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CASE REPORT

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Rupture of a thoracic aortic aneurysm: a rare adverse reaction following systemic tissue plasminogen activator infusion

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Abstract We present a patient with rupture of a thoracic aortic aneurysm occurring after systemic infusion of tissue plasminogen activator for the treatment of acute ischemic stroke, which was successfully treated with the placement of an endovascular stent-graft.

Key words Aortic aneurysm · Ruptured aorta · Graft and prostheses · Thrombolysis · Tissue plasminogen activator

Introduction

Tissue plasminogen activator (tPA) is an in vivo biologically active substance that has a high affinity with fibrin and acts to convert plasminogen to plasmin in a thrombus. Since the fibrinolytic activity of tPA is markedly enhanced in the presence of fibrin, it is expected to localize fibrinolysis with limited systemic proteolysis. However, intracranial and gastrointestinal hemorrhage, as well as hemorrhage into the retroperitoneal space, have been reported as adverse reactions following the administration of tPA.[1–7] We report a patient with rupture of a thoracic aortic aneurysm occurring after the systemic infusion of tPA for the treatment of acute ischemic stroke, which was successfully repaired with the placement of endovascular stent-grafts.

Case report

A 67-year-old man with a history of atrial fibrillation and liver function disturbance was urgently admitted to our Department of Neurology, complaining of aphasia and right hemiplasia that suddenly developed during a business meeting. Unpon admission, the patient was awake but was slightly disorientated. There was no chest pain or other symptoms or signs that might have indicated the aneurysm was unstable. Laboratory findings showed no evidence of anemia: the red blood cell (RBC) count was $484 \times 10^4\,mm^{-3}$, hemoglobin (Hg) was 15.3 g/dl, and hematocrit (Ht) was 47%. Chest radiographs revealed a large mass in the left upper mediastinum, suggesting a thoracic aortic aneurysm (Fig. 1A). A computed tomography (CT) scan of the head showed no evidence of intracranial hemorrhage, leading to a diagnosis of acute ischemic stroke. Two hours after the onset of the aphasia and hemiplasia, a total of $1\,800 \times 10^4$ IU ($30 \times 10^4\,IU\,kg^{-1}$) of Nataplase (Milyzer: Mitsui Pharmaceutical, Japan), a recombinant single-chain tPA, was intravenously administered by drip infusion over the course of 1 h. Heparin was not utilized.

Laboratory findings on the second day revealed rapidly progressing anemia: the RBC count was $383 \times 10^4\,mm^{-3}$, Hg was 12.5 g/dl, and Ht was 35.2%. Nevertheless, there were no apparent changes in hemodynamics nor complaint of chest pain so follow-up observation was continued. On the 5th day, there was no improvement of the anemia, and left pleural effusion was seen on the chest radiographs (Fig. 1B). On the 7th day, there was mild further progression of anemia: the RBC count was $359 \times 10^4\,mm^{-3}$, Hg was 11.2 g/dl, and Ht was 33%. The patient also complained of dyspnea. The attending neurologist consulted our department for the purpose of clarifying the cause of the anemia.

A precontrast chest CT on the 7th day revealed left pleural effusion with high attenuation areas within the posterior side. High-attenuation areas were also detected within the mural thrombus of the aortic aneurysm (Fig. 2A). A contrast-enhanced CT demonstrated an aortic aneurysm, 6 cm in diameter, at the proximal descending aorta (Fig. 2B). Based on these CT findings, acute rupture of the aortic aneurysm with a massive left hemothorax was diagnosed. Over 1 000 ml of hemorrhagic pleural effusion was drained after the insertion of a chest tube into the left pleural cavity. Since liver and renal function disturbances developed and further aggravated the general condition of the patient, surgical intervention, including the placement of an inter-

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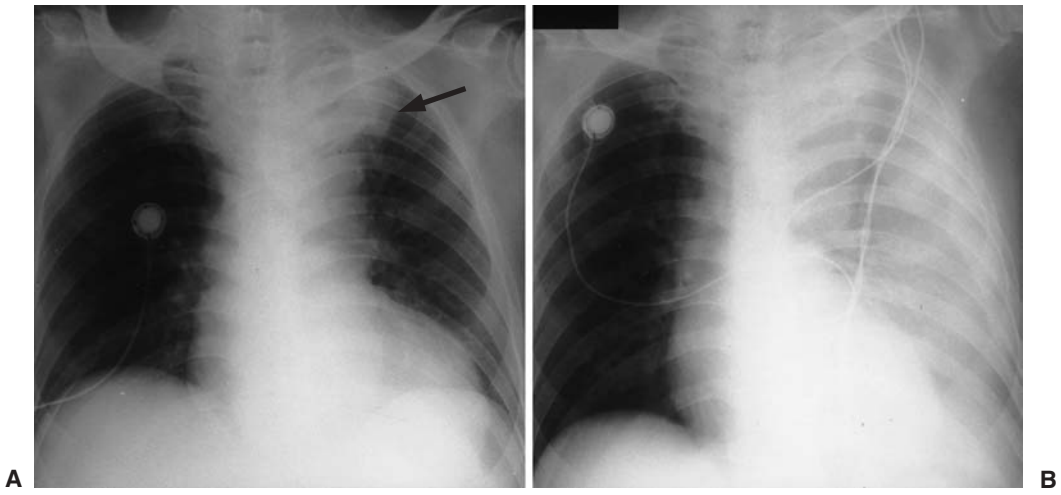

Fig. 1. **A** A chest radiograph taken on admission shows a large mass in the left upper mediastinum as well as obscuration of the aortic arch (*arrow*). **B** A chest radiograph taken on the 5th day after admission demonstrates massive opacification of the left hemithorax, suggesting pleural effusion

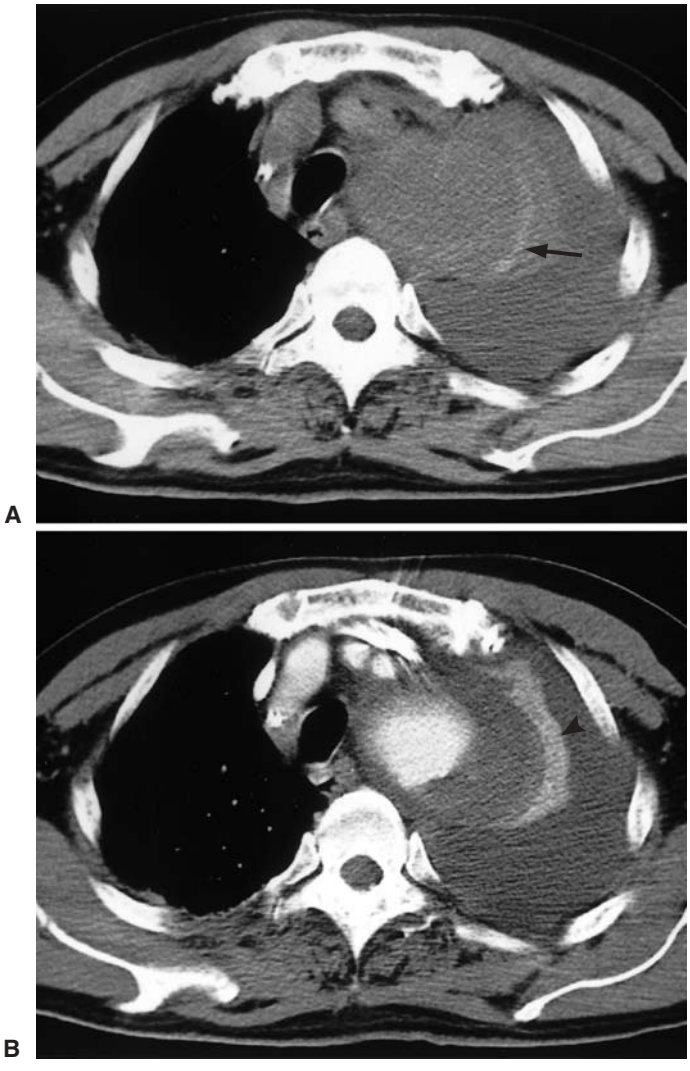

Fig. 2. **A** A precontrast chest computed tomography (CT) image depicts massive hemothorax. A high-attenuation area, which represents acute hemorrhage, is also demonstrated within the mural thrombus of the aneurysm (*arrow*). **B** A contrast-enhanced CT image demonstrates an aneurysm at the proximal descending aorta. *Arrowhead* indicates atelectasis

position graft via a thoracotomy, was considered to be ill-advised. Emergency repair of the ruptured aortic aneurysm by placement of endovascular stent-grafts was then performed.

Two stent-grafts were utilized in the procedure: a polyester-fiber graft-covered Spiral Z stent (Medico's Hirata, Tokyo, Japan), which was a 115 mm long (20 mm bare part on the proximal side) with the diameter tapered from 40 to 24 mm, and a 65-mm long by 30-mm diameter polyester-fiber graft-covered modified Z stent (hand-made). The sizes of the stent-grafts were determined on the basis of contrast-enhanced CT images. Since the proximal aortic neck between the origin of the left subclavian artery and the aortic aneurysm was short, the bare part of the Spiral Z stent was placed at the orifice of the left subclavian artery. The modified Z stent was then placed in a stent-in-stent manner at the distal side of the Spiral Z stent. Although aortography immediately after stent-graft placement revealed an endoleak from the proximal site of the aneurysm, an additional procedure, of aneurysmal packing with metallic coils (Cook, Bloomington, IN, USA), was performed (Fig. 3).

After the endovascular stent-graft repair of the aneurysm, draining of the hemorrhagic pleural effusion via a chest tube decreased significantly and stopped 12 h later. The dyspnea was resolved and no further progression of the anemia was observed. Complete thrombosis of the aneurysm was confirmed with contrast-enhanced CT on the 30th day after the endovascular stent-graft treatment. Although the patient's condition was subsequently complicated by repeated pneumonia, drug-induced liver dysfunction, renal failure, and acute pancreatitis, he was discharged 2 months after the endovascular stent-graft treatment.

Discussion

Intravenous administration of tPA is considered to be useful because this treatment can improve neurological recov-

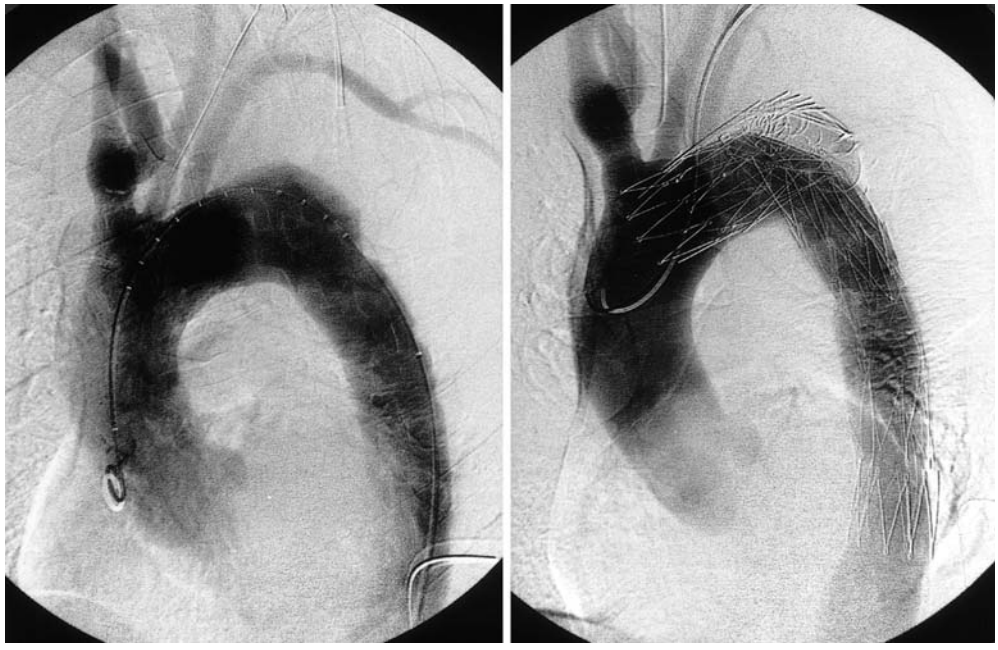

Fig. 3. Intra-arterial digital subtraction angiographic images before (**A**) and after (**B**) endovascular stent-graft placement with aneurysmal packing with metallic coils. The aortic aneurysm at the proximal descending aorta is successfully excluded

ery and reduce the incidence of disability in cases of acute ischemic stroke.[4] Tissue plasminogen activator has a high degree of affinity with fibrin. It is believed to develop clot-specific, more effective local fibrinolysis without activating systemic proteolysis, thereby reducing adverse reactions, such as hemorrhage, compared to urokinase. However, superficial and internal bleeding involving the intracranial, gastrointestinal, and retroperitoneal spaces, and the genitourinary or respiratory tracts, has been reported.[1–7] The incidence of hemorrhage after intravenous administration of tPA is reported to be similar to that of intravenous urokinase administration.[5]

To the best of our knowledge, this is the first clinical report of a case in which aortic aneurysm rupture occurred as a potentially lethal adverse reaction following systemic tPA infusion. The mechanisms of the rupture of the thoracic aortic aneurysm after the tPA infusion are not clear. The aortic wall in abdominal aortic aneurysms is degraded by a synergistic combination of macrophages, plasminogen activators, and matrix metalloproteases.[8] It is, therefore, speculated that tPA infusion might lead to the rupture of the aortic aneurysm. Tissue plasminogen activator is contraindicated in several conditions, including the presence of an intracranial hemorrhage or the suspicion of subarachnoid hemorrhage, because of the increased risk of bleeding, which can result in significant disability or death.[6,7] The presence of aortic aneurysm is, to date, not included in the contraindications of tPA therapy. However, in view of this rupture case, the presence of an aortic aneurysm should be considered by physicians prior to tPA therapy, and the risk-to-benefit ratio determined. The risk of aortic rupture should be listed in the precautions on tPA therapy.

The repair of aortic aneurysms using endovascular stent-grafts was initially employed for the treatment of abdominal aortic aneurysm, but was later applied to thoracic aortic aneurysms.[9,10] Semba et al. reported success with the use of endovascular stent-grafts in 11 patients in the repair of an acute rupture of a descending thoracic aortic aneurysm.[11] They reported that exclusion of the ruptured thoracic aneurysms was successful in all patients without any complications. In the present case, draining of the hemorrhagic pleural effusion via a chest tube decreased significantly and finally stopped, and no further progression of anemia was observed after the placement of the endovascular stent-grafts. This novel procedure may be an effective, less invasive alternative to surgery in patients with an acute rupture of an aortic aneurysm.

The occurrence of acute rupture of an aneurysm after systemic tPA infusion is considered a rare but potentially life-threatening adverse reaction. Physicians should be aware of the presence of an aortic aneurysm prior to tPA therapy. When the existence of an aortic aneurysm is suspected, tPA therapy should be performed carefully, taking into consideration the risk-to-benefit ratio. If an aortic rupture should occur, endovascular stent-graft repair may be a therapeutic alternative to conventional surgery in patients considered at high risk.

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