PAPER

Ischaemic stroke with malignancy may often be caused by paradoxical embolism

Y Iguchi, K Kimura, K Kobayashi, Y Ueno, T Inoue

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See end of article for authors' affiliations

Correspondence to: Y Iguchi, Department of Stroke Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki City, Okayama, 701–0192, Japan; yigu@med.kawasaki-m.ac.jp

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Background: Although ischaemic stroke with malignancy occasionally occurs, the mechanisms of stroke in such cases have not been investigated in detail.
Objective: To examine the mechanisms of ischaemic stroke with malignancy, particularly in relation to right-to-left shunt (RLS).
Methods: Consecutive patients with ischaemic stroke within 24 h of stroke onset were prospectively studied. Contrast saline transcranial Doppler examination was carried out for all patients, to investigate the presence of RLS. When patients with stroke had RLS, deep venous thrombosis (DVT) or pulmonary embolism was assessed to diagnose paradoxical brain embolism.
Results: Participants comprised 184 consecutive patients (115 men and 69 women) with a mean (standard deviation (SD)) age of 73 (11.8) years and mean (SD) National Institutes of Health Stroke Scale (NIHSS) score of 8 (7.4). RLS was detected in 32 of 184 (18%) patients. Malignancy was present in 11 (5%) patients. RLS was more frequent in patients with malignancy than in patients without malignancy (55% *v* 15%, respectively; p = 0.001). All six patients with RLS and malignancy displayed DVT or pulmonary embolism with severe disability (modified Rankin Scale 4–5) before stroke onset.
Conclusion: Paradoxical brain embolism should be considered to be an important mechanism in patients with stroke and malignancy.

Several causes of ischaemic stroke associated with malignancy have been reported previously, such as hypercoagulability and non-bacterial thrombotic endocarditis (NBTE).[1] However, making a definite diagnosis of NBTE is difficult, as cardiological investigations cannot always detect vegetations in the heart.[2] NBTE is attributed to a disorder of coagulation and endothelial dysfunction.[3] Paradoxical brain embolism has recently been considered to be a potential cause of cerebral infarction of unknown aetiology. Deep venous thrombosis (DVT) is the main embolic cause of paradoxical brain embolism and readily occurs under hypercoagulable conditions.[4] Although both NBTE and DVT are likely to be found in patients with malignancy, attention has not been paid to paradoxical brain embolism. Our study aimed to investigate the frequency of paradoxical brain embolism among patients with malignancy and to examine clinical characteristics in these patients.

PARTICIPANTS AND METHODS

Participants comprised consecutive patients with acute ischaemic stroke who were admitted to our stroke centre (Stroke Center, Kawasaki Medical School, Okayama, Japan) within 24 h of stroke onset between May 2004 and August 2005. On arrival at the emergency department or stroke unit, patients underwent contrast-transcranial Doppler examination (c-TCD) to detect right-to-left shunt (RLS), electrocardiography and magnetic resonance studies including diffusion-weighted imaging and magnetic resonance angiography. Information about patient history and drugs was obtained, as follows:

- presence of malignancy;
- cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidaemia and smoking);
- atrial fibrillation; and
- previous illness (coronary heart disease, transient ischaemic attack, cerebral infarction and cerebral haemorrhage).

Cardiovascular risk factors identified were: (1) hypertension, use of antihypertensive agents, systolic blood pressure ⩾160 mm Hg or diastolic blood pressure ⩾95 mm Hg on admission; (2) diabetes mellitus, use of oral hypoglycaemic agents, insulin or glycated haemoglobin >6.4%; (3) hypercholesterolaemia, use of antihyperlipidaemic agents or serum cholesterol level >240 mg/dl; and (4) smoking, any lifetime experience of cigarette use. Using Trial of ORG 10172 in Acute Stroke Treatment criteria, stroke subtype was categorised into four groups: (1) small-vessel disease; (2) large-vessel disease; (3) cardioembolic stroke; and (4) other or undetermined cause of stroke.[5] Stroke severity on admission was assessed using the NIHSS score. Outcome was also measured using the modified Rankin Scale.

Ultrasound study

Standard transcranial Doppler (TCD) examination was carried out to assess the intracranial arteries using a standard scanning protocol as reported previously.[6] The middle cerebral artery (MCA) was insonated from the temporal window at a depth of 50–55 mm using a 2 MHz handheld transducer (DWL MultiDop T; Lindau, Germany) when the MCA and anterior cerebral artery were both detectable. After identifying the patent MCA, continuous monitoring of MCA flow signals was carried out using a Marc 500 head frame (Spencer Technology, Seattle, Washington, USA) maintaining a tight position and constant angle of insonation. If no temporal window was found to detect both MCAs, the right internal carotid artery was insonated through the orbital window at a depth of 60–65 mm (as short as possible). Standard TCD recording with the addition of an intensity

Abbreviations: c-TCD, contrast-transcranial Doppler; c-TEE, contrast-enhanced transoesophageal echocardiography; DVT, deep venous thrombosis; MCA, middle cerebral artery; NBTE, non-bacterial thrombotic endocarditis; NIHSS, National Institutes of Health Stroke Scale; PFO, patent foramen ovale; RLS, right-to-left shunt; TCD, transcranial Doppler

Table 1 Baseline characteristics of 11 patients with stroke and malignancy

	n = 11
Male, n	8
Age, years (SD)	68.2 (10.1)
Primary lesion of malignancy (n)	
Stomach	4
Liver	3
Kidney	1
Pancreas	1
Breast	1
Leukaemia	1
Interval from diagnosis of malignancy, months (SD)	2.3 (1.2)
Recent weight loss (5 kg/m), n	9
Continous fever, n	4
Previous treatment (n)	
Chemotherapy	2
Operation	4
Both chemotherapy and operation	3
No treatment	2
Diagnosis of RLS	6
DVT or PE (n)	
DVT	3
PE	1
Both DVT and PE	2

DVT, deep venous thrombosis; PE, pulmonary embolism; RLS, right-to-left shunt.

threshold of >6 dB was carried out for 20 min. The Doppler audio signals of both the standard and c-TCD examination were recorded on digital audiotape. Microembolic signals were identified by their typical visual appearance on the spectral display and their characteristic sounds, according to standard consensus criteria.[7] A contrast agent study was conducted by mixing saline solution (9 ml) and air (1 ml), agitated between two 10-ml syringes connected by a three-way stopcock. An indwelling catheter was placed in the anterior cubital vein. A bubble containing saline was then injected under two conditions: (1) no Valsalva manoeuvre and (2) Valsalva manoeuvre for 5 s starting 5 s after the beginning of bubble-mixed saline injection. Patients were trained in the Valsalva manoeuvre before the procedure. Satisfactory performance of the Valsalva manoeuvre was verified by consecutive reductions in blood flow velocity.[8] Each of these tests was continued for ⩾2 min after bolus injection of the saline containing bubbles. RLS was diagnosed if ⩾1 microbubble was recorded in one vessel within 40 s after injection.[9] Even if the Valsalva manoeuvre was unsatisfactory, RLS could be detected in 80% of patients by using c-TCD.[10] Therefore, when a patient could not perform the Valsalva manoeuvre because of neurological manifestation or agitation, c-TCD and contrast-enhanced transoesophageal echocardiography (c-TEE) without Valsalva manoeuvre only were performed in our series.

When patients were diagnosed with embolic stroke based on neuroimaging and the embolic source was unknown, transoesophageal echocardiography was performed to evaluate the presence of patent foramen ovale (PFO), complicated lesions in the aorta or abnormal structures in the heart, such as embolus or vegetation. Trained echocardiographers from the department of cardiology and neurology performed TEE after informed consent was obtained from the patient or spouse. PFO was also diagnosed when microbubbles obviously increased after performance of the Valsalva manoeuvre, or PFO was directly confirmed by c-TEE examination. If the patient displayed RLS, radionuclide venography and venous ultrasonography were performed to assess DVT, and pulmonary perfusion–ventilation scintigraphy was used to examine the presence of pulmonary embolism. Paradoxical brain embolism was defined by: (1) the presence of RLS; (2) the presence of DVT or pulmonary embolism; (3) embolic stroke on neuroimaging, such as cortical and multiple infarcts on diffusion-weighted imaging; (4) lack of other cardiac diseases, such as atrial fibrillation, acute myocardial infarction, old myocardial infarction with intraventricular thrombosis, mitral valve disease, prosthetic valve implication, pacemaker or dilated cardiomyopathy; and (5) lack of arterial disease with >50% stenosis in the affected artery.

Carotid duplex ultrasonography was also performed to detect the atherosclerotic change in extracranial cerebral vessels. Stenosis (>70% according to the criteria of North American Symptomatic Trial Collaborators) of internal carotid artery was diagnosed when peak systolic flow was >200 cm/s.[11] Carotid arterial occlusion was defined as previously.[12]

Malignancy survey

Malignancy was defined as a patient having received treatment for malignancy for ⩽6 months before stroke onset. Furthermore, when a patient showed abnormal findings on routine laboratory examination, occult blood in stool, continued fever without any identifiable infection or weight loss >5 kg/month, a blood sample was examined for tumour markers such as carcinoembryonic antigen, carbohydrate antigen 19–9, prostate-specific antigen for men and carbohydrate antigen 125 for women, using commercially available kits, along with abdominal ultrasonography and gastrointestinal and colonic fibrescopy. When a diagnosis of malignancy had already been made, these investigations were not performed. A definite diagnosis of malignancy was based on the pathological findings.

RESULTS

Participants comprised 184 consecutive patients (115 men and 69 women) with a mean (standard deviation (SD)) age of 73 (11.8) years and a mean NIHSS score of 8 (7.4). The stroke subtypes were small-vessel disease (n = 48); large-vessel disease (n = 28); cardioembolic stroke (n = 62), including 16 paradoxical brain embolisms; and other determined or unknown causes of stroke (n = 46). Malignancy was identified in 11 of the 184 (5%) patients (table 1). The tumour site for these 11 patients with stroke and malignancy was as follows: stomach (n = 4); liver (n = 3); pancreas (n = 1); colon (n = 1); breast (n = 1); and kidney (n = 1). Our hospital did not have an oncology unit. Seven patients were managed in a surgical unit before stroke onset. Four patients were managed by internal medicine. Pulmonary embolism or DVT was observed in 6 of the 11 patients. Other hypercoagulable states, such as cerebral sinus thrombosis, arterial thrombosis, disseminated intravascular coagulation and thrombotic thrombocytopenic purpura, were investigated but not found in any of our patients. Cardioembolic stroke was found in seven patients (including six patients with paradoxical brain embolisms) and four patients had small-vessel disease. Transoesophageal echocardiography was performed on 10 patients and autopsy was conducted in 1 patient. No evidence of NBTE was observed in any of the 11 patients. c-TCD examinations were carried out within 24 h from stroke onset and mean (SD) examination time from onset was 14.3 (6.8) h. c-TCD data on all 184 patients were analysed (135 patients with a temporal window and 49 with an orbital window), and RLS was detected in 32 of 184 (18%) patients by cTCD or c-TEE. c-TEE was conducted in 121 of 184 (66%) patients. Whereas c-TEE confirmed PFO in 28 of 32 patients with RLS detected by c-TCD, two patients had atrial septal deficit. We could not perform c-TEE in two other patients. RLS was observed in 6 of the 11 (55%) patients with malignancy, compared with 26

Table 2 Clinical characteristics of patients with both malignancy and right-to-left shunt

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	Male	Male	Male	Male	Female	Female
Age, years	59	79	59	68	76	73
Malignancy, pathology	Stomach, AC	Stomach, AC	Liver, AC	Pancreas, AC	Breast, AC	Liver, AC
Location of stroke	Right MCA	Left MCA	Right MCA	Bilateral MCA	Putamen, pons, cerebellum	Bilateral MCA
Multiple lesions	+	+	+	+	+	+
Drugs before stroke onset	–	–	–	–	–	–
Standard TCD	No MES	No MES	No MES	No MES	No temporal window	No temporal widow
History of TIA or brain infarction	–	–	–	–	–	–
Risk factor	HT	HT, HL	–	HT	–	–
NIHSS on admission	20	24	22	2	15	12
Modified Rankin Scale before onset	4	4	4	4	4	4
DVT or PE	+	+	+	+	+	+
TAT (normal, ⩽3.0 ng/ml)	14.2	10.3	11.2	20	40	33.3
D-dimer (normal, ⩽1.0 μg/ml)	4.3	4.4	3.4	3.9	14.4	6.4
Dead in hospital	Yes	Yes	Yes	Yes	Yes	Yes

AC, adenocarcinoma; DVT, deep venous thrombosis; DWI, diffusion-weighted imaging; HL, hyperlipidemia; HT, hypertension; MCA, middle cerebral artery; MES, microembolic signals; NIHSS, National Institutes of Health Stroke Scale; PE, pulmonary embolism; TAT, thrombin–antithrombin III complex; TCD, transcranial Doppler; TIA, transient ischaemic attack.
No temporal window, transcranial Doppler could not detect any blood flow signals from temporal insonation window.

of the 173 (15%) patients without malignancy ($p = 0.001$). Table 2 shows clinical characteristics of the six patients (four men, two women) with malignancy and RLS in detail (mean (SD) age, 68 (8.6) years; mean (SD) NIHSS score, 15.8 (8.1)). As microembolic symbols were obviously increased in all six patients just after the Valsalva manoeuvre, we diagnosed them as having PFO. Malignancy was diagnosed before stroke onset and cancers included adenocarcinoma of the stomach (patients 1 and 2), liver (patients 3 and 6), pancreas (patient 4) or breast (patient 5). All six patients with both malignancy and PFO displayed DVT or pulmonary embolism. Transoesophageal echocardiography was performed in six patients and no vegetation in the heart valves, embolus or aortic complicated lesions were found. In patient 2, c-TCD and c-TEE were conducted without the Valsalva manoeuvre because of severe neurological deficit. As intrathoracic pressure was increased by a mechanical ventilation system, we diagnosed the patient as having RLS. No arterial diseases or other cardiogenic embolic sources were identified. Although TCD could detect bilateral MCAs through the patent temporal window in four patients, no microembolic signals were found in standard TCD recording. Finally, we diagnosed six patients with malignancy and RLS as having paradoxical brain embolism because there was no apparent embolic source despite the presence of multiple cortical lesions. Magnetic resonance imaging and computed tomography of all patients did not show any brain metastases. Activities of daily life before stroke onset were restricted by the patients' general condition (modified Rankin Scale ⩾4). D-dimer and thrombin-antithrombin complex were increased in all six patients, indicating the activation of both fibrinolytic and thrombin activity. All six patients died during hospitalisation within 3 months of stroke onset. Figure 1 shows the findings for patient 4, in whom venography of the lower limbs showed DVT and diffusion-weighted imaging showed multiple infarctions.

DISCUSSION

Cerebral ischaemia associated with malignancy is well known as NBTE.[3] NBTE has been best diagnosed using either transthoracic or transoesophageal echocardiography.[2] In the present series, 6 of 11 patients with malignancy were diagnosed with paradoxical brain embolism. In patients with malignancy, thrombosis is related to increased activity of the coagulation system, as evidenced by markers of accelerated thrombin generation and increased platelet reactivity.[13] As D-dimer and thrombin–antithrombin complex had already been increased at stroke onset in six patients with RLS and malignancy, DVT might occur before stroke and also contribute to the occurrence of paradoxical brain embolism. Interestingly, all six patients experienced restricted activities of daily life or were bedridden before stroke onset. These conditions may also contribute to the formation of DVT.

TCD is a reliable and non-invasive technique that can display intracranial haemodynamic changes. In addition, c-TCD has found a place as a useful, repeatable, bedside tool for detecting the presence of RLS in patients with unknown cause of embolic stroke.[14] When the cause of cerebral ischaemia is unknown in patients with malignancy, c-TCD should be conducted immediately. If c-TCD demonstrates RLS, investigation of DVT is warranted to prevent recurrent paradoxical brain embolism and pulmonary embolism.

In our series, all patients with both RLS and malignancy showed advanced adenocarcinoma. This suggests that advanced adenocarcinomas have the potential to promote DVT. Indeed, patients with advanced gastric and pancreas cancer have been reported with DVT or pulmonary embolism in a previous report.[15] Previous studies where no pathological investigations have been carried out have reported that adenocarcinomas are likely to cause not only NBTE but also venous thrombosis.[3] Histopathology in patients with malignancy when they have ischaemic stroke should therefore be investigated.

The present study has various limitations. Firstly, although autopsy is necessary to certify the presence of NBTE, autopsy was conducted in only one patient. Secondly, we were uncertain as to the frequency of DVT in this series, because DVT and pulmonary embolism were not investigated for all patients without RLS. Nevertheless, DVT or pulmonary embolism was detected in all patients with stroke and RLS, and 6 of 16 (38%) patients with a paradoxical brain embolism showed malignancy. We suspect that DVT and RLS have an important role in the aetiology of stroke with malignancy. Thirdly, skilful sonographers safely performed TEE examination even though patients could not swallow a TEE probe because of severe neurological deficits. In fact, in our study, there were no medical complications during TEE examination even if patients had severe neurological manifestations.

Conclusions

In conclusion, in >50% of patients, stroke and malignancy seem to be accompanied by RLS and DVT or pulmonary embolism. Paradoxical brain embolism seems likely to represent one mechanism of stroke in patients with

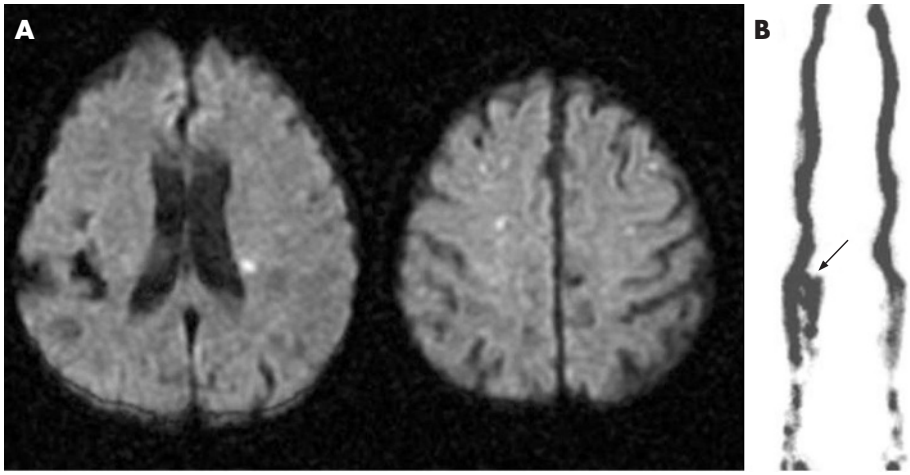

Figure 1 Patient 4. (A) Diffusion-weighted imaging shows multiple hyperintense lesions in both right and left middle cerebral artery areas. (B) Venography of the lower limb 5 days after stroke onset shows abnormal collateral flow (arrow) in the leg vein, indicating deep venous thrombus.

malignancy. When no embolic sources are identifiable in patients with stroke and malignancy and the source is unknown, c-TCD examination should be performed to detect the presence of RLS.

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Authors' affiliations

Y Iguchi, K Kimura, K Kobayashi, Y Ueno, T Inoue, Department of Stroke Medicine, Stroke Center, Kawasaki Medical School, Kurashiki, Japan

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