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Association between nonbacterial thrombotic endocarditis and hypoxigenic pulmonary diseases

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Abstract Observation of patients with nonbacterial thrombotic endocarditis (NBTE) in the setting of hypoxia from various lung diseases raised the question of a possible pathogenetic relationship between hypoxia and the development of NBTE. We reviewed 50 autopsied patients with NBTE and compared them with 50 age/race/gender-matched control patients without NBTE. We noted the lung weight and graded the histopathological severity of lung involvement by disease, clinical respiratory compromise, and the extent of any cancer present. Patients with NBTE had heavier lungs ($P<0.01$) and histologically and clinically more severe pulmonary disease (both $P<0.005$). There was no statistically significant difference in the extent of metastatic cancer between the NBTE patients and the controls ($P>0.5$). When patients with cancer were excluded from the group of NBTE cases, there was still a statistically significant preponderance in the mean lung injury and clinical compromise scores of the NBTE patients (both $P<0.05$), but the difference in lung weight was no longer statistically significant ($P>0.05$). The study suggests that, in some patients, hypoxia may lead to NBTE, possibly through altered coagulation states.

Keywords Nonbacterial thrombotic endocarditis · Hypoxia · Lung disease · Malignant neoplasms · Disseminated intravascular coagulation

Introduction

Nonbacterial thrombotic endocarditis (NBTE), or marantic endocarditis, is a disease characterized by the presence of vegetations on cardiac valves, which consist of fibrin and platelet deposits and are devoid of bacteria or inflammation. First referred to as "thrombo-endocarditis" in 1888 by Zeigler [14], it was originally thought to be an agonal phenomenon in the debilitated, terminal cancer patient (thus the term "marantic") [16, 24, 27]. Over the years, however, NBTE has become increasingly recognized as a condition accompanying numerous diseases and a potentially life-threatening source of thromboemboli to the brain, kidney, heart, and other important organs [24, 27, 37].

NBTE has been found in association with malignant tumors, especially adenocarcinomas [1, 9, 19, 24], bone marrow transplantation [17, 22, 29], acquired immunodeficiency syndrome [4, 15, 18, 31], snake bites [35], thrombotic thrombocytopenic purpura [36], certain autoimmune disorders [10, 28], major trauma [33], and septicemia and burns [24]. In many cases, disseminated intravascular coagulation (DIC) was present in patients with NBTE [1, 16, 19, 24].

Damage to the endothelium of the cardiac valves may play an important role in the pathogenesis of NBTE. For example, NBTE is associated with indwelling cardiac catheters [11]. In addition, structural abnormalities of the valves may be involved, such as in cases of mitral prolapse [6, 12]. There is a report of NBTE in three members of the same family, in which a possibility of an inherited valvular defect was suggested [23]. Turbulent flow, to which edges of the valves are exposed, may cause hemodynamic trauma and lead to local fibrin deposition [24]. Other causes of NBTE may also exist.

We have observed several autopsy cases in which NBTE coexisted with severe pulmonary disease in patients without other obvious predisposing factors, such as a malignancy. We decided to investigate a possible correlation between hypoxigenic lung diseases and NBTE using the autopsy database of The Johns Hopkins Hospital.

Methods

Between 1979 and 1998, 8042 autopsies were performed at our institution. We selected 50 cases from among the total of 74 cases of NBTE encountered during that time (25 consecutive cases, each

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from the beginning and the end of the period). For each of the cases, the next age/race/gender-matched NBTE-free patient from the same autopsy pool was identified to serve as a control. We reviewed the detailed patient histories recorded in the autopsy files, the gross organ description protocols, and all available microscopic sections of the lungs. As a rule, one section was generated from each lobe of each lung at the time of autopsy, with additional sections of any discovered lesions. Since a majority of cases had significant lung pathology, most of them had more than the basic five sections.

From the gross autopsy protocols, we recorded the combined weight of the lungs in each case. We estimated the degree of impairment of the gas exchange function of the lungs based on our study of the histologic sections. Each case was graded on a semiquantitative scale, the final score being the result of a consensus between both observers (A.T. and G.H.). The scores were assigned as follows: 0, no pathologic diagnosis; 1, mild or moderate disease involving one or two sections; 2, moderate disease involving three or four sections or severe disease in one section; and 3, moderate disease in more than four sections or severe disease in two or more sections.

The degree of clinical impairment of the respiratory function was graded on a semiquantitative scale as follows: 0, no impairment; 1, mild respiratory problems requiring no treatment or an occasional administration of oxygen; 2, moderate dyspnea requiring frequent or constant oxygen supplementation by mask or nasal cannula; and 3, severe impairment requiring intubation and artificial ventilation. In addition, the degree of spread of any malignancy anywhere within the body was graded on a semiquantitative scale as follows: 0, no evidence of malignancy; 1, tumor involving one organ; 2, regional spread of the tumor with or without lymph node involvement; and 3, widely metastatic tumor. The differences between cases and controls were assessed using two-tailed, nonpaired analysis using the Student's *t*-test.

Results

The incidence of NBTE in our series, spanning 19 years, was 0.92%, which is similar to previously reported data [24]. The mean age of the subjects was 52.5 years (10–81 years). Of the cases, 56% were white, 42% were black, and 2% were Asian. In addition, 56% of the cases were males.

Malignancies among the NBTE subjects included seven cases of acute myelogenous leukemia (14%), five cases of non-Hodgkin's lymphoma (10%), four cases of squamous cell carcinoma (8%), three pancreatic carcinomas (6%), two cases of acute lymphoblastic leukemia (4%), and one case (2%) each of gastric and breast carcinomas, rhabdomyosarcoma, Hodgkin's lymphoma, and undifferentiated carcinoma.

Table 1 summarizes the number of the NBTE lesions in each heart, the sides of the heart, and the specific valves affected. The left side of the heart alone was most frequently involved (58%). The majority of the hearts had NBTE lesions on one valve only (60%). The mitral valve was most often affected (50%). The cusps of three of the aortic valves and of one mitral valve, in addition to having NBTE, were also found to be thickened. There was no evidence of rheumatic valvular disease, however.

Pulmonary diseases among the NBTE patients are summarized in Table 2. In all, only three patients with NBTE (6%) had no histologic evidence of lung disease. The patients with NBTE had heavier lungs (mean 1758.5 g vs 1409.6 g, $P<0.01$). The pathological severity of lung disease was significantly higher among the NBTE cases (mean score 2.32 vs 1.34, $P<0.0001$). Likewise, the degree of clinical respiratory compromise was higher among those with NBTE (2.24 vs 1.58, $P<0.005$). Of the cases and controls, 52% and 40%, respectively, had cancer, but there was no statistically significant difference in the degree of spread of any malignancy between the two groups (mean score 1.12 vs 1.02, $P>0.5$).

When all 26 patients with NBTE and cancer, together with their matched controls, were excluded from the investigation, the resulting mean lung disease score was still higher among the NBTE patients (2.25 vs 1.29, $P<0.05$). The degree of clinical respiratory impairment was also higher in the NBTE group (2.2 vs 1.5, $P<0.05$). However, the difference in lung weight was no longer statistically significant (1540.6 g vs 1227.9 g, $P>0.05$).

Table 1 Location of nonbacterial thrombotic endocarditis (NBTE) lesions

Side of the heart	Incidence (%)
Right	18
Left	58
Right and left	24
Number of valves	**Incidence (%)**
One	60
Two	28
Three	10
Four	2
Valves affected	**Incidence (%)[a]**
Mitral	50
Aortic	42
Tricuspid	42
Pulmonic	20

[a] The sum exceeds 100%, because several lesions can be present in the same case

Table 2 Incidence of pulmonary lesions in nonbacterial thrombotic endocarditis (NBTE) patients

Pulmonary lesion	Incidence (%)[a]
Organizing diffuse alveolar damage	26
Emphysema	20
Pneumonia	18
Diffuse alveolar damage	16
Interstitial fibrosis	16
Cancer	14
Infarct	10
Hemorrhage	10
Thromboembolism	8
Edema	2

[a] The sum exceeds 100%, because several lesions can be present in the same case

Discussion

Coexistence of NBTE with hypoxigenic lung diseases has been frequently reported, although not emphasized, in the medical literature. Horowitz and Ward [16] described a case in which NBTE coexisted with diffuse alveolar damage and DIC. Krous [21] reported two newborn infants with respiratory distress syndrome and NBTE, one of whom suffered from meconium aspiration, pneumothorax, and DIC, and the other had hyaline membrane disease and atelectasis. Patterson [30] described NBTE in a patient with adult respiratory distress syndrome, diffuse alveolar damage, and DIC resulting form an overdose of a cold medication. Young and Zalneraitis [37], in their series of seven children and young adults with NBTE, found significant hypoxigenic pulmonary lesions in six, including severe pneumonia, fat embolization, and a bronchial tear. All of their subjects also had some coagulation defects, including DIC. Jerman and Fick [17] observed two bone marrow transplant recipients who subsequently developed NBTE. One of them suffered from *Pneumocystis* pneumonia and diffuse alveolar damage, and the other had organizing interstitial pneumonia, pulmonary hyaline membranes, bacterial and viral pneumonia, and respiratory failure. Kollef et al. [20] reported a case of NBTE associated with gold-induced pulmonary disease. Diez-Martin et al. [7] discovered NBTE in two bone marrow transplant patients, both of whom also suffered from respiratory failure. Lastly, Sharma et al. [33] described fatal cerebral embolization from NBTE in a patient with major trauma, adult respiratory distress syndrome, sepsis, and DIC.

In a series of 31 patients with NBTE and cancer reported by Bedikian et al. [1], there was a 64.5% incidence of pneumonia. The immediate cause of death was pneumonia in 34.5% of the cases, and chronic pulmonary failure in 12.9%. There were also cases of lung carcinoma and pulmonary embolization. The focus of their work, however, was an association between NBTE and DIC (see discussion below).

Experimental evidence of an association between hypoxia and NBTE also exists. Nakanishi et al. [25] demonstrated a greatly increased incidence of NBTE in rats subjected to a hypoxic environment simulating high altitude dwelling (an equivalent of 5500 m elevation). The incidence of NBTE was 33% at 4 weeks and 100% at 12 weeks of exposure to hypoxia. In addition, they reported a significant decrease in platelet counts, prolongation of the prothrombin and partial thromboplastin times, and a decrease in the levels of several individual coagulation factors. Later, Nakanishi et al. [26] repeated the experiment, finding the incidence of NBTE of 33, 29, 65, and 100% at 4, 6, 8, and 12 weeks, respectively. The experimental group showed a significantly higher level of the plasma tissue factor (TF) activity. An accumulation of TF in macrophages, stromal cells, few endocardial cells, the extracellular matrix of the cardiac valves, and in macrophages within the thrombus was also noted.

Our study demonstrates a correlation between the severity of hypoxigenic lung diseases and NBTE. This relationship is evident from the increased lung weight of the subjects with NBTE, their higher degree of pulmonary histopathology, and a more severe clinical respiratory impairment. Based on these and the above-cited clinical and experimental data, one can suggest a causal relationship between hypoxia and NBTE.

It appears that NBTE results from abnormal interactions between the coagulation system, platelets, and endothelial cells. A systemic release or an increased endothelial expression of TF in response to hypoxia could lead to activation of the extrinsic pathway of coagulation. There is evidence that hypoxia can also activate platelets [32, 34]. In other experiments, hypoxia led to activation of endothelial cells, manifested by an increased expression of adhesion molecules and major histocompatibility complex class II molecules [8]. Alterations in these three systems, i.e., coagulation, platelets, and endothelium, lead to the formation of NBTE. The location of the resulting fibrin-platelet thrombi on the edges of cardiac valves may be caused by a high degree of hemodynamic stress to which the valvular endocardium is subjected.

The relationship between NBTE and DIC is still unclear. DIC, with its numerous causes, is characterized by concomitant systemic activation of thrombosis and fibrinolysis. The degree of DIC may range from a severe, life-threatening process to a low-grade, compensated coagulopathy. Chronic, low-grade DIC in a setting of cancer is called Trousseau's syndrome [3]. It is thought that abnormal TF expression is central to the pathogenesis of DIC [5]. It appears that TF may be secreted into the circulation by promyelocytic leukemia cells [13] and constitutively expressed on the surface of adenocarcinoma cells [3]. In addition, cytokines (interleukin-1 and tumor necrosis factor) are reported to enhance the expression of TF by endothelial cells [5]. The resulting prothrombotic activity, coupled with activation of fibrinolysis, leads to the clinical picture of DIC.

NBTE frequently coexists with DIC, and the clinical spectra of these two disorders appear to overlap. Kim et al. [19] found histologic evidence of DIC in 50% of patients with NBTE in their autopsy series. Bedikian et al. [1] found histologic evidence of DIC in 71% of their patients with NBTE and cancer. However, a prospective study of cancer patients by Edoute et al. [9] found no statistically significant increase in the incidence of D-dimer elevation among patients with valvular vegetations compared with those without vegetations. At this time, it is probably reasonable to assume that frequently the same conditions that cause DIC can also cause NBTE, probably through activation of TF. Whether hypoxia-related NBTE is always accompanied by DIC remains to be determined, and experimental animal studies similar to ones mentioned above [25, 26] would be best suited for resolving this question.

Interestingly, there was no difference in the degree of spread of any malignancy between the NBTE cases and

the controls in our study. According to Bell et al. [2], severe coagulopathies in cancer patients can be produced by tumors minute in size. Moreover, in our series, even exclusion of the patients with cancer from the NBTE group still produced a statistically significant preponderance of the severity scores of lung injury and the degree of clinical respiratory compromise of the patients with NBTE over those without cardiac vegetations. This shows that the presence or absence of cancer is not a confounding factor for our conclusion.

In a handful of cases from our series, there may have been an influence of indwelling catheters on the formation of NBTE. More specifically, in two of the cases where NBTE lesions were found on the tricuspid and pulmonic valves only, the presence of a Swan-Ganz catheter was documented in the gross protocol. However, such cases are a distinct minority, because most of the NBTE lesions were present in the left heart (Table 1), where one does not expect to find any indwelling lines. Moreover, not every patient with an intracardiac line develops NBTE, which shows that other factors must be operating to contribute to the development of these lesions.

In summary, we have demonstrated a positive association between the severity of hypoxigenic lung diseases and NBTE. The effect of the former may be mediated by alterations in the coagulation system, platelets, and endothelial cells. Further research is needed to delineate the relationship between NBTE, hypoxia, cancer, and DIC.

References

1. Bedikian A, Valdiviesco M, Luna M, Bodey GP (1978) Nonbacterial thrombotic endocarditis in cancer patients: comparison of characteristics of patients with and without concomitant disseminated intravascular coagulation. Med Pediatr Oncol 4:149–157
2. Bell WR, Starksen NF, Tong S, Porterfield JK (1985) Trousseau's syndrome. Devastating coagulopathy in the absence of heparin. Am J Med 79:423–430
3. Callander N, Rapaport SI (1993) Trousseau's syndrome. West J Med 158:364–371
4. Cammarosano C, Lewis W (1985) Cardiac lesions in acquired immune deficiency syndrome (AIDS). J Am Coll Cardiol 5:703–706
5. Carey MJ, Rodgers GM (1998) Disseminated intravascular coagulation: clinical and laboratory aspects. Am J Hematol 59:65–73
6. Cook DJ, Tanser PH (1989) Nonbacterial thrombotic endocarditis complicating mitral valve prolapse presenting as Parinaud's syndrome – a case report. Angiology 40:494–497
7. Diez-Martin JL, Habermann TM, Gastineau DA, Solberg LA Jr, Letendre L (1988) Nonbacterial thrombotic endocarditis in autologous bone marrow transplantation. Am J Med 85:742–744
8. Dore-Duffy P, Balabanov R, Beaumont T, Hritz MA, Harik SI, LaManna JC (1999) Endothelial activation following prolonged hypobaric hypoxia. Microvasc Res 57:75–85
9. Edoute Y, Haim N, Rinkevich D, Brenner B, Reisner SA (1997) Cardiac valvular vegetations in cancer patients: a prospective echocardiographic study of 200 patients. Am J Med 102:252–258
10. Ferrans VJ, Rodriguez ER (1985) Cardiovascular lesions in collagen-vascular diseases. Heart Vessels [Suppl]1:256–261
11. Ford SE, Manley PN (1982) Indwelling cardiac catheters. An autopsy study of associated endocardial lesions. Arch Pathol Lab Med 106:314–317
12. Geyer SJ, Franzini DA (1979) Myxomatous degeneration of the mitral valve complicated by nonbacterial thrombotic endocarditis with systemic embolization. Am J Clin Pathol 72:489–492
13. Gralnick HR, Abrell E (1973) Studies of the procoagulant and fibrinolytic activity of promyelocytes in acute promyelocytic leukaemia. Br J Haematol 24:89–99
14. Gross L, Friedberg CK (1936) Nonbacterial thrombotic endocarditis. Classification and general description. Arch Int Med 58:620–640
15. Herskowitz A (1996) Cardiomyopathy and other symptomatic heart diseases associated with HIV infection. Curr Opin Cardiol 11:325–331
16. Horowitz CA, Ward PCJ (1971) Disseminated intravascular coagulation, nonbacterial thrombotic endocarditis and adult pulmonary hyaline membranes – an interrelated triad? Report of a case following small bowel resection for a strangulated inguinal hernia. Am J Med 51:272–280
17. Jerman MR, Fick RB Jr (1986) Nonbacterial thrombotic endocarditis associated with bone marrow transplantation. Chest 90:919–922
18. Kaul S, Fishbein MC, Siegel RJ (1991) Cardiac manifestations of acquired immune deficiency syndrome: a 1991 update. Am Heart J 122:535–544
19. Kim HS, Suzuki M, Lie JT, Titus JL (1977) Nonbacterial thrombotic endocarditis (NBTE) and disseminated intravascular coagulation (DIC). Autopsy study of 36 patients. Arch Pathol Lab Med 101:65–68
20. Kollef MH, Irvine T, Cragun WH (1988) Nonbacterial thrombotic endocarditis associated with gold-induced pulmonary disease. Ann Intern Med 108:903–904
21. Krous HF (1979) Neonatal nonbacterial thrombotic endocarditis. Arch Pathol Lab Med 103:76–78
22. Kupari M, Volin L, Suokas A, Timonen T, Hekali P, Ruutu T (1990) Cardiac involvement in bone marrow transplantation: electrocardiographic changes, arrhythmias, heart failure and autopsy findings. Bone Marrow Transplant 5:91–98
23. Leung KL, Milewicz DM, Phillips MD, Barasch E (1997) Nonbacterial thrombotic endocarditis in three members of a family. N Engl J Med 336:1677–1678
24. Lopez JA, Ross RS, Fishbein MC, Siegel RJ (1987) Nonbacterial thrombotic endocarditis: a review. Am Heart J 113:773–784
25. Nakanishi K, Tajima F, Nakata Y, Osada H, Sugiyama K, Maruta H, Kawai T, Suzuki M, Torikata C (1997) Hypercoagulable state in a hypobaric, hypoxic environment causes nonbacterial thrombotic endocarditis in rats. J Pathol 181:338–346
26. Nakanishi K, Tajima F, Nakata Y, Osada H, Ogata K, Kawai T, Torikata C, Suga T, Takishima K, Aurues T, Ikeda T (1998) Tissue factor is associated with the nonbacterial thrombotic endocarditis induced by a hypobaric hypoxic environment in rats. Virchows Arch 433:375–379
27. Olney BA, Schattenberg TT, Campbell JK, Okazaki H, Lie JT (1979) The consequence of the inconsequential: marantic (nonbacterial thrombotic) endocarditis. Am Heart J 98:513–522
28. Paik ML, MacLennan GT, Seftel AD (1999) Embolic testicular infarction secondary to nonbacterial thrombotic endocarditis in Wegener's granulomatosis. J Urol 161:919–920
29. Patchell RA, White CL, Clark AW, Beschorner WE, Santos GW (1985) Nonbacterial thrombotic endocarditis in bone marrow transplant patients. Cancer 55:631–635
30. Patterson FK (1980) Delayed fatal outcome after possible Ru-Tuss overdose. J Forensic Sci 25:349–352
31. Pinto AN (1996) AIDS and cerebrovascular disease. Stroke 27:538–543
32. Ponicke K, Sternitzky R, Mest HJ (1987) Stimulation of aggregation and thromboxane A2 formation of human platelets by hypoxia. Prostaglandins Leukot Med 29:49–59

33. Sharma S, Mayberry JC, Deloughery TG, Mullins RJ (2000) Fatal cerebroembolism from nonbacterial thrombotic endocarditis in a trauma patient: case report and review. Mil Med 165:83–85
34. Shen D, Wang Y (1994) Effects of hypoxia on platelet activation in pilots. Aviat Space Environ Med 65:646–648
35. Singh S, Dass A, Jain S, Varma S, Bannerjee AK, Sharma BK (1998) Fatal non-bacterial thrombotic endocarditis following viperine bite. Intern Med 37:342–344
36. Vilanova JR, Norenberg MD, Stuard ID (1975) Thrombotic thrombocytopenic purpura. Systemic embolization from nonbacterial thrombotic endocarditis. NY State J Med 75:2246–2248
37. Young RSK, Zalneraitis EL (1981) Marantic endocarditis in children and young adults: clinical and pathological findings. Stroke 12:635–639