ACUTE ISCHEMIC STROKE IN PATIENTS WITH CANCER: RISK FACTORS, CLINICAL AND IMAGING OUTCOMES

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ABSTRACT

Introduction*: Cancer patients have higher risk of stroke compared with the normal population. The relationship between this increased risk and traditional vascular risk factors is not known exactly. The aims of this study were to investigate ischemic strokes, who had a history of cancer or diagnosed cancer during etiologic scanning, in terms of the cancer type, likely causes of stroke and demographic data.*

Materials and methods*: In this retrospective study, the stroke patients with known cancer or diagnosed with cancer during follow-up were selected by screening the data of 1002 acute ischemic stroke patients who were followed-up in the hospital between 2012 and 2015 and demographic, clinical and imaging findings were recorded. Temporal association between cancer type, presence of metastasis, treatment administered, response to therapy, cancer and stroke, possible stroke etiology and stroke risk factors of the patients were investigated.*

Results*: An association was determined between acute ischemic stroke and cancer in 58 (5.8%) of our patients. Sixty-nine percent of our patients were males and the mean age was 66.5-year. Cancers most commonly found were lung (20.7%), colorectal (15.5%) and prostate cancer (13.8%). The most frequently found risk factors for ischemic stroke were hypertension and diabetes mellitus. Twelve point one percent of the patients did not have any traditional risk factors for ischemic stroke. Eight point six percent of the patients had ischemic stroke as a presenting symptom of cancer. Sixty-eight point nine percent of the patients had supratentorial infarcts and 10.3% of them infratentorial infarcts. Supratentorial infarcts were most commonly located in the middle cerebral region, and infratentorial infarcts were located in the brainstem.*

Conclusion*: Cancer patients with ischemic stroke showed different risk factors, stroke etiology and infarct localizations. Therefore, cancers need to be particularly studied in patients who do not have traditional risk factors for ischemic stroke.*

Keywords*: Ischemic stroke, cancer, traditional risk factor, imaging.*

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Introduction

Cancer and stroke are among the leading causes of morbidity and disability associated with diseases in developed countries. Approximately 7% of cancer patients have symptomatic stroke during the clinical course, and 15% have cerebrovascular lesions at autopsy[(1)]. The incidence of stroke is approximately 1.5 times higher in cancer patients than normal population[(2)].

Retrospective study showed that 6%-12% of acute ischemic stroke (AIS) patients have concomitant malignancies. These findings indicate a higher incidence of stroke in the cancer patients compared to the general population[(1-4)]. Cancer patients with stroke are presenting neurologic symptoms and signs included hemiparesis (74%), aphasia/ dysarthria (51%), visual field deficit (26%) ataxia (11%), headache (8%), seizure (8%)[(5)]. When cancer occurs in stroke patients, neurological outcomes worsen and

prognosis tends to be poor. The median survival was only 4.5 months and strongly correlated with initial neurologic disability[2, 3].

The prevelance of cancer was higher among stroke patients compared with the general population for all age groups, especially younger than 70 years[4]. The AIS ratio due to cancer is thought to be 1.5 times higher in male than female[5]. Many factors such as advancing age, cigarettes, obesity physical inactivity and hypercoagulability, which are risk factors both for stroke, and cancer might be reasons for this[6, 7]. However, traditional vascular risk factors are not determined in some of AIS patients[3, 8]. Possible mechanisms of AIS in these patients are direct pressure of tumor on the vessel or vascular invasion of tumor, tumor associated embolism, coagulation disorders and effect of administered drugs[1, 9].

In this study, frequency of cancer was investigated in AIS patients and demographic characteristics, stroke risk factors, stroke etiology, imaging findings, cancer type, cancer treatment administered and the period between cancer and stroke of these patients were examined.

Materials and methods

The patients with known cancer or diagnosed with cancer during follow-up were included in this retrospective study by screening the data of all patients who were followed-up with diagnosis of AIS in our clinic between January 2012 and April 2015. Acute infarct was defined to be hyperintensity on diffusion-weighted imaging (DWI) and hypointensity on Apparent Diffusion Coefficient (ADC) map. The patients with hemorrhagic stroke, the patients without acute infarct on DWI and the patients with watershed infarct were excluded from the study.

Demographic characteristics, laboratory and imaging findings were recorded from patient registries. Involved organ, presence of metastasis, administered cancer treatment (radiotherapy, chemotherapy), response to cancer treatment, period between cancer and stroke were evaluated in the patients with known cancer. In all patients, hypertension (HT) (blood pressure ≥ 140/90 mmHg), diabetes mellitus (DM) (blood glucose ≥ 126 mg/dL), hyperlipidemia (HL) (total cholesterol ≥ 220 mg/dL or very low-density lipoprotein-cholesterol ≥ 140mg/dL), atrial fibrillation (AF), coronary artery disease (CAD), and presence of previous stroke were recorded as risk factors for stroke (10). Laboratory results (complete blood count, liver and renal function tests, sedimentation, coagulation tests), electrocardiogram (ECG), transthoracic echocardiogram, duplex sonography of carotid and vertebral arteries findings, were recorded. The results of transesophageal echocardiography, holter ECG, magnetic resonance angiography, computerized tomography angiography, prothrombotic profile (protein C, protein S, antithrombin, lupus antibodies, anticardiolipin antibodies, D-dimer level etc.) were also recorded whenever performed.

The patients were assessed according to the criteria of Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification for presence of stroke etiology other than cancer and presence of large vessel atherosclerosis (LAA), cardioembolism (CE) and small vessel occlusion (SVO) were recorded (11). Size and localization of infarct on DWI was recorded for all patients. The infarcts were classified as supratentorial and infratentorial according to their localizations. Supratentorial infarcts were classified as middle cerebral artery (MCA), anterior cerebral artery (ACA) and posterior cerebral artery (PCA) infarcts. Infratentorial infarcts were classified as brainstem and cerebellar infarcts. The infarcts with a diameter of <15mm were classified as lacunar infarcts and those with a diameter of >15 mm were classified as non-lacunar infarcts.

The local ethic committee approved the study. Since it was a retrospective study, patient consent forms were not constituted.

Results

Fifty-eight (5.8%) patients determined to have association with cancer by screening the data of 1002 AIS patients were included in this study. Forty of these patients were males and 18 of them were females. The age of the male patients ranged between 38 and 90 years (mean age: 66.5±13.6) and the age of the female patients ranged between 53 and 90 (mean age: 73.2± 12.5). AIS associated with cancer was more commonly seen in the males (40/18). There was no difference between the female and male patients regarding age (p=0.079). Ten patients (17.2%) had a previous ischemic stroke. Four of these patients were taking an anti-aggregating agent and one of them was taking an oral anticoagulant drug. NIHSS score was determined to be average 6.36±4.38 during first presentations of the patients.

Most commonly determined cancers were lung (20.78%) and colorectal cancers (15.5%) (Figure 1). Other organs involved were prostate (8 patients), lar-

ynx (6 patients), stomach (4 patients), skin (3 patients), urinary bladder (2 patients), gynecological organs (2 patients), breast (1 patient), pancreas (1 patient), brain (1 patients), hepatobiliary system (1 patient) and nasopharynx (1 patient). Hematological malignancy was detected in 7 patients (lymphoma 4 patients, leukemia 3 patients). Sixteen patients (27.6%) had distant organ metastases. Underlying pathological diagnoses of the patients with lung cancer were as followings: small cell lung cancer (SCLC) in six patients, squamous cell carcinoma in one patient and adenocarcinoma in five patients.

Average platelet count of the patients was 273±136.27 k/μL (32-669 k/μL). Two patients had thrombocytosis. Fifteen patients had INR values higher than normal (>1.1). Other laboratory tests performed were within normal limits.

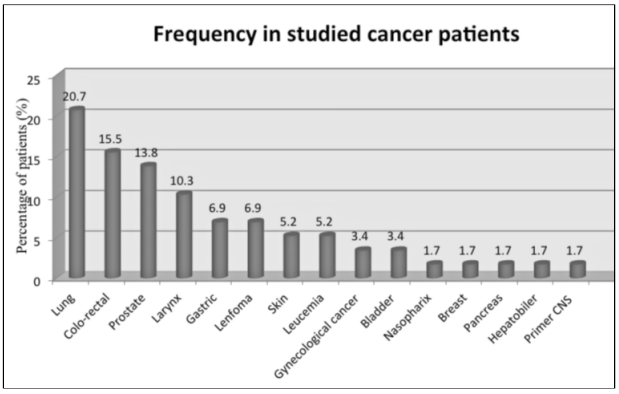

Figure 1: The frequency of different types of cancer in our stroke/cancer population studied.

Table 1 revealed the risk factors determined in the patients and the relationship between etiologies and imaging findings with cancer types. The most commonly determined risk factors for ischemic stroke were HT (37.5%) and DM (37.5%). Ten patients were determined to have HL, 6 patients CAD, 7 patients AF (5 patients had isolated AF and 2 patients had AF with left ventricular hypokinesia). No risk factor for traditional ischemic stroke was determined in 7 patients (12.1%). Organs involved and cancer types in these patients were colorectal adenocarcinoma (1 patient), SCLC (1 patient), non-Hodgkin's lymphoma (1 patient), hepatocellular carcinoma (1 patient), gastric adenocarcinoma (1 patient), prostate adenocarcinoma (1 patient) and pancreatic adenocarcinoma (1 patient). Two of these patients received chemotherapy in the last 3 months and radiotherapy was administered in one patient due to brain metastasis.

Radiotherapy was administered in 9 of our patients. The number of patients receiving chemotherapy was 22 (37.9%). Five of these patients had AIS in the first 6 months after receiving chemotherapy and two of these patients had no risk factor for stroke. Ten patients had AIS after cure was provided.

				TOAST			DWI		
Cancer	HT	DM	HL	LAA	CE	SVO	AC	PC	Multiple
Lung	4	3	3	1	2	1	9	1	2
Colo-rectal	2	5	4	-	-	2	5	2	2
Prostate	3	3	-	2	4	-	6	2	-
Larynx	3	1	-	2	-	1	6	2	-
Gastric	3	2	1	-	-	1	1	1	2
Lymphoma	1	2	-	-	-	-	3	1	-
Skin	1	2	1	-	2	-	2	-	1
Leucemia	2	-	-	-	1	1	1	1	1
Gynecological	2	1	-	1	-	-	1	-	1
Bladder	1	1	1	1	-	1	1	-	1
Other	5	3	1	-	1	-	2	1	2

Table 1: Risk factors, stroke etiology and infarct localization.
HT:Hypertension; DM:Diabetes mellitus; HL:Hyperlipidemia; TOAST:Trial of Org 10172 in Acute Stroke Treatment; LAA: Large Artery Atherosclerosis; CE:Cardioembolism; SVO: Small Vessel Occlusion; DWI:Diffusion Weighted Imaging AC:Anterior circulation PC: Posterior circulation)

According to the TOAST criteria, LAA was determined in 7 patients (12.1%), CE in 10 patients (17.2%) and SVO in 7 patients (12.1%). Cancer types in the patients determined to have LAA were prostate adenocarcinoma (2patients), larynx squamous carcinoma (2 patients), SCLC, gynecologic, urinary bladder adenocarcinoma; cancer types in the patients determined to have CE were prostate adenocarcinoma (3 patients), lung cancer (2 patients), skin cancer (2 patients), leukemia, breast cancer, cancer types in the patients determined to have SVO were colon adenocarcinoma (2 patients), lung adenocarcinoma, larynx adenocarcinoma, leukemia, urinary bladder adenocarcinoma and gastric adenocarcinoma. The causes of CE were as followings: AF in 6 patients, akinetic left ventricular segment in 1 patient, left ventricular hypokinesia and multiple cardiac reasons in 1 patient.

Ischemic stroke was the first presenting symptom of cancer in 5 patients (8.6%). Cancers determined in these patients were malignant melanoma (2 patients), undifferentiated gastric adenocarcinoma (1 patients), prostate adenocarcinoma (1 patients) and

pancreatic adenocarcinoma (1 patients). Two of these patients had AF and HT, one of them had HT and DM. No risk factor for ischemic stroke was determined in the other two patients. Three patients (2 SCLC, 1 colon adenocarcinoma) died in the hospital during follow-up period.

Forty patients (68.9%) had supratentorial infarcts and 6 patients (10.3%) had infratentorial infarcts. Infarct was determined both in supratentorial and infratentorial regions in 12 patients (20.8%). Infarct was located in the MCA region in 34 (85%) of patients with supratentorial infarcts, in the PCA region in 4 patients (10%) and in the ACA region 2 patients (5%). Infratentorial infarcts were located in the brainstem in 4 patients and in the cerebellum in 2 patients. Multiple acute infarcts were seen most commonly in lung and colon cancer. While infarct was determined in supratentorial region in 9 of 12 patients with lung cancer, only 1 patient had an infarct in infratentorial region. Hemorrhagic transformation (1 prostatic squamous cell cancer, 1 SCLC) developed in 2 patients during follow-up. Ten patients (17.2%) had lacunar infarcts.

Discussion

Thromboembolic events develop in approximately 20% of cancer patients[1, 12]. It is reported that ischemic strokes develop in 3-3.5% of cancer patients (2, 12,13). In our study, an association was determined between AIS and cancer in 5.8% of our patients. AIS associated with cancer was seen more commonly in male patients (69% versus 31%). Age was similar among female and male patients. Lung cancers (20.78%) and colorectal cancers (15.5%) were most commonly determined in our patients. Cancer type was SCLC in half of our patients with lung cancer. Also in the previous studies, it was reported that most commonly determined cancers in stroke patients were gastrointestinal (19%-32%), lung (11%-38%), gynecological (21%), brain (9%) and prostate cancers (9%) (2, 5, 6; 8, 9, 14-16)

Possible mechanisms of AIS in cancer patients are direct pressure of tumor on the vessel or vascular invasion of tumor, tumor associated embolism, release of the mucin or procoagulant factors, coagulation disorders and effect of administered treatments (surgery, radiotherapy, chemotherapy)[1, 9, 17]. The cause of AIS in one of our patients with nasopharynx cancer was local pressure due to invasion of carotid artery. Vascular injury occurring during surgery might cause AIS by causing tissue factor release and radiotherapy might cause AIS by causing endothelial injury[9, 17, 18]. The risk for AIS increases 10-fold following the application of radiotherapy on to the brain and neck[19]. It was reported that also chemotherapeutic drugs and especially cisplatin, cyclophosphamide and 5-fluorouracil were causes of AIS[5]. Radiotherapy was administered in 15.5% of our patients. Chemotherapy was administered in 37.9% of our patients. Five of these patients had AIS in the first 6 months after receiving chemotherapy and two of these patients had no risk factor for stroke. We determined a primary central nervous system tumor in one of our patients. It was reported that also neovascularization occurring due to growth of tumor in primary brain tumors might cause ischemic stroke[20].

Stroke may develop after diagnosis of cancer in cancer patients or stroke might be presentation symptom of cancer. It is reported that particularly pancreatic adenocarcinoma may be manifested by stroke by increasing the tendency toward thrombosis[13]. AIS was the first presenting symptom of cancer in 5 (8.6%) of our patients. Cancer was pancreatic adenocarcinoma in one of these patients and malignant melanoma, mucinous carcinoma of cervix, undifferentiated gastric adenocarcinoma and prostatic adenocarcinoma were determined in the other patients.

The most commonly determined risk factors in our patients were HT and DM. No risk factor for ischemic stroke was determined in 12.1% of our patients. In the study performed by Lee et al., it was reported that HT was the most commonly determined risk factor also in cancer-AIS patients[15]. It is not exactly known whether the frequency of traditional risk factors for stroke in cancer patients developing AIS is different from the one in cancer patients without AIS. It was reported in many studies that the frequency of risk factors was determined to be similar in both patient groups[9, 13]. In the study performed by Shwarzbach et al., it was reported that HL and HT were less commonly determined in cancer-AIS patients and DM and the other vascular risk factors were determined with similar frequency in AIS patients without cancer[6]. Additionally, the most commonly determined risk factors in our patients diagnosed with cancer after stroke were HT (60%) and AF (40%).

According to the TOAST criteria, CE and LAA were determined in 17.2% and 12.1% of our patients, respectively. In the study performed by Zhang et al., it was reported that cardio-embolic etiology was most commonly determined etiology in AIS patients

with cancer[21]. LAA and CE etiologies were determined in 1 and 3 of our patients who were diagnosed with cancer after stroke. In the previous studies, LAA was most commonly determined in the patients who were diagnosed with cancer after stroke[3, 15].

It was reported that infarcts developed in supratentorial region and especially in MCA region in cancer patients (6, 22). While infarct was most commonly determined in supratentorial region (68.9%) and especially in MCA region in our patient group, isolated infratentorial infarct was determined only in 6 (10.3%) of our patients. Consistent with the previous studies, 12 (20.8%) of our patients had both supratentorial and infratentorial infarct[6, 23]. Multiple acute infarcts were most commonly seen in lung and colon cancers. Multiple acute infarcts were seen most commonly in lung and colon cancer. Seventeen point two percent of our patients had lacunar infarcts. In the study performed by Shwarzbach et al., lacunar infarct was determined in 20% of the patients[6]. Hemorrhagic transformation developed in only 2 (3.4%) of our patients.

The limitations of our study is its retrospective nature and some patients has missing tests (D-dimer, fibrinogen, etc.), not being able to find CT and RT starting dates clearly on those who have received it and exclusion of those with watershed infarcts. Watershed infarcts were reported to occur due to many various etiological reasons such as especially local invasion of neck region tumors, effect of RT on large vessels, hypoperfusion during cancer surgery[24].

In conclusion, an association with cancer is not rare in AIS patients. Therefore, research of cancers as well as traditional risk factors for stroke in AIS patients is important for determination of both treatment and prognosis.

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