

# Nonbacterial Thrombotic Endocarditis—A Rare Case of Acute Libman-Sacks Endocarditis Complicated by Multiple Cerebral Infarcts: Case Report and Literature Review



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## INTRODUCTION

Nonbacterial thrombotic endocarditis (NBTE), which was originally reported by Ziegler<sup>1</sup> in 1888, is a deposit of thrombi and fibrin on cardiac valves. NBTE develops as a spectrum of conditions that arise from multiple underlying causes. Since the first report by Trousseau<sup>2</sup> in 1865, known as Trousseau's syndrome, malignancy has been recognized as a major cause of NBTE. Other causes of NBTE include autoimmune diseases, such as Libman-Sacks endocarditis (LSE) associated with systemic lupus erythematosus (SLE), which was reported in 1924.<sup>3</sup> The etiology of NBTE is due to a hypercoagulable state and an inflammatory response. This hypercoagulable state is relevant to malignancy, and the inflammatory response is linked to autoimmune diseases. NBTE was discovered in 80% of patients with cancer in a postmortem study<sup>4</sup> and in 46% of patients with autoimmune diseases in an antemortem study.<sup>5</sup> The thrombi consist of platelet-rich fibrin. NBTE clot formation may be augmented by multiple abnormal coagulation mechanisms. Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) are useful methods for detecting NBTE. We report a case of acute NBTE due to LSE complicated by multiple coagulopathies leading to cerebral infarction detected on TTE and TEE.

## CASE PRESENTATION

A 23-year-old man was admitted to our hospital because of persistent cough and fever (37.3°C). Two weeks before admission, he had undergone a tooth extraction because of caries, and 1 week later a nonproductive cough developed, along with fever. Approximately 5 years before admission, he began to receive warfarin and immunosuppressant therapy for SLE, antiphospholipid syndrome, lupus nephritis, protein S (PS) deficiency, homocysteinemia, deep vein

thrombosis, and chronic thromboembolic pulmonary hypertension. The patient's compliance was good, and an appropriate dose of warfarin was administered to control the prothrombin time international normalized ratio within a range of 2.0 to 3.0. The patient had been in his usual state of health until approximately 4 months before this presentation at our hospital, when he had left popliteal artery thrombosis. Anticoagulant therapy was changed from warfarin to rivaroxaban, and he was treated conservatively. However, 1 month later he had an acute myocardial infarction caused by left anterior descending coronary artery thrombosis and underwent emergent percutaneous intervention with aspiration of the thrombus. Aspirin therapy was added, and the patient was scheduled for admission for follow-up coronary angiography and peripheral artery angiography.

On the day of admission, laboratory tests revealed an elevated white blood cell count (11,600/ $\mu$ L), elevated C-reactive protein (1.09 mg/dL), elevated creatinine (1.33 mg/dL), elevated D-dimer (1.1  $\mu$ g/mL), prolongation of activated partial thromboplastin time (69.6 sec), a stable mildly elevated level of anti-double-stranded deoxyribonucleic acid antibody (51 IU/mL) with range of 30 to 50 IU/mL for >1 year, and a stable slightly low level of total hemolytic complement (24.0 U/mL) with range of about 20 to 30 U/mL for >1 year. Chest radiography showed a cardiothoracic ratio of 49%, clear lung fields, and a sharp costophrenic angle. The patient underwent TTE, which revealed a low-echoic mass (13  $\times$  11 mm) around the left ventricle to the side of the aortic valve (Figure 1A, Video 1). This prompted us to immediately perform TEE. The low-isoechoic mass was attached to the basal part of the right coronary cusp (Figure 1B, Video 2) on TEE. A zoom view showed a mass (29  $\times$  6 mm) extending from the right to the left coronary artery via the commissure, which moved to the left ventricular side during diastole and to the aortic side during systole (Figures 1C and 1D, Videos 3 and 4). The margin was rough, and the internal structure was inhomogeneous. A three-dimensional zoom view showed the mass extending linearly, mainly from the basal part of the right coronary leaflet partially to the basal part of the left coronary leaflet via the commissure, which moved to the left ventricular side during diastole and to the aortic during systole (Figure 1E, Video 5). There was no degeneration of the aortic valve, but mild aortic regurgitation was detected. On the basis of the clinical course and echocardiographic findings, a diagnosis of infective endocarditis (IE) or NBTE was considered. Follow-up coronary angiography was canceled. Blood cultures were collected, and a continuous infusion of heparin (10,000 U/day) and antibiotics was initiated. A total of three sets of blood cultures were negative. On the second day of admission, white blood cell count (9,400/ $\mu$ L) and C-reactive protein level (0.9 mg/dL) decreased. On the third day of admission, the patient reported a slight sensory impairment of the right upper limb and

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## VIDEO HIGHLIGHTS

**Video 1:** TTE with an isoechoic mass around the left ventricular side of the aortic valve.

**Video 2:** TEE with a low-isoechoic mass attached to the basal side of the right coronary cusp.

**Video 3:** Zoom view on TEE with a low-isoechoic inhomogeneous mass attached to the basal side of the right coronary cusp moving to the left ventricular side in diastolic phase and to the aortic side in systolic phase. The margin is rough, and the internal structure is inhomogeneous.

**Video 4:** Zoom view on TEE with a low-isoechoic inhomogeneous mass attached to the basal side of the right coronary cusp via commissure to the basal side of the left coronary cusp.

**Video 5:** TEE, three-dimensional zoom view, depicting a low-isoechoic mass attached linearly from mainly the basal part of the right coronary cusp via the commissure to partly on the basal part of the left coronary cusp.

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mild dysarthria. Magnetic resonance imaging of the head revealed an acute infarction of the left insular cortex and left parietal lobe. Heparin infusion was increased to 15,000 U/day, and emergent surgery was scheduled. However, while preparing for surgery, inconsistent behavior of the patient was observed. Magnetic resonance imaging showed new lesions at the subcortex of the right parietal lobe and right parietal lobe (Figure 2A). Emergent transcatheter revascularization was performed. Cerebral angiography showed infarction of the middle cerebral artery (Figure 2B). The embolus was removed successfully (Figure 2C). Sequential emergent aortic valve replacement was performed. Macroscopic findings of the aortic valve showed regional degeneration of the left ventricular side of the right and left coronary cusps, to where the thrombus attached. The aortic side was intact (Figure 3A). Pathologically, the regional degeneration of the right coronary cusp where the thrombus was attached showed a displacement of fibroblast and collagen fibers (Figure 3B). The thrombus consisted of fibrin and platelets. Neutrophils or bacteria were not found (Figure 3C). The embolus removed from the middle cerebral artery by emergent transcatheter revascularization was similar to the thrombus attached to the aortic valve. On the basis of these findings, a diagnosis of NBTE was established. A mechanical valve was implanted in the aortic valve position. Rivaroxaban was switched to warfarin, and immunosuppressant therapy for SLE was strengthened to prevent thrombosis. The postoperative course was uneventful. After sufficient rehabilitation, no permanent damages from the cerebral infarction were seen. The patient was discharged home on the 30th day after surgery.

## DISCUSSION

LSE, a potential complication of SLE, is a type of NBTE sometimes caused by autoimmune diseases, especially by SLE complicated

with antiphospholipid syndrome.<sup>6</sup> Cardiac valve disease associated with SLE is categorized into two types: leaflet thickening and LSE. Forty-eight percent of patients with SLE who undergo TEE are reported to have leaflet thickening.<sup>7</sup> On the other hand, 10% of patients with SLE are reported to develop LSE. Leaflet thickening and LSE overlap. Almost all cases of LSE show damage to the left-sided cardiac valves. Sixty-three percent of LSE cases involve the mitral valve, and 34% involve the aortic valve.<sup>8</sup> Circulating immune complexes in SLE induce inflammation and injury to the entire valve surface.<sup>9</sup> Formation of LSE-associated thrombus is also triggered by immune complexes, especially consisting of antiphospholipid antibodies. Antiphospholipid antibodies are detected in half of patients with SLE, and 40% of these patients have valvular lesions.<sup>10</sup> In our patient, antiphospholipid antibody was found to be positive.

In addition to circulating immune complexes, we should consider several conditions that predispose to the development of widespread thrombosis or embolism to multiple vascular territories in this patient. PS deficiency is a common cause of venous thromboembolism. However, certain types of PS mutation are reported to induce arterial thrombosis.<sup>11</sup> Homocysteinemia is also a well-known risk factor for venous thromboembolism. The interaction of elevated homocysteine levels and other predisposing factors facilitates the formation of arterial thromboembolism.<sup>12</sup> The failure rate of warfarin therapy for venous thromboembolism was reported to be 8%, even when the prothrombin time international normalized ratio is controlled within a range of 2.0 to 3.0.<sup>13</sup> In our patient, compliance with warfarin was good and the prothrombin time international normalized ratio was controlled within the therapeutic range. However, the interaction of multiple factors (LSE, antiphospholipid antibody, PS deficiency, and elevated homocysteine) might have triggered the arterial thromboembolism.

It is sometimes difficult to differentiate NBTE from IE-associated vegetation. On echocardiography, LSE-associated thrombi can be differentiated from IE-associated vegetations by their locations as well as the appearance and mobility pattern. LSE-associated thrombi are located near the leaflet base, while IE-associated vegetations are located at the leaflet line of closure.<sup>7</sup> In our patient, IE was considered on the basis of his medical history. TEE showed a mass attached to the base of the aortic valve, which was suggestive of LSE. However, LSE could sometimes be complicated by IE.<sup>8</sup> Therefore, assessing the presence of IE and initiating antibiotic therapy is essential.

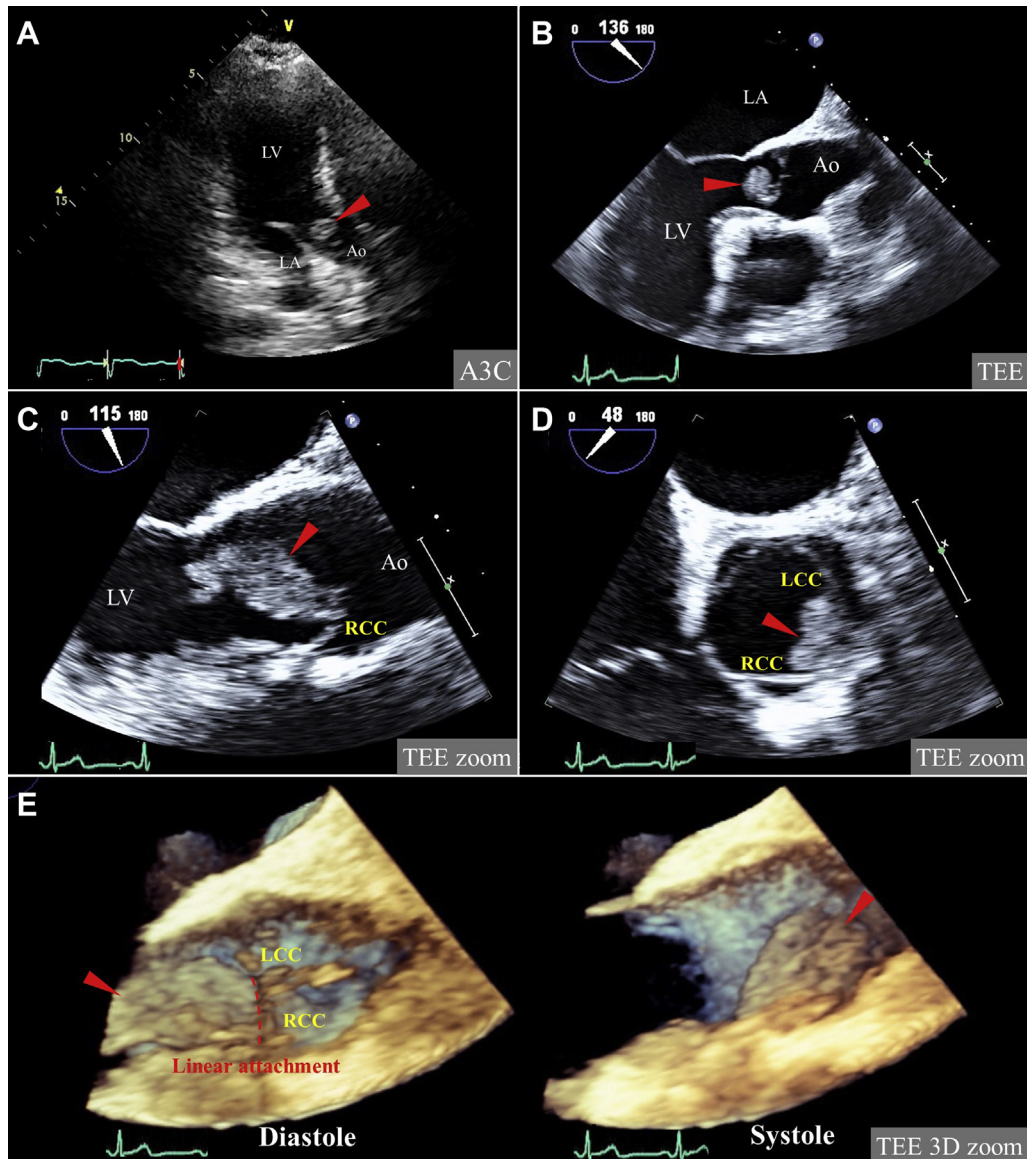
In our patient, the appearance of LSE on echocardiography was rather atypical. The chronic phase of typical LSE is often detected on the basis of associated leaflet or cusp commissural fusion with iso-high heterogenous echogenicity. The thrombus detected in this patient involved the commissure with iso-low heterogenous echogenicity, indicating that it was in the acute phase. However, the location of typical LSE is at the atrial side of the mitral valve or vessel side of the aortic valve. The thrombus was located at ventricular side in this patient. The attached area of typical LSE was rather wide and poorly mobile. However, the thrombus of this patient attached linearly and was mobile. The mean size of atrial thrombus caused by typical LSE is reported to be  $3.9 \pm 1.3$  mm, with a maximum size of 10 mm, which is smaller than what was seen in our patient (29 mm).<sup>14</sup> Typical LSE sometimes involves not only one small thrombus but also multiple small thrombi. On the other hand, this patient had only one large thrombus. Development of LSE is associated with SLE activity

and other risk factors, as in this patient. However, typical LSE is usually asymptomatic in the acute phase and initially manifests only when an embolic event results in neurologic symptoms.<sup>15</sup> This patient developed multiple embolic events in the acute phase, even though SLE activity was ambiguous. These characteristics indicated acute NBTE as a result of multiple factors due to LSE. Periodic echocardiographic follow-up is important to detect acute and asymptomatic typical LSE, especially when SLE-related marker levels are increased or related systemic symptoms develop.<sup>15</sup> TTE is also indispensable to detect acute NBTE, even when the systemic symptoms are ambiguous. In our patient, the

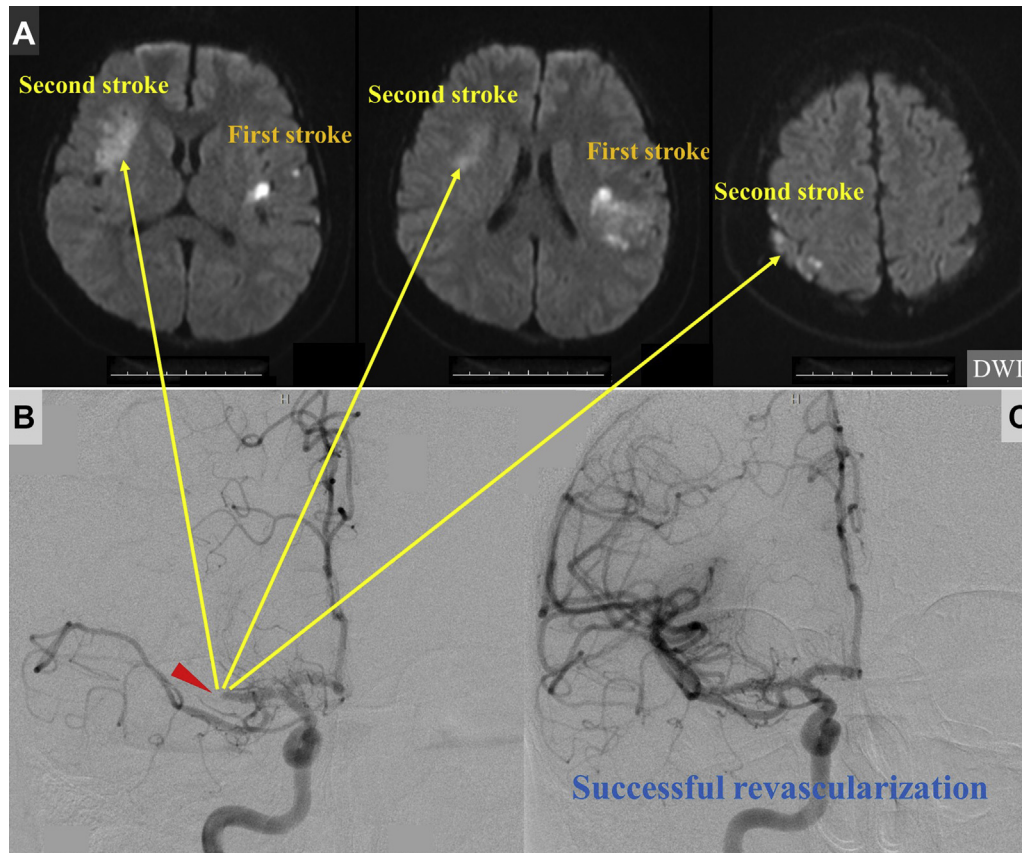
maximum size of the NBTE thrombus measured by TTE was 13 mm. However, the maximum size as evaluated by TEE was 29 mm. TEE allows a more accurate evaluation of the entire size of NBTE. A combination of TTE and TEE is necessary to screen and investigate NBTE.

### CONCLUSION

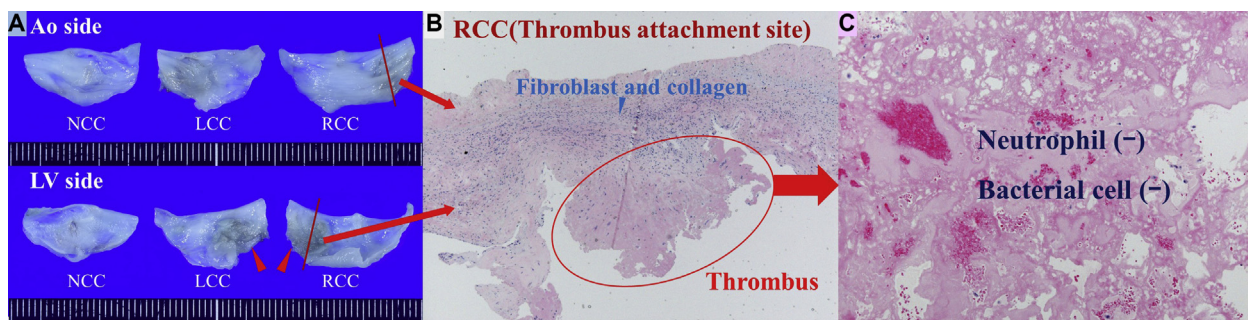
We diagnosed a case of acute NBTE resulting from multiple coagulopathies triggered by LSE leading to cerebral infarction detected using



**Figure 1** (A) TTE shows an isoechoic mass (13 × 11 mm) around the left ventricular side of the aortic valve (red arrowhead). (B) TEE shows the low-isoechoic mass attached to the basal part of the right coronary cusp (red arrowhead). (C) Zoom view on TEE shows the intact aortic valve and the low-isoechoic mass (29 × 6 mm) attached to the basal side of the right coronary cusp (RCC) (red arrowhead). The margin is rough, and the internal structure is inhomogeneous. (D) Zoom view on TEE shows the low-isoechoic mass attached to the RCC via the commissure to the basal side of the left coronary cusp (LCC) (red arrowhead). (E) Three-dimensional zoom view on TEE shows the mass attached linearly from the basal part of RCC via the commissure partially to the basal part of the LCC (red arrowhead). A3C, Apical three-chamber view; Ao, aorta; LA, left atrium; LV, left ventricle.



**Figure 2** (A) Magnetic resonance imaging of the head shows an acute infarction of the left insular and left parietal lobe cortex (first stroke) and hyperacute lesions in the right parietal lobe subcortex (second stroke). (B) Cerebral angiography shows infarction of the middle cerebral artery (*red arrowhead*). (C) Acute revascularization of the right middle cerebral artery was successful. DWI, Diffusion-weighted imaging.



**Figure 3** (A) Macroscopic findings of the aortic valve show regional degeneration of the left ventricular side of the right coronary cusp (RCC) and left coronary cusp (LCC), where the thrombus is attached (*red arrowhead*). The aortic side is intact. (B) The regional degeneration of the RCC where the thrombus attached shows the displacement of fibroblasts and collagen fiber. (C) Hematoxylin and eosin staining of the removed mass shows a thrombus consisting of fibrin and platelets; neutrophils and bacteria are not found. NCC, Non-coronary cusp.

TTE and TEE. Echocardiography is indispensable to screen and detect LSE as well as NBTE in asymptomatic patients with SLE.

#### SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.case.2020.09.005>.

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