

Acute Cerebral Infarction during Combination Chemotherapy with S-1 and Cisplatin for a Young Patient with a Mucin-Producing Adenocarcinoma of the Stomach

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Abstract

We report a 29-year-old woman with gastric cancer who developed Trousseau's syndrome, a malignancy-related thromboembolism, during chemotherapy. She was diagnosed with a mucin-producing adenocarcinoma of the stomach, and chemotherapy with S-1 and cisplatin was commenced. During treatment, she developed a sudden onset of right hemiplegia. Magnetic resonance imaging showed an acute cerebral infarction of the left cerebral hemisphere. The underlying pathophysiology is thought to be chronic disseminated intravascular coagulation due to mucin-producing adenocarcinomas. However, cisplatin-induced vascular toxicity and hypercoagulability caused by decreased plasma protein C activity, elevated plasma von-Willebrand factor levels, and hypomagnesemia has also been proposed to be associated with thrombogenicity.

Key words: Trousseau's syndrome, cisplatin-based chemotherapy, thromboembolism, mucin-producing adenocarcinoma, cerebral infarction

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Introduction

Thrombosis is one potential complication in patients with malignancies who undergo surgery, radiation, or chemotherapy (1). The relationship between neoplasms and thromboembolic diseases was first described by Trousseau in 1865, when he reported a high frequency of venous thrombosis in a series of patients with gastric carcinomas (2). Trousseau's syndrome is defined as spontaneous, recurrent or migratory episodes of venous thrombosis, migratory thrombophlebitis or arterial emboli due to non-bacterial thrombotic endocarditis, or any combination of these, occurring in patients with underlying or undiagnosed malignancy (2). Thus, the term Trousseau's syndrome is used broadly to refer to any form of excessive coagulation associated with cancers (3). The most commonly associated tumors are mucin-producing adenocarcinomas originating in the lungs, breasts, or alimentary tract (4), which frequently cause mi-

croangiopathies induced by hypercoagulability and resultant disseminated intravascular coagulation (5, 6). Moreover, the vascular toxicity caused by the chemotherapy may in itself increase the risk of stroke (7). Since the first report in 1983 (8), a number of patients with an ischemic cerebrovascular complication have been reported after antineoplastic treatment including cisplatin alone or in combination (9-14). The frequency of this complication was reported to be very rare, counting less than one in 2,000 treated patients (12). Indeed, the occurrence of Trousseau's syndrome in the course of combination chemotherapy with S-1 (TS-1[®]) and cisplatin has not been described. Here, we report a case of acute cerebral infarction that developed in a young patient with a mucin-producing signet ring cell adenocarcinoma of the stomach during combination chemotherapy with S-1 and cisplatin, and discuss the mechanisms of thrombotic complications.

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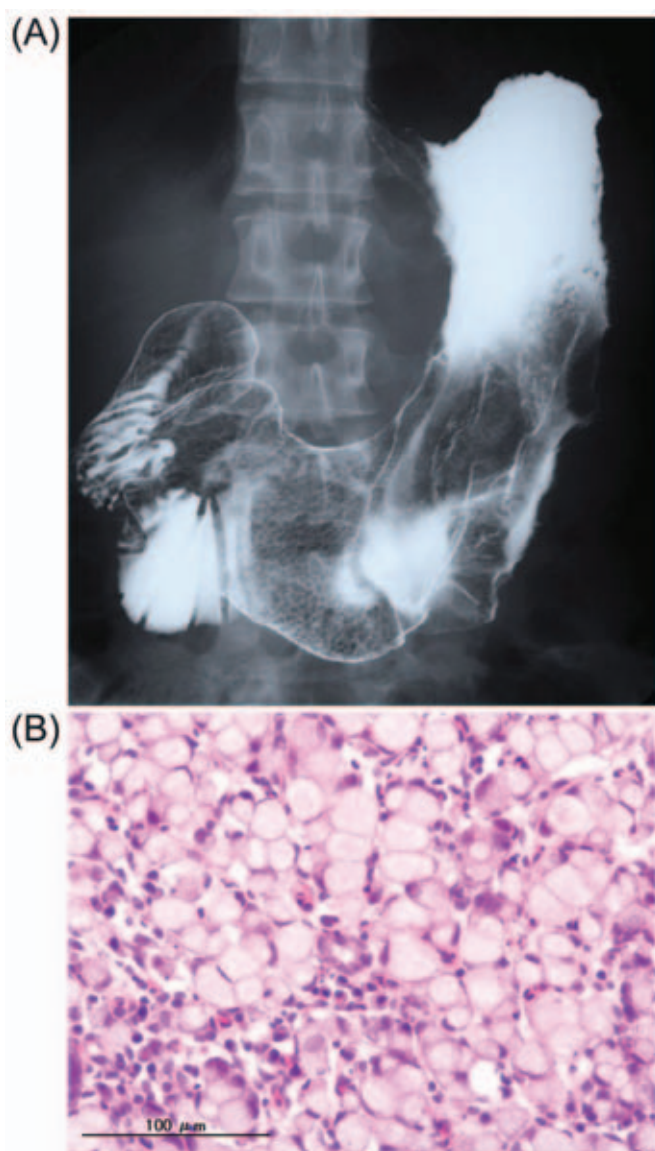


Figure 1. (A) Double-contrast barium image of the stomach with the patient in the supine position, showing loss of distensibility of the stomach and a gastric carcinoma of scirrhous type involving the entire body and the cardia of the stomach. (B) Histological findings of biopsy specimens of the stomach before chemotherapy. Signet ring cells with marked mucin production in the cytoplasm were found. (HE stain, $\times 400$).

Case Report

A 29-year-old woman was admitted to our hospital in November 2002, suffering with a loss of appetite. The patient did not have any other medical diseases or cardiovascular risk factors such as hypertension, hypercholesterolemia, or diabetes. She had no history of smoking. A physical examination showed no particular findings. Laboratory investigation revealed anemia (hemoglobin: 8.5 g/dL) and marked elevations of carcinoembryonic antigen (CEA; 52 ng/mL, normal range below 5 ng/mL) and carbohydrate antigen

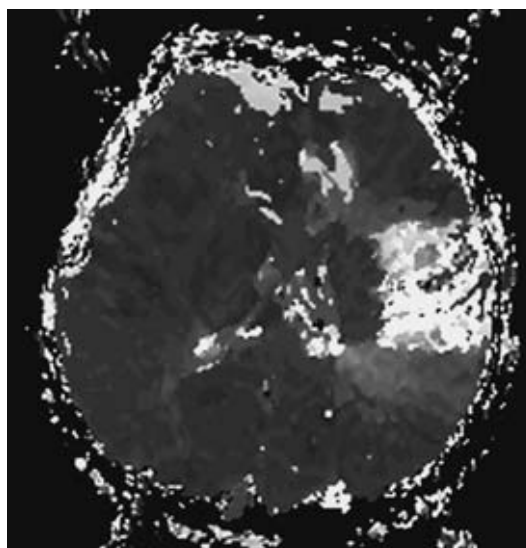


Figure 2. A diffusion magnetic resonance image taken 1 hour after the onset of right hemiplegia. The bright area of the left cerebral hemisphere demonstrated acute ischemic cerebral infarction.

(CA) 19-9 (352 U/mL, normally <37 U/mL). Coagulation markers such as platelet count, prothrombin time, partial thromboplastin time, antithrombin-III, and protein C activity were all within normal limits. Her electrocardiogram was normal without atrial fibrillation. Upper gastrointestinal endoscopy showed an advanced gastric carcinoma on the entire body and fornix of the stomach. An upper gastrointestinal series revealed loss of distensibility of the stomach (Fig. 1A). Histological examination of the biopsy specimens showed a signet ring cell adenocarcinoma with marked mucin production in the cytoplasm (Fig. 1B). Abdominal ultrasonography and computed tomography demonstrated ascites in the pelvic cavity and paracentesis revealed the infiltration of signet ring cell carcinoma cells in the ascitic fluid. From these findings, the patient was diagnosed as having a stage IV gastric carcinoma according to the UICC classification (15). Chemotherapy with a combination of S-1 and cisplatin was commenced after the patient gave written informed consent.

S-1 (80 mg/m²) was administered orally on days 1 to 21, and cisplatin (60 mg/m²) was infused for 6 hours on day 8 according to the literature (16). On day 15 in the first course of chemotherapy, the patient complained of transient palsy of the fingers of both hands and dizziness, but these symptoms disappeared immediately. Before the start of the second course, the CEA and CA19-9 levels decreased to 20.0 ng/mL and 267 U/mL, respectively. On day 13 in the second course, the patient suddenly developed an acute onset of confusion and right-sided weakness. A physical examination confirmed right hemiplegia accompanied by facial nerve palsy, generalized hyperreflexia, and global aphasia. Diffusion-weighted magnetic resonance images showed acute ischemic cerebral infarctions of the left cerebral hemisphere involving the region of the left middle cerebral artery

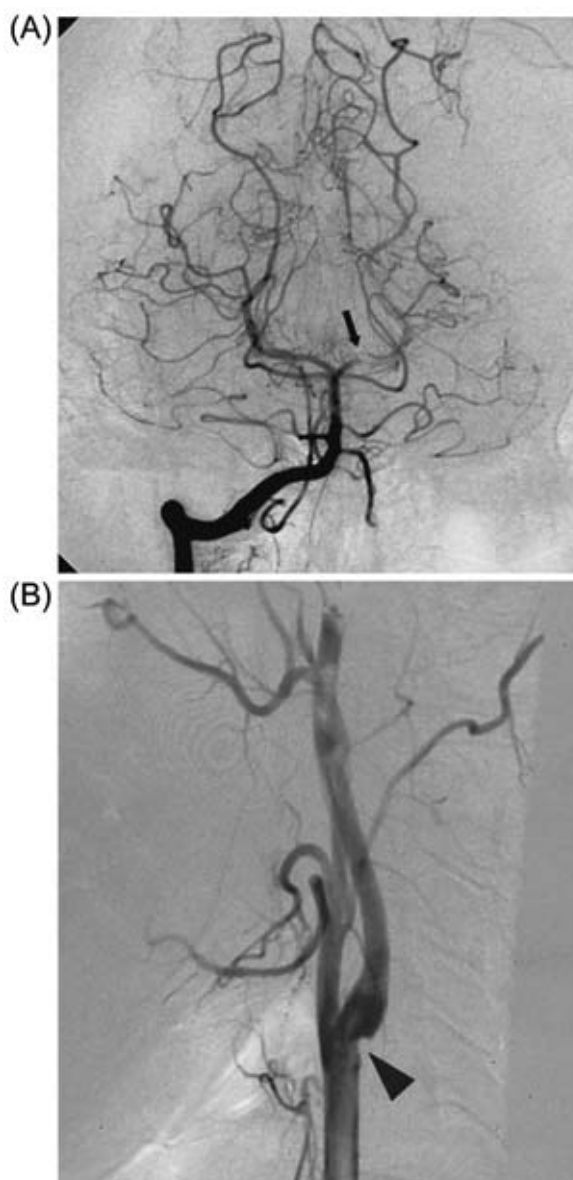


Figure 3. Cerebral angiographic findings. (A) The M1 segment of the left middle cerebral artery “(arrow)” was occluded. (B) A partial defect in the left internal carotid artery “(arrowhead)” suggested the presence of a thrombus.

(MCA; Fig. 2). Four-vessel cerebral angiography revealed occlusion of the left M1 segment of the MCA (Fig. 3A). Carotid angiography also demonstrated irregularity of the orifice of the left internal carotid artery (Fig. 3B). Moreover, vascular ultrasonography of the left carotid artery demonstrated a manifest carotid plaque at the orifice of the left internal carotid artery (Fig. 4), although the presence of endocardial disease or valvular dysfunction was ruled out by echocardiography. As such ischemic events may be related to the hypercoagulability, coagulation markers such as the plasma levels of protein C activity and von Willebrand factor (vWf), and serum magnesium level were measured. The plasma protein C activity and serum magnesium level were reduced to 48 and 1.5 mg/dL, respectively, and plasma vWf level was elevated to 251, whereas other coagulation mark-

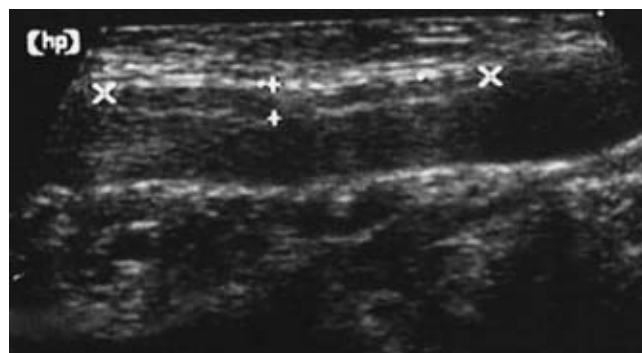


Figure 4. Vascular ultrasonography of the left internal carotid artery. A thrombus (3 mm thickness) was found in the orifice of the left internal carotid artery.

Table 1. Laboratory Data and Coagulation Parameters at the Onset of Right Hemiplegia

Parameters		normal range
Platelet count	$33.9 \times 10^4/\mu\text{L}$	$(11.0 - 40.0 \times 10^4/\mu\text{L})$
PT	12.4 seconds	$(10.2 - 12.1 \text{ seconds})$
APTT	29.9 seconds	$(26.2 - 39.3 \text{ seconds})$
Protein C activity	48%	$(64 - 146\%)$
Von Willebrand factor	251%	$(60 - 170\%)$
Fibrinogen	240 mg/dL	$(150 - 400 \text{ mg/dL})$
Magnesium	1.5 mg/dL	$(1.8 - 2.3 \text{ mg/dL})$
D-Dimer	8.2 $\mu\text{g/mL}$	$(< 1.0 \mu\text{g/mL})$
Anti-CL- β 2GPI	$< 1.2 \text{ U/mL}$	$(< 3.5 \text{ U/mL})$
Uric acid	3.7 mg/dL	$(3.6 - 7.8 \text{ mg/dL})$
Creatinin	0.6 mg/dL	$(0.4 - 0.8 \text{ mg/dL})$

Footnote: Anti-CL- β 2GPI, antibodies against cardiolipin and β 2glycoprotein I; APTT, activated partial thromboplastin time; PT, prothrombin time; U, units.

ers, such as platelet count, were normal (Table 1).

Chemotherapy was discontinued and conservative therapy including free radical scavenging, low-molecular-weight dextran, low-molecular-weight heparin, and glycerol were started. Thrombolytic treatment was not performed because of the high risk of thrombolysis-related hemorrhagic infarction. Three weeks later, plasma protein C activity and serum magnesium level had normalized to 93% and 2.1 mg/dL, respectively, but the plasma vWf level was still elevated to 249%. Despite the intensive treatment, the patient's right hemiplegia continued and she died five months later.

Discussion

We describe here a case of acute cerebrovascular ischemic events during combination chemotherapy with S-1 and cisplatin for a patient with mucin-producing signet ring cell adenocarcinoma of the stomach. Considering the vascular ir-

regularity of the left internal carotid artery observed in angiography in spite of her young age, malignancy-related thromboembolism was suspected as previously reported as Trousseau's syndrome. The prevalence of clinically apparent thromboembolism in cancer patients may be up to as high as 15% (17). Although the precise mechanism of this syndrome is not yet proven, we can suggest several possibilities for this patient receiving cisplatin-based chemotherapy.

First, there may have been cisplatin-induced vascular toxicity (18). Direct endovascular damage induced by cisplatin has been reported (19). Free radical-induced lipid peroxidation may also play an important role in the pathogenesis of cisplatin-induced endothelial injury (19). Such endothelial injuries cause intimal thickening (20), and can lead to platelet aggregation at the site of endothelial injury. This can cause the local accumulation of several mediators that promote platelet aggregation and vasoconstriction (21), and lead finally to the occurrence of a thrombus. Therefore, it is reasonable to argue that cisplatin-induced vascular endothelial injury might have been present at the orifice of the left internal carotid artery and contributed to the production of a thrombus.

Second, this patient had a mucin-producing signet ring cell adenocarcinoma of the stomach. Such tumors may secrete abnormally glycosylated mucins and mucin fragments into the blood stream, which are associated with coagulopathies (22). As Trousseau's syndrome was originally reported to be associated with mucin-producing adenocarcinomas (23), some early studies suggested that secreted mucin might act as a procoagulant for hypercoagulopathy (5). Moreover, the interactions of circulating mucins derived from carcinoma cells with platelet P-selectin are suggested to be strongly associated with Trousseau's syndrome, and mucins may act as templates to aggregate activated platelets via P-selectin (3). Accordingly, we speculate that destruction of the tumor cells by chemotherapy may have caused mucin influx into the circulation, leading to a hypercoagulable state.

Third, cisplatin-induced hypercoagulability caused by decreased activity of anticoagulant protein C, an inhibitor of coagulation, and elevated plasma vWf level following cisplatin treatment may be suspected. Cisplatin can cause

changes in these coagulation factors (18), which are also considered to be associated with endothelial injuries (10, 24, 25), although the precise mechanism remains unclear. Indeed, protein C can be modified by proteolytic enzymes released by endothelial injuries (26). Moreover, cisplatin-induced hypomagnesemia resulting from renal tubular injury increases vascular smooth muscle contraction and contributes to hypercoagulability (18). The incidence of hypomagnesemia was reported as ranging from 76% to 87% after cisplatin-based chemotherapy (27, 28). Such coagulation abnormalities and hypomagnesemia were also identified in the present patient. Considering the recovery of protein C activity and the serum magnesium level three weeks after the discontinuance of chemotherapy, such cisplatin-induced hypercoagulability might be associated with the pathophysiology of acute cerebrovascular ischemic events.

Combination chemotherapy with S-1 and cisplatin for advanced gastric cancer is widely used and its clinical efficacy is well demonstrated (29, 30). Thus, although the incidence of Trousseau's syndrome is not high, we should be aware that patients receiving such chemotherapy against mucin-producing cancers might have a particular risk for developing Trousseau's syndrome and we must observe them carefully for subtle evidence of thrombosis during treatment. In retrospect, in the present case, as her symptoms of finger palsy and dizziness in the first course of chemotherapy were likely signs of transient ischemic attack, we should have discontinued cisplatin-based chemotherapy earlier. However, the efficacy of prophylactic anticoagulation therapy using low molecular weight heparin has been disputed (31), and further study is needed.

In conclusion, we should be aware that vascular events are critical complications of cisplatin-based chemotherapy particularly for mucin-producing cancers, even in the absence of overt risk factors for cardiovascular diseases. Once a vascular event has occurred, discontinuation of cisplatin-based chemotherapy is mandatory. Early prediction of the risk of vascular events through laboratory measure abnormalities, such as decreased plasma protein C activity, elevated plasma vWf levels, and hypomagnesemia, should be attempted to prevent this life-threatening toxicity.

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