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Arterial Changes after Thrombolysis and Percutaneous Transluminal Angioplasty in Vertebrobasilar Thrombosis

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Summary: We present clinicopathologic findings in a patient treated with intraarterial thrombolysis and angioplasty for vertebrobasilar thrombosis. Autopsy revealed a marked inflammatory infiltrate within the vertebral artery at the site of catheter manipulation. This finding may have important implications for the use of interventional angiography in cerebrovascular disease.

Index terms: Arteries, transluminal angioplasty; Thrombolysis

We present autopsy findings in a patient with vertebrobasilar thrombosis who underwent technically successful thrombolysis followed by angioplasty of an underlying region of arterial stenosis in the intracranial portion of the left vertebral artery.

Case Report

A 46-year-old man with multiple risk factors for cerebrovascular disease suffered a symptomatic left parietal lobe infarct. Subsequent imaging studies showed a silent infarct of the left cerebellar hemisphere. Two months later, vertigo, tinnitus, and diplopia developed, and the patient was admitted to the hospital for treatment with heparin. Angiography revealed complete occlusion of the right vertebral artery proximal to the posterior inferior cerebellar artery and very high grade stenosis of the left vertebral artery. Collateral flow was minimal. Despite anticoagulation, signs indicative of left pontine ischemia developed and the patient was transferred to our institution for thrombolytic therapy. He was intubated for airway protection but was alert and following commands upon arrival. Neurologic examination was remarkable for intermittent abducens and facial nerve dysfunction on the left.

Repeat angiography 5 hours after symptomatic progression revealed complete occlusion of the vertebrobasilar system proximal to the posterior inferior cerebellar arteries bilaterally (Fig 1A). Five hundred thousand units of urokinase (Abbott, Chicago, Ill) were infused into the left vertebral arterial clot over 1 hour via a 3F microcatheter with restoration of vertebrobasilar blood flow (Fig 1B). Despite recanalization, the patient's neurologic status continued to deteriorate, and fixed deficits of left pontine and medullary function were apparent following the 500 000-unit infusion. Significant residual arterial stenosis (85%) due to underlying atherosclerotic disease was evident upon recanalization. The arterial infusion of urokinase was continued for 6 hours (total dose, 1 500 000 units). The left vertebral artery stenosis was reduced to 30% via angioplasty to optimize basilar flow and reduce chances of rethrombosis (Fig 1C). Approximately 1 hour after angioplasty, signs of right pontine ischemia developed and the patient became unresponsive. Transcranial Doppler ultrasonography at this time revealed normal flow through the left vertebral and basilar arteries. Emboli were detected on sonograms of the basilar artery. Approximately 12 hours later, less than 24 hours after arrival, brain death ensued. Anticoagulation was maintained throughout the course of the patient's hospitalization and throughout all angiographic procedures. Five hours after determination of brain death, neither vertebral artery could be identified by transcranial Doppler sonography and only trickle flow was identified in the basilar artery. Flow through the anterior circulation was normal. Life support was withdrawn 36 hours after the start of thrombolysis.

Gross examination of the brain revealed an organizing cerebral infarct in the left lateral parietal lobe and diffuse softening and friability of the parenchyma throughout the posterior circulation. Microscopically, the cerebellum, occipital cortex, hippocampus, and brain stem all showed diffuse edema and acute hypoxic injury to neurons.

Gross and microscopic examinations of the circle of Willis and its major branches showed focal areas with moderate to severe stenosis resulting from atherosclerosis. The basilar artery was diffusely stenotic (75%). The right vertebral artery was almost completely occluded, with acute thrombosis in a lumen compromised by diffuse atherosclerosis (>75%). The catheterized left vertebral artery was examined from the level of the C1-2 vertebrae to the

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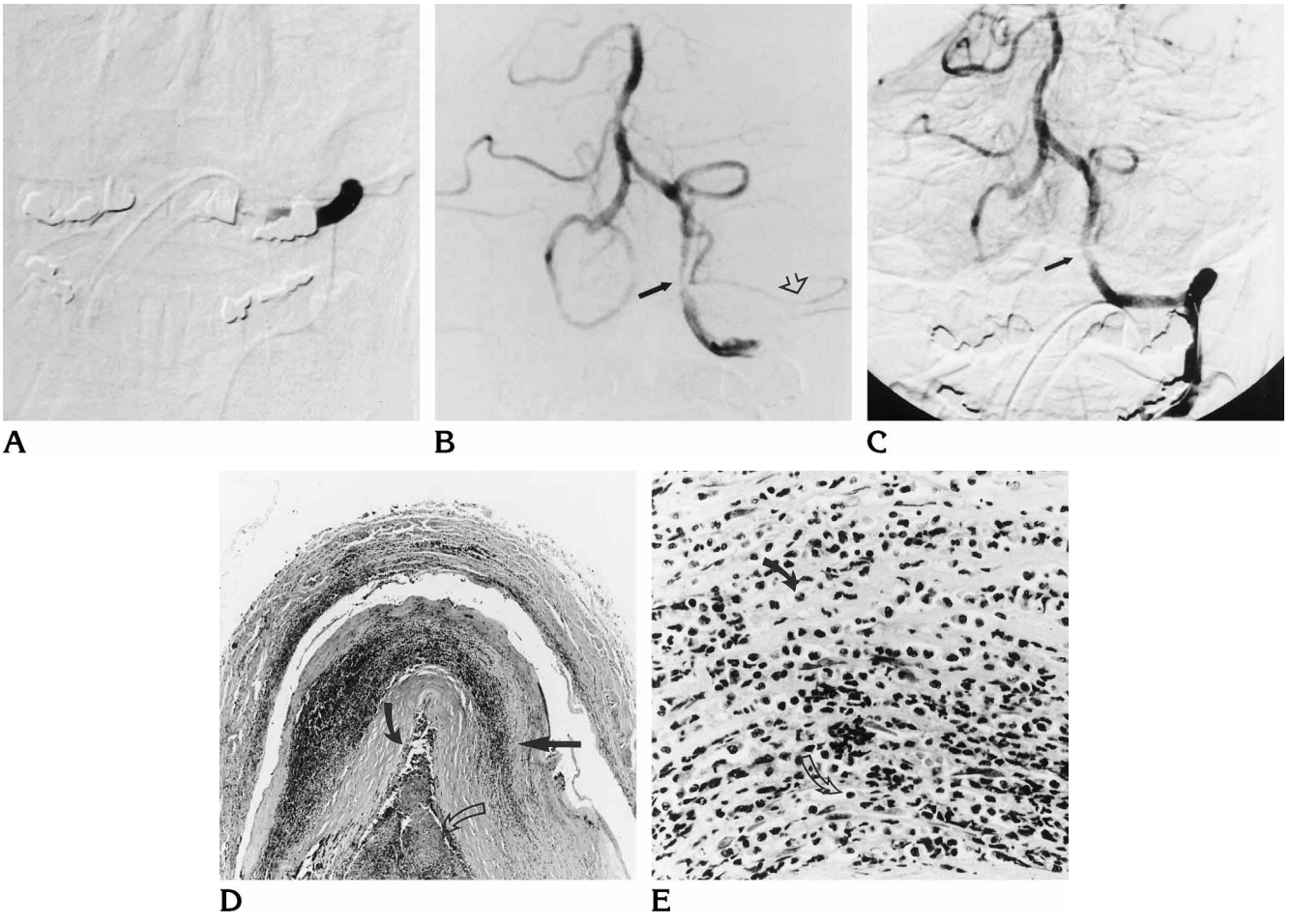

Fig 1. A 46-year-old man with signs and symptoms of brain stem ischemia.

A, Initial anteroposterior vertebral angiogram shows occlusion of the vertebrobasilar system.

B, Angiogram after urokinase infusion (1 500 000 units) into the thrombus shows marked residual stenosis (*solid arrow*). The distal branches of the posterior inferior cerebellar artery are seen (*open arrow*).

C, Angiogram after percutaneous transluminal angioplasty shows reduction of stenosis (*arrow*). Note the poor opacification of the left anterior inferior cerebellar artery and the distal branches of the posterior inferior cerebellar arteries.

D, Photomicrograph of vertebral artery shows inflammatory infiltrate within the thrombus (*open curved arrow*), intima (*solid curved arrow*), and media (*straight arrow*) (original magnification ×40).

E, Histologic section of the media shows polymorphonuclear (*solid arrow)* and lymphocytic (*open arrow*) infiltrates (original magnification ×400).

basilar artery. The lumen of the extradural portion of the artery was narrowed by partial thrombosis superimposed on atherosclerosis. The thrombus was adherent to the vessel wall and consisted of an admixture of inflammatory cells, red blood cells, and fibrin forming lines of Zahn. Like the extradural segment, the intracranial left vertebral artery contained atherosclerosis with acute thrombosis, although sections from the distal left vertebral artery had less marked atherosclerosis than the proximal segments. The vascular wall in the distal portions of the vessel had a marked inflammatory infiltrate within the intima and media (Fig 1D and E), characterized by abundant polymorphonuclear cells and mature lymphocytes. The site of the inflammatory reaction corresponded to the site in the vessel where the catheter was positioned for angioplasty and infusion of thrombolytics. There was no evidence of vasculitis within the remainder of the cerebral vasculature. No microemboli were seen.

Discussion

Clinicopathologic Correlation

Thrombosis of the vertebrobasilar system is often fatal and may warrant aggressive therapy, such as thrombolysis and angioplasty. Our experience with intraarterial thrombolysis in ver-

tebrobasilar occlusion has failed to show significant clinical benefit, largely because of high rates of rethrombosis (1). In the coronary circulation, rethrombosis tends to occur in vessels with high-grade residual stenosis (>75%) (2, 3). In an effort to decrease this risk in the present case, we opted to decrease the degree of residual stenosis within the left vertebral artery via angioplasty. Although technically successful (arterial recanalization was achieved within 7 hours of symptom progression), the patient's condition continued to worsen. The progression was characterized by exacerbation of existing symptoms and addition of new symptoms, indicating widespread bilateral brain stem ischemia. It is clear from the final transcranial Doppler ultrasonographic examination and autopsy findings that rethrombosis occurred. However, because neurologic deterioration occurred despite a patent basilar artery, another mechanism of injury must be invoked. The fact that the new signs and symptoms reflected involvement of vessels remote from those responsible for the presenting signs and symptoms argues against the allegation that recanalization occurred too late to salvage those neurons from ischemic injury, as there was no indication of ischemia in this part of the brain stem prior to recanalization.

A possible explanation for the neurologic deterioration, which is in part supported by the transcranial Doppler ultrasonographic findings, is that catheter manipulation of the arterial clot and atherosclerotic plaque caused diffuse microembolization. Indeed, this process must have occurred, since the arterial stenosis was reduced from 85% to 30%. As the ultrasonography was performed approximately 1 hour after angioplasty, the emboli, in part, must have been related to arterial wall damage and subsequent clot formation. The final angiogram (Fig 1C) does show a widely patent basilar artery and left vertebral artery, but the left anterior inferior cerebellar artery and the distal branches of the posterior inferior cerebellar arteries were not well opacified, suggesting either incomplete lysis or distal thrombi. The posterior inferior cerebellar arteries are seen better on the preangioplasty study (Fig 1B), suggesting that embolization may have occurred after the left vertebral clot disruption and angioplasty.

The lack of microemboli at autopsy may be related to endogenous fibrinolysis, since the autopsy was performed about 20 hours after the emboli were detected. In embolic stroke, angiographic documentation of arterial occlusion is often difficult unless angiography is performed within 6 hours of symptom onset (4, 5). Further, given the presumably small size of these emboli, and thus the large surface area–to–volume ratio, the process of fibrinolysis would be enhanced.

The most significant pathologic finding was the striking acute inflammatory response that was seen within the left vertebral artery at the level of catheter placement during angioplasty and thrombolysis. Because neutrophils and other white blood cells bind to activated endothelium and elaborate biologically active substances that result in disruption of the blood-brain barrier (6, 7) and promote coagulation (8–10), the presence of inflammation and thrombosis in the treated vessel of this patient has possible implications for the use of intravascular techniques in the treatment of cerebrovascular disease.

Effects of Angioplasty and Thrombolysis

In addition to their intended effects, angioplasty procedures and thrombolysis can activate both leukocytes and endothelial cells. After angioplasty is performed in extracranial vessels, endothelial cells express high levels of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and class II major histocompatibility antigens (11). Within hours after injury, neutrophils infiltrate the injured vessel wall, with peak infiltration achieved by 12 hours (12). Myocardial angioplasty leads to elevations of plasma elastase (13) and leukocyte integrins (14) within the coronary sinus, indicating local activation of neutrophils. Neutrophils taken from the coronary sinus also evidence activation with increased surface expression of the adhesion molecule CD11b and increased elastase production (15). Urokinase and streptokinase are both potent chemotactic factors for polymorphonuclear cells (16, 17). As a result of reperfusion, polymorphonuclear cells develop increased adhesiveness toward endothelium (18). In blood vessels that have been damaged by angioplasty, the propensity for white cell–endothelial cell interactions is increased.

A major consequence of the vascular inflammatory response following any interventional angiographic procedure is that of the propensity for rethrombosis. Activated white cells secrete

cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor, which promote coagulation (8–10) and further enhance neutrophil-endothelial cell interactions (19). The products of neutrophil activation, such as elastase, defensins, and lactoferrin, may also inhibit endogenous fibrinolysis (20, 21) and anticoagulation (22). But interventional angiography within the brain also carries with it problems that are unique to the brain. Urokinase alters the morphology of microvascular endothelial cells, which can disrupt the blood-brain barrier (23). The elaboration of cytokines by leukocytes at the level of the vessel wall can also disrupt the blood-brain barrier (6, 7), resulting in direct exposure of central nervous system tissue to the neurotoxic effects of cytokines (24) as well as to the toxic superoxide products of white cell activation.

Conclusions

The remarkable pathologic finding in this case is the degree of focal arterial inflammation at the site of catheter manipulation. It is not clear whether the precipitating factor for leukocyte infiltration was related to the primary disease process, mechanical injury, urokinase, or a combination of factors. What is illustrated, however, is that adequate treatment of stroke depends on more than revascularization. Catheter trauma and reperfusion both lead to upregulation of various cellular adhesion molecules, which promote leukocyte aggregation, adhesion, and migration across the endothelium. White cells may promote breakdown of the blood-brain barrier, enhance the possibility of rethrombosis, and cause damage by virtue of oxidative activity and cytokine production. Since urokinase is a potent chemoattractant for polymorphonuclear cells, vascular damage incurred through angioplasty may be confounded by concomitant thrombolysis. Simple recanalization, then, cannot be expected to be sufficient therapy for stroke. Mechanisms regulating inflammation need to be investigated to better prevent the occurrence of rethrombosis and limit neuronal injury.

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