

CASE REPORT

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# Trousseau syndrome in a patient with advanced oral squamous cell carcinoma: a case report

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## Abstract

**Background:** Trousseau syndrome is known as a variant of cancer-associated thrombosis. Trousseau syndrome commonly occurs in patients with lung or prostate cancer. Hypercoagulability is thought to be initiated by mucins produced by the adenocarcinoma, which react with leukocyte and platelet selectins to form platelet-rich microthrombi. This is the first report of Trousseau syndrome in a patient with oral cancer.

**Case presentation:** Here, we describe the case of a 61-year-old Japanese man diagnosed as having advanced buccal carcinoma (T4bN2bM1; the right scapula, erector spinae muscles, and the right femur), who experienced aphasia and loss of consciousness. Although magnetic resonance imaging showed cerebral infarction, carotid invasion by the tumor and carotid sheath rupturing, cardiovascular problems, and bacterial infection were not present, which indicated Trousseau syndrome.

**Conclusions:** Trousseau syndrome in oral cancer is rare, but we must always consider cancer-associated thrombosis in patients with advanced stages of cancer regardless of the primary site of the cancer and take steps to prevent it.

**Keywords:** Trousseau syndrome, Oral squamous cell carcinoma, Cancer-associated thrombosis

## Background

It is well known that patients with advanced malignant disease are at risk of a hypercoagulable condition, and may develop cancer-associated thrombosis (CAT) [1].

Trousseau syndrome (TS) is a known state of CAT and often occurs in patients with advanced solid cancers [2]. TS is defined as chronic disseminated intravascular coagulation (DIC) associated with non-bacterial thrombotic endocarditis. Recovery is rare in patients with TS and there is no established evidence regarding the effects of anticoagulant treatment on this condition [1, 3]. TS is currently used to describe a hypercoagulation disorder in patients with malignancy, similar to CAT [1, 3]. TS commonly occurs in pulmonary, digestive, gynecology, or urinary cancer [1, 3, 4], and no such condition has been reported in a patient with oral cancer.

Here, we described a case of TS in a patient with buccal squamous cell carcinoma (SCC).

## Case presentation

In 2017, a 61-year-old Japanese man was referred to an oral and maxillofacial surgeon in Tokai University Hospital, Isehara, Japan, because of trismus and general fatigue. He complained of gradually worsening trismus and a painful ulcerated wound in the right buccal mucosa that had failed to heal for the past 6 months. He was on medication for hypertension and had no other specific systemic disease. On physical examination, facial swelling without redness was observed on the middle right side of his face, and trismus was noted (inter-incisor distance was 17 mm). Ulceration was observed in the right buccal mucosa, and an indurated mass could be palpated on the skin of his right cheek. Multiple palpable cervical lymphadenopathies were observed. He underwent workup for suspected malignancy of the

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buccal mucosa. There were no neurological and cardiologic abnormalities.

Computed tomography (CT) showed a mass in the right buccal mucosa that extended superiorly destructing the lateral wall of the maxillary sinus, inferiorly to the retromolar trigone, and laterally to the buccinator and anterior border of the masseter muscles, with multiple cervical lymph node enlargements (Fig. 1a and b). Whole-body  $^{18}\text{F}$ -fludeoxyglucose (FDG) positron emission tomography (PET)/CT was performed. The PET scan showed increased uptake of FDG in multiple lymph nodes in the right cervical area, scapula and erector spinae muscles, and the right femur (Fig. 1c).

Laboratory tests on admission showed high white blood cell count (13,400 cells/ $\mu\text{L}$ ) and elevated levels of SCC marker (4.5 ng/mL), but did not show any disorder in other tests including blood coagulation tests and tumor markers: cancer antigen (CA) 19-9, 31 U/ml; and carcinoembryonic antigen (CEA), 1.0 ng/ml.

An incisional biopsy of the right buccal mucosa was performed, which confirmed the diagnosis of SCC. He was given a diagnosis of right buccal carcinoma (T4bN2bM1). Induction chemotherapy was planned, and he was admitted at our hospital. Five days after hospitalization and prior to the initiation of chemotherapy, he experienced aphasia and lost consciousness. He had right hemiparesis with right upper and lower extremities manual muscle test (MMT) grade 0 [5, 6], and his National Institute of Health Stroke Scale (NIHSS) was 19 [7, 8].

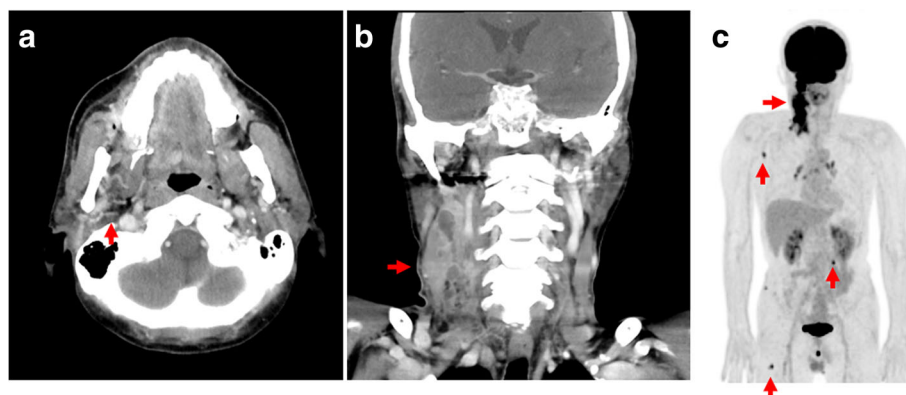
The first set of laboratory tests right after onset revealed a platelet count of  $31.1 \times 10^4/\mu\text{L}$ , a prothrombin time-international normalized ratio (PT-INR) of 1.06, and high levels of fibrinogen degradation product (FDP) at 9.2  $\mu\text{g}/\text{ml}$  and D-dimer at 5.4  $\mu\text{g}/\text{mL}$ . No marked abnormality was observed on other blood chemistry tests,

and the condition did not fulfill the diagnostic criteria for DIC. Brain CT, 30 minutes after the onset of symptoms, showed scattered hyperdense curvilinear areas suggestive of developing petechial hemorrhage in the region of his right middle cerebral artery (MCA) (Fig. 2a). Magnetic resonance imaging (MRI) was performed 100 minutes after the onset of symptoms. Diffusion-weighted image (DWI) showed a scattered lesion affecting the cortical part of the region supplied by his right MCA and perfusion imaging showed corresponding deficit (Fig. 2b). Head magnetic resonance angiography (MRA) showed attenuated flow-related signal in his right MCA region beyond the M1 segment, but its superior division was not visible (Fig. 2c). All imaging findings indicated right MCA infarction. A Doppler ultrasound scan of his neck revealed thrombosis of his left internal jugular vein (IJV), and compression of his right IJV by metastatic lymph nodes (Fig. 2d and e). He was diagnosed as having TS by multifocal cerebral infarction.

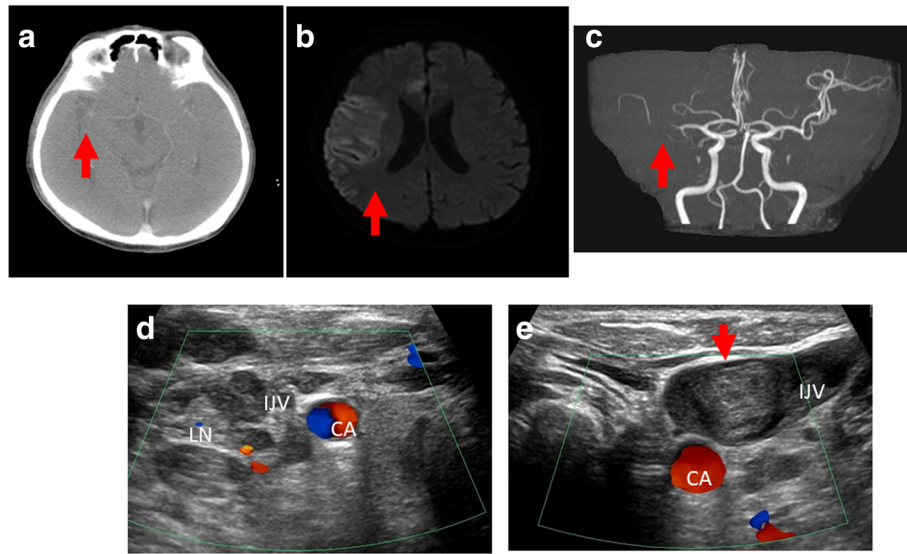
Intravenous recombinant tissue plasminogen activator (t-PA) (alteplase 0.6 mg/kg) was administered directly after the MRI scan. Electrocardiogram (ECG), Holter monitoring, echocardiography, and blood culture tests did not show any abnormalities. A head CT on 1, 3, and 7 days after onset showed that the infarction in his right MCA area had not recovered. Seven days after the onset of brain infarction, systemic heparinization was started (PT-INR, 1.5 to 2.0). He did not recover from his cerebral infarction and died 16 days after admission, 21 days after diagnosis, due to pneumonia. A pathological autopsy was not performed as the family did not consent. Family consent was obtained for this case report.

## Discussion

TS was first described in 1865 as migratory superficial thrombophlebitis in patients experiencing cancer [2]. TS



**Fig. 1** Patient computed tomography scan and positron emission tomography/computed tomography images. **a** and **b**) Computed tomography showed a mass in the right buccal mucosa (red arrow) that extended superiorly to destruct the lateral wall of the maxillary sinus, inferiorly to the retromolar trigone, and laterally to the buccinator muscle and the anterior border of the masseter muscles, with multiple cervical lymph node enlargement. **c**) Whole-body  $^{18}\text{F}$ -fludeoxyglucose positron emission tomography/computed tomography showed increased uptake in multiple lymph nodes in the right cervical area, right scapula and erector spinae muscles, and right femur (red arrows)



**Fig. 2** Patient computed tomography scan images after onset of aphasia and loss of consciousness. **a** Scattered hyperdense curvilinear areas (red arrow) suggestive of developing petechial hemorrhage in the region of the right middle cerebral artery. **b** Diffusion-weighted image showed a scattered lesion (red arrow) affecting the cortical part supplied by the right middle cerebral artery with corresponding deficit. **c** Head magnetic resonance angiography showed attenuated flow-related signal in middle cerebral artery beyond the M1 segment, while its superior division was not visible (red arrow). **d** A Doppler ultrasound scan of the neck revealed that the right internal jugular vein was compressed by metastatic lymph nodes. **e** A thrombosis was detected in the left internal jugular vein (red arrow). CA carotid artery, IJV internal jugular vein, LN metastatic lymph node

commonly occurs in lung (17%), pancreas (10%), colon and rectum (8%), kidneys (8%), and prostate (7%) cancers [4]. This is the first report on TS in a patient with oral cancer or SCC. Recent reports suggested that TS is considered a condition which induces stroke due to the hypercoagulability state associated with malignancy; with non-bacterial and non-circulation thrombotic endocarditis reported as the common causative factor [9–12]. In this case, although we could not carry out transesophageal echocardiography because of trismus, there were no signs

of thrombotic or bacterial endocarditis (normal ECG and echocardiography and negative blood culture). In addition, carotid invasion by the tumor and carotid sheath rupturing was ruled out by Doppler ultrasound given the fact that this is the most common cause of head and neck SCC (HNSCC)-associated cerebrovascular attack [13, 14], leading us to the diagnosis of TS in this patient.

TS is described as a chronic disseminated intravascular coagulopathy associated with microangiopathy, verrucous endocarditis, and arterial emboli in patients with cancer,

**Table 1** Khorana Risk Score criteria for assessing venous thromboembolism in patients with cancer

Risk factor	Points	Present patient
Site of primary cancer		
Very high risk (stomach, pancreas)	2	
High risk (lung, lymphatic system, reproductive organs, bladder, testicular)	1	
Low risk (all other sites)	0	0
Other characteristics		
Platelet count $\geq 350,000/\mu\text{l}$	1	
Hemoglobin level $< 10$ g/dl or use of red cell growth factors	1	
White blood cell count $> 11,000/\mu\text{l}$	1	1
Body mass index $\geq 35$ kg/m <sup>2</sup>	1	
Risk category	Score (Total points)	Risk of symptomatic VTE
High risk	$\geq 3$	7.1%
Intermediate risk	1 or 2	2.1%
Low risk	0	0.8%

VTE venous thromboembolism

**Table 2** Risk Scoring System of cancer-associated thrombosis criteria for assessing venous thromboembolism in patients with cancer

Risk factor	Point		Present patient
Age and sex			
40 to 80-year-old female	1		
> 80 years old	-1		
Prior history of VTE	3		
Cancer subtypes			
Low VTE propensity			
Head and neck, endocrine	-2		-2
Esophagus, breast	-1		
High VTE propensity			
Lung, gynecologic, sarcoma, metastasis unknown origin	1		
Myeloma, prostate	2		
Intermediate VTE propensity			
Other cancer subtypes	0		0
Risk category	Score (Total points)	Incidence of VTE	
High risk	3-	8.7%	
Intermediate risk	1-2	1.5%	
Low risk	=0	0.9%	
Very low risk	-4 to -1	0.5%	-2

**VTE venous thromboembolism**

which often occurs in mucin-positive carcinomas of the lung or prostate. Hypercoagulability is thought to be initiated by mucins produced by the adenocarcinoma, which will then react with leukocyte and platelet selectins to form platelet-rich microthrombi [12]. However, the etiology of TS is not known and multiple factors including thromboplastin-like substances, fibrin deposition, direct activation of factor X by tumor proteases, tissue factor, cysteine protease, tumor hypoxia, tumor-induced inflammatory cytokines, are believed to be responsible for this phenomenon in murine models [11, 15–18] of mucinous carcinoma. Although the present case lacks the typical findings of mucin-producing carcinoma, such as intracytoplasmic mucin or extracellular mucin pools, serum tumor markers CA 19-9 and CA-125 were markedly elevated in the tumor, according to immunohistochemical findings.

A recent study, using a large population-based database, indicated that the risk of stroke was significantly higher in patients with HNSCC. However, the risk of stroke in these patients was dependent on age, with the highest rate observed in patients younger than 40 years. The risk was also higher in those patients who had received both radiotherapy and chemotherapy [19]. Our patient did not have any of these risk factors. Thromboprophylaxis in hospitalized patients with cancer is almost universally recommended and two risk scoring systems for venous thromboembolism (VTE) in patients with cancer, namely the Khorana Risk Score (KRS) and

Risk Scoring System of CAT (RSSC), are widely used [17, 18, 20, 21]. Although both scoring systems recommend the use of thromboprophylaxis in patients with high or intermediate risk of VTE, both classify patients with head and neck cancer as low risk. This is because both systems are heavily dependent on the site of primary cancer, with gastric and pancreatic cancers scoring the highest on the KRS (2 points), followed by lung, lymphoma, gynecologic, bladder, and testicular cancers (scoring 1); with all other sites, including head and neck, gaining 0 points (Table 1). A similar point system can be observed in RSSC, with myeloma and prostate topping the list with 2 points, lung and gynecologic cancers and sarcoma receiving 1 point, esophagus and breast scoring 1, head and neck and endocrine having a 2-point score, and all other sites are scored as 0 (Table 2). In the present case, the risk of symptomatic VTE was calculated as 0.5–2.1% putting our patient in the intermediate group on the KRS scale and at very low risk on the RSSC. Although both systems recommend anticoagulation in high-risk groups to prevent VTE, patients with HNSCC are rarely categorized as high risk because both systems strongly rely on the primary site of the tumor.

Recovery in TS is slow and there is no established evidence supporting anticoagulant treatment in TS. Controlling the causative tumor and providing immediate systemic anticoagulation are the main steps for the treatment of TS. Systemic heparinization is considered an effective treatment strategy [3, 12, 22, 23].

## Conclusions

Based on our experience with this case, further investigations are required to prevent TS in cases of patients with head and neck carcinoma. If a patient has advanced cancer, there must be discussion concerning whether to use anticoagulation therapy to prevent VTE or not, regardless of the tumor primary site and histological type.

## Abbreviations

CA: Cancer antigen; CAT: Cancer-associated thrombosis; CEA: Carcinoembryonic antigen; CT: Computed tomography; DIC: Disseminated intravascular coagulation; DWI: Diffusion-weighted image; ECG: Electrocardiogram; FDG: <sup>18</sup>F-fludeoxyglucose; FDP: Fibrinogen degradation product; HNSCC: Head and neck squamous cell carcinoma; IJV: Internal jugular vein; KRS: Khorana Risk Score; MCA: Middle cerebral artery; MMT: Manual muscle test; MRA: Magnetic resonance angiography; MRI: Magnetic resonance imaging; NIHSS: National Institute of Health Stroke Scale; PET: Positron emission tomography; PT-INR: Prothrombin time-international normalized ratio; RSSC: Risk Scoring System of CAT; SCC: Squamous cell carcinoma; t-PA: Tissue plasminogen activator; TS: Trousseau syndrome; VTE: Venous thromboembolism

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## Authors' contributions

KA drafted the manuscript. MT, MU, YO, AK, and YOt provided figures and critical revision of the manuscript. YN provided figures and legends and critical revision of the manuscript. TAR and TAo were involved in general supervision, critical revision, and final approval of the manuscript before submission. All authors read and approved the final manuscript.

## Consent for publication

Written informed consent was obtained from the patient's next-of-kin for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

## Competing interests

The authors declare that they have no competing interests.

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