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Nonbacterial Thrombotic Endocarditis in Cancer Patients: Pathogenesis, Diagnosis, and Treatment

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Key Words. Nonbacterial thrombotic endocarditis • Cancer • Anticoagulation

LEARNING OBJECTIVES

1. Enumerate procoagulant factors present in malignancy and the risk for thromboembolic events.
2. Describe the morbidity associated with nonbacterial thrombotic endocarditis.
3. List the recommended evaluations and treatments for nonbacterial thrombotic endocarditis.

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ABSTRACT

Thrombophilia is a well-described consequence of cancer and its treatment. The pathogenesis of this phenomenon is complex and multifactorial. Nonbacterial thrombotic endocarditis (NBTE) is a serious and potentially underdiagnosed manifestation of this prothrombotic state that can cause substantial morbidity in affected patients, most notably recurrent or multiple ischemic cerebrovascular strokes. Diagnosis of NBTE requires a high degree of clinical suspicion as well as the judicious use of two-dimensional echocardiography to document the presence of valvular thrombi. In the absence of contraindications to therapy, treatment consists of systemic anticoagulation, which may ameliorate symptoms and prevent further thromboembolic episodes, as well as control of the underlying malignancy whenever possible. The Oncologist 2007;12:518–523

Disclosure of potential conflicts of interest is found at the end of this article.

INTRODUCTION

Since the seminal observation by Armand Trousseau in 1865 [1], numerous studies have confirmed the common association between cancer and thromboembolism. Contemporary estimates indicate that 15% of cancer patients suffer a thromboembolic event during their clinical course and as many as 50% of cancer patients have evidence of venous thromboembolism on postmortem examination [2, 3]. The etiology of the hypercoagulable state in cancer is multifactorial (Table 1). Contributing factors include procoagulant alterations associated with the malignancy (tissue factor and cancer procoagulant expression by tumor cells, vascular compression by tumor masses) and the host’s inflammatory response (monocyte tissue factor expression, increased levels of factor VIII, fibrinogen, and von Willebrand factor) as well as adverse procoagulant effects associated with can-
cancer treatment (surgery, chemotherapy, radiotherapy). Although venous thromboembolism is the most common manifestation, cancer-associated thrombophilia may also present as a migratory superficial thrombophlebitis (the original syndrome described by Trousseau), arterial thrombosis, disseminated intravascular coagulation (DIC), a thrombotic microangiopathy or nonbacterial thrombotic endocarditis (marantic endocarditis). The purpose of this article is to review the pathogenesis, incidence, clinical manifestations, and management of nonbacterial thrombotic endocarditis (marantic endocarditis).

It has been estimated that one in seven hospitalized cancer patients who succumb to their disease do so from pulmonary embolism [4]. Of these patients, 60% have localized cancer or limited metastatic disease, which would have allowed for longer survival in the absence of a fatal embolic event. According to the Medicare Provider Analysis and Review Record, a database that records the primary discharge diagnosis and an additional four discharge diagnoses in the U.S., the rate of initial or recurrent thromboembolism in patients with cancer greatly exceeds that recorded in those without malignancy, and occurs with similar frequencies among cancers of virtually all body systems [5]. The true rate of thromboembolic disease in cancer patients is impossible to determine, largely because most thromboses are subclinical and diagnosed only at the time of autopsy.

The majority of thrombotic episodes occur spontaneously, that is, in the absence of triggering factors that commonly account for thromboembolic complications in patients without cancer [6]. This is confirmed by the high frequency of patients with known malignancy referred to clinicians for the development of venous thromboembolism (VTE) [7]. The most common situations that make cancer patients at a higher risk for VTE include immobilization, surgery, chemotherapy with or without adjuvant hormone therapy, and the presence of indwelling of central venous catheters [8].

The strong association between cancer and thrombophilia is further emphasized by the high rate of cancer development in patients with venous thrombosis. Those who present with an idiopathic thrombosis are consistently found to have a risk of cancer four to five times higher than those who develop secondary thromboses [8]. These data have recently found important confirmation in three large, retrospective, population-based studies [9–11]. It is interesting to note that although the risk for developing cancer is particularly high in the first 6 months following the diagnosis of VTE, the relative risk for a cancer diagnosis remains elevated for up to 10 years following the sentinel thrombotic episode, suggesting that either a malignant disorder can induce hypercoagulability many years prior to its overt clinical presentation or that cancer and thrombosis share common risk factors.

### Definition and Pathogenesis

Originally described by Ziegler in 1888, the lesions of NBTE were considered to be fibrin thrombi deposited on normal or superficially degenerated cardiac valves [12]. In 1936, Gross and Friedberg introduced the term nonbacterial thrombotic endocarditis [13]. In 1954, Angrist and Marquis first called attention to the frequent association of systemic emboli with this disease [14]. Numerous reports have identified the relationship between NBTE and a variety of different inflammatory states, including chronic diseases like malignancy and autoimmune disease [15–17]. It has also been demonstrated to occur in patients with acute fulminant disease states, like septicemia or burns [18, 19].

NBTE (formerly known as marantic endocarditis) is characterized by the deposition of thrombi on previously undamaged heart valves in the absence of a bloodstream bacterial infection and by the increased frequency of arte-
The pathogenesis of NBTE is incompletely understood. Nevertheless, several clues to the etiology of NBTE can be gleaned from the results of previous pathological studies in humans and animal models. The lesions of NBTE are classically found in areas of high flow on valvular leaflets; therefore, blood flow likely contributes to the location if not the initiation of these valvular lesions. Elevated levels of circulating cytokines associated with cancers, such as tumor necrosis factor or interleukin-1, may also result in local tissue damage that instigates vegetation formation. Perhaps the most important factor in the formation of these valvular vegetations is the hypercoagulable state associated with malignancies. An animal model of NBTE found that increasing levels of circulating tissue factor and increased expression of tissue factor mRNA by valvular monocytes were closely associated with vegetation formation [24]. These findings suggest that synergy between local physical and cytokine-mediated valvular damage and excessive platelet and coagulation factor activity likely contribute to the pathogenesis of NBTE.

A recent investigation has indeed provided direct genetic evidence for the link between oncogene activation and hemostasis [25].

**INcidence and Clinical Features**

While NBTE has been reported in every age group, it most commonly affects patients between the fourth and eighth decades of life. No sex predilection has been reported. The incidence of systemic emboli varies widely (14%–91%, with an average of 42%) [22].

The incidence of NBTE is largely unknown. The largest autopsy series published more than 30 years ago included 65 cases of NBTE discovered at autopsy during a 10-year period, an incidence of 1.6% in the adult autopsy population. In 51 cases, one or more malignant neoplasms were associated with NBTE; adenocarcinoma was the most frequent histologic type of related neoplasm. Lung, pancreas, and gastric cancer, and adenocarcinoma of unknown primary site are the most common cancers associated with NBTE. Coagulation abnormalities suggestive of DIC were present in 18.5% of the cases. Valvular and peripheral intravascular thromboses were sequelae of the abnormal coagulation of DIC. Arterial thrombosis with infarction occurred in many peripheral organs. Splenic and renal infarctions were most frequent, but cerebral and cardiac consequences were the most likely to reveal the diagnosis, as well as result in significant morbidity and mortality [18]. A more recent autopsy series from the early 1990s looked at the incidence of NBTE. There were 10 cases of NBTE among 1,640 adult patients autopsied over a 24-year period. Eight of those 10 patients had an underlying malignancy. NBTE was more common in cancer patients than in patients without malignancy (1.25% versus 0.2%; \( p < .05 \)). Patients with adenocarcinoma were at a higher risk than patients with other malignant processes (2.70% versus 0.47%; \( p < .05 \)), especially in cases of pancreatic cancer in comparison with other adenocarcinomas (10.34% versus 1.55%; \( p < .05 \)). Systemic embolization was the main cause of morbidity [26].

**Clinical Manifestation and Diagnosis**

The major clinical manifestations of NBTE result from systemic emboli rather than valvular dysfunction. These vegetations are easily dislodged because there is little inflammatory reaction at the site of attachment. Common sites of embolization include the spleen, kidney, and extremities, but the most significant morbidity arises from emboli to the central nervous system and coronary arteries [27]. Ischemic strokes resulting in focal or diffuse neurologic abnormalities may be seen.
There are no pathognomonic symptoms or signs that suggest the diagnosis of NBTE. Cardiac murmurs are infrequently noted [28, 29]. When present, these murmurs are nonspecific soft systolic murmurs located at the left lower sternal border. The presence of a new murmur or a change in a previously noted murmur is probably more helpful, but this finding is even more infrequent. Nonetheless, a murmur noted in the setting of known malignancy or with laboratory evidence of DIC should make the clinician strongly consider the diagnosis of NBTE.

Systemic emboli occur in nearly 50% of patients with NBTE and usually result in the presenting symptom, with the cerebral, coronary, renal, and mesenteric circulations being the most frequently affected [30–32]. The most common (and certainly most devastating) clinical presentation of NBTE is a sudden neurological deficit (either localized or diffuse). Patients with advanced cancer who develop a neurological deficit should be evaluated for the presence of cerebral metastases with either magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CT) of the brain. MRI has a higher sensitivity and specificity in diagnosing embolic strokes than CT, and should therefore be employed preferentially should the suspicion of stroke arise. The diagnosis of NBTE should be strongly suspected in any stroke patient with a known or suspected malignancy. Diffusion-weighted MRI (DWI) patterns can help to differentiate between cardioembolic strokes resulting from infective endocarditis and NBTE. In a study by Singhal et al. [33], in which DWI was used to compare patterns of acute and recurrent stroke in infective endocarditis and NBTE including lesion size, number, and location, four stroke patterns were identified—pattern 1, a single lesion, suggesting a solitary embolus; pattern 2, multiple closely spaced lesions in a single arterial territory, “territorial infarction;” pattern 3, multiple punctate disseminated lesions; and pattern 4, multiple small and medium or large disseminated lesions. All nine patients with NBTE exhibited pattern 4, whereas the 27 patients with infective endocarditis exhibited patterns 1, 2, 3, and 4 \( (p = .013) \). The authors concluded that patients with NBTE uniformly have multiple, widely distributed, small and large strokes, whereas those with infective endocarditis exhibit a panoply of stroke patterns. The size of the valvular vegetations did not correlate with the size, number, or pattern of strokes. NBTE probably results in this pattern of involvement because vegetations in NBTE have little cellular organization and therefore have a higher potential for fragmentation and embolization [34]. NBTE can result in peripheral emboli affecting any organ; thus hematuria may signal renal artery emboli with resultant renal infarcts, left upper quadrant pain may betray a splenic infarct, and peripheral emboli to extremities may result in a cold, cyanotic, or pulseless limb. Despite the proclivity of the aortic and mitral valves to be affected by vegetations in NBTE, the pulmonary circulation is also frequently involved in the embolic process. In one study, pulmonary emboli were noted in 50% or more of patients with NBTE, although it is difficult to ascribe all observed pulmonary emboli to underlying NBTE in patients with advanced malignancy and systemic thrombophilia [18].

NBTE is difficult to diagnose if the underlying disease is accompanied by fever, a not uncommon occurrence in patients with advanced or occult cancer, or in those with a concurrent febrile illness secondary to a separate infectious or noninfectious process. Moreover, the small friable vegetations frequently embolize, leaving only small remnants to be identified on the valve. As noted above, cardiac murmurs, a hallmark of bacterial endocarditis, are frequently absent, thus adding to the difficulty in diagnosing this condition. Therefore, if a diagnosis of endocarditis is made, but the cultures and serology are negative, and there is no response to antibiotic treatment, then NBTE should be strongly considered.

The first step in diagnosing NBTE in a patient with cancer is to be cognizant of the condition. A high degree of suspicion is required. Patients with newly acquired murmurs should be evaluated with two-dimensional echocardiography to elucidate the presence of valvular vegetations. Despite the invasive nature of transesophageal echocardiography (TEE), TEE is thought to be more sensitive in detecting valvular vegetations than transthoracic echocardiography (TTE) and is thus the preferred diagnostic test for this condition. The potential value of TEE in diagnosing NBTE was illustrated in a series of 51 consecutive cancer patients with cerebrovascular events who were referred for TEE [35]. Almost one half of the patients had a definite cardiac source of embolism. Nonbacterial vegetations were detected in nine patients (18%); TTE was performed in seven of these patients and was negative in four. Sources of embolism other than NBTE included left atrial thrombus, complex aortic atheroma, and a patent foramen ovale or atrial septal defect in the presence of venous thromboembolism. Needless to say, selection of patients for TEE is important. Such patients would principally include those without end-stage malignancies, with a performance status of three or more on the Eastern Cooperative Oncology Group scale, and a cerebrovascular event that has not resulted in profound incapacitation, provided that any significant esophageal pathology and bleeding diathesis are excluded or reversed. Echocardiographic studies prospectively evaluating cancer patients for NBTE have yet to be performed [36].

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MANAGEMENT
Treatment of patients with NBTE is challenging. In general, treatment of NBTE consists of therapy directed at the underlying malignancy and systemic anticoagulation. Unfortunately, in many cases of NBTE associated with cancer, the disease is metastatic and thus, curative options are limited. The most effective anticoagulant appears to be unfractionated heparin, which has been shown to be effective in reducing the incidence of recurrent episodes of thromboembolism [22, 37–39]. When delivered in therapeutic doses, both i.v. and s.c. heparin therapy has been effective. Although experience is more limited, low molecular weight heparin has also been useful. In the authors’ anecdotal experience with patients suffering from Trousseau’s syndrome, occasional patients who have failed low molecular weight heparin therapy have been successfully managed with unfractionated heparin. In contrast to heparins, vitamin K antagonists such as warfarin should not be used in patients with malignancy-associated NBTE, as recurrent thromboembolic events while on warfarin are common [22, 38, 39]. Although the exact reason for warfarin’s inability to control the coagulopathy associated with NBTE is not precisely known, the presence of non–vitamin K dependent agents that induce the thrombotic coagulopathy has been suggested by some investigators [40]. It remains unknown whether newer anticoagulants such as the synthetic indirect factor Xa inhibitor, fondaparinux, or the direct thrombin inhibitors will be effective. Anticoagulation must be continued indefinitely in patients suffering from NBTE, because recurrent thromboembolism has occurred in patients following discontinuation of heparin therapy. Although most patients do not require surgery to address NBTE valvular lesions, cardiac surgery is a reasonable intervention in selected circumstances where the risk–benefit balance is favorable.

CONCLUSIONS
Cancer is associated with a significant hypercoagulable state that increases the risk of thromboembolism fivefold. NBTE is an uncommon but devastating manifestation of malignancy-associated thrombophilia. NBTE should be considered in any cancer patient suffering an episode of arterial thromboembolism. NBTE vegetations are platelet- and fibrin-rich thrombi that most commonly affect the aortic and mitral valves. TEE and DWI are useful imaging modalities in the diagnosis of NBTE. Definitive therapy includes antitumor therapy directed at the underlying malignancy and indefinite anticoagulation with unfractionated or low molecular weight heparin. Vitamin K antagonists such as warfarin are ineffective and should not be employed in management. The efficacy of newer alternative anticoagulants such as fondaparinux and direct thrombin inhibitors remains unknown. The long-term outcome for most patients with malignancy-associated NBTE is poor, because it is typically associated with disseminated and incurable malignancies. Nevertheless, antitumor and anticoagulant therapies often have significant palliative benefit and so should be used for most patients with NBTE.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST
M.S. has acted as a consultant for Sanofi-Aventis and GlaxoSmithKline.

REFERENCES