Hyperlipidemia as a risk factor for Trousseau syndrome-related cerebral infarction in patients with advanced gastrointestinal cancer

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Received December 27, 2021; Accepted June 15, 2022

DOI: 10.3892/ol.2022.13437

Abstract. Trousseau syndrome-related cerebral infarction rarely occurs during chemotherapy in patients with gastrointestinal (GI) cancer, and its clinical features remain unclear. The present study aimed to examine the clinical features of Trousseau syndrome-related cerebral infarction developed during chemotherapy for GI cancer. The present retrospective cohort study consecutively enrolled 878 patients with unresectable GI cancer who received chemotherapy at the Multidisciplinary Treatment Cancer Center, Kurume University Hospital (Kurume, Japan) between April 2014 and March 2020. Patients with colorectal cancer (n=308) were the most common, followed by those with pancreatic (n=242), gastric (n=222) and biliary tract (n=59) cancer, neuroendocrine tumors (n=34) and duodenal cancer (n=11). Among the 878 patients, Trousseau syndrome-related cerebral infarction occurred in 8 (0.9%) patients with a median age of 70.5 years (range, 58-75 years), and 50% of the patients were male (4/8). In total, 3 patients had gastric cancer, 3 had pancreatic cancer and 2 had biliary tract cancer. A greater percentage of patients with Trousseau syndrome-related cerebral infarction had hyperlipidemia (38.0%) than those without (8.2%; P=0.005). Hyperlipidemia was a risk factor for occurrence of Trousseau syndrome-related cerebral infarction with an odds ratio of 7.009 (95% confidence interval, 1.785-27.513). Trousseau syndrome-related cerebral infarction developed during GI chemotherapy was rare and hyperlipidemia may predict its onset.

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Key words: cerebral infarction, Trousseau syndrome, hyperlipidemia

Introduction

An association between malignancies and venous thromboembolism (VTE) was first reported by the French physician Armand Trousseau in 1865 (1). Since its identification, the combination of cancer and conditions of hypercoagulation is often termed Trousseau syndrome (cancer-associated thrombosis). Cancer-associated thrombosis, including deep vein thrombosis (DVT), pulmonary embolism and visceral thrombosis, are classified as VTE (2). VTE is a frequent and burdensome complication in patients with active cancer, and its estimated overall 12-month incidence rate is 6-8% (3,4). Risk factors for VTE in these patients include patient-related factors such as obesity, lying down for too long, primary cancer site, staging, comorbidities and histopathological subclass, as well as treatment-related factors such as surgery, chemotherapy, molecular targeted agents and central venous catheter placement (5-7). Trousseau syndrome-related cerebral infarction is a relatively rare complication of malignant disease compared with those related to DVT or pulmonary embolism; however, its prognosis is markedly poor (median survival, 4.5 months from diagnosis) (2,3,8). The mechanisms underlying stroke due to Trousseau syndrome include hypercoagulopathy, disseminated intravascular coagulation (DIC), nonbacterial thrombotic endocarditis and production of tissue factors (9,10).

In a previous study of 3,426 autopsy cases of malignant tumors conducted in 1985, 14.6% of cases had combined cerebrovascular accidents, of which 51% had cerebral infarction and 49% had cerebral hemorrhage (11). Malignant tumors and thromboembolism have been reported to be strongly associated with mortality, and thromboembolism has been reported as the second leading cause of mortality in patients with malignant tumors (5,12,13). It is known that, in patients with Trousseau syndrome, those with cerebral infarction have

a higher mortality rate than those with only VTE, and treatment and prevention of cerebral infarction reduce mortality and improve patient quality of life (6,14,15). However, effective treatment methods and predictors of its onset have not been established. It is important to understand these clinical features, since thrombosis associated with cancer is not just an accidental complication but also a major cause of morbidity and mortality directly associated with malignancy (15).

A large-scale epidemiological study demonstrated that patients with brain tumors, hematological malignancies and adenocarcinomas of the lung, pancreas, stomach and ovary are at a markedly high risk of developing VTE; however, the actual prevalence of Trousseau syndrome has not been clarified thus far (16). Few reports have examined the clinical features of Trousseau syndrome-related cerebral infarction developed during chemotherapy in patients with ovarian, pancreatic and colorectal cancers (17-21); however, the information on patients with gastrointestinal (GI) cancer is limited.

The present study aimed to investigate the prevalence and detailed clinical features of patients with Trousseau syndrome who developed cerebral infarction during chemotherapy for GI cancer. In addition, the current study investigated the factors associated with the occurrence of Trousseau syndrome-related cerebral infarction under chemotherapy.

Materials and methods

Patients. The present retrospective study consecutively enrolled 878 patients with unresectable pathologically-diagnosed GI cancer who received chemotherapy at the Multidisciplinary Treatment Cancer Center of Kurume University Hospital (Kurume, Japan) between April 2014 and March 2020. Patients (aged ≥18 years) were eligible if they had histologically confirmed advanced gastrointestinal cancer (colorectal cancer, pancreatic cancer, gastric cancer, biliary tract cancer, neuroendocrine tumor, duodenal cancer) and a performance status of 0-2. Patients were excluded if they had a perfromance status of 3 and multiple cancers. The following data were collected from medical charts and reviewed: Age, sex, performance status, type of comorbid malignancies, cancer stage [according to the 8th edition of the Union for International Cancer Control (UICC) TNM classification] (22), risk factors for cerebrovascular accident, number of days from onset of cerebral infarction to mortality, serum C-reactive protein (CRP), carcinoembryonic antigen (CEA), carbohydrate antigen (CA)19-9, treatment method and outcome. Risk factors for cerebrovascular accidents, including diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease (CKD), Khorana VTE risk score and DIC score, were evaluated. Serum markers (CRP, CEA, CA19-9) and risk factors (diabetes, hypertension, hyperlipidemia, CKD, performance status, Khorana VTE risk score) at the time of initiating chemotherapy were evaluated. DIC score were evaluated at the time of Trousseau syndrome-related cerebral infarction.

Definition of diabetes mellitus, hypertension, hyperlipidemia, CKD, Khorana VTE risk score and DIC score. Subjects were confirmed to have diabetes mellitus if they had fasting plasma glucose ≥126 mg/dl and hemoglobin A1c ≥6.5% (23). Hypertension was regarded as present if a patient had a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg (24). Hyperlipidemia was defined as present if the serum triglyceride levels were ≥240 mg/dl and/or the serum low-density lipoprotein cholesterol level was ≥160 mg/dl (25). Subjects were defined as patients with CKD if they had CKD stage ≥3 (26). The serum D-dimer level measured within 48 h from the diagnosis of cerebral infarction was used to evaluate blood coagulability. The risk of VTE was evaluated using the Khorana VTE risk score (0 points, low risk; 1-2 points, moderate risk; and 3 points, high risk) (12). The diagnosis for DIC was based on the Japanese Association for Acute Medicine DIC diagnostic criteria (0-3 points, not DIC; 4-8 points, DIC) (27).

Definition of Trousseau syndrome-related cerebral infarction. Patients who presented with acute cerebral infarction on brain magnetic resonance imaging (MRI) with neurological symptoms were further diagnosed with cerebral infarction by neurology specialists, and were diagnosed with Trousseau syndrome-related cerebral infarction.

Statistical analysis. Data are presented as the median (range) or n (%). Each parameter was compared between patients without Trousseau syndrome-related cerebral infarction groups and patients with Trousseau syndrome-related cerebral infarction groups using the Fisher's exact test or categorical variables and Mann-Whitney U-test for continuous variables. Firth's logistic regression was performed to assess the association between Trousseau syndrome-related cerebral infarction and possible risk factors, and to reduce biases of ordinal logistic regression in the analysis of rare events such as Trousseau syndrome-related cerebral infarction (28). $P<0.05$ was considered to indicate a statistically significant difference. Data analysis was performed using JMP Pro version 15.0 and SAS9.4 (both from SAS Institute, Inc.).

Results

Baseline patient characteristics. Of the 878 patients, 39% were female (341/878). The median age was 67 years (range, 23-86 years). Colorectal cancer (35%; 308/878) was the most common malignancy, followed by pancreatic (28%; 242/878), gastric (25%; 222/878) and biliary tract (7%; 61/878) cancer, as well as neuroendocrine tumors (4%; 34/878) and duodenal cancer (1.3%; 11/878) (Table I). The majority of patients in the study had a performance status of 0 and 89 patients had a performance status of 1 (Table I). Only 0.9% (8/878) of the patients developed Trousseau syndrome-related cerebral infarction during chemotherapy. There were no significant differences in age or sex between patients with and without Trousseau syndrome-related cerebral infarction. In all patients who developed Trousseau syndrome-related cerebral infarction, the tumor stage was IV (8th edition of the UICC TNM classification). According to their cancer type, Trousseau syndrome-related cerebral infarction occurred in 3.28% (2/61) of patients with biliary tract cancer, 1.35% (3/222) of patients with gastric cancer and 1.24% (3/242) of patients with pancreatic cancer. By contrast, no patients with colorectal cancer or neuroendocrine tumors were diagnosed with Trousseau syndrome-related cerebral infarction (Table I).

Table I. Baseline clinical characteristics of the patients (n=878).

Characteristic	Total	Patients without Trousseau syndrome-related cerebral infarction (n=870)	Patients with Trousseau syndrome-related cerebral infarction (n=8)	P-value
Age, years	67 (23-86)	67 (23-86)	70.5 (58-75)	0.64
Sex female/male	341 (39)/537 (61)	337 (39)/533 (61)	4 (50)/4 (50)	0.72
Performance status 0/1/2	789 (90)/89 (10)/0 (0)	781 (90)/89 (10)/0 (0)	8 (100)/0(0)/0 (0)	>0.99
Type of cancer and staging[a]				
Colorectal cancer	308 (35)	308 (35)	0 (0)	0.06
Stage IIA/IIIA/IIIB/IVA/IVB	1/11/8/204/73	1/11/8/204/73	0/0/0/0/0	
Pancreatic cancer	242 (28)	239 (27)	3 (38)	0.69
Stage III/IV	52/190	52/187	0/3	
Gastric cancer	222 (25)	219 (25)	3 (38)	0.42
Stage IIIA/IIIB/IIIC/IV	2/1/5/214	2/1/5/211	0/0/0/3	
Biliary tract cancer	61 (7)	59 (7)	2 (25)	0.10
Stage IV/other	61/0	59/0	2/0	
Neuroendocrine tumor	34 (4)	34 (4)	0 (0)	>0.99
GIST/NET/NEC	7/17/10	7/17/10	0/0/0	
Duodenal cancer	11 (1.3)	11 (1.3)	0 (0)	>0.99
Stage IV/other	11/0	11/0	0/0	

Values are expressed as the median (range), n or n (%). [a]8th Edition of the Union for International Cancer Control TNM classification. GIST, gastrointestinal stromal tumor; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma.

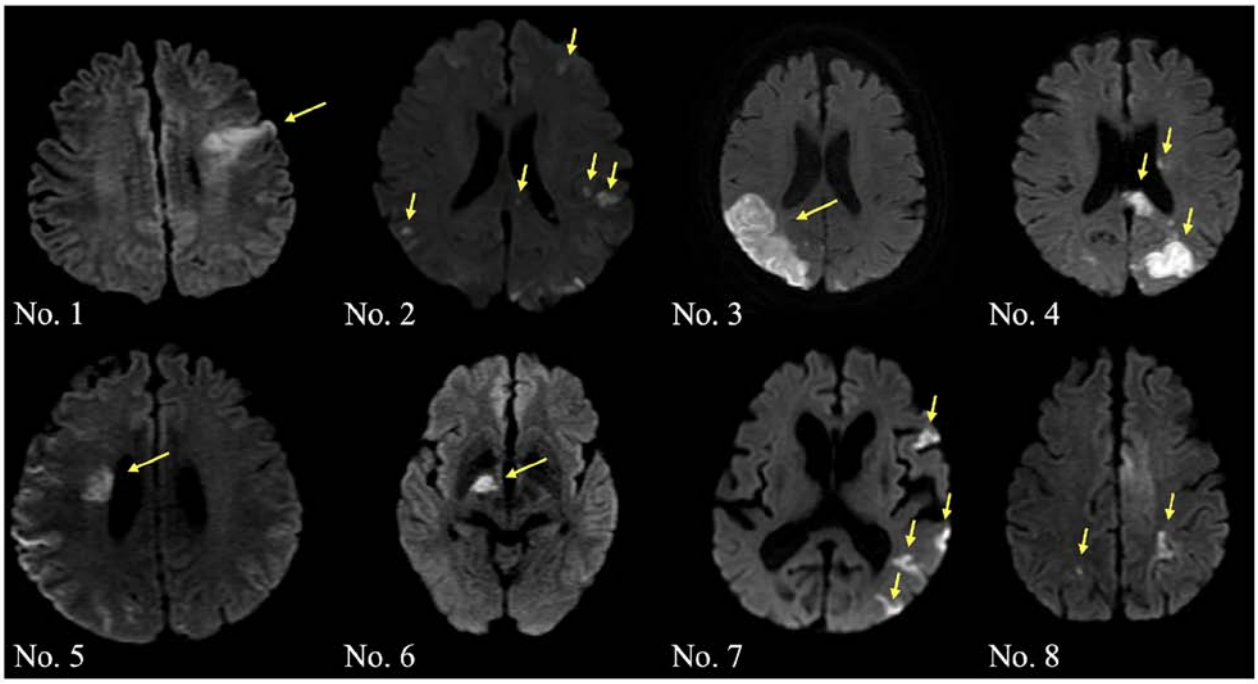

Figure 1. Diffusion-weighted image for each patient. Cases 1, 3, 5 and 6 showed a single lesion of cerebral fraction, while cases 2, 4, 7 and 8 showed multiple lesions of cerebral fraction. Arrows represent the infarction lesions.

Symptoms and radiographic findings of cerebral infarction in patients with Trousseau syndrome-related cerebral infarction. The cerebral infarction lesions detected by MRI of the brain (diffusion-weighted image) were as follows: Single lesion in one vascular territory infarction in 4 cases (cases 1, 3, 5 and 6) and multiple infarctions in 4 cases (cases 2, 4, 7 and 8) (Fig. 1). Neurological symptoms at onset were as follows: Disorientation in 5 cases, hemiparesis in 3 cases, dysarthria in 3 cases and loss of consciousness in 1 case.

Table II. Clinical characteristics of patients with Trousseau syndrome-related cerebral infarction.

Case no.	Age, years	Sex	Performance status	Primary cancer site	Metastatic lesions	Histopathological diagnosis	D-dimer, μg/ml	Duration from onset to diagnosis, days	DIC score	Acute-phase treatment for cerebral infarction	Chemotherapy regimen
1	64	F	0	Gastric cancer	Peritoneum	Poorly differentiated adenocarcinoma	19.4	1	1	Edaravone	Nivolumab (3rd line)
2	58	M	0	Gastric cancer	Liver	Tubular adenocarcinoma	10.5	2	1	Heparin	S1 + CDDP (1st line)
3	75	M	0	Gastric cancer	Liver	Poorly differentiated adenocarcinoma	1.3	3	0	Heparin	S1 + CDDP (1st line)
4	71	F	0	Pancreatic cancer	Peritoneum	Adenocarcinoma	0.1	3	4	Edaravone	GEM + Nab-PTX (1st line)
5	72	F	0	Pancreatic cancer	Liver	Adenocarcinoma	28.4	1	6	Thrombectomy	GEM (2nd line)
6	70	F	0	Pancreatic cancer	Liver	Adenocarcinoma	5.5	7	4	Anti-platelet drug	GEM + Nab-PTX (1st line)
7	74	M	0	Biliary tract cancer	Liver	Adenocarcinoma	4.3	4	1	Anti-platelet drug	GEM + CDDP (1st line)
8	63	M	0	Biliary tract cancer	Liver	Adenocarcinoma	1.3	7	3	Heparin	GEM + CDDP (1st line)

F, female; M, male; CDDP, cisplatin; GEM, gemcitabine; PTX, paclitaxel; Nab-PTX, nanoparticle albmin-bound-paclitaxel; S1, tegafur/gimeracil/oteracil; DIC, disseminated intravascular coagulation.

Figure 2. Clinical course for each patient. ♦, initiation of treatment for cerebral fraction; §, point of Trousseau syndrome-related cerebral infarction recurrence (no. 8); †, deceased.

Clinical characteristics of patients with Trousseau syndrome-related cerebral infarction. The clinical characteristics of the patients with Trousseau syndrome-related cerebral infarction are summarized in Table II. Among the 8 patients who developed Trousseau syndrome-related cerebral infarction, the median age was 70.5 years (range, 58-75 years), and 50% were females. Although the histological differentiation of the different malignancies was not the same, all cases were adenocarcinoma. In almost all patients (87.5%; 7/8), elevated serum D-dimer levels were observed (median serum D-dimer level, 8.925 μg/ml; normal range, <1.0 μg/ml) at disease onset. Metastatic lesions were found in the liver in 6 cases and in the peritoneum in 2 cases (Table II). There were no patients with lung and/or brain metastases. In total, 3 cases (37.5%) were diagnosed with DIC at onset (Table II). Notably, all these characteristics were observed in patients with pancreatic cancer (Table II). The line of therapy at the time of onset was as follows: A total of 6 cases (75.0%) were on first-line chemotherapy, 1 case (12.5%) was on second-line chemotherapy and 1 case (12.5%) was on third-line chemotherapy (Table II). In total, 5 patients underwent a chemotherapy regimen using gemcitabine, while 4 patients underwent chemotherapy using cisplatin. As acute-phase treatment for cerebral infarction, 3 cases were treated with heparin, 2 with anti-platelet drugs, 2 with edaravone (a free radical scavenger) and 1 with thrombectomy (Table II).

Clinical course of each patient with Trousseau syndrome-related cerebral infarction. In the 8 patients who developed Trousseau syndrome-related cerebral infarction, the median time from the initiation of chemotherapy to onset of Trousseau syndrome-related cerebral infarction diagnosis was 59.5 days (range, 7-263 days), and 62.5% (5/8) of these patients were diagnosed within 60 days (Fig. 2). In addition, the median survival time after Trousseau syndrome-related cerebral infarction occurrence was 17.5 days (range, 5-455 days), and 62.5% (5/8) of these patients succumbed to disease within 20 days (Fig. 2). By contrast, long-term survival, defined as >120 days after Trousseau syndrome-related cerebral infarction diagnosis, was observed in 3 cases (cases 6, 7 and 8). The median time from onset to diagnosis, which was the same as the initiation of treatment, was 3 days (range, 1-7 days). Cases 6 and 7 were able to continue chemotherapy without

Table III. Risk factors for Trousseau syndrome-related cerebral infarction.

Risk factor	Patients without Trousseau syndrome-related cerebral infarction (n=870)	Patients with Trousseau syndrome-related cerebral infarction (n=8)	Odds ratio	95% CI	P-value
Hypertension	214 (24)	1 (13)	0.612	0.105-3.570	0.585
Hyperlipidemia	72 (8.2)	3 (38)	7.009	1.785-27.513	0.005
Chronic kidney disease	31 (3.6)	0 (0)	1.568	0.085-29.005	0.763
Diabetes	158 (18)	2 (25)	1.726	0.396-7.527	0.467
Performance status >1	89 (10)	0 (0)	0.514	0.029-9.112	0.650
Khorana VTE risk score					
Low	300 (34)	2 (25)	1.000	Ref.	Ref.
Intermediate	433 (50)	4 (50)	1.248	0.263-5.910	0.796
High	137 (16)	2 (25)	2.185	0.373-12.821	0.373
CRP >0.3 mg/dl	440 (51)	4 (50)	0.977	0.262-3.639	0.973
CEA >5 ng/ml	473 (56)	4 (50)	0.795	0.213-2.962	0.733
CA19-9 >37.0 ng/ml	416 (49)	5 (63)	1.620	0.421-6.241	0.483

Values are expressed as n (%). VTE, venous thromboembolism; CRP, C-reactive protein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CI, confidence interval.

sequelae, and survived for 455 and 136 days, respectively. Case 8 resumed chemotherapy upon recovering from a stroke; however, the patient had a recurrence of a stroke associated with Trousseau syndrome 5 months later (Fig. 2).

Association between risk factors and Trousseau syndrome-related cerebral infarction. The associations between risk factors and their occurrence were assessed to explore the predictive factors for Trousseau syndrome-related cerebral infarction development. The prevalence of hyperlipidemia in patients with Trousseau syndrome-related cerebral infarction (38%; 3/8) was significantly higher than that in patients without Trousseau syndrome-related cerebral infarction (8.2%; 72/870; P=0.005) (Table III). Hyperlipidemia was found to be a risk factor for occurrence of Trousseau syndrome-related cerebral infarction with an odds ratio of 7.009 [95% confidence interval (CI), 1.785-27.513] (Table III). By contrast, there were no significant differences between the groups for other factors, including prevalence of hypertension, CKD, diabetes mellitus, performance status, Khorana VTE risk score, serum CRP, and serum tumor markers such as CEA and CA19-9 (Table III).

Discussion

A recent population-based study of patients with different cancer types showed that the standardized mortality ratio of fatal stroke, including cerebral infarction, was 2.17 (95% CI, 2.15-3.21). The highest ratio was observed in patients with brain or GI cancer (29). In addition, it has also been reported that cancer treatment options, including chemotherapy and molecular-targeted therapy, aggravate the risk of stroke (29). In the present study, which analyzed 878 patients with unresectable GI cancer on chemotherapy, only 0.9% of patients developed Trousseau syndrome-related cerebral infarction. Notably, of the 308 cases of colorectal cancer, none of the patients were diagnosed with Trousseau syndrome-related cerebral infarction. However, its occurrence rate has been reported to be 10-12% in patients with this malignancy (21). In the present study, the occurrence rate of Trousseau syndrome-related cerebral infarction developed during chemotherapy was 1.24, 1.35 and 3.28% in patients with pancreatic, gastric and biliary tract cancer, respectively. Previous studies have reported an occurrence rate of 6-8% in patients with pancreatic cancer and of 4-6% in patients with gastric cancer (19,20). The majority of patients examined in the present study had a good general condition, with a performance status of 0 and a low Khorana VTE score, suggesting that the risk of thrombosis may have been lower than previously reported (19,20). Furthermore, the current study did not include cases with Trousseau syndrome-related cerebral infarction before diagnosis of cancer, which likely led to the observed differences in prevalence rates. Therefore, including various cancer stages in the evaluation of prospective trials is desirable.

In the present study, common risk factors for cerebral infarction, including hypertension, CKD and diabetes mellitus, were not associated with the development of Trousseau syndrome-related cerebral infarction. Consistent with a previous study in which hyperlipidemia was an independent predictor of cerebrovascular events such as stroke (30), only hyperlipidemia was detected as a predictive factor for Trousseau syndrome-related cerebral infarction in the present study. It has been demonstrated that hyperlipidemia induces endothelial dysfunction and oxidative stress, leading to endothelial damage, resulting in an increased risk of thromboembolism (31). Furthermore, lowering cholesterol is important to prevent cerebral infarction in patients with hyperlipidemia (31). Lowering cholesterol in patients with cancer may also be important for preventing the development of Trousseau syndrome-related cerebral infarction. Adenocarcinomas that secrete mucus are one of the risk factors for Trousseau

syndrome (32). Since mucin-related tumor markers such as CA19-9, CA125 and CA15-3 are considered to trigger thrombotic events, particularly in ovarian cancer (31), the serum levels of CA19-9 and CEA were assessed in the current study. However, these tumor markers were not found to be predictive factors for the occurrence of Trousseau syndrome-related cerebral infarction.

Cancer may mediate the pathophysiology of stroke either directly or via coagulation disorders and infections (33). D-dimer, a degradation product of fibrin thrombus produced by the action of thrombin, activated factor XIII and plasmin, is known to be a highly sensitive index for thrombosis (34). D-dimer is also nonspecifically elevated in various conditions, including DVT, pregnancy, DIC and aortic dissection (35). Trousseau syndrome, which is caused by cancer-related hypercoagulability, has been reported to present with higher D-dimer values than accidental cerebral infarction not associated with hypercoagulability, and is often accompanied by DIC (12,36). Consistent with a previous study reporting that solid tumors, particularly hepatocellular carcinoma, lung cancer and pancreatic cancer, are more likely to cause DIC, all cases diagnosed with DIC at the onset of Trousseau syndrome in the present study were cases of pancreatic cancer (37). Recently, it has been reported that D-dimer and CRP are potential biomarkers for diagnosing Trousseau syndrome in patients with cerebral embolism (38). Consistent with the previous report, the serum D-dimer levels in almost all patients (87.5%; 7/8) with Trousseau syndrome-related cerebral infarction in the present study were elevated. However, not all patients were evaluated for serum D-dimer levels, and D-dimer levels could not be evaluated as predictors in the current study. In addition, serum CRP levels were not significantly different between the group with Trousseau syndrome-related cerebral infarction and the group without Trousseau syndrome-related cerebral infarction. Although it depends on the histopathological subclass and primary cancer site, the incidence rate of cancer-related VTE has been reported to be 6-8% (3,4). According to the Khorana VTE score, which was introduced in 2008 to stratify the risk of VTE and select cases requiring therapeutic intervention (12,39), the incidence of VTE was 5.7% in the low-risk group, 8.6% in the medium-risk group and 14% in the high-risk group, showing a positive association between the Khorana VTE score and the incidence of VTE (40). By contrast, the Khorana VTE score could not be used as a predictor in the present study. It is known that malignant cells activate coagulation through multiple mechanisms such as tissue factor production and inflammatory cytokines (41). Tissue factor is one of the principal initiators of the extrinsic coagulation cascade and directly converts factor VII to factor VIIa (42). Furthermore, inflammatory cytokines can also promote the coagulation cascade by inducing tissue factors from vascular cells, monocytes and macrophages (41).

In the current retrospective study, almost all patients who developed Trousseau syndrome-related cerebral infarction underwent chemotherapy with gemcitabine and/or cisplatin. Gemcitabine is a widely used anticancer drug for patients with different types of cancer, including pancreatic, biliary tract and lung cancer (43). Several case reports have demonstrated the occurrence of Trousseau syndrome under chemotherapy using gemcitabine (44,45). A previous study revealed that gemcitabine kills proliferating endothelial cells by activating acid sphingomyelinase (46). Cisplatin is also a widely approved anticancer drug for patients with different types of cancer, including gastric, lung and ovarian cancer (47). *In vitro* examination using human endothelial cells revealed that exposure to cisplatin upregulated the production of inflammatory proteins, which were assumed to initiate vascular inflammation and endothelial dysfunction (48). It was suggested that these drugs may damage endothelial cells, resulting in an increased risk of thromboembolism.

It has been reported that infarcts involving multiple vascular areas detected by diffusion-weighted imaging are highly sensitive to Trousseau syndrome-related cerebral infarction (18). A previous study that assessed the radiological features of 31 patients with Trousseau syndrome-related cerebral infarction showed that multiple lesions in multiple vascular territories were the most frequent pattern (87.1%; 27/31) (36). By contrast, only 50% of the patients in the present study exhibited this feature. Due to the small number of cases, further research on patterns of cerebral infarction in patients with GI cancer in a large number of patients is needed.

In patients with Trousseau syndrome-related cerebral infarction, the median survival time has been reported to be 4.5 months, with 25% of patients succumbing to the disease within 30 days (8). Consistent with this report, the prognoses of the patients in the present study were remarkably poor, and 62.5% (5/8) of them succumbed to the disease within 20 days. Only 2 patients were able to continue chemotherapy without sequelae. Notably, 62.5% (5/8) and 87.5% (7/8) of these patients developed cerebral infarction within 60 and 110 days, respectively. These results indicated that Trousseau syndrome-related cerebral infarction may develop soon after the initiation of chemotherapy. Heparin, a standard treatment for Trousseau syndrome-related cerebral infarction, is preferred over oral anticoagulants (4). In the physiology of Trousseau syndrome, warfarin potassium is considered ineffective due to the suggested presence of vitamin K-independent coagulation abnormalities (49). In a study regarding the efficacy of direct oral anticoagulants, it was reported that dabigatran was not effective in suppressing the recurrence of Trousseau syndrome-related cerebral infarction (50). Case accumulation is desired for optimal management and long-term survival of patients with Trousseau syndrome-related cerebral infarction.

To the best of our knowledge, the present study was the first to reveal the prevalence and clinical features of Trousseau syndrome-related cerebral infarction in patients with unresectable GI cancer. However, the current study has several limitations. In total, >800 patients with unresectable GI cancer who received chemotherapy were assessed. The prevalence of Trousseau syndrome-related cerebral infarction was calculated, and the risk factors associated with its occurrence were evaluated. However, the number of cases in the Trousseau syndrome-related cerebral infarction group was small, which may have led to bias in the results. Therefore, a future study with a large number of cases is required. In the present retrospective study, DVT was not confirmed on transesophageal echocardiography prior to chemotherapy. Furthermore, the smoking status (which is known to be strongly associated with stroke), such as current or never smokers, could not be evaluated. In addition, D-dimer was not determined in all of

the patients. Therefore, clinical trials that address these issues require to be performed in the future.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

ToT and HS conceived the study and wrote the manuscript. KM, HK, YA and TaT made substantial contributions to the conception and design of the study. TU, SN, MF, KI, TN, HI, AM and TS collected the clinical data and were involved in the raw data analysis. KM was involved in the raw data statistical analysis and revised the manuscript. All authors discussed the results and contributed to the final manuscript. ToT, HS and KM confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki, and was reviewed and approved by the Ethics Committee of Kurume University School of Medicine (Kurume, Japan; approval no. 21166). Written informed consent was obtained from all patients regarding treatment; however, the requirement for patient consent for participation in the study was waived due to the retrospective design of the current study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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