	Fourth Mitral Valve Replacement	Fifth Mitral Valve Replacement
Time after first mitral valve replacement (months)		0	2	3	30	32
Implanted mitral valve		Sorin bicarbon fitline 31 mm	Sorin bicarbon fitline 31 mm	Carbomedics 33 mm + bovine pericardial patch	Carpentier-Edwards Perimount 33 mm	St. Jude Medical 33 mm + bovine pericardial patch
Type of valve (mechanical vs bio prothesis)		Mechanical	Mechanical	Mechanical	Bioprothesis	Mechanical
Medical treatment prior to mitral valve replacement		None	Acenocoumarol	Acenocoumarol and ceftriaxone (1 day before surgery)	Prednisone, intravenous immunoglobulin, ciprofloxacin and acenocoumarol	Prednisone, intravenous immunoglobulin, Anakinra and Fenprocoumon
Medical treatment after mitral valve replacement		Unknown	Voriconazole, ciprofloxacin, doxycycline (all were discontinued when cultures were negative) and acenocoumarol	Ceftriaxone, ciprofloxacin, and vancomycin	Fenprocoumon, prednisone, ciprofloxacin, and rituxan	Fenprocoumon, ticagrelor, prednisone, and anakinra
Medical treatment in outpatient clinic		Acenocoumarol	Acenocoumarol	Acenocoumarol, ticagrelor, prednisone, and ciclosporin (later switched to adalimumab, hydroxycarbamide, and rituxan)	Fenprocoumon, prednisone, and rituxan	Fenprocoumon, ticagrelor, prednisone, and anakinra
Clinical presentation						
Key symptoms		Exercise intolerance and fatigue	Dysarthria and vertigo	Dyspnea, fever, and atrial flutter	Fatigue and diplopia	No symptoms
Diagnosis of key symptoms		Endocarditis lenta	Multiple lacunar infarctions due to vegetations on mitral valve	Vegetations on mitral valve	Transient ischemic attacks and vegetations on mitral valve	Routine transesophageal echocardiography: vegetations on mitral valve
Fever ( $\geq 38.5$ °C)		No	No	Yes	No	No
Largest vegetation (mm)		15	Unknown	18	19	31
(Para)valvular dysfunction		Moderate mitral valve regurgitation	Unknown	Massive paravalvular leakage	Mild valvular leakage	Mild paravalvular leakage
White blood cell count ( $\times 10^9/L$ )	4-10	10.9	11.3	12.8	15.6	16.3
Neutrophil count ( $\times 10^9/L$ )	1.6-8.3	-	-	9.61	14.3	12.9
C-reactive protein (mg/mL)	0-10	8.6	21	29	8.4	12
Creatine kinase (U/L)	0-145	-	165	21	28	26
Troponin T ( $\mu g/L$ )	0-0.014	-	0.037	-	-	-
Troponin I (ng/L)	0-45	-	-	-	28	7
Hemoglobin (mmol/L)	7.4-9.6	-	6.5	7	8.8	7.9
Haptoglobin (g/L)	0.3-2	-	-	-	-	-
Sodium (mmol/L)	136-146	-	144	138	140	135
Potassium (mmol/L)	3.8-5.0	-	3.7	3.6	4.2	4
Urea (mmol/L)	3.0-7.5	-	-	5.6	8.4	7.1
Creatinine (mmol/L)	49-90	-	70	67	91	94
Estimated glomerular filtration rate (mL/min/1.73 m <sup>2</sup> )	>80	-	-	>90	>90	>90
Total bilirubin ( $\mu mol/L$ )	3-21	-	-	10	14	17
Aspartate transaminase (U/L)	0-30	-	-	23	25	32
Albumin (g/L)	35-50	-	-	43.3	43.1	-

**FIGURE 2** Vegetations Versus Immunosuppressive Agents



Mitral valve vegetations plotted against the use of immunosuppressive medication and prednisone. **Asterisks** indicate a mitral valve replacement.

reaction to the bovine bioprosthetic valve could be possible.

Inasmuch as our patient was adequately treated with anakinra, an interleukin-1 antagonist, extensive interleukin release of unknown origin triggering an innate immune response was thought to be causative of the endocarditis.

## FOLLOW-UP

Twenty-two months after the fifth MVR, transthoracic echocardiography has repeatedly shown a 5-mm large structure on the posterior annulus, which has been stable since the last TEE (Figure 3D, Video 5) and has been considered to be a suture. To date, the patient is free of TIAs, atrial fibrillation, and dyspnea. The patient continues to use anakinra and has tapered off the prednisone dose to 5 mg daily.

## CONCLUSIONS

We report a rare case of an ill-understood repetitive immune-mediated noninfectious endocarditis. On the basis of this case, we suggest considering treating patients with an unexplained repetitive

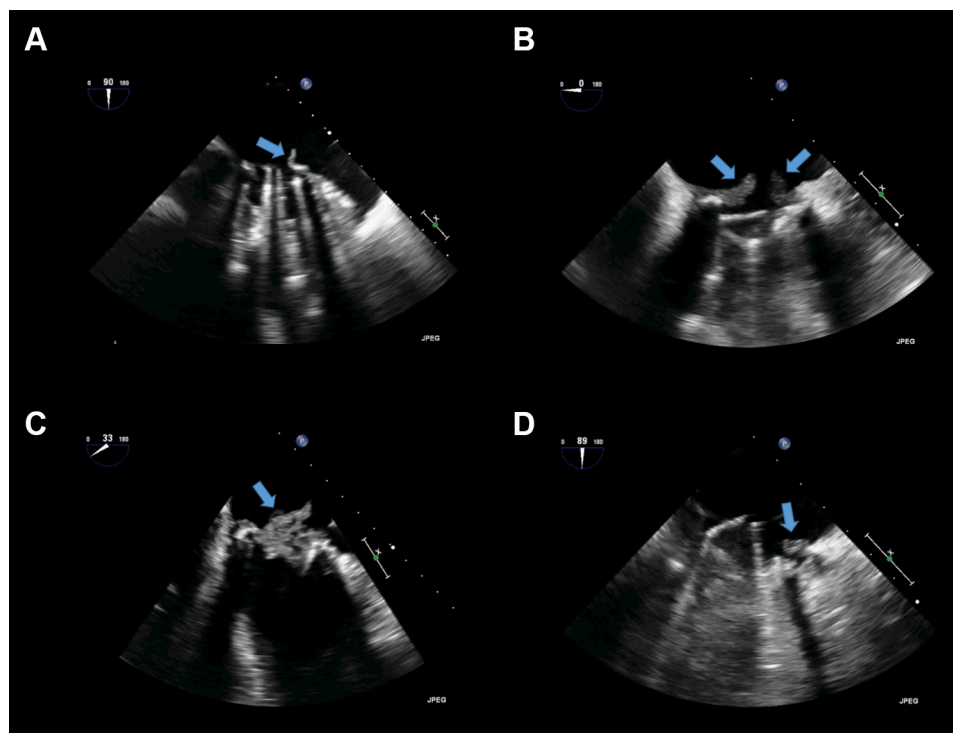
immune-mediated noninfectious endocarditis with high doses of prednisone initially and anakinra. Our case shows that, despite extensive diagnostic efforts, even in the current era it is sometimes challenging to establish a fitting diagnosis and consequently an appropriate treatment.

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**FIGURE 3** Vegetations on the Mitral Valve Before Mitral Valve Replacements

(A) Transesophageal echocardiography (TEE) before the third mitral valve replacement (MVR), showing an 18-mm mobile vegetation attached to the mitral valve (MV) ring. (B) TEE before the fourth MVR, visualizing mobile and irregular vegetations on the anterior and posterior MV ring. (C) TEE before the fifth MVR, showing a very large (31-mm) irregular and mobile vegetation seemingly attached to both MV leaflets. (D) TEE 2 weeks after the fifth MVR, visualizing a small (5-mm) structure in the posterior annulus. **Arrows** indicate the vegetations.

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**KEY WORDS** Anakinra, autoimmune, endocarditis, mitral valve replacement, repetitive

**APPENDIX** For a supplemental table, figures, and videos, please see the online version of this paper.