

Ruptured Arteriovenous Malformation Complicating Thrombolytic Therapy With Tissue Plasminogen Activator

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● It is thought that the clot-specific activity of tissue plasminogen activator, used in the treatment of acute myocardial infarction, makes bleeding complications less common than does the use of either streptokinase or urokinase. The incidence of intracerebral hemorrhage complicating the use of tissue plasminogen activator has been estimated to be 0.68%. This is a report of the rupture of an intracranial arteriovenous malformation complicating the use of tissue plasminogen activator therapy. Theories for the mechanism of hemorrhage in this instance are presented, as are suggestions for future use of the enzyme.

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Tissue plasminogen activator is a clot-selective enzyme that has largely supplanted nonspecific streptokinase and urokinase in the treatment of acute myocardial infarction. Its greater specificity is thought to contribute to its lower incidence of bleeding complications, especially central nervous system hemorrhage.^{1,2} Detailed analysis of intracranial bleeding during treatment with tissue plasminogen activator has only been carried out in one previous study, to our knowledge.³ We report a case of cerebral hemorrhage that occurred secondary to a ruptured arteriovenous malformation during intercurrent tissue plasminogen activator treatment.

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REPORT OF A CASE

A 65-year-old man with a history of intermittent angina and controlled hypertension was admitted with substernal chest pain radiating into the left arm and electrocardiographic evidence of an acute inferior wall myocardial infarction. His initial blood pressure reading was 180/100 mm Hg. Nitrates and morphine sulfate were administered, without relief.

Subsequently the patient received a 6-mg bolus of tissue plasminogen activator followed by an infusion of 54 mg/h for 1 hour and then 20 mg/h for 2 subsequent hours. A 5000-U bolus of heparin was given during the first hour, followed by a 1000-U/h infusion.

Seven hours after initiation of the protocol, the patient developed a left hemiplegia and became unresponsive. Computed tomography revealed a massive intracerebral hematoma (Fig 1). After administration of protamine and fresh-frozen plasma, the patient underwent a right frontal craniotomy and evacuation of the hematoma. In the base of the cavity, an arteriovenous malformation with signs of recent hemorrhage was discovered and excised using a microsurgical technique. A postoperative arteriogram demonstrated no residual malformation. A subsequent computed tomographic scan showed the right frontal cavity containing the clips used to excise the arteriovenous malformation (Fig 2). Pathologic analysis revealed the characteristic features of an arteriovenous malformation (Fig 3).

The patient made an uneventful recovery despite his left hemiplegia.

Comment

The incidence of intracerebral hemorrhage in a pooled worldwide review of clinical protocols utilizing tissue plasminogen activator has been reported as 0.68%.³ Recent protocols have suggested the use of a lower rec-

ommended maximum dose of tissue plasminogen activator, recognizing that this may diminish the occurrence of intracranial hemorrhage.⁴ This inclination is based on studies demonstrating the production of a systemic fibrinolytic state with higher doses, longer infusion times, and higher infusion rates.^{5,6} An association between these fibrinolytic disorders and bleeding complications, including central nervous system hemorrhage, has been reported.⁷

In general, tissue plasminogen activator is relatively clot specific due to its high affinity for the fibrin-plasminogen complex.^{5,8,9} Cerebral arteriovenous malformations are congenital

Fig 1.—Noncontrast computed tomogram of the head reveals a massive right frontal hemorrhage extending to, and distorting, the ventricular system. This is characteristic of bleeding secondary to a ruptured arteriovenous malformation.





Fig 2.—Postoperative computed tomogram shows no residual blood and a low-density cavity where the previous clot was evacuated. Clips, used to ligate the vessels of the arteriovenous malformation, are seen within this region.



Fig 3.—Photomicrograph demonstrates the thin-walled dilated arteries and veins characteristic of an arteriovenous malformation with evidence of recent hemorrhage from the vessels (hematoxylin-eosin, $\times 100$).

anomalies composed of localized congeries of arteries and veins with deranged and premature connections. Although they are generally asymptomatic and predisposed to spontaneous rupture, with resultant intracerebral hemorrhage, episodes of repeated thrombosis within the lesion are probably more common, as are subclinical episodes of microhemorrhage.¹⁰ These have been attributed to both the abnormal fragility of the arteriovenous malformation vessels and the dramatic turbulence within the arteriovenous shunts.¹¹ Spontaneous clots or those formed in response to small bleeding occurrences might be quite susceptible to dissolution by tissue plasminogen activator.

Patients harboring asymptomatic arteriovenous malformations, as in the present case, or central nervous

system neoplasms may be particularly prone to hemorrhage when they are given the fibrinolytic enzyme. Tissue plasminogen activator may lyse fibrin clots within these lesions and result in massive intracerebral hemorrhage.

As part of the entry criteria for introduction into a tissue plasminogen activator protocol, it may be useful to obtain both noncontrast and contrast-enhanced computed tomograms of the head. Identification of an unsuspected intracranial lesion prior to induction of therapy may alter the plan of action.

The presence of such an intracranial entity may dissuade one from the use of tissue plasminogen activator in an individual case. If such use is deemed necessary, the evidence in our case may further support the use of lower dose protocols in some patients. In addition, intensive neurologic monitor-

ing should be implemented in all patients receiving tissue plasminogen activator therapy.

Finally, it should be emphasized that the risk of cerebral hemorrhage may be equally inherent in the use of other thrombolytic therapies, including streptokinase. If time constraints during an acute myocardial infarction mandate that thrombolytic therapy must be initiated immediately, before a computed tomogram can be obtained, a thorough neurologic history and physical examination should be performed to screen for patients with underlying intracranial lesions. Subsequently, the patients can be followed up on clinical grounds, and further diagnostic testing may be carried out when time permits.

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