

Ischemic Stroke in Cancer Patients With and Without Conventional Mechanisms A Multicenter Study in Korea

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Background and Methods—To assess the precise mechanisms of stroke in cancer patients, we analyzed the data for cancer patients with acute ischemic stroke registered from 6 centers in South Korea. Clinical features, risk factors, diffusion-weighted imaging lesion patterns, and laboratory findings including D-dimer levels were compared between patients with conventional stroke mechanisms (CSMs) and cryptogenic group.

Results—A total of 161 patients were included in this study: 97 (60.2%) patients in the CSM group and 64 (39.8%) in the cryptogenic group. Patients in the CSM group were older and vascular risk factors were more prevalent than in the cryptogenic group. Diffusion-weighted imaging patterns of multiple lesions involving multiple arterial territories were observed more frequently in the cryptogenic group than in the CSM group. In addition, levels of the D-dimer were higher in the cryptogenic group than in the CSM group (11.5 ± 14.6 versus 3.6 ± 10.3 $\mu\text{g/dL}$). In multivariate analysis, the diffusion-weighted imaging lesion pattern of multiple vascular territories (odds ratio, 11.2; 95% CI, 3.74 to 33.3), and D-dimer levels of >1.11 $\mu\text{g/dL}$ (odds ratio, 10.6; 95% CI, 3.29 to 33.8) were associated independently with the cryptogenic group.

Conclusions—Stroke outside of CSM occurred in a large number in cancer patients. In stroke patients with cancer, D-dimer levels and diffusion-weighted imaging lesion patterns may be helpful in early identification of non-CSMs (especially coagulopathy associated with cancer) and possibly in guiding preventive strategies for stroke. (*Stroke*. 2010;41:798-801.)

Key Words: ischemic stroke ■ hypercoagulopathy ■ magnetic resonance imaging ■ cancer

Both systemic cancer and ischemic stroke are common in old age. In addition, cerebrovascular disease occurs commonly in cancer patients, with 15% of cancer patients experiencing thromboembolic events during their clinical course.¹ Systemic cancer is related to ischemic stroke via various mechanisms;²⁻⁴ however, the characteristics of stroke in cancer patients have been largely unknown. Previous studies reported that the stroke patterns and vascular risk factors in cancer patients were not significantly different compared with the general population.⁵⁻⁷ Autopsy studies demonstrated that the most common cause of ischemic stroke (78% asymptomatic) in patients with cancer was atherosclerosis.¹ On the contrary, others reported that embolisms, not including those of cardiac origin, were the most common cause of ischemic stroke in cancer patients.⁸

Early identification of stroke mechanisms may be important in cancer patients. Although patients with systemic

cancer usually show poor outcomes, survival of cancer patients is increasing with the development of cancer medicine. Stroke mechanisms in cancer patients may differ from those in stroke patients without cancer. Thus, treatment and preventive strategies in these 2 groups may differ.

In the present study, we aimed to assess the prevalence and characteristics of stroke involving mechanisms possibly related to cancer. Using data from a multicenter registration of cancer patients with cerebrovascular events, we studied the clinical, laboratory, and neuroimaging features and then compared these findings in patients with and without conventional stroke mechanisms (CSMs).

Methods

Between January 2006 and August 2008, we prospectively studied consecutive patients registered from 6 centers in South Korea with active cancer who experienced acute ischemic stroke. Patient selection is shown in Figure 1. Active cancer was defined as a diagnosis

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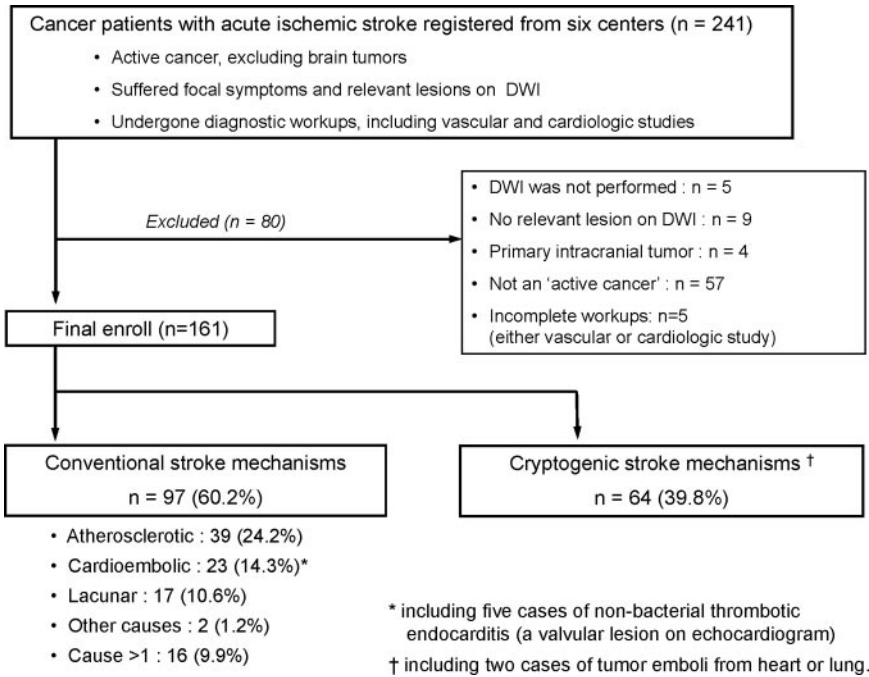


Figure 1. Patient selection.

of cancer, within 6 months before enrollment, any treatment for cancer within the previous 6 months, or recurrent or metastatic cancer, as described previously.⁹ The local institutional review boards approved the study, and all patients provided informed consent with regard to participation in the study.

Age, gender, and stroke risk factors were collected for all patients. Data relating to cancer, including type and extent of cancer and time interval from diagnosis of cancer to stroke, were also recorded. All patients underwent MRI, vascular study, routine blood tests and coagulation studies, electrocardiography, and echocardiography. D-dimer levels were performed within 24 hours of symptoms onset in most patients (up to 48 hours). Stroke mechanisms were assigned using the Trial of Org 10172 in Acute Stroke Treatment classification, and patients were classified as either CSM group or cryptogenic group. We compared the inpatient ischemic stroke population observed at the Stroke Center at Samsung Medical Center using the same time interval (n=1036) with respect to the stroke subtype.

We analyzed diffusion-weighted imaging (DWI) data in all patients. DWI patterns were classified as single/multiple lesions involving one arterial territory and multiple lesions involving multiple arterial territories.

Results

Of the 241 cancer patients with stroke, 161 patients were eventually identified (Figure 1). Among the 161 patients (57 female; mean age 67.2 years [range 56 to 78 years]), 97 (60.2%) patients were assigned to the CSM group, and 64 (39.8%) were assigned to the cryptogenic group. On the contrary, 6796 stroke patients without cancer were identified from 6 centers during the study period; 1154 (18.0%) were cryptogenic stroke.

Patient characteristics with respect to stroke mechanism are shown in the Table. The risk factors for stroke were more prevalent in the CSM group than in the cryptogenic group. Patients with stroke had different primary cancers that were not different between the groups; lung cancer was the most common form (29.2%), followed by gastric and colorectal cancer (Figure 2A). The presence of metastasis at the time of

stroke was more prevalent in the cryptogenic group than in the CSM group ($P<0.001$).

We then compared the mechanism of stroke between the CSM group and stroke patients without cancer. The stroke mechanisms in the CSM group were not different from those of stroke patients without cancer (Figure 2B).

DWI patterns of multiple lesions involving multiple arterial territories were more frequently observed in the cryptogenic group, whereas single/multiple lesions involving one arterial territory were observed more frequently in the CSM group ($P<0.001$). The levels of D-dimer were higher in the cryptogenic group than in the CSM group ($P=0.001$). D-dimer levels of $>1.11 \mu\text{g/mL}$ forecasted the cryptogenic group, with sensitivity of 78.8% (95% CI, 66.1 to 88.6%) and specificity of 71.8% (95% CI, 59.4 to 81.2%).

Multiple logistic regression revealed that after adjusting for risk factors for stroke and cancer characteristics, DWI pattern of multiple vascular territories and D-dimer levels of $>1.11 \mu\text{g/mL}$ were associated independently with the cryptogenic group (Table).

Discussion

This was the largest clinical data study involving stroke patients with cancer. In our study, CSMs were absent in $\approx 40\%$ of the stroke patients with cancer, a higher frequency of cryptogenic mechanism than in stroke patients without cancer (18%). Interestingly, among the patients exhibiting CSMs, tumor-specific mechanisms were unlikely to play a role in the development of stroke given that the distribution of a stroke subtype in cancer patients in the CSM group was similar to stroke patients without cancer.

A hypercoagulable state is a common condition in cancer patients. In the present study, we hypothesized that laboratory findings suggesting coagulopathy may predict possible tumor-specific stroke mechanisms. We used D-dimer levels to

Table. Patient Characteristics and Odds Ratios for Cryptogenic Group

	CSM Group (n=97)	Cryptogenic Group (n=64)	Estimated Odds Ratio for Cryptogenic Group		
			Crude	Adjusted (95% CI)	P
Risk factor profiles					
Age	70.0±10.3	63.0±10.6‡	0.967	...	
Male gender	58 (59.8%)	46 (71.9%)	4.760*	...	
Hypertension	59 (60.8%)	20 (31.3%)‡	0.641	...	
Diabetes	26 (26.8%)	8 (12.5%)*	0.430	...	
Smoking	28 (28.9%)	22 (34.4%)	
Alcohol	17 (20.7%)	14 (24.6%)	
Dyslipidemia	14 (14.6%)	8 (12.5%)	
Atrial fibrillation	20 (20.6%)	0 (0%)‡	N/A	...	
Ischemic heart disease	9 (12.3%)	6 (12.0%)	
Distant metastasis	21 (24.4%)	32 (54.2%)‡	1.912	...	
DWI patterns					
Single vascular territory	77 (79.4%)	19 (29.7%)	Reference	Reference	
Multiple vascular territories	20 (20.6%)	45 (70.3%)‡	10.73‡	11.16 (3.74–33.28)	<0.001
Laboratory findings					
D-dimer levels, µg/mL	3.6±10.3	11.5±14.6†			
D-dimer levels of >1.11 µg/mL	29 (39.7%)	45 (81.8%)‡	11.79‡	10.55 (3.29–33.84)	<0.001

* $P<0.05$; † $P<0.01$; ‡ $P<0.001$.

measure the coagulation status. D-dimer level is a direct measure of activated coagulation and was used in many previous studies as a measure of hypercoagulability.³ In the present study, most patients without conventional risk factors had elevated D-dimer levels, which were an independent predictor for stroke involving non-CSMs. Our data suggest that coagulopathy could be a major pathophysiologic mechanism of stroke related to tumors. However, treatment of

cancer, cancer itself, and stroke itself can cause elevated D-dimer levels,¹⁰ and it could be difficult to attribute a stroke definitively to hypercoagulability based on D-dimer only.⁸ Substances in tumor cells such as cysteine proteases and tissue factor have procoagulant, or thromboplastin-like, activity.⁴ Additional studies regarding the precise molecular mechanisms of cancer-related coagulopathy and longitudinal follow-up data with anticoagulant use are needed.

MRI findings in cancer patients with stroke were seldom reported. Recent studies demonstrated that concealed cancer should be considered in patients who exhibit multiple infarcts on DWI.¹¹ In the present study, patients with CSMs frequently exhibited single arterial territorial involvement patterns, whereas patients without CSMs showed multiple lesions within multiple arterial territories, suggesting embolic stroke.

It is important to differentiate stroke mechanisms (conventional versus cancer related) in cancer patients because preventive strategies targeting coagulopathy should be tailored to the stroke mechanism in each patient. Our clinical, laboratory, and DWI data suggest that stroke patients with unconventional mechanisms could be regarded as “cancer-related” stroke patients. On the contrary, stroke patients with conventional mechanisms were unlikely to have cancer-related mechanisms because the mechanisms of stroke in those patients were not different from stroke patients without cancer. Thus, these patients should be treated according to the stroke subtypes, such as atherosclerotic, lacunar, etc. Our present data suggest that data regarding D-dimer levels and DWI lesion patterns may guide early management with anticoagulation in stroke patients with cancer who are suspected to have coagulation abnormalities.

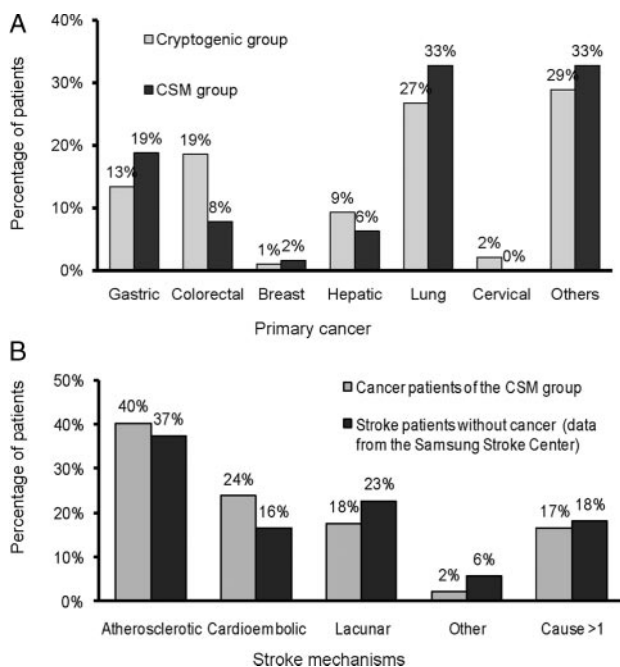


Figure 2. Cancer types in cryptogenic vs CSM group (A) and stroke subtype in patients with vs patients without cancer (B).

The extent of cancer, certain primary cancers, and the time interval between the diagnosis of cancer and the onset of stroke might be associated more frequently with cancer-related mechanism. The cancer stage and time interval between cancer and stroke diagnosis could not be directly compared because of diverse types of primary cancer, and distant metastasis did not show independent association with cancer-related stroke because of a small number of patients. Additional studies with more patients are needed.

The strength of our study lies in the consecutive recruitment of a relatively large, well-phenotyped group of patients, a multicenter enrollment, and a comparison of stroke patients without cancer. However, these are data from Korean patients with cancer, and additional studies in different study populations are warranted.

In conclusion, stroke without conventional mechanisms occurred in a large number of cancer patients. Our results suggest the importance of differentiation of stroke mechanisms in cancer patients with stroke. Laboratory findings and DWI lesion patterns were helpful in the early identification of non-CSMs (ie, hypercoagulopathy) in cancer patients.

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Disclosures

None.

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