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Case Series

# Cerebral Amyloid Angiopathy: A Hidden Risk for IV Thrombolysis?

Ryan J. Felling[1,3#]*, Roland Faigle[1#], Cheng-Ying Ho[2], Rafael H. Llinas[1] and Victor C. Urrutia[1]

[1]Department of Neurology, Johns Hopkins University School of Medicine, USA
[2]Department of Pathology, Johns Hopkins University School of Medicine, USA
[#]These authors contributed equally to this work

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**Corresponding author**
Ryan J. Felling, Johns Hopkins University, and Director, Pediatric Stroke Program, 200 N. Wolfe Street, Baltimore, MD 21287, Tel: 410-955-4259; Fax: 410-614-9807; E-mail: rfellin2@jhmi.edu

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**Abstract**

Recombinant tissue plasminogen activator (t-PA) is the only FDA approved therapy for acute ischemic stroke. Cerebral microbleeds (CMBs) or cerebral amyloid angiopathy (CAA) are currently not contraindications, however, data regarding this complex issue are limited. We report 2 cases of fatal intracerebral hemorrhage (sICH) after IV t-PA, each with evidence of CAA. Patients with CAA may have increased risk for IV thrombolysis-associated sICH. We highlight the severe and catastrophic pattern of ICH, which may be a defining characteristic, and discuss the limitations of our current understanding of the risk of thrombolysis-associated ICH in patients with CAA and/or CMBs.

## INTRODUCTION

Intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (t-PA) is the cornerstone of acute ischemic stroke therapy [1]. sICH complicates IV thrombolysis in 4.5 to 10% of patients [2,3]. It most commonly occurs in the infarct core within 36 hours of t-PA administration and remains the most devastating complication of thrombolysis with an associated mortality rate of up to 47% [4].

Cerebral amyloid angiopathy (CAA) is an important cause of primary lobar ICH in the elderly [5]. Deposition of amyloid beta increases the fragility of vessel walls causing spontaneous hemorrhages that commonly remain clinically silent. Diagnostic criteria for CAA (Boston criteria) exist, but definitive diagnosis requires pathologic examination. The premortem diagnosis of CAA relies on identification of lobar cerebral microbleeds (CMBs) with susceptibility-weighted (or T2*) MRI. The presence of CMBs is not a generally accepted predictor of increased risk for symptomatic ICH after IV thrombolysis, and few studies have prospectively studied this risk. We report 2 cases of sICH after t-PA, one with pathology-confirmed CAA and another with probable CAA. We discuss the risk-benefit analysis of thrombolysis in patients with CAA and propose that IV t-PA may be relatively contraindicated in patients who carry a diagnosis of at least probable CAA and/or have a high burden of CMBs. We also draw attention to the catastrophic pattern of these hemorrhages and suggest that it may be characteristic of IV t-PA-associated sICH in the presence of CAA.

## CASE PRESENTATION

### Case 1

An 81 year old African American woman with hypertension, hyperlipidemia, diabetes mellitus, and a prior transient ischemic attack presented with the acute onset of right face/arm weakness and difficulty speaking. Her NIH Stroke Scale (NIHSS) was 4. With good localization of symptoms to the left MCA territory, her presumptive diagnosis was ischemic stroke due to multiple vascular risk factors. She did not have a history of atrial fibrillation, and her symptoms did not suggest multifocal embolic infarctions. CT scan did not show any hemorrhage. In the absence of contraindications she received IV t-PA beginning 120 minutes after the onset of symptoms. Her symptoms improved during the infusion, but at the end she developed a moderate headache with confusion and new language deficits. Repeat CT scan demonstrated multifocal subdural, subarachnoid, and intraparenchymal hemorrhage (Figure 1A). Despite aggressive medical management, she progressed to herniation and brain death. On postmortem examination, the superficial cerebral and leptomeningeal small vessels showed diffuse wall thickening with eosinophilic deposits, and the involved vessels were remarkable for cracking in the wall and replacement of the medial layer by amyloid, creating a “vessel-within-vessel” or “double barreling” appearance (Figure 1B, C), consistent with grade 3 CAA [6].

### Case 2

An 84 year old man with hypertension, diabetes mellitus, hyperlipidemia, and dementia presented with acute onset left-

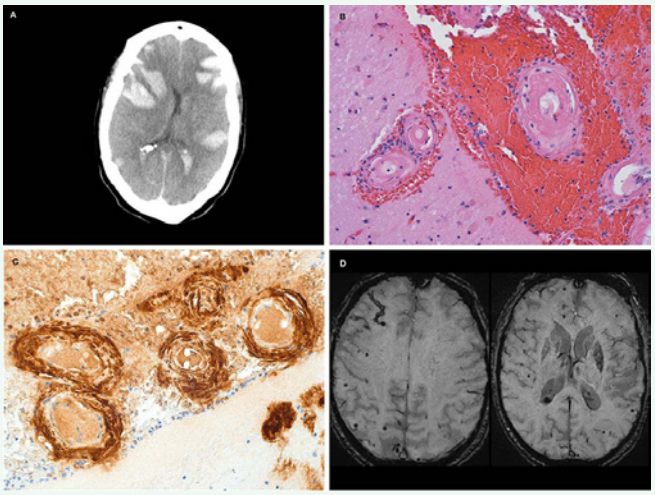

**Figure 1** (A) CT scan of patient 1 demonstrating multifocal ICH including subarachnoid, intraparenchymal, and intraventricular components. (B) Hematoxylin and eosin stain demonstrating hemorrhage and "double-barrel" appearance of vessels in amyloid angiopathy from patient 1. (C) Immunohistochemistry demonstrating amyloid beta deposition in the vessel walls of patient 1. (D) Susceptibility-weighted MRI of patient 2 demonstrating numerous lobar microhemorrhages.

sided weakness, left gaze deviation, dysarthria, and neglect. His NIHSS was 14. Head CT showed an old left PCA stroke, but no hemorrhage. He was presumptively diagnosed with a focal ischemic stroke secondary to multiple vascular risk factors. He did not have clinical symptoms or a history of atrial fibrillation to strongly suggest multifocal embolic strokes. Without contraindications IV t-PA was administered 150 minutes after symptom onset symptoms. After initial improvement he developed increasing lethargy, nausea, and vomiting 3 hours after the infusion. Repeat head CT demonstrated multifocal ICH. Despite aggressive supportive measures, he suffered brain herniation and expired. A prior MRI showed extensive lobar CMBs sparing the thalamus, basal ganglia, and pons. With the history of dementia, this is consistent with probable CAA per Boston criteria (Figure 1D).

## DISCUSSION

The cases above suggest a possible increased risk of hemorrhagic complications in patients with CAA. Moreover, it draws attention to the severity of the hemorrhage with multifocal, multispace (intraparenchymal, subarachnoid and subdural) distribution, as a possible clinical marker of CAA-associated hemorrhage after IV t-PA. While the hemorrhagic conversion of multifocal embolic strokes could be an alternative explanation for the distribution of hemorrhages, neither patient presented a clinical picture consistent with multifocal strokes, nor did either have a known risk factor for cardioembolic stroke such as atrial fibrillation.

Evaluating the risk of thrombolysis-related sICH in CAA is difficult due to the lack of definitive diagnosis without pathology. In their review, McCarron et al. examined reported cases of thrombolysis-associated sICH. Of 50 cases with ICH 10 had available pathology, with 7 having evidence of CAA [7]. Other studies have examined the risk of hemorrhage following thrombolysis in patients with CMBs, but not necessarily CAA. The large, prospective BRASIL study found no significant increase in the risk of sICH following thrombolysis in patients with CMBs [8]. A recent meta-analysis demonstrated a trend toward increased risk of ICH in patients with CMBs, but none of the individual studies reached statistical significance [9].

There are important limitations in applying the above evidence to thrombolysis in the setting of acute stroke. First and foremost, many studies looking specifically at pathologic evidence of CAA in the setting of hemorrhage were done in patients receiving thrombolysis for cardiac disease rather than stroke, and patients with parenchymal brain injury prior to t-PA administration likely have very different risks of hemorrhage. The studies specifically investigating stroke patients largely utilize the presence of CMBs which lacks diagnostic specificity. CAA is one of the primary diagnoses along with hypertensive angiopathy, but the differential diagnosis includes cavernous malformations, diffuse axonal injury, and other rare causes. These studies do not address the burden or location of CMBs which may help to differentiate between etiologies [10]. It is plausible that the underlying pathology of CMBs relates to the risk of hemorrhage, and animal models indicate a specific propensity for hemorrhage after thrombolysis in CAA [11].

The cases presented here contribute important additional evidence suggesting a relationship between CAA and t-PA-related sICH. Case 1 is, to our knowledge, the first reported pathology-confirmed case of CAA in t-PA-associated hemorrhage in the setting of acute stroke, and illustrates the difficulty of making this diagnosis clinically in the emergency setting as this patient did not have a good history of cognitive decline. In order to differentiate risk due to specific underlying pathology, further study is warranted to better characterize whether the pattern and burden of CMBs is associated with increased risk of thrombolysis-associated sICH. This will require prospective studies with pre-thrombolysis MRI, and a cost-benefit analysis is necessary, considering the cost and time delay of pre-treatment MRI versus prevention of sICH. Meanwhile, the potential for increased risk of t-PA-related sICH in patients with a high probability of CAA should be an additional factor considered in clinicians' decisions to treat with thrombolysis.

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