*Case Report*

Risk factors of diffuse alveolar hemorrhage after acute ischemic stroke treated with tissue-type plasminogen activator. The effectiveness of activated recombinant factor VII treatment

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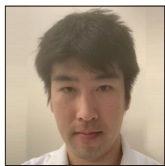
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ABSTRACT

Background: Diffuse alveolar hemorrhage (DAH) is a rare and frequently life-threatening complication of a variety of conditions. DAH may result from coagulation disorders, inhaled toxins, or infections. We report a series of patients who developed DAH after receiving a tissue-type plasminogen activator (tPA) for acute cerebral infarction. We aimed to find risk factors of DAH in patients receiving tPA and the effectiveness of activated recombinant factor VII (rFVIIa) treatment for the same.

Case Description: A total of 1023 acute ischemic stroke (AIS) patients who received tPA in our department from January 2006 to December 2018 were enrolled in this study. Four of the 1023 patients (0.39%) developed DAH. The modified Rankin scale was used to assess clinical severity. Infarction volume was assessed upon follow-up using DWI (diffusion-weighted imaging). Atherothrombotic brain infarction cases were excluded from the study. The age, sex, occlusion site, area of infarction, emphysema, intracranial hemorrhage, and neurological outcomes were analyzed. Patients who developed DAH were more likely to have a history of emphysema. We administered rFVIIa to three DAH patients with good prognosis.

Conclusion: The inclusion/exclusion criteria of tPA were based on the AHA/ASA Guidelines for the early management of patients with AIS. These patients had no evidence of infections, bronchoscopy, autoimmune diseases, HIV, and transplantations. Our study suggests that systemic administration of rFVIIa for DAH is effective. Emphysema may be a risk factor for the development of DAH following tPA. When we use tPA for emphysema patients, we must be careful about DAH enough.

Keywords: Activated recombinant factor VII, Acute ischemic stroke, Diffuse alveolar hemorrhage, National Institutes of Health Stroke Scale, Tissue-type plasminogen activator

INTRODUCTION

Diffuse alveolar hemorrhage is an uncommon but acute and life-threatening event. A number of diseases can cause pulmonary bleeding, and it can accompany Wegener granulomatosis, microscopic polyangiitis, Goodpasture syndrome, connective tissue disorders, antiphospholipid antibody syndrome, infectious or toxic exposures, and neoplastic conditions.[2,4] In addition, the administration of tPA can also cause such bleeding. Glycoprotein IIb/IIIa inhibitors and other

antiplatelet drugs have been the most commonly reported drugs associated with alveolar hemorrhage.[6] Kalra *et al.* reported that 0.27% (14/5412) of patients who underwent coronary procedures with tPA[7] developed DAH. We report a series of four patients who developed DAH due to tPA. In our study, rFVIIa (NovoSeven®, Novo Nordisk A/S, Bagsværd, Denmark) administration was very effective in treating DAH. This is the first report to show the effectiveness of rFVIIa on DAH due to tPA.

CASE DESCRIPTION

Case 1

A 68-year-old man with the left hemiparesis from 2 h previously visited the emergency room. His medical history included hypertension and bilateral emphysema due to heavy smoking. Vital sign assessment revealed tachycardia; examination of the heart revealed atrial fibrillation (AF). Neurological examination revealed left hemiparesis and mild disturbance of consciousness. The National Institutes of Health Stroke Scale (NIHSS) score was 12. A magnetic resonance imaging (MRI) (diffusion-weighted image) showed right corona radiate infarction [Figure 1a]. MR angiography (MRA) revealed right middle cerebral artery (MCA) occlusion [Figure 1b]. Chest X-ray showed no remarkable findings on admission. Initial investigations performed included a white blood cell (13.9×10^9/L; normal $4-11 \times 10^9$/L), hemoglobin (14.6 g/dL; normal 13.1–17.3 g/dL), and platelet (147×10^9/L; normal $130-400 \times 10^9$/L) count. Prothrombin time (16 s; normal 11.5–14.5 s), activated partial thromboplastin time (40.1 s; normal 27.5–41 s), D-dimer (<0.5 mg/mL; normal <0.5 mg/mL), arterial blood gas (room air; pH 7.35), PaO_2 (89.0 mmHg), and $PaCO_2$ (45.1 mmHg) were also analyzed. The patient was negative for antineutrophilic cytoplasmic antibody. Intravenous tPA was administered according to the accelerated regimen (0.6 mg/kg) 3.5 h after onset. Four hours later, consciousness gradually improved, the right MCA recanalized [Figure 1c], and volume of infarction was not changed. The patient experienced hemoptysis and mild shortness of breath 18 h later, with no chest pain or fever. Oxygen saturation dropped from 97 to 90%. Chest computed tomography (CT) revealed multifocal

diffuse ground-glass attenuation and patchy consolidation in both lungs [Figure 2a and b]. Immediate chest X-ray revealed bilateral upper lobe intra-alveolar infiltrate [Figure 2c]. The hemoptysis gradually improved after treatment with dopamine, corticosteroids, and bronchodilators, followed by fluid replacement, mechanical ventilation (MV), and administration of rFVIIa (75 mg/kg) with corticosteroids. The improvement was noted on day 3 and resolved completely by day 4. Hemoglobin dropped from 14.9 g/dl on admission to 11.7 g/dl on day 5, with no evidence of bleeding in other sites. Two weeks later, he was put off of the artificial respirator. After 1 month, the chest X-ray was normal [Figure 2d]. He was transferred to a rehabilitation hospital after 6 weeks of hospitalization with modified Rankin scale (mRS) score of 3.

Case 2

A 54-year-old male, previously healthy, nonsmoking, presented with the right hemiparesis from 1.5 h with a body temperature of 36.1°C and room air oxygen saturation of 95%. Cardiac examination showed arterial fibrillation. His white blood cell count was 6.3×10^9 cells/L, hematocrit was 39%, and platelet count was 196×10^9 cells/L. The APTT was not prolonged at 35 s and PT and INR were normal. Serologies for ANA, c- and p-ANCA, and anti-GBM antibodies were negative. IgG ACA and anti-2GPI antibodies were persistently negative. Urinalysis was normal. The NIHSS score was 10. Initial brain CT excluded bleeding. tPA was administered 3 h after symptom onset. After tPA, there was no improvement in the NIHSS score.
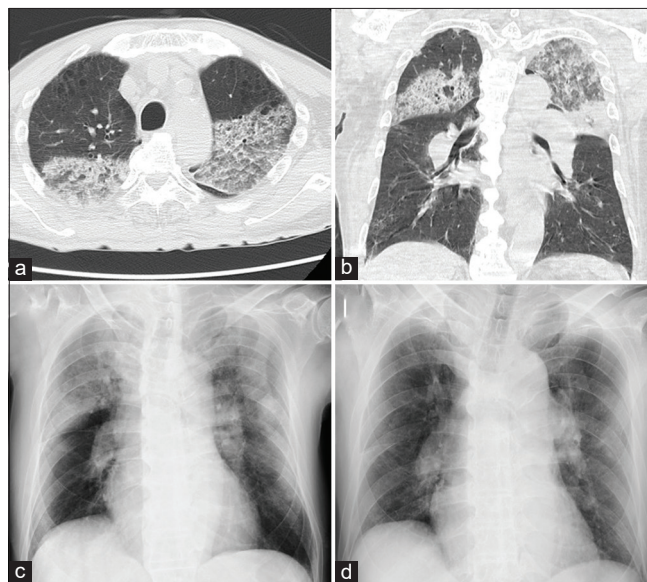

Figure 1: (a) MRI (diffusion-weighted image) showing right corona radiate infarction. (b) MR angiography (MRA) reveals right middle cerebral artery (MCA) occlusion. (c) Four hours after tPA administration, the right MCA was recanalized.

Figure 2: (a-c) Thorax CT and chest X-ray performed 18 h after intravenous tPA in the 68-year-old man (Case 1) shows bilateral infiltrations in the middle and superior lobes suggesting diffuse alveolar hemorrhage (DAH). (d) Chest X-ray which performed 1 month after tPA shows full recovery of DAH.

Six hours after ITT, he presented with acute dyspnea, hypoxemia, and hemoptysis. Chest radiography showed bilateral alveolar infiltrates and emphysema, but there were no pulmonary emboli seen on CT evaluation of the pulmonary vasculature. His hemoglobin level dropped from 11.6 to 9.8 g/dL. Bronchoscopy revealed DAH. He was diagnosed as having tPA-associated alveolar hemorrhage and treated by administering intrapulmonary rFVIIa (75 mg/kg) with corticosteroids. Within 5 days, he had near-complete resolution of symptoms and radiographic findings. After 3 weeks, he was extubated and discharged with an mRS score of 2 at the end of 1 week. A control thorax CT performed after 6 months showed complete resolution of the infiltrates, and the mRS score was 1.

Case 3

A 71-year-old female was admitted to the emergency room 90 min after acute onset of the right hemiplegia and global aphasia. Her medical history revealed that she had mitral stenosis and AF for several years. She was not using an anticoagulant drug. The NIHSS score was 22. Initial brain CT excluded bleeding. Initial laboratory findings showed no abnormality in routine biochemical, coagulation, and complete blood count parameters. tPA was administered 3 h after symptom onset. After tPA administration, there was no improvement in the NIHSS score. Follow-up brain CT at 24 h showed a large ischemic lesion in the area of the left MCA.

Eight hours after tPA, she was experiencing shortness of breath, an oxygen saturation on room air of 88%, and bilateral rales. Her hemoglobin level dropped from 12.5 to 7.2 g/dL. She received 4 units of fresh frozen plasma and 2 units of packed red blood cells. Chest radiographs showed new bilateral alveolar infiltrates and no evidence of pulmonary emboli. We performed bronchoscopy with bronchial alveolar lavage (BAL). The returned lavage fluid was bloody from aliquot to aliquot [Figure 3a]. She underwent endotracheal intubation for MV. She was diagnosed with alveolar hemorrhage. Heparin therapy was stopped. Because of severe hypoxemia, extracorporeal membrane oxygenation was started; however, subsequently, the patient suddenly collapsed. Despite changing the extracorporeal membrane oxygenation to percutaneous cardiopulmonary bypass, the patient died the same day. An autopsy was performed at the request of the family. Lung tissue obtained during autopsy showed neutrophilic septal infiltrates and associated alveolar hemorrhage [Figure 3b].

Case 4

A 75-year-old male presented with the right hemiparesis and motor aphasia from 1 h. He had not previously been diagnosed with undifferentiated connective tissue disease.
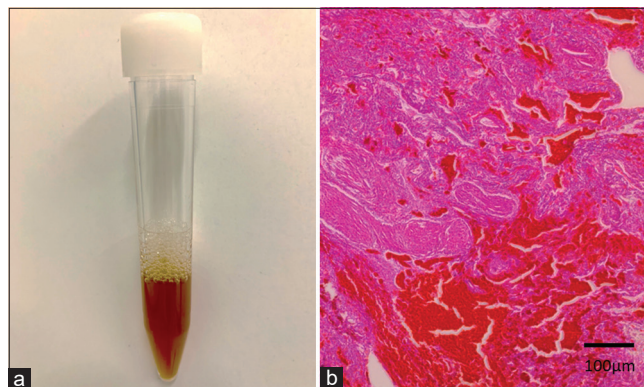

Figure 3: (a) Bronchoalveolar lavage (BAL) was performed in the left upper lobe (Case 3). We observed progressive hemorrhagic BAL. BAL fluid analysis shows an increase in red blood cells. (b) Autopsy of the lung tissue (×20) (Case 3) showing inflammatory cell infiltrate of septae and extravasation of red blood cells into alveolar spaces.

He had a 50 pack-year smoking history. His medical history revealed that he had prosthetic mitral valve AF detected on electrocardiogram. Initial laboratory findings showed no abnormality in routine biochemical, coagulation, and complete blood count parameters. The NIHSS score was 15. Initial brain CT had not shown intracranial bleeding. Two hours after symptom onset, tPA was administered. Five hours after tPA administration, there was improvement in the NIHSS score (15–10). He was afebrile and had a room air oxygen saturation of 84%. Basilar rales were present on lung examination. Chest radiography showed bilateral alveolar infiltrates and emphysema; CT scan of the chest showed no pulmonary emboli. Bronchoscopy was significant for bilateral alveolar hemorrhage without evidence of infection. His hemoglobin level dropped from 13.6 to 10.1 g/dL. He received 4 units of packed red blood cells. Control chest X-ray performed after 1 month showed complete resolution of the infiltrates. The patient was transferred to palliative care unit 1 month after tPA with a modified Rankin scale (mRS) score of 4.

DISCUSSION

Thrombolytic therapy induces a marked hemostatic defect by combined actions on blood components, the vessel wall, and the hemostatic plug resulting in hemorrhagic complications in the central nervous system, GI and GU tracts, retroperitoneum, and at vascular access sites.[9]

Symptomatic intracerebral hemorrhage is a well-known complication of antiplatelet or anticoagulant therapy; however, there are limited data regarding extracranial hemorrhage, especially DAH in AIS. Alveolar hemorrhage (AH) is characterized by accumulation of red blood cells within acinar lung units derived from alveolar capillaries or venules.[10] It originates from the pulmonary

microcirculation rather than the bronchial circulation and parenchymal abnormalities. Its local form may be secondary to local infection. The diffuse form (DAH) is associated with pathologies such as systemic vasculitis including granulomatosis with polyangiitis, microscopic polyangiitis, and anti-glomerular basement membrane (GBM). Antibody disease and connective tissue diseases such as systemic lupus erythematosus and rheumatoid arthritis also form part of the diffuse form of DAH. Exposure to toxins and drugs, left ventricle dysfunction, mitral stenosis, coagulation disorders, idiopathic pulmonary hemosiderosis, bone marrow transplant, and infections such as HIV are also associated with DAH.[10]

The cause of our patients' intra-alveolar bleeding remains unknown. However, it was interesting that most of our patients had emphysema. Prior emphysema might have been a risk factor for this adverse effect. Fibrinolysis induced by tPA causes hemostatic plug disintegration and bleeding from sites of emphysema. It is possible, however, that prior emphysema contributed to tPA-related bleeding because of the presence of fragile line blood vessels (angiogenesis) in the scar.

Diffuse alveolar hemorrhage syndrome has three main histological appearances: (1) pulmonary capillaritis characterized by neutrophilic infiltration of the interstitium leading to capillary damage; (2) bland hemorrhage into the alveolar space without inflammation; and (3) diffuse alveolar damage similar to acute respiratory distress syndrome.

In the third pattern, there is hemorrhage in alveolar spaces with alveolar damage. This pattern is associated with anticoagulant therapy, idiopathic pulmonary hypertension, and emphysema.[11] DAH that appears as a complication of medical therapy is a direct consequence of the drug and this is called as "drug-induced DAH." Drugs may cause DAH by causing hypersensitivity reactions or direct toxicity, and some drugs such as thrombolytic agents, anticoagulants, platelet glycoprotein IIb/IIIa inhibitors, and platelet aggregation inhibitors may cause DAH by causing coagulation defects. The clinical presentation is usually acute, but sometimes may be subacute.[11,13]

The most important laboratory finding is the decrease in hematocrit, especially in acute-onset patients. Anti-neutrophil cytoplasmic antibodies, anti-double-stranded DNA, antinuclear antibodies, anti-GBM antibodies, coagulation studies, and peripheral smear should be assessed for diagnosis and urinalysis; serum urea and creatinine should be assessed for renal involvement.[10] Bronchoscopy is necessary to exclude endobronchial lesions. Sequential bronchoalveolar lavage (BAL) aliquots taken from the same location through flexible bronchoscopy are progressively more hemorrhagic in DAH, which is

diagnostic.[10] BAL is also needed to exclude infection, and cytological examination differentiates DAH from pulmonary bleeding due to metastasis. Recently, it has been reported that administering rFVIIa as a rescue therapy resulted in good results in the treatment of DAH.[3,8] Therapy of the DAH syndrome seems to be simple because DAH is the common denominator of multiple underlying diseases and conditions. It is most important to separate the treatment of the alveolar bleeding from the optimization of underlying disease such as plasmapheresis, steroids, and antibiotics. Intravenous administration of FVIIa is suggested as an adjuvant therapy for the treatment of the underlying disease. Taking into consideration, the adverse effects of high-dose steroids often used in patients with DAH and further the risk of acquiring irreversible pulmonary fibrosis due to insufficient iron clearance, FVIIa seems to be far less risky in spite of such an intervention.[1]

Our study demonstrates low mortality rate after administering intrapulmonary rFVIIa [Table 1]. There are case reports in the literature showing that ITT with streptokinase or alteplase might result in DAH in patients with acute myocardial infarction (MI).[12,14]

Data from 10 cases with MI showed that DAH occurred within 3 h–12 h following ITT and that previous pneumonia, pulmonary, or cardiac catheterization, defibrillation or cardiopulmonary resuscitation, arrhythmia, heart failure, and chronic obstructive pulmonary disease such as emphysema were comorbidities that increased the development of DAH.[14] We calculated incidence of DAH due to tPA in our patients with AIS. This was 0.39% (95% CI =0.25–0.44). In the literature, it was reported in patients with acute MI receiving coronary arteriography and treatment with GP IIb/IIIa inhibitors.[7] In our case series, 3 of 4 patients with DAH had emphysema which suggests that emphysema may be a risk factor for the development of DAH following ITT as previously reported.[5] Overall, 31 of 1023 non-DAH patients had emphysema. This is clearly significantly different.

Only one patient died within 1 week of massive DAH and respiratory failure. The other three patients survived, and DAH recovered completely. The most important laboratory finding of DAH, decreased hemoglobin, was observed in all patients. We believe that the use of rFVIIa may be effective in the treatment of DAH following ITT in patients with AIS. In this study, rFVIIa administration was very effective. Development of DAH due to tPA in three patients with AIS with emphysema and showing effectiveness of rFVIIa was reported for the 1st time. Systemic administration of FVIIa for use for the uncontrollable life-threatening hemorrhage may become an effective treatment even in patients with AIH.

Table 1: Clinical data of the patients.

Case	Age	Sex	Occluded artery	NIHSS	tPA administration after onset (h)	Volume of infarction (mm³)	Etiology	Side of DAH	On admission Hb	Follow-up Hb	Emphysema	rFVIIa	Prognosis (mRS)
1	68	M	Rt-ICA	12	3.5	21	Af	Bil	14.9	11.7	+	+	3
2	54	F	Rt-MCA	8	3	28	Af	Bil	11.6	9.8	+	+	1
3	71	M	Lt-MCA	22	3	72	Af	Rt	12.6	7.2	+	-	6
4	74	F	Lt-MCA	15	2	63	Af	Bil	13.6	10.1	-	+	4

CONCLUSION

Caution should be exercised when using tPA on emphysema patients, we must be careful about DAH. The documented therapy of FVIIa has demonstrated a sustained and immediate hemostatic effect in DAH, however, still only in a small number of patients.

Larger studies are warranted, taking into account the high mortality of the DAH syndrome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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