Table 1. *Baseline characteristics in patients with nonvalvular atrial fibrillation and control subjects*

	n	NVAF	n	Control	*P* value
Age	71	74.4 ± 9.9	71	73.7 ± 8.2	.658*
Chronic AF	29	40.8%	—	—	—
Paroxysmal AF	42	59.2%	—	—	—
Hypertension	45/71	63.4%	41/71	57.7%	.492†
Diabetes mellitus	20/71	28.2%	19/71	26.8%	.851†
Hypercholesterolemia	25/71	35.2%	30/71	42.3%	.389†
Aspirin intake	39/71	54.9%	36/71	50.7%	.614†
Warfarin intake	22/71	31.0%	1/71	1.4%	<.001†
Smoking‡	19/68	27.9%	23/57	40.4%	.144†
Drinking‡	22/63	34.9%	26/53	49.1%	.124†
BMI‡	56	23.5 ± 3.0	54	22.6 ± 3.3	.170*
Max IMT‡	36	2.3 ± 1.0	57	2.1 ± 1.0	.185§
LAD‡	49	3.9 ± 1.0	6	3.3 ± 0.4	.036§
TAT‡	22	1.5 ± 1.0	14	1.4 ± 0.5	.28§
D-dimer‡	21	1.3 ± 4.1	14	0.8 ± 1.2	.34§
β-TG‡	38	39.0 ± 23.1	37	34.1 ± 12.9	.33§

Abbreviations: β-TG, β-thromboglobulin; AF, atrial fibrillation; BMI, body mass index; max IMT, maximum intima-media thickness of carotid artery; LAD, left atrial diameter; TAT, thrombin-antithrombin III complex.

Values are mean ± SD. $P < .05$ was considered statistically significant.

*Differences compared with control subjects using the Student independent *t* test.

†Chi-square test.

‡Subject numbers were different between 2 groups because of missing data. We analyzed only the available data.

§Mann–Whitney *U* test.

Results

Background Characteristics

Background characteristics in the control and NVAF groups are shown in Table 1. The respective frequencies of risk factors in the control and NVAF groups were 57.7% and 63.4% for hypertension, 26.8% and 28.2% for diabetes, and 42.3% and 35.2% for hypercholesterolemia, respectively, with none of the differences being significant. The respective percentages of oral intake of antiplatelet agents in the control and NVAF groups were 50.7% and 54.9%, with no difference observed, but the respective percentages of oral intake of anticoagulants (warfarin) were 1.4% and 31.0%, significantly higher in the NVAF group. There were no differences for smoking, drinking, BMI, and max IMT, but the NVAF group had a significantly higher LAD value. There were no significant differences between the two groups in TAT, D-dimer, or β-TG.

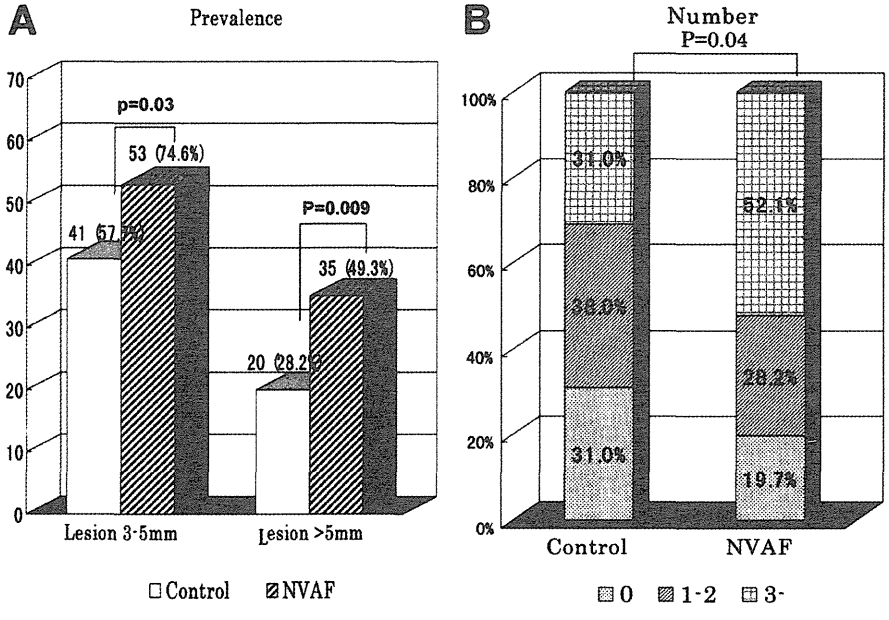

Figure 1. *Prevalence and number of silent cerebral infarction (SCI) by size on magnetic resonance imaging. (A) The percentage of patients with at least 1 SCI with a size of 3 to 5 mm or >5 mm were significantly higher in the nonvalvular atrial fibrillation (NVAF) group (lined columns) than in the control group (open columns). (B) The number of SCIs was also significantly larger in the NVAF group than in the control group. Statistical analysis was performed using the Chi-square test (A) and the Mann–Whitney U test (B).*

Table 2. *Prevalence of risk factors for silent cerebral infarction*

	SCI (3-5 mm)					SCI (>5 mm)				
	(−)		(+)			(−)		(+)		
Risk factor	n = 48		n = 94		*P* value	n = 87		n = 55		*P* value
Age <75 y	18	37.5%	52	55.3%	.04	35	40.2%	35	63.6%	<.01
Male	34	70.8%	62	66.0%	.56	61	70.1%	35	63.6%	.42
Hypertension	27	56.3%	59	62.8%	.45	51	58.6%	35	63.6%	.55
Hypercholesterolemia	20	41.7%	35	37.2%	.61	38	43.7%	17	30.9%	.13
Diabetes mellitus	13	27.1%	26	27.7%	.94	24	27.6%	15	27.3%	.97
NVAF	18	37.5%	53	56.4%	.03	36	41.4%	35	63.6%	.01
Aspirin intake	22	45.8%	53	56.4%	.23	49	56.3%	26	47.3%	.29
Warfarin intake	4	8.3%	19	20.2%	.07	10	11.5%	13	23.6%	.06

Abbreviations: NVAF, nonvalvular atrial fibrillation; SCI, silent cerebral infarction.
Differences compared with control subjects by Chi-square test.
Values are mean ± SD.
$P < .05$ was considered statistically significant.

Silent Cerebral Infarcts

The proportions of patients in the NVAF group with at least 1 SCI 3 to 5 mm in size and >5 mm in size were 74.6% and 49.3%, respectively, compared with 57.7% and 28.2%, respectively, for the control group. The positive percentages in both sizes of SCI were significantly higher in the NVAF group than in the control group. The numbers of SCIs were also significantly larger in the NVAF than the control group (Figure 1).

No significant difference between chronic and paroxysmal atrial fibrillation was seen in either the proportion of patients with the presence of SCIs or the numbers of SCIs.

A comparison of the presence or absence of SCIs with age and other factors showed that age and NVAF were significant factors for both 3 to 5 mm and >5 mm sizes of SCIs (Table 2).

Multiple logistic regression analysis was also performed to investigate the relationships between risk factors and SCIs. In this issue, NVAF was observed to be correlated with oral anticoagulant intake, so it was excluded from the factors. The results also showed that age and NVAF were significant factors for both sizes of SCIs (Table 3).

In the NVAF group, 31.0% of SCIs were seen in the cortex/subcortex and 56.3% in the deep white matter, which were more frequent than those in the control group (9.9% in the cortex/subcortex and 22.5% in the deep white matter). On the other hand, there were no significant differences in the thalamus/basal ganglia, brain stem, and cerebellum (Figure 2).

Spearman correlation analysis revealed that CHADS2 scores were associated with the number of SCIs in the cortex/subcortex (r = 0.277; 95% confidence interval [CI], 0.05-0.48; $P < .01$). By contrast, in the deep white matter, thalamus/basal ganglia, brain stem, or cerebellum, there was no association with CHADS2 score and the number of SCIs. The CHADS2 score were not assessed by multivariate analysis because the scheme takes age and hypertension into account.

Table 3. *Multiple logistic regression analysis of risk factors for silent cerebral infarction*

	SCI (3-5 mm)			SCI (>5 mm)		
Risk factor	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.07	1.02-1.12	<.01	1.08	1.03-1.13	<.01
Male	0.84	0.37-1.93	.68	0.77	0.35-1.72	.52
Hypertension	0.98	0.46-2.11	.97	0.89	0.41-1.90	.74
Hypercholesterolemia	0.79	0.36-1.71	.54	0.58	0.26-1.27	.17
Diabetes mellitus	0.82	0.35-1.93	.65	0.89	0.38-2.07	.78
NVAF	2.18	1.03-4.61	.04	2.53	1.21-5.30	.01
Aspirin intake	1.61	0.77-3.43	.22	0.68	0.32-1.44	.32

Abbreviations: CI, confidence interval; NVAF, nonvalvular atrial fibrillation; OR, odds ratio; SCI, silent cerebral infarction.
$P < .05$ was considered statistically significant.

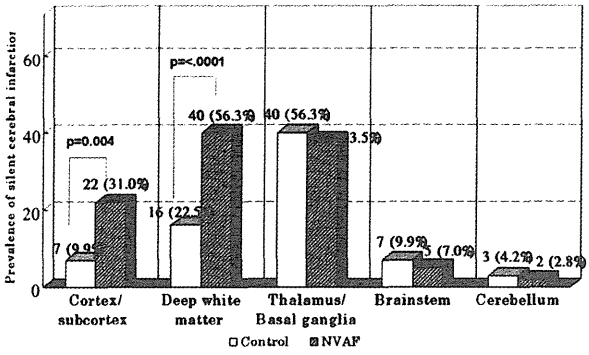

Figure 2. *Location of silent cerebral infarction (SCI) on magnetic resonance imaging. SCIs in the cortex/subcortex and in the deep white matter were more frequent in the nonvalvular atrial fibrillation group (lined columns) than those in the control group (open columns). There were no significant differences in the thalamus/basal ganglia, brainstem, or cerebellum. Statistical analysis was performed using the Chi-square test.*

Cerebral White Matter Lesions

No difference in grade between the control and NVAF groups was seen for PVH, but the DSWMH grade was significantly higher in the NVAF group (Fig 3).

A comparison of the presence or absence of PVH and DSWMH with age and other factors showed that age was significantly higher and hypertension significantly more frequent in patients with PVH, while age was significantly higher and NVAF significantly more frequent in patients with DSWMH (Table 4).

Multiple logistic regression analysis was conducted in the same way as for SCIs to investigate the relationship with risk factors. Age alone was an independent risk factor for PVH, whereas for DSWMH not only age but also NVAF was an independent risk factor (Table 5).

Discussion

In this study, NVAF patients had a higher rate of SCIs than the control patients. In previous studies, the rate of SCIs has been found to be 8% to 28% in healthy individuals[5,17] and 8% to 57% in patients with cardiovascular disease, hypertension, and diabetes mellitus.[17]

In the present study, the percentages of patients in the control group with SCIs from 3 to 5 mm and >5 mm were 57.7% and 28.2%, respectively, while the NVAF group had higher rates (74.6% and 49.9%, respectively). The rate of SCIs was thought to be higher relatively because this study was hospital-based and the subjects were older than those in previous studies.

The NVAF group had also significantly larger number of SCIs than the control group, and high rates of SCIs were observed in the cortex/subcortex and in the deep white matter in patients with NVAF.

Previous research has shown that approximately 80% of microthrombi injected into the carotid artery embolize to gray matter regions.[18] In addition, it has been reported that multiple small infarcts in the cortex seen on MRI diffusion-weighted images are actually embolisms or small embolic fragments.[19,20] From these, high rates of SCIs in the cortex/subcortex in NVAF patients may be small silent cardiogenic embolism to preferentially occur in those with than without NVAF.

On the other hand, it is possible that deep white matter SCIs may reflect in situ small vessel disease. It has previously been reported that the administration of aspirin, which has an antiplatelet effect, resulted in the reduction of deep white matter and basal ganglia SCIs in patients with NVAF, and, because no change was seen in the cortex/subcortex, the authors speculated that SCIs in the deep white matter and basal ganglia region were not

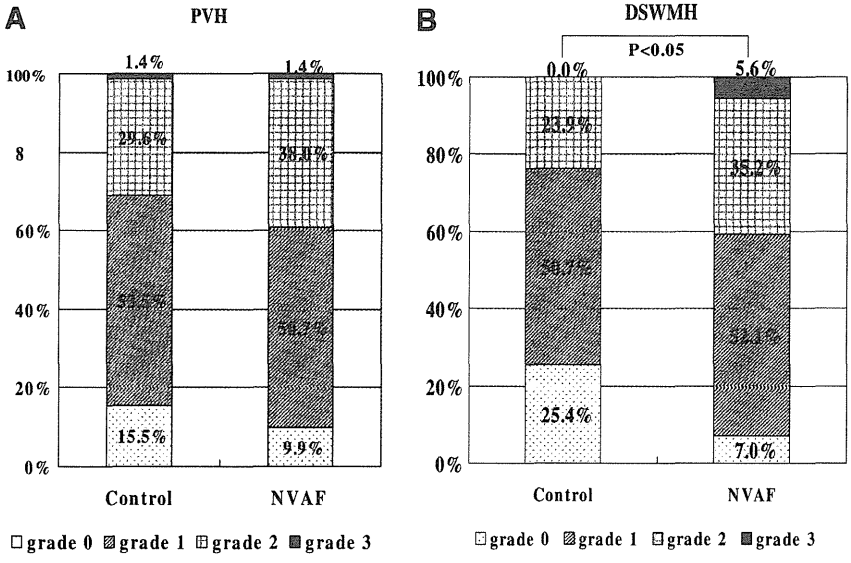

Figure 3. *Prevelance of periventricular hyperintensity (PVH) and deep and subcortical white matter hyperintensity (DSWMH). (A) There was no difference for PVH grade between the control group and the nonvalvular atrial fibrillation (NVAF) group. (B) The DSWMH grade was significantly higher in the NVAF group than in the control group. Statistical analysis was performed using the Chi-square test.*

Table 4. *Prevalence of risk factors for periventricular hyperintensity and deep and subcortical white matter hyperintensity*

	PVH (%)					DSWMH (%)				
	(−)		(+)			(−)		(+)		
Risk factor	n = 18		n = 124		*P* value	n = 23		n = 119		*P* value
Age >75 y	5	27.8%	65	52.4%	.04	6	26.0%	64	53.8%	.02
Male	14	77.8%	82	66.1%	.32	18	78.3%	78	65.5%	.23
Hypertension	7	38.9%	79	63.7%	.04	10	43.5%	76	63.9%	.06
Hypercholesterolemia	5	27.8%	50	40.3%	.45	8	34.8%	47	39.5%	.67
Diabetes mellitus	1	5.6%	38	30.6%	.05	3	13.0%	36	30.3%	.09
NVAF	7	38.9%	64	51.6%	.31	5	21.7%	66	55.5%	<.01
Aspirin intake	10	55.6%	65	52.4%	.80	10	43.5%	65	54.6%	.32
Warfarin intake	2	11.1%	21	16.9%	.77	2	8.7%	21	17.6%	.44

Abbreviations: DSWMH, deep and subcortical white matter hyperintensity; NVAF, nonvalvular atrial fibrillation; PVH, periventricular hyperintensity.

Values are mean ± SD.

$P < .05$ was considered statistically significant. Differences compared with control subjects using the Chi-square test.

caused by fibrin clots, but rather platelet thrombi probably formed on the deep perforating arteries.[21]

Because deep white matter constitutes the boundary zone for cerebral blood flow, hemodynamic mechanisms give rise to ischemia and to form of secondary thrombi. Caplan and Hennerici[22] have hypothesized that embolism and low perfusion exert a synergistic effect. Low perfusion reduces the blood flow for washing emboli away, while emboli block the blood supply, further worsening ischemia. These suggest that the deep white matter SCIs seen in the NVAF patients were probably the result of a combination of low perfusion caused by hemodynamic mechanisms and microthrombi.

In our results, there was no significant difference in the basal ganglia/thalamus SCIs between the NVAF and control groups. Recent reports indicated that risk factors for the basal ganglia infarcts are different from those for deep white matter infarcts, and carotid artery stenosis and coronary artery disease were significant and independent predictors of the basal ganglia infarcts.[23-25] Therefore, the SCIs in the basal ganglia were more likely to be paralleled with a background systemic atherosclerosis.

Most previous studies showed that hypertension was associated with SCIs, but it was not a significant risk factor in this study. The results showed that age and NVAF but not hypertension was significant factor for SCIs. The reason for this discrepancy between the previous studies and our study was that the hypertension percentage of the subjects in both groups of this study was higher than in the previous studies, and because half of the subjects were NVAF patients. These differences in the proportions of hypertension and NVAF between the previous studies and this study might have affected the results of statistical analysis.

We also found that, compared with the control group, NVAF patients had a significantly higher DSWMH grade,

Table 5. *Multiple logistic regression analysis of risk factors for periventricular hyperintensity and deep and subcortical white matter hyperintensity*

	PVH			DSWMH		
Risk factor	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.08	1.01-1.15	.02	1.13	0.83-0.95	<.01
Male	0.54	0.15-1.95	.34	0.43	0.66-8.34	.20
Hypertension	2.01	0.66-6.10	.22	1.69	0.59-4.91	.33
Hypercholesterolemia	1.73	0.52-5.78	.37	1.01	0.33-3.11	.99
Diabetes mellitus	7.28	0.88-60.14	.07	2.58	0.61-10.89	.20
NVAF	1.91	0.62-5.90	.26	7.34	2.04-26.41	<.01
Aspirin intake	0.64	0.21-1.98	.44	1.48	0.51-4.27	.47

Abbreviations: CI, confidence interval; DSWMH, deep and subcortical white matter hyperintensity; NVAF, nonvalvular atrial fibrillation; OR, odds ratio; PVH, periventricular hyperintensity.

$P < .05$ was considered statistically significant.

while there was no difference in the PVH grade. Multiple logistic regression analysis showed that age was a significant independent risk factor for PVH, whereas not only age but also NVAF was a significant independent risk factor for DSWMH. In a comparison of the 2 groups, patients with PVH were significantly older and had a higher frequency of hypertension, a result consistent with previous reports.[7,8]

Pathologically, PVH is associated with other age-related changes, such as pallor of the myelin sheath and expansion of the perivascular space, which manifests on MRI scans as rim, caps, or a smooth halo, although they are not regarded as abnormal findings.[26]

In DSWMH, small infarct areas are mixed with age-related changes, and these are regarded as reflecting atherosclerosis of perforators. They are seen in elderly people with vascular risk factors and are recognized as chronic ischemia.[26,27]

The present study found the frequency of DSWMH to be significantly higher in NVAF patients, suggesting the existence of small artery disease. It has been proposed that for SCIs, the cause lies in the low cerebral perfusion by reduced cardiac output in NVAF patients.[28,29] It has previously been reported that chronically low perfusion affects cerebral white matter lesions[30] and a higher rate of cerebral white matter lesions observed in atrial fibrillation accompanied by left ventricular hypertrophy has also been reported.[28]

According to recent reports, the irregular heartbeat of atrial fibrillation gives rise to turbulence in the blood flow and damages the vascular endothelial cells, reducing production of nitric oxide, which has an antithrombotic effect.[31] It has also been shown that shear stress generated by atrial fibrillation affects the vascular endothelium and inhibits nitric oxide synthesis, and that the nitric oxide synthase inhibitor asymmetric dimethyl arginine increases.[32] Furthermore, there have also been reports on platelet activation in atrial fibrillation as a result of expression of the platelet adhesion molecule P-secretin[33] and blood hypercoagulation in the early stages after atrial fibrillation.[34,35]

From these facts, not only does cerebral blood flow diminish but also antithrombotic action decreases in NVAF patients and these effects may combine to generate a high rate of deep white matter lesions.

The CHADS2 score was an independent prognostic factor for cerebral infarction in NVAF patients as reported.[36] In our study, the number of SCIs in the cortex/subcortex was significantly increased according to the increase of CHADS2 score. Our results revealed that this scoring system was an effective scheme not only in stroke risk but also in risk of SCI.

Conclusions

A high rate of cortical/subcortical and deep white matter SCIs was observed in NVAF patients, and the mechanism for their generation is thought to consist of the synergistic effect of microthrombi and hemodynamic abnormalities. High-grade white matter lesions were also common in NVAF patients, and diminished cerebral blood flow and reduced antithrombotic action may be involved in their pathogenesis. The CHADS2 score was a useful scheme of evaluating not only stroke risk but also risk of SCI in Japanese NVAF patients.

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ORIGINAL ARTICLE

Cancer-associated ischemic stroke is associated with elevated D-dimer and fibrin degradation product levels in acute ischemic stroke with advanced cancer

Tomoyuki Kono, Toshiho Ohtsuki, Naohisa Hosomi, Ikuko Takeda, Shiro Aoki, Yoshimasa Sueda, Kayoko Ishihara, Takeshi Nakamura, Takemori Yamawaki and Masayasu Matsumoto

Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical Sciences, Hiroshima, Japan

Aim: Although several studies have reported various causes of ischemic stroke in patients with cancer, only a few have evaluated the clinical relevance of ischemic stroke pathogenesis to cancer. The aim of the present study was to elucidate the clinical characteristics of cancer-associated ischemic stroke.

Methods: We evaluated 154 ischemic stroke patients without cancer and 57 ischemic stroke patients with cancer who had either received continuous treatment for cancer within 5 years before to the onset of ischemic stroke, or who had been diagnosed with cancer within 1 year after the onset of ischemic stroke. Cancer patients were grouped into "cancer-associated ischemic stroke," the "conventional ischemic stroke," or "other."

Results: A total of 15 patients (26%) were classified into the cancer-associated ischemic stroke in cancer patients. In univariate analysis of the cancer-associated ischemic stroke and the others, there were significant differences in the prevalence of hypertension, hyperlipidemia and advanced cancer (clinical stage IV), and the levels of D-dimer, fibrin degradation product and hemoglobin. With multivariate regression analysis of those factors, the prevalence of hypertension, hyperlipidemia and advanced cancer (clinical stage IV), and the levels of D-dimer and fibrin degradation product remained as statistically independent factors, which were associated with cancer-associated ischemic stroke ($n = 111$, $\chi^2 = 67.21$, $P < 0.0001$).

Conclusion: In acute ischemic stroke, the cancer-associated ischemic stroke is associated with elevated D-dimer and fibrin degradation products, even after controlling hypertension, hyperlipidemia and advanced cancer (clinical stage IV). **Geriatr Gerontol Int 2012; ••: ••–••.**

Keywords: cancer, D-dimer, fibrin degradation product, ischemic stroke.

Introduction

Systemic thromboembolism associated with cancer was first described by Armand Trousseau and colleagues in 1865. In a more recent autopsy study of 3426 cancer cases, excluding primary brain tumors, 15% of the cases examined had experienced cerebrovascular events.[1] The

Accepted for publication 15 November 2011.

Correspondence: Dr Naohisa Hosomi MD PhD, Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima, Hiroshima 734-8551, Japan. Email: nhosomi@hiroshima-u.ac.jp

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doi: 10.1111/j.1447-0594.2011.00796.x

causes of ischemic stroke in patients with cancer might differ from those in patients without cancer. Cancer can predispose patients to hypercoagulable states and might cause the development of deep vein thrombosis (DVT) and non-bacterial thrombotic endocarditis (NBTE).[2] NBTE is one of the most common causes of ischemic stroke in cancer patients,[3] and it has been found in 27% of cancer patients with ischemic stroke on post-mortem analysis.[1]

A number of previous studies have evaluated the characteristics of ischemic stroke patients with cancer. Cestari *et al.* classified the subtypes of ischemic stroke with cancer and found conventional ischemic stroke in just 35 of 96 patients (36%).[4] In addition, there were 36 of 52 patients (69%) with NBTE or embolism of an undetermined source in the subtype of embolic stroke.[4] In another study, embolic signals were detected with transcranial Doppler (TCD) in 45.9% of ischemic stroke patients with cancer.[5] In embolic stroke patients with cancer, a hypercoagulable state attributable to the cancer might have been one of the major causes of ischemic stroke.

However, these studies included a large number of elderly cancer patients, and it is possible that there was a certain proportion of these elderly patients in whom conventional ischemic stroke might have been attributable to atrial fibrillation (Af), atherosclerotic disease or other causes. This highlights the possibility that the causes of ischemic stroke in cancer patients are more complex than previously anticipated. To effectively detect and prevent ischemic stroke in cancer patients, it is necessary to define the causal relationship between ischemic stroke and cancer. However, the characteristics of ischemic stroke attributable to cancer that might allow its discrimination from conventional ischemic stroke remain undetermined.

The aim of the present study was to elucidate the clinical characteristics of cancer-associated ischemic stroke to differentiate it from the other type of ischemic stroke.

Methods

Design

This was a retrospective study of acute ischemic stroke patients admitted to Hiroshima University Hospital, Hiroshima, Japan, between January 2006 and August 2010. Ischemic stroke was confirmed by computed tomography (CT) and/or magnetic resonance imaging (MRI). We classified the patients as with cancer if they had active cancer or had been diagnosed with any cancer within 1 year after the onset of ischemic stroke, excluding primary intracranial tumors. Active cancer was defined by the presence of any continuous treatment for cancer within 5 years before the onset of ischemic stroke. The patients were classified as non-cancer patients if they had never been diagnosed with cancer, had undergone surgical removal of cancer more than 5 years before stroke onset and had shown no recurrence of cancer until their stroke onset, or had no clinical information regarding their cancer.

Data collection

Patients were classified as hypertensive when they had been diagnosed with hypertension before stroke onset, and/or were taking antihypertensive medication. Patients were classified as having diabetes mellitus (DM) if they had glycated hemoglobin (HbA_{1c}) ≥ 6.5% and fasting blood glucose ≥126 mg/dL, and/or were taking oral hypoglycemic agents or insulin. Patients were classified as hyperlipidemic if they had total cholesterol ≥220 mg/dL, low-density lipoprotein cholesterol ≥140 mg/dL and triglyceride level ≥150 mg/dL, and/or were taking antihyperlipidemic medication. Af was diagnosed with a standard electrocardiogram (ECG), 24-h ECG recording or 14-day ambulatory ECG monitoring.[6] The clinical stage of cancer was evaluated at the onset of ischemic stroke based on the tumor–node–metastasis (TNM) classification (for solid cancer) or the modified Ann Arbor (Cotswold's) staging (for malignant lymphoma).[7] In cases with an onset of ischemic stroke before cancer diagnosis, the clinical stage of cancer was evaluated at the time of cancer diagnosis. When a patient had multiple primary cancers, we evaluated the most advanced cancer.

Blood cell counts and blood coagulation factors (e.g. prothrombin time [PT; s], PT international normalized ratio [PT–INR], activated partial thromboplastin time [APTT; s], fibrinogen [mg/dL], D-dimer [μg/mL], fibrin degradation product [FDP; μg/mL], and antithrombin 3 [AT3; %]) were evaluated within 24 h of admission. D-dimer levels were measured by the latex agglutination method using a Sysmex XE7000 and the RIAS AUTO D-dimer NEO reagent (Kobe, Japan).

Ischemic stroke subtypes were classified by two stroke neurologists using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria and imaging examinations (e.g. brain MRI, carotid ultrasonography, transthoracic echocardiography [TTE]), which were carried out within 1 week after hospitalization.[8] In addition, patients with the cancer-associated ischemic stroke were further categorized in accordance with the patients for whom no causes of stroke other than cancer could be identified in the subtype of undetermined etiology, despite extensive evaluations including brain MRI, carotid ultrasonography and TTE. Patients were classified as conventional ischemic stroke if their ischemic stroke was a lacunar infarction or if they had Af, myocardial infarction, rheumatic valvular disease, valvular replacement, cardiomyopathy, severe stenosis

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(>50%) of the infarct-related artery, arterial dissection or aortitis.

Statistical analysis

Medians (minimum to maximum) were used to describe continuous data, and frequency and percentage were used for categorical data. Univariate analyses were carried out to evaluate differences among the groups with regards to baseline characteristics, risk factors and laboratory data. Statistical analysis was carried out using JMP software version 9.0 for Windows (SAS Institute, Cary, NC, USA). Values were compared between patient groups using Fisher's exact test for categorical variables. Differences in continuous variables among the groups were examined using the Kruskal–Wallis test. When there was a statistically significant difference, the Wilcoxson signed rank test was applied to examine the difference between each group. Multivariate logistic regression was utilized to assess the relative importance of variables found to be related to the cancer-associated ischemic stroke, in initial univariate analyses. All analyses were two-tailed, and a value of $P < 0.05$ was considered statistically significant.

Results

A total of 211 consecutive acute ischemic stroke patients (79 women and 132 men) were identified between January 2006 and October 2010. The median age was 73 years (range 25–92). The patients' baseline characteristics are listed in Table 1. With our classifications, 15 patients (26%) were in the cancer-associated ischemic stroke group, 39 (68%) were in the conventional ischemic stroke group and three (6%) were not assigned to either classification among the cancer patients. No patient in the present study was assigned to both classifications. Of the three patients not assigned to either classification, one was classified as having a stroke of an undetermined etiology, because the general condition of the patient deteriorated before further evaluation. The two other patients in this group showed disseminated intravascular coagulation (DIC). There were no significant differences in prevalence of vascular risk factors in the cancer patients compared with that in the non-cancer patients. The most common vascular risk factor in the cancer patients was hypertension. It was similar to non-cancer patients. Ischemic stroke onset preceded cancer diagnosis in eight patients. The median duration from cancer diagnosis to stroke onset was 8 months (range –11 to 120) in the cancer patients. The patients in the cancer-associated ischemic stroke group had a lower rate of hypertension and hyperlipidemia than those in the conventional ischemic stroke group ($P < 0.05$).

Table 1 Baseline characteristics

		Non-cancer ($n = 154$)	Cancer ($n = 57$)	CAIS ($n = 15$)	CIS ($n = 39$)	Other ($n = 3$)
Age, years median (range)		73 (25, 92)	75 (50, 91)	74 (50, 87)	76 (56, 91)	67 (56, 86)
Sex	Female, *n* (%)	65 (42)	14 (25)	6 (40)	7 (20)	1 (33)
Risk factors	Hypertension, *n* (%)	100 (65)	33 (58)	5 (33)	26 (67)	2 (67)
	DM, *n* (%)	54 (35)	19 (33)	3 (20)	16 (41)	0 (0)
	Hyperlipidemia, *n* (%)	74 (48)	17 (30)	1 (7)	16 (41)	0 (0)
	Af, *n* (%)	55 (36)	19 (33)	0 (0)	19 (49)	0 (0)
Ischemic stroke subtypes	Small-vessel disease, *n* (%)	22 (14)	5 (9)	0 (0)	5 (13)	0 (0)
	Large artery atherosclerosis, *n* (%)	30 (20)	12 (21)	0 (0)	12 (31)	0 (0)
	Cardioembolism, *n* (%)	62 (40)	18 (32)	0 (0)	18 (46)	0 (0)
	Other determined etiology, *n* (%)	16 (10)	6 (10)	0 (0)	4 (10)	2 (67)
	Undetermined etiology, *n* (%)	24 (16)	16 (23)	15 (100)	0 (0)	1 (33)
Duration from cancer diagnosis to ischemic stroke onset, month median (range).		NA	8 (–11, 120)	13 (0, 69)	7 (–11, 120)	7 (0, 11)

Af, atrial fibrillation; CAIS, cancer-associated ischemic stroke; CIS, conventional ischemic stroke; DM, diabetes mellitus; NA, not assessed.

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Table 2 Distributions of primary cancers

	Cancer ($n = 57$)	CAIS ($n = 15$)	CIS ($n = 39$)	Other ($n = 3$)
Lung	8	2	6	0
Stomach	7	1	6	0
Liver	6	2	4	0
Colon	5	0	5	0
Prostate	4	0	4	0
Malignant lymphoma	4	1	3	0
Pancreas	3	2	0	1
Gall bladder	3	2	1	0
Kidney	3	2	1	0
Esophagus	3	0	2	1
Pharynx	2	0	1	1
Breast	3	1	2	0
Others	6	2†	4‡	0

†These two patients had uterus cancer and malignant melanoma. ‡These four patients had thyroid cancer, gastrointestinal stromal tumor, bladder cancer or soft tissue tumor of the elbow. CAIS, cancer-associated ischemic stroke; CIS, conventional ischemic stroke.

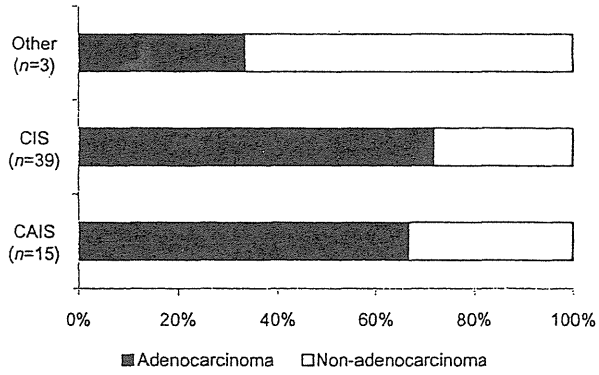

Figure 1 Histological types of primary cancer in the ischemic stroke classification in association with cancer. The difference in the distribution of adenocarcinoma between the cancer-associated ischemic stroke (CAIS) group and the conventional ischemic stroke (CIS) group was not significant.

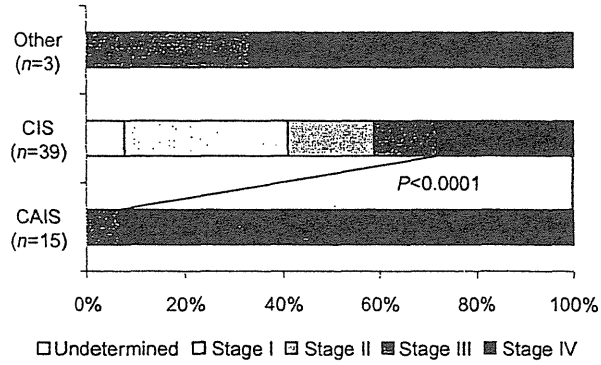

Figure 2 Clinical stage of primary cancer in the cancer-associated ischemic stroke group. There was a higher prevalence of advanced cancer (clinical stage IV) in patients with cancer-associated ischemic stroke (CAIS) compared with patients with conventional ischemic stroke (CIS).

The distributions of the primary cancers are shown in Table 2. Primary cancers were located in the lung in eight patients (14%) and in the stomach in seven patients (12.2%). Through histological classification, it was determined that 39 patients (68%) had adenocarcinoma. There was no significant difference in the distribution of adenocarcinoma between the cancer-associated ischemic stroke and the conventional ischemic stroke groups (Fig. 1). There was a higher prevalence of advanced cancer (clinical stage IV) in the cancer-associated ischemic stroke group than in the conventional ischemic stroke group ($P < 0.0001$; Fig. 2).

Blood cell counts, including hemoglobin and platelet counts, were evaluated in all patients. D-dimer and FDP levels were evaluated in 177 (84%) and 118 patients (56%), respectively. There was no significant difference in platelet counts among the groups. Hemoglobin was low in both cancer groups compared with that of the non-cancer group. D-dimer and FDP levels were significantly higher in the cancer-associated ischemic stroke group than in the non-cancer group and conventional ischemic stroke group ($P < 0.05$; Fig. 3). To assess the association between blood coagulation and clinical stage of primary cancer, differences between D-dimer and FDP levels were evaluated in the different clinical stages. Levels of D-dimer and FDP in the patients with cancer of clinical stage IV were significantly higher than those in patients of clinical stages I–III (D-dimer: 1.3 μg/mL [0.1–29.0] in stages I–III and 8.3 μg/mL [0.4–81.5] in stage IV and FDP: 3.1 μg/mL [0.8–50.5] in stages I–III and 15.1 μg/mL [1.2–100.2] in stage IV, $P < 0.05$, respectively).

In univariate analysis on the cancer-associated ischemic stroke and the other groups, there were significant differences in the prevalence of hypertension, hyperlipidemia, and advanced cancer (clinical stage IV) and the levels of D-dimer, FDP and hemoglobin. Then, we carried out multivariate logistic regression analysis on the cancer-associated ischemic stroke and the others with those factors. As a result, the prevalence of hypertension, hyperlipidemia, and advanced cancer (clinical stage IV), and the levels of D-dimer and fibrin degradation product remained as statistically independent factors, which associated with cancer-associated ischemic stroke ($n = 111$, $\chi^2 = 67.21$, $P < 0.0001$; Table 3).

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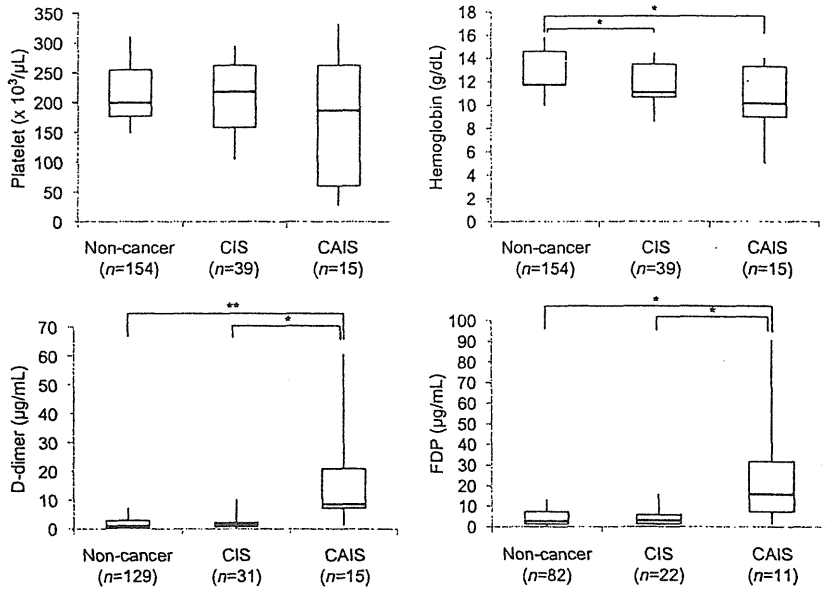

Figure 3 Blood cell counts and coagulation factors in the cancer-associated ischemic stroke group. There was no significant difference in platelet counts between the cancer-associated ischemic stroke (CAIS) and the conventional ischemic stroke (CIS) groups. Although hemoglobin level was low in both cancer patient groups compared with that of the non-cancer patients, there was no significant difference between the patients with CAIS and those with CIS. D-dimer and fibrin degradation product (FDP) levels were significantly higher in the CAIS group than the other groups. Boxplot graph was made with median, 10th, 25th, 75th and 90th values. Significant differences among groups: $*P < 0.05$, $**P < 0.0001$.

Table 3 Multivariate logistic regression analysis on the cancer-associated ischemic stroke and the others

Factors	χ^2	*P*-value
Hypertension	11.13	0.0008
Hyperlipidemia	4.16	0.0414
Advanced cancer	48.47	<0.0001
D-dimer	12.60	0.0004
FDP	9.24	0.0024
Hemoglobin	2.15	0.9988

$n = 111$, $\chi^2 = 67.21$, $P < 0.0001$. FDP, fibrin degradation product.

Discussion

In the present study, we evaluated the clinical characteristics of ischemic stroke patients with cancer. Of the 58 patients examined, 16 (28%) were classified as having cancer-associated ischemic stroke. The characteristics of cancer-associated ischemic stroke were evaluated by comparison with the non-cancer group and conventional ischemic stroke group. There was no significant difference in the prevalence of adenocarcinoma between the cancer-associated ischemic stroke and the conventional ischemic stroke groups. However, there was a higher prevalence of advanced cancer (clinical stage IV) in patients with cancer-associated ischemic stroke than in patients with conventional ischemic stroke. There was a lower prevalence of hypertension and hyperlipidemia in patients with the cancer-associated ischemic stroke than in patients with the conventional ischemic stroke. There were no significant differences between the two groups in hemoglobin and platelet counts. FDP and D-dimer levels were significantly higher in patients with the cancer-associated ischemic stroke than in the non-cancer group and the conventional ischemic stroke group. In acute ischemic stroke, cancer-associated ischemic stroke was associated with elevated D-dimer and fibrin degradation products, even after controlling hypertension, hyperlipidemia and advanced cancer (clinical stage IV).

In the present study, we attempted to select the patients with cancer-associated ischemic stroke using the TOAST criteria. Kim *et al.* have also tried to classify ischemic stroke patients with cancer using conventional and cryptogenic stroke mechanisms.[9] In their classification, ischemic stroke patients with undetermined etiologies according to the TOAST criteria were categorized solely with reference to cryptogenic stroke mechanisms. Although their classification method is almost equal to our method, they classified five NBTE patients as a conventional ischemic stroke mechanism. NBTE is widely recognized as a unique cause of cardioembolism frequently observed in cancer patients, as has been reported in a post-mortem series.[1] Although transesophageal echocardiography (TEE) is the most appropriate method to diagnose cardiac sources of embolism, such as NBTE,[10] it is difficult to carry out TEE in all cancer patients, as TEE is an invasive examination. In the present study, we carried out TEE in just 37% of the patients who were suspected to have had a cardioembolic stroke from the results of imaging analysis and who could tolerate esophageal intubation. Although our execution rate of TEE was higher than that in previous reports,[4,11] it is quite likely that there is a selection bias. Therefore, we tried to classify cancer-associated ischemic stroke without using the finding of TEE. As a

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result, three patients with NBTE in the cancer-associated ischemic stroke group were included, because there were not embolic sources, despite extensive examination without TEE. From this result, this classification method could be adequate in a clinical site.

D-dimer is a plasmin-derived degradation product of cross-linked fibrin that is elevated in patients with hypercoagulability. D-dimer levels were elevated in a wide variety of conditions with intravascular clotting, including ischemic stroke itself. Previous studies have reported that D-dimer is higher in stroke patients with cancer than in stroke patients without cancer.[4] In the present study, we have shown that, among ischemic stroke patients, D-dimer levels were more elevated in patients with cancer-associated ischemic stroke than non-cancer and conventional ischemic stroke. The patients with NBTE showed high D-dimer levels. There were three patients with NBTE found with TEE in the cancer-associated ischemic stroke group. Their D-dimer levels were 8.7 μg/mL, 23.1 μg/mL and 55.5 μg/mL; these values were markedly higher than those of the other patients in this group. It might be because NBTE can result from a hypercoagulable stage. Furthermore, we investigated the possibility that patients with advanced cancer show high levels of D-dimer. Interestingly, the levels of D-dimer were higher in the patients with stage IV cancer than in those with clinical stages I–III. From the present results, D-dimer and FDP remained as independently significant, even after controlling the prevalence of hypertension, hyperlipidemia and advanced cancer (clinical stage IV). Therefore, although the elevation of blood coagulation factors in the patients with the cancer-associated ischemic stroke might be attributable to a higher clinical stage of primary cancer, it was independently associated with the cancer-associated ischemic stroke.

Uemura *et al.* reported that hemoglobin levels were reduced in cancer patients compared with patients with no malignancy.[12] Their explanation for the reduced hemoglobin levels in cancer patients was the general condition of these patients as a result of cancer cachexia or gastrointestinal bleeding in gastrointestinal cancer patients. The present results support those of Uemura *et al.*; hemoglobin levels in the cancer groups were lower than the non-cancer group in the present study. However, there was no significant difference in hemoglobin levels between the patients with cancer-associated ischemic stroke and those with conventional ischemic stroke. The present results suggested that hemoglobin levels cannot be a marker used to distinguish between cancer-associated ischemic stroke and conventional ischemic stroke in cancer patients.

Circulating mucinous material has been reported in embolic stroke patients with mucin-producing adenocarcinomas.[13–15] Seok *et al.* reported that embolic signal was observed in patients with metastasis or adenocarcinoma.[5] Of the patients in the present study, 68% were adenocarcinoma patients. However, there was no significant difference in histological types between the cancer-associated ischemic stroke and the conventional ischemic stroke patients. These results require confirmation in a larger number of patients.

In the present results, there was a significant difference in the clinical stage of cancer, but not the histological type between the patients with cancer-associated ischemic stroke and those with conventional ischemic stroke. A few previous reports have evaluated the relationship between cancer-associated ischemic stroke and its clinical stage. Kim *et al.* showed a high prevalence of distant metastasis in cryptogenic stroke mechanisms.[9] This report supports the present results in that there was a high prevalence of advanced cancer in the patients with cancer-associated ischemic stroke.

The present study has some limitations. First, this was a single-center retrospective study. Our hospital functions as both a regional cancer center and an advanced emergency center. The proportion of ischemic stroke patients with cancer might differ between our hospital and the general population. Therefore, there might be a selection bias for ischemic stroke patients with cancer. Second, the method of classifying cancer-associated ischemic stroke is not generalized. With our classification system, all of the ischemic stroke patients with Af were classified as having cardioembolism in conventional ischemic stroke. However, there is a possibility that some of these stroke cases might have been attributable to a hypercoagulable state as a result of cancer rather than to Af. Further selection criteria are necessary to select the Af patients in whom the ischemic stroke was a result of hypercoagulability as a result of cancer. Therefore, further research investigating the association between ischemic stroke and cancer is needed. Finally, although TEE is necessary to diagnose NBTE, TEE cannot be carried out in all cases because of patients' general conditions, anatomical reasons (e.g. esophageal or gastric cancer and esophageal varix) and/or lack of patient cooperation.

In conclusion, 26% of the patients studied were classified as having cancer-associated ischemic stroke. Based on our results, elevated D-dimer and FDP levels can be associated with cancer-associated ischemic stroke, even after controlling hypertension, hyperlipidemia and advanced cancer (clinical stage IV).

Acknowledgments

This study was partially supported by a research grant from Mitsubishi Pharma Research Foundation.

Disclosure statement

None.

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Ulcerated Carotid Plaques with Ultrasonic Echolucency Are Causatively Associated with Thromboembolic Cerebrovascular Events

Tomomi Nakamura, MD,*† Yukiko Tsutsumi, MD,* Yuko Shimizu, MD,* and Shinichiro Uchiyama, MD*

The presence of ulcerated carotid plaques is a risk factor for ischemic stroke, which is associated with thromboembolism. We evaluated the relationship between ulcerated carotid plaques and cerebrovascular events in patients with acute ischemic stroke or transient ischemic attack. We extracted 48 consecutive patients with ulcerated carotid plaques from a cohort of 1111 patients with acute ischemic stroke or transient ischemic attack. All patients were evaluated by carotid ultrasonography and diffusion-weighted magnetic resonance imaging. We defined thromboembolic events by excluding potential cardiac sources of embolism, stroke in posterior circulation, contralateral lesions, and single and small (<1.5 cm) subcortical lesions, and we considered the remaining patients with cortical lesions or multiple or large subcortical lesions as having experienced a thromboembolic cerebrovascular event. We compared ultrasonographic findings in the patients with and those without a thromboembolic cerebrovascular event. A relationship with thromboembolic events was suspected in 10 patients (21%) with ulcerated carotid plaques. The proportion of smokers was significantly higher in the group of patients with a thromboembolic event (90% vs 53%; $P = .03$). Logistic regression demonstrated a significant association between thromboembolic events and the presence of echolucent ulcerated plaques (odds ratio, 9.34, 95% confidence interval, 1.65-53.0), even though maximum intima-media thickness and other variables of ulcerated plaques (eg, depth of ulcers, thickness of the plaque, or the degree of stenosis) did not differ significantly between the 2 groups. Our findings indicate that although cerebrovascular events are closely associated with echolucent ulcerated carotid plaques, the prevalence of thromboembolism was not very high (~20%) in our cohort of Japanese patients with ulcerated carotid plaques. **Key Words:** Ulcerated carotid plaque—ultrasonography—cerebrovascular event—thromboembolism—diffusion-weighted magnetic resonance imaging.
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From the *Department of Neurology, Neurological Institute, Tokyo Women's Medical University, Tokyo, Japan; and †Department of Neurology, Itabashi Chuo Medical Center, Tokyo, Japan.

Received April 5, 2011; revision received June 16, 2011; accepted June 19, 2011.

Address correspondence to Tomomi Nakamura, MD, Department of Neurology, Neurological Institute, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. E-mail: tnakamur@nij.twmu.ac.jp.

1052-3057/$ - see front matter
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doi:10.1016/j.jstrokecerebrovasdis.2011.06.015

Atherosclerotic carotid artery disease is an established risk factor for ischemic stroke, and the presence of plaques with surface irregularities or ulcerations increases the risk.[1-3] These plaques are more prevalent in patients with a history of stroke or transient ischemic attack (TIA).[4-8] Moreover, the detection of microembolic signals (MES) by transcranial Doppler (TCD) is closely associated with the presence of ulcerated carotid plaques.[9-11] In view of the mechanism of development from ulcerated carotid plaques to cerebrovascular events, ulcerated carotid plaques are considered to be traces of plaque rupture or

fragmentation or sources of emboli generated at the cavity due to stagnated blood flow.[12] The causative relationship between ulcerated carotid plaques and the development of stroke remains controversial, however.[13] Some investigators have reported that ulcerated carotid plaques are not necessarily associated with ipsilateral symptoms, although ulceration is more frequent in symptomatic patients than in asymptomatic patients.[14,15] Another study failed to show correlations between neurologic symptoms and carotid plaque surface irregularities.[16] Yet another study found that the presence of MES is not associated with the characteristics of carotid plaques, even though emboli arose more frequently in symptomatic patients than in asymptomatic patients.[17]

Carotid endarterectomy (CEA) and carotid artery stenting are treatment options for patients with ≥50% stenosis to prevent further cerebrovascular events.[18] But because a causative relationship between cerebrovascular events and ulcerated carotid plaques as a source of thromboembolism (TE) remains obscure, little information regarding treatment for ulcerated carotid plaques is available despite the established risk for ischemic stroke. Diffusion-weighted magnetic resonance imaging (DWI) is the most sensitive tool available for detecting fresh ischemic lesions and identifying the lesions responsible for acute neurologic symptoms. Thus, the use of DWI might help clarify the causative relationship between ulcerated carotid plaques and cerebrovascular events in patients with acute ischemic stroke.

In the present study, we distinguished ulcerated carotid plaques as a source of TE from those without a direct correlation to cerebrovascular events using DWI during the acute phase of ischemic stroke or TIA. We then compared the ultrasonographic findings of ulcerated carotid plaques that were likely to be causatively related to cerebrovascular events with those that were unrelated to these events.

Methods

Patients with ulcerated carotid plaques detected by carotid ultrasonography were enrolled out of a total of 1111 consecutive patients admitted to the Itabashi Chuo Medical Center between January 2005 and December 2008 because of acute ischemic stroke or TIA. All patients were diagnosed with ischemic stroke or TIA by trained neurologists. On admission, each patient underwent a baseline 12-lead electrocardiography, biochemical and hematologic measurements, chest X-ray, magnetic resonance imaging (MRI) including DWI, magnetic resonance angiography (MRA) if without contraindications, and high-resolution duplex carotid ultrasonography. Arrhythmias responsible for cardioembolism, such as paroxysmal atrial fibrillation, were investigated using Holter electrocardiography. The presence of traditional cardiovascular risk factors, including age, sex, hypertension (casual blood pressure ≥160/95 mm Hg or receipt of antihypertensive medication), diabetes mellitus (fasting plasma glucose ≥7.77 mmol/L or receipt of medication), hyperlipidemia (serum total cholesterol ≥5.70 mmol/L or receipt of medication), and cigarette smoking (within the past 5 years or habitually smoking ≥10 cigarettes a day for >1 year, determined from self-report), was recorded. Patients who were diagnosed with TIA without DWI-positive lesions were excluded from the study, because the causative relationship between ischemic brain lesions and ulcerated carotid plaques via TE-related mechanisms could not be clarified.

Carotid Ultrasonography

An experienced examiner who was blinded to patient data performed high-resolution duplex carotid ultrasonography using a 7.5-MHz duplex scanner (Aplio XG; Toshiba, Tokyo, Japan). The common and internal carotid arteries were scanned cross-sectionally and longitudinally, to estimate the presence and distribution of atherosclerotic plaques. The entire common carotid arteries and internal carotid arteries up to approximately 20 mm distal from the tip of carotid bifurcation were scanned bilaterally. Maximum intima-media thickness (IMT) measurements were obtained to identify the thickest region of the arterial wall. Thereafter, the surface appearance of the plaques was scrutinized from several directions. Optimal insonation angles were determined to clearly visualize identified excavations. Ulcers were diagnosed by color-Doppler imaging as the presence of large obvious craters (≥2 mm deep) with a well-defined back wall at the base and reversed or stagnated blood flow in the craters according to an international consensus report.[19]

Carotid plaques with ulcers and the ulcers themselves were analyzed further by ultrasonography. The depth of the ulcers and maximal thickness of the ulcerated plaques were measured (Fig 1). The degree of stenosis at ulcerated plaques was calculated according to the criteria of the North American Symptomatic Carotid Endarterectomy Trial (NASCET).[20] The echogenicity of ulcerated plaques was also evaluated according to previous reports.[19,21] In brief, optimal images of ulcerated plaques were digitized using an Epson ES-8000 scanner (Epson, Tokyo, Japan). Individual ulcerated plaques were then outlined using the computer mouse and analyzed using Adobe Photoshop CS software (Adobe Systems, Mountain View, CA). The gray-scale content (assuming 0-5 for the bloodstream and 185-195 for the intimal lining) was determined and expressed as the mean, median, standard deviation, and total pixel count. The gray-scale median (GSM) was used as a measure of overall plaque echogenicity.[21] Each ulcerated plaque was classified as either echolucent or other based on the GSM value. An echolucent plaque was indicated by a GSM of <50, which was considered equivalent to being uniformly anechoic (class I) or predominantly hypoechoic or anechoic (class II).[19,21]

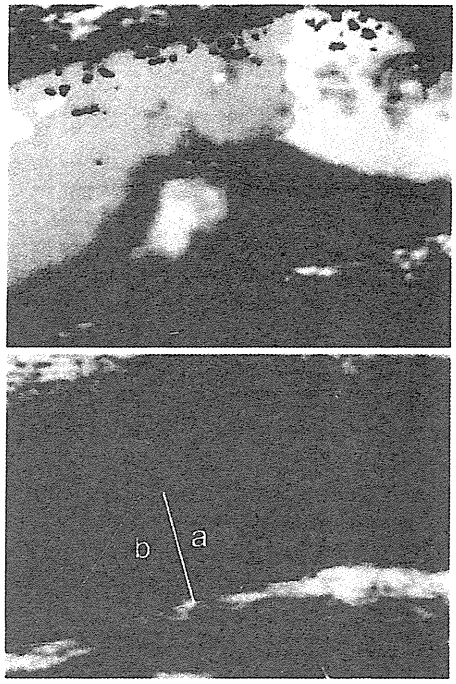

Figure 1. *Example of an ulcerated carotid plaque. Ulcers diagnosed as large obvious craters and reversed or stagnated blood flow within craters on color-Doppler imaging images (upper). The thickness of plaques with ulcers (a) and depth of ulcers (b) were measured at the maximum point (lower). The echogenicity of ulcerated carotid plaques was evaluated by outlining plaques (yellow line) and analyzing gray-scale content.*

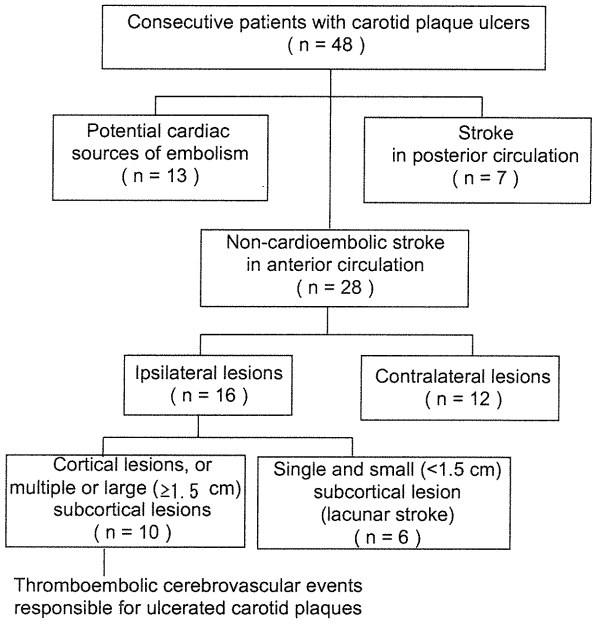

Figure 2. *Criteria for a diagnosis of TE.*

Criteria for TE

To identify patients with thromboembolic cerebrovascular events, we excluded patients with ischemic stroke in the posterior circulation confirmed by DWI and those with potential cardiac sources of embolism according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification from the patients with ulcerated carotid plaques,[22] because a causative relationship between ulcerated carotid plaques and stroke in the posterior circulation or cardioembolic stroke was unlikely. We also excluded patients with DWI-positive lesions contralateral to the ulcerated carotid plaques for the same reason. Finally, we excluded patients with single small (<1.5 cm) DWI-positive subcortical lesions (equivalent to lacunar stroke) because of the low likelihood of an embolus at an ulcerated carotid plaque entering a perforating branch artery from the middle cerebral artery without affecting leptomeningeal arteries.[23,24] We diagnosed a thromboembolic cerebrovascular event in the remaining patients with a cortical lesion or multiple or large (≥1.5 cm) subcortical lesions (Fig 2).

Statistical Methods

Differences in background factors between patients with and without a thromboembolic event were statistically compared using the Student independent *t*-test for age and the χ^2 test for sex and traditional cardiovascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia, and cigarette smoking. Differences in the ultrasonographic characteristics of ulcerated lesions were also compared using the Student independent *t*-test for the maximum IMT, ulcer depth, and ulcerated plaque thickness and the χ^2 test for >50% stenosis of ulcerated plaque and echolucent ulcerated plaque. An association between those plaque features and thromboembolic events was further analyzed using a logistic regression model to determine independent variables as ultrasonographic characteristics of ulcerated lesions. Statistical significance was taken at a level of 5% using SPSS 17.0 (SPSS Japan, Tokyo, Japan).

Results

Forty-eight of the 1111 consecutive patients with acute stroke or TIA (4.3%) had ulcerated carotid plaques detected by high-resolution duplex carotid ultrasonography. Among these 48 patients, 13 (27%) had potential cardiac sources of embolism, and 7 (15%) had sustained posterior circulatory stroke. Of the remaining 28 patients with non-cardioembolic stroke in the anterior circulation, 12 (25%) had sustained stroke contralateral to ulcerated carotid plaques and 6 (13%) had small (<1.5 cm) individual subcortical lesions.

Cerebrovascular events were considered causatively related to ulcerated carotid plaques by thromboembolic mechanisms in 10 of the 48 patients (21%) with stroke and ulcerated carotid plaques (Fig 2). Figure 3 shows the DWI images from these 10 patients. Seven of these 10 patients developed symptomatic stroke and 3

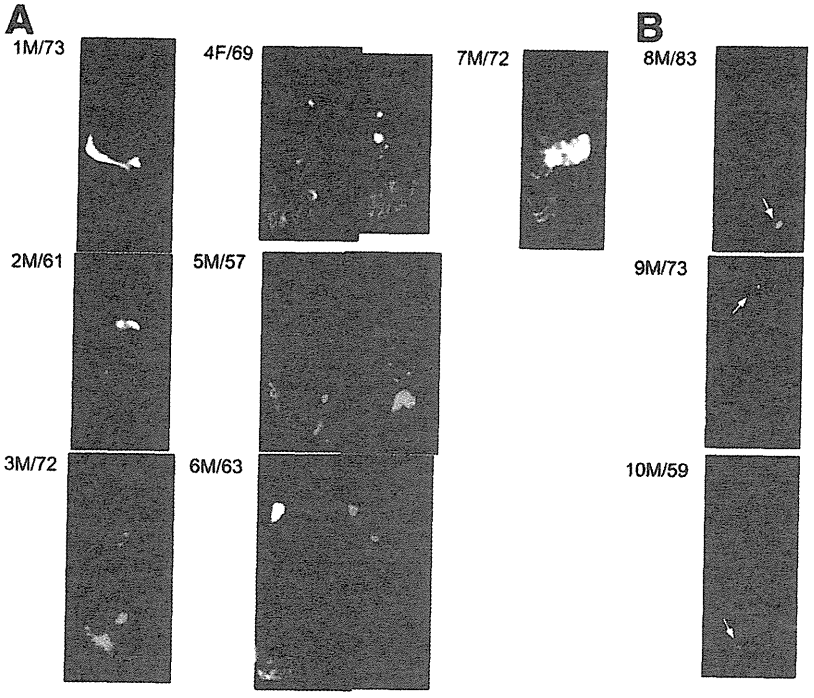

Figure 3. *Diffusion-weighted magnetic resonance imaging in 10 patients with acute ischemic stroke (A) or TIA (B) generated by thromboembolic mechanisms from carotid plaque ulcerations. Numbers indicate patients. Arrows in the TIA images in (B) indicate punctuate high-signal lesions.*

developed TIA, including 1 patient with amaurosis fugax. The patients with DWI-positive lesions were divided into 2 groups based on size and location. All patients in the group with relatively large (≥1.5 cm) single or multiple cortical and/or subcortical lesions (Fig 3A) developed symptomatic stroke, whereas all patients in the other group with punctuated lesions at the cerebral cortex (Fig 3B) developed TIA.

Background characteristics of patients with ulcerated carotid plaques and ultrasonographic ulcer characteristics are presented in Table 1. Univariate analysis found a significantly younger mean age in the patients with a thromboembolic event compared with those without a thromboembolic event (68 ± 8 years vs 77 ± 9 years; $P = .005$). Although all cardiovascular risk factors were more frequent and the proportion of smoking was significantly higher in the patients with a thromboembolic event (90% vs 53%; $P = .03$) events, maximum IMT as an indicator of individual atherosclerotic degree did not differ between the 2 groups. On the other hands, the proportion of echolucent ulcerated carotid plaques was significantly higher among patients with than without thromboembolic events (70% vs. 24%; $P = .006$). Other features of ulcerated carotid plaques did not differ significantly between the 2 groups. We also compared the ultrasonographic features of ulcerated plaques using a logistic regression model and found a significant association between thromboembolic cerebrovascular events and echolucent ulcerated plaques (odds ratio, 9.34; 95% CI, 1.65-53.0), with no significant difference in other variables (Table 2).

Discussion

In the present study, 48 of 1111 patients with stroke or TIA (4.3%) had ulcerated carotid plaques detected by high-resolution duplex carotid ultrasonography. A previous Japanese ultrasonographic study reported the presence of ulcerated carotid plaques in 21 of 214 patients (10%) with at least one risk factor for stroke and atherosclerosis or a history of stroke.[1] Another Japanese study using ultrasonography showed that 52 of 1076 patients (4.8%) had ulcerated carotid plaques at the time of carotid ultrasound assessment of secondary stroke prevention or perioperative risk evaluation.[25] Two major studies outside Japan have described the frequency of ulcerated carotid plaques based on angiographic data. The European Carotid Surgery Trialists (ECST) study identified carotid plaque ulcerations in 14% of 3007 symptomatic carotid arteries in patients with TIA or minor stroke,[26] and the NASCET study found ulceration in 35% of symptomatic carotid arteries with >70% stenosis.[2] Extracranial carotid artery disease is more prevalent in Western populations than in Asian populations,[27] and thus the frequency of thromboembolic cerebrovascular events might be more prevalent in Western populations.

According to our criteria for thromboembolic cerebrovascular events, the proportion of patients with ischemic lesions attributable to carotid ulcers was unexpectedly low (~20%) among patients with ulcers and ischemic stroke or TIA. Although the presence of ulcerated carotid plaques is an established risk factor for ischemic stroke,[1-3] our findings imply that ulcers are not frequently

Table 1. *Background characteristics in patients with carotid plaque ulcers and ultrasonographic ulcer findings*

	TE	NonTE	*P*
Number of patients	10	38	
Age, years, mean ± SD	68 ± 8	77 ± 9	.005
Male sex, n (%)	9 (90)	25 (66)	NS
Medical history, n (%)			
Hypertension	7 (70)	25 (66)	NS
Diabetes mellitus	4 (40)	11 (29)	NS
Hyperlipidemia	5 (50)	9 (24)	NS
Smoking habit	9 (90)	20 (53)	.03
Previous antiplatelet therapy	3 (30)	15 (39)	NS
Carotid ultrasonography findings			
Maximum IMT, mm, mean ± SD	4.3 ± 1.0	4.5 ± 1.2	NS
Depth of ulcer, mm, mean ± SD	2.5 ± 0.9	2.7 ± 0.8	NS
Thickness of ulcerated plaque, mm, mean ± SD	3.9 ± 1.5	3.9 ± 1.1	NS
>50% stenosis at ulcerated plaque, n (%)	4 (40)	7 (18)	NS
Echolucent ulcerated plaque, n (%)	7 (70)	9 (24)	.006

Abbreviation: NS, not significant.

associated with the development of cerebrovascular events. Based on previous reports indicating a relationship between carotid plaque ulcerations and MES,[9-11] we assume that carotid plaque ulcerations are traces of plaque fragmentation or sources of emboli formed by clots generated inside the cavity. The question then arises as to the end of the emboli. Stork et al[17] postulated that smaller platelet aggregates and smaller emboli (ie, fibrin clots and subendothelial matrix) comprise small (20-100 μm), asymptomatic microemboli that are macroscopically invisible but detectable by TCD. Indeed, carotid plaque ulcerations represent vulnerable or high-risk plaques, but the majority of emboli generated at the point of ulcerations might be too small to cause symptomatic events.

Table 2. *Odds ratios of ulcer findings for thromboembolic cerebrovascular events*

	OR (95% CI)	*P*
Maximum IMT	0.83 (0.36-1.95)	.67
Depth of ulcer	0.88 (0.16-4.75)	.88
Thickness of ulcerated plaque	0.63 (0.20-1.96)	.42
>50% stenosis at ulcerated plaque	4.01 (0.51-31.3)	.19
Echolucent ulcerated plaque	9.34 (1.65-53.0)	.01

In the present study, we performed MRI, including DWI, in all patients during the acute phase of stroke or TIA to define recent ischemic lesions and investigate a causative relationship between ischemic brain lesions and carotid ulcerations. To the best of our knowledge, the features of systematic MRI findings in patients with thromboembolic cerebrovascular events arising from carotid plaque ulcerations have not been well described. Seven of 10 patients with thromboembolic events in the present study had multiple DWI-positive cortical and/or subcortical lesions (Fig 3A) that were obvious as MRI findings of TE. In addition, the finding of punctuate cortical lesions on DWI in patients with thromboembolic TIA (Fig 3B) is intriguing. The frequency of DWI-positive findings in patients with TIA has ranged from 16% to 67% in 19 previous DWI studies.[28] Those studies investigated clinical predictors for early stroke (DWI-positive lesions) after TIA and described the duration of symptoms, motor symptoms, atrial fibrillation, or high-grade carotid stenosis as the positive predictors for DWI-positive lesions.[28] However, none of those studies included carotid plaque ulceration as a positive predictor for DWI-positive lesions. Our results indicate that punctuate cortical lesions on DWI in patients with TIA and ulcerated carotid plaques should be carefully considered because they might be overlooked by other MRI sequences.

The prevalence of carotid plaque ulcerations causing thromboembolic events was not high in the present study. However, echolucent ulcerated carotid plaques were closely associated with thromboembolic cerebrovascular events. This finding indicates that ulcerations on fragile or vulnerable plaques constitute a higher risk of symptomatic stroke. Echolucent carotid plaques are an established significant risk factor;[29,30] that is, carotid plaques with an ultrasonographic echolucent appearance correlate with lesions containing intraplaque hemorrhage or rich in lipids, which present a greater risk for ischemic stroke than hyperechogenic lesions consisting primarily of fibrous tissue.[31] Other investigators also have shown a higher prevalence of echolucent carotid plaques in patients with MES detected by TCD.[32] Thus, ulcerations on echolucent plaques are more likely to be genuine traces of plaque rupture or fragmentation to generate large emboli comprising cholesterol crystals or clotted blood that progress to symptomatic events.

In present study, neither the thickness nor the frequency of ulcerated plaques with >50% stenosis was associated with thromboembolic events, although the risk of stroke is greater with moderate- or high-grade carotid stenosis than with low-grade carotid stenosis.[18] Little is understood about the risk for symptomatic stroke among patients with carotid plaque ulcerations on low-grade carotid stenosis. Our findings suggest that the echogenicity of plaques at the point of ulceration is more relevant to the risk of stroke than the grade of stenosis or thickness of plaque in patients with ulcerated carotid plaques. Our

results are consistent with a case report by Kobayashi et al,[33] who described 2 patients with ischemic stroke events that were refractory to medical treatment. These patients had echolucent ulcerated plaques with mild carotid stenosis (<50%), and ischemic stroke did not recur after CEA. Although the value of surgical intervention for low-grade carotid stenosis remains uncertain, surgery should at least be considered for patients with echolucent ulcerated plaques even when the stenosis in such plaques is of low grade.

This study has several possible limitations. We did not perform transesophageal echocardiography in all patients to detect thrombus or plaques in the ascending aorta and aortic arch. TE originating from the aorta is also an important mechanism of stroke,[34] and TE from the aorta could not be excluded. Moreover, we might not have precisely differentiated TE from cardioembolism. Because we classified patients with potential cardiac sources of embolism primarily as having a cardioembolism, this study included patients with both cardiac sources of embolism and carotid plaque ulcerations among those with cardioembolic stroke. However, differentiating carotid embolism from aortic embolism or cardioembolism still might have been difficult even if transesophageal echocardiography had detected atherosclerotic plaques at the aorta or intracardiac thrombus. Furthermore, we excluded patients with single and small (<1.5 cm) DWI-positive subcortical lesions from thromboembolic cerebrovascular events. Although small emboli can indeed enter perforating arteries and cause lacunar stroke,[24,35] the possibility of emboli entering perforating arteries is considered low. In an animal model, only 1.4%-6% of microspheres (mean diameter, 31-92 μm) injected via an internal carotid artery entered small penetrating vessels.[24] Therefore, we excluded patients with single and small subcortical lesions from the group with thromboembolic cerebrovascular events to ameliorate the specificity of thromboembolic events.

In conclusion, we have demonstrated that the proportion of thromboembolic cerebrovascular events is not as high as expected in patients with carotid plaque ulcers, whereas echolucent ulcerated carotid plaques are closely associated with such events irrespective of carotid stenosis. Therefore, CEA or carotid artery stenting should be considered for patients with echolucent ulcerated carotid plaques who are refractory to antithrombotic therapy regardless of the degree of carotid stenosis present. A large multicenter study is needed to identify treatment strategies for patients with ulcerated carotid plaques and low-grade stenosis.

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