Stroke and Cancer

The Importance of Cancer-Associated Hypercoagulation as a Possible Stroke Etiology

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Background and Purpose—The importance of cancer-associated hypercoagulability as a possible stroke etiology in patients with cancer has received relatively little attention to date. A recent study has suggested that cancer-associated hypercoagulation may be of special importance in the absence of conventional stroke mechanisms.

Methods—We identified patients with ischemic stroke sequentially admitted to our stroke center with the additional diagnosis of active and malignant cancer from 2002 to 2011. By using our prospectively collected stroke, MRI, and laboratory data banks, the etiology and risk factors of stroke, types of cancer, deep vein thrombosis/pulmonary embolism, D-dimer levels, and diffusion-weighted imaging lesion patterns were compared to an age- and sex-matched control group. Patients with cancer with a conventional stroke etiology and patients with an unidentified and/or cancer-associated stroke etiology were analyzed separately.

Results—One hundred forty patients with cancer and 140 control subjects were included. Unidentified stroke ($P<0.001$) and infarction in multiple vascular territories ($P<0.001$) were significantly more frequent and D-dimer levels significantly higher ($P<0.05$) in patients with cancer. Vice versa, risk factors such as hypertension ($P<0.05$) and hyperlipidemia ($P<0.01$) were more prevalent in control subjects. Deep vein thrombosis and pulmonary embolism were more frequent ($P<0.01$) and D-dimer levels higher ($P<0.01$) in the patients with unidentified and/or cancer-associated stroke etiology compared to the patients with cancer with a conventional stroke etiology. Lung and pancreatic cancer were significantly overrepresented and D-dimer levels higher in these patients compared with other patients with cancer ($P<0.01$).

Conclusions—Our data confirm the concept of cancer-associated hypercoagulation as a widely underestimated important stroke risk factor in patients with cancer, especially in those with severely elevated D-dimer levels and in the absence of conventional risk factors. **(*Stroke*. 2012;43:3029-3034.)**

Key Words: cancer and stroke ■ coagulopathy ■ D-dimer ■ embolic stroke ■ etiology ■ risk factors

A causal relationship between malignant cancer and thrombosis has been known since the 19th century, when Armand Trousseau in 1865 first described migratory thrombosis as the first manifestation of occult gastric cancer.[1,2] The association between cancer and excessive blood coagulation has since then attracted much attention. Today the concept of "Trousseau's syndrome" is commonly used not only to describe migratory thrombosis that precedes the diagnosis of occult cancer, but also any "hypercoagulable state associated with malignant cancer."[3]

Nevertheless, the importance of paraneoplastic hypercoagulability as a possible stroke etiology in patients with cancer has received relatively little attention to date. This may be because it is difficult to diagnose in patients with stroke because etiologies may concur in the usually elderly and multimorbid patients and malignancy may represent a simple coincidence. Furthermore, the underlying mechanisms of paraneoplastic hypercoagulability are complex, of high interindividual variability, and still not fully understood.[4,5]

A small number of earlier studies on this topic generated conflicting results.[6–12] The largest study including 161 patients by Kim et al in 2010 differentiated between patients with cancer+stroke with and without conventional stroke etiologies and renewed the idea of cancer-associated hypercoagulation as an important stroke etiology.[13] Significantly higher D-dimer levels as well as a significantly higher rate of multiply affected vascular territories in the group of patients without conventional stroke etiology supported the idea of cancer-associated hypercoagulation with resulting cerebral embolism. This was promoted by a higher prevalence of

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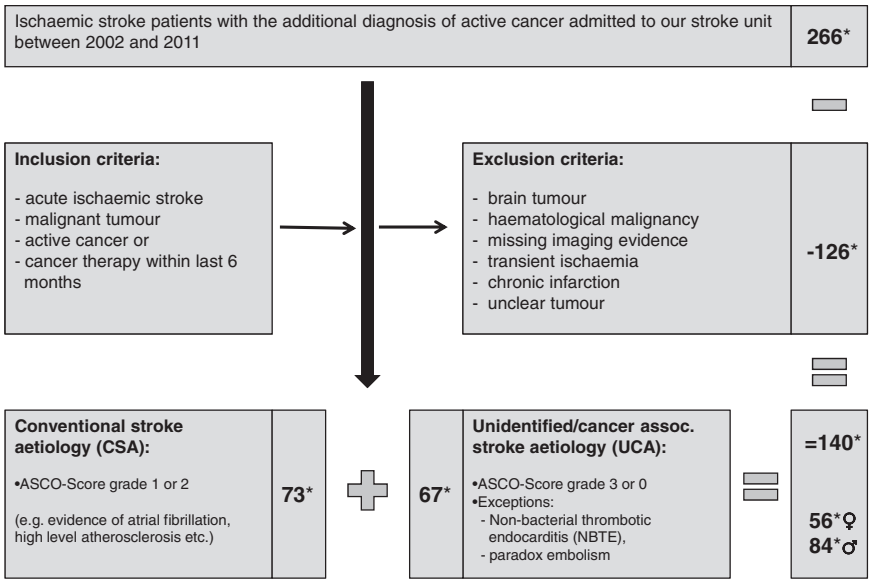

Figure 1. Selection of patients with cancer showing inclusion and exclusion criteria as well as subgroup assignment and patient numbers.

high-intensity transient signals in transcranial Doppler recordings. Suggesting microembolic mechanisms in those patients, the incidence of high-intensity transient signals correlated significantly with D-dimer levels in patients not displaying conventional stroke mechanisms.[14] These results have recently been reviewed by Bang et al in 2011[15]; however, neither study included a control group and both studies are still expecting replication outside South Korea.

According to the hypothesis that paraneoplastic hypercoagulation plays an important role in the pathophysiology of stroke in patients with cancer without conventional stroke mechanisms, we wondered whether similar findings could be observed in a large cancer+stroke population versus a matched control group.

Methods and Patients

Patient Selection

Patients with ischemic stroke with the additional diagnosis of solid and active malignancy admitted to our stroke center (Department of Neurology, UniversitätsMedizin Mannheim, University of Heidelberg, Heidelberg, Germany) were identified by reviewing our prospectively collected stroke data bank for the years 2002 to 2011 (n=140 [56 female, 84 male]). Active cancer was defined as confirmed malignancy treated or untreated in the last 6 months before stroke. Diagnosis of cancer was confirmed by given medical records or, in case of newly diagnosed or recurrent cancer, by histological evidence and oncologist expertise. Twenty-four patients with cancer received chemotherapy, 17 hormonotherapy, and 10 radiotherapy before stroke. Patients with cancer (CP) with an uncertain status or degree of malignancy were excluded as were patients with transient ischemia or who displayed no evidence of acute infarction or chronic infarction on neuroimaging. Patients with hematologic malignancies or primary brain tumor were also not included in the study, because these patients were considered to represent a subgroup with different underlying stroke mechanisms. Moreover, none of the included patients or control subjects showed imaging evidence or clinical syndrome suggestive of cerebral vein thrombosis as patients with cerebral vein thrombosis were not considered in the study per se. Further inclusion and exclusion criteria are given in Figure 1.

A control group presenting with ischemic infarction was established by one-to-one assignment of age- and sex-matched control subjects (n=140 56 female, 84 male). To avoid bias due to time-dependent differences in the diagnostic workup over the years, control subjects were further selected with respect to the date of admission. Consequently, the first age- and sex-matched patient with stroke before the index patient's admission to the hospital was chosen as the control subject. Clinical data were determined in the same manner for control subjects as for patients with cancer except for malignancy-associated variables (online-only Data Supplement Figure I). The mean age was 73 years (±9.76 [45–91]) in both groups.

Clinical Management and Data Acquisition

Clinical history and risk factors of atherosclerosis, stroke lesion patterns, outcome values measured by clinical assessment scores (see subsequently), type of cancer, presence of metastatic disease or concomitant deep vein thrombosis/pulmonary embolism, and first diagnosis of cancer were identified consistently by reviewing each patient. In addition, D-dimer levels were assessed with D-dimer levels obtained >10 days after stroke onset or possibly being affected by recombinant tissue-type plasminogen activator treatment being excluded from analysis (number of CP=70 of 140 [50%]; number of control subjects [CS]=33 of 140 [24%]).

Clinical assessment and diagnostic workup were performed according to our standardized stroke care protocol. Neurological and physical examination usually took place every 6 hours on the first 3 days after admission and were documented using the National Institutes of Health Stroke Scale, modified Rankin Scale, and Barthel Index for clinical assessment. In addition, the modified Rankin Scale and Barthel Indices before stroke (n=249 of 280) estimated at admission and modified Rankin Scale, Barthel Index, and National Institutes of Health Stroke Scale at the time of dismissal (n=161 of 280) from the hospital were documented. Diagnostic workup usually included cerebral MRI scans including diffusion-weighted imaging with sequential application of 3 separate diffusion-sensitizing gradients in perpendicular directions, T1- and T2-weighted studies, fluid attenuation recovery, T2* as well as 3-dimensional time-of-flight MR angiography. Where MRI was not possible for individual reasons, cerebral CT was used. In case of clinical evidence for deep vein thrombosis and/or pulmonary embolism, ultrasound scanning and/or CT imaging of the chest was performed (number of CP=36 of 140 [26%]; number of CS=7 of 140 [5%]). Full stroke workup further included extra- and intracranial Doppler and duplex

Table 1. The ASCO Phenotypic Classification of Stroke

A	Atherosclerosis
S	Small-vessel disease
C	Cardiac disease
O	Other causes
1	Definitely a potential cause of the index stroke
2	Causality uncertain
3	Not likely a direct cause of the index stroke (but disease is present)
0	Disease is not present
9	Insufficient workup

sonography of brain-supplying arteries, electrocardiography on admission, 72-hours electrocardiographic and vital sign monitoring, transthoracic (number of CP=43 of 140 [31%]; number of CS=72 of 140 [51%]) or transesophageal echocardiography (number of CP=17 of 140 [12%]; number of CS=15 of 140 [11%]), and laboratory tests (routine hematology and biochemistry, including coagulation test) as standard procedures according to stroke unit management recommendations (European Stroke Organization Guidelines, 2008). Additionally, transcranial Doppler ultrasound monitoring for high-intensity transient signal monitoring was performed in a small number of patients (number of CP=18 of 140 [13%]; number of CS=23 of 140 [16%]), but only one CS presented with positive transcranial Doppler high-intensity transient signal monitoring due to high-level atherosclerosis.

For comparative purposes to general epidemiological cancer data, we used a government publication provided by the Robert Koch Institute and Society for Epidemiological cancer registry in Germany ("Robert Koch Institut & Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V.").[16]

Stroke Etiology

After stroke workup, the data were analyzed and patients were phenotypically classified according to the ASCO score.[17] The new ASCO phenotypic classification of stroke has shown good concordance with the most widely used Trial of ORG 10172 in Acute Stroke Treatment classification but reflects important additional information.[18] The ASCO classification code is illustrated in Table 1. We established 2 subgroups of patients with cancer+stroke according to the presence of a potential stroke etiology expressed by the ASCO score. Patients with ASCO Grade 1 or 2 in any category reflecting the presence of a "definite potential cause of index stroke" (1) or at least an "uncertain causality" (2) were attributed to the conventional stroke etiology group (CSE group). Patients with unidentified stroke etiology (without ASCO Grade 1 or 2 in any category; see Table 1) and/or cancer-associated stroke etiology (evidence for nonbacterial thrombotic endocarditis or paradox embolism irrespective of the ASCO score) were attributed to the unidentified/cancer-associated stroke etiology group (UCE group).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Science (SPSS Version 19.0; IBM). Differences in frequency of categorical variables were reviewed using the χ^2 test or Fisher exact test. Outcome values were compared using *t* tests and general linear model analysis, respectively. As expected, D-dimer levels tended not to show a Gaussian distribution ($P<0.1$) and inhomogeneity of variance; therefore, comparison of D-dimer levels was performed using the Mann-Whitney *U* test for independent variables. All statistical analysis performed followed preformulated hypotheses.

Results

In 102 of 140 (73%) of the CS, a definite/probable stroke etiology expressed by an ASCO Grade 1 or 2 could be identified versus only 73 of 140 (52%) in patients with cancer. Consequently, unidentified stroke etiology was significantly more frequent in the cancer group (67 of 140 [48%]) than in the control group (38 of 140 [27%]; $P<0.001$).

Table 2. Comparison of D-Dimer Levels and Prevalence of DVT/PE

	Patients With Cancer	Control Subjects	Significance
D –dimer, μg/mL	6.15±8.58	1.39±1.9	<0.001
	UCE (unidentified/ cancer association)	CSE (conventional stroke etiology)	Significance
D-dimer, μg/mL	8.39±9.59	3.91±6.87	<0.05
	CP With Metastatic Disease	CP Without Metastatic Disease	Significance
D-dimer, μg/mL	8.12±9.97	2.88±3.77	<0.01
	Lung, pancreatic, gastric cancer	Other cancer	Significance
D-dimer, μg/mL	7.64±8.91	5.36±8.4	<0.05
	Patients With Cancer	Control Subjects	Significance
DVT+PE	8+3=1 (8%)	1+0=1 (1%)	<0.01
	UCE (unidentified/ cancer association)	CSE (conventional stroke etiology)	Significance
DVT+PE	7+3=10 (15%)	1+0=1 (1%)	<0.01

DVT indicates deep vein thrombosis; PE, pulmonary embolism; UCE, unidentified and/or cancer-associated stroke etiology; CP, patients with cancer; CSE, patients with cancer with a conventional stroke etiology.

The prevalence of deep vein thrombosis and pulmonary embolism was significantly higher in patients with cancer (11 of 140 [8%]) than in control subjects (one of 140 [1%]; $P<0.01$) and in patients with cancer with an unidentified and/or cancer-associated stroke etiology (UCE group; 10 of 67 [15%]) compared with patients with cancer with a definite/probable stroke etiology (CSA group; one of 73 [1%]; $P<0.01$; Table 2). D-dimer levels varied significantly, especially in the cancer group, with normal values up to 35 μg/mL, but were significantly higher in the cancer group than in the control group ($P<0.001$; for numbers see Table 2; Figure 2). D-dimer levels were also significantly higher in the UCE group compared with the CSE group of patients with cancer ($P<0.05$) as well as in patients with cancer presenting with metastatic disease than patients with cancer without ($P<0.01$; Table 2). Metastatic disease itself was significantly more frequent in patients with cancer with unidentified and/or stroke-associated stroke etiology (59%) than in patients with cancer with conventional stroke etiology (28%; $P<0.05$). Furthermore, small embolic infarction was significantly more frequent ($P<0.05$) and infarction in multiple vascular territories at least tended to be more frequent in patients with metastatic disease ($P<0.1$; for additional data, see online-only Data Supplement Table IV). Chemo-, radio-, or hormonotherapy before stroke did not influence D-dimer levels and distribution of patients was not significantly different between the UCE and CSE groups.

There was a significant difference, however, concerning vascular risk factors between patients with cancer and control

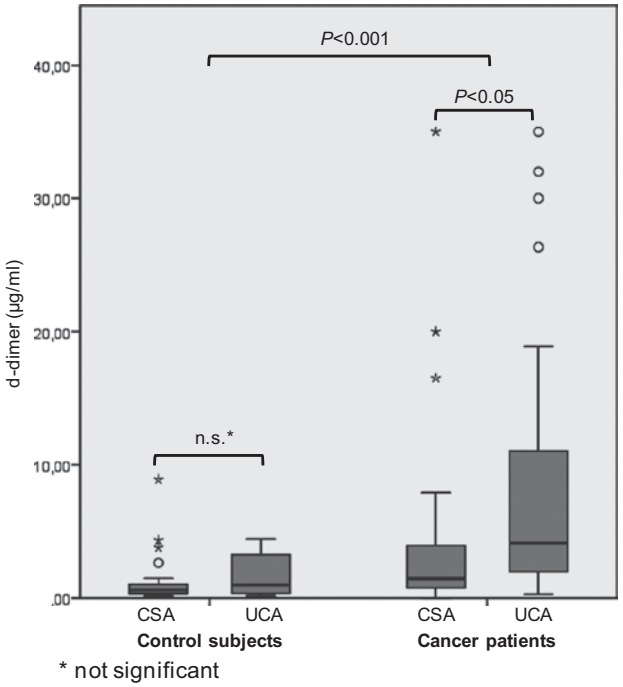

Figure 2. Distribution of D-dimer levels among control subjects, patients with cancer with conventional stroke etiology (CSE), and patients with cancer with unidentified/cancer-associated stroke etiology (UCE).

subjects. Hypertension (P<0.05) as well as hyperlipidemia (P<0.01) were significantly more prevalent in the control group than in the cancer group (for numbers, see Table 3). On the other hand, there was no significant difference in the prevalence of diabetes (P=1) or smoking (P=0.226) between the 2 groups.

We compared stroke lesion patterns between patients with cancer and control subjects (for numbers, see Table 3). Infarction in multiple vascular territories (P<0.05) and small embolic infarction (P<0.001), defined as cortical infarction <1 cm in diameter, were significantly more frequent in patients with cancer, whereas lacunar infarction was more or less of the same prevalence in both groups. On the other hand, significantly more control subjects than patients with cancer showed a territorial lesion pattern (P<0.05). Finally 19 of 140 (14%) control subjects and 10 of 140 (7%) patients with cancer presented with other lesion patterns such as brain stem or watershed infarction. Additionally, infarction in multiple vascular territories was also more frequent in the UCE than in the CSE group (P<0.01). Otherwise lesion pattern did not differ significantly between the 2 groups (for numbers, see Table 3). Furthermore, patients with cancer presenting with infarction in multiple vascular territories (P<0.001) as well as patients with cancer presenting with small embolic infarction (P<0.001) did show significant higher D-dimer levels compared with patients with other lesion patterns.

Prevalences of different tumor types in our studied population are given in Figure 3. Lung (P<0.001) and pancreatic cancer (P<0.01) in particular were significantly overrepresented in our population compared with the standard prevalence in the German population. The comparison is also visualized in Figure 3. D-dimer levels were significantly higher in patients presenting with lung, pancreatic, and gastric cancers than in the other patients with cancer (P<0.05; Table 2).

Table 3. Risk Factors and Lesion Patterns in Patients With Cancer and Control Subjects

	Patients With Cancer	Control Subjects	Significance
Risk factors			
Hypertension	108 (77%)	123 (88%)	<0.05
Hyperlipidemia	38 (27%)	62 (44%)	<0.01
Smoking	23 (16%)	31 (22%)	NS
Diabetes	46 (33%)	46 (33%)	NS
Lesion pattern			
Infarction in multiple vascular territories	34 (24%)	20 (14%)	<0.05
Territorial infarction	57 (41%)	75 (54%)	<0.05
Small embolic infarction	48 (34%)	22 (16%)	<0.001
Lacunar infarction	28 (20%)	29 (21%)	NS
Brain stem/watershed infarction	10 (7%)	19 (14%)	NS
	UCE (unidentified/ cancer association)	CSE (conventional stroke etiology)	
Infarction in multiple vascular territories	23 (34%)	11 (15%)	<0.01
Small embolic infarction	27 (40%)	21 (29%)	NS
Territorial infarction	26 (39%)	31 (43%)	NS
Lacunar infarction	15 (22%)	14 (19%)	NS
Brain stem/watershed infarction	3 (5%)	7 (10%)	NS

NS indicates not significant; UCE, unidentified and/or cancer-associated stroke etiology; CSE, patients with cancer with a conventional stroke etiology.

In-hospital mortality tended to be higher in patients with cancer (14 of 140 [10%] versus 6 of 140 [4%]). Otherwise National Institutes of Health Stroke Scale, modified Rankin Scale, and Barthel Index neither differed at the time of admission nor at the time of dismissal from the hospital significantly between patients with cancer and control subjects (online-only Data Supplement Table II). The first diagnosis of cancer was made in 34 of 140 (24%) patients with cancer. Nonbacterial thrombotic endocarditis was only described in a single patient with cancer and only one control subject.

Discussion

The high prevalence of unidentified stroke etiologies in our cancer group compared with the control group on the one hand, and the lower prevalence of some important vascular risk factors such as hypertension and hyperlipidemia on the other hand, suggests that besides conventional stroke mechanisms, also specific cancer-associated stroke mechanisms like hypercoagulation take effect in patients with cancer,

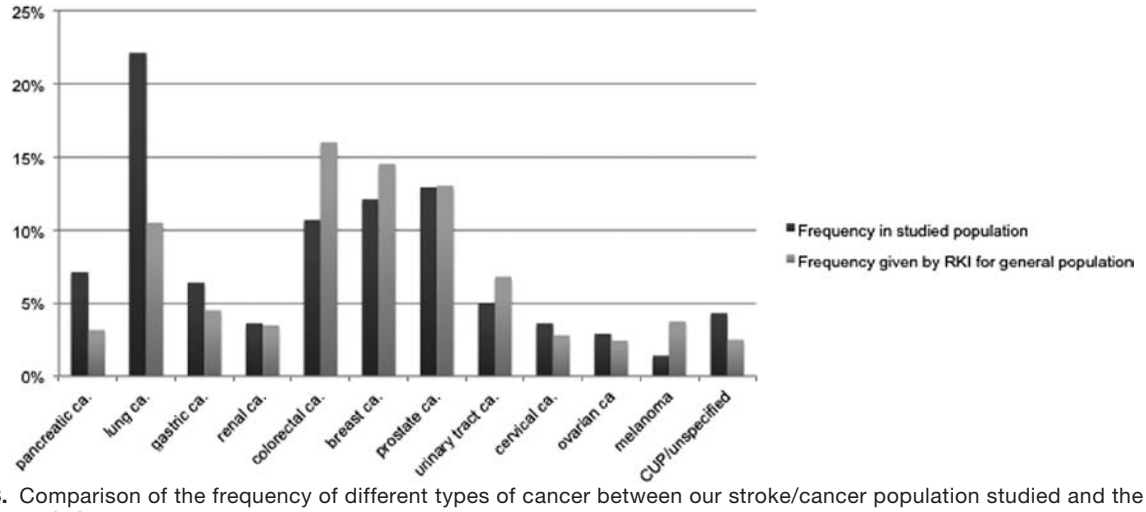

Figure 3. Comparison of the frequency of different types of cancer between our stroke/cancer population studied and the general German population.

which results in a different distribution of risk factors in this group of patients.

Cancer-associated risk factors for stroke include several direct or indirect tumor influences like tumor embolism, vessel infiltration or compression, surgery, septic embolism, or simply immobilization. Also chemotherapy and the aftermath of radiation contribute to the large range of possible cancer-related stroke etiologies. A comprehensive overview concerning the various cancer-associated stroke mechanisms and the risk of chemotherapy and radiation in this context is given elsewhere. [19–22] Thromboembolic complications in patients with cancer are of special importance among these.[2,3,5,22,23] Nevertheless, this association is often underestimated, in particular in those patients who are not known to have cancer once the stroke signs and symptoms occur. The several different mechanisms involved range from carcinoma mucins interacting with P- and L-selectins resulting in selectin-dependent microangiopathy and finally generating platelet-rich microthrombi to an exaggerated fluid phase thrombosis in which tissue factor and cysteine proteases (commonly referred to as cancer procoagulants) play an important role by independently activating the coagulation cascade.[23] Other mechanisms discussed involve tumor hypoxia or oncogene activation.[3]

D-dimers are a product of degradation of fibrin clots that result from various fibrinolytic activity and are therefore a sensitive but unspecific measure of the activation of the coagulation cascade and thrombus formation. [24] The significant difference in D-dimer levels between patients with cancer and control subjects in our study supports the growing evidence that cancer-associated hypercoagulation not only increases the risk of venous thromboembolism in these patients, but also the risk for ischemic stroke. The significant difference of D-dimer levels and of deep vein thrombosis/pulmonary embolism between patients with cancer with conventional stroke etiology and patients with cancer with unidentified and/or cancer-associated stroke etiology further leads to the conviction that cancer-associated hypercoagulation must be taken into account, especially in the absence of conventional stroke etiology.

However, cancer-associated hypercoagulation is difficult to diagnose in the individual because the common coagulation markers including D-dimers lack specificity and sensitivity.[4] To simplify the diagnosis of cancer-associated stroke, it is therefore important to identify associated predisposing factors. In our study this was particularly the case for the presence of metastatic disease. The interaction between metastatic disease and blood coagulation have been the object of extensive research leading to the perception that circulating tumor cells may not just accelerate clot formation but that successful metastasis of several tumor cell types actually depends on activation of coagulation.[25] D-dimer levels were significantly higher in patients with metastatic disease, indicating that cancer-associated hypercoagulation is more prevalent in this group of patients. Metastatic disease was also significantly more frequent in patients presenting with an unidentified stroke etiology. Patients with cancer with metastatic disease therefore represent a subgroup with a higher risk for cancer-associated hypercoagulation and subsequent stroke.

Furthermore, cancer-associated hypercoagulation should be taken into account if a patient with cancer presents with infarction in multiple vascular territories or focal lesions on MRI, which is commonly recognized as a marker for proximal embolism.[26] The significantly higher prevalence of infarction in multiple vascular territories in patients with cancer compared with control subjects as well as in the UCE compared with the CSE group of patients with cancer therefore supports the concept of proximal embolism potentially due to cancer-associated hypercoagulation. In addition, the evidence of elevated D-dimer levels in these patients also strengthens this hypothesis.

We also recorded the different types of cancer in our population under study, attempting to identify types of cancer associated with an elevated incidence of ischemic stroke. For this purpose, we compared our data with general epidemiological numbers for cancer prevalence in Germany, which are published on a regular basis by the Robert Koch Institute and Society for Epidemiological cancer registry in Germany ("Robert Koch Institut & Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V."). [16] Our data show that

lung and pancreatic cancers were significantly overrepresented in the stroke+cancer population studied. An increased risk of stroke has recently been described for patients with lung cancer in a population-based cohort study [27] and lung as well as pancreatic and gastric cancer are well known to be associated with an increased risk of thromboembolic events.[28–30] This concept of "thromboembolic cancer" is further supported by the fact that D-dimer levels in patients with the mentioned 3 cancer types were significantly higher compared with the other patients with cancer.

To our knowledge, this is the largest case-controlled study so far that examines the association of stroke and cancer in a collective of patients with stroke including a control group. Our results are in line with the results of the earlier and largest study so far by Kim et al.[13] The significance of this study, however, was limited by the fact that it did not include a control group but compared patients with cancer with and without a conventional stroke etiology.

Of course one must be aware of the inherent limitations of our study approach being case-controlled and that care must be taken if conclusions are drawn by the results of a single study. Furthermore, D-dimer levels were only present in approximately half of the patients with cancer and one fourth of the control subjects. Given the frequent coincidence of stroke and malignant diseases, these data are nevertheless of great interest and general importance. We strongly encourage replication of our results because the topic still awaits a large-scale prospective trial and therapeutic options in this group of patients may differ.

Our data support the concept of cancer-associated hypercoagulation as a relevant stroke etiology in patients with cancer in multiple ways. We identified patients at increased risk for cancer-associated stroke, namely patients with elevated D-dimer levels in the absence of other conventional stroke etiologies and/or infarction in multiple vascular territories or small embolic infarction. Patients presenting with lung or pancreatic cancer as well as patients with metastatic disease are at highest risk for cancer-associated stroke. We propose that diagnostic workup should include a broad laboratory assessment of hypercoagulability including D-dimer levels in all patients with cancer+stroke.[31] In addition, patients with suspected cancer-associated hypercoagulability should also be screened for other thromboembolic complications such as deep vein thrombosis, which is of utmost therapeutic relevance.

Disclosures

None.

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