Severe Aortic Regurgitation by Nonbacterial Thrombotic Endocarditis Treated with Anticoagulation Therapy

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INTRODUCTION

Nonbacterial thrombotic endocarditis (NBTE) is a rare condition that forms noninfectious thrombotic lesions on the heart valves, usually without clinically significant valve dysfunction.[1]

We report a case of NBTE that mimics infective endocarditis, causing severe valvular regurgitation and cerebral embolization. The case was successfully treated with anticoagulation therapy, avoiding surgical intervention.

CASE PRESENTATION

A 48-year-old woman who was recently diagnosed with lung adenocarcinoma presented to our hospital. Magnetic resonance imaging (MRI) performed for the screening of metastatic lesions revealed small cerebral infarctions in multiple cerebral regions (Figure 1). Computed tomography performed at the same time as MRI showed diffuse microthrombi in peripheral pulmonary arteries (Figure 2). A transthoracic echocardiogram (TTE) that was requested to identify an intracardiac source of the cerebral infarctions showed no valvular dysfunction or obvious intracardiac thrombus. At this point, edoxaban 60 mg was started for pulmonary embolism and cerebral infarction.

One month later, a physician noticed a new diastolic murmur that was absent at the first presentation, and a repeat TTE was performed that showed new severe aortic regurgitation (AR). The aortic valve leaflets appeared thickened with associated echogenic material suggestive of infectious endocarditis (IE); severe AR was also present (Figure 3, Video 1). Transesophageal echocardiography (TEE) revealed irregularly shaped echogenic masses adherent to the coapting edges of all three aortic valve leaflets. These masses were low echoic and minimally mobile. The maximum size was 16.0 × 6.7 mm (width × height). The AR jet arose from the center of the valve without apparent valvular destruction such as leaflet prolapse, bending, or perforation (Figure 4, Videos 2 and 3).

VIDEO HIGHLIGHTS

Video 1: Transthoracic echocardiography at 1 month. Zoomed parasternal long-axis images **(A)** and parasternal short-axis images **(B)** of the aortic valve and the apical long-axis view **(C)** display thickened valve leaflets associated with severe AR.

Video 2: Transesophageal echocardiography of aortic valve, short-axis view. This biplane image displays irregularly shaped echogenic masses adherent to the coapting edges of all three aortic leaflets *(left)* and severe central AR *(right)*.

Video 3: Transesophageal echocardiography of aortic valve, long-axis view. This biplane image displays multiple low-echoic and nonmobile echogenic masses attached to the aortic valve *(left)* with associated severe AR *(right)*; the maximum mass size was 16.0 × 6.7 mm (width × height).

Video 4: Transthoracic echocardiography after anticoagulation. The parasternal long-axis view *(top)* and the parasternal short-axis views *(bottom)* of the aortic valve show resolution of the echogenic masses and a dramatic reduction in AR severity to mild.

Video 5: Transthoracic echocardiography of pre- and post-anticoagulation therapy. Apical long-axis view of pre- *(left)* and post- *(right)* anticoagulation shows a dramatic reduction in AR severity.

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Other than lung adenocarcinoma, she had no particular medical history, including no drug abuse, alcohol consumption, or family history of similar presentation. She did not experience fever or heart failure symptoms prior to this event.

Differential diagnoses of these echogenic masses included IE, NBTE, papillary fibroelastoma, and Lambl's excrescence.

For the diagnosis of IE, further investigations were performed based on the modified Duke criteria.[2] Her body temperature was 36.6°, and her blood pressure was 138/62 mm Hg. A careful physical examination did not find any evidence of immunologic, embolic, or vascular phenomena such as Janeway lesions, Roth spots in the retina, or Osler nodules. Repeatedly performed blood culture examinations were negative. Laboratory investigations showed elevated white blood cell count (10,400 × $10^9/\mu$L), C-reactive protein (1.3 mg/dL), and D-dimer level (9.6 μg/mL). Thrombophilic evaluation including antinuclear body and

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Conflicts of Interest: None.

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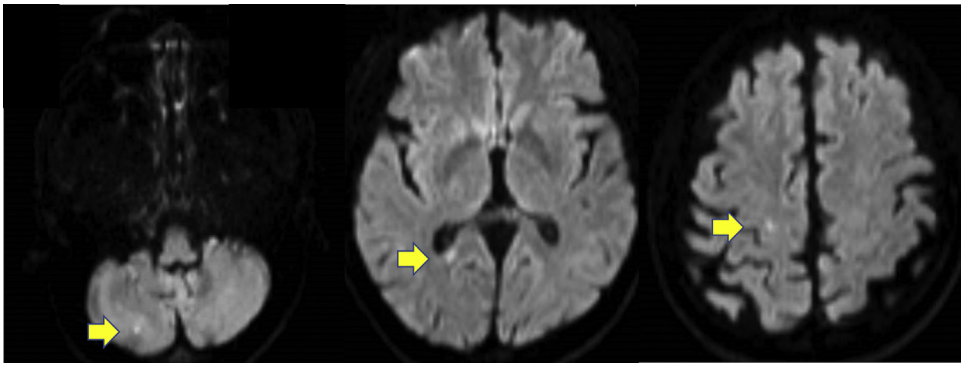

Figure 1 Brain MRI at diagnosis. Small cerebral infarctions (*yellow arrows*) in multiple cerebral regions are shown.

antiphospholipid antibody was normal. Overall, modified Duke criteria for IE were rejected with only one major criterion met: echocardiogram positive for IE, with low-echoic, minimally mobile, independent masses.

Since the masses were multiple and large, the likelihood of Lambl's excrescence, which typically are mobile, thin, and filiform structures, was considered low. Papillary fibroelastoma was also considered less likely because it is usually highly mobile and is attached to the valve leaflet with a stalk-like structure.[3] Furthermore, there was no evidence suggesting an underlying autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome; therefore, NBTE associated with her lung adenocarcinoma was suspected. Edoxaban was discontinued, and anticoagulation therapy with subcutaneous injection of low-dose unfractionated heparin was started. Her D-dimer level had gradually decreased to a normal range, and the follow-up TTE on day 13 showed shrinkage of masses and improvement in AR severity from severe to moderate. On day 33, a repeat TTE showed that the masses attached to the aortic leaflets finally became undetectable. The degree of AR was dramatically reduced to mild (Figure 5, Videos 4 and 5). During this period, the patient did not experience any complications despite no antibiotic therapy. The follow-up MRI showed no evidence of new embolization. As for lung adenocarcinoma, chemotherapy concurrently administered with anticoagulation was effective. After 3 months of chemotherapy, chest X-ray showed shrinkage of right hilar lymph nodes and right lower lobe mass shadow (Figure 6). Currently, the patient is continuing chemotherapy and heparin treatment as an outpatient.

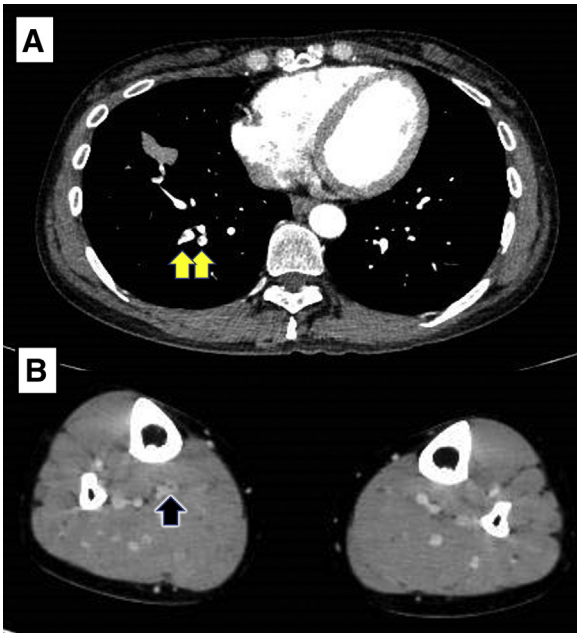

Figure 2 Chest computed tomography at diagnosis. Diffuse microthrombi (*yellow arrows*) in peripheral pulmonary arteries **(A)** and deep vein thrombosis (*black arrow*) in right lower extremity **(B)** are shown.

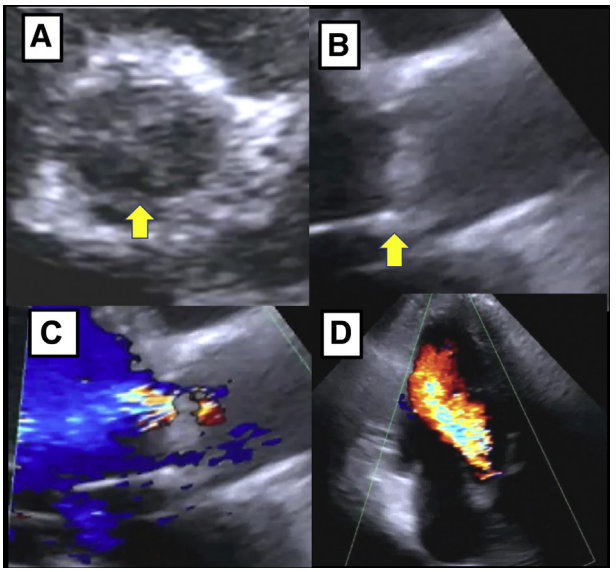

Figure 3 Follow-up transthoracic echocardiography. Zoomed parasternal short-axis view **(A)** and zoomed parasternal long-axis view of the aortic valve showing thickened aortic valve leaflets, predominately of the noncoronary cusp (*arrow*) **(B)**. Zoomed parasternal long-axis view of the aortic valve with color Doppler imaging shows the AR jet with flow convergence noted on the aortic side of the aortic valve **(C)**; AR vena contracta = 9.8 mm; AR jet/left ventricular outflow tract ratio = 55%. Zoomed apical long-axis view of aortic valve with color Doppler imaging showing severe AR **(D)**.

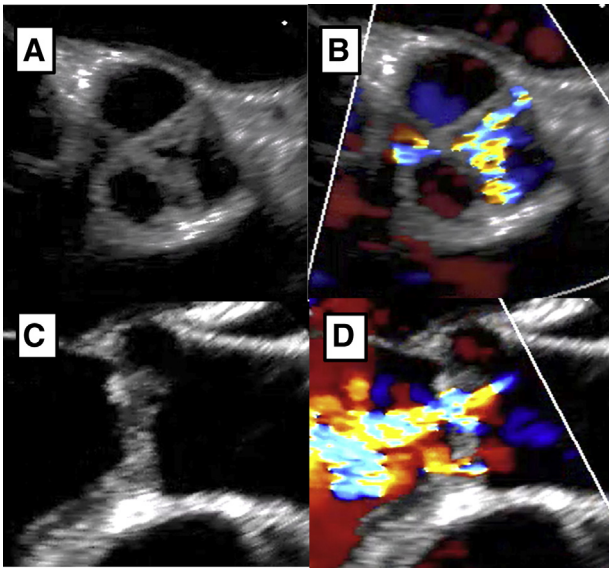

Figure 4 Transesophageal echocardiography. Short-axis **(A)** and long-axis **(C)** images of the aortic valve showing low-echoic, irregularly shaped masses adherent to the coapting edges of all three aortic leaflets. The maximum size was 16.0 × 6.7 mm (width × height). Severe AR is noted on the corresponding color Doppler images **(B, D)**.

DISCUSSION

NBTE, also known as marantic endocarditis, is a rare condition that forms noninfectious, thrombotic lesions on the heart valves, often associated with underlying malignancy or autoimmune disease and succeeding hypercoagulable states.[4] NBTE is composed of clots formed by platelets and fibrin,[5] and the underlying valvular tissue is either entirely normal or shows subtle histologic evidence of abnormal collagen and elastic fibers. Thus, NBTE does not usually destroy valve structure or cause clinically significant valvular heart disease.[1] In this case of NBTE with atypical severe valvular regurgitation, anticoagulation therapy resolved the valvular dysfunction by shrinking the vegetation and recovering the valve coaptation.

Unfractionated heparin is reported to be the most effective anticoagulant, which has been shown to be effective in reducing the incidence of recurrent episodes of thromboembolism.[1] However, the use of vitamin K antagonists such as warfarin in patients with NBTE may not be effective as the presence of non–vitamin K–dependent agents may induce the thrombotic coagulopathy in NBTE treated with warfarin.[6] A couple of case reports suggest the inefficacy of direct oral anticoagulants in the treatment of NBTE.[7] Our case also supports these reports. The image quality between the first and second TTE in our case was comparable, and the vegetation had grown in size during this period between the two TTEs despite the use of edoxaban. Accordingly, we chose unfractionated heparin, which successfully ameliorated the vegetation in this case.

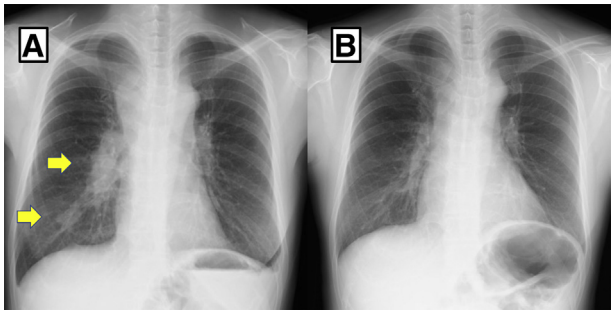

Figure 6 Chest X-rays before and after chemotherapy. Comparison of chest X-rays **(A)** before and **(B)** after chemotherapy displays notable shrinkage of the right hilar lymph nodes and right lower lobe mass shadow (*arrows in A*).

The most important differential diagnosis with an echogenic mass attached to the heart valves on an echocardiogram is IE, which often causes severe valvular regurgitation associated with destruction of the valve. Such severe valvular regurgitation generally requires surgical treatment, which can be high risk for sick patients with malignancy, as in our case.[8] Therefore, the differential diagnosis between NBTE and IE in our case was critical for therapeutic planning.

In general, NBTE does not usually cause severe valvular dysfunction, as the valve structure usually remains intact. However, a similar case of NBTE with AR and multiple embolic events found fibrinous aggregation and scattered inflammatory cells without evidence of structural deterioration at surgery.[9]

In our case with severe AR and the relatively large mass, surgical intervention would be indicated if there were associated structural valve destruction due to infection.[7] Echocardiography was useful in our case as it showed no clear evidence of obvious valvular destruction such as perforation. Previous studies reported that TEE is more sensitive in identifying a cardiac embolic source than TTE and thus is the preferred diagnostic test for NBTE.[10,11] In addition, our careful examinations and negative blood culture indicated that IE was rather unlikely. Anticoagulation therapy with unfractionated heparin undergoing frequent serial assessment with echocardiography successfully led to diminished vegetations and AR.

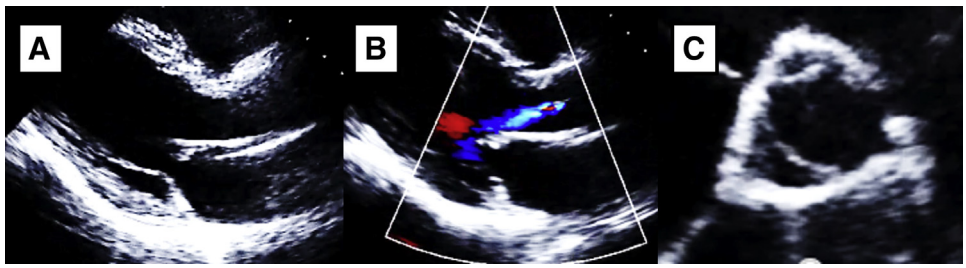

Figure 5 Transthoracic echocardiography after anticoagulation therapy. The parasternal long-axis view **(A)** and the parasternal short-axis view **(C)** of the aortic valve show resolution of the echogenic masses. The color Doppler image from the parasternal long-axis view shows a dramatic reduction in AR severity to mild **(B)**.

The patient has had no hospital admissions over the previous year under continuous anticoagulation therapy with low-dose unfractionated heparin and chemotherapy for lung adenocarcinoma. Repeated TTEs after hospitalization have shown no recurrence of NBTE. Since the risk of recurrent thromboembolism persists with the presence of malignancy,[10] we planned to continue anticoagulation.

CONCLUSION

We experienced a case of NBTE with severe AR mimicking IE that was successfully treated with unfractionated heparin alone. Our report highlights the importance and difficulty of differentiating NBTE from IE. Although it is very rare, valve dysfunction can occur due to noninfectious vegetation impairing valve coaptation in NBTE, and proper medical treatment with unfractionated heparin may improve valvular disease and avoid surgical intervention in these cases. While echocardiography is the cornerstone of the differential diagnosis, other clinical findings and careful history taking play the fundamental role in the diagnosis, and repeat TTE and TEE are essential.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online https://doi.org/10.1016/j.case.2022.04.002.

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