Massive Spontaneous Symptomatic Hemorrhagic Transformation Following Pontine Infarction – A Case Report

Yu-Hsiang Su, Sheng-Feng Sung

Abstract

Purpose: Spontaneous hemorrhagic transformation is common in anterior circulation infarction, but is rarely seen in brainstem infarction. We report a case of massive symptomatic brainstem hemorrhagic transformation in a patient with pontine infarction treated with only antiplatelet agents.

Case Report: A 59-year-old man presented with acute dysarthria and right sided weakness. His Glasgow coma scale was E3 V5 M6. His pupils were pinpoint in size and minimally reactive to light. He showed complete horizontal gaze palsy, right facial weakness, severe dysarthria, dysphagia, and right hemiplegia. Computed tomography showed a dense basilar artery sign without evidence of acute infarction or hemorrhage. After treated with aspirin and dipyridamole, he had massive symptomatic brainstem hemorrhagic transformation on the next day. After medical treatment, he survived but remained in locked-in state with occasional drowsiness.

Conclusion: Hemorrhagic transformation following brainstem infarction is a rare yet potentially devastating condition in patients without thrombolytic therapy. It should be considered when neurological deterioration develops in patients with brainstem infarction. Follow-up brain imaging studies are warranted because antithrombotic agents should be discontinued in case of hemorrhagic transformation.

Key Words: Brainstem infarction, hemorrhagic transformation

Acta Neurol Taiwan 2016;25:27-32

INTRODUCTION

Spontaneous hemorrhagic transformation (HT) is common in supratentorial and cerebellar infarction, but is rarely seen in brainstem infarction. Although petechial hemorrhage may exist in brainstem infarction, massive HT is very rare[1]. Up to now, only sparse cases of massive brainstem HT have been reported[1-3], therefore its frequency is difficult to be evaluated. In an international prospective observational registry study of basilar artery occlusion (BAO), only one of 183 patients who were treated with antithrombotic therapy had symptomatic HT[4]. We herein present a case of massive spontaneous symptomatic HT after pontine infarction.

From the Division of Neurology, Department of Internal Medicine, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Taiwan.
Received November 26, 2015. Revised January 21, 2016
Accepted February 3, 2016.

Corresponding Author: Sheng-Feng Sung, MD, MS Division of Neurology, Department of Internal Medicine, Ditmanson Medical Foundation Chia-Yi Christian Hospital, 539 Zhongxiao Road, East District, Chiayi City 60002, Taiwan.
E-mail: sfsung@seed.net.tw

CASE REPORT

A 59-year-old man presented with acute dysarthria and right sided weakness. The patient had a prior right supratentorial infarction nine years ago, with sequelae of slight hemiparesis on the left side. He had been a smoker for more than 30 years, but did not have the habit of consuming alcohol. He did not have a history of chronic kidney disease, liver disease, cardiac arrhythmia, head trauma, or intracranial hemorrhage, and he was not on any medications. He arrived at the emergency department at 5.5 hours after onset of symptoms, with a blood pressure of 174/101 mm Hg, a regular heart rate of 77 per minute, and a respiratory rate of 24 per minute. On neurological examination, his Glasgow coma scale was E3 V5 M6. His pupils were pinpoint in size and minimally reactive to light. He showed complete horizontal gaze palsy, right facial weakness, severe dysarthria, dysphagia, and right hemiplegia. He also complained of blurry vision but did not cooperate with detailed visual testing. He denied having headache or neck pain at onset and he had not experienced neck injury or chiropractic manipulation recently.

Computed tomography (CT) of brain (Fig. 1A and 1B) at 5.5 hours after onset revealed no evidence of infarction or hemorrhage, although it showed a dense basilar artery sign. The laboratory data at the emergency department were within normal limits, except for a mild leukocytosis (12.750×10^9/L) with a normal differential count, and hyperglycemia (16.915 mmol/L). His electrocardiography showed normal sinus rhythm with a rate of 70 per minute. He was treated with 100 mg of aspirin after CT examination. Because of the presence of bilateral pinpoint pupils, horizontal gaze palsy, severe bulbar palsy and right hemiplegia, a clinical diagnosis of pontine infarction was made and BAO was suspected. Then he was admitted to the intensive care unit. After admission, he was treated with aspirin 300 mg per day, dipyridamole 75 mg twice per day, and subcutaneous insulin for sugar control. No evidence of atrial fibrillation was observed on the electrocardiogram monitor during the hospitalization course. His systolic blood pressure was between 113 and 148 mm Hg and diastolic blood pressure below 90 mm Hg, so no antihypertensive was administered.

On the next day, just before scheduled magnetic resonance imaging (MRI) scan, he suddenly lapsed into coma with a surge of blood pressure, reaching 205/90 mm Hg 33 hours after stroke onset. The neurological examination showed a Glasgow coma scale of E1 V1 M2, bilateral pinpoint and non-reactive pupils, absence of oculocephalic reflexes, and absence of sucking reflex. He was immediately intubated for protection of his airway. Follow-up CT (Fig. 1C and 1D) performed 33.5 hours after onset disclosed massive pontine hemorrhage with extension to the midbrain and rupture into the fourth ventricle. He had remained comatose during the subsequent hospital stay. The blood chemistry tests revealed hyperlipidemia and an elevated hemoglobin A1c of 9.2%. The echocardiography did not show any evidence of valvular heart disease or intracardiac thrombus formation. He survived the stroke after conservative treatment without tracheostomy. He was transferred to a chronic care unit at 18 days. One month after stroke, he could breath spontaneously after removal of the

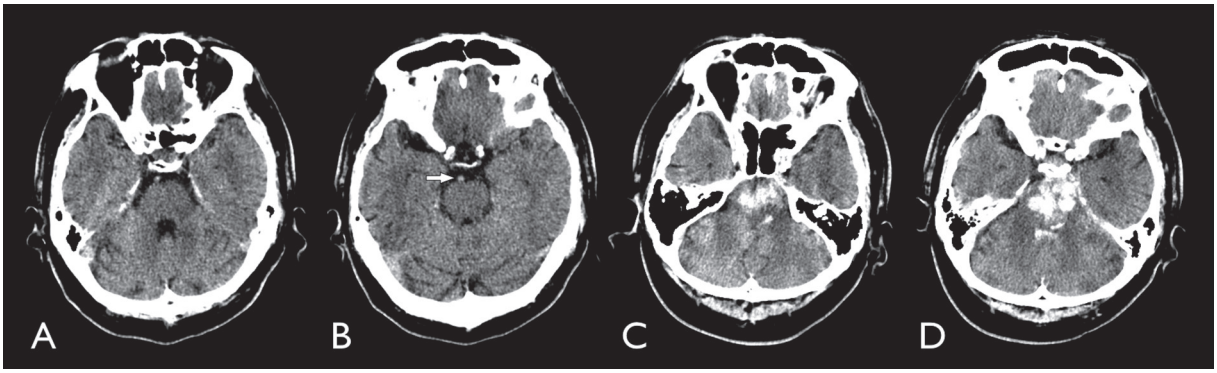

Figure 1. Computed tomography (CT) of brain (A, B) at 5.5 hours after stroke onset shows a dense basilar artery sign. Follow-up CT (C, D) at 33.5 hours discloses massive pontine hemorrhage.

endotracheal tube although he was still stuporous.

DISCUSSION

HT is a well-known and dreadful complication of acute ischemic stroke because it is associated with an adverse outcome[5]. Regarding the mechanism of HT, it has been proposed that the disruption of the blood-brain barrier with dysfunction of autoregulation of cerebral vessels, which is highly dependent on the duration of ischemia, predisposes to blood extravasation during the reperfusion[6]. Currently, the identified risk factors of HT include large size of infarcts, use of thrombolytic agents or anticoagulants, and infarctions due to cardioembolism or specific etiologies other than large artery atherothrombosis and lacunar infarction[5]. A migratory embolism theory has been proposed to explain why embolic infarctions are prone to HT[7].

The incidence of HT varies widely from 4% up to 68.6%[8]. The wide range of reported incidences may be due to multiple factors including duration of follow-up, type of neuroimaging, choice of treatment, selection of patients (limited to cardioembolic stroke or inclusive of all etiologies), and protocol of follow-up imaging (performed routinely or following neurological deterioration)[8]. Although the outcome of posterior circulation infarction did not differ from that of anterior circulation infarction[9], HT infrequently occurred in posterior circulation infarction. In one study, the incidence of HT within the first week in large anterior circulation infarction is 28.8%, and the incidence of HT in large posterior circulation infarction is 7.0%[5]. In another study, the incidence of HT after ischemic stroke is 40.4% (59/146) in middle cerebral artery infarction, 36% (9/25) in anterior cerebral artery infarction, 28.6% (6/21) in posterior cerebral artery infarction, 33.3% (2/6) in cerebellar infarction, and 0% (0/4) in brainstem infarction[10].

From the literature review, we identified only three case reports of massive brainstem HT in the past 20 years[1-3]. All of them had embolic infarction. Even though previous studies indicated that female accounted for approximately one third of BAO cases[4,11], the three previously reported cases and the present one are male. In addition, whereas only 22% of symptomatic HT occurred within 3 days after ischemic stroke[12], all the four cases had HT within 48 hours after ischemic stroke. In two of these cases, HT was found on routine follow-up imaging studies without causing neurological deterioration. In other words, HT could have been missed if follow-up imaging studies had not been done. Because patients with extensive brainstem infarction generally presented with severe neurological deficits, it may be difficult to identify any neurological deterioration even when the size of HT is substantial. Furthermore, even if neurological deterioration

Table 1. Clinical characteristics and outcomes of reported cases of brainstem hemorrhagic transformation.

Case	Age	Sex	Risk factors	Stroke mechanism	Initial consciousness	Pupillary and oculomotor abnormalities	Weakness	Dense basilar artery sign	Treatment	Timing of HT	Outcome	Reference
1	59	M	Hypertension, diabetes, hyperlipidemia	Atherosclerosis	E3 V5 M6	Pinpoint, minimally reactive pupils, horizontal gaze palsy	Right hemiplegia	Yes	Aspirin and dipyridamole	33 hours	Survived	The present case
2	79	M	AF	Embolic	Comatose	Fixed pupils, complete gaze palsy	Quadriplegia	Yes	None	12 hours*	Expired at 9 days	Kimura et al[10]
3	66	M	Hypertension	Embolic	E1 V1 M1	Small pupils with sluggish reflex, complete gaze palsy	Quadriplegia	Yes	Enoxaparin	2 days	Expired at 4 days	Hsiao, et al[2]
4	79	M	Hypertension, CAD, CKD	Embolic	E1 V1 M4	Fixed dilated pupils, complete gaze palsy	Quadriplegia	Yes	Aspirin	8 hours*	Expired at 8 days	Willey, et al[1]

AF = atrial fibrillation; CAD = coronary artery disease; CKD = chronic kidney disease; HT = hemorrhagic transformation.

*Found on routine follow-up neuroimaging studies without clinical neurological deterioration.

happens, it may be attributed to other common causes of early neurological deterioration, such as progressive stroke, edema, and recurrent stroke[13]. As a result, the occurrence of HT following brainstem infarction might be underestimated.

Unlike the previously reported cases, our patient was presumed to have brainstem infarction due to basilar artery atherothrombosis rather than cardioembolism because he had multiple risk factors for large artery atherosclerosis, including hypertension, hyperlipidemia and diabetes. Moreover, his echocardiography and electrocardiography did not show any evidence suggestive of cardioembolism. However, we could not exclude the possibility of artery-to-artery embolism. To our best knowledge, our case is also the only one who survived such massive HT after brainstem infarction. All the three previously reported cases died within 4 to 9 days, but our case survived. The different outcomes may be partially explained by their varying initial stroke severity. A previous study found that patients with BAO or basilar artery stenosis had poor prognosis if they had stupor or coma, dysarthria, pupillary disorder, and lower cranial nerve involvement on admission[11]. The three previous cases presented with coma, partially or completely impaired light reflex, complete gaze palsy, and quadriplegia. Apparently, our case had milder initial neurological deficits, including drowsiness, sluggish pupillary reflex, horizontal gaze palsy with spared vertical eye movements, and right hemiplegia. These findings suggested that our case had a less extensive infarction in the brainstem, which could be attributed to the underlying stroke etiology. Patients with brainstem infarction due to atherosclerotic lesions could have smaller infarction and less severe symptoms if the circulation can adapt whereas sudden embolic occlusions typically causes extensive infarction and severe neurological deficits[14]. Cardioembolic etiology has been shown to be a predictor for poor outcome in patients with BAO or basilar artery stenosis[11].

Because use of thrombolytic agents is a risk factor for HT[5], the incidence of HT has risen in the era of thrombolytic therapy[4]. However, patients with posterior circulation infarction still have a lower risk of symptomatic intracranial hemorrhage than those with anterior circulation infarction (0% versus 5%) after intravenous thrombolytic therapy[15]. Another study also found no symptomatic intracranial hemorrhage in patients with BAO[16]. The lower rate of HT in posterior circulation stroke may make prediction models of post-thrombolytic hemorrhage inaccurate in patients with posterior circulation infarction[17]. On the other hand, HT is only seen in 0.5% (1/183) of patients with brainstem infarction who were treated with either antitcoagulants or antiplatelet agents[4]. Because anticoagulant therapy generally carries a higher risk for HT than antipalatelet therapy[18], we believe that the risk of HT in patients of brainstem infarction with antiplatelet therapy alone is even lower.

Several hypotheses might explain why HT seldom occurs in posterior circulation infarction, especially in brainstem infarction. First, posterior circulation strokes tend to have smaller infarct size while large infarct size is a risk factor for HT. Second, the brainstem is well supplied by small end-arteries with collateral flow, which may result in a slower evolution of irreversible ischemia in posterior circulation strokes with proximal artery occlusion[19]. Third, pretreatment T2* permeability derangement on magnetic resonance permeability imaging, an indicator of blood-brain barrier disruption, is a powerful predictor of HT after revascularization therapy in both anterior and posterior circulation infarction[20]. Such permeability derangement is less frequently seen in posterior circulation infarction than in anterior circulation infarction (7% versus 22%)[21].

A previous study found that large artery dissection was one of the most common etiologies of posterior circulation stroke in Taiwan population[22]. A vertebrobasilar dissecting aneurysm or berry aneurysm could theoretically cause brainstem infarction and hemorrhage at the same time. However, hemorrhagic complications due to vertebrobasilar artery dissection or aneurysms are more likely to be subarachnoid hemorrhage rather than parenchymal hemorrhage. Although simultaneous subarachnoid hemorrhage and posterior circulation infarction have been found in cases with vertebrobasilar dissection or aneurysms[23,24], only one case of brainstem hemorrhage due to an aneurysm in the vertebrobasilar system has been reported in the past 40 years[25]. Moreover, this unique case is quite different from ours in that this case presented with brainstem hemorrhage from the beginning whereas our case had brainstem infarction at onset followed by hemorrhagic transformation. Because of

lacking MRI and angiography studies, we were unable to determine whether the rare manifestation of hemorrhagic transformation following brainstem infarction in our case was due to vertebrobasilar dissection or aneurysms.

In conclusion, our case reminds clinicians that spontaneous HT after brainstem infarction is rare but does happen, even in a patient treated only with antiplatelet therapy. In addition to progressive stroke, edema, and recurrent stroke, HT should be considered when neurological deterioration develops in patients with brainstem infarction. Follow-up brain imaging studies are warranted because antithrombotic agents should be discontinued in cases of HT.

ACKNOWLEDGEMENT

We sincerely thank Ms. Li-Ying Sung for her contribution to English editing.

REFERENCES

1. Willey JZ, Harrison DM, Schumacher HC. Early spontaneous brainstem hemorrhage following widespread brainstem ischemia. J Postgrad Med 2008;54:336-337.
2. Hsiao M-C, Lee JD, Lee M, Weng H-H. Massive pontine hemorrhagic transformation associated with an anticoagulant for basilar artery occlusion. Neurol India 2006;54:431-433.
3. Kimura K, Ogata J, Minematsu K, Yasaka M, Yamaguchi T. Massive pontine hemorrhagic infarction associated with embolic basilar artery occlusion. Intern Med 2001;40:658-661.
4. Schonewille WJ, Wijman CAC, Michel P, Rueckert CM, Weimar C, Mattle HP, Engelter ST, Tanne D, Muir KW, Molina CA, Thijs V, Audebert H, Pfefferkorn T, Szabo K, Lindsberg PJ, de Freitas G, Kappelle LJ, Algra A; BASICS study group. Treatment and outcomes of acute basilar artery occlusion in the Basilar Artery International Cooperation Study (BASICS): a prospective registry study. The Lancet Neurology 2009;8:724-730.
5. Paciaroni M, Agnelli G, Corea F, Ageno W, Alberti A, Lanari A, Caso V, Micheli S, Bertolani L, Venti M, Palmerini F, Biagini S, Comi G, Previdi P, Silvestrelli G. Early hemorrhagic transformation of brain infarction: rate, predictive factors, and influence on clinical outcome: results of a prospective multicenter study. Stroke 2008;39:2249-2256.
6. Sussman ES, Connolly ES. Hemorrhagic transformation: a review of the rate of hemorrhage in the major clinical trials of acute ischemic stroke. Front Neurol 2013;4:69.
7. Fisher M, Adams RD. Observations on brain embolism with special reference to the mechanism of hemorrhagic infarction. J Neuropathol Exp Neurol 1951;10:92-94.
8. Terruso V, D'Amelio M, Di Benedetto N, Lupo I, Saia V, Famoso G, Mazzola MA, Aridon P, Sarno C, Ragonese P, Savettieri G. Frequency and determinants for hemorrhagic transformation of cerebral infarction. Neuroepidemiology 2009;33:261-265.
9. Libman RB, Kwiatkowski TG, Hansen MD, Clarke WR, Woolson RF, Adams HP. Differences between anterior and posterior circulation stroke in TOAST. Cerebrovasc Dis 2001;11:311-316.
10. Okada Y, Yamaguchi T, Minematsu K, Miyashita T, Sawada T, Sadoshima S, Fujishima M, Omae T. Hemorrhagic transformation in cerebral embolism. Stroke 1989;20:598-603.
11. Devuyst G, Bogousslavsky J, Meuli R, Moncayo J, de Freitas G, Van Melle G. Stroke or transient ischemic attacks with basilar artery stenosis or occlusion: clinical patterns and outcome. Arch Neurol 2002;59:567-573.
12. Tan S, Wang D, Liu M, Zhang S, Wu B, Liu B. Frequency and predictors of spontaneous hemorrhagic transformation in ischemic stroke and its association with prognosis. J Neurol 2014;261:905-912.
13. Siegler JE, Martin-Schild S. Early Neurological Deterioration (END) after stroke: the END depends on the definition. Int J Stroke 2011;6:211-212.
14. Mattle HP, Arnold M, Lindsberg PJ, Schonewille WJ, Schroth G. Basilar artery occlusion. Lancet Neurol 2011;10:1002-1014.
15. Sarikaya H, Arnold M, Engelter ST, Lyrer PA, Mattle HP, Georgiadis D, Bonati LH, Fluri F, Fischer U, Findling O, Ballinari P, Baumgartner RW. Outcomes of intravenous thrombolysis in posterior versus anterior circulation stroke. Stroke 2011;42:2498-2502.

16. Pagola J, Ribo M, Alvarez-Sabín J, Rubiera M, Santamarina E, Maisterra O, Delgado-Mederos R, Ortega G, Quintana M, Molina CA. Thrombolysis in anterior versus posterior circulation strokes: timing of recanalization, ischemic tolerance, and other differences. J Neuroimaging 2011;21:108-112.
17. Sung S-F, Chen C-H, Chen Y-W, Tseng M-C, Shen H-C, Lin H-J. Predicting symptomatic intracerebral hemorrhage after intravenous thrombolysis: Stroke territory as a potential pitfall. J Neurol Sci 2013;335:96-100.
18. Bogousslavsky J, Regli F. Anticoagulant-induced intracerebral bleeding in brain ischemia. Evaluation in 200 patients with TIAs, emboli from the heart, and progressing stroke. Acta Neurol Scand 1985;71:464-471.
19. Ostrem JL, Saver JL, Alger JR, Starkman S, Leary MC, Duckwiler G, Jahan R, Vespa P, Villablanca JP, Gobin YP, Vinuela F, Kidwell CS. Acute basilar artery occlusion: diffusion-perfusion MRI characterization of tissue salvage in patients receiving intra-arterial stroke therapies. Stroke 2004;35:e30-e34.
20. Bang OY, Saver JL, Alger JR, Shah SH, Buck BH, Starkman S, Ovbiagele B, Liebeskind DS; UCLA MRI Permeability Investigators. Patterns and predictors of blood-brain barrier permeability derangements in acute ischemic stroke. Stroke 2009;40:454-461.
21. Lee M, Saver JL, Alger JR, Hao Q, Starkman S, Ali LK, Kim D, Ovbiagele B, Vespa PM, Froehler MT, Tenser MS, Salamon N, Villablanca JP, Jahan R, Duckwiler GR, Tateshima S, Gonzalez N, Vinuela F, Liebeskind DS. Blood-brain barrier permeability derangements in posterior circulation ischemic stroke: frequency and relation to hemorrhagic transformation. J Neurol Sci 2012;313:142-146.
22. Chung C-P, Yong C-S, Chang F-C, Sheng W-Y, Huang H-C, Tsai J-Y, Hsu H-Y, Hu H-H. Stroke etiology is associated with outcome in posterior circulation stroke. Ann Clin Transl Neurol 2015;2:510-517.
23. Murakami K, Takahashi N, Matsumura N, Umezawa K, Midorikawa H, Nishijima M. Vertebrobasilar artery dissection presenting with simultaneous subarachnoid hemorrhage and brain stem infarction: case report. Surg Neurol 2003;59:18-22.
24. Androdias G, Hermier M, Turjman F, Honnorat J, Nighoghossian N. Simultaneous subarachnoid hemorrhage and cerebellar infarct revealing vertebral artery aneurysm: acute magnetic resonance imaging assessment. Arch. Neurol 2005;62:1158-1159.
25. Ono N, Imai S, Zama A, Hosaka T, Onada K, Wakao T. Successful treatment of a basilar aneurysm presenting as a brainstem hemorrhage. Surg Neurol 1984;22:365-370.