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Original Article

Evaluation of stroke risk factors and characteristics in the comorbidity of cancer

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Abstract

Aim: Stroke and cancer can be followed together and in the presence of cancer, there may be changes in classical stroke characteristics. The aim of this study was to determine the effect of cancer on stroke risk factors, radiological and clinical features.
Materials and Methods: Patients who were hospitalized with the diagnosis of stroke between 2014-2020 were included in the study retrospectively. By examining the stroke and cancer characteristics of the patients; The differences in demographic findings, stroke risk factors, and radiological features of stroke between patients with and without cancer were examined. The anti-cancer treatments used and the characteristics of cancer were evaluated in stroke patients.
Results: 281 stroke patients were evaluated and cancer was detected in 52 patients. There was no significant difference in terms of demographic characteristics of the patients. No significant difference was observed in stroke patients with cancer in terms of risk factors except smoking and alcohol use. Multiple ischemic lesions were more evident on magnetic resonance imaging (MRI) in stroke patients with cancer. The most common cancer was lung cancer.
Conclusion: Stroke and cancer are increasingly common comorbidities. As the time between stroke and cancer development decreases, while the risk factors for cancer are more prominent, classical risk factors for stroke are observed less frequently.

Keywords: Cancer; disease duration; risk factors; stroke

INTRODUCTION

Stroke and cancer are among the diseases that are increasing in prevalence worldwide and are considered as the causes of serious morbidity and mortality (1-3). Cancer is a risk factor for stroke patients and ischemic stroke has been reported in 15% of cancer patients, but this rate has been found to be lower than 0.08% in recent studies (4,5). Stroke is thought to have a negative effect on survival in cancer patients, and it has been reported that the average life span of cancer patients is 4.5 months after stroke (6).

Coexistence of cancer and stroke; Many mechanisms are blamed in the etiopathogenesis: direct tumor effect, hypercoagulability, cancer treatment (chemotherapy and radiotherapy) are among these factors (4,7,5,8). Atherosclerosis, which is the best known in the pathogenesis of stroke, is thought to increase the risk of stroke by potentializing hypercoagulability due to cancer (9).

In the presence of cancer; Classic risk factors for stroke (hypertension, diabetes mellitus, hyperlipidemia, family history, smoking, atrial fibrillation) and cancer-related risk factors such as cancer type and treatments for cancer may be effective in the occurrence of stroke. In the absence of classical risk factors, stroke has often been associated with cancer (10). However, studies evaluating which group of risk factors are more common for stroke in cancer patients are limited and contradictory (4,11).

The relationship between cancer and ischemic stroke has been reported in many types of cancer; It is seen most frequently in lung and pancreatic cancers (7). Determining the cancer groups in which stroke is observed more frequently and analyzing risk factors are important in terms of the course of both diseases. Our aim in this study; To examine the risk factors and stroke characteristics in stroke and cancer association.

MATERIALS and METHODS

Patients

Two hundred and eighty-one patients over 18 years of age who were hospitalized with a diagnosis of acute ischemic stroke between 2014 and 2020 were included in the study. The diagnosis of all patients was confirmed by clinical

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and diffusion brain magnetic resonance imaging (MRI) by the presence of acute ischemic brain lesions. Those followed with the diagnosis of intracerebral hematoma and transient ischemic attack were excluded from the study.

Data were obtained retrospectively. Clinical and laboratory information was obtained from an electronic database.

Fifty-two patients had a diagnosis of cancer. Neurological, systemic and cardiological examinations of all patients were evaluated. Among the laboratory and imaging methods, computerized brain tomography, diffusion MRI, electrocardiogram, transthoracic echocardiography, rhythm holter, carotid and vertebral artery Doppler ultrasonography, brain and cervical computed tomography angiography and blood tests were evaluated for risk factors.

The patients were divided into two groups according to the presence of cancer as stroke patients with cancer and stroke patients without cancer. Age, gender, risk factors for stroke, cancer presence, cancer duration, chemotherapy and radiotherapy treatment were evaluated as risk factors for stroke in all patients. Study was performed in accordance with the ethical standards of the 1964 Helsinki declaration. Ethics committee approval was obtained from the ethics committee of Istanbul Medipol University with the decision dated 04.09.2020 and numbered 661.

Cancer Features

For cancer disease, the cancer type, location, histopathology, presence of any metastasis were examined. Anticancer treatments used at the diagnosis of acute ischemic attack were grouped as chemotherapy and radiotherapy. Time to stroke were grouped as pre-cancer diagnosis, with cancer diagnosis, and post-cancer diagnosis. The time between cancer and stroke diagnoses was calculated in months and divided into 4 groups as <3 months, 3-6 months, 6-12 months and >12 months.

Stroke Characteristics

Classical risk factors for stroke were determined for patients with and without cancer. Clinical findings that occur acutely in patients after stroke were examined.

Laboratory Evaluation

The laboratory tests of the patients performed within the first 24 hours after stroke were evaluated. Complete blood count, glycated Hemoglobin (Hemoglobin A1c), LDL, total cholesterol and triglyceride values were examined to evaluate the stroke risk factors of the patients.

Radiology Examinations

Ischemic lesion was defined as acute stroke with hyperintensity in the brain region corresponding to the artery area in diffusion-weighted MRI examinations and presence of hypo intenseness in the ADC sequence. The vascular system (anterior / posterior) affected by the stroke and the side where it was placed (right / left / bilateral) were determined with the diffusion MRI. Anterior system strokes were evaluated as ischemia of the middle cerebral artery, anterior cerebral artery, internal carotid artery and its branches, while ischemia of the posterior cerebral artery, basilar artery, vertebral artery and its branches were classified as posterior system strokes.

Statistical Analyis

IBM SPSS version 25 program was used to evaluate the data. Frequency, percentage, median, and 25-75 quartile values were used to evaluate the descriptive data. Chi-square analysis was used to examine categorical variables. Statistical significance was accepted as $p < 0.05$.

RESULTS

Of the 281 patients included in our study, 52 (18.5%) had cancer with stroke (cancer (+) stroke),229 of them (81.5%) were non-cancer stroke (cancer (-) stroke). The mean age of the patients with cancer (-) stroke was 68 (56-75), and the mean age of those with cancer (+) stroke was 66 (55-73). There was no difference between the two groups in terms of mean age ($p = 0.288$).

169 (60.1%) of the patients were male and 112 (39.9%) were female. The patients were divided into two groups according to the presence of cancer and risk factors were compared. There was no significant difference between the two groups in terms of age, gender, presence of atrial fibrillation, and family history of stroke. However, it was observed that the prevalence of HT, DM, CAD, HL was lower, and smoking and alcohol use was higher in patients with cancer (+) stroke ($p < 0.001$ for each). (Table 1).

Table 1. Evaluation of stroke risk factors in the presence of cancer

			Cancer (-) stroke	Cancer (+) stroke	Z/X^2; p
Age	**Median (IQR 25-75)**		68 (56-75)	66 (55-73)	10.062; 0.288
Gender	n (%)	Male	139 (60.7)	30 (57.7)	0.160; 0.689
		Female	90 (39.3)	22 (42.3)	
Hypertension	n (%)	(-)	70 (30.6)	31 (59.6)	**15.530; <0.001**
		(+)	159 (69.4)	21 (40.4)	
Diabetes mellitus	n (%)	(-)	122 (53.3)	40 (76.9)	**9.707; 0.002**
		(+)	107 (46.7)	12 (23.1)	
Coronary artery disease	n (%)	(-)	151 (65.9)	43 (82.7)	**5.565; 0.018**
		(+)	78 (34.1)	9 (17.3)	
Atrial fibrillation	n (%)	(-)	178 (77.7)	46 (88.5)	3.019; 0.082
		(+)	51 (22.3)	6 (11.5)	

Hyperlipidemia	n (%)	(-)	116 (50.7)	39 (75.0)	**10.155; 0.001**
		(+)	113 (49.3)	13 (25.0)	
Smoking	n (%)	(-)	205 (89.5)	41 (78.8)	**4.427; 0.035**
		(+)	24 (10.5)	11 (21.2)	
Alcohol use	n (%)	(-)	228 (99.6)	49 (94.2)	**8.588; 0.003**
		(+)	1 (0.4)	3 (5.8)	
Family history of stroke	n (%)	(-)	222 (96.9)	51 (98.1)	0.197; 0.657
		(+)	7 (3.1)	1 (1.9)	

The most common cancers in patients were lung cancer (n = 17, 32.7%), breast cancer (n = 6, 11.5%), prostate cancer (n = 4, 7.7%) and colon cancer (n = 4,. 7.7%). While 30.8% of the patients received radiotherapy, the rate of those who received chemotherapy was 71.2%. At least one metastatic focus was detected in 61.5% of the patients. In 63.5% of the patients, the time between cancer development and stroke was found to be longer than 12 months (Table 2).

When the radiological features of stroke are examined among individuals with and without cancer; there was no statistical difference for the vascular system in which the stroke was localized, the side of the stroke, hemorrhagic transformation, and stroke clinical findings (p> 0.05). However, the frequency of multiple stroke lesions in cancer (+) stroke patients was higher than in patients with cancer (-) stroke (p = 0.013) (Table 3).

Considering the time between stroke and cancer development, when the patients with this time less than 6 months and longer than 6 months are compared; there was no statistical difference between the groups in terms of gender, presence of HT, DM, coronary artery disease or AF, smoking and alcohol use, history of stroke, cancer type, presence of metastasis, radiotherapy and chemotherapy use (p> 0.05). The frequency of HL was evaluated to be higher in individuals whose stroke development lasted longer than 6 months (p = 0.016).

Table 2. Cancer characteristics in stroke patients

		N	%
Cancer localization	Lung	17	32.7
	Brain	3	5.8
	Endometrium	1	1.9
	Pituitary cancer	1	1.9
	Large intestine	4	7.7
	Large intestine and bladder	1	1.9
	Lymphoma	3	5.8
	Breast	6	11.5
	Breast and ovarian	1	1.9
	Bladder	1	1.9
	Gastric	2	3.8
	Gastric and leukemia	1	1.9
	Multiple myelom	1	1.9
	Ovarian	1	1.9
	Pancreas	1	1.9
	Prostate	4	7.7
	Rectum	1	1.9
	Thyroid	3	5.8
Radiotherapy	(-)	36	69.2
	(+)	16	30.8
Chemotherapy	(-)	15	28.8
	(+)	37	71.2
Metastasis	(-)	20	38.5
	(+)	32	61.5
Time between cancer and stroke diagnosis (months)	<3 months	9	17.3
	3-6 months	4	7.7
	6-12 months	6	11.5
	>12 months	33	63.5

Table 3. Comparison of the radiological and clinical features of stroke

		Cancer (-) stroke		Cancer (+) stroke		X^2; p
		N	%	N	%	
System affected in stroke (anterior/posterior)	Posterior system	78	34.1	16	30.8	0.345; 0.842
	Anterior system	140	61.1	34	65.4	
	Anterior and posterior system	11	4.8	2	3.8	
Side of stroke	Bilateral	60	26.2	17	32.7	5.478; 0.140
	Right	71	31.0	14	26.9	
	Left	98	42.8	20	38.5	
Clinical features of stroke	Ataxia	32	14.0	9	17.3	8.774; 0.067
	Visual disturbance	4	1.7	2	3.8	
	Speach disturbance	48	21.0	19	36.5	
	Cranial nerve dysfunction	1	0.4	0	0.0	
	Weakness	144	62.9	22	42.3	
Multiple lesions in MRI	Not Multiple	144	62.9	23	44.2	**6.114; 0.013**
	Multipl	85	37.1	29	55.8	
Hemorrhagic transformation on MRI	(-)	209	91.3	45	86.5	1.091; 0.296
	(+)	20	8.7	7	13.5	

DISCUSSION

In cancer patients, prolongation of life expectancy with treatment increases the incidence of stroke relatively. In addition, both diseases have similar risk factors such as age, smoking, and obesity (12).

In autopsy studies performed in cancer patients, the most common finding after metastasis is stroke, but most of these cases are asymptomatic (13). Coexistence of cancer and stroke was observed in 18.5% of the patients in this study, this rate was higher than the rates observed in the literature (5). One reason for this may be that the center where the study was conducted is an oncology center and therefore we have the opportunity to evaluate and follow up more oncology patients. In addition, increasing rates of cancer and stroke worldwide, and the effects of newly added chemotherapy and radiotherapy protocols on the vascular system may also be effective. However, the prolongation of life expectancy in cancer patients with anti-cancer treatments may be associated with a higher incidence of stroke.

In many studies, no significant difference was observed between stroke patients with and without cancer in terms of the presence of classic stroke risk factors (14). However, in patients without classical risk factors, the relationship between cancer and stroke has been reported more clearly (10). Hyperlipidemia and hypertension have been observed less frequently in stroke patients with cancer (15). In addition, vascular risk factors were observed less frequently in patients with active cancer (16). In this study, revealing the risk of cancer on stroke; in stroke patients with cancer, classical risk factors for stroke were lower except smoking and alcohol use, which are risk factors for both stroke and cancer. However, hyperlipidemia was observed more frequently in patients whose time between cancer and stroke was longer than 6 months. Therefore, it was thought that the longer the time between cancer and stroke, the more important atherosclerotic risk factors in terms of stroke risk. Based on this, it was thought that hyperlipidemia, which is one of the classic risk factors of stroke, may be more effective in stroke patients with cancer as the time between cancer and stroke gets longer (17).

Studies have defined the relationship between cancer and stroke in many ways. Especially when cancer-related stroke pathogenesis is evaluated; paraneoplastic mechanism, direct cancer-related effect, hypercoagulability, and complication of cancer treatments can be listed among the mechanisms (18). However, when patients with active cancer are evaluated, the presence of unidentified stroke was reported more frequently (19,20). Similarly, the study population consisted of patients with active cancer, most of them metastatic and being followed up with a diagnosis of advanced stage cancer, and in support of previous studies, classical risk factors were observed less frequently in this group.

While trying to explain the causes of stroke in cancer patients with many factors, it is reported that the cancer type and the presence of chemotherapy may also be effective. Chemotherapy protocol with a single or more than one agent, hormonal therapy, and the use of hematopoietic growth factors change the incidence (21). Treatment-related stroke has been frequently reported in prostate and breast cancer, which are less thrombogenic and more benign types of cancer and where hormonal therapies are used (22). Although atherosclerosis in the brain and cervical arteries secondary to radiation is also a cause, it is thought that stroke in cancer patients is multifactorial (23). The most common type of cancer in this study was lung cancer. Although lung cancer is reported as the most common type of cancer with stroke, different rates are reported in different ethnic groups. For example, gastric cancer in Asia, and colorectal cancer in the Norwegian study group is the most common cancer type (7,10,16,24). Among the factors that determine the association of stroke cancer, the prevalence of cancer types observed in the society may be effective in addition to the characteristics of cancer and cancer treatment.

Studies on the time between cancer diagnosis and stroke have yielded various results. Stroke may occur as the first sign of cancer, and the time between cancer and stroke can be expressed in years (5,25,26,17). In patients with treated cancer, the mean time between cancer and stroke was found to be 6.8 years longer (17). Concomitantly, the risk of stroke has been found to be higher in patients with advanced cancer (27). The presence of advanced stage cancer has been found to be associated with hypercoagulability that may cause embolic events. Especially increased serum angiogenic factors in patients have been associated with the risk of stroke in cancer patients, although they have not been clearly defined (28). All of the patients in the study group were active cancer patients, 63% of the patients had longer than 12 months between cancer and stroke, the mean time between cancer and stroke was 29 months (0-144 months), and it was shorter than the literature. This situation was explained by the presence of active, metastatic cancer and the higher use of chemotherapy in our study group.

MRI features are also thought to be important in defining the effects of cancer on stroke. Studies have shown that multiple ischemic lesions are more common in stroke patients accompanying cancer (10,27). The reason for being multiple is often explained pathophysiologically to embolic causes. The rate of multiple lesions in patients with stroke was higher in stroke patients with cancer, similar to the literature. Therefore, it was thought that MRI features might be important in evaluating the etiology in the evaluation and management of these patients.

LIMITATIONS

The main limitations of this study are that it is retrospective, we follow a relatively large number of oncological patients and it is single center.

CONCLUSION

Stroke and cancer are multifactorial diseases that have an increasing prevalence all over the world and cause

serious disability in combination. In the presence of stroke accompanying cancer, cancer-related pathophysiological mechanisms are more prominent than classical risk factors for stroke. As the time between cancer and stroke increases, the classical risk factors for stroke can be observed more frequently.

Competing Interests: The authors declare that they have no competing interest.

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REFERENCES

1. Wolf PA, D'Agostino RB, Belanger AJ, et al. Probability of stroke: a risk profile from the Framingham study. Stroke 1991;22:312-8.
2. Howlader N, Noone AM, Krapcho M, et al. SEER cancer statistics review, 1975-2008. Bethesda, MD: National Cancer Institute. Available at: http://seer.cancer.gov/csr/ 1975_2008/. Accessed November 18, 2011
3. Bethesda, MD: National Cancer Institute. Available at: http://seer.cancer.gov/csr/ 1975_2008/. Accessed November 18, 2011
4. Graus F, Rogers LR, Posner JB. Cerebrovascular complications in patients with cancer. Medicine (Baltimore) 1985;64:16-35.
5. Taccone FS, Jeangette SM, Blecic SA. First-ever stroke as initial presentation of systemic cancer. J Stroke Cerebrovasc Dis 2008;17:169-74.
6. Adams HP Jr, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology 1999;53:126-31.
7. Cestari DM, Weine DM, Panageas KS, et al. Stroke in patients with cancer: incidence and etiology. Neurology 2004;62:2025-30.
8. Levine SR. Hypercoagulable states and stroke: a selective review. CNS Spectrums 2005;10:567-578, Bick RL. Cancer-associated thrombosis. New Engl J Med 2003;349:109-11.
9. Sanossian N, Djabiras C, Mack WJ, Ovbiagele B. Trends in cancer diagnoses among inpatients hospitalized with stroke. J Stroke Cerebrovasc Dis 2013;22:1146-50.
10. Kim SG, Hong JM, Kim HY, et al. Ischemic stroke in cancer patients with and without conventional mechanisms: a multicenter study in Korea. Stroke 2010;41:798-801.
11. Chaturvedi S, Ansell J, Recht L. Should cerebral ischemic events in cancer patients be considered a manifestation of hypercoagulability? Stroke 1994;25:1215-8.
12. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: Defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006;4:2137
13. Grisold W, Oberndorfer S, Struhal W. Stroke and cancer: a review. Acta Neurol Scand 2009;119:1-16.
14. Zhang Y, Cordato D, Shen Q, et al. Risk factor, pattern, etiology and outcome in ischemic stroke patients with cancer: a nested case-control study. Cerebrovasc Dis 2007;23:181-7.
15. Schwarzbach CJ, Schaefer A, Ebert A, Held V, Bolognese M, Kablau M, et al, Stroke and Cancer: The importance of Cancer-Associated Hypercoagulation as a Possible Stroke Aetiology. Stroke 2012;43:3029-34.
16. Lee EJ, Nah HW, Kwon JY, Kang DW, Kwon SU, Kim JS. Ischaemic Stroke in patients with cancer: is it different from usual strokes? Int J Stroke 2014;9:406-12.
17. Selvik HA, Thomassen L, Logallo N, Næss H. Prior cancer in patients with ischemic stroke: the Bergen NORSTROKE study. J Stroke Cerebrovasc Dis 2014;23:919-25.
18. Stefan O, Vera N, Otto B, et al. Stroke in cancer patients: a risk factor analysis. J Neurooncol 2009;94:221-26.
19. Navi BB, Singer S, Merkler AE, et al. Recurrent thromboembolic events after ischemic stroke in patients with cancer. Neurology 2014;83:26-33.
20. Karlińska AG, Gromadzka G, Karliński MA, Członkowska A. The activity of malignancy may determine stroke pattern in cancer patients. J Stroke Cerebrovasc Dis. 2015;24:778-83.
21. Lee AY, Levine MN. The thrombophilic state induced by therapeutic agents in the cancer patient. Semin Thromb Hemost 1999;25:137-45.
22. Azoulay L, Yin H, Benayoun S, et al. Androgen-deprivation therapy and the risk of stroke in patients with prostate cancer. Eur Urol 2011;60:1244-50
23. Chu CN, Chen SW, Bai LY, et al. Increase in stroke risk in patients with head and neck cancer: a retrospective cohort study. Br J Cancer 2011;105:1419-23.
24. Kim JM, Jung KH, Park KH, Lee ST, Chu K, Roh JK. Clinical manifestation of cancer related stroke: retrospective case-control study. J Neurooncol 2013;111:295-301.
25. Borowski A, Ghodsizad A, Gams E: Stroke as a first manifestation of ovarian cancer. J Neurooncol 2005;71: 67-9
26. Cornuz J, Bogousslavsky J, Schapira M, Regli F, Camenzind E: Ischemic stroke as the presenting manifestation of localized systemic cancer. Schweiz Arch Neurol Psychiatr 1988;139:5-11.
27. Kwon MH: Stroke as the first manifestation of concealed cancer. J Neurol Sci 2007;258:80-3
28. Dirix LY, Salgado R, Weytjens R, et al. Plasma fibrin D-dimer levels correlate with tumour volume, progression rate and survival in patients with metastatic breast cancer. Br J Cancer 2002;86:389-95.