

Intravenous Tissue Plasminogen Activator for an Ischemic Stroke with Occult Double Primary Cancer

Yukihiro Yoneda^a Akira Fukuda^a Tomohiro Yamazaki^b Natsuhi Sasaki^c
Masahiko Ohta^a Yasufumi Kageyama^a

Divisions of ^aNeurology, ^bGastroenterology and ^cNeurosurgery, Hyogo Prefectural Amagasaki Hospital, Amagasaki City, Japan

Key Words

Cancer · Ischemic stroke · Stroke · Thrombolysis

Abstract

Background: In patients with advanced-stage cancer, systemic thrombolysis with tissue plasminogen activator (tPA) for hyperacute ischemic stroke is not strictly off-label, but it is at higher risk of complications (including bleeding). **Case Report:** A 71-year-old male with unrecognizable malignancy developed a hemispheric ischemic stroke and received intravenous tPA within 4.5 h of onset, followed by anticoagulation treatment after 24 h of thrombolysis. Two days later, the patient had tarry stool and progressive anemia, receiving a blood transfusion. The systemic workup documented the presence of double primary cancers with advanced stage gastric and rectal cancers, and the patient subsequently received palliative care. The outcome at 3 months was a modified Rankin Scale of 5, and the patient died 6 months after the stroke. **Discussion:** Although systemic thrombolysis with tPA for ischemic stroke in patients with advanced-stage cancer may be performed relatively safely, optimal post-thrombolysis management is important to prevent the complications.

© 2014 S. Karger AG, Basel

Introduction

In patients with hyperacute ischemic stroke and current active cancer, systemic thrombolysis with tissue plasminogen activator (tPA) is not strictly a contraindication [1–3], but it may carry a higher risk of complications (including bleeding). Recent studies have shown

Yukihiro Yoneda, MD
Division of Neurology, Hyogo Prefectural Amagasaki Hospital
1-1-1 East-Daimotsu
Amagasaki City, Hyogo 660-0828 (Japan)
E-Mail y-yoneda@hp.pref.hyogo.jp

that aggressive thrombolytic reperfusion therapy is relatively safe and effective in stroke patients with cancer [4–8].

Case Report

A 71-year-old right-handed male with a long-term history of heavy smoking, currently taking anti-hypertensive medication at a general practitioners' clinic, suddenly developed stupor and left hemiparesis and arrived at our hospital 130 min after symptom onset. Upon presentation, the National Institute of Health Stroke Scale (NIHSS) score was 10 points. A baseline brain CT was perfectly normal. On the 1.5-T MR scanner (Signa, General Electric, USA), diffusion-weighted image, scanned 154 min after onset, demonstrated a subtle focal high-signal intensity area around the right caudate nucleus, and MR angiography (MRA) documented an occlusion of the right internal carotid artery (ICA) (fig. 1). The electrocardiogram showed no arrhythmia. The blood test showed moderate anemia with hemoglobin values of 8.5 g/dl, a red blood cell count of $342 \times 10^4/\mu\text{l}$, and his hematocrit was 27.8%. Other hematological profiles, including platelet cell count, international normalized ratio and D-dimer, were all normal. Although a suspicion of a hematological disorder or gastrointestinal bleeding arose, general physical examinations, including checking the appearance of his skin and his underwear, did not show any signs of skin purpura or bloody stool, and his family members did not report any history of bleeding. Neither a digital rectal examination nor the placement of a nasogastric tube to search for active gastrointestinal bleeding was performed. Finally, after obtaining written informed consent from his family members, the patient received intravenous thrombolysis with a tPA of 0.6 mg/kg alteplase according to the Japanese guidelines [2, 3, 9] 203 min after symptom onset.

The neurological status remained unchanged with an NIHSS score of 13 points at 24 h and an anemic state with hemoglobin values of 8.4 g/dl, a red blood cell count of $334 \times 10^4/\mu\text{l}$, and a hematocrit of 27.0%. The status did not deteriorate after thrombolysis. Intravenous anticoagulation with the direct thrombin inhibitor argatroban, which has been licensed for ischemic stroke in Japan [2, 3], was started 24 h after thrombolysis. Two days after thrombolysis, the patient suddenly had tarry stool and progressive anemia with hemoglobin values of 6.8 g/dl, a red blood cell count of $289 \times 10^4/\mu\text{l}$, and a hematocrit of 22.4%. The patient received a blood transfusion of 4 units after the discontinuation of the intravenous argatroban infusion. The systemic workup, including systemic CT scans and endoscopic gastroscopy and colonoscopy, documented the presence of double primary malignancy with advanced-stage gastric and rectal cancers, associated with multiple remote lymph node metastases (fig. 1). The histopathology showed a tubular adenocarcinoma in the rectal specimen and a poorly differentiated adenocarcinoma in the stomach specimen, indicating synchronous double primary advanced-stage malignancy. The transthoracic echocardiography documented no embolic source. Eight days later, the fluid-attenuated inversion recovery image on the 3T MR scanner (Achieva, Phillips, The Netherlands) showed a moderate-sized infarction in the right middle cerebral artery (MCA) territory with no hemorrhagic transformation. MRA demonstrated mildly anterograde blood flow of the MCA via the contralateral anterior cerebral artery (fig. 1). The neck MRA showed an occlusion of the right ICA at the cervical portion, suggesting an atherothrombotic large artery stroke as an etiological mechanism for this stroke. The NIHSS score was 16 points with left dense hemiplegia and spatial neglect.

The patient was then transferred to receive palliative treatment. The outcome at 3 months was a modified Rankin Scale of 5, and the patient died from systemic dissemination of the cancers 6 months after the stroke.

Discussion

In this patient with occult types of synchronous double primary advanced-stage cancers in the stomach and rectum, systemic thrombolysis with tPA was performed relatively safely, but delayed gastrointestinal bleeding occurred during post-thrombolysis anticoagulation treatment.

Because net benefits decrease over time in stroke thrombolysis, the latest guidelines [1–3] have strongly encouraged urgent thrombolysis without extra investigations, delaying an initiation of thrombolysis and without procedures that are associated with an excessive risk of bleeding. In this patient with asymptotically pretreated moderate anemia, although any hematological disorder or gastrointestinal bleeding was suspected before thrombolysis, we could not sufficiently rule out the risk of active bleeding at sites of the occult gastric and rectal cancers. Therefore, earlier post-thrombolysis non-invasive investigations such as systemic CT scans to search for bleeding risks might have at least prevented the delayed gastrointestinal bleeding. Apart from urgent stroke thrombolysis, a patient with an unrecognized tumor who received local thrombectomy and thrombolysis with tPA for acute limb artery ischemia developed rectal bleeding, leading to the diagnosis of colorectal cancer [10].

According to the largest cancer registry in Japan [11], the incidence of synchronous multiple primary cancers was 4.5% (2,219 patients) of all 49,751 cancer patients. The combination of synchronous gastric and rectal cancers occurred only in 42 patients, representing 0.08% of all 49,751 cancer patients and 1.9% among 2,219 patients harboring synchronous multiple primary malignancy [11].

In patients with hyperacute ischemic stroke receiving thrombolytic reperfusion therapy, the proportion of patients with cancer represented 1.6–5% [4–8], showing a relatively safe and effective profile. In 1 study [7], 2 out of 11 thrombolized cancer patients had an occult malignancy, 1 of whom had a sigmoid colon cancer that bled locally and the patient also showed a moderately decreased hemoglobin level. Since patients with known advanced-stage cancer usually do not receive aggressive stroke treatments [5, 7], to the best knowledge, this is the first thrombolized patient with synchronous double primary advanced-stage cancers. In ischemic stroke patients hospitalized within 7 days of onset, the incidence of occult malignancy was relatively high at 3%, and a correct diagnosis of cancer was made after several investigations during hospitalization [12].

Before urgent stroke thrombolysis, in routine clinical practice, it may be difficult to promptly make a correct diagnosis for occult type of multiple or metastatic malignancy. However, optimal post-thrombolysis management is important to at least minimize the complications.

Disclosure Statement

The authors declare no conflicts of interest.

References

- 1 Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW Jr, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H: Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44:870–947.
- 2 Shinohara Y, Yanagihara T, Abe K, Yoshimine T, Fujinaka T, Chuma T, Ochi F, Nagayama M, Ogawa A, Suzuki N, Katayama Y, Kimura A, Minematsu K: Cerebral infarction/transient ischemic attack (TIA) (Japanese guidelines for the management of stroke). *J Stroke Cerebrovasc Dis* 2011;20(suppl):S31–S73.
- 3 Minematsu K, Toyoda K, Hirano T, Kimura K, Kondo R, Mori E, Nakagawara J, Sakai N, Shiokawa Y, Tanahashi N, Yasaka M, Katayama Y, Miyamoto S, Ogawa A, Sasaki M, Suga S, Yamaguchi T: Guidelines for the intravenous application of recombinant tissue-type plasminogen activator (alteplase), the second edition, October 2012: a guideline from the Japan Stroke Society. *J Stroke Cerebrovasc Dis* 2013;22:571–600.
- 4 Stefan O, Vera N, Otto B, Heinz L, Wolfgang G: Stroke in cancer patients: a risk factor analysis. *J Neurooncol* 2009;94:221–226.
- 5 Masrur S, Abdullah AR, Smith EE, Hidalgo R, El-Ghandour A, Rordorf G, Schwamm LH: Risk of thrombolytic therapy for acute ischemic stroke in patients with current malignancy. *J Stroke Cerebrovasc Dis* 2011;20:124–130.
- 6 Graber JJ, Nayak L, Deangelis LM: Use of recombinant tissue plasminogen activator in cancer patients with acute stroke. *J Neurooncol* 2012;107:571–573.
- 7 Cappellari M, Carletti M, Micheletti N, Tomelleri G, Ajena D, Moretto G, Bovi P: Intravenous alteplase for acute ischemic stroke in patients with current malignant neoplasm. *J Neurol Sci* 2013;325:100–102.
- 8 Murthy SB, Karanth S, Shah S, Shastri A, Rao CP, Bershad EM, Suarez JI: Thrombolysis for acute ischemic stroke in patients with cancer: a population study. *Stroke* 2013;44:3573–3576.
- 9 Yamaguchi T, Mori E, Minematsu K, Nakagawara J, Hashi K, Saito I, Shinohara Y; for the Japan Alteplase Clinical Trial (J-ACT) Group: Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 h of onset. *Stroke* 2006;37:1810–1815.
- 10 Schellhammer F, Pourhassan S, Topp S, Fürst G: Diagnosis of colo-rectal cancer revealed by haemorrhagic complication of intraarterial thrombolysis. *Vasa* 2007;36:143–144.
- 11 Kaneko S, Yamaguchi N: Epidemiological analysis of site relationships of synchronous and metachronous multiple primary cancers in the National Cancer Center, Japan, 1962–1996. *Jpn J Clin Oncol* 1999;29:96–105.
- 12 Uemura J, Kimura K, Sibazaki K, Inoue T, Iguchi Y, Yamashita S: Acute stroke patients have occult malignancy more often than expected. *Eur Neurol* 2010;64:140–144.

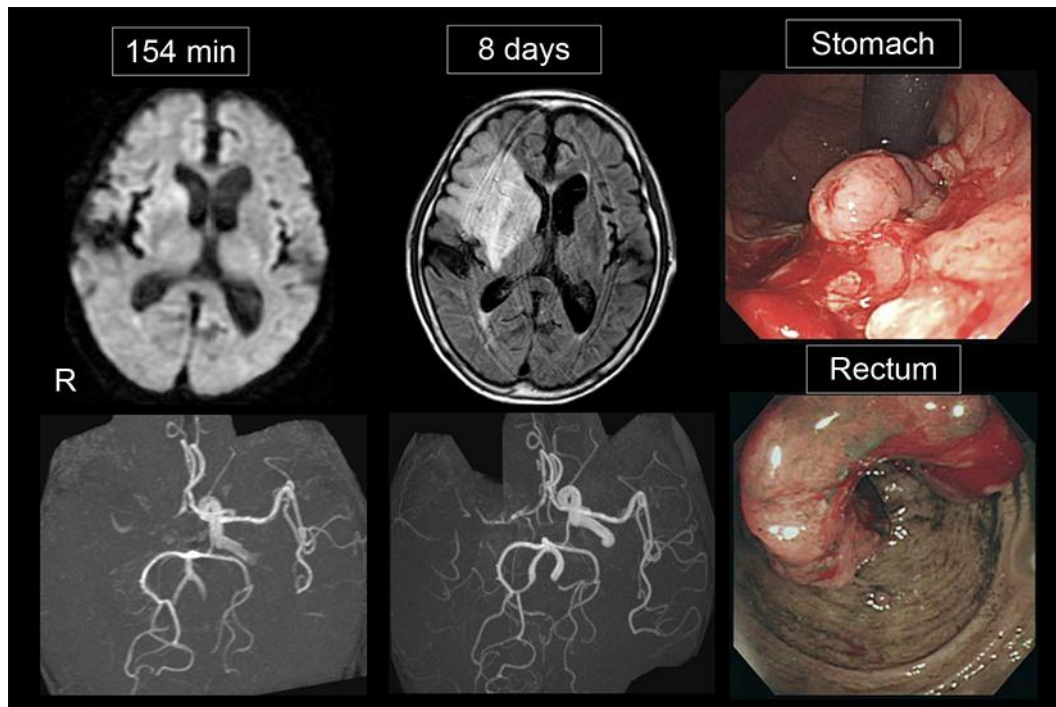


Fig. 1. Brain MR images and endoscopic examinations of the stomach and rectum. Prior to thrombolysis, diffusion-weighted image demonstrates a subtle high-signal intensity area around the right caudate nucleus, and MRA displays an occlusion of the right ICA (left column). The fluid-attenuated inversion recovery image 8 days later shows a moderate-sized high-signal intensity area in the right MCA territory. The MRA displays partially anterograde blood flow in the right MCA via contralateral anterior cerebral artery, but the right ICA remains in occlusion (middle column). Endoscopic examinations of the stomach and rectum performed 5 and 9 days after thrombolysis show both advanced-stage malignant tumors with blood oozing (right column).