Administration of Tissue Plasminogen Activator (tPA) during an Orthotopic Heart Transplant

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Citation

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Abstract

A 56yr old female with nonischemic cardiomyopathy and a remote unsubstantited history of lupus anticoagulant presented for orthotopic heart transplant. During the decannulation, the cardiopulmonary pass pump showed signs of clot. Simultaneously Bispectral Analysis neurological monitoring indicated a sudden and significant deterioration. The Neuro-interventional service diagnosed diffuse clot of the cerebral circulation and attempted treatment with Tissue Plasminogen Activator administration and mechanical thrombolysis.

CASE DESCRIPTION

The patient was a 56 year old woman with a diagnosis of nonischemic cardiomyopathy admitted for an orthotopic heart transplant. Her past medical history included the following: At 28, she was treated medically for an irregular heart rhythm. Then she had a stroke with resultant left sided weakness at age 44. Mitral valve prolapse was also diagnosed at that time. Three years later a pacemaker was implanted after a syncopal episode when she was found to have AV block. Echocardiogram showed a reduced ejection fraction (EF) and mitral and tricuspid insufficiency.

At 48, the patient underwent mitral and tricuspid valve repair. Three years later the patient was admitted for increased arrhythmias (chronic atrial fibrillation/flutter). Amiodarone was started; however it was discontinued due to elevated liver functions. Her EF at that time was 15-20%. At age 55, she had an automatic cardiac defibrillator implanted (AICD). Four days after the AICD placement, she suffered a transient ischemic attack and required stent placement in her right subclavian artery.

Two months prior to this admission, the patient was hospitalized with progressive heart failure; EF was 5-10%. She discharged on Coumadin and placed on the transplant list. There was noted difficulty in stabilizing her coagulation status. The cardiologists believed this may have been due to increased leafy green vegetable ingestion and also fluid retention causing hepatic congestion. In a previous admission, a lupus anticoagulant (LA) was mentioned although no information or basis for the diagnosis was recorded.

The patient quit smoking 12 years ago. She had had three normal uncomplicated pregnancies and no known drug allergies. Daily medications included: Warfarin, Lasix, Ecotrin, Folic Acid, Calcium, Aldactone, Alprazolam, Nasacort and Vitamin B 12. She was also taking Lisinopril, Carvedilol, and Hydroxyzine twice a day.

Physical examination: Blood pressure 96/66, pulse 68, and afebrile. The patient did not have JVD or carotid bruits. Breath sounds were clear but decreased at the bases. Cardiac examination revealed S1, S2 with a S3 gallop and a 2/6 systolic murmur ausculated at the left subcostal area. Peripheral pulses were full and equal in all extremities with some mild pedal edema. Abdominal ultrasound was unremarkable and a chest CT showed cardiomegaly and emphysematous lungs. Pulmonary function tests demonstrated mild obstructive disease unresponsive to bronchodilators.

Preoperative laboratory values were PT of 31.6, PTT of 38.6; her CBC and Electrolytes were normal and a urine analysis was unremarkable.

OPERATIVE COURSE

Anesthesia was induced with a combination of fentanyl, etomidate, and midazolam. Intubation was facilitated with succinylcholine. Pavulon (Pancuronium bromide) was given for muscle relaxation during the procedure. A pulmonary

artery catheter and a transesophogeal echocardiogram probe were inserted. After 1.5 hours of surgery an aminocaprioic acid infusion was initiated.

Surgery proceeded without incident. T3 was given as a bolus approximately forty-eight minutes before cross clamp removal and continued as an infusion. Bypass time was 156 minutes, cross clamp 149 minutes. The venous cannulas were removed after half of the protamine had been given. At that time it was noted that there was stranding in the aortic cannula indicating significant clot burden. Simultaneously, the Bispectral Analysis neurological monitoring reading dropped to below 10. The patient's pupils were examined and were found to be unequal, dilated and poorly responsive to light.

Immediately the blood pressure was elevated and the patient cooled. A neurosurgical consultant came to the operating room. Using a right femoral artery approach and a portable fluoroscopy machine, a catheter and guide wire were advanced into the left common carotid and the left internal carotid artery (ICA). Angiography showed a thrombus occluding the distal left M1 branch. The catheter was then directed into the right common carotid artery revealing complete occlusion of the right ICA. Left vertebral artery angiography showed a thrombus in the basilar artery. At that point a decision was made to administer Tissue Plasminogen antigen (tPA).

A wire was placed across the thrombus of the right ICA and tPA was injected along with mechanical thrombolysis. However, a follow up angiogram failed to demonstrate improvement. Additional tPA was infused to the right middle cerebral artery and the right ICA for a total of 10 mg of tPA to the right side. The catheter was then directed to the left Middle Cerebral Artery clot. tPA was injected (total 5mg) and attempts at mechanical thrombolysis were performed. Finally the catheter and wire were directed into the left vertebral artery, and 5mg of tPA was injected in the basilar artery.

The neurosurgeon then reexamined the left ICA. There was no improvement; in fact the clot seemed to have increased. Balloon angioplasties were also unsuccessful. At this point it was agreed that there was nothing to be gained by further attempts and the catheters were removed.

The surgeons then reevaluated the surgical field; there were significant raw surfaces that required further electrocautery. Bleeding was diminished but not fully controlled so the patient was transported to the intensive care unit with the skin but not the sternum closed. Chest tube drainage, while deemed more than normal, did not require further surgical intervention.

POSTOPERATIVE COURSE

Doppler examination showed complete thrombosis of the right brachial and radial arteries; the left radial and ulnar arteries and the right lower extremity's arteries were all patent.

Three screening tests for LA were obtained; a phospholipid-dependent inhibitor, PTT-LA., Hexagonal Phase and DRVV (viper venom test). Only the DRVV test was positive thus the results were not conclusive for LA.[1]

CT scans of the brain were performed after surgery. They showed "diffuse cerebral edema with loss of the gray-white differentiation consistent with sequelae of global hypoxic injury". A neurology consult concluded ischemic encephalopathy without any signs of brainstem activity. Per the family's wishes, the patient was returned to the operating room for donation of liver and kidneys.

DISCUSSION

In a few years the patient had gone from actively working and three normal pregnancies to a NYHA class IV. It was later postulated that this rapid progression was a result of microthrombosis. There was one mention in the patient's chart about a possible history of LA. Careful review of all available documents revealed no explanation or basis for this comment. (As noted above, tests for LA were not definitive). The patient had previous open heart surgery and apparently no hypercoagulable events at that time. Yet, she had several transient ischemic attacks and a subclavian artery that required stenting. Unfortunately the patient's medical records were not clear as to the etiology of her transient ischemic attacks or to the subclavian artery problem.

It was only after half of the protamine had been administered that that signs of problems were noted. This might have been underestimated had not the BIS monitor's readings dropped simultaneously. It was certainly surprisingly that even with attempts at manual thrombolysis, balloon angioplasty and administration of tPA, there was no resolution of the thrombi. In fact there seemed to have been enhancement of the occlusions.

Studies have reported the incidence of neurologic complications following a heart transplant as 13.7-31%.[2-4]

These studies reported up to a 5% risk of cerebrovascular complications,[2] with the most frequent being ischemic stroke.[3] Significant risk factors were valvular disease, diabetes mellitus and chronic renal failure.[4]

The use of antifribinolytics to limit blood loss especially on reoperations had been a common practice. While aprotinin has been withdrawn from use because of serious end organ damage,[5] aminocaproic acid is still in wide spread use and was not found to be associated with increased risk of renal, cardiac or cerebral events.[5] Researchers in Texas did report patients with inherited hypercoaguability are predisposed to overwhelming clot burden by using antifibrinolytics.[6] Patients with LA do not fit the conventional criteria of inherited hypercoaguability. However they are clearly prone to thrombosis and as such may fall into the categories outlined by Ramsey et al.[6]

Patients with a known diagnosis of LA have undergone cardiopulmonary bypass surgery without incident.[7] Use of the activated clotting time in these patients is not reliable.[7] Customary empiric dosages of heparin and protamine (monitored with heparin concentration) have resulted in an unremarkable course.[8] While it is known that LA may prolong the aPTT, LA is not generally a cause of bleeding in general or cardiac surgical procedures.[9] Almost all case reports or series of cases of patients with LA undergoing CPB focus on the intraoperative problem of anticoagulation. There are evidence linking antiphospholipid syndromes with unexplained perioperative thromboembolic complications such as graft occlusion.[10] Massoudy et al described five patients with Antiliphospholipid syndrome during cardiac surgery. Only two survived, one received one-half of the normal dose of protamine and the other received no protamine at all in order to avoid possible perioperative thrombotic events.[10]

Our case raised many questions that remain unanswered. During a heart transplant, other agents are administered which differ from routine valvular surgery including mycophenolatemofetil (Cellcept®) and OKT3. Is it possible that the malignant hypercoagulable state may have been caused by heparinization, subsequent reversal with protamine combined with one or both of those agents? Did our patient have an Antiliphospholipid syndrome exacerbated by the protamine? Could the aminocaproic acid been contributory to this process and the apparent resistance to tPA?

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