

Original Article



Cerebral infarction caused by Trousseau syndrome associated with cervical cancer

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ABSTRACT

Objective: The combination of cancer and hypercoagulable states is often called Trousseau syndrome. In particular, cerebral infarction caused by Trousseau syndrome is reported to have a poor prognosis. In gynecology, there are many reports of ovarian cancer and a few of uterine cancer. Since there has been no comprehensive report of Trousseau syndrome in cervical cancer, we aimed to summarize Trousseau syndrome in cervical cancer.

Methods: Cerebral infarction caused by cancer-related arterial thrombosis was defined as Trousseau syndrome. Patients with cervical cancer diagnosed at our hospital between January 2014 and December 2021 were retrospectively reviewed using the hospital's medical records.

Results: A total of 1,432 patients were included in the study. Trousseau syndrome occurred in 6 patients (0.4%). The mean age of patients with Trousseau syndrome was 63 years (range: 53–78 years). Of the 6 patients who developed Trousseau's syndrome, 4 patients had it before or during initial treatment, and 2 during recurrent/relapsed disease treatment. The 4 patients who developed the syndrome before or during initial treatment had advanced disease: 1 in stage IIIC and 3 in stage IVB. In all cases, the disease was associated with progressive distant metastasis. The median survival time from the onset of Trousseau syndrome was 1 month (range: 0–6 months).

Conclusion: Cervical cancer causes Trousseau syndrome in cases of advanced disease with a short time between the onset of the syndrome and mortality.

Keywords: Cervical Cancer; Cerebral Infarction; Thromboembolism; Lymph Node Metastasis; Tissue Factor

Synopsis

This is the first comprehensive report of cerebral infarction caused by Trousseau syndrome in cervical cancer. Patients with Cerebral infarction caused by Trousseau syndrome had advanced or recurrent cervical cancer. The time from the onset of cerebral infarction caused by Trousseau syndrome to death was short.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: K.M.; Data curation: K.M., F.A., A.A., N.H.; Investigation: K.M.; Project administration: K.H.; Supervision: Y.M., K.H.; Writing - original draft: K.M.; Writing - review & editing: Y.M., F.A., A.A., N.H., K.H.

INTRODUCTION

Trousseau syndrome was first described by Armand Trousseau in 1865 as migratory superficial thrombophlebitis [1]. In 1977, Sack reported that Trousseau syndrome is a chronic disseminated intravascular coagulation syndrome with nonbacterial thrombotic endocarditis (NBTE) and arterial thrombosis in patients with cancer [2]. Abnormal coagulation due to cancer has been reported as venous thrombosis, arterial thrombosis, and NBTE. Currently, the combination of cancer and hypercoagulable conditions is broadly defined as Trousseau syndrome [3].

Cerebral infarction caused by cancer-related arterial thrombosis or NBTE is a condition of Trousseau syndrome in the narrow sense. Notably, many studies on the association between cancer and venous thrombosis have been reported [4,5], and recently, accumulating evidence suggests an association between cancer and arterial thrombosis [6,7]. Cancer-induced arterial thrombosis is reported in 2.6% of patients, 41% of whom have myocardial infarction, and 33% have cerebral infarction [6]. Cerebral infarction due to Trousseau syndrome is reported to have a poor prognosis [8,9], with an in-hospital mortality rate of approximately 20% that is 3.5 times higher than that of general stroke [9].

Cerebral infarction caused by Trousseau syndrome is more common in lung, gastrointestinal (stomach and pancreas), and breast cancers [6,8]. The histological type is frequently adenocarcinoma, and mucin-mediated induction of platelet aggregation in circulating plasma has been reported in mucin-producing tumors [3,8]. In gynecology, there are many reports of ovarian cancer [10,11], followed by endometrial cancer [12]. Since there are no comprehensive studies on cervical cancer, we now report cases of cerebral infarction due to Trousseau syndrome in patients with cervical cancer at our hospital.

MATERIALS AND METHODS**1. Patients**

The medical records of patients admitted to our hospital between January 2014 and December 2021 and diagnosed with cervical cancer were retrospectively studied. The data reviewed included physical examination records, laboratory blood tests, imaging scans, chemotherapy records, radiation records, pathology reports, and prognostic information. Patients with other comorbidly active cancers, those who underwent initial treatment at other hospitals, and those transferred to different hospitals during treatment were excluded.

2. Clinical background of patients

We used the International Federation of Gynecology and Obstetrics 2018 guidelines for stage classification [13] and the World Health Organization 2014 guidelines for histology [14]. Risk factors for underlying systemic complications or lifestyle-related diseases were assessed. The patients investigated were selected from previous reports of known risk factors [7,8,10]. Hypertension, hyperlipidemia, and diabetes mellitus were defined in patients before cervical cancer treatment or in untreated participants: hypertension was defined as having a systolic blood pressure of 140 mmHg or higher; hyperlipidemia as having a low-density lipoprotein ≥ 150 mg/dL or triglyceride ≥ 150 mg/dL; and diabetes as having a blood sugar ≥ 200 mg/dL or hemoglobin HbA1c $\geq 6.5\%$ at any time. The smoking coefficients were calculated by adding the number of cigarettes smoked per day to the number of years smoked [15].

3. Diagnosis and treatment of Trousseau syndrome

We defined Trousseau syndrome as cancer-related cerebral infarction that develops after cervical cancer diagnosis. We collaborated with a nearby affiliated hospital to perform tests to rule out the possibility of noncancer-related strokes, such as atherosclerotic or cardiogenic cerebral infarction. Tests included magnetic resonance imaging, computed tomography, electrocardiography, cardiac ultrasonography, and transesophageal ultrasonography. NBTE diagnosis was confirmed by transesophageal ultrasonography that confirmed the presence of verrucae, and by the culture of a blood clot taken to treat a stroke that confirmed it was not of bacterial origin. Stroke treatment was performed at a nearby affiliated hospital, and after stroke treatment, rehabilitation, and cancer treatment were continued at the outpatient hospital.

4. Ethics statement

All participants provided informed consent before participating in this study. We conducted this study by following the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the Cancer Institute at Ariake Hospital, Japanese Foundation for Cancer Research, Japan (approval number: 2023-GB-039).

RESULTS

Six (0.4%) of the 1,432 patients developed cerebral infarction due to Trousseau's syndrome. The overall mean age was 48.8 years (range: 17–89 years), whereas in patients with Trousseau syndrome it was 63 years (range: 53–78 years).

According to histopathology examinations, Trousseau syndrome was found in 2 of 904 (0.2%) squamous cell carcinomas (SCC) and 3 of 230 (1.3%) adenocarcinomas of the usual type (**Table 1**).

Six cases of Trousseau syndrome occurred, 4 before or during the initial treatment and 2 during recurrent/relapsed treatment. The 4 patients who developed the disease before or during initial treatment were advanced cases: 1 in stage IIIC and 3 in stage IVB (**Table 1**).

Table 1. Clinical characteristics

Characteristics	All patients (n=1,432)	Trousseau's syndrome (n=6)	
Age (yr)	48.8 (17–89)	63 (53–78)	
Histological type			
SCC	904 (63.1)		2
Adeno-usual type	230 (16.1)		3
Adeno-SCC	145 (10.1)		0
Other	153 (10.7)		1
FIGO 2018		Primary of cancer	Recurrence of cancer
IA	266 (18.6)		
IB	455 (31.8)		1
IIA	54 (3.8)		
IIB	112 (7.8)		
IIIA	8 (0.6)		
IIIB	34 (2.4)		
IIIC	397 (27.7)	1	
IVA	15 (1.0)		
IVB	91 (6.4)	3	1

Data shown are mean (range) or number (%).

Adeno-SCC, Adenosquamous carcinoma; Adeno-usual type, endocervical adenocarcinoma usual type; FIGO, International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma.

Trousseau syndrome in cervical cancer

Table 2. Histopathological characteristics of patients with Trousseau's syndrome

Patient No.	Age	FIGO 2018	Histology	Cancer treatment	Disease condition	Cancer site	Symptom of onset	Localization of cerebral infraction
1	66	IVB	Adeno-usual type	Primary	Progression	Lung, LYM (abdominal, extra abdominal)	Dysarthria	Left middle cerebral artery
2	57	IVB	SCC	Primary	Before treatment	Lung, LYM (abdominal, extra abdominal)	Gait disturbance	Multiple
3	63	IVB	SCC	Recurrence	Progression	LYM (abdominal, extra abdominal)	Left hemiplegia	Right middle cerebral artery
4	53	IVB	Other	Primary	Progression	LYM (abdominal, extra abdominal)	Dysarthria	Left middle cerebral artery
5	78	IIIC	Adeno-usual type	Primary	Progression	Lung, pleura, liver, bone	Disarthria, right hemiplegia	Left middle cerebral artery, multiple
6	67	IB	Adeno-usual type	Recurrence	Progression	Lung, pleura, liver, bone	Dysarthria	Left middle cerebral artery

Adeno-usual type, endocervical adenocarcinoma usual type; FIGO, International Federation of Gynecology and Obstetrics; LYM, lymph node metastasis; NEC, neuroendocrine carcinoma; SCC, squamous cell carcinoma.

Table 3. Clinical characteristics of patients with Trousseau's syndrome

Patient No.	BMI	BI	HT	HL	DM	HU	MI	AF	PFO	DVT	Anticlotting drug	Dehydration	Infarction	BEV
1	16.3	20	Yes	Yes	No	No	No	No	No	No	No	No	No	Yes
2	ND	740	No	No	No	No	No	No	No	No	No	Yes	No	No
3	21.3	840	No	No	No	No	No	No	No	No	No	No	Yes	No
4	18.8	580	No	No	No	No	No	No	No	Yes	No	No	No	Yes
5	17.2	150	No	No	No	No	No	No	No	Yes	Yes	No	No	No
6	24.3	0	Yes	Yes	Yes	No	No	No	No	Not	No	Yes	No	No

AF, atrial fibrillation; BEV, bevacizumab administration; BI, Brinkman index; BMI, body mass index; DM, diabetes mellitus; DVT, deep vein thrombosis; HL, hyperlipidemia; HT, hypertension; HU, hyperuricemia; MI, myocardial infarction; ND, no data; PFO, patent foramen ovale.

Patients with stage IIIC had pulmonary, pubic, or hepatic metastases due to exacerbation during the initial treatment. Notably, all patients displayed progressive distant metastases (**Table 2**).

The risk factors for cancer-related cerebral infarction included a history of smoking in 5 patients and of hypertension in 3. There was no history of atrial fibrillation or myocardial infarction. Deep venous thrombosis (DVT) was present in 2 patients; 1 had been under treatment. Dehydration was present in 2 patients at the time of cerebral infarction, and 1 had a concurrent urinary tract infection (**Table 3**).

Hematological tests show that 4 patients with non-SCC had elevated tumor markers: either carcinoembryonic antigen, carbohydrate antigen 19-9 (CA19-9), or cancer antigen 125 (CA125). Low hemoglobin levels (<10 g/dL) were found in 4 patients, and low serum albumin (Alb) levels (<3.5 g/dL) were found in 5 patients (**Table 4**). Median survival time from the onset of Trousseau syndrome was 1 month (range: 0–6 months) (**Table 4**). In 1 case, which occurred prior to first treatment, the patient died from progression of cervical cancer during treatment of Trousseau's syndrome. The remaining 5 patients were on third-line or higher therapy, but their cervical cancer progressed before their general condition improved from stroke treatment.

DISCUSSION

Cerebral infarction caused by cancer-induced arterial thrombosis or NBTE is defined as Trousseau syndrome. This is the first comprehensive report of cerebral infarction due to Trousseau syndrome in cervical cancer.

Table 4. Biochemical characteristics and survival of patients with Trousseau's syndrome

Patient No.	Hb (g/dL)	Platelet (*10 ⁴ /ul)	D-dimer (ul/mL)	Alb (g/dL)	CEA (ng/mL)	CA19-9 (U/mL)	CA125 (U/mL)	Transesophageal echo	Treatment of cerebral infarction	OS of after Trousseau
1	6.5	8.2	18.9	2.6	108.6	3,553.7	858.1	Verrucae on M valve	Endovascular treatment	1 month
2	10.9	48.9	11.2	1.6	6.1	25.8	ND	Not performed	Antithrombotic therapy	2 months
3	8.5	8	ND	3.3	4.9	ND	ND	Verrucae on M valve	Endovascular treatment	1 month
4	10.9	10.4	2.5	3.9	358.5	31.3	155.5	Not performed	Antithrombotic therapy	6 months
5	7.7	15.1	26.3	3.1	ND	50,000	538.5	Verrucae on M valve	Endovascular treatment	0 month
6	7.9	10.9	31.6	3.1	ND	14	484.3	Verrucae on M valve	Antithrombotic therapy	1 month

Alb, albumin; CEA, carcinoembryonic antigen; Hb, hemoglobin; CA125, cancer antigen 125; CA19-9, carbohydrate antigen 19-9; ND, no data; OS, overall survival.

Recently, evidence has accumulated suggesting an association between cancer and arterial thrombosis [6,7], with cancer-induced arterial thrombosis reported to occur in 2.6% of patients, 41% of whom were at risk for myocardial infarction and 33% were at risk for cerebral infarction [6]. Cerebral infarction occurring in cancer patients is reported to have a poor prognosis [8,9], with an in-hospital mortality rate of approximately 20%, 3.5 times higher than that of general cerebral infarction [9]. In our present report, patients with cerebral infarction due to Trousseau syndrome did not die from stroke, but their cervical cancer progressed rapidly, and all died within 1 month (range: 0–6 months) after onset.

The Incidence of cerebral infarction due to Trousseau syndrome in ovarian cancer has been reported as 1.1%–3.2% [10,11], whereas for cervical cancer, our report was 0.4%. However, this may be an underestimate. Takano et al. [10] reported that in ovarian cancer, 1.7% of patients developed the disease before treatment and 1.5% after treatment initiation. Notably, all other previous reports, including those on different types of cancer, included cases in which the cancer was diagnosed after the onset of stroke. This is due to the increased risk of thrombogenesis approximately 1 year before cancer diagnosis [7,9,16]. However, since our neurology department does not treat cerebral infarction and we have not encountered patients diagnosed with cancer due to cerebral infarction, we only included patients diagnosed with Trousseau syndrome after developing cervical cancer. Therefore, it is possible that the number reported here may be an underestimate. This is a limitation of this study because Trousseau syndrome is an event that occurs during the course of cancer and requires long-term follow-up, making it difficult to study the patients prospectively.

There are no comprehensive reports on cervical cancer and its association with arterial thrombosis; however, Matsuo et al. reported that distant metastasis, local progression, and hypoalbuminemia are risk factors for venous thrombosis [17]. In our report, all 6 patients had distant metastasis or local progression, including initial and recurrent disease. In 5 of the 6 patients, hypoalbuminemia with Alb <3.5 g/dL was present. Previous reports on arterial thrombosis in other cancers have reported that male gender, hypertension, smoking, and adenocarcinoma are risk factors [6-8]. In the present report, 5 of 6 patients (83.3%) had a smoking history, and 3 (50.0%) had adenocarcinoma. Tumor markers were elevated in all 4 non-SCC cases, including the adenocarcinoma markers CA19-9 and CA125. Mucin produced by adenocarcinoma has been reportedly involved in thrombus production [3,8]; however, cerebral infarction due to Trousseau syndrome was observed in 2 of 904 SCC patients (0.4%). Tissue factor (TF), also known as platelet coagulation factor III, is a member of the human coagulation factor family. TF expression has been confirmed as a biomarker for preoperative diagnosis and prognosis of malignant tumors [18]. TF has been reported to be one of the risk factors for Trousseau syndrome [3]. In cervical cancer, increased TF has been reported in patients with lymph node metastases, regardless of histologic type [19]. The present study

found lymph node metastasis in 4 of 6 patients with Trousseau syndrome, including 2 of the 2 SCC cases; more attention may be needed in SCC cases with multiple lymph node metastasis.

Trousseau syndrome can also occur in cervical cancer and is seen in advanced and recurrent cases; however, it is infrequent. Patients with adenocarcinoma or lymph node metastases may require special attention. The prognosis of patients with cerebral infarction due to Trousseau syndrome is poor. In the 6 cases presented here, symptoms such as dysarthria and hemiplegia were observed. There were no deaths due to cerebral infarction because the patients came to the hospital early in their illness and were treated for cerebral infarction. However, because the underlying disease progressed rapidly and was refractory to treatment, all patients died of the underlying disease within 0–6 months after the stroke.

In conclusion, cervical cancer causes Trousseau syndrome in cases of advanced disease with a short time between the onset of the syndrome and mortality.

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