Case Report

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Thromboembolic complications following tissue plasminogen activator therapy in patients of acute ischemic stroke - Case report and possibility for detection of cardiac thrombi

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Abstract: Many reports focus on the probability of intracranial hemorrhage as a complication after recombinant tissue plasminogen activator (rt-PA) therapy. However, thromboembolic complications are not well discussed. We experienced a case in which severe thromboembolic complications occurred in the right radial and right ulnar artery. Arterial fibrillation was observed in this case. If multiple thrombi exist in the atrium or ventricle, multiple small embolic particles may appear following thrombolytic therapy, and that may be a potential risk of secondary thromboembolic complications due to incomplete dissolution of thrombi. Transesophageal echocardiography is a standard method to detect intracardiac sources of emboli in the case of arterial fibrillation. Transesophageal echocardiography is, however, an invasive method for patients with ischemic stroke during rt-PA therapy. High resolution enhanced CT could be a useful tool and may be a reliable alternative to transthoracic echocardiography. Careful assessment of thromboembolic complications following rt-PA therapy in patients with arterial fibrillation is needed. In this case report and mini review, we would like to discuss about the accurate diagnostic methods to detect cardiac or undetermined embolic sources and provide expedited stroke care. These embolic sources may be more readily discovered during rt-PA therapy within the limited therapeutic time window.

Keywords: Thromboembolic complications; acute ischemic stroke; Arterial fibrillation; Tissue plasminogen activator therapy; Detection of cardiac thrombi

1 Introduction

Patients suffering from an acute ischemic stroke were given an intravenous infusion of recombinant tissue plasminogen activator (rt-PA; Alteplase) within 4.5 hours and were reported to have an improved outcome for neurological function [1, 2]. Complications after rt-PA therapy in patients with ischemic stroke result in worsened prognosis. Many reports [1, 2], including the J-ACT trial [3], focus primarily on the probability of intracranial hemorrhage. However, other critical complications have not been well discussed. We would like to present the following case in which severe thromboembolic complications occurred. Arterial fibrillation (AF) was observed in this case. In this paper, we explore the possibility of new measures targeting early detection to prevent thromboembolic complications following rt-PA therapy in ischemic stroke patients.

2 Case report

A male in his 50s was untreated for AF.

At 8:50 a.m. the patient suddenly lost consciousness, which was witnessed by his family. He also had left hemiparesis and speech disturbance. On admission to the hospital at 9:13 a.m., the patient's conscious level

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was equal to a GCS (E3V3M5) score of 11 and his blood pressure was 224/152mmHg, which gradually decreased to 130/80mmHg without any treatment. His initial measurement on the National Institutes of Health Stroke Scale (NIHSS) was 16 points and his ECG revealed AF. Initial brain CT scans indicated no early ischemic signs on admission. The patient was diagnosed as having suffered an acute ischemic stroke. Activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR) were reported in the normal range and there were no other contraindications, making the patient eligible for thrombolysis. Transthoracic echocardiography gave an ejection fraction measurement of 31% and was not able to reveal the evidence of cardiac thrombus. The patient was given rt-PA (Alteplase: 0.6mg/kg) intravenously 2 hours 38 minutes (at 11:28 a.m.) from onset according to Japanese guideline for thrombolysis in patients with acute ischemic stroke [3]. Following administration of rt-PA, the patient's conscious level had recovered to a GCS score (E3 V5 M6) of 14 and blood pressure was 126/80mmHg, but left hemiparesis persisted. However, he felt numbness and was complaining of motor weakness in his right arm at 1:00 p.m. following administration of rt-PA. Approximately 6 hrs after rt-PA therapy, the physicians noticed that his right radial artery and right ulnar artery had no pulse. An ultrasonographic doppler flow test performed immediately afterwards indicated no flow in his right radial and right ulnar artery. An acute brachial artery obstruction was diagnosed and an emergency surgical procedure (removal of embolic thrombus) was performed. Although the patient recovered full consciousness the next morning, his hemiparesis remained. However, brachial artery obstruction recurred. Enhanced CT scans of the chest revealed multiple thrombi in the left atrium and ventricle (figure 1). After 26 hrs of rt-PA therapy, this patient was given continuous intravenous heparin, and warfarin was started on day 6. Thrombi were not observed in his cardiac atrium and ventricle using transesophageal echocardiography after warfarin treatment, and the patient was discharged on day 38, still with left hemiparesis.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Informed consent: Informed consent has been obtained from all individuals included in this study.

3 Discussion

Among ischemic strokes, cardiogenic embolism causes approximately 20% of all cases. Of these, non-valvular AF is responsible for approximately 50%, and left ventricular thrombi are detected in only one third of the cases [4]. Data to evaluate the risk of systemic thromboembolic complications due to thrombolysis in ischemic stroke patients are scarce. According to a study on acute myocardial infarction, in which did not consider ischemic strokes, thromboembolic complications are observed in 1.5% of patients receiving systemic thrombolysis [5]. Case reports on thromboembolic complications during thrombolysis in patients with ischemic stroke were gathered, and thromboembolic complications such as acute myocardial infarction [6-9], recurrent embolic stroke [10], and upper (our case) /lower limb artery occlusion [11] after rt-PA therapy were serious and their influence on patient outcome gradually became apparent. In our case, the patient suffered untreated AF. Recently, a report demonstrated that patients with AF have worse outcomes than patients without AF [12]. In addition, covert AF is the most prevalent cause with embolic stroke of an undetermined source, whereas AF can be detected after repeated ECG monitoring during critical care in some cases [13]. This means that normal sinus rhythm at admission in patients with stroke cannot dismiss the possibility of covert AF. If so, the risk of recurrent stroke or systemic secondary thromboembolic complications is still present in patients with embolic stroke. If subclinical multiple thrombi in the aorta, atrium or ventricle are present, multiple small embolic particles would appear after thrombolytic therapy due to the incomplete dissolution of thrombi. For these reasons, the possibility of thromboembolic complications cannot be ignored since the outcome would be serious. Discussion of more concrete therapeutic plans for early detection and for the prevention of thromboembolic complications after rt-PA therapy is needed.

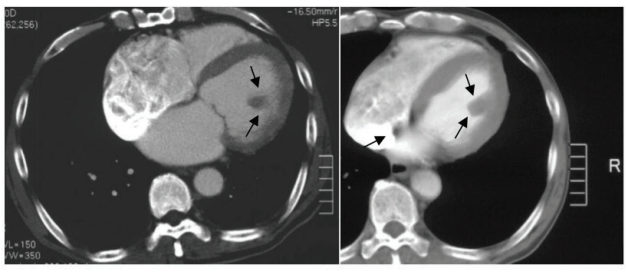

Figure 1: A: Chest CT findings after administration of rt-PA.
B: Chest CT scans reveal multiple thrombi (arrows) in the left ventricle.

However, subsequent administration of anticoagulants and platelet anti-aggregated agents are currently contraindicated during the first 24 hours following intravenous rt-PA therapy. Therefore, a risk for secondary systemic thromboembolic complications caused by incomplete dissolution of thrombi following rt-PA therapy in patients with a "high-risk" group is possible, particularly by estimating $CHADS_2$ and CHA_2DS_2-VASc scores for AF [14]. In those patients, early detection following rt-PA therapy in embolic stroke patients with AF or undetermined embolic sources is considered needed. If an appropriate diagnosis of cardiac or undetermined embolic sources can quickly be determined by any diagnostic method, improvement in treatment results and reduction in the risk of secondary systemic thromboembolic complications related to rt-PA therapy in embolic stroke patients may be possible.

4 Echocardiography

Transthoracic echocardiography is used to detect possible intracardiac sources of emboli. However, definitive cardiac lesions associated with embolism such as left atrial clots, left ventricular thrombi, or mitral valve thrombi and vegetation are visualized in only 3-8% of patients presented with embolic stroke [15-17]. On the contrary, transesophageal echocardiography (TEE) can detect cardiac thrombus in up to 26% of consecutive patients admitted for examination for transient ischemic attack (TIA) or ischemic stroke [18]. Although covert AF is a risk factor for recurrence emboli, there is also the risk that AF is not observed at the time of hospital admission [13]. First, assessment of possible cardiac thrombi is not part of routine examination in cases of ischemic stroke before and after rt-PA therapy. TEE is widely available and is currently a useful method to detect left atrial thrombus [19-21]. However, TEE does not allow for sufficient performance of the Valsalva maneuver or patient consent in case of unconsciousness. It is also considered to be potentially invasive under limited clinical conditions during rt-PA therapy. Effective procedures modified to TEE to detect possible cardiac thrombi during rt-PA therapy are expected.

5 Contrast-enhanced computed tomography

Interestingly, enhanced CT scan could detect multiple thrombi in the left atrium and ventricle after rt-PA therapy in our case. Patients with AF are at risk of ischemic stroke from a left atrium and left atrial appendage thrombus [22, 23]. Recently, contrast-enhanced multidetector computed tomography allows accurate and consistent imaging of left atrial thrombus [24, 25], including with additional methods of CT scanning [26, 27] or scoring [24]. From these results, according to recent meta-analysis [28] for CT diagnosis of cardiac thrombus, mean sensitivity and specificity were 81% (95% CI: 70-90%) and 90% (95% CI: 88-91%), respectively. In cases of "high-risk" patients, such as AF [12, 13, 23], AF with cardiac dysfunction [23] or embolic stroke of undetermined source [13, 14], evaluation by high resolution enhanced CT could be a useful tool and may be a reliable alternative to TEE [29, 30] in the evaluation of cardiac or undetermined embolic source during rt-PA therapy which cause secondary systemic thromboembolic complications within a limited therapeutic time window. By combining methods, efficacy and accuracy in the detection of embolic sources in cardiac or systemic will increase, and may reduce morbidity and mortality caused by secondary systemic thromboembolic complications during rt-PA therapy.

6 Conclusion

We reviewed the possibility of efficacy for embolic stroke patients with AF in detecting cardiac or arterial embolic sources using echocardiography or high resolution enhanced CT together with conventional diagnostic methods. Such cases could provide useful input in the consideration of rt-PA therapy when evaluating ischemic embolic stroke patients. High resolution enhanced CT may be useful as a detector of small incomplete dissolution of thrombi after rt-PA therapy, instead of TEE. Discussion of more concrete therapeutic plans for early detection and prevention of thromboembolic complications following rt-PA therapy in ischemic embolic stroke patients with undetermined embolic sources is needed. As the risk of venous thrombosis after rt-PA therapy was also not discussed in this mini review, further consideration of detection methods for secondary thromboembolic sources is also needed.

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