

## Case Report

## Fatal Contralateral Cardioembolic Stroke Promoted by Systemic Thrombolysis with rtPA in Ischemic Stroke

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## Abstract

**Background and Purpose:** Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) is the most effective and the only approved causal treatment in acute ischemic stroke.

**Summary of Case:** We treated an 88-year-old male woman with atrial fibrillation and acute left middle cerebral artery (MCA) infarction with intravenous thrombolysis. Directly thereafter, she developed an epileptic status. Immediate CT scan was normal. Fourteen hours later, it showed a normal left hemisphere but a fatal space-occupying contralateral MCA and anterior cerebral artery (ACA) infarction. Autopsy revealed thrombi in atria, large right MCA and ACA ischemia, and occlusion of two major visceral arteries.

**Conclusion:** RtPA, though effective for the initial infarction, caused a rarely observed fatal adverse event, i.e. cardioembolism by detachment of atrial thrombi fragments, with an uncommon presentation as epileptic status. Stroke physicians' awareness of this potential course will allow treatment in time.

**Keywords:** Thrombolysis therapy; Cardioembolic stroke; serious adverse event

## Abbreviations

rtPA: Recombinant Tissue Plasminogen Activator; AF: Atrial Fibrillation; NIHSS: National Institute of Stroke Scale score; MCA: Middle Cerebral Artery; CT: Computed Tomography; ACA: Anterior Cerebral Artery; IV: Intravenous

## Abstract

Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) is the most effective and the only approved causal treatment within the first 4.5 hours of acute ischemic stroke [1]. Its most dreaded adverse event is symptomatic intracranial hemorrhage, which occurs in 2.4% [1] to 5.2% [2] of patients. Hence, most exclusion criteria are aimed to reduce bleeding risks. In contrast, cardioembolism to other vascular territories during or in direct course of thrombolysis for stroke is rarely observed in atrial fibrillation (AF) [3-5] and presence of intracardiac thrombus [6]. Although not systematically reported in large randomized controlled trials, up to 6.8% of thrombolysis patients with AF may have clinically significant cardioembolic strokes in other cerebrovascular territories possibly linked to rtPA [3]. Still, it is not the focus of stroke physicians which may oftentimes delay diagnosis and therapy [5].

## Case Presentation

We report an 88-year-old woman who still attended to most of her daily needs until she developed acute right-sided brachiofacial hemiparesis, slight dysarthria, and a hypaesthetic right leg (National Institute of Stroke Scale score (NIHSS) 8) due to acute left middle cerebral artery (MCA) infarction. Cerebral CT scan confirmed our clinical diagnosis by time-to-peak prolongation in a small part of the MCA territory (Figure 1A-D). There were no early ischemic signs or

evidence of carotid artery or MCA occlusion on CT angiography. Formerly unknown tachyarrhythmia AF indicated cardioembolic etiology.

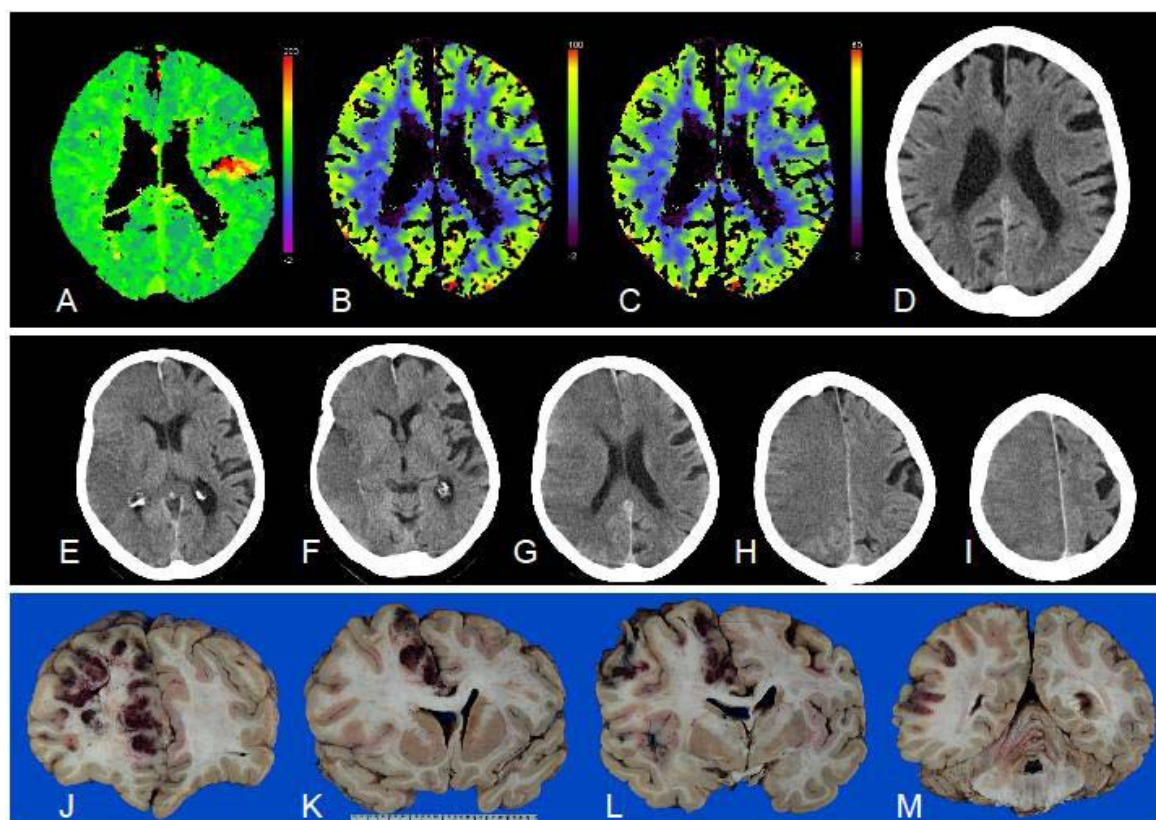
After exclusion of contraindications, information about the off-label use regarding her age, and the patient's informed consent, intravenous thrombolysis with rtPA was immediately started 210min after symptom onset. During thrombolysis, neurological status and vital signs were stable.

Instantly after the end of thrombolysis, the patient developed persistent tonic gaze deviation to the right and simultaneous tonic extension of all extremities. Immediate cerebral CT-scan did not reveal any new aspects. The epileptic status was terminated within 30min after i.v. administration of 6mg lorazepam and 1.2g valproic acid. The patient stayed in coma (NIHSS 23) which made elaborate clinical judgment impossible. Fourteen hours later, CT scan did not show any infarction of the initially affected left hemisphere. In contrast, we diagnosed a large space-occupying MCA and anterior cerebral artery (ACA) infarction of the contralateral right hemisphere, which in retrospect had caused the epileptic status (Figure 1E-I) and finally was fatal through transtentorial herniation 48 hours after thrombolysis.

Autopsy revealed a massive load of thrombi in the left and right cardiac atria, large ischemia of the right MCA and ACA territory, only very limited evidence of the initial left MCA infarction (Figure 1J-M), superior mesenteric artery occlusion and right renal infarction.

## Discussion/Conclusion

Despite successful thrombolysis of the initial left MCA infarction, rtPA also promoted left atrial thrombus fragmentation. This resulted



**Figure 1:** Cerebral CT scan confirmed acute left middle cerebral artery (MCA) infarction by (A) time-to-peak prolongation and mismatch between cerebral (B) blood flow and (C) blood volume in a small part of the MCA territory. (D) There were no early ischemic signs. (E-I) Cerebral CT scan fourteen hours after the clinical deterioration showed an unremarkable initially affected left hemisphere but a large space-occupying MCA and ACA infarction of the contralateral right hemisphere. (J-M) Coronal cerebral sections revealed large ischemia of the right MCA and ACA territory and no evidence of the initial left MCA infarction.

in fatal embolic occlusion of the contralateral MCA and ACA and of two major visceral arteries. The close temporal context supports this pathophysiology. AF and cardiac thrombi may increase the risk of secondary embolism during and after thrombolysis. Given the high percentage of AF (32.4%) [3] and small proportion of cardiac thrombi (2.7%) [6] among stroke patients receiving rtPA in two single center studies about early recurrent ischemic stroke, the rate of comparable fulminant and fatal embolism to other cerebrovascular territories in the rapid succession to i.v. thrombolysis (5.4% [3] to 0% [6]) is low. Still, if contralateral stroke occurs, its course is frequently fatal [3]. No reports exist on the frequency of extra-cerebral embolism.

To our best knowledge, only one report resembles ours in terms of presence of AF, time course, and presentation of symptoms at time of neurological deterioration [5]. Larger contralateral MCA and ACA infarction disguised as epileptic seizure occurred during thrombolysis. Diagnosis was delayed despite clinical hints. In contrast, this stroke was not fatal but highly disabling, the patient was 8 years younger rendering thrombolysis an approved treatment, and it is unknown whether subclinical embolism occurred to other vascular territories, while our patient had subclinical occlusion of two major visceral arteries.

Fatal outcomes immediately following i.v. thrombolysis for stroke have been reported in three cases with AF and/or atrial or ventricular thrombus due to secondary cardioembolic myocardial infarction [7,8]. Still, in comparison with these 'strategic' embolisms, the extent

of embolism and the fatal end of our patient remains remarkable and is the only case we know of that was confirmed by autopsy [3,5,7,8].

We do not consider the patient's advanced numerical age the relevant factor for this adverse event but the supposedly high quantity of intracardiac thrombi at the initiation of thrombolysis. Thrombolysis is a safe and effective treatment above the age of 80 years [9]. The fulminate embolism could neither have been foreseen nor prevented. More restrictive rtPA administration in the elderly or in cardioembolic stroke is inappropriate.

The main lesson to learn is that stroke physicians should keep in mind this rarely observed adverse event of further cardioembolism during thrombolysis and its uncommon presentation as epileptic status. In case of early diagnosis, immediate mechanical revascularization of the right MCA and ACA might have prevented the fatal outcome. Still, thrombectomy may have been unfeasible as carotid arteries of the elderly are oftentimes elongated and impassible with the catheter.

Furthermore, this case calls for higher alertness in AF detection and ample primary preventive prescription of oral anticoagulants in patients with high cardioembolic and moderate bleeding risk. This may have prevented the ultimately fatal stroke. Prior to this stroke, the patient had scored 5 on the CHA<sub>2</sub>DS<sub>2</sub>-VASc and 2 on the HASBLED score indicating a high cardioembolic and low major bleeding risk.

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