

Nonbacterial thrombotic endocarditis presenting as intracerebral hemorrhage

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Summary Nonbacterial thrombotic endocarditis is a rare cause of valvular heart disease, most commonly associated with advanced malignancy. The morbidity of this kind of endocarditis lies in its tendency to embolize, while the valve function is usually preserved. The central nervous system is the most common site of embolization, leading to ischemic stroke. We report a case of nonbacterial thrombotic endocarditis complicated by intracerebral hemorrhage as the first manifestation of adenocarcinoma of the lung. The endocarditis led to severe aortic regurgitation. In view of the advanced stage of lung cancer, the patient refused further therapy. He passed away 3 weeks after first diagnosis of the adenocarcinoma.

Keywords Endocarditis · Marantic · Stroke · Lung neoplasms · Aortic regurgitation

Case report

Nonbacterial thrombotic endocarditis (NBTE) is a rare condition affecting patients with advanced cancer or other entities with hypercoagulable states.

We present the case of a 66-year-old patient presenting at the emergency department for nausea and vomiting of sudden onset accompanied by a headache and blurred vision. The patient was on acetylsalicylic acid for coronary heart disease. Physical examination revealed hemianopsia to the left. A diastolic murmur at the left sternal border was present. A computed tomography (CT) scan of the head showed an intracere-

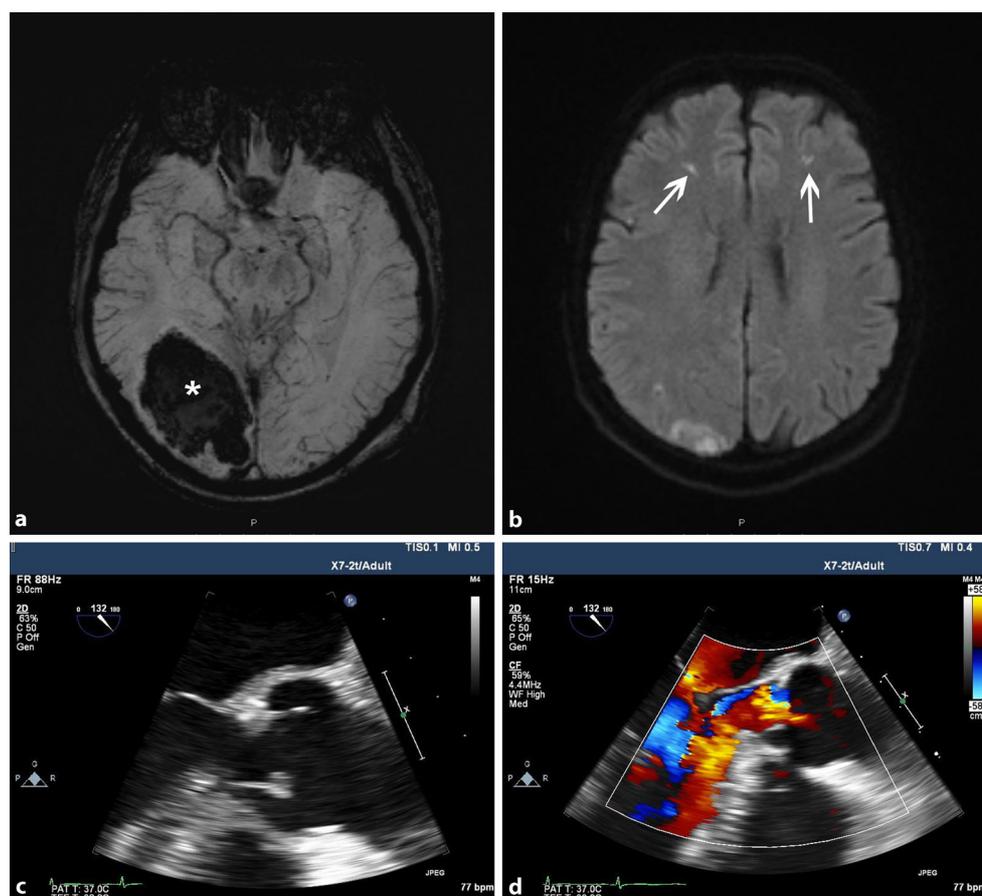
bral parieto-occipital hemorrhage (estimated 25 ml). Because of the stable clinical status no surgical intervention was necessary.

Laboratory tests were unremarkable with the exception of a consumption coagulopathy including reduced levels of fibrinogen, clotting factors, and platelets and an increased D-dimer level and INR. Magnetic resonance imaging (MRI) of the brain demonstrated in addition to the intracerebral hemorrhage multiple bilateral ischemic brain lesions (Fig. 1a, b). Transesophageal echocardiography (TOE) showed a mobile structure of 6 × 6 mm attached to the right coronary cusp of the aortic valve accompanied by moderate aortic regurgitation (Fig. 1c, d). Antibiotic therapy with high-dose amoxicillin–clavulanate was initiated for presumptive bacterial endocarditis despite a low white blood cell count and C-reactive protein level. The slight consumption coagulopathy was interpreted in the context of the intracranial hemorrhage.

Four days later, the patients developed fever and a neurological deterioration. Repeat MRI of the brain showed new subacute bilateral ischemic infarctions and a new hemorrhage of 2.5 cm in diameter in the right cuneus. At this point, TOE detected severe aortic regurgitation with a new echo-dense structure on the noncoronary cusp. As blood cultures remained sterile, the patient's condition was reassessed. Blood tests were negative for antinuclear, antineutrophil cytoplasmic, anticardiolipin, antimitochondrial, and antismooth muscle antibodies. A thoracic and abdominal CT scan showed enlarged mediastinal lymph nodes and an unclear consolidation in the left lower pulmonary lobe. Cytological samples obtained from bronchoscopic lavage showed cells compatible with adenocarcinoma. We interpreted the aortic valve lesions as NBTE caused by non-small cell lung cancer. The positron emission tomography (PET CT) scan

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Fig. 1 Susceptibility-weighted imaging (SWI) of the brain shows the susceptibility artifacts caused by the hemorrhage in the right occipital lobe (*asterisk, a*). Diffusion-weighted-imaging (DWI) reveals multiple areas with restricted diffusion due to recurrent embolization (*arrows, b*). Long-axis views from transesophageal echocardiography showing the vegetation on the right coronary cusp (*c*) and relevant aortic regurgitation (*d*)



demonstrated left hilar lymph node metastases as well as osteolytic foci in the left-sided acetabulum leading to the diagnosis of stage IV lung cancer. The patient refused further therapy and his condition deteriorated rapidly including new paralysis of the right arm and finally the loss of consciousness. The patient passed away 3 weeks after had been diagnosed with adenocarcinoma.

Discussion

This report demonstrates an uncommon presentation of adenocarcinoma of the lung. NBTE (marantic endocarditis) is a rare condition occurring in the setting of advanced malignancy and hypercoagulable states [1]. Before the era of echocardiography, NBTE was diagnosed following autopsy. In a large autopsy study, NBTE was found in 1.6 % of the adult autopsy population [2]. In 51 of 65 cases, malignancies were associated with NBTE of which adenocarcinoma represented the most frequent type. Adenocarcinoma of the lung, the pancreas, and the ovaries represent the most common entities and at the time of diagnosis of NBTE, most of the malignancies have metastasized [3]. In a recent study, in 4.3 % of a total of 1,282 ischemic stroke patients with no history of cancer, cancer was diagnosed after stroke, lung cancer being the

most common tumor type [4]. The exact prevalence of NBTE in cancer is unknown. In a prospective ultrasound study, valvular vegetations consistent with NBTE were identified in 38 of 200 cancer patients [5]. The morbidity of the disease lies in its tendency for embolization, the frequency is estimated as being up to 50–76 % [6]. Sites of embolization are the central nervous system (CNS), but the spleen, kidneys, and the coronary arteries are also frequently affected [7].

The valvular lesions of NBTE are sterile, consisting of degenerating platelets and fibrin strands. As there is no underlying inflammation, they are very friable, leading to a high prevalence of embolization [1]. Most frequently, the aortic and mitral valve are affected, but the right-sided and prosthetic heart valves are also not spared [3, 6, 8].

The pathogenesis of NBTE is incompletely understood. However, mechanisms are considered to be similar to the ones underlying cancer hypercoagulability [9]. Interleukins, tumor necrosis factor, and tissue factor are released in response to the interaction between macrophages and monocytes with the malignant cells. Along with thrombogenesis, these factors can cause endothelial damage, making the heart valves susceptible to vegetation formation.

With the development of echocardiography, antemortem diagnosis of NBTE has gained importance.

In several studies, TOE outperformed transthoracic echocardiography in the ability to detect NBTE in stroke patients [10]. The vegetations do not usually destroy the valvular leaflets and the frequency of relevant valvular regurgitation is not higher compared with controls [5, 10]. Since the routine use of echocardiography to detect cardiac sources of stroke, the diagnosis of NBTE frequently precedes the diagnosis of the cancer.

Treatment of NBTE is the correction of the underlying cause. Unfortunately, there is no curative approach in the majority of cases since causative tumors are usually detected at an advanced stage. Nevertheless, valve malfunction may be attenuated by chemotherapy as suggested for aortic regurgitation caused by NBTE [11]. Anticoagulation is important, and heparins seem to be effective in preventing further thromboembolism [12, 13]. Cardiac surgery is rarely necessary and should be restricted to patients in congestive heart failure due to valvular dysfunction or to patients with recurrent embolism despite adequate anticoagulation.

Our case describes the rare constellation that neurological symptoms due to intracerebral hemorrhage most likely secondary to asymptomatic embolism of cardiac origin precede the diagnosis of an adenocarcinoma. To the best of our knowledge, no case of an intracerebral hemorrhage as initial presentation of an adenocarcinoma with NBTE has been published to date. Fujishima et al. described a case of a secondary hemorrhage after ischemic stroke with diagnosis of an adenocarcinoma of the lung post mortem [14]. A second rarity of our case is the development of relevant valve regurgitation, caused by a deficient leaflet coadaptation due to multiple vegetations. Early diagnosis of NBTE associated with cancer is crucial since anticoagulation can help prevent recurrent, often devastating, embolism.

Conflict of interest O. Wigger, S. Windecker, and S. Bloechlinger declare that they have no competing interests.

References

1. El-Shami K, Griffiths E, Streiff M. Nonbacterial thrombotic endocarditis in cancer patients: pathogenesis, diagnosis, and treatment. *Oncologist*. 2007;12(5):518–23.
2. Deppisch LM, Fayemi AO. Non-bacterial thrombotic endocarditis: clinicopathologic correlations. *Am Heart J*. 1976;92(6):723–9.
3. Biller J, Challa VR, Toole JF, Howard VJ. Nonbacterial thrombotic endocarditis. a neurologic perspective of clinicopathologic correlations of 99 patients. *Arch Neurol*. 1982;39(2):95–8.
4. Selvik HA, Thomassen L, Bjerkreim AT, Naess H. Cancer-associated stroke: the Bergen NORSTROKE study. *Cerebrovasc Dis Extra*. 2015;5(3):107–13.
5. Edoute Y, Haim N, Rinkevich D, Brenner B, Reisner SA. Cardiac valvular vegetations in cancer patients: a prospective echocardiographic study of 200 patients. *Am J Med*. 1997;102(3):252–8.
6. Sack GH, Levin J, Bell WR. Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: clinical, pathophysiologic, and therapeutic features. *Medicine (Baltimore)*. 1977;56(1):1–37.
7. Tiong IS, Williams MJ, Perez DJ. Nonbacterial thrombotic endocarditis with ST-elevation myocardial infarction treated with percutaneous coronary aspiration thrombectomy. *Heart Lung Circ*. 2013;22(5):386–9.
8. Yasutake H, Sugano Y, Ikeda Y, Ohara T, Hasegawa T, Kanzaki H, et al. First case report of the antemortem diagnosis of nonbacterial thrombotic endocarditis of a mechanical prosthetic valve. *Intern Med*. 2016;55(3):255–7.
9. Lee AY. Cancer and thromboembolic disease: pathogenic mechanisms. *Cancer Treat Rev*. 2002;28(3):137–40.
10. Dutta T, Karas MG, Segal AZ, Kizer JR. Yield of transesophageal echocardiography for nonbacterial thrombotic endocarditis and other cardiac sources of embolism in cancer patients with cerebral ischemia. *Am J Cardiol*. 2006;97(6):894–8.
11. Colchero T, Lopez-Sanchez FA, Dominguez-Perez L, Rodriguez-Padial L. Nonbacterial thrombotic endocarditis and severe aortic valve regurgitation. Resolution after chemotherapy. *Med Clin (Barc)*. 2012;138(6):271–2.
12. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med*. 2003;349(2):146–53.
13. Salem DN, Stein PD, Al-Ahmad A, Bussey HI, Horstkotte D, Miller N, et al. Antithrombotic therapy in valvular heart disease – native and prosthetic: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest*. 2004;126(457):82.
14. Fujishima S, Okada Y, Irie K, Kitazono T, Saku Y, Utsunomiya H, et al. Multiple brain infarction and hemorrhage by nonbacterial thrombotic endocarditis in occult lung cancer – a case report. *Angiology*. 1994;45(2):161–6.