

Thrombolysis-related Multiple Lobar Hemorrhaging in Cerebral Amyloid Angiopathy with Extensive Strictly Lobar Cerebral Microbleeding

Makoto Eriguchi¹, Yusuke Yakushiji¹, Jun Tanaka¹, Masashi Nishihara² and Hideo Hara¹

Abstract

A hemi-paralyzed 86-year-old man was diagnosed with ischemic stroke and underwent thrombolysis. Pre-thrombolysis brain magnetic resonance imaging revealed extensive strictly lobar cerebral microbleeding (CMB). Post-thrombolytic computed tomography revealed asymptomatic multiple intracerebral hemorrhaging (ICH). His age, CMB topography, and decreased cerebral spinal fluid amyloid- β 40 and 42 levels were compatible with a diagnosis of cerebral amyloid angiopathy (CAA). There is no consensus on the safety of thrombolysis for acute stroke patients with CAA. Patients with CAA might have a higher incidence of thrombolysis-related ICH than those without CAA.

Key words: cerebral infarction, intracerebral hemorrhaging, cerebral amyloid angiopathy, cerebral microbleeding, thrombolysis

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Introduction

Cerebral amyloid angiopathy (CAA) is a common small-vessel disease of the brain characterized by progressive deposition of amyloid- β (A β) protein in the walls of small vessels of the cerebral cortex and overlying leptomeninges. The most common clinical presentation is symptomatic spontaneous lobar intracerebral hemorrhaging (ICH) in elderly people (1), which appears to be exacerbated by antithrombotic agents (2). However, little is known about whether or not CAA is a risk factor for thrombolysis-related ICH. We herein report a case of clinically probable CAA, based on the Boston criteria (3), that developed thrombolysis-related ICH.

Case Report

An 86-year-old, right-handed man was referred to our hospital with a chief complaint of acute-onset, right-sided weakness. He had a history of hypertension and arrhythmia

and was taking aspirin and antihypertensive agents. His blood pressure was 163/103 mmHg with an irregular heart rate of 102 beats per minute. Electrocardiogram revealed atrial fibrillation. His neurologic symptoms included consciousness disturbance (Glasgow coma scale 11, E4 V1 M6), right sensorimotor disturbance, and global aphasia, and his National Institutes of Health stroke scale (NIHSS) score was 28. The first brain computed tomography (CT) scan showed no early ischemic changes nor any hemorrhagic lesions. Laboratory tests revealed no contraindications to thrombolysis. Subsequent brain magnetic resonance imaging (MRI) showed a high-intensity area in the left frontal lobe on diffusion-weighted imaging with distal M2 occlusion on magnetic resonance angiography (Fig. 1) and multiple parieto-occipital-dominant lobar cerebral microbleeding (CMB) on susceptibility-weighted imaging (Fig. 2). Based on a diagnosis of cardioembolic stroke, intravenous thrombolysis (recombinant tissue plasminogen activator, 0.6 mg/kg) was administered 4 hours after symptom onset. Follow-up brain CT performed 24 hours after thrombolysis revealed multiple points of ICH in the right frontotemporal lobe and

¹Division of Neurology, Department of Internal Medicine, Saga University Faculty of Medicine, Japan and ²Department of Radiology, Saga University Faculty of Medicine, Japan

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Correspondence to Dr. Makoto Eriguchi, eriguchm@cc.saga-u.ac.jp

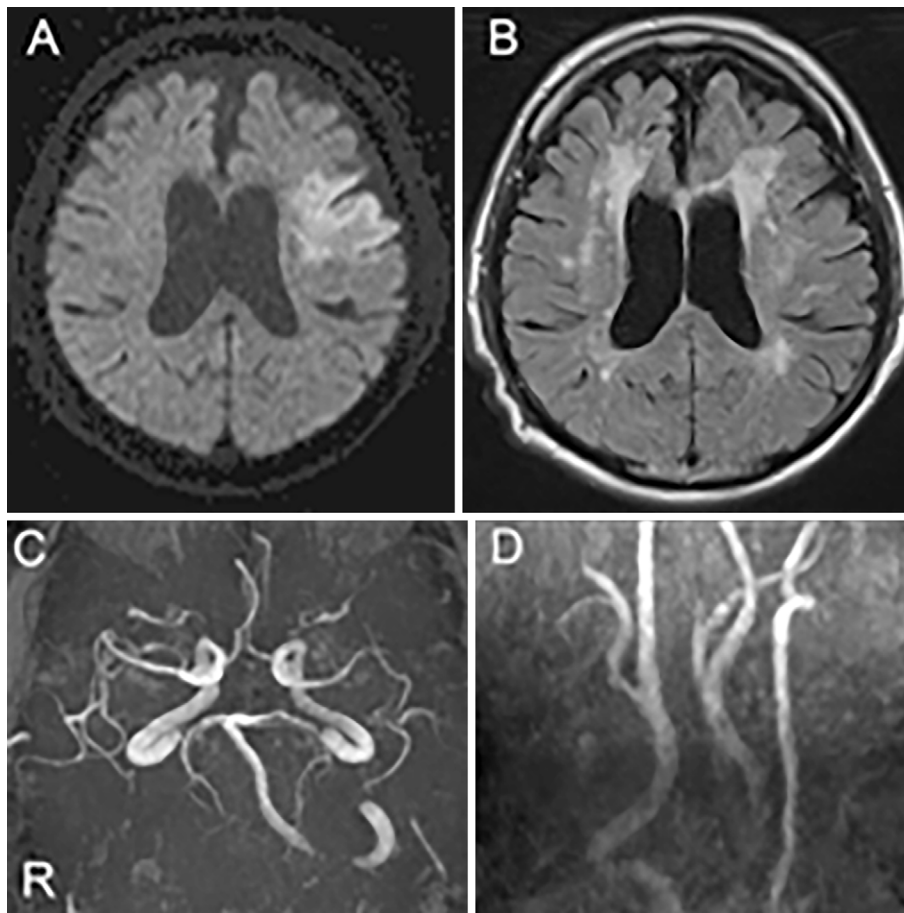


Figure 1. (A), (B) Pre-thrombolysis magnetic resonance images show a high-intensity area on the diffusion-weighted image and an iso-intensity area in the left frontal lobe on fluid-attenuated inversion recovery. (C), (D) Distal middle cerebral artery (M2) occlusion without responsive artery stenosis between the common carotid artery and proximal middle cerebral artery (M1) is documented on magnetic resonance angiography.

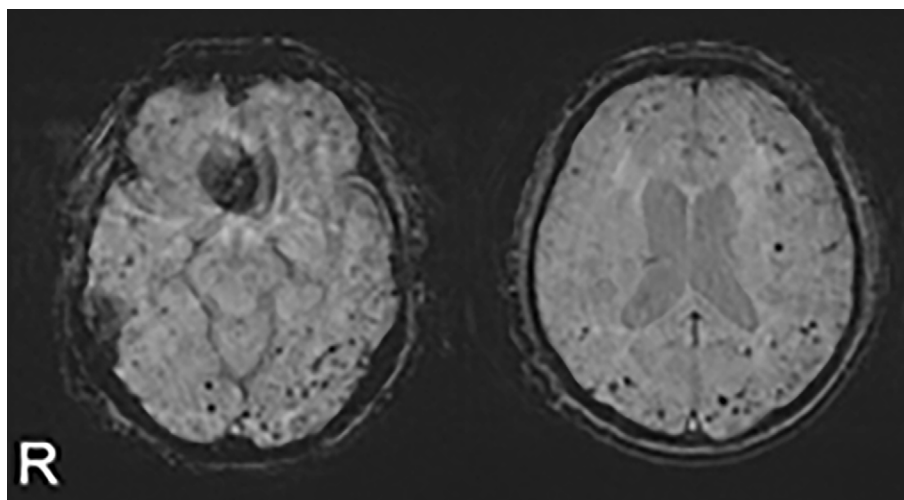


Figure 2. Pre-thrombolysis magnetic resonance images on susceptibility-weight image show multiple strictly lobar cerebral microbleeds suggestive of probable cerebral amyloid angiopathy based on the Boston criteria.

cerebellar hemisphere without neurologic deteriorations 1,185 (4)) and A β 42 levels (89 pg/mL, reference 838 \pm 253 (4)). Decreased A β 40 (1,663 pg/mL, reference 4,003 \pm 253 (4)) in the cerebrospinal fluid (CSF) were compatible

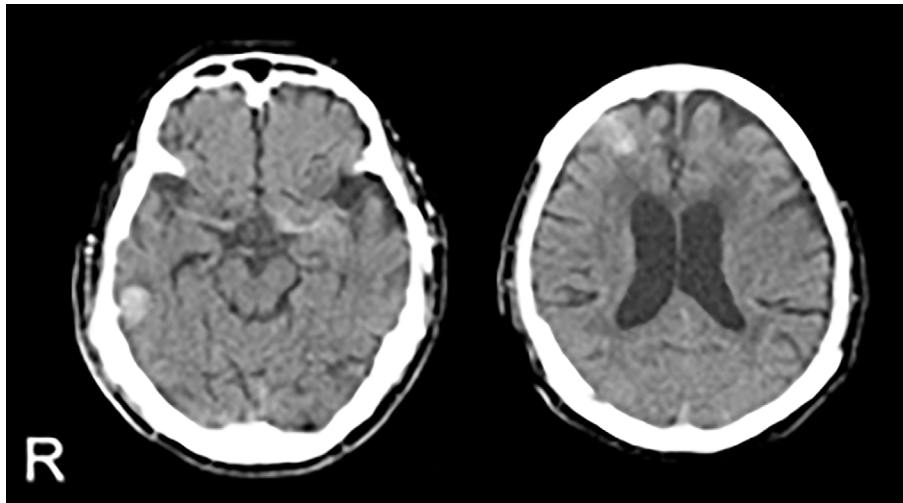


Figure 3. Post-thrombolysis head computed tomographics show multiple thrombolysis-related lobar hemorrhages.

with CAA. Three months after onset, he had no recurrence of stroke but was still bedridden (modified Rankin Scale score of 5).

Discussion

We herein reported a patient with ischemic stroke with extensive strictly lobar CMB, suggesting CAA. The patient had several predisposing common factors that may have contributed to ICH after thrombolysis: older age (85 years), a severe neurologic deficit at baseline [The National Institutes of Health Stroke Scale (NIHSS) 28], and taking aspirin. These factors must be considered before the administration of thrombolysis, due to their potential associated bleeding risks, but are not considered definitive contraindications for thrombolysis in the latest Japanese guidelines published in 2012 (5).

CMB has been shown to be associated with thrombolysis-related ICH, although such associations are still controversial. A recent meta-analysis demonstrated a trend toward an increased incidence of thrombolysis-related ICH in patients with CMB (6, 7). Pathological differences in CMB by distribution are now well-known, an CMB in deep regions (deep CMB) is considered to be associated with hypertensive microangiopathy, whereas strictly lobar CMB shares risk factors with CAA (8). According to the consensus (3), our patient, who was ≥ 55 years of age with multiple points of strictly lobar CMB, was diagnosed with probable CAA. This diagnosis was supported by the decreased A β levels in the CSF.

Recently, particular interest has been paid to whether or not there is an association between CAA and thrombolysis-related ICHs, as CAA often affects elderly patients at a high risk for cortico-subcortical hemorrhaging; however, data on whether or not CAA, which is clinically diagnosed by age and strictly lobar CMB on paramagnetic MRI, is associated with thrombolysis-related ICH or a poor outcome are still

limited.

There have been two case reports of thrombolysis-related ICH in CAA patients (9, 10). Both cases were elderly women >70 years of age who showed thrombolysis-related lobar ICH within 24 hours after onset and were treated by intravenous thrombolysis for right frontal lobe infarcts. Both patients died, and autopsies revealed pathologic evidence of definite CAA (9, 10). These cases imply that patients with CAA have a high risk of thrombolysis-related ICH and its associated poor outcome. However, a recent European prospective study examined the association between CMB presence and number or location and the functional outcome after thrombolysis (11). In that study, 717 consecutive patients with ischemic stroke, including 45 (6.3%) with strictly lobar CMB, a characteristic finding of CAA, and 60 (8.3%) with presumed underlying vasculopathy had CAA. All patients were treated by intravenous thrombolysis alone. A logistic regression analysis showed no association between the presence or number of CMBs on pre-thrombolysis MRI and a poor outcome 3 months after therapy, despite a substantial incidence of thrombolysis-related ICH (at least 4% of subjects). In a sensitivity analysis, patients with strictly lobar CMB, as well as with a presumed underlying vasculopathy of CAA, also showed no association with poor outcomes. Such results seem to support the clinical course of our patient, as his subsequent ICH after thrombolysis did not affect his neurologic symptoms.

Of note, there was a difference in the diagnostic accuracy of CAA between the above two case reports and the patients with a poor outcome in the European study (11) as well as our own patient: the former had pathological evidence of CAA, while the latter did not. In light of the imperfect sensitivity and specificity of the Boston criteria for the clinical diagnosis of CAA (3), the European study as well as our own case may have misclassified some patients as having CAA-related ICH when their ICH was actually related to hypertensive arteriopathy.

In conclusion, we experienced a patient that was clinically diagnosed with CAA and had thrombolysis-related ICH without neurologic deterioration. For now, clinically diagnosed CAA using MRI findings is not a contraindication for thrombolysis, but we should consider that patients with CAA supportive findings might be at a higher risk of developing thrombolysis-related ICH than patients without these findings.

The authors state that they have no Conflict of Interest (COI).

Authors' contributions

Dr. Eriguchi: Study concept and design, analysis and interpretation of data, drafting/revising the manuscript for content

Dr. Yakushiji: Study concept and design, analysis and interpretation of data, drafting/revising the manuscript for content

Dr. Tanaka: Analysis and interpretation of data

Dr. Nishihara: Analysis and interpretation of data

Prof. Hara: Drafting/revising the manuscript for content

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