

Fatal Intracranial Hemorrhage after Intravenous Thrombolytic Therapy for Acute Ischemic Stroke Associated with Cancer-related Nonbacterial Thrombotic Endocarditis

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Nonbacterial thrombotic endocarditis (NBTE) is associated with hypercoagulability in patients with inflammatory states such as cancer and autoimmune diseases. Cardiac vegetations caused by NBTE often lead to life-threatening systemic thromboembolism that most frequently affects the brain, spleen, and kidneys. A 54-year-old woman diagnosed with ovarian cancer suddenly developed back pain and left hemiparesis. Although intravenous alteplase (rt-PA) therapy was administered to treat hyperacute ischemic infarction detected by magnetic resonance imaging, intracranial hemorrhage occurred in the left hemisphere several hours later as the patient started to lose consciousness. Transthoracic echocardiography then detected aseptic vegetations on the mitral and aortic valves, indicating NBTE associated with ovarian cancer. Because therapies for NBTE are limited to heparinization and control of underlying diseases, thrombolytic therapy for acute embolic stroke in NBTE has not yet been validated. We postulated that thrombolytic therapy for cancer-related NBTE might easily cause hemorrhagic complications because cancer-related NBTE is often similar to the state of disseminated intravascular coagulation. **Key Words:** Nonbacterial thrombotic endocarditis—marantic endocarditis—alteplase—ischemic infarction—thrombolytic therapy—disseminated intravascular coagulation.

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Nonbacterial thrombotic endocarditis (NBTE; also known as marantic endocarditis) is defined as noninfectious cardiac valvular vegetations with negative blood cultures,¹ and it is most commonly caused by an underlying malignancy. The presenting symptom of NBTE is sys-

temic or pulmonary embolization,² and the most common neurologic complication is ischemic stroke.³ The safety and effectiveness of thrombolytic therapy for acute ischemic stroke due to NBTE have not been established. We describe a patient with NBTE-associated stroke in whom severe intracranial hemorrhage (ICH) developed after undergoing thrombolytic therapy. Thrombolytic therapy for cancer patients should need careful consideration of risks and benefits, because thrombolytic therapy in patients with NBTE-associated stroke might be associated with very poor outcomes.

Case Report

A 54-year-old woman diagnosed with ovarian cancer was scheduled to undergo elective surgery (Fig 1). She had no history of valvular heart disease, dental surgery,

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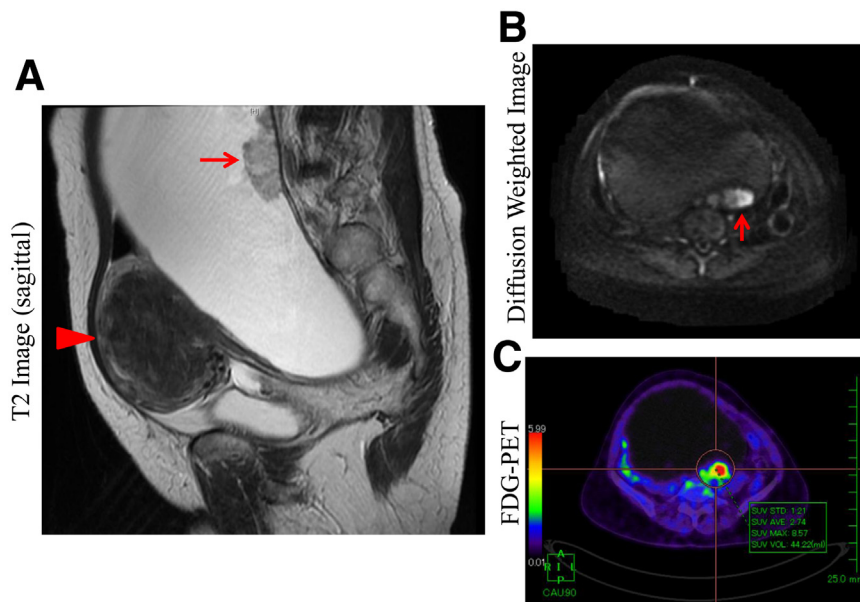


Figure 1. Magnetic resonance (MR) and [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) images of patient with ovarian cancer. Sagittal T2-weighted MR image (A) of pelvis shows giant cystic lesion with solid tumor arising from right ovary (arrow). Uterine fibroid is also evident in muscular wall of uterus (arrowhead). Diffusion-weighted image (B) shows high signal intensity in solid tumor. (C) Increased cellular activity in solid tumor on FDG-PET image indicates ovarian cancer.

or medication use. Ten days before the elective procedure, she suddenly developed back pain with left-sided weakness and was immediately admitted to our hospital. Left hemiparesis and unilateral spatial neglect with a National Institutes of Health Stroke Scale score of 7 were evident on arrival at the emergency department. Initial laboratory findings were almost within normal limits, except for elevated D-dimer (41.6 $\mu\text{g}/\text{mL}$) and decreased fibrinogen (104 mg/dL). Diffusion-weighted magnetic resonance images showed high-intensity areas in the middle cerebral artery (Fig 2, A) and magnetic resonance angiography revealed an occluded right middle cerebral artery (Fig 2, B). DWI-ASPECTS (diffusion-weighted imaging the Alberta Stroke Program Early Computed Tomography) score of the initial diffusion-weighted imaging was 7 points of 11. Computed tomography of the thorax and abdomen also revealed pulmonary embolism and small renal and splenic infarctions. After obtaining informed consent, alteplase (rt-PA) was intravenously administered per standard protocol within 4.5 hours after the onset of neurologic symptoms. Blood pressure before and after rt-PA remained at about 120/70 mm Hg without any antihypertensive agent and blood pressure elevation was not detected during the clinical course. About 5 hours after rt-PA treatment, she developed loss of consciousness and right hemiparesis with a massive ICH on the left hemisphere (Fig 2, C). Transthoracic echocardiography after admission showed mobile vegetations on the mitral and aortic valves (Fig 2, D). Repeated blood cultures remained sterile, indicating a diagnosis of nonbacterial thrombotic endocarditis (NBTE). Anticoagulation therapy for NBTE could not be started because of the ICH and the elective surgery was canceled. Her general condition gradually worsened after admission and disseminated intravascular coagulation (DIC) was also

diagnosed based on new findings of thrombocytopenia with a platelet count of less than 50,000, hypofibrinogenemia, a significantly prolonged prothrombin time, and increased levels of FDP (fibrin degradation products). Despite supportive therapy, the patient died 3 weeks after the onset of ischemic stroke.

Discussion

Intravenous rt-PA for hyperacute ischemic stroke was the established therapy on current clinical guidelines.⁴⁻⁶ These guidelines indicate administering thrombolytic therapy only for selected patients to minimize the risk of major bleeding complications. Most contraindications for thrombolytic therapy in acute ischemic stroke have been established from the study protocols of randomized controlled trials to reduce the risk of hemorrhagic complications and are thus based on expert opinion rather than on empirical medical evidence.⁷ Whether thrombolytic therapy is safe and effective for patients with cancer is important to be validated because ischemic stroke is a relatively common complication in such patients. However, little is known about the hemorrhagic complications of thrombolytic therapy in patients with cancer, because they have usually been excluded from clinical trials of such therapy to rule out the possibility that morbidity due to cancer might influence stroke outcomes. Recent studies have found that thrombolytic therapy does not seem to increase symptomatic bleeding complications in patients with cancer,⁸⁻¹¹ but the numbers of patients in these reports were limited.

To the best of our knowledge, this is the first description of ICH caused by thrombolytic therapy for ischemic stroke associated with cancer-related NBTE. This condition is characterized by thrombus deposition on previously

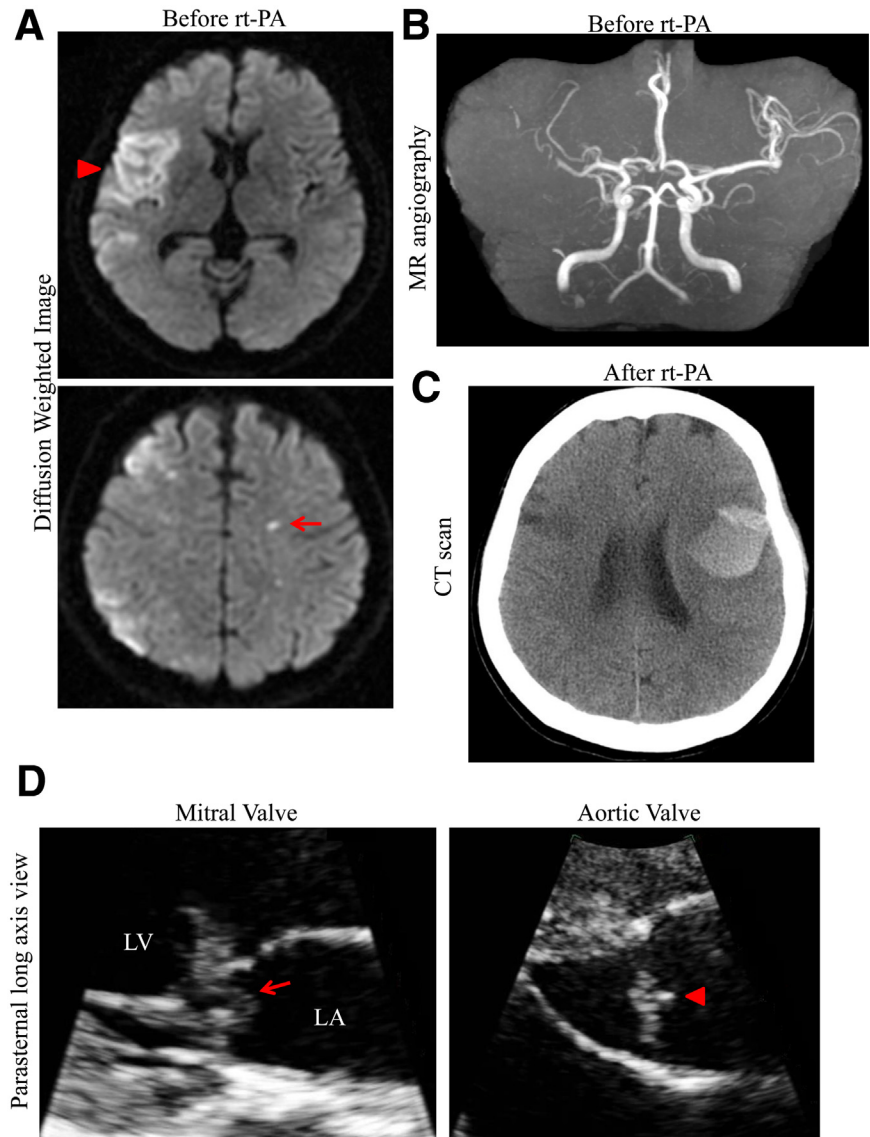


Figure 2. (A-C) Brain magnetic resonance images, magnetic resonance angiography (MRA) images before, and computed tomography (CT) image of patient after rt-PA therapy. Large (A, arrowhead) and small (A, arrow) hyperintense lesions in right and left middle cerebral artery (MCA) area, respectively, revealed by DWI are consistent with acute cerebral infarction. Occlusion in distal M1 segment of right MCA revealed by MRA (B). Brain CT image of patient after rt-PA therapy shows intracranial hemorrhage in left hemisphere (C). (D) Transthoracic echocardiographic images of mitral and aortic valves. Mobile vegetation measuring about 8 × 5 mm (arrow) is attached to P2 and P3 segments of posterior leaflet on mitral valve. Small vegetation (arrowhead) is attached to aortic valve.

undamaged heart valves in the absence of a bloodstream bacterial infection and by an increased frequency of arterial embolic events in patients with chronic underlying diseases.¹ The pathogenesis of NBTE has not been fully elucidated. However, cytokines such as tumor necrosis factor, interleukin-1, and interleukin-6 released from interaction between macrophages and malignant cells cause endothelial damage that generates a thrombogenic surface on the vascular lining, resulting in the generation of thrombin and thrombosis via an activated coagulation cascade.¹² Valvular and peripheral intravascular thromboses are the sequelae of the disrupted coagulation associated with DIC.¹³ DIC plays an important pathogenic role in the development of NBTE, especially when linked with cancer. The relationship between NBTE and cancer should be carefully considered because it might result in bleeding diathesis. Although a large-scale analysis with a sufficient sample size is needed to determine the value of thrombolytic ther-

apy for acute ischemic stroke associated with NBTE, this case might be a warning for the idea that thrombolytic therapy is not so dangerous for ischemic stroke patients with cancer.⁸⁻¹¹ Careful consideration should be needed before deciding to administer thrombolytic therapy for cancer patients who suddenly develop neurologic symptoms and other embolic manifestations, because thrombolytic therapy in patients with NBTE-associated stroke might be associated with very poor outcomes.

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