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CASE REPORT

INTERMEDIATE

CLINICAL CASE

Quadravalvular Noninfectious Endocarditis

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ABSTRACT

Nonbacterial thrombotic endocarditis is characterized by sterile thrombi on cardiac valves. This report describes the case of nonbacterial endocarditis without pathologic findings of fibrin or platelet deposition. Quadrivalvular endocarditis was found to be due to immunoglobulin M heavy chain deposition. This was a case of nonbacterial, nonthrombotic quadrivalvular endocarditis, which was termed noninfective endocarditis. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2019;1:350–4) © 2019 The Authors. 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/).

Nonbacterial thrombotic endocarditis (NBTE) is characterized by the presence of sterile thrombi composed of platelets interwoven with strands of fibrin on cardiac valves (1). No inflammation or microorganisms are detected. The present report discusses what may be the first description of quadrivalvular endocarditis due to the deposition of immunoglobulin M (IgM) heavy chain, with extensive systemic embolization. This study also introduces the term noninfective endocarditis (NIE), which describes the finding of a nonbacterial and nonthrombotic endocarditis.

HISTORY OF PRESENTATION

A 70-year-old male presented with chest discomfort. On physical examination, he was afebrile and comfortable. Systolic and diastolic murmurs were auscultated throughout the precordium. Electrocardiography showed anterolateral ST-segment depressions. Troponin I concentration was 1.49 ng/ml; white blood cell count was 5.8 × 10^9 cells/l; hemoglobin was 14.6 g/dl; creatinine was 1.1 mg/dl; and erythrocyte sedimentation rate was 78 mm/h. A transthoracic echocardiogram revealed normal ventricular function and extensive thickening of all 4 cardiac valves and vegetations, measuring 1.5 to 1.7 cm long (**Figure 1**, Videos 1, 2, 3, and 4).

MEDICAL HISTORY. Hypertension, cerebral microinfarctions, and carotid stenosis. The patient was empirically treated for infective endocarditis, and his chest discomfort was attributed to septic emboli. A transesophageal echocardiogram showed erratically moving echo densities on all 4 valves, with the left atrium and left atrial appendage lined with a fimbriated mass (**Figure 1**). The ascending aorta had evidence of this process as well. Infectious workup, including cultures for fungus and HACEK organisms (including "*Haemophilus*, *Aggregatibacter* [previously *Actinobacillus*], *Cardiobacterium*, *Eikenella*, *Kingella*"), was negative.

LEARNING OBJECTIVES

- To introduce the term, NIE, which describes the finding of a nonbacterial and nonthrombotic endocarditis.
- To make a differential diagnosis for NIE in the setting of a hematologic malignancy.

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INVESTIGATIONS. As a result, the working definition of the patient's condition was changed to NBTE. He was treated with anticoagulant agents with unfractionated heparin. Hypercoagulable and vasculitis workups were unrevealing. Age-appropriate cancer screening results were negative. Serum protein electrophoresis demonstrated 2 monoclonal proteins, IgM lambda and IgM kappa, with associated lambda and kappa Bence-Jones proteins identified by urine protein electrophoresis, raising the possibility of a plasma cell dyscrasia. Bone marrow biopsy was performed. The patient had recurrent episodes of chest discomfort with associated ST-segment depressions. Coronary computed tomographic angiography (Figure 2) revealed calcific plaque in the left anterior descending coronary artery (LAD) and circumflex artery as well as soft plaque in all 3 epicardial vessels with near-total occlusion of the proximal right coronary artery.

ABBREVIATIONS AND ACRONYMS

AV = atrioventricular

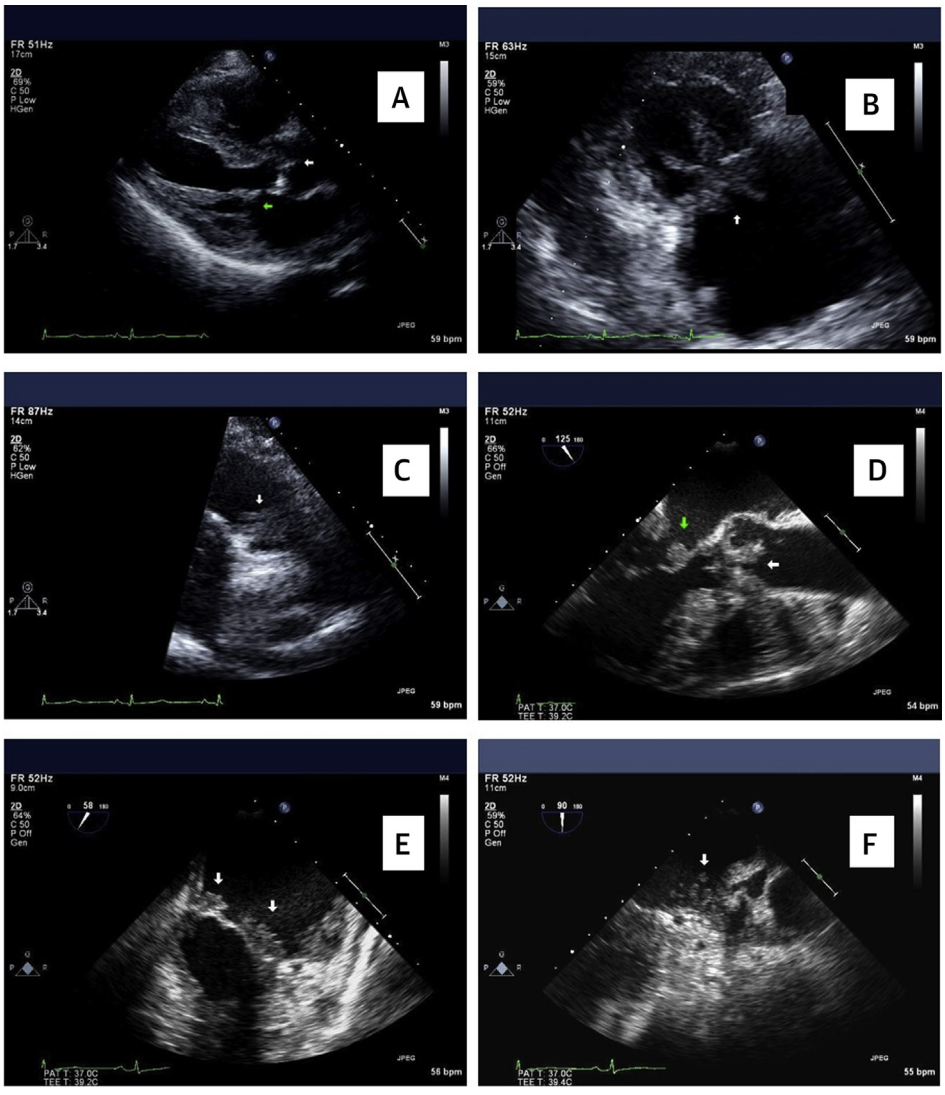
LAD = left anterior descending coronary artery

LHCDD = light and heavy chain deposition disease

NBTE = Nonbacterial thrombotic endocarditis

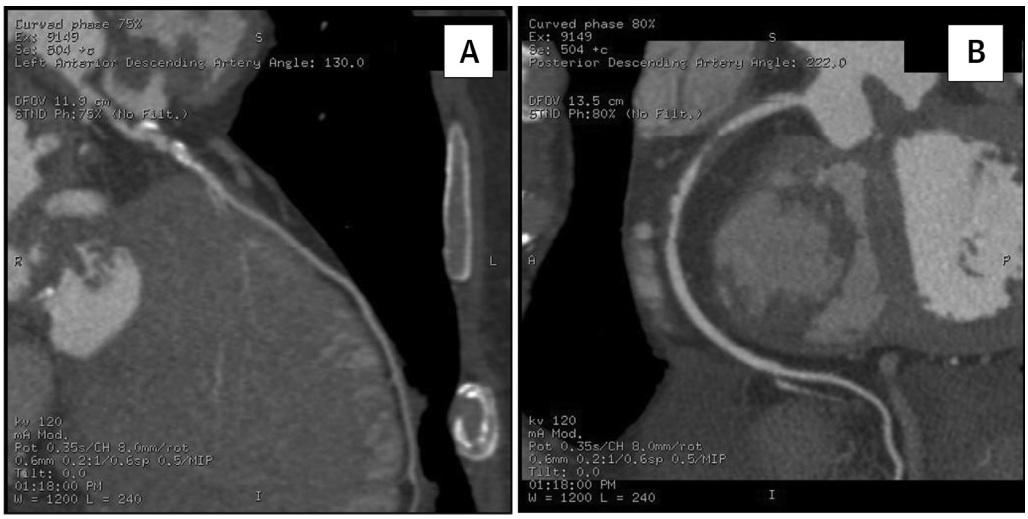
NIE = noninfective endocarditis

FIGURE 1 Transthoracic and Transesophageal Echocardiogram



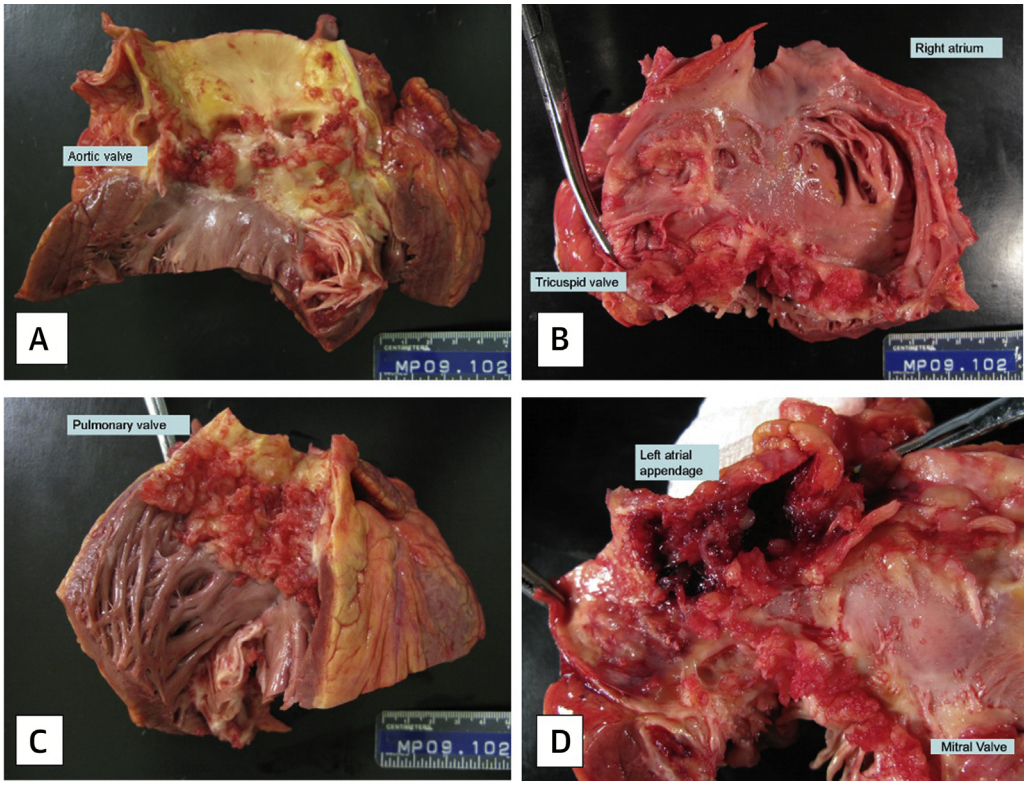
(A) TTE, parasternal long axis view of aortic **(white arrow)** and mitral valve vegetations **(green arrow)**. **(B)** TTE, parasternal right ventricular inflow view of tricuspid valve vegetations. **(C)** TTE, parasternal right ventricular outflow view of pulmonary valve vegetations. **(D)** TEE, aortic **(green arrow)** and mitral valve vegetations **(white arrow)**. **(E)** TEE, mitral valve vegetations. **(F)** TEE, fungating mass in the left atrial appendage. See Videos 1, 2, 3, and 4. TEE = transesophageal echocardiogram; TTE = transthoracic echocardiogram.

FIGURE 2 Coronary CT Angiography



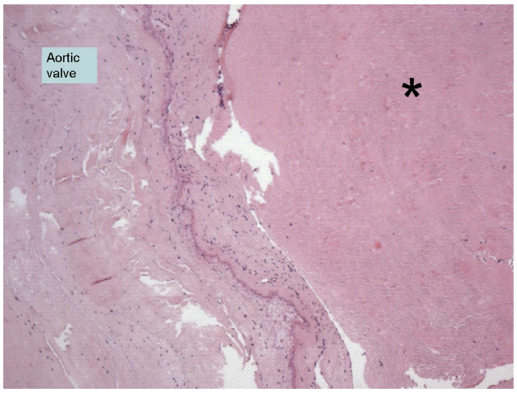
CT angiography of the left anterior descending artery with mixed calcific and soft plaque with 50% to 70% stenosis **(A)** and the right coronary artery with soft plaque and subtotal occlusion **(B)**. CT = computed tomography.

FIGURE 3 Pathology



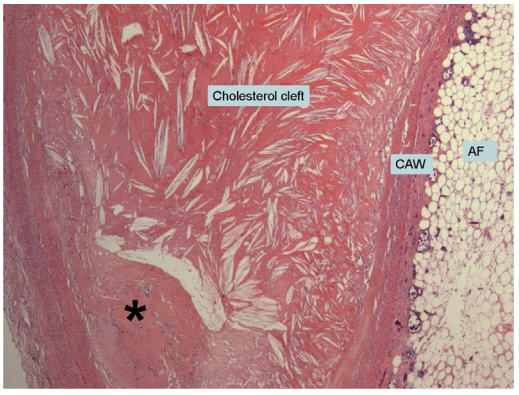
Vegetations found on the aortic valve **(A)**, tricuspid valve **(B)**, pulmonary valve **(C)**, and left atrial appendage with fungating mass **(D)**.

FIGURE 4 Aortic Valve Vegetation



Hematoxylin and eosin stain of the aortic valve with IgM deposition. *Vegetation consisting of IgM.

FIGURE 5 Left Anterior Descending Coronary Artery Occlusion



Hematoxylin and eosin stain of the LAD with complete occlusion by atherosclerotic plaque and IgM embolism. *IgM embolism. AF= adventitial fat; CAW = coronary artery wall; LAD = left anterior descending artery.

MANAGEMENT. The patient was offered valve replacement and debulking with coronary artery bypass surgery, but he declined. His bone marrow biopsy returned nondiagnostic results, so a repeat biopsy was performed. Two hours later, the patient had chest pain with ST-segment elevation and atrioventricular (AV) block. Asystole ensued, and the patient died.

An autopsy demonstrated extensive deposition of amorphous, eosinophilic material on the 4 cardiac valves (Figure 3) and the walls of the atria, pulmonary artery, and aorta. There was embolization to the kidney, spleen, liver, and lungs. The material was found to be nonamyloid IgM heavy chain and lambda light chain without any fibrin or platelets (Figure 4). Atherosclerosis of the coronary arteries with no evidence of rupture was present, with complete occlusion of the LAD by IgM deposition (Figure 5). Bone marrow examination revealed small $CD20^{+}$ lymphocytes (B-cells) and IgM deposition consistent with an underlying low-grade B-cell lymphoproliferative disorder (Figure 6).

FOLLOW-UP. Deceased.

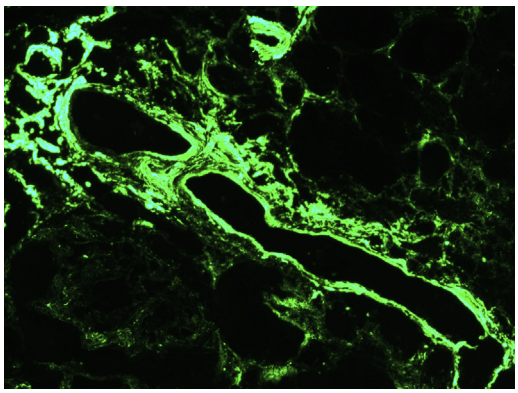
DISCUSSION

NBTE has been variably referred to as marantic endocarditis, Libman-Sacks endocarditis, and verrucous endocarditis. NBTE is a noninfectious condition marked by the sterile accumulation of fibrin and platelets on the surface of a cardiac valve. It is most often associated with mucin-producing adenocarcinomas or lymphomas, collagen-vascular disease, and hypercoagulable states. The main mechanism for thrombi deposition begins with endothelial damage and the exposure of subendothelial connective tissue to circulating platelets. Current guidelines recommend using intravenous administration of unfractionated heparin or subcutaneous low-molecular-weight heparin in NBTE with systemic or pulmonary emboli as a grade 2C recommendation (2). Valvular surgery has not been evaluated by prospective studies. However, it remains an option in patients with large vegetations, valve dysfunction, or recurrent embolic events while they are receiving anticoagulation.

Thrombus deposition must be present by definition in NBTE. There are only 6 cases of quadrivalvular NBTE reported in published reports, each with evidence of valvular thrombosis (3–8). This report describes what the present authors believe to be the first description of a nonbacterial, nonthrombotic endocarditis of all 4 cardiac valves due to the deposition of IgM heavy chain. There was no evidence of any thrombi at pathology examination. This case demonstrates that NIE is a better descriptor for NBTE, unless there is pathology confirmation of fibrin and platelet deposition.

DIFFERENTIAL DIAGNOSIS. In the present patient, after infective endocarditis was ruled out with microbiologic data, the diagnosis was changed to NBTE. A search for a hypercoagulable state and solid malignancy did not reveal a cause. The serum and urine protein electrophoreses results suggested that a hematologic malignancy might have been present, particularly a plasma cell dyscrasia. However, the first

FIGURE 6 Immunofluorescence



Immunofluorescence performed on the kidney, used to confirm IgM.

bone marrow biopsy result was nondiagnostic. Unfortunately, the repeated bone marrow biopsy results were returned after the patient died. The pathology finding of small B-cells extended the underlying differential diagnosis to include Waldenstrom macroglobulinemia, amyloidosis, and light and heavy chain deposition disease (LHCDD).

In addition to the presence of an IgM paraprotein, Waldenstrom macroglobulinemia is characterized by anemia, hyperviscosity, and peripheral neuropathy. An increase of 10% or more of the bone marrow biopsy sample must show the infiltration of small lymphocytes with plasmacytoid or plasma cell differentiation in an intertrabecular pattern (9). These clinical findings and pathologic findings were not present in this case. Primary (AL) amyloidosis is characterized by the deposition of amorphous, eosinophilic material. However, amyloidosis is diagnosed by demonstrating apple-green birefringence under polarized light to Congo red staining which was not seen in this case. Also, cardiac amyloidosis, although associated with valvular thickening, typically presents clinically with a restrictive cardiomyopathy (10). LHCDD is associated with deposition of IgM and lymphoproliferative disorders; however, it is marked by prominent renal involvement with proteinuria and renal failure. When there is cardiac involvement in LHCDD, diastolic dysfunction and conduction system diseases are seen. Although AV blockage was seen immediately antemortem, the other findings of LHCDD were not present. Therefore, the most appropriate diagnosis for this patient is low grade B-cell lymphoproliferative disorder with extensive deposition of paraprotein causing quadrivalvular NIE with embolization to the LAD.

CONCLUSIONS

To the best of the present authors' knowledge, this is the first case of nonbacterial, nonthrombotic quadrivalvular endocarditis caused by deposition of heavy chain IgM. This case highlights the need for a more accurate description of NBTE. Noninfective endocarditis or NIE should be used in cases of cardiac vegetations without evidence of infection or thrombus deposition.

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KEY WORDS B-cell lymphoproliferative disorder, nonbacterial thrombotic endocarditis, noninfective endocarditis

APPENDIX For supplemental videos, please see the online version of this paper.