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Potential Pathogenesis and Biomarkers of Kidney Cancer-Related Stroke

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Background: Stroke risk and stroke recurrence are increased in cancer patients, but the pathogenesis and biomarkers of kidney cancer-related stroke (KCS) are generally unclear. The aim of the present research was to investigate the pathogenesis and plasma biomarkers of kidney cancer-related stroke.

Material/Methods: A retrospective review was conducted on acute stroke patients with kidney cancer (KC) who were admitted to the hospital between January 2006 and December 2015. A total of 106 patients with KCS (active KC patients with acute stroke but without conventional vascular risks) were identified. In addition, 106 age- and sex-matched patients with KC alone were recruited.

Results: KCS patients had higher plasma D-dimer, cancer antigen (CA) 125, and CEA levels and greater proteinuria levels than did KC patients. Multiple logistic regression analysis showed that the risk of stroke in patients with KC increased independently by 0.8% (odds ratio [OR] 1.008; 95% confidence interval [CI] 1.002, 1.013; p=0.004) with a 1 ng/mL increase in D-dimer levels, by 1.2% (OR 1.012; 95% CI 1.007, 1.018; p=0.000) with a 1 U/mL increase in CA125, by 2.5% (OR 1.025; 95% CI 1.012, 1.038; p=0.000) with a 1 U/mL increase in CEA by 1.4% (OR 1.014; 95% CI 1.005, 1.024; p=0.004) with a 1 mg increase in urine protein in 24 hours.

Conclusions: Elevated plasma D-dimer, CA125 and CEA levels, and increased urine protein levels might lead to hypercoagulability and then KCS; however, they may also be biomarkers of KCS.

MeSH Keywords: Biological Markers • Kidney Neoplasms • Pathology • Stroke

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Background

Ischemic stroke and malignant cancer both are leading causes of death and disability. Stroke risk and stroke recurrence are increased in cancer patients [1,2]. Previous studies have suggested that some strokes are induced by cancer via an underlying physiopathologic mechanism known as cancer-related stroke [3,4]. Cancer-related stroke is characterized by multiple lesions in multiple arterial territories in the brain. Occasionally, cancer cells invade the left atrium and the blood vessels nearby, induce cardiovascular thrombus and non-bacterial thrombotic endocarditis (NBTE), and then cause cardiac thrombus, indicating that cancer directly causes thrombotic stroke [5–7]. However, most strokes in cancer patients are associated with elevated plasma D-dimer [8–10]. Furthermore, elevated plasma D-dimer, high-sensitivity C-reactive protein, fibrinogen, and pro-brain natriuretic peptide levels could be regarded as biomarkers of cancer-related stroke [11,12]. However, most previous studies have been conducted on cancer patients, and cancer patients are a heterogeneous group that includes patients with different types of cancers. Cancer cells are also heterogeneous, and the local sites and status of cancer in the body are diverse, indicating that the pathogenesis and biomarkers of cancer-related stroke should vary. Therefore, research on specific cell types in cancer patients may be the most suitable for the investigation of the pathogenesis and biomarkers of cancer-related stroke.

Kidney cancer (KC) is one of the most common cancers in the urinary system [13]. Metastasis of renal cell carcinoma has been observed to invade the pulmonary vein and pass into the heart cavity, leading to cerebral infarction [6]. Strokes occurring in some patients with KC may be related to the KC itself, namely, kidney cancer-related stroke (KCS). However, the pathogenesis and biomarkers of KCS are generally unclear. In the present study, our aim was to obtain a better understanding of the pathogenesis and plasma biomarkers of KCS. We performed a systemic retrospective study by reviewing the clinical data of KC patients with acute ischemic stroke. Additionally, we selected the same number of age- and sex-matched KC patients without stroke as the control group.

Material and Methods

Patients

This study was reviewed and approved by the Guangxi Medical University Review Board. A total of 8923 KC patients were recruited from the First Affiliated Hospital of Guangxi Medical University, the Fourth Affiliated Hospital of Guangxi Medical University, and the Ninth Affiliated Hospital of Guangxi Medical University between January 2006 and December 2015. Among them, there were 106 patients who met the criteria for KCS. The diagnosis of KC for all patients was pathologically confirmed. The diagnosis of acute stroke was based on the American Heart Association diagnostic criteria for stroke [14], which is patients presenting with a sudden onset of slurred speech, hemiplegic paralysis, and limb numbness, or other focal neurological deficits. Computed tomography (CT) images showed no cerebral hemorrhage, and magnetic resonance imaging (MRI) showed hyperintense lesions on T2- and diffusion-weighted images (DWI). The etiology of stroke was determined according to the TOAST criteria [15].

In actuality, it is very difficult to identify KCS in modern clinical practice. Based on the definition of cancer-related stroke in previous studies [3,4], in the present study, KCS was defined as acute stroke in patients with active KC. The KCS group met the following criteria: 1) patients diagnosed with KC and having KC in the active phase (i.e., treatment for KC not yet started, treatment failed to meet the criteria for clinical cure, or having confirmed recurrence or metastasis of KC) and who developed acute ischemic stroke without conventional vascular risk factors, such as hypertension, diabetes, and hyperlipemia; and 2) patients with acute ischemic stroke who were first diagnosed with KC during anti-stroke therapy. The exclusion criteria were: 1) patients with conventional risk factors; 2) patients with primary or metastatic intracranial malignant tumors; 3) patients with other malignant conditions; and 4) patients with cerebral vascular disease other than cerebral infarction.

The patients in the KC alone group had been diagnosed with KC, had KC in the active phase, did not have acute stroke, and were age- and sex-matched with the KCS patients. The exclusion criteria were: 1) patients with conventional vascular risk factors; 2) patients with brain metastasis; and 3) patients with other cancers.

Collection of clinical data

The general demographic characteristics in both groups, such as age and sex, were collected. Moreover, data were collected from blood tests, including routine blood examinations and blood biochemical assays, and proteinuria was assessed after testing from a 24-hour urine collection. Data on KC were collected, including the clinical manifestations; pathological types; metastasis; treatment information, including radiotherapy, chemotherapy and surgical resection; and tumor markers, such as cancer antigen (CA) 125, CA153, and CA199. Information on acute ischemic stroke, including clinical manifestations and the severity of focal neurological deficits as assessed with the National Institutes of Health Stroke Scale (NIHSS), were also collected. In addition, data from imaging endpoints, including echocardiography (ECG), transcranial Doppler ultrasound, cranial CT, CT angiography (CTA), MRI, and MR angiography

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(MRA), were also collected. The prognosis of patients on the 30th day after stroke symptom onset was based on the modified Rankin scale (mRS).

Statistical methods

All statistical analyses were performed using SPSS 18.0 software. Independent-samples *t* tests were used for quantitative data, and chi-square tests were used for qualitative data. Multivariable logistic regression analysis was performed to predict the independent contributions of factors in KCS versus KC. Significant variables with $p<0.05$ in univariate analyses were considered explanatory variables and were entered together into multivariable models. A p value <0.05 was considered statistically significant.

Results

A total of 106 KCS patients were identified, accounting for 1.19% of the total KC patients. Of the 106 KCS patients, 75 (70.75%) were male and 31 (29.25%) were female. Their average age (mean ± standard deviation) was 62.40±7.82 years. Similarly, the 106 KC patients had an average age of 60.88±6.26 years. As expected, no significant differences in age or sex were observed between these 2 groups. The demographic characteristics are listed in Table 1.

Among the KCS patients, 87 (82.08%) developed stroke in the first 6 months after the diagnosis of KC, 5 (4.72%) patients developed stroke 6 months to 1 year later, and 6 (5.66%) patients developed stroke more than 1 year after KC diagnosis. However, there were 8 (7.54%) patients with acute cerebral infarction as the first manifestation; these patients were first diagnosed with KC during anti-stroke therapy. There were 92 (86.88%) KCS patients with more than 1 lesion on brain MRI (Figure 1).

As a result of the inclusion and exclusion criteria, there was no significant difference in the types of KCs in the KCS and KC patients. When the clinical characteristics of the KCS patients were compared with those of the KC patients, most blood routine and coagulation values were not significantly different. However, blood test endpoints showed that KCS patients had higher plasma D-dimer, CA125, and CEA levels and greater proteinuria levels than did the KC patients. In addition, more KCS patients than KC patients had KC metastasis. Moreover, more KC patients than KCS patients underwent surgical resection treatment, but there were no significant differences between the 2 groups regarding chemoradiotherapy. In addition, more KCS patients died during hospitalization for KC (Table 1).

To identify the risk factors for KCS, we used multivariate logistic regression analysis to investigate 6 potentially important variables: D-dimer, CA125, CEA, proteinuria, KC metastasis, and surgical therapy. However, only D-dimer, CA125, CEA, and proteinuria were entered into the final models. The multiple model can be described using the following equation: logit $p=\ln(p/1-p)=\beta 0+\beta 1X1+\beta 2X2+\beta 3X3+\beta 4X4$. The final regression equation was as follows: logit $p=-10.969+1.008X1+1.021X2+1.025X3+1.014X4$. The risk of stroke in patients with KC increased independently by 0.8% (odds ratio [OR] 1.008; 95% confidence interval [CI] 1.002, 1.013; $p=0.004$) with an increase in the D-dimer level of 1 ng/mL; increased independently by 1.2% (OR 1.012; 95% CI 1.007, 1.018; $p=0.000$) with an increase in CA125 of 1 U/mL; increased independently by 2.5% (OR 1.025; 95% CI 1.012, 1.038; $p=0.000$) with an increase in CEA of 1 U/mL; and increased by 1.4% (OR 1.014; 95% CI 1.005, 1.024; $p=0.004$) with an increase in urine protein of 1 mg/24 h. These data revealed that elevated plasma D-dimer, CA125, and CEA levels, as well as increased levels of urine protein, may be independent risk factors for KCS (Table 2).

Discussion

Cancer increases the risk of stroke [2]. The incidence of stroke in cancer patients differs for different types of cancer. For example, the incidence of stroke within 3 months after the diagnosis of cancer was 5.1% in patients with lung cancer, 3.4% in patients with pancreatic cancer, 3.3% in patients with colorectal cancer, 1.5% in patients with breast cancer, and 1.2% in patients with prostate cancer [16]. In the present study, KCS was diagnosed in 1.19% of all patients with KC, and stroke occurred within 6 months after the diagnosis of KC in most of the KCS patients, indicating that as soon as KC is diagnosed, precautions should be taken to prevent stroke.

However, to effectively prevent cancer-related stroke, the mechanism of cancer-related stroke must be understood. Previous research has suggested that cancer-related stroke might occur via an unconventional mechanism. Occasionally, lung cancer cells have been found to directly cause thrombotic stroke by invading the left atrium, and kidney cells have been found to cause thrombotic stroke by invading the right inferior pulmonary vein [5,6]. In addition, cancer-related NBTE directly leading to thrombotic stroke has been documented [7,17]. Cancer patients with acute stroke often show no evidence that cancer cells directly cause stroke. However, accumulating studies have revealed that most cancer-related stroke patients have elevated plasma D-dimer levels, and some patients have more signs of microthrombus in their internal carotids when assessed by transcranial Doppler sonography. As a result, cancer-related hypercoagulability is regarded as the main mechanism of cancer-related ischemic stroke [18–21]. In the present study, KCS patients also had higher plasma D-dimer levels than did KC patients. Moreover, multivariate logistic regression analysis

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Table 1. The clinical features of KCS compared to KC.

Characteristics	KCS (n=106)	KC (n=106)	P value
Age	62.40±7.82	60.88±6.26	0.120*
Gender			
Male (n,%)	75 (70.75)	75 (70.75)	1.000#
Female (n,%)	31 (29.25)	31 (29.25)	1.000#
Blood tests			
RBC ($\times 10^{12}$/L)	4.21±0.80	4.30±0.62	0.343*
HGB (g/L)	124.04±21.33	119.08±17.93	0.068*
PLT ($\times 10^{9}$/L)	214.73±55.15	204.47±47.17	0.147*
MPV (fl)	8.08±0.39	7.99±0.49	0.121*
TT (s)	12.75±0.88	12.94±0.84	0.103*
PT (s)	12.56±1.47	12.35±1.66	0.327*
APTT(s)	30.94±2.96	31.60±2.35	0.073*
INR	1.02±0.15	1.04±0.23	0.450*
FIB (g/l)	4.83±0.73	4.68±0.65	0.104*
UREA (mmol/L)	5.69±2.14	5.97±2.29	0.345*
CREA (umol/L)	106.01±25.27	110.64±30.11	0.226*
Proteinuria(mg/24 h)	164.33±51.43	114.84±49.84	0.000
D-dimer (ng/m L)	511.35±129.53	356.45±107.89	0.000*
CA 125 (U/ml)	289.46±119.72	119.75±84.81	0.000*
CA 199 (U/ml)	88.34±21.16	83.22±21.97	0.085*
CEA(U/ml)	196.33±82.41	87.97±37.58	0.000*
Type of therapy			
Chemoradiotherapy	40 (37.74)	33 (31.13)	0.312#
Surgery	42 (39.62)	59 (55.66)	0.019#
Not treated	24 (22.64)	14 (13.21)	0.073#
Kidney cancer metastasis (n,%)	51 (48.11)	20 (18.87)	0.000#
Type of kidney cancer (n,%)			
Suprarenal epithelioma	48 (45.28)	46 (43.40)	0.782#
Papillary cell carcinoma	32 (30.19)	30 (28.30)	0.763#
Chromophobe kidney cancer	18 (16.98)	21 (19.81)	0.595#
Bellini collecting duct carcinoma	8 (7.54)	9 (8.49)	0.800#
Death during hospitalization for kidney cancer	22 (20.75)	3 (2.83)	0.000#

* With two independent samples t-test; # with chi-square test. Values are presented as mean ± SD.CRF, conventional risk factors; RBC – red blood cells; HGB – hemoglobin; PLT – platelet; MPV – mean platelet volume; TT – thrombin time; PT – prothrombin time; APTT – activated partial thromboplastin time; INR – international normalized ratio; FIB – fibrinogen; UREA – carbamide; CREA – creatinine; Proteinuria – 24 hour urine microalbumin.

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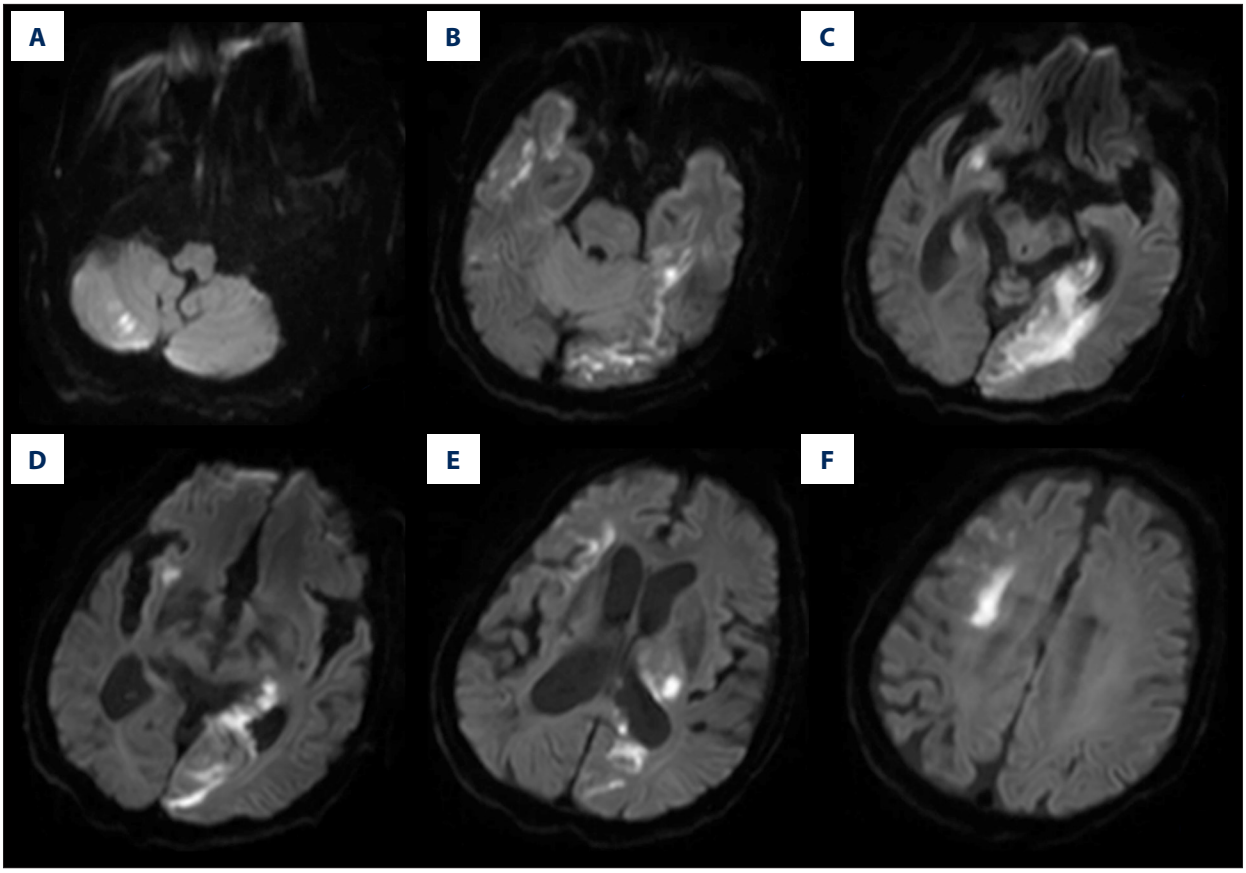

Figure 1. Classical magnetic resonance imaging (MRI) samples from a kidney cancer related stroke patient. The patient developed stroke in three weeks after the diagnosis of kidney cancer, and the diffusion weighted imaging(DWI) of MRI showed that there were multiple lesions in multiple arterial territories in the brain (**A–F**).

Table 2. Multivariate Logistic regression analysis.

Factors	β	SE (β)	Wals	Df	P	OR	95% CI
D dimer	0.008	0.003	8.085	1	0.004	1.008	1.002–1.013
CA125	0.012	0.003	19.323	1	0.000	1.012	1.007–1.018
CEA	0.025	0.006	14.647	1	0.000	1.025	1.012–1.038
Proteinuria	0.014	0.005	8.433	1	0.004	1.014	1.005–1.024
Constant	–10.969	1.686	42.325	1	0.000	0.000	

SE – standard error; OR – odds ratio; CI – confidence interval.

revealed that elevated levels of plasma D-dimer may independently increase the risk of stroke in KC patients, which also indicates that hypercoagulability plays an important role in KCS. Previous studies have shown that elevated plasma levels of CA125 in cancer patients are associated with an increased risk of stroke [22]. In addition, animal experiments have determined that mucins secreted by cancer cells trigger the reciprocal activation of platelets and neutrophils, leading to the formation of microthromboembolism in the blood [23]. In the present study, compared to KC patients, KCS patients had elevated plasma cancer marker levels, including CA125 and CEA, and multivariate logistic regression analysis revealed that the elevated levels of CA125 and CEA independently increase the risk of stroke in KC patients. The results suggest that KC cells introduce mucinous substances, such as CA125 and CEA, into the bloodstream to induce a hypercoagulable state, which in turn leads to embolic stroke. In addition, previous studies have shown that many types of chronic kidney disease are associated with increased proteinuria and venous thromboembolism [24,25]. Severe proteinuria was not only found to be an

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independent risk factor for stroke, but was also an independent predictive factor for a poor prognosis of stroke [26–28]. Patients with KC may have increased urine protein levels [29], but the relationship between proteinuria and cancer-related stroke has been unclear. In the present study, compared to KC patients, KCS patients had higher proteinuria levels, and multivariate logistic regression analysis revealed that the increased urine protein levels may independently increase the risk of stroke in KC patients. Therefore, a possible explanation might be that proteinuria leads to a hypercoagulable state and then to stroke. Future research should address the role of elevated plasma D-dimer, CA125, CEA, and proteinuria levels in the development of stroke in patients with KC.

Cancer-related stroke may have specific biomarkers. Previous studies have revealed that cancer-related stroke is characterized by elevated plasma D-dimer levels and multiple lesions distributed in multiple vascular regions [11,12]. In addition, elevated plasma D-dimer, fibrin degradation product (FDP), brain natriuretic peptide (BNP), fibrinogen, and C-reactive protein (CRP) levels are known to be biomarkers of cancer-related stroke [11,12,30]. Based on this finding, Ito et al. [31] successfully differentiated cancer-related stroke using elevated plasma D-dimer levels from atrial fibrillation-related acute multifocal embolic stroke, but it was still necessary to determine whether substantiated cancer-related stroke had specific biomarkers. In the present study, KCS patients showed elevated plasma D-dimer, CA125 and CEA levels, and increased urine protein levels, which might be distinct clinical features of KCS patients, or they may be biomarkers of KCS, indicating that elevated plasma CA125 and CEA levels, together with increased proteinuria levels, may also be used to differentiate KCS from other types of cancer-related stroke or other conventional stroke. Therefore, in the present study, the patients who had stroke as their first manifestation would be diagnosed with KC and KCS based on elevated plasma CA125 and CEA levels, together with increased proteinuria levels. For cancer-related stroke with stroke as the first manifestation or for stroke patients with concealed cancers [32–34], biomarkers and their forms found in the present study may be useful for physicians in clinical practice. However, further prospective investigations with more patients are needed to confirm our findings.

Conclusions

Although more details about the mechanism still need to be determined, this study demonstrates that elevated plasma D-dimer, CA125 and CEA levels, together with increased proteinuria levels, might lead to hypercoagulability and KCS and might also be biomarkers of KCS.

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