

[ CASE REPORT ]

## Trousseau's Syndrome Presenting as Multiple Cerebral Infarctions Caused by Mucin-producing Bladder Micropapillary Urothelial Cancer

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### Abstract:

We herein report a 70-year-old man with recurrent multiple cerebral infarctions under warfarin therapy who was finally diagnosed with Trousseau's syndrome resulting from advanced bladder cancer. A histological examination of the mesenteric lymph nodes revealed metastasis of micropapillary urothelial cancer with positive mucin markers CA125 and MUC1. Blood examinations also indicated elevated tumor markers, such as CA19-9 and CA125. To our knowledge, this is the first report of Trousseau's syndrome in a patient with bladder micropapillary urothelial cancer in which mucin involvement was clearly proven by histological and serological examinations.

**Key words:** Trousseau's syndrome, bladder cancer, cerebral infarction, micropapillary urothelial cancer, mucin

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### Introduction

Cancer-related stroke is a common condition, and several mechanisms have been reported in association with it, such as treatment-related, tumor occlusion, medical comorbidities, and cancer-associated hypercoagulopathy (1, 2). Among these, cancer-related coagulopathy may also be referred to as Trousseau's syndrome, which was originally defined by Armand Trousseau to indicate migratory superficial thrombophlebitis. The term is now used to indicate chronic-disseminated intravascular coagulopathy associated with microangiopathy, verrucous endocarditis, and arterial emboli in patients with cancer, especially in those with mucin-positive carcinomas (3, 4).

Recently, Trousseau's syndrome has been recognized as a cause of stroke of unknown etiology, although no specific biomarkers are available for this syndrome. While elevated D-dimer levels sometimes suggest Trousseau's syndrome, this condition is not specific. Considering the association be-

tween this syndrome and mucin-positive carcinomas, mucin-related tumor markers, such as CA19-9 and CA125, may act as potential markers of Trousseau's syndrome, especially in cases with cancer that are usually considered not associated with Trousseau's syndrome, including bladder cancer (3, 5, 6).

We herein report for the first time a case of Trousseau's syndrome presenting as multiple cerebral infarctions (CIs) in a patient with bladder micropapillary urothelial cancer, a rare subtype of bladder cancer, in which mucin involvement was clearly proven by mucin-associated staining, including CA125 and MUC1, and the measurement of mucin-related tumor markers, such as CA19-9 and CA125.

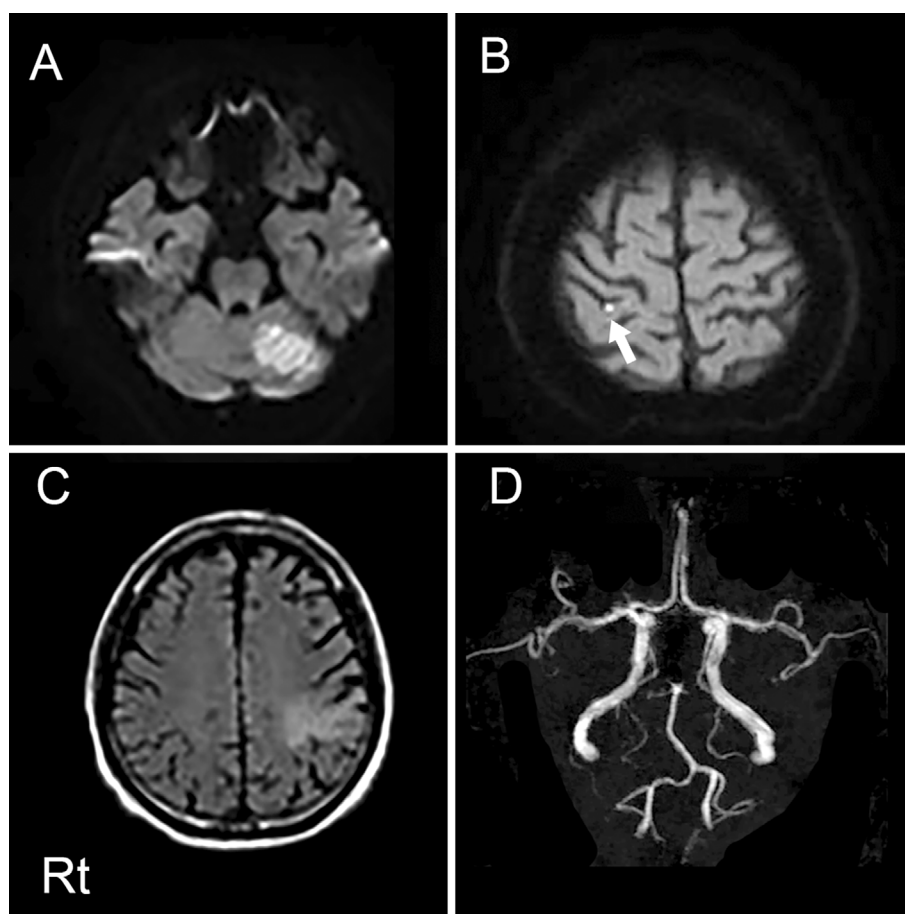
### Case Report

A 70-year-old man visited a hospital due to frequent urination, where he was diagnosed with stage IV bladder cancer. Surgery was not recommended because of multiple lymph node metastases, so chemotherapy was selected in-

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**Figure 1.** Diffusion-weighted brain magnetic resonance image revealing newly developed multiple cerebral infarctions in the left cerebellum (A) and in the right parietal lobe (arrow in panel B). Fluid-attenuated inversion recovery imaging revealed hyperintensity in the left parietal lobe, indicating a previous cerebral infarction that developed a month ago (C). Magnetic resonance angiography revealed no atherosclerotic lesion (D).

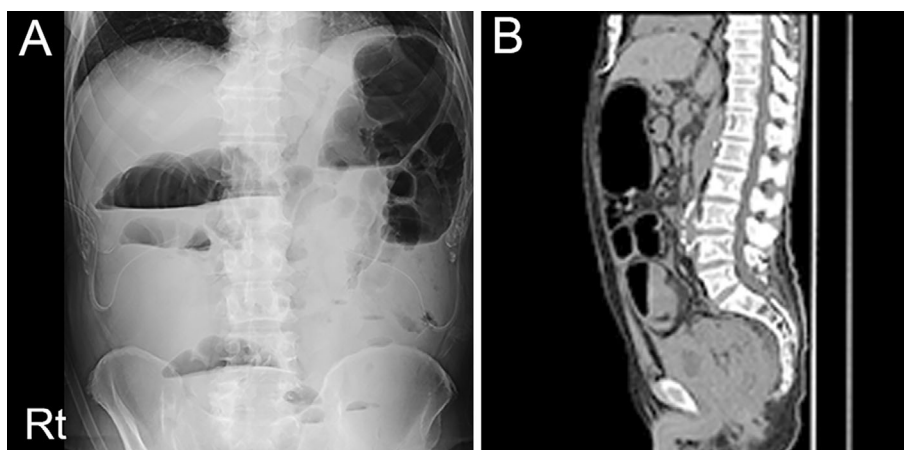
stead. After a year, he developed CI in the left parietal lobe and was admitted to another hospital. During the admission, his right upper and lower limb paralyses nearly completely improved, and he was discharged with a modified Rankin Scale (mRS) of 2. Although the etiology of this CI remained unknown, warfarin potassium was started for secondary prevention.

One month after the first CI, the patient visited our hospital due to consciousness disturbance, and head magnetic resonance imaging (MRI) showed newly developed multiple CIs (Fig. 1). A neurological examination revealed limb ataxia, dysarthria, and aphasia with mild consciousness disturbance, and he was assigned a National Institute of Health Stroke Scale of 4. He was a past smoker and was undergoing medication for diabetes mellitus and hypertension, with no significant family history.

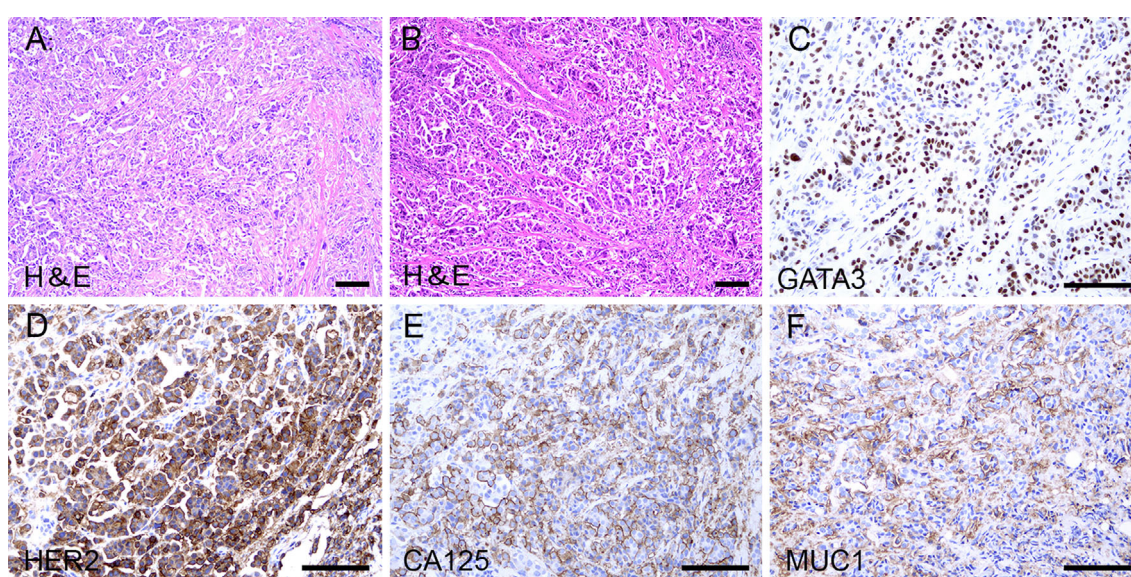
His electrocardiogram and echocardiography revealed no remarkable findings that indicated cardioembolism. Carotid ultrasonography and three-dimensional (3D) computed tomography (CT) angiography revealed no atherosclerotic lesion. His blood test indicated a prolonged prothrombin time (international normalized ratio=1.60) under warfarin therapy

and elevated D-dimer level (7.4  $\mu\text{g/mL}$ ). Although recurrent stroke under warfarin therapy and elevated D-dimer level suggested the possibility of Trousseau's syndrome, bladder cancer has been infrequently reported as a cause of this syndrome. Furthermore, as we did not perform transthoracic echocardiography, we could not exclude the possibility of paradoxical embolism due to a right-to-left shunt; a previous study reported that ischemic stroke is often caused by paradoxical embolism in patients with malignancies (7). After considering these points, we tentatively initiated anticoagulation therapy with a subcutaneous injection of heparin. The D-dimer level decreased to 2.3  $\mu\text{g/mL}$  after heparin injection was initiated.

On the 17th hospital day, the patient experienced a loss of appetite, and abdominal X-ray and CT revealed ileus-like images (Fig. 2). Given the elevation of his serum tumor markers, including carcinoembryonic antigen (CEA), CA19-9, and CA125 at 44.8 ng/mL, 638.2 U/mL, and 97.9 U/mL, respectively, we first suspected concurrent colorectal cancer. However, colon fiberoscopy revealed colon obstruction due to compression from outside of the colon. We found that the colon obstruction had been caused by peritoneal dissemi-



**Figure 2.** Abdominal X-ray (A) and computed tomography (B) images showing ileus-like images.



**Figure 3.** Histological examinations of mesenteric lymph nodes obtained during surgery with Hematoxylin and Eosin staining (A) showing similar findings to those of specimens obtained in a previous hospital (B). Positive staining for GATA3 (C) and HER2 (D) indicated micropapillary urothelial cancer. Positive staining for CA125 (E) and MUC1 (F) suggested mucin production. Scale bar=100  $\mu$ m.

nated lesions of bladder cancer, and accordingly, colostomy with double orifices was performed as a palliative surgery.

The histopathological findings of the mesenteric lymph nodes obtained during surgery (Fig. 3) indicated micropapillary urothelial cancer with positive staining for GATA3 [which is usually positive in urothelial and breast cancers (8)] and HER2 (indicating micropapillary cancer, usually positive in breast cancer, ovarian cancer, stomach cancer, and bladder cancer); these findings were similar to those of specimens obtained in a previous hospital. Furthermore, cancer cells were also positive for mucin-associated staining, such as CA125 and MUC1, with remarkable vascular infiltration of MUC1-positive cancer cells (Fig. 3).

Considering the clinical course as well as the histological and serological examinations that indicated mucin-producing cancer, we finally diagnosed the stroke subtype in this case

as Trousseau's syndrome. The patient eventually died four months after admission due to the progress of bladder cancer without any recurrence of CIs under heparin injection therapy.

## Discussion

We reported for the first time a case of Trousseau's syndrome that presenting as multiple CIs due to bladder micropapillary urothelial cancer with mucin production; these findings were verified both histologically and serologically.

Trousseau's syndrome has been regarded as thrombosis associated with hypercoagulability in association with malignant tumors (3). Several mechanisms have been speculated to induce Trousseau's syndrome, including mucin-related hypercoagulability. Carcinoma mucins are believed to inter-

**Table.** Cases of Cerebral Infarction in Patients with Bladder Cancer Reported as Trousseau's Syndrome.

Reference No	Year published	Age / Gender	Histological type of bladder cancer	CA19-9 (U/mL)	CA125 (U/mL)	D-dimer ( $\mu\text{g/mL}$ )	Treatment
15	1995	67 /Male	Transitional cell carcinoma	not reported	not reported	not reported	Heparin
14	2016	38 /Female	Transitional cell carcinoma	63	376	1.0	Heparin
12	2018	71 /Female	Squamous cell carcinoma	not reported	not reported	0.4	Warfarin
13	2019	46 /Male	Transitional cell carcinoma	not reported	not reported	21.6	No anticoagulant therapy
our case	2020	70 /Male	Micropapillary urothelial cancer	638.2	97.9	7.4	Heparin

CI: cerebral infarction

act with P- and L-selectins and produce mucin-mediated platelet aggregation without thrombin production as well as to promote the formation of microthrombus (9). Supporting this speculation, Trousseau's syndrome has been reported to be predominant in adenocarcinomas, such as lung cancer, pancreatic cancer, gastric cancer, ovarian cancer, and breast cancer, especially in mucin-producing tumors (1, 5). In a previous study, the examination of 613 cases of non-bacterial thrombotic endocarditis showed that most of the patients had adenocarcinomas (6).

Trousseau's syndrome in patients with bladder cancer, most of which are transitional cell carcinoma, is considered uncommon. A recent multi-center retrospective study investigated bladder cancer-related ischemic stroke and found that approximately 1.29% of the patients with bladder cancer also had ischemic stroke (10). In another study, urogenital carcinoma was reported as the fourth-most frequent cancer that presented with stroke (11). However, these reports included all cancer-related stroke cases, including those induced by drugs, dehydration, and Trousseau's syndrome (cancer-associated hypercoagulopathy). If the subjects had been limited to those with Trousseau's syndrome, we speculate that the frequency would have been less than that in the present report. To our knowledge, only five cases (including the present case) of Trousseau's syndrome with CI in patients with bladder cancer have been reported thus far (Table) (12-15), and some may not have had cancer-associated hypercoagulopathy, since the D-dimer level in those cases was not elevated.

In the present case, a histological examination revealed micropapillary urothelial cancer, which was first reported in 1994 as a rare subtype of bladder cancer, accounting for < 2% of all bladder cancer cases, and is often advanced at the time of the diagnosis (16, 17). Micropapillary urothelial cancers tend to show higher positive rates for mucin-associated staining, such as CA125 and MUC1, than normal urothelial cancers (18). MUC1 is a transmembrane mucin that correlates with the incidence of thromboembolism by increasing the blood viscosity (19). Our patient actually showed positive staining for CA125 and MUC1, which indicated mucin production. Furthermore, the levels of mucin-related serum

markers, such as CA19-9 and CA125, were also elevated in our patient, indicating mucin secretion. Several studies have suggested that serum CA19-9 and CA125 levels may be generally useful predictors of the onset of CI in patients with cancer (20, 21). However, a recent study that targeted cases with bladder cancer (including any histopathological type) indicated that an elevated serum CEA level was an independent risk factor of CIs, whereas the serum CA19-9 and CA125 levels showed no significant correlations with the occurrence of CIs (10). While whether the discrepancy between the results in our case and those in the aforementioned recent study is due to differences in the histopathological type or patient-specific features is unclear, examinations of serum tumor markers, such as CA19-9 and CA125, are not usually performed routinely for cases of bladder cancer (as shown in the Table), so data that might be useful for addressing this topic are still lacking.

Nevertheless, to our knowledge, this is the first report of Trousseau's syndrome in a patient with bladder micropapillary urothelial cancer, in which the involvement of mucin production and secretion was clearly proven by histological and serological examinations. Our experience with the present case suggested that mucin-related hypercoagulability should be considered in cases where findings are suggestive of mucin production, even in cases with cancer that are otherwise not considered to be associated with Trousseau's syndrome. Although no specific biomarkers for Trousseau's syndrome are currently available, an active search for mucin-related markers may be useful for investigating the possibility of Trousseau's syndrome.

**The authors state that they have no Conflict of Interest (COI).**

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