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Systemic embolization due to non-bacterial thrombotic endocarditis: An autopsy case report and mini review of the literature

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Abstract

Nonbacterial thrombotic endocarditis is a rare, non-infectious complication associated with hypercoagulable states, such as malignancies and autoimmune diseases. Due to the difficulty distinguishing marantic endocarditis from infective endocarditis, the diagnosis is often delayed or even a postmortem finding. We present the case of a 70-year-old Caucasian female with marantic endocarditis secondary to metastatic duodenal adenocarcinoma. The patient presented with a short history of memory deficits, personality disturbances, and left homonymous hemianopia. Diffusion-weighted magnetic resonance imaging showed multi-territorial bihemispheric cerebral infarctions. Transthoracic echocardiography revealed native mitral valve endocarditis, and serial blood cultures remained negative. Despite antibiotic therapy, the patient's condition continuously deteriorated, and she died within 3 weeks after her initial presentation. Postmortem examination showed a non-bacterial thrombotic endocarditis. Early clinical suspicion and prompt diagnosis are of decisive importance for the survival of the patients.

Keywords

Marantic endocarditis, nonbacterial thrombotic endocarditis, hypercoagulable states, malignancies, embolic complications, postmortem diagnosis

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Learning points

- NBTE, or marantic endocarditis, is strongly associated with cancer-related hypercoagulability, especially mucin-releasing adenocarcinomas.
- Marantic endocarditis often goes undiagnosed due to its subtle symptoms and similarity to infective endocarditis. Early clinical suspicion is critical.
- NBTE frequently leads to systemic embolization, with cerebral infarctions being one of the most common complications, often resulting in permanent neurological deficits.

Introduction

Marantic endocarditis, also known as nonbacterial thrombotic endocarditis (NBTE), verrucous endocarditis, or Libman-Sacks endocarditis, is a rare form of endocarditis, characterized by the presence of sterile vegetations composed of platelets and fibrin on the heart valves.[1] The vast majority of the cases occur in the context of cancer-associated hypercoagulability; however, the disease may also complicate other hypercoagulable medical entities, for example, chronic inflammatory conditions and myeloproliferative disorders.[2–5]

The fact that patients remain asymptomatic for an extended period partly explains why the disease often escapes timely diagnosis,[1] frequently representing an autopsy finding.[6] However, due to the friability of the thrombotic vegetations, patients with marantic endocarditis tend to have systemic embolization with cerebral infarctions, representing the most

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common embolic complications commonly associated with permanent neurological deficits.[7,8]

To raise awareness among physicians, we highlight a case involving a 70-year-old Caucasian female exhibiting embolic multi-territorial bihemispheric cerebral infarctions attributed to marantic endocarditis secondary to metastatic duodenal adenocarcinoma. Given the challenges regarding the diagnosis of NBTE, we have also conducted a brief literature review summarizing the approach to cancer-associated marantic endocarditis, its pathophysiology, current research evidence in the literature, and potential differential diagnoses and diagnostic dilemmas.

Case presentation

A 70-year-old Caucasian woman presented to our emergency department with a 1-day history of memory deficits and personality changes. Her medical history included duodenal adenocarcinoma stage IV with liver metastases, arterial hypertension, thyroiditis Hashimoto, and vitamin B-12 deficiency. Simultaneously with the diagnosis of duodenal carcinoma a year earlier, a right-sided segmental pulmonary embolism, as well as renal and splenic arterial infarctions caused by paraneoplastic coagulopathy, was diagnosed. During this time, the patient was under anticoagulation treatment with rivaroxaban due to a previously diagnosed deep vein thrombosis of the right leg. At the time of presentation, her medication included fluorouracil, folinic acid, irinotecan, and aflibercept as second-line palliative systemic treatment, apixaban, lisinopril, pantoprazole, and levothyroxine.

There were no further significant findings on physical examination except for left homonymous hemianopia. More specifically, vital signs were normal, and there were no further neurologic deficits, cardiac murmurs, or peripheral stigmata of endocarditis.

Blood testing revealed moderate thrombocytopenia (62G/l, n.v. 140–370), elevated C-reactive protein (68 mg/l, normal value (n.v.) < 0.5), slightly elevated transaminases, gamma-glutamyl transferase, and alkaline phosphatase, hyponatremia (133 mmol/l, n.v. 136–145), acute renal failure (creatinine 134 µmol/l, n.v. 45–84), and a remarkable elevation of cardiac troponin T (627 ng/l, n.v. <14). The initial electrocardiogram was normal. Computer tomography (CT) of the head demonstrated a solitary lesion parietal right with enhancement without evidence of bleeding, which did not explain the clinical picture. Diffusion-weighted MRI showed multi-territorial bihemispheric cerebral infarctions, including a large left-sided occipital ischemia matching the clinical picture. Transthoracic echocardiography (TTE) revealed a degeneratively altered mitral valve with thickening of both mitral valve leaflets and partial destruction of the posterior mitral valve leaflet with evidence of floating vegetation on the posterior mitral valve leaflet measuring approximately 11×6 mm and severe concomitant insufficiency. Moreover, echocardiographic findings were suggestive of moderate tricuspid regurgitation and significantly high pulmonary hypertension, most likely being postcapillary by severe mitral regurgitation. Left ventricular size and systolic function were normal. Blood cultures were taken before the initiation of antibiotic therapy. Subsequently, according to the guidelines, antimicrobial treatment with amoxicillin/clavulanic acid was started. Anticoagulation with apixaban was initially continued; however, on hospital Day 2, it was replaced by unfractionated heparin in prophylactic doses. On hospital Day 9, we restarted apixaban. Despite 10 days of incubation, the blood cultures showed no bacterial growth. Thus, additional tests regarding blood culture-negative endocarditis (*Bartonella* sp, *Brucella, Coxiella burnetii, Mycoplasma pneumoniae*, and *Aspergillus fumigatus*), including eubacterial polymerase chain reaction and search for *Tropheryma whipplei* were performed, which also proved negative. Despite antibiotic treatment, the patient's condition continuously deteriorated with the development of clinical symptoms and signs of severe heart failure. Moreover, inflammation blood markers significantly worsened. The CT abdomen showed progressive disease of the tumor manifestations and minimal pulmonary infiltrates. To objectify the heart failure and monitor endocarditis progression, a second TTE was performed, which revealed a severe progressive destructive mitral regurgitation. Given the palliative situation, a cardiosurgical revision could not be performed. For better control, heart failure therapy was extended. In this context, no improvement of the symptomatology could be achieved. A round table discussion with the patient and her family was held to discuss the precarious situation, and it was decided to switch to palliative comfort therapy. The patient died on hospital Day 19. An autopsy indicated NBTE (Figure 1). Microscopy demonstrated a fibrin-rich thrombus without bacterial growth or tumor tissue (Figure 2).

Discussion

NBTE, formerly marantic endocarditis, is a rare disease entity associated with hypercoagulability states, complicating the clinical course of cancer patients and being considered a paraneoplastic phenomenon.[9,10] Eighty percent of all cases of NBTE are linked to malignancies, whereas the rest 20% is observed in patients with hypercoagulability induced by other inflammatory conditions (e.g., systemic lupus erythematodes, antiphospholipid syndrome, and myeloproliferative diseases).[2–4] Common malignancies associated with NBTE include lung, pancreas, ovary, breast carcinomas, and malignant melanoma.[7,11] The disease was first described by Ziegler in 1888 in cadavers and refers to the formation of sterile, friable, thrombotic vegetations on normal or degenerated cardiac valves.[12]

Although the pathogenesis of hypercoagulable states in cancer patients is complex and not completely elucidated, it appears that multiple pathophysiologic mechanisms contribute to its development, including leukocytosis,

thrombocytosis, enhanced inflammatory responses, and elevated expression of phospholipids, and tissue factor. Moreover, factors associated with a patient's characteristics and treatment (e.g., immobility, operative procedures, hospitalization, radiation therapy, central venous catheters, and chemotherapy-associated endothelial toxicity) participate further in its pathophysiology.[11] Endothelial injury is postulated to play a cardinal role in the pathogenesis of marantic endocarditis, leading to platelet deposition and activation and migration of inflammatory mononuclear cells to generate thrombi consisting of platelets, fibrin, and immune complexes.[13] Accumulating data show that malignant cells express cytokines, such as tumor necrosis factor-a, interleukin (IL)-1, and IL-6, which, apart from their relation to inflammation, are procoagulant factors, causing sloughing of vascular endothelial cells as well as increased blood sludging.[14,15] Moreover, the above-mentioned cytokines trigger the monocytes, the endothelial, and the neoplastic cells to tissue factor, potentially activating the coagulation cascade.[15] Indeed, it is hypothesized that secondary endothelial damage—generated in the context of inflammatory reactions, local blood flow turbulence, and hypoxia—activates the formation and subsequent deposition of aggregates consisting of platelets and fibrin on cardiac valves.[7] Moreover, another hypothesis postulates that cancer-induced enhanced thrombomodulin levels could reduce thrombomodulin levels at endothelial niveau, where it acts as an anticoagulant under physiologic conditions. Moreover, malignancies can increase the levels of the von Willebrand factor and thus strengthen platelet endothelium interactions.[16]

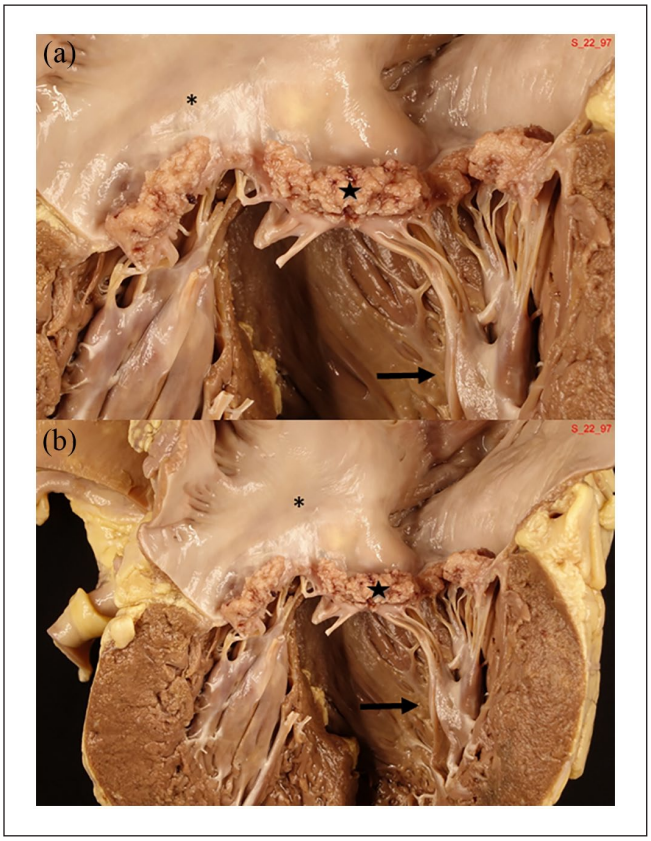

Figure 1. Autopsy findings of a patient with underlying malignancy and mitral valve nonbacterial thrombotic endocarditis. Note the left ventricle with prominent myocardial hypertrophy. Asterisk: left atrium, star: mitral valve vegetation, arrow: papillary muscle left ventricle.

Marantic endocarditis is considered a rare disease, with adult autopsy studies reporting a low incidence of 0.9% to 1.6% among all cases of endocarditis.[6] However, echocardiographic studies in patients with malignancies highlight that almost one-fifth of the patients who did not suffer cardiologic clinical manifestations revealed sterile valve vegetations,[17] indicating that marantic endocarditis may represent an underestimated clinical entity.

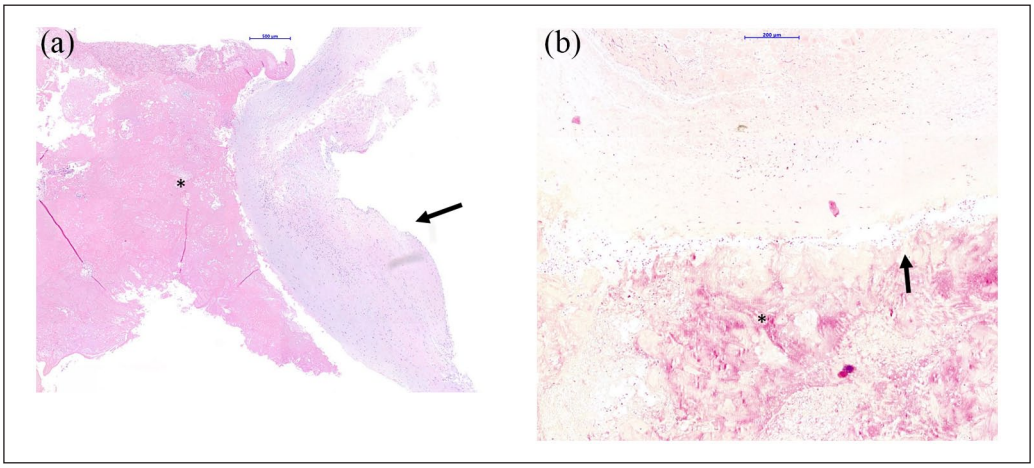

Figure 2. Mitral valve with fibrin-rich organizing thrombus. Hematoxylin and eosin (a) stained section demonstrated an organizing thrombus formed of fibrin and platelets (asterisk), valve seen on the right. There is a lack of significant inflammatory infiltrate and subsequent stains for infectious microorganisms (Gram-stains, b) were negative.

Although patients with NBTE are commonly asymptomatic, they can develop symptoms in the context of valve heart disease and heart failure, depending on the degree of destruction of the affected valve and the extension of the thrombotic aggregate.[13,18] Indeed, the study of Zmaili and co-workers (2021) highlights an association between numerous NBTE lesions and differing levels of valvular regurgitation. While valvular dysfunction was generally mild in the majority of cases, a subset of patients exhibited substantial valvular regurgitation, necessitating surgical valvular intervention. Other distinctive patterns observed in their patient population involved the widespread thickening of the mitral valve leaflets or aortic valve cusps, absent commissural fusion, or doming—a characteristic feature typically associated with rheumatic valve lesions.[19] However, due to the friability of these vegetations, explained through the in situ inflammation,[7] they tend to systemic embolization with detrimental consequences, for example, cerebrovascular events, which represent the most common embolic complication and are frequently associated with permanent neurological deficits.[8] Indeed, a recent retrospective study of 48 patients with marantic endocarditis demonstrated that almost 80% of the patients presented an embolic complication within 1 month after NBTE diagnosis.[20] The fact that cerebrovascular phenomena constitute the predominant observed embolic manifestation of NBTE can probably be explained by the extensive diagnostic investigations performed in the context of stroke.[21] NBTE is primarily a disease of the left-sided valves, whereas affection of tricuspid and pulmonary valves represent a rarity.[10] The affection of more than one valve is reported in 15% of the cases.[11]

Given that NBTE is usually an incidental clinical diagnosis or a postmortem finding, a high clinical suspicion is needed to enhance premortem diagnosis and, thus, prognosis.[22] Indeed, an intensive search for NTBE should be performed early in patients with embolic events and an underlying disease associated with hypercoagulability as malignancies and autoimmune diseases.[23] In the vast majority of cases, TTE represents the initial diagnostic approach. However, due to its restrictive ability to detect vegetation <3 mm, transesophageal echocardiography may also be necessary.[23,24] The reported vegetation size varies, ranging from 1 mm to up to 20 mm.[25] In patients presenting with stroke, the MRI pattern of the lesions may also be helpful. Strokes due to infective endocarditis are often single or present as focal lesions and territorial infarctions, occasionally with a single vascular distribution, whereas strokes of thrombotic origin are commonly multiple and widely distributed with simultaneous presentation of small and large ischemic lesions.[7] As stated above, marantic endocarditis is frequently a postmortem finding. The microscopic characteristics of the vegetation are phase-dependent and include a combination of platelets, fibrin, hematoxylin bodies, and granular tissue.[7] Moreover, in association with the chronicity of the lesions, signs of chronic injury, such as calcifications and fibrosis, may also be found.[13,21]

The most important differential diagnosis of non-bacterial thrombotic endocarditis is infective endocarditis. Separating the two clinical situations is significant as it determines therapeutic management.[5] Indeed, implantable central venous access port devices in patients with malignancies serve to administer chemotherapy and improve patients' quality of life. However, their use is accompanied by complications, for example, site and bloodstream infection,[26–28] making these patients susceptible to the development of infective endocarditis. In addition, due to an immunocompromised state and invasive procedures performed, patients with cancer are particularly predisposed to the development of infective endocarditis.[29] Nevertheless, the clinical suspicion of NBTE should be raised from the clinical history of hypercoagulable states and clinical findings, including the absence of Osler's nodes, Roth's spots, and cardiac murmur. Laboratory findings can further contribute to the correct diagnosis. Indeed, serial blood cultures, microbial serologies, and immunologic markers according to the Modified Duke's Criteria[30] can, if positive, lead to the diagnosis of endocarditis, whereas laboratory findings compatible with disseminated intravascular coagulation, especially elevated D-dimers orientate to the diagnosis of NBTE.[5] By definition, negative blood cultures and microbial serologies must exclude the primary differential diagnosis, that is, infective endocarditis.[31] Furthermore, the distribution and pattern of ischemic lesions in brain MRI in patients with stroke may also be helpful.[5] In addition, histological examination with the growth of bacteria in histologic sections and culture is also indicative of infective endocarditis. Finally, the clinical criterion of response to antibiotic treatment is also suggestive of infective endocarditis.[5]

Regarding the therapy of NBTE, treatment of the underlying pathology, particularly malignancy, and the associated hypercoagulable state represent the cornerstones of its therapeutic strategy.[32,33] Based on the pathophysiology of NBTE, heparin therapy has been used in the vast majority of cases. However, randomized controlled trial data do not exist.[34] Both unfractionated heparin and low molecular weight heparin (LMWH) have been highlighted to be effective in limiting the progression and the recurrence of thromboembolism in patients with malignancies.5 Moreover, based on the flexibility of the use of LMWH in ambulatory settings, in combination with recent data supporting treatment failure with vitamin-K antagonists (VKAs), makes the long-term use of LMWH a considerable therapeutic choice.[32,33,35] Indeed, a meta-analysis indicates that LMWH, compared to VKAs, significantly reduces the risk of recurrent events in venous thromboembolism (VTE) without a significant increase in major bleeding. However, despite LMWH's advantages, such as fewer drug interactions and reliable pharmacokinetics, its need for frequent injections and higher costs may impact patient adherence.[36,37] Encouragingly, recent evidence

supports the consideration of direct oral anticoagulants (DOACs) as a viable option for both treating and preventing secondary thrombotic complications in individuals with cancer.[38,39] Indeed, in a recent study in adults diagnosed with cancer and VTE, DOACs demonstrated noninferiority to LMWH in preventing recurrent VTE throughout a 6-month observation period supporting the utilization of DOACs as a viable option for preventing recurrent VTE in cancer patients.[39] However, the use of DOACs in treating cancer-associated NBTE should be further evaluated.

Even though specific recommendations regarding the role of surgery in patients with marantic endocarditis are lacking, surgical therapy may be considered in selected patients with recurrent embolic events, despite anticoagulation, big size of the vegetation, valvular dysfunction, and history of the prosthetic valve, taking, however, into account the underlying disease and the associated prognosis.[11,21,40,41]

Conclusions

In conclusion, marantic endocarditis is a rare form of endocarditis characterized by the formation of sterile, fibrin vegetations on heart valve leaflets. The vast majority of the cases occur in the context of cancer-associated hypercoagulability. However, the disease may also complicate other diseases associated with hypercoagulable states, for example, chronic inflammatory conditions and myeloproliferative disorders. Differentiating from classic infective endocarditis, particularly during the early stages, represents a diagnostic challenge. NBTE may result in severe complications, including valvular dysfunction, heart failure, and embolic events. Diagnosis is based on the clinical history of malignancy and clinical, echocardiographic, laboratory, histological, and radiologic findings. Treatment of the underlying disease, systemic anticoagulation, and surgical therapy in selected cases are the cornerstones of the therapeutic management of the disease.

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Author's contributions

The study was designed by D.E. and M.Z. D.E., M.F., and P.S. were involved in the diagnosis and management. M.F. edited the pictures. C.T., P.S., and M.Z. searched the articles and drafted the manuscript. M.Z. revised the manuscript. All authors read and approved the final manuscript.

Data Availability

Data sharing does not apply to this article as no data sets were generated or analyzed during the present study.

Declaration of conflicting interests

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Ethics approval

The project did not meet the definition of human subject research.

Informed consent

Written informed consent was obtained from the patient's legally authorized representative for publication of the details of this medical case and any accompanying images.

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