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Intravenous Recombinant Tissue Plasminogen Activator (Rt-PA) Induced Life-Threatening Angioedema

Szu-chi Chen, MD[1], Yue-Ying Li, MD[1], Hung-Kai Lo, MD[1], Hann-Yeh Shyu, MD[2,3], Ming-Hua Chen, MD[2,3] and Po-Jen Hsiao, MD, PhD[4,5,6]

[1]Department of Internal Medicine, Taoyuan Armed Forces General Hospital, Taoyuan, Taiwan

[2]Division of Neurology, Department of Internal Medicine, Taoyuan, Armed Forces General Hospital, Taoyuan, Taiwan

[3]Department of Neurology, Tri-Service General Hospital, National Defense Medical University, Taipei, Taiwan

[4]Division of Nephrology, Department of Internal Medicine, Taoyuan, Armed Forces General Hospital, Taoyuan, Taiwan

[5]Division of Nephrology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical University, Taipei, Taiwan

[6]Department of Life Sciences, National Central University, Taoyuan, Taiwan

***Corresponding author:**

Po-Jen Hsiao, MD,
Division of Nephrology, Department of Internal Medicine, Taoyuan Armed Forces General Hospital, Taiwan No.168, Zhongxing Rd., Longtan Dist., Taoyuan City 325, Taiwan

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1. Abstract

An 85-year-old woman with a prior cerebrovascular accident presented with sudden right-sided weakness and aphasia (NIHSS 15). She received intravenous recombinant tissue plasminogen activator (rt-PA) followed by successful mechanical thrombectomy for an acute left M1 occlusion. Within two hours, she developed right-sided neck swelling, ecchymosis, dyspnea, and stridor. Prophylactic endotracheal intubation was performed, and methylprednisolone and diphenhydramine were administered. Her airway stabilized without haemorrhagic complications. Neurological function gradually improved, and she was extubated after 10 days. The patient achieved a satisfactory recovery and remained well without sequelae at 6-month follow-up. rt-PA induced neck angioedema is rare but may be life-threatening. Early recognition of rt-PA–induced angioedema associated complications and prompt management are crucial to prevent fatal complications.

2. Introduction

Angioedema without accompanying urticaria is a recognized and potentially serious complication in patients receiving the recombinant tissue-type plasminogen activator (r-tPA) alteplase or its modified form, Tenecteplase, for acute ischemic stroke, with reported incidence ranging from 0.4% to 5.1% [1-5]. This condition manifests as nonpitting, nonpruritic swelling of the skin or mucous membranes resulting from transient increases in vascular permeability. When induced by r-tPA, angioedema typically affects the head and neck region, posing a significant risk of airway compromise and potentially fatal obstruction. Multiple biological pathways can lead to angioedema, and several mediators have been implicated, including bradykinin, histamine, substance P, prostaglandins, and leukotrienes. Because the effectiveness of treatment differs across these mechanisms, accurately identifying the predominant mediator is essential for guiding appropriate, individualized therapy.

Although existing clinical guidelines advise the initial use of epinephrine and antihistamines when managing isolated r-tPA–induced angioedema, growing evidence suggests that this strategy may not fully address the underlying pathophysiology in many cases. Increasing data indicate that bradykinin plays a central role in r-tPA–associated angioedema, especially given its involvement in vasodilation and increased vascular permeability. Therefore, the experts advocate for therapeutic approaches that prioritize modulation of the bradykinin pathway [6], such as agents targeting bradykinin receptors or inhibiting its production or downstream effects. This shift in focus may improve outcomes by offering more targeted control of the angioedema process, particularly in patients who do not respond adequately to conventional antihistamine- and epinephrine-based regimens. Overall, optimizing the management of r-tPA–induced angioedema requires greater attention to the underlying mechanisms, with growing support for bradykinin-cantered strategies as a more physiologically appropriate and potentially more effective first-line treatment option.

3. Case Report

An 85-year-old woman with a history of an old cerebrovascular accident presented to the outpatient department with sudden onset of right-sided weakness and aphasia. She was immediately transferred to the emergency department for further evaluation. On arrival, her National Institutes of Health Stroke Scale (NIHSS) score was 15. After consultation with a neurologist, intravenous recombinant tissue plasminogen activator (rt-PA) was administered. The patient subsequently underwent endovascular thrombectomy, which revealed an acute occlusion of the left middle cerebral artery (M1 segment), and successful mechanical thrombectomy was performed. Within two hours after rt-PA administration, non-pitting swelling and ecchymosis over the right side of her neck were noted (Figure 1). Physical examination revealed obvious dyspnea and stridor. For airway protection, prophylactic endotracheal intubation was performed after discussion with the patient and her family. Intravenous methylprednisolone (125 mg) and diphenhydramine (60 mg) were administered immediately in addition to airway management. Following the above interventions, gradual improvement in muscle strength on the right side was observed. No hemorrhagic complications occurred during hospitalization. The patient was successfully extubated after 10 days. She was discharged with a satisfactory recovery. After a 6-month follow-up, she remained well without sequelae.

Figure 1: Non-pitting swelling and ecchymosis over the right side of the neck developed within two hours after administration of intravenous recombinant tissue plasminogen activator (rt-PA).

4. Discussion

Angioedema has been reported to occur in patients treated with alteplase or Tenecteplase for acute ischemic stroke [1-6]. It is typically mild, transient, and often manifests contralateral to the ischemic hemisphere. rt-PA-induced angioedema usually involves the head and neck region, where it may lead to airway obstruction and potentially life-threatening complications [3, 4]. Because upper airway compromise can develop rapidly, clinicians should maintain a high index of suspicion and initiate prompt airway protection when necessary.

The onset of angioedema has been reported to range from 5 to 189 minutes after the initiation of rt-PA infusion, with a median onset time of approximately 65 minutes [7, 8]. Therefore, close monitoring of patients for several hours following rt-PA administration is strongly recommended to detect any early signs of airway involvement. The proposed mechanism of rt-PA–induced angioedema involves vasodilation and increased vascular permeability mediated by inflammatory pathways, primarily through bradykinin activation. Patients receiving angiotensin-converting enzyme (ACE) inhibitors and those with computed tomogra-

phy (CT) evidence of ischemia involving the frontal and insular cortex appear to have an increased risk of developing angioedema [9]. Consequently, the use of ACE inhibitors for blood pressure control should be avoided immediately prior to rt-PA administration. Although current guidelines recommend initial management with epinephrine and antihistamines for isolated rt-PA-induced angioedema, several reports suggest that treatment targeting the bradykinin-mediated pathway may provide a more effective therapeutic approach [10]. Further research is warranted to establish optimal management strategies for this potentially fatal complication.

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