RESEARCH ARTICLE

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Risk Factors, Biomarkers, Etiology, Outcome and Prognosis of Ischemic Stroke in Cancer Patients

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Abstract

Introduction: Cerebrovascular disease is the second most common complication in individuals with tumours. The aim of this study was to investigate risk factors, biomarkers, etiology and prognosis of ischemic stroke in cancer patients (ISCPs). **Methods:** The medical records of 619 consecutive patients who were admitted with acute ischemic stroke from January 2012 to November 2014 were retrospectively evaluated. The patients were divided into two groups (group 1, patients with an active cancer prior to the onset of ischemic stroke; group 2, patients without an active cancer history). The demographic data, risk factors, NIHSS scores, thrombocyte count, D-dimer, fibrinogen and C reactive protein (CRP) level at admission, modified Rankin Scale (mRS) scores in the follow-up period and location of lesions on DWI were recorded. The Mann-Whitney U test, chi-squared test and logistic regression was used for analyzing data, $p<0.05$ being considered statistically significant. **Results:** A total of 46 (7.4%) ISCPs were included. Hyperlipidemia was significantly lower in the ISCP group ($p=0.001$). Elevated thrombocyte counts, D-dimer, fibrinogen and CRP levels at admission, acute multiple ischemic lesions, other causes, mortality in hospital and worse outcome were significantly related to ISCP ($p<0.05$). On logistic regression analysis, follow up mRS>3, acute multiple ischemic lesions located in more than one vascular territory (AMIMCT) and other causes were significantly associated with ISCP ($p<0.001$). **Conclusion:** In our study, other causes, AMIMCT and mRS>3 were more common in the ISCP group. We consider that CCS could be more suitable for detecting other causes than TOAST. Biomarkers could be important in the ISCP group.

Keywords: Ischemic stroke- cancer- biomarkers

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Introduction

Cancer and stroke are common in elderly and they are most common causes of death in developed countries. However, cerebrovascular disease is the second most common central nervous system complication in cancer patients (Graus et al., 1985). The causes of ischemic stroke in patients with and without cancer may be different. The pathogenesis of stroke in cancer patients could be related to cancer-mediated hypercoagulability or complications of oncological treatments (Blom et al., 2005; Caineet al., 2002; Cestariet al., 2004; Dammaccoet al., 2013; Goet al., 2013;Khorana and Fine, 2004; Kim et al., 2010; Navi et al., 2014; Parpiaet al., 2011; Rogers, 2010).

D-dimer, fibrinogen, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are significantly increased in patients with ischemic stroke (Alvarez-Perez et al., 2011; Kim et al., 2013; Kim et al., 2014; Montaneret al., 2008; Seoket al., 2010). Some of previous studies reported that these biomarkers had statistically significant higher in cancer patients with ischemic stroke compared to non-cancer patients with ischemic stroke (Bang et al., 2011; Kono et al., 2012; Seoket al., 2010; Schwarzbachet al., 2012). Otherwise, some of previous studies found that there was no statistically significant difference in these biomarkers between cancer and non-cancer patients with ischemic stroke (Kim et al., 2013).

The aim of this study was to investigate risk factors, biomarkers, etiology and prognosis of ischemic stroke in cancer patients (ISCP) compared to non-cancer patients with ischemic stroke.

Materials and Methods

The medical records of 619 consecutive patients who were admitted with acute ischemic stroke from January 2012 to November 2014 were retrospectively evaluated. Approval was obtained from the research ethic committee in advance of the study. The patients were divided into two groups; group 1 (ISCP) included patients with active cancer prior to the onset of ischemic stroke at any time

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before stroke onset and group 2 (non-ISCP) included patients without active cancer history.

Patient demographics and medical risk factors, including history of hypertension, diabetes, hyperlipidemia, atrial fibrillation, congestive heart failure, coronary artery disease, previous transient ischemic attack, previous stroke, the National Institutes of Health Stroke Scale (NIHSS) scores at admission, thrombocyte count, D-dimer, fibrinogen and C reactive protein (CRP) level were collected using a standard data collection form and entered into an institutional database. All patients had diffusion-weighted imaging (DWI).Hypertension was defined as blood pressure >=140/90 mmHg on repeated measurements or prior use of antihypertensive medication, diabetes mellitus as fasting blood glucose level >=126 mg/dl on repeated measurements or the use of medications to lower blood glucose, atrial fibrillation by previous history or if detected on ECG or Holter. Coronary artery disease included any history of angina, myocardial infarction or coronary revascularization.

Acute multiple ischemic lesions located in more than one vascular territories (AMIMCT) was defined as multiple acute infarcts either in bilateral anterior circulations, or in anterior and posterior circulations, simultaneously. The patients with AMIMCT were selected based on diffusion-weighted imaging (DWI).

A single rater (MHS) determined etiologic stroke subtypes using the automated Causative Classification System (CCS, available at https://ccs.mgh.harvard.edu) (Ay at al., 2005). The CCS subtypes included supra aortic large artery atherosclerosis, cardio-aortic embolism, small artery occlusion, other causes and undetermined causes. Etiologic work-up included vascular imaging studies, such as carotid Doppler ultrasonography, computerized tomography angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA), transthoracic or transesophageal echocardiography, 24-hour cardiac rhythm monitoring, and laboratory tests for hypercoagulability and vasculitis. The modified Rankin Scale (mRS) scores were recorded according to follow-up visits of the patients.

Statistical Anaylsis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 11.5 version (SPSS Inc. Chicago, Illinois, USA). Descriptive statistics were expressed as means±standard deviations and median (minimum-maximum) for quantitative variables and the number (percent) for qualitative variables. The Mann-Whitney U test was used to compare differences between two independent groups when the dependent variable was a numerical, but not normally distributed. The group rates were compared using a chi-squared test. Logistic regression was used for analyzing of independent variables that determine to the risk factors for a dependent qualitative variable with two categories, was a statistically significant risk factor for this variable. $p<0.05$ was considered to be statistically significant.

A sample size of 554 achieves 99.9% power to detect an effect size (W) of 0,2370 using a 1 degree of freedom Chi-Square Test with a significance level (alpha) of 0,05.

Results

A total of 46 (7.4%) patients with ISCP (29 males [63.0%] and 17 females [37.0%]; mean age 70.70±11.04[44-96] years) and 573 patients with non-ISCP (300 males [52.4%] and 273 females [47.6 %]; mean age 69.30±13.52 [23-103] years) were included in the study Table 1.

The types of primary cancer in patients with ischemic cancer are as follows: bladder cancer in 9 (19.6%) patients, gastric cancer in 6 (13.1%) patients, lung cancer in 6 (13.1%) patients, chronic myeloid leukemia in 6 (13.1%) patients, breast cancer in 3 (6.5%) patients, non-Hodgkin lymphoma in 3 (6.5%) patients, colon cancer in 2 (4.3%) patients, multiple myeloma in 2 (4.3%), overian cancer in 2 (4.3%) patients, pancreatic cancer in 2 (4.3%) patients, esophageal cancer in 1 (2.2%) patient, nasal cavity cancer in 1 (2.2%) patient, tongue cancer in 1 (2.2%) patient, larynx cancer in 1 (2.2%) patients and hepatobiliary cancer in 1 (2.2%) patient. Metas¬tasis was present in 8 (17.4%) patients Table 2.

No between-group differences in history of hypertension, diabetes mellitus (DM) atrial fibrillation, atrial fibrillation, congestive heart failure, coronary artery disease, previous transient ischemic attack or previous stroke were observed ($p>0.05$). Hyperlipidemia was significantly lower in the ISCP group compared to others ($p=0.001$) Table 1.

The mean NIHSS score was 7.48± 4.40 (0-15) at admission in group 1 and 5.95±4.50 (0-26) at admission in group 2 ($p=0.824$). The mean admission thrombocyte count, D-dimerand C reactive protein (CRP) level at admission were significantly higher in ISCP group compared to other group ($p<0.05$) Table 1.

The patients with AMIMCT were 16 (34.8%) in ISCP group and 62 (10.8%) in non-ISCP group. AMIMCT was significantly associated with ISCP ($p<0.001$).

The etiologic stroke subtypes in Group 1 were large-artery atherosclerosis (LAA) in 8 (17.4%) patients, cardio-aortic embolism in 14 (30.4%) patients, small artery occlusion in 3 (6.5%) patients, other causes in 12 (26.1%) patient (hyperviscosity syndrome n=12) and undetermined causes in 9 (19.6%) patients. The etiologic stroke subtypes in Group 2 were large-artery atherosclerosis (LAA) in 144 (25.1%) patients, cardio-aortic embolism in 242 (42.2%) patients, small artery occlusion in 29 (5.1%) patients, other causes in 23 (4.0%) patient and undetermined causes in 135 (23.6%) patients. Other causes were more common in Group 1 compared to Group 2 ($p<0.001$) Table 1.

Mortality in hospital was 21.7% (n=10) in group 1 and 9.9% (n=57) in group 2. It was significantlyassociated with ISCP group ($p=0.013$). The follow-up information was accessible for 21 patients in ISCP group and 287 patients in non-ISCP group. The mean follow-up time of the patients was 9 (1-32) months and the mean mRS was 4.27±2.07 (0-6) in group 1 and 2.38±2.31 (0-6) in group 2 at follow-up period. The outcome was significantly worse in ISCP group than non-ISCP group ($p=0.027$). Recurrent stroke occurred in 1 (2.2%) patients in group1 and 12 (2.1%) patients in group 2 ($p=0.97$) Table 1.

Table 1. Epidemiologic and Clinical Characteristics of Patients with ISC and Without ISC

Variables	ISCP n=46	Non-ISCP n=573	p value
Age, year, Mean±SD	70.70±11.04	69.30±13.52	0.776
Sex, n (%)			
Female	17 (37.0)	273 (47.6)	0.162
Male	29 (63.0)	300 (52.4)	
Medical history			
-Hypertension , n (%)	27 (58.7)	405 (70.7)	0.089
-Diabetes mellitus, n (%)	17 (37.0)	166 (29.0)	0.253
-Atrial fibrillation , n (%)	7 (15.2)	118 (20.6)	0.382
-Hyperlipidemia, n (%)	2 (4.3)	156 (27.2)	0.001
-CAD, n (%)	10 (21.7)	134 (23.4)	0.799
-CHF, n (%)	3 (6.5)	67 (11.7)	0.287
-Previous stroke history, n (%)	8 (17.4)	98 (17.1)	0.960
-Previous TIA history, n (%)	4 (8.7)	44 (7.7)	0.804
CCS classification, n (%)			
-Large-artery atherosclerosis	8 (17.4)	144 (25.1)	0.480
-Cardio-aortic embolism	14 (30.4)	242 (42.2)	0.200
-Small artery occlusion	3 (6.5)	29 (5.1)	0.260
-Other causes	10 (24.4)	20 (3.9)	<0.001
-Undetermined causes	9 (19.6)	135 (23.6)	0.950
Admission NIHSS, Median (Min-Max)	7.5 (0.0-15.0)	5.0 (0.0-26.0)	0.013
Recurrent stroke, n (%)	1 (2.2)	12 (2.1)	0.97
Mortality in hospital, n (%)	10 (21.7)	57 (9.9)	0.013
Follow up mRS, Median (Min-Max)	5.0(0.0-6.0)	1.0 (0.0-6.0)	<0.001
Follow up mRS> 3, n (%)	20 (76.9)	117 (34.0)	<0.001
Thrombocyte count/mm^3, Median (Min-Max)	218.0 (34.0-651.0)	229.5 (6.0-877.0)	0.529
CRP mg/dl, Median (Min-Max)	12.0 (0.0-248.0)	8.4 (0.0-303.0)	0.014
D-dimer, Median (Min-Max)	1,519.0 (362.0-12,487.0)	590.5 (42.0-3,191.0)	0.003
Multiple infarct, n (%)	16 (34.8)	62 (10.8)	<0.001

ISCP, ischemic stroke patients with cancer; SD, Standard Deviation; CAD, Coronary Artery Disease; CHF, congestive heart failure; TIA, transient ischemic attack; CCS, Causative Classification System; mRS, The modified Rankin Scale; NIHSS, the National Institutes of Health Stroke Scale; CRP, C reactive protein

Table 2. The Types of Primary Cancer in Patients with Ischemic Stroke

The types of primary cancer	ISCP n =46
bladder cancer, n (%)	9 (19.6%)
gastric cancer, n (%)	6 (13.1%)
lung cancer, n (%)	6 (13.1%)
chronic myeloid leukemia, n (%)	6 (13.1%)
breast cancer, n (%)	3 (6.5%)
non-Hodgkin lymphoma, n (%)	2 (2.8%)
colon cancer, n (%)	2 (4.3%)
multiple myeloma, n (%)	2 (4.3%)
overian cancer, n (%)	2 (4.3%)
pancreatic cancer, n (%)	2 (4.3%)
esophageal cancer, n (%)	1 (2.2%)
nasal cavity cancer, n (%)	1 (2.2%)
tongue cancer, n (%)	1 (2.2%)
larynx cancer, n (%)	1 (2.2%)
hepatobiliary cancer, n (%)	1 (2.2%)
Metastasis, n (%)	8 (17.4%)

ISCP, ischemic stroke in cancer patients

Logistic Regression analysis was performed for independent variables of risk factors with dependent cancer categorical variables, including gender, HT, DM, HL, other causes, AMIMCT, CRP and mRS > 3 and p values of these variables were found to be 0.165, 0.092, 0.256, 0.004, <0.001, <0.001, 0.012, <0.001, respectively. The model was constructed by using variables of other causes, AMIMCT and mRS > 3 which were both statistically significant and clinically meaningful and p values of these variables were found to be <0.001, <0.001 and <0.001, respectively. The model was cancer = 4.416 + 2.391 * Other causes + 1.828. AMIMCT + 1.851 * mRS > 3 Table 3.

Table 3. Logistic Regression Analysis of ISCP

	OR	95%, CI	p value
Other causes	10.920	3.201 - 37.249	<0.001
AMIMCT	6.219	2.265 – 17.074	<0.001
mRS > 3	6.367	2.290 – 17.709	<0.001

CCS,Causative Classification System; AMIMCT, acute multiple ischemic lesions located in more than one vascular territories; mRS, modified Rankin Scale

Discussion

Most reports have found no differences in common stroke risk factors between cancer and non-cancer patients with ischemic stroke (Cestari et al., 2004; Grisold et al., 2009; Stefanet al., 2009; Zhang et al., 2004). However, some of studies have found low incidences of hypertension and hyperlipidemia in cancer patients with ischemic stroke compared to those of the non-cancer group (Kono et al., 2012; Schwarzbach et al., 2012). Moreover, no significant differences in hyperlipidemia and atrial fibrillation incidences have been reported, but a tendency for lower incidence in cancer patients with ischemic stroke (Zhang et al., 2006). Kim et al., (2014) reported that the cancer group had a lower incidence of hypertension, atrial fibrillation, hyperlipidemia, and ischemic heart disease when they compared non-cancer and cancer patients with ischemic stroke. In our study, only hyperlipidemia was significantly lower in the ISCP group compared to others (p=0.001)

D-dimer is a marker for hypercoagulability and increased D-dimer level was associated with ischemic stroke (Wildeet al., 1989; Montaneret al., 2008).

In previous studies, D-dimer levels have statistically significant higher in cancer patients with ischemic stroke compared to non-cancer patients with ischemic stroke (Banget al., 2011; Kim et al., 2013; Konoet al., 2012; Seoket al., 2010; Schwarzbachet al., 2012). Some of them were hypothesized that coagulopathy and emboli in cancer patients may be the etiology for ischemic stroke (Bang et al., 2011; Kim et al., 2010; Stefanet al., 2009).

Increased fibrinogen is another biomarker related to ischemic stroke (Rothwell et al., 2004). Previous studies reported that increased fibrinogen levels were associated with cancer patients with ischemic stroke (Alvarez-Perez et al., 2011; Prugger et al., 2013). Otherwise, Kim et al., (2013) found that there was no statistically significant difference in fibrinogen levels between cancer and non-cancer patients with ischemic stroke.

C-reactive protein is associated with inflammation and atherosclerotic disease (Pasceriet al., 2000).

Increased CRP level is related to acute ischemic stroke (Alvarez-Perez et al., 2011; Montaneret al., 2008). Kim et al., (2014) reported no significant difference in CRP levels between cancer and non-cancer patients with ischemic stroke (Kim et al., 2013). On the other hand, Kim et al. found statistically significant higher CRP concentrations in cancer patients with ischemic stroke.

We found significantly higher levels of biomarkers such as CRP, fibrinogen, and D-dimer in the cancer with ischemic stroke group than the non-cancer ischemic stroke group. The high levels of biomarkers may be associated with the presence of both cancer and ischemic stroke.

Recent studies demonstrated that multiple infarcts within multiple arterial territories on DWI were related to cancer patients with ischemic stroke (Kim et al., 2010; Kwonet al., 2007). We found a significant difference between AMIMCT and cancer patients with ischemic stroke.

In previous studies, etiology of stroke subtypes has been classified according to the TOAST. Cestari et al., (2004) found that thrombotic strokes (54%) including cardio-aortic embolic strokes (15%) more common than non-thrombotic strokes (46%), including those due to undetermined causes (19%), atherosclerotic causes (10%), small-artery occlusion (12%), and other determined causes (5%) in cancer patients with ischemic stroke. Kim et al., (2014) found that etiology of stroke subtypes were large-artery atherosclerosis (41%), small artery occlusion (28.8%), cardio-aortic embolism (17.3%), undetermined etiology (8.3%), and other determined etiology (4.5%) in cancer patients with ischemic stroke. However, stroke subtypes were not statistically significant between cancer and non-cancer patients with ischemic stroke (Bang et al., 2011; Zhang et al., 2006; Zhang et al., 2007).

In our study, other causes were more common in ISCP group compared to others (p<0.001). We think that CCS could be more suitable for detecting other causes than TOAST for cancer patients with ischemic stroke.

Zhang et al., (2006) found that admission and follow up mRS was similar in cancer and non-cancer patients with ischemic stroke. Otherwise, they reported that died in hospital was significantly higher in stroke patients with cancer. In another study, there was no statistically significant difference in follow up mRS and mortality between cancer and non-cancer patients with ischemic stroke. We found that follow up mRS>3 was significantly higher in ISCP group compared to others.

There are several limitations of our study, including its retrospective design, and a relatively short follow up duration. In addition, this is a restriction of the cohort to a single medical center. However, all of our patients underwent a detailed work-up for determining causative mechanism of ischemic stroke. Acute ischemic lesions were identified with diffusion weighted imaging in all patients. In contrast to the previous studies, etiologic subtypes of ISCP have been determined systematically according to the CCS in our patients.

In conclusion, - D-dimer, fibrinogen and C-reactive protein (CRP) could be related to ISCP. Further studies with larger patient numbers are needed to clarify this issue. - Other causes were more common in ISCP group compared to others (p<0.001). We think that CCS could be more suitable for detecting other causes than TOAST for cancer patients with ischemic stroke. - AMIMCT was significantly associated with ISCP. - Follow up mRS>3 was significantly higher in ISCP group.

Conflict of interest

The authors do not have any conflict of interest.

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