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Case Report

Clinical characteristics of breast cancer complicated by cerebral infarction

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Abstract: Objective: This study aimed to investigate the clinical characteristics of breast cancer complicated by cerebral infarction, as well as the potential pathogenesis. Methods: Retrospective analysis was conducted on clinical data of breast cancer patients that had developed cerebral infarction during hospitalization, and patients that had been diagnosed as breast cancer during treatment for acute cerebral infarction. Results: A total of 16 patients (0.34%) with active breast cancer complicated by cerebral infarction were screened out from 4,737 patients. The selected 16 subjects were all females aged 28-65 years (49.44±11.00 years on average). There was one or more conventional brain stroke risk factors in 4 patients (25.00%), while none in the other 12 patients (75.00%). Cerebral infarction was found in 14 patients (87.50%) 7-180 d after the diagnosis of breast cancer, while the other 2 patients (12.50%) were first diagnosed as breast cancer during hospitalization and treatment for acute cerebral infarction. As per cancer types, 11 cases were identified as invasive ductal carcinoma, 3 as intraductal carcinoma, and 2 as invasive lobular carcinoma. Metastasis was confirmed in 6 patients (37.50%). Biochemical indicator tests revealed elevated levels of D-dimer in 13 patients, CA153 in 11 patients, CEA in 10 patients, and CA125 in 9 patients. Single lesion shown as intracranial high-intensity signal in MRI diffusion weighted imaging (DWI) was detected in 6 patients (37.50%), and multiple lesions with various arterial supplies in 10 patients (62.50%). Conclusion: Most patients with breast cancer complicated by cerebral infarction lack conventional brain stroke risk factors, with abnormal biochemical indicator levels, as well as multiple intracranial lesions with various arterial supplies. And the pathogenesis may be relevant to the hypercoagulability in such patients.

Keywords: Breast cancer, cerebral infarction, clinical characteristics, pathogenesis

Introduction

The fact that cancer may add up to the risk of developing cerebral infarction [1, 2] suggests a correlation between the incidence of cerebral infarction and the underlying cancer condition. Recent studies have revealed a lack of conventional risk factors, elevated level of D-dimer in peripheral circulation, as well as multiple intracranial lesions with various arterial supplies among patients with cancer-related cerebral infarction [3, 4], and the pathogenesis may be mostly related to the hypercoagulable condition [3-5]. The latest report by the International Agency for Research on Cancer (IARC) indicates that breast cancer is the most common type of cancer in women around the world, and China is one of the countries with high incidences of breast cancer [6, 7]. Breast cancer may also lead to increased risk of cerebral infarction [8, 9]. However, there have been so far no reports on the clinical characteristics and potential pathogenesis of breast cancer complicated by cerebral infarction. This study performed a retrospective analysis on the clinical data of patients that had been hospitalized, and treated in the First Affiliated Hospital of Guangxi Medical University for active breast cancer complicated by cerebral infarction between 2003 and 2013, and preliminarily investigated the clinical characteristics and potential pathogenesis.

Materials and methods

Diagnosis and inclusion criteria

Diagnosis criteria: Based on the criteria by Horii et al. [10], active breast cancer was defined as pathologically diagnosed breast cancer that

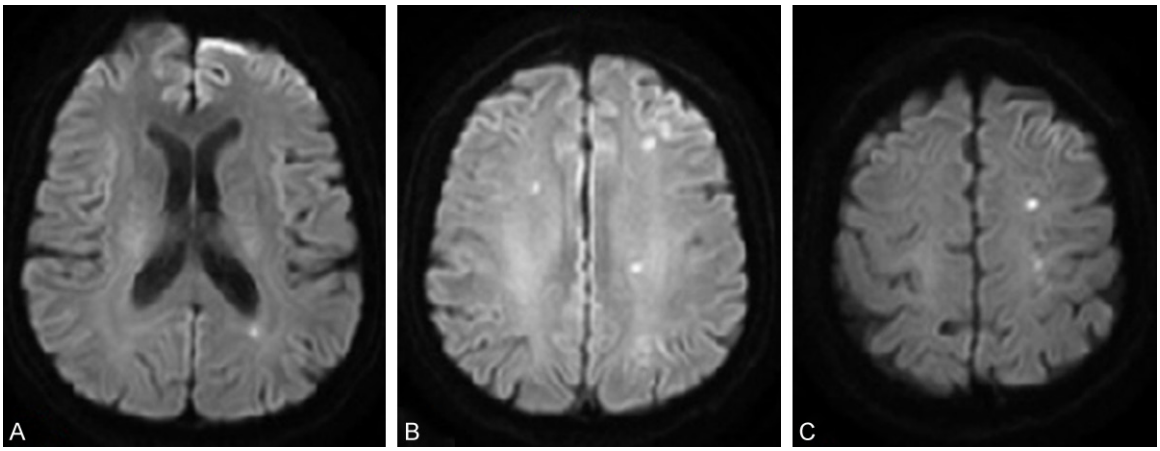

Figure 1. Cranial MRI diffusion weighted imaging (DWI) of Case 4. Multiple infarction lesions - A: 1 lesion near left posterior horn of lateral ventricle; B: 3 lesions in left centrum semiovale, 1 in right centrum semiovale; C: 2 lesions in left parietal lobe.

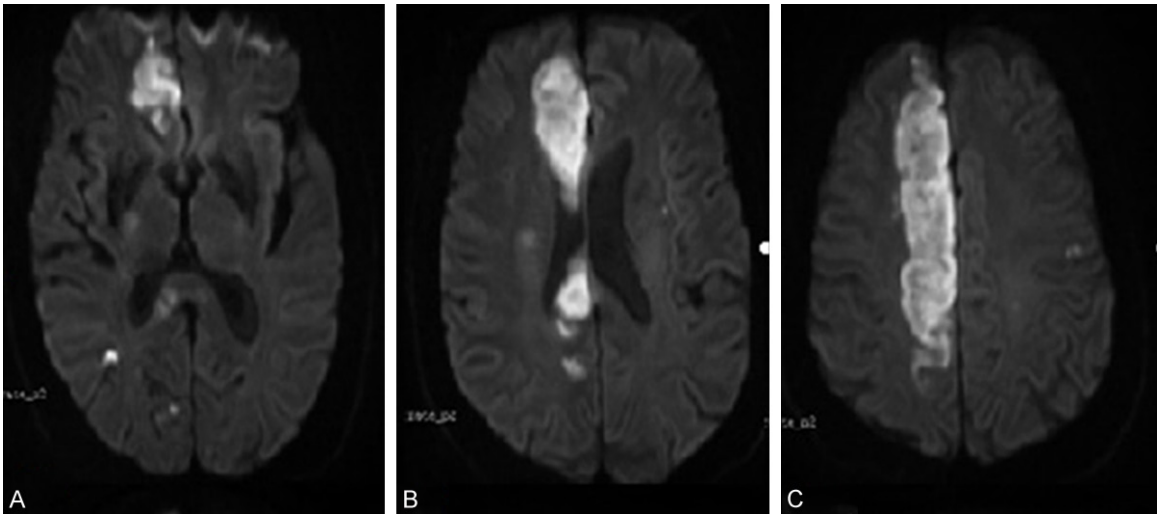

Figure 2. Cranial MRI diffusion weighted imaging (DWI) of Case 15. Multiple infarction lesions: 1 in right frontal and parietal lobes, 1 in left parietal lobe.

didn't meet the standard of clinical cure, and those with confirmed metastasis, or recurrent cancer. The criteria of acute cerebral infarction were in accordance with the most recent diagnostic standard revised by the American College of Cardiology (ACC) [11].

Inclusion criteria: Patients were continually included if pathologically diagnosed as breast cancer that hadn't been clinically cured, with confirmed metastasis, recurrent cancer, or abrupt symptoms of localized neurological deficit such as limb asthenia, numbness, alalia etc. Fresh lesions accounting for relevant symptoms were observed via cranial CT or MRT unenhanced and diffusion weighted imaging (DWI) scans, and confirmed as cerebral infarction changes by unenhanced MRI scan and DWI 21 d later. Patients were also included if first diagnosed with breast cancer during hospitalization and treatment for acute cerebral infarction. Exclusion criteria: Patients were excluded if breast cancer had intracranial metastasis or was complicated by other malignant tumors, hematological diseases, or cerebral hemorrhage; and also if diagnosed with cerebral infarction more than 5 years after cancer onset, without evidence of recurrence or metastasis (non-active breast cancer patients). Patients lacking adequate case records were excluded as well. Cases were selected as per the ICD-10 standard. Clinical data of breast cancer pati-

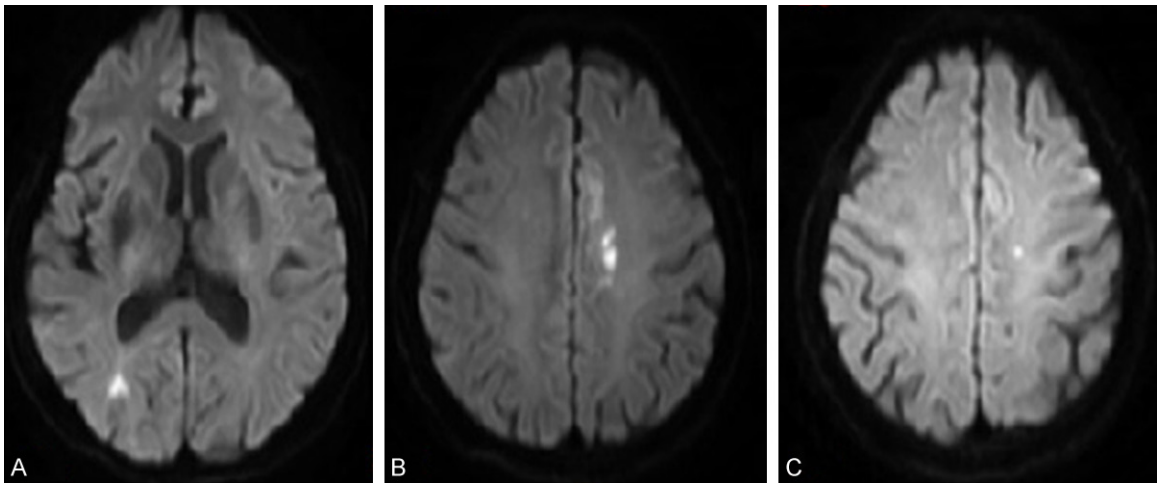

Figure 3. Cranial MRI diffusion weighted imaging (DWI) of Case 13. Multiple infarction lesions - A: 1 lesion in right occipital lobe; B: 1 lesions in left centrum semiovale; C: 1 lesion in left parietal lobe.

ents were first extracted by C50, and then the data of patients with breast cancer complicated by cerebral infarction by C50 and I63. The selection was jointly reviewed and determined by 3 experts blinded to this study and specializing in oncology, neurology and neuroimaging respectively.

Collection of clinical data

Demographic data such as age, gender etc., as well as cerebral infarction risk factors such as hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking and alcohol abuse, limb embolism history, stroke personal and family histories etc. were all collected. The severity of neurological deficit while complicated by acute cerebral infarction was assessed using the National Institutes of Health Stroke Scale (NIHSS). Thirty-day prognosis was evaluated using the modified Rankin Scale (mRS) in order to avoid the influence of breast cancer development on patient activities of daily living and functional capacity. And unfavorable prognosis was suggested if mRS ≥ 3 points. Patient data on pathological type and stage, metastasis and breast cancer therapy etc.; blood test results including routine blood test, biochemical indicator levels, erythrocyte sedimentation rate (ESR), blood coagulation activity, blood viscosity, and levels of D-dimer and other tumor markers; examination results of electrocardiogram (ECG), ultrasonic cardiogram (UCG), chest CT, neck vessels' Doppler scan, neck and cranial CT angiography (CTA), cranial CT and MRI, magnetic resonance angiography (MRA) etc. were all collected.

Results

A total of 16 patients (0.34%) with active breast cancer complicated by cerebral infarction were screened out from 4,737 patients. The selected 16 subjects were all females aged 28-65 years (49.44±11.00 years on average). There were brain stroke risk factors such as hypertension, diabetes, hyperlipidemia, cerebral artery stenosis etc. in 4 patients (25.00%), while none observed in the other 12 patients (75.00%). Cerebral infarction was found in 14 patients (87.50%) 7-180 d (average, 59.29±55.94 d; median, 40 d) after the diagnosis of breast cancer, while the other 2 patients (12.50%) were first diagnosed as breast cancer during hospitalization and treatment for acute cerebral infarction. All patients underwent acute onsets of symptoms and signs of localized neurological deficit such as alalia, limb asthenia, sensory disturbance, etc. to various extents; 1 patient developed disorder of consciousness. The NIHSS scores assessing neurological deficit ranged from 2 to 19 points (7.19±4.02 on average). Thirty days after the onset of cerebral infarction, 11 patients (68.75%) were above-moderately disabled, and 1 patient (6.25%) died from cerebral infarction. In the acute phase of cerebral infarction onset, cranial MRI DWI indicated single lesion with high-intensity signal in 6 patients (37.50%), while multiple lesions with various arterial supplies in 10 patients (62.50%, **Figures 1-3**). Cranial MRI of all patients 1 month later confirmed the changes of intracranial lesion signals were consistent with cerebral infarction, without intracranial tumor or metastasis of breast cancer

Table 1. Results on cerebral infarction

Serial number	Gender	Age (years)	Clinical manifestation	Risk factor	NIHSS score	mRS score (30 d)	Lesion count and location	Head-and-neck MRA/CTA	Time elapsed since breast cancer diagnosis
1	Female	47	Asthenia of right limbs	N	2	0	1 lesion in left centrum semiovale	N	15 d
2	Female	50	Asthenia of right limbs, hypomnesia, blurred vision	N	6	3	4 lesions, in bilateral basal ganglia, as well as left frontal, temporal and parietal lobes	N	-7 d
3	Female	58	Asthenia of right limbs, alalia, blurred vision	N	5	3	3 lesions, in bilateral parietal lobes and left basal ganglion	N	112 d
4	Female	38	Asthenia of bilateral limbs	N	5	1	7 lesions, in bilateral centrum semiovalae, left parietal lobe, and near the left posterior horn of lateral ventricle	N	7 d
5	Female	60	Asthenia, numbness and ataxia of right limbs	N	11	4	6 lesions, in bilateral occipital lobes, right cerebellum, left parietal lobe and left thalamus	N	180 d
6	Female	60	Asthenia of left limbs	Hypertension and diabetes	6	3	1 lesion in right basal ganglion	Atherosclerosis and localized stenosis of bilateral internal carotid arteries	-8 d
7	Female	61	Mental confusion, alalia, asthenia of right limbs	N	19	6	3 lesions in bilateral frontal lobes and left temporal lobe	-	60 d
8	Female	46	Asthenia and numbness of right limbs	N	4	2	1 lesion in left thalamus	N	30 d
9	Female	65	Asthenia and numbness of left limbs	Hypertension and diabetes	3	1	1 lesion in right thalamus	N	45 d
10	Female	60	Asthenia of right limbs, blurred vision	N	7	4	3 lesions in left frontal lobe, right parietal lobe, and left corona radiate	N	13 d
11	Female	40	Asthenia of right limbs, cough and hoarseness while drinking	N	10	3	3 lesions in left pons and bilateral basal ganglia	N	160 d
12	Female	56	Asthenia and numbness of right limbs	Diabetes	5	3	1 lesion in left thalamus	Atherosclerotic plaque and localized stenosis in left middle cerebral artery	90 d
13	Female	46	Asthenia of left limbs, blurred vision	N	8	3	3 lesions in left centrum semiovale, left parietal lobe, and right occipital lobe	N	50 d
14	Female	28	Asthenia of right limbs, left facial paralysis	Hyperglycemia	7	3	1 lesion in left pons	Atherosclerotic plaques and stenoses in bilateral vertebral arteries, internal carotid arteries and middle cerebral arteries	15 d
15	Female	35	Asthenia and sensory disturbance of left limbs	N	10	4	2 lesions in left frontal and parietal lobes, and right parietal lobe	N	18 d
16	Female	41	Asthenia of right limbs, blurred vision	N	7	3	2 lesions in left centrum semiovale, and right parietal lobe	N	35 d

Note: "N" for normal; "-" for unavailable test; mRS=6: Patient died; cerebral infarction lesions in long T1 and T2, high-intensity DWI signal; CTA: Cranial CT angiography; MRA: Cranial MRI angiography.

Table 2. Results on breast cancer

Serial number	Gender	Age (years)	Pathological type	TNM Stage	Metastasis	Breast cancer Relevant therapy	CA153 (U/ml)	CA125 (U/ml)	CEA (ng/ml)	D-dimer (ng/ml)
1	Female	47	Invasive ductal carcinoma	$T_1N_0M_0$ (Stage I)	No	Modified radical mastectomy, chemotherapy^{CMF}, endocrine therapy^{T}	42.10	112.74	2.70	-
2	Female	50	Invasive lobular carcinoma	$T_2N_3M_0$ (Stage IIIC)	Ipsilateral supraclavicular and infraclavicular lymph nodes	Modified radical mastectomy, chemotherapy^{CMF}, radiotherapy, endocrine therapy^{L}	143.21	6.10	15.26	2415
3	Female	58	Invasive ductal carcinoma	$T_2N_0M_0$ (Stage IIA)	No	Modified radical mastectomy, chemotherapy^{CMF}	10.17	31.20	10.08	1650
4	Female	38	Invasive ductal carcinoma	$T_2N_0M_0$ (Stage IIA)	No	Modified radical mastectomy, chemotherapy^{CMF}, endocrine therapy^{T}	34.89	342.05	21.00	1780
5	Female	60	Invasive ductal carcinoma	$T_2N_3M_0$ (Stage IIIC)	Ipsilateral supraclavicular and infraclavicular lymph nodes	Modified radical mastectomy, chemotherapy^{CMF}, radiotherapy	107.34	30.10	9.12	1246
6	Female	60	Invasive lobular carcinoma	$T_1N_0M_0$ (Stage I)	No	Modified radical mastectomy, endocrine therapy^{L}	69.05	13.15	12.57	4450
7	Female	61	Invasive ductal carcinoma	$T_2N_3M_0$ (Stage IIIC)	Ipsilateral axillary and supra-clavicular lymph nodes	Modified radical mastectomy, chemotherapy^{TAC}, radiotherapy	312.58	561.43	11.69	1340
8	Female	46	Intraductal carcinoma	$TisN_0M_0$ (Stage 0)	No	Segmental mastectomy	28.09	10.02	11.31	-
9	Female	65	Intraductal carcinoma	$TisN_0M_0$ (Stage 0)	No	Segmental mastectomy	16.45	4.90	1.54	974
10	Female	60	Invasive ductal carcinoma	$T_2N_0M_1$ (Stage IV)	Sternum	Chemotherapy^{TAC}	186.09	747.56	31.25	5888
11	Female	40	Invasive ductal carcinoma	$T_1N_0M_0$ (Stage I)	No	Modified radical mastectomy, chemotherapy^{CMF}, endocrine therapy^{T}	21.24	45.06	3.74	1644
12	Female	56	Invasive ductal carcinoma	$T_2N_0M_1$ (Stage IV)	Sternum	Chemotherapy^{TAC}	214.64	898.05	28.56	1700
13	Female	46	Invasive ductal carcinoma	$T_2N_0M_0$ (Stage IIA)	No	Modified radical mastectomy, chemotherapy^{CMF}	24.65	38.70	8.87	2996
14	Female	28	Intraductal carcinoma	$TisN_0M_0$ (Stage 0)	No	Segmental mastectomy	19.52	13.20	5.64	3320
15	Female	35	Invasive ductal carcinoma	$T_2N_3M_0$ (Stage IIIC)	Ipsilateral supraclavicular lymph nodes	Modified radical mastectomy, chemotherapy^{TAC}, radiotherapy, endocrine therapy^{T}	456.23	264.34	27.98	-
16	Female	41	Invasive ductal carcinoma	$T_2N_0M_0$ (Stage IIA)	No	Modified radical mastectomy, chemotherapy^{CMF}, endocrine therapy^{T}	50.80	58.13	19.37	6655

Note: "-" for unavailable test; D-dimer normal reference value, 0-450 ng/mL; CA, cancer antigen; CA153 normal reference value, 0.00-25.00 U/ml; CA125 normal reference value, 0.00-35.00 U/ml; Carcino-embryonic antigen (CEA) normal reference value, 0.00-10.00 ng/mL; TNM Stage, the internationally applied classification system of malignant tumors; T, Primary tumor; N, Lymph node metastasis; M, Distant metastasis; chemotherapy^{CMF}, cyclophosphamide, methotrexate and fluorouracil; chemotherapy^{TAC}, docetaxel, pirarubicin and cyclophosphamide; ^{T}, Tamoxifen; ^{L}, Letrozole.

(**Table 1**). Among the 16 patients, 11 (68.75%) were identified as invasive ductal carcinoma, 2 (12.50%) as invasive lobular carcinoma, and 3 (18.75%) as intraductal carcinoma. Metastasis was confirmed in 6 patients (37.50%), including 2 with ipsilateral supraclavicular and infraclavicular lymphatic metastases, 1 with ipsilateral metastases in axillary and supraclavicular lymph nodes, 1 with ipsilateral metastases in supraclavicular lymph nodes, and 2 with sternum metastasis. As per breast cancer stages, there were 3 patients (18.75%) in Stage 0 subgroup, 3 patients (18.75%) in Stage I, 4 patients (25.00%) in Stage II, 4 patients (25.00%) in Stage III, and 2 patients (12.50%) in Stage IV. Surgical treatment was adopted in 14 patients, while chemotherapy, endocrine therapy and radiotherapy in 12, 7 and 5 patients respectively. Peripheral serum examination on biochemical indicators revealed elevated levels of D-dimer, cancer antigen 153 (CA-153), CA125 and carcino-embryonic antigen (CEA) in 13, 11, 9 and 10 patients respectively (**Table 2**).

Discussion

Cancer condition may add up to the risk of developing cerebral infarction, and a certain pattern exists in the onset of cerebral infarction among cancer patients. According to the 1987-2008 national cancer censoring results reported by Swedish scholar Zöller et al. in 2012, the incidence of cerebral infarction within 6 months since the diagnosis of cancer is 1.6%, the incidence of cerebral infarction within 6-12 months is 1.1%, and the incidence of cerebral infarction during 1 to 5 years is 1.1%. Those findings suggest that cancer may significantly increase the risk of cerebral infarction, and the onset of the latter is also as per a certain pattern of time. As in this study, the incidence of cerebral infarction was 0.34% among the hospitalized patients with active breast cancer, suggesting cerebral infarction might be one of the common complications, which took place within the latter half of a year after breast cancer diagnosis in such patients. Therefore, there was a certain time pattern with regard to the occurrence of breast cancer complicated by cerebral infarction.

Compared with normal population, an apparent clinical concern is on the very possibility of different characteristics of cerebral infarction among cancer patients. To address such a concern in 2014, Kim et al. [3] analyzed the clinical data of all the patients with acute cerebral infarction treated by the Pusan General Hospital in the Republic of Korea from January 2003 to December 2012. Active cancer complicated by cerebral infarction was found in 156 patients. And when compared with cerebral infarction without cancer, cancer patients with the complication of cerebral infarction usually lacked conventional brain stroke risk factors, and partial patients had elevated levels of plasma fibrinogen, C-reactive protein (CRP) and D-dimer, as well as multiple intracranial lesions of infarction with various arterial supplies. Also in 2014, another Korean study conducted by Lee et al. [4] discovered that the clinical characteristics of cancer complicated by cerebral infarction included lacking conventional stroke risk or pathogenic factors, elevated level of plasma D-dimer, and multiple intracranial lesions with various arterial supplies in a single infarction onset. In this study, there were also the characteristics of lacking conventional stroke risk factors, elevated D-dimer level and multiple intracranial lesions with various arterial supplies in a single infarction onset etc. among most patients with breast cancer complicated by cerebral infarction. Moreover, significantly elevated levels of CA153, CA125 and CEA were observed as well, suggesting that like other types of cancer complicated by cerebral infarction, breast cancer with cerebral infarction also had its own characteristics.

Additionally, 2 patients in this study had been diagnosed as breast cancer during hospitalization and treatment for acute cerebral infarction. Cerebral infarction may be the first clinical manifestation of pancreatic cancer, adenocarcinomas of the lung, the ovary, and the biliary duct etc. [12-14]; and as revealed by this study, partial breast cancer patients might also share this characteristic. Therefore, cancer tests are necessary for patients with cerebral infarction that are not accounted for.

The pathogenesis of how cancer leads to cerebral infarction is worth more in-depth study. There were two kinds of patients per the results of this study-patients with conventional brain stroke risk factors and single intracranial infarction lesion, as well as those without conventional stroke risk factors but with multiple lesions under various arterial supplies in a single onset

of cerebral infarction. The pathogenesis of the former might be the same or resemble that of conventional cerebral infarction, while cerebral infarction in the latter is probably related to breast cancer. Several studies have indicated elevations in the level of plasma D-dimer, suggesting that cancer may lead to cerebral infarction via altering patients' blood coagulability [3, 4]. To make this clearer, in the study of Seok et al. [15] on cancer complicated by cerebral infarction, transcranial Doppler (TCD) is used to spot microthrombi in bilateral carotid arteries. As a result, more microthrombus signals are found in carotid arteries among patients without conventional stroke risk factors but with elevated D-dimer level and multiple cerebral infarction lesions, which more directly suggests that cancer may change the coagulative state in patients to bring about microthrombosis, and eventually cerebral infarction. Jovin et al. [16] study the relationship between CA125 and cerebral infarction and find that CA125 levels significantly increase in patients with cancer complicated by cerebral infarction. Hypercoagulability is also present in such patients, suggesting CA125 with its mucoprotein characteristic may lead to the hypercoagulable state which can be related to the pathogenesis of cerebral infarction in cancer patients. In this study, most patients had significantly increased levels of D-dimer, CA153, CEA and CA125, as well as multiple cerebral infarction lesions under various arterial supplies. These blood test abnormalities might be also related to the incidence of cerebral infarction in cancer patients. Recent studies pointed out that breast cancer treatment may increase the chance to develop cerebral infarction [8, 9]. Moreover, cancer may also result in cerebral infarction through invading adjacent vessels and causing non-bacterial thrombotic endocarditis (NBTE) etc. [17, 18].

There's no applicable prevention or treatment for breast cancer complicated by cerebral infarction at the present time since the pathogenesis remains unclear. However, the latest studies have indicated that thrombotic event is a common complication in cancer patients [19, 20], and preventive antiplatelet and anticoagulant medications may effectively reduce the incidence of such thrombotic events [21, 22]. According to Suenaga et al.'s study on microthrombus Doppler detection [23], the use of warfarin may significantly reduce signals of deep vein thrombosis (DVT) in cancer patients. Seok et al. [13] have also reported similar findings in their study on Doppler detection of microthrombi in carotid arteries among cancer patients. Therefore, based on the studies above, preventive antiplatelet and anticoagulant medications may reduce the incidence of cerebral infarction in cancer patients though such conclusion needs to be further verified through more researches. Recently accomplished retrospective research has also found that the thrombolytic therapy via the use of recombinant tissue plasminogen activator (rt-PA) is both safe and effective in patients with malignant tumor-related cerebral infarction [24-26], suggesting positive significance in exploring prognostic improvement for patients with cancer complicated by cerebral infarction.

There are several limitations of this study mainly due to its retrospective nature, relatively smaller sample size, and patient data during hospitalization restricted by specific necessities of clinical diagnosis. Future prospective multicenter studies targeting community populations are needed to further elucidate the clinical characteristics and pathogenesis of breast cancer-related cerebral infarction.

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Disclosure of conflict of interest

None.

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