Multi-valve Libman-Sacks's endocarditis-related multiple, massive and fatal systemic embolization. A case report and a review of diagnostic work-up

Vito Maurizio Parato,[1,2] Sara Belleggia,[2] Andrea Giovanni Parato,[3] Umberto Ianni,[1] Michela Molisana,[1] Germana Gizzi,[1] Simone D'Agostino,[1] Melissa Dottori,[4] Marco Di Eusanio[5]

[1]Cardiology and Rehabilitation Unit, Emergency Department, Madonna del Soccorso Hospital, San Benedetto del Tronto; [2]Post-Graduation School of Cardiovascular Diseases, School of Medicine, Università Politecnica delle Marche, Ancona; [3]Cardiology Division and Chair, "Tor Vergata" University Hospital, Rome; [4]Cardiology Unit and Echolab, Cardiovascular Sciences Department, University Hospital Lancisi-Salesi, Ancona; [5]Cardiac Surgery Unit and Cardiovascular Sciences Department, University Hospital Lancisi-Salesi, Università Politecnica delle Marche, Ancona, Italy

Correspondence: Vito Maurizio Parato, Cardiology and Rehabilitation Unit, Emergency Department, Madonna del Soccorso Hospital, AST-AP, Via Luciano Manara 7, 63074 San Benedetto del Tronto (AP), Italy.
Tel./Fax: +39 0735793277
E-mail: vitomaurizio.parato@sanita.marche.it

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Abstract

We reported a case of non-bacterial thrombotic endocarditis (NBTE) in a 37-year-old woman who presented with signs and symptoms of cardio-embolic cerebral stroke caused by a prothrombotic state due to underlying advanced uterine cancer. Multimodal imaging, including 3D-ecocardiography, as well as laboratory and cultural tests, were critical in making the diagnosis. After starting anticoagulation therapy with low molecular weight heparin, the patient underwent surgical aortic valve replacement due to worsening aortic valve function, initial left ventricle enlargement, increasing dimensions, and mobility of vegetations. Unfortunately, vegetations relapsed on the aortic valve bio-prosthesis as well as the mitral leaflets, resulting in a final picture of multi-valve NBTE. The fatal outcome was due to a massive multiple limb embolism, which resulted in leg amputations and septic complications. Starting with the case, we present a brief overview of the pathology's presentation, treatment, management, and prognosis, as well as the diagnostic work-up.

Introduction

Non-bacterial thrombotic endocarditis (NBTE), also known as marantic, Libman-Sacks, thrombotic, or verrucous endocarditis, is a rare condition of non-infective endocarditis characterized by the formation of aggregates of platelets and fibrin that usually affects undamaged heart valves in the absence of bacteremia and mostly occurs in patients with a predisposing state like hypercoagulability [1-3]. NBTE is usually associated with advanced malignancy (typically adenocarcinomas), and autoimmune/rheumatologic diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. Diagnosis is often *post-mortem*. Clinical manifestations are usually related to systemic embolization, with cerebrovascular stroke as the most common first presentation. We describe a case of NBTE in a young woman affected by advanced uterine cancer.

Case Report

A 37-year-old female patient, diagnosed with advanced uterine cancer (poorly differentiated human papillomavirus-related adeno-

carcinoma) and recently presenting with left popliteal deep vein thrombosis complicated by pulmonary embolism, presented to our emergency department with recurrent episodes of dysarthria and blurred vision.

Upon admission, she was referred to the neurological unit for comprehensive assessment. The patient denied any previous history of fever or cardiovascular symptoms. Physical examination disclosed mild dysarthria and left buccal rhyme hypokinesia.

Laboratory tests showed low hemoglobin concentration (9.6 g/dL; normal range: 12.5-16.0 g/dL), elevated D-dimer levels (22.5 mg/mL; normal range <0.5 mg/dL), and an elevated C-reactive protein level (18.3 mg/dL; normal range <0.5 mg/dL). Kidney function was normal (estimated glomerular filtration rate: 90 mL/min/1,73 m^2). Liver function was normal (glutamate pyruvate transminase: 26 U/L, normal range: 7-45; serum glutamic oxaloacetic transaminase: 21 U/L, normal range: 8-43). Coagulation parameters were normal: activated partial thromboplastin time 32 sec; international normalized ratio 1. Procalcitonin and blood cultures – for both aerobic and anaerobic bacteria - were negative. Serological tests for immunity, such as rheumatoid factor, antinuclear antibody, and anticardiolipin antibody, were negative.

Imaging studies, including chest and abdomen computed tomography (CT), demonstrated pulmonary embolism with an extended area of parenchymal infarction, the appearance of splenic infarction, enlargement of the uterine mass with lymphnodes, and caval vein invasion. Additionally, a CT-brain scan showed new cortical-subcortical hypodensities indicative of recent ischemic lesions, which were confirmed by brain magnetic resonance imaging, suggesting cerebral embolism.

Due to the potential source of emboli, the patient was referred to the cardiology unit. Transthoracic echocardiography (TTE) revealed mild aortic insufficiency. To rule out the presence of a patent foramen ovale (PFO), a TTE bubble test was performed with a negative result. Therefore, a 2D-transesophageal echocardiography (TEE) with bubble test was conducted, which turned out negative for PFO. However, TEE surprisingly revealed an oval-shaped isoechoic thickening of the aortic valve cusp tips, leading to mild aortic insufficiency with double jet regurgitation.

Given the patient's clinical history, laboratory results, and echocardiographic findings, there was a suspicion of marantic endocarditis. The patient was initiated on anticoagulation therapy using low molecular weight heparin (enoxaparin, 100UL/kg bid) and also received carboplatin and paclitaxel chemotherapy for the management of advanced cancer. Bevacizumab was excluded from the treatment plan due to the thromboembolic condition. Additionally, empiric antibiotics were administered.

Two weeks later, the TEE exam showed multiple isoechoic masses involving all the aortic cusps, which had increased in size. The largest mass, measuring 15×4 mm, demonstrated significant mobility with projection into the outflow tract during diastole and onto the aortic valve during systole (Figure 1 A,B and *Supplementary Video 1*). The abnormal thickening of the valve-free margin caused leaflet retraction leading to significant aortic insufficiency due to the coaptation gap (Figure 1 C,D and

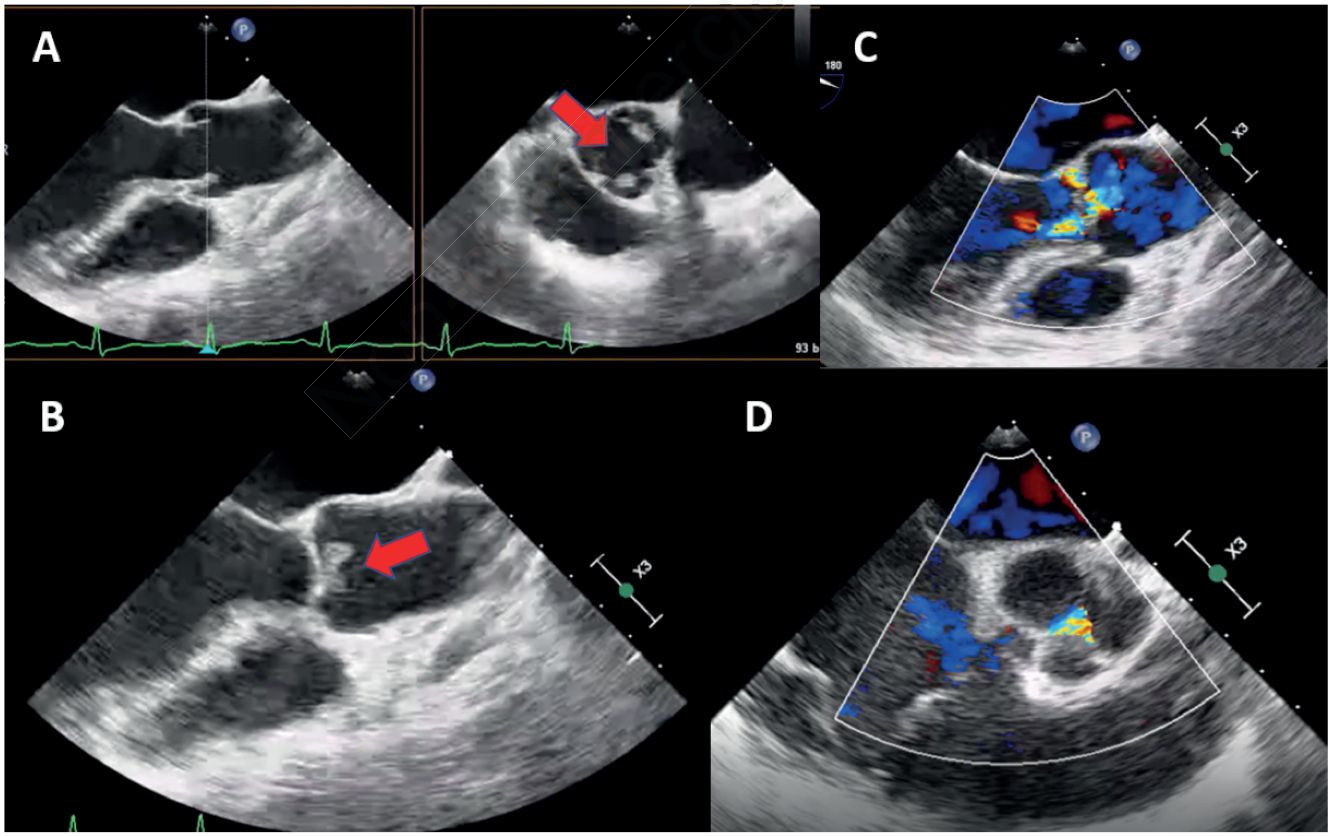

Figure 1. Non-bacterial thrombotic endocarditis in a 37-year-old woman with uterine metastatic adenocarcinoma. A,B) 2D-transesophageal echocardiogram, apical long axis with X-plane view, demonstrating thickening of the aortic valve leaflets together with small isoechoid masses attached to free margin (arrow); C,D) transesophageal echocardiogram aortic valve apical long axis and short axis view demonstrating mild aortic insufficiency with double jet regurgitation.

Supplementary Video 2). No masses were found on the remaining valves.

Considering the poor response to medical therapy and the worsening valvular function with initial left ventricle enlargement (end-systolic diameter of 47 mm), the patient was referred to the cardiac surgery unit. The patient underwent aortic valve replacement with a bio-prosthesis (Carpentier-Edwards Magna Ease N. 21).

The surgical specimen was sent for histological analysis. The result was: finely granular, fibrinous eosinophilic material, containing cellular debris including nuclear remnants, neutrophils, and lymphocytes.

However, 2 months later, she presented severe limb ischemia, which led to the amputation of both legs. 2D-3D-TEE demonstrated a relapse of new vegetations on the prosthetic aortic valve (Figure 2 A,B and *Supplementary Videos 3 and 4*) and on both mitral leaflets (Figure 2 C,D and *Supplementary Videos 5 and 6*). The largest mitral vegetation was 12×9 mm, and at the transgastric short-axis view (0°) a moderate regurgitation with a central jet was visible (*Supplementary Video 7*).

Infective endocarditis was definitely excluded because of the lack of Duke's criteria according to the latest guidelines [4].

Despite efforts to manage the situation, the patient's condition continued to deteriorate, and the patient died because of refractory sepsis one month later.

Discussion

NBTE, also known as *marantic*, Libman-Sacks, thrombotic or verrucous endocarditis, is a form of non-infective endocarditis characterized by the formation of aggregates of platelets plus fibrin. It usually affects undamaged heart valves without the presence of bacteremia and usually occurs in patients with a specific predisposition, such as hypercoagulability [5,6].

NBTE is usually associated with advanced malignancies (80% of cases) typically adenocarcinomas, autoimmune/rheumatic diseases such as SLE and rheumatoid arthritis [1,3,7].

The diagnosis of NBTE can be challenging, and it is often made *post-mortem* (with rates ranging from 0.9 to 1.6%) [8-13]. The most frequent clinical presentations are related to systemic embolization of the friable vegetations, leading to conditions such as cerebrovascular transient ischemic attacks and strokes (the most common),

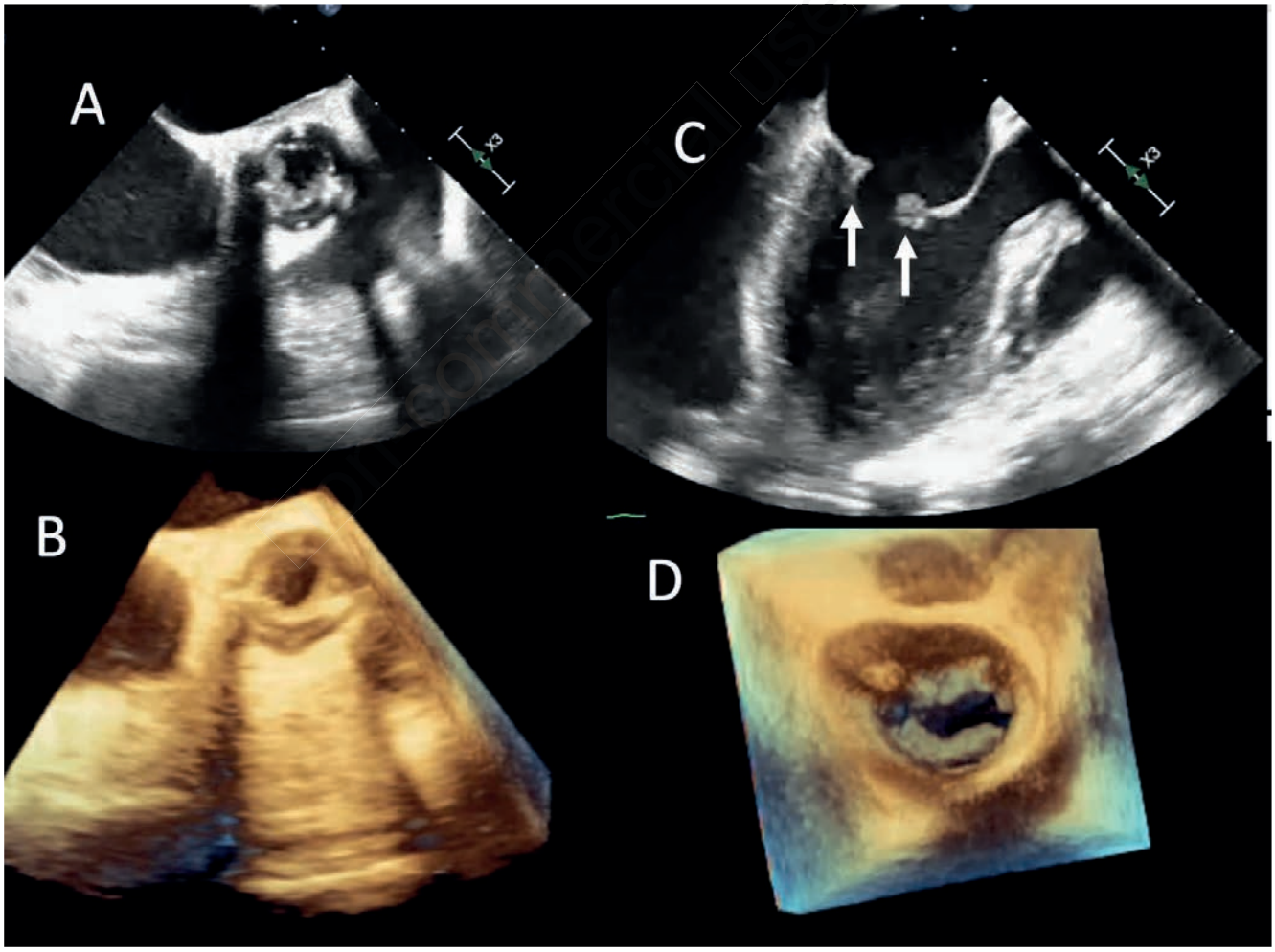

Figure 2. Non-bacterial thrombotic endocarditis in a 37-year-old woman with uterine metastatic adenocarcinoma. A,B) 2D- and 3D-transesophageal echocardiogram (short axis view) demonstrating pathological thickening of the aortic bio-prosthetic valve leaflets together with small isoechoid masses attached to the prosthetic leaflets; C,D) 2D- and 3D-transesophageal echocardiogram, 180° and surgical view respectively, demonstrating non-bacterial vegetations on both mitral leaflets (arrows).

myocardial ischemia, spleen infarction, hematuria, limb ischemia, and ischemic skin manifestations [6,14,15].

To diagnose NBTE, it is crucial to exclude infective endocarditis (IE), considering the possibility of culture-negative IE. NBTE should be suspected in patients with malignancies or autoimmune diseases who develop embolic complications. Cancer screening (*e.g.*, chest and abdomen CT) is mandatory in many cases, and autoimmune tests should be included in the diagnostic work-up [1,15].

TTE and TEE represent the first-choice imaging modalities for the diagnosis of NBTE. The most common echocardiographic finding is the presence of small hyperechoic (isoechoic in our case) masses, typically attached to the low-pressure side of the heart valves, with or without oscillating motion. The mitral valve is involved in two-thirds of cases, while the aortic valve is affected in up to a quarter of cases [6,16]. Atypical presentations with larger lesions or diffuse leaflet thickening affecting multiple valves are also possible [15]. Unlike IE, local complications such as abscesses, pseudoaneurysms, and fistulas are typically absent [17]. According to Roldan *et al*. [18], the use of 3D-TEE, compared to 2D-TEE, provides additional information about the aortic valve more often than the mitral valve. In fact, the number of vegetations identified and the different locations of vegetation might be higher using 3D-TEE as compared with 2D-TEE, and these differences are generally most remarkable for the aortic valve (this is likely explained by the superior visualization of the bodies of the aortic cusps using 3D-TEE). Moreover, 3D-TEE detects more often associated commissural fusion of the mitral leaflets or aortic cusps.

Galzerano *et al*. said that anatomic imaging and, hence, anatomy-based vocabulary make 3D-TEE the echographic modality better able to improve communication within the endocarditis team [19]. Furthermore, the authors suggest performing it routinely in institutions in order to fill the gap between 2D-echocardiography and anatomy.

The management of NBTE involves anticoagulation therapy to reduce the risk of embolic manifestations. Heparin (unfractionated or low molecular weight) is preferred to vitamin K antagonists [6,20,21]. The routine use of direct oral anticoagulants for this indication has not been adequately evaluated [17], and recurrent thromboembolism after anticoagulant discontinuation has been reported, suggesting long-term continuation of anticoagulation [21,22].

Additionally, the treatment of the underlying disease (*e.g.*, malignancy or autoimmune disorder) should be promptly initiated [6].

Surgical indications for valve intervention are not well-defined but seem to align with those of IE, such as heart failure or acute valve rupture, and valve preservation may be possible, unlike in IE [6].

If antibiotics are initiated, they can be discontinued unless there is a suspicion of IE with negative blood cultures.

The optimal follow-up is not well-established, but it is advisable to repeat echocardiographic evaluations to monitor the progression or resolution of valvular vegetations [23]. Prognosis is generally poor and closely related to the underlying disease, especially in cases of advanced malignancies, with a mortality rate of 38.1% [17].

Conclusions

We have reported a case of NBTE presenting with signs and symptoms of cardioembolic cerebral stroke and related to a prothrombotic state due to underlying advanced uterine cancer. Besides laboratory and cultural tests, multimodal imaging, including 3D-ecocardiography, was crucial for the diagnosis. Unlike other published cases [23], given the worsening aortic valve function with initial hemodynamic impact on left ventricle volumes, increasing dimensions, and mobility of vegetations, after starting anticoagulation therapy, the patient underwent surgical aortic valve replacement.

Unfortunately, this resulted in a failing decision since a relapse of vegetations occurred on the aortic valve bio-prosthesis and, additionally, on the mitral leaflets with a final picture of multi-valve NBTE. A massive multiple limb embolism caused leg amputations and septic complications, resulting in death.

The uniqueness of our case is the multi-valve involvement and the high burden of multisite peripheral embolism caused by a significant hypercoagulable status, resulting in deep vein thrombosis and pulmonary embolism, splenic infarction, and a massively embolizing NBTE.

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Online supplementary material:

Supplementary Video 1. 2D-transesophageal echocardiography X-plane view, demonstrating oval-shaped isoechoic and mobile masses on aortic valve.

Supplementary Video 2. 2D-transesophageal echocardiography short-axis view (60°) demonstrating aortic valve regurgitation.

Supplementary Video 3. 2D-transesophageal echocardiography short-axis view (60°) demonstrating new onset pathological thickening of aortic bio-prosthetic leaflets.

Supplementary Video 4. 3D-transesophageal echocardiography short-axis view (60°) demonstrating new onset pathological thickening of aortic bio-prosthetic leaflets.

Supplementary Video 5. 2D-transesophageal echocardiography X-plane view demonstrating oval-shaped isoechoic masses on both mitral leaflets.

Supplementary Video 6. 3D-transesophageal echocardiography surgical view demonstrating pathological thickening and masses on both mitral leaflets.

Supplementary Video 7. 2D-transesophageal echocardiography trans-gastric view (0°) demonstrating mitral valve involvement with significant regurgitation.