TPA-induced angioedema involving the posterior cerebral artery; a case presentation

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Introduction:

- Tissue plasminogen activator (t-PA, or Alteplase) is commonly used in the treatment of acute ischemic stroke, pulmonary embolism, and ST-elevation myocardial infarctions.
- Since its approval in 1996, utilization has marked improved stroke recovery and decreased hospital stay.
- Major concerns with administering t-PA are intracranial hemorrhage and brain herniation, however hospital staff should be vigilant for other severe reactions such as angioedema, hemopericardium, cardiac tamponade, and anaphylaxis.
- TPA-induced angioedema, though rare, is a potentially fatal outcome of thrombolysis.
  - It primarily occurs in patients with the following:
    - Infarction of the middle cerebral artery.
    - Concomitant use of ACE-inhibitors.
    - C1 esterase deficiency.
- It is usually self-limited, and treatment is mostly supportive.
  - Treatment:
    - Anti-histamines, steroids, and epinephrine.
    - Refractory cases: complement inhibitors.
- Due to severity and possible progression to airway restriction, it is crucial to closely monitor these patients, especially if they are known to have increased risk factors, such as ACE-inhibitor use or C1 esterase deficiency, for this phenomena.

Case Presentation:

We present an 84-year-old female with a history of hypertension managed with lisinopril, chronic obstructive pulmonary disease, atrial fibrillation without anticoagulation for approximately three months due to gastrointestinal bleed, lung cancer with subsequent left upper lobectomy who presented to our emergency department for right-sided weakness, slurred speech, and right-sided hemianopsia after collapsing onto the floor. She did not have convulsions, loss of consciousness, or any prodromal symptoms.

Upon arrival to our emergency department, she was found to have 2/5 strength in her right-sided extremities as well as right-sided neglect. An urgent CT of the head was performed and revealed a subacute infarct of the left pons (Picture 1). A CTA head was obtained which confirmed these findings.

After determination of thrombolytic candidacy, Alteplase was given. Within 30 mins of initial administration the patient complained of oral swelling. Soon after, she required emergent intubation for airway protection.

Neurology and the critical care team helped coordinate her care. Treatment included methylprednisolone 125mg IV, diphenhydramine 50mg IV, and famotidine 20mg IV to treat the angioedema. There was marked improvement of her angioedema and she was subsequently extubated the following morning. Repeat CT of the head revealed an acute to subacute infarct with encephalomalacia of the left occipital lobe (Picture 2). Echocardiography did not reveal an atrial shunt. She was started on full dose aspirin as well as duloxetine 20mg for stroke recovery. She began to work with physical therapy and had some improvement in her motor skills as well as her vision. Subsequent MRI illustrated infarct in the region of the posterior cerebral artery circulation without evidence of hemorrhagic conversion.

During her hospitalization, she had persistent nausea and vomiting which was controlled with promethazine. As per neurology recommendations, her anticoagulation was restarted 10 days after the onset of her stroke. Ultimately, the patient was discharged home with hospice at the request of patient and family. Her discharge medications included morphine sulfate, lorazepam, fluoxetine, and promethazine. She expired a week thereafter.

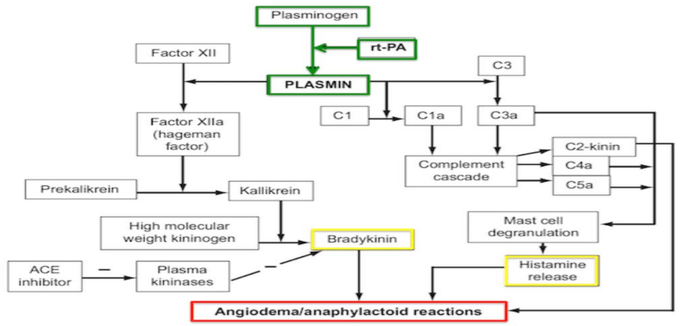
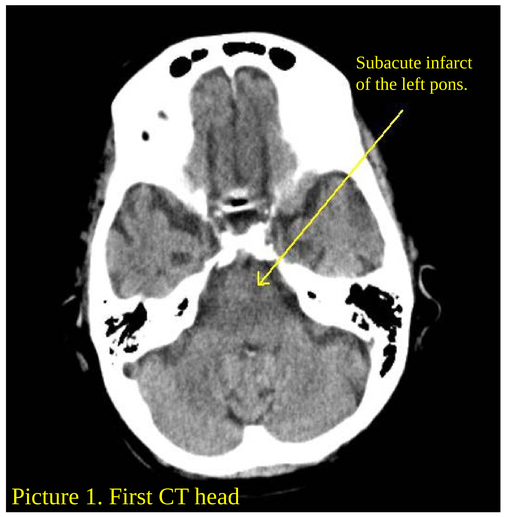
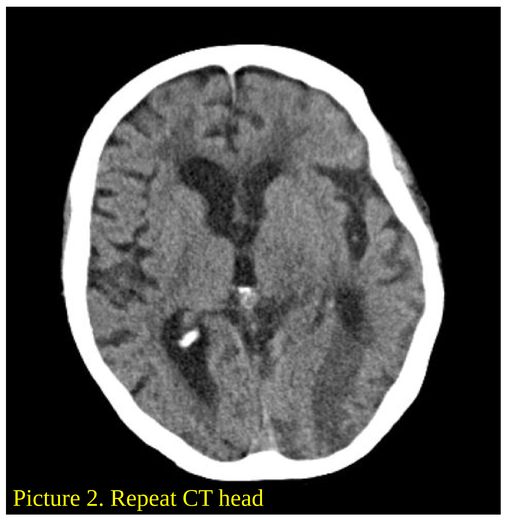


Table 1. Hypotheses



Picture 1. First CT head



Picture 2. Repeat CT head

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Discussion:

- Angioedema is a rare but potentially fatal complication of administering t-PA.
  - Occurs in approximately 1-5% of patients receiving t-PA after an ischemic stroke [1].
  - Usually observed within an hour of completing the t-PA infusion. [2]
- The mechanism behind this phenomena is still unclear, however there are several hypotheses used to explain this occurrence (Table 1).
  - Theories suggest that it may be a bradykinin-mediated pathway as t-PA increases the production of bradykinin thus increasing vascular permeability, as well as histamine, causing vasodilation [1]. Another source suggests that t-PA may activate the complement pathway leading to increased complement levels, therefore increasing mast cell and basophil degranulation leading to angioedema [3].
- The relative risk of developing t-PA-induced angioedema in patients who take ACE-inhibitors, is 13.6, as both these medications increase levels of circulating bradykinin [2,4,5]. This was demonstrated in our case as our patient was taking lisinopril making her more susceptible to developing t-PA-induced angioedema.
- There have been studies performed to determine other risk factors for development of t-PA-induced angioedema, such as the location of the ischemic stroke.
  - It has been hypothesized that right-sided insular ischemic infarcts pose the greatest risk of developing angioedema as compared to other cerebral infarctions with a relative risk of 6.4.
  - It is postulated that insular infarcts augment sympathetic hyperactivity due to impaired autonomic function, which in turn intensifies proinflammatory cytokine production and vascular permeability that can cause orolingual edema [1].
  - Our patient, however, had a posterior cerebral artery (PCA) infarct which is not consistent with these hypotheses, making our case more unusual. A retrospective institutional study done by Sczepanski et al showed that of the 4 patients who had t-PA-induced angioedema (out of 147), only one of these 4 had ischemia to the PCA.
- Hospital staff should be prepared to recognize the first signs of t-PA-induced angioedema and follow the 2018 Guidelines for proper management [4] .
  - Discontinue the t-PA infusion.
  - Administer:
    - IV methylprednisolone 125 mg, diphenhydramine 50 mg, ranitidine 50 mg or famotidine 20 mg.
    - If symptoms persist, epinephrine can be used, however, it should be given cautiously as it may suddenly increase blood pressure and increase the risk of intracranial hemorrhage.
    - Other options, include the C1-esterase inhibitor icatibant, a selective bradykinin B2 receptor antagonist.

Conclusion:

T-PA-induced angioedema is a rare but potentially fatal outcome of thrombolysis occurring in 1 of 50 patients, which increases to 1 of 10 in insular infarcts and 1 of 6 in those who are concomitantly using ACE-inhibitors at the time of thrombolysis [6]. Angioedema typically presents within the hour of t-PA administration and can quickly lead to airway compromise. Due to its severity, it is imperative to closely monitor these individuals, as prompt treatment is essential. Our patient, though exposed to ACE-inhibitors, was found to have an infarct of her posterior cerebral artery which has rarely been documented in the literature, making this case unique.

References:

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