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Case Report

A Case of Gallbladder Cancer with Trousseau Syndrome Successfully Treated Using Radical Resection

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Trousseau syndrome is characterized by cancer-associated systemic thrombosis. We describe the first case of a successfully treated gallbladder adenocarcinoma accompanied by Trousseau syndrome. A 66-year-old woman presented with right hemiplegia. Magnetic resonance imaging identified multiple cerebral infarctions. Her serum carbohydrate antigen 19-9 and D-dimer levels were markedly elevated, and a gallbladder tumor was detected via abdominal computed tomography. Venous ultrasonography of the lower limbs revealed a deep venous thrombus in the right peroneal vein. These findings suggested that the brain infarctions were likely caused by Trousseau syndrome associated with her gallbladder cancer. Radical resection of the gallbladder tumor was performed. The resected gallbladder was filled with mucus and was pathologically diagnosed as an adenocarcinoma. Her postoperative course was uneventful, and she received a one-year course of adjuvant therapy with oral S-1. No cancer recurrence or thrombosis was noted 26 months postoperatively. Despite concurrent Trousseau syndrome, a radical cure of the primary tumor and thrombosis could be achieved with the appropriate treatment.

Key words: gallbladder cancer, Trousseau syndrome, radical surgery

Trousseau syndrome is characterized by systemic thrombosis, associated with venous thromboembolism (VTE) due to an underlying malignancy [1]. Because there is no national surveillance program for VTE, current prevalence and incidence estimates for cancer-associated VTE are based on population cohort studies or claims data and coding [2]. The incidence of cancer-associated VTE tends to be high for particularly aggressive cancers, such as pancreas and brain cancer [2]. Cancer patients with VTE fare worse, and patients with lung, liver, or pancreas cancer are more likely to develop distant metastases within one year following a VTE episode [3].

Trousseau syndrome is associated with advanced cancer and has an extremely poor prognosis. The median survival after onset is 4.5 months, with 25% of cases dying within 30 days of onset [4].

Most reports of malignant tumors with Trousseau syndrome involve unresectable diseases [5,6]. To our knowledge, this is the first reported case of a patient successfully treated for gallbladder adenocarcinoma with secondary Trousseau syndrome.

Case Presentation

A 66-year-old woman presented with right-sided hemiplegia. She had no risk factors for stroke, except

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for hypertension. Brain magnetic resonance imaging at her previous hospital revealed multiple cerebral infarctions (Fig. 1). Because contrast-enhanced computed tomography (CECT) upon admission at the previous hospital also revealed irregular wall thickening in the body of the gallbladder (Fig. 2), she was referred to our department for treatment of gallbladder cancer. She received oral antiplatelet agents, and was referred to our hospital for slight weakness of the right upper extremity. On admission at our department, laboratory examination showed elevated levels of carbohydrate antigen 19-9 (CA19-9) (299.8 U/mL) and D-dimer (13.1 pg/mL) (Table 1). Other coagulation or fibrinolysis parameters were unremarkable, and no other tumor markers were positive. Venous ultrasonography of the lower limbs showed a deep venous thrombus (DVT) in the right peroneal vein (Fig. 3). No arrhythmias were noted on 12-lead electrocardiography, and no abnormalities suggesting thrombotic endocarditis were demonstrated on transthoracic echocardiography. She was clinically diagnosed with Trousseau syndrome due to the presence of a malignant tumor, multiple cerebral infarctions, and DVT. No evidence of hepatic invasion, regional lymph node metastasis, or distant metastasis was observed, and she was finally diagnosed with resectable

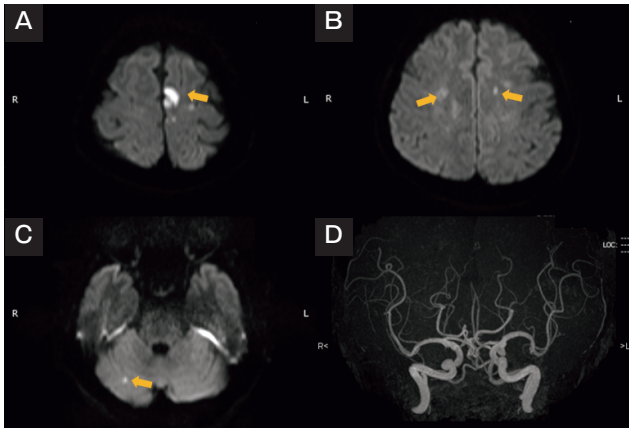

Fig. 1 **A**, **B**, **C**, Diffusion-weighted imaging showed multiple cerebral infarctions (Arrow); **D**, Magnetic resonance angiography did not detect stricture of cerebral artery.

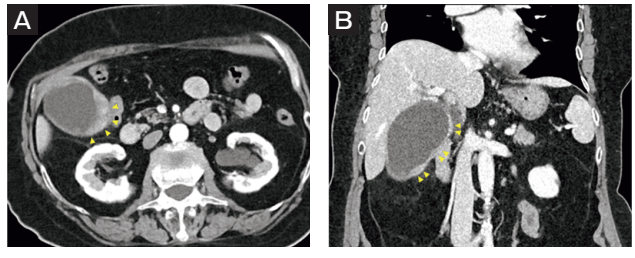

Fig. 2 Contrast enhanced computed tomography. Irregular wall thickening with contrast effect in the body of the gallbladder (arrowheads). **A**, axial view; **B**, coronal view.

Table 1

Hematology		Biochemistry		Coagulation	
WBC	8,540 /uL	TP	8.7 g/dL	PT-INR	1.14
RBC	438 $\times 10^4$/uL	T-Bil	0.5 mg/dL	APTT	26.7 sec
Hb	12.7 g/dL	AST	24 IU/L	D-dimer	13.1 Ug/mL
Ht	38.5 %	ALT	22 IU/L	Aint-CLAb	3.6 U/mL
Plt	22.1 $\times 10^3$/uL	LDH	316 IU/L	LAC	0.8
Serology		BUN	14.5 mg/dL	AT-III	74 %
CRP	2.1 mg/dL	Cr	0.8 mg/dL	Protein-C	104 %
ANA	<40 Fold	Na	140 mEq/L	Protein-S	83 %
CEA	1.0 ng/mL	K	4.3 mEq/L		
CA19-9	299.8 U/mL	Cl	101 mEq/L		

WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; Plt, platelet; CRP, C-reactive protein; ANA, antinuclear antigen; CEA, carcinoembryonic antigen; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time; Anti-CLAb, anticardiolipin antibody; LAC, lupus anticoagulant; AT-III, antithrombin III.

gallbladder cancer with secondary Trousseau syndrome.

One week before the operations, the patient's oral antiplatelet agent was suspended, and intravenous heparin was initiated. Two weeks after the diagnosis of gallbladder cancer, segment 4a+5 hepatic resection with bile duct resection and biliary reconstruction was performed. The total operative time was 215 min, and the intraoperative blood loss was 1,445 mL. Intravenous heparin was continued for one week following surgery, then switched to direct oral anticoagulant therapy with edoxaban. On gross examination of the resected specimen, the gallbladder was mucus-filled, and the mucosal surface was covered with multiple nodular masses (Fig. 4). High-grade biliary intraepithelial neoplasia was noted, and tumor invasion was detected at six sites, with a maximum tumor depth reaching the subserosa (Fig. 5). There was no involvement of the hepatic parenchyma or extrahepatic duct, but one regional lymph node metastasis was detected. The final histopathological diagnosis was pathological Stage IIIb gallbladder adenocarcinoma according to the TNM classification [7], and negative tumor margins were achieved.

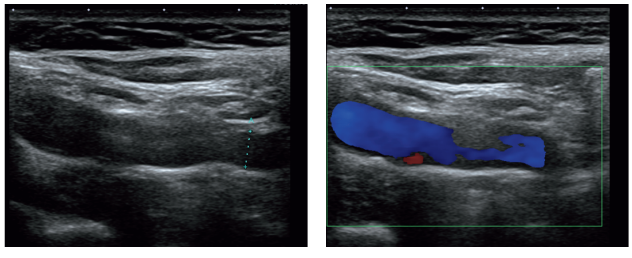

Fig. 3 Ultrasound sonography showed deep venous thrombosis.

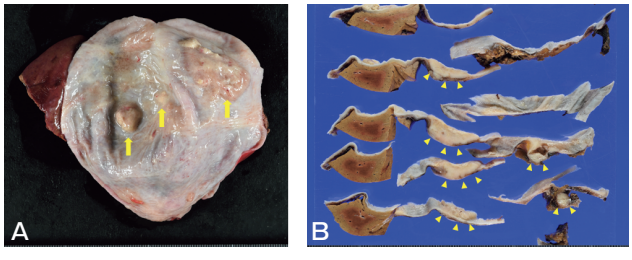

Fig. 4 Specimen. **A**, Macroscopic findings. Mucosal surface of the gallbladder was covered with multiple nodular masses (arrow); **B**, Cut surface of the specimen. (The location of tumors was indicated by arrowheads).

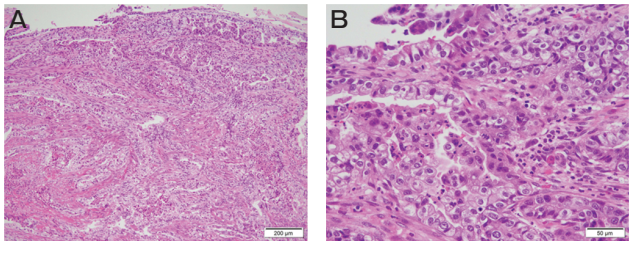

Fig. 5 Pathological tissue portraits (Hematoxylin-Eosin staining). The tumor histology was tubular adenocarcinoma. **A**, Scale bar = 200 μm; **B**, Scale bar = 50 μm.

Her postoperative course was uneventful, and she was discharged on the 14th postoperative day. Her neurological deficit had fully recovered when she was discharged from our hospital. As adjuvant therapy, S-1 was administered orally at 80 mg/day for 14 consecutive days, followed by a 7-day rest period, for one year. She continued to take anticoagulation agent. No cancer recurrence or new thrombotic episode had been observed at 26 months postoperatively.

Discussion

We report a case of gallbladder cancer with secondary Trousseau syndrome, successfully managed with radical resection with adjuvant chemotherapy. This case demonstrates that radical treatment of gallbladder cancer is allowable despite secondary Trousseau syndrome. Recurrence-free survival for more than 26 months was achieved for both the tumor and cerebral infarction.

Trousseau syndrome is a condition in which stroke occurs due to increased blood coagulation associated with malignancy. The incidence of embolism varies depending on the cancer's histological type, with adenocarcinomas and pancreatic cancers being the most frequent cause of VTE [8, 9]. Patients who develop Trousseau syndrome often have advanced cancer. Since the primary disease is often challenging to treat, the prognosis is often poor. However, there are only a few reports of patients suffering from gallbladder carcinoma with secondary Trousseau syndrome; scant information on the prognosis of these patients has been available [10].

Several mechanisms underlying cancer-related VTE have been proposed [11]. The factors involved in hypercoagulation in patients with advanced cancers include tissue factors, cysteine protease, tumor hypoxia, tumor-induced inflammatory cytokines, and carcinoma mucin [10]. Carcinoma production of mucin is believed to play an essential role in the onset of Trousseau syndrome because histopathologic examina-

tion revealed adenocarcinoma of the gallbladder with mucin production. However, in our case, we did not reveal evidence of mucinous production in the resected specimen. Elevated serum D-dimer levels have been reported to be associated with Trousseau syndrome and increased mucin tumor markers such as CA125 and CA19-9 [12]. In our case, the patient's preoperative D-dimer and CA19-9 levels were elevated, consistent with previous findings of Trousseau syndrome in patients with gallbladder carcinoma.

Gallbladder cancer is a malignancy with a relatively poor prognosis, with advanced stages such as the current case having a reported five-year survival rate of 9-27% [13]. It has, however, been reported that six months of oral S-1 as postoperative adjuvant chemotherapy after curative resection can significantly prolong survival [14]. Early thrombosis treatment and malignancy control are prognostic factors in treating Trousseau syndrome. However, when physical function is impaired due to the development of cerebral infarction or pulmonary embolism, surgery is often impossible, or chemotherapy must be discontinued [15]. In our case, radical resection was performed within two weeks of the diagnosis of gallbladder cancer with Trousseau syndrome. The ability to initiate adjuvant chemotherapy using S-1, without postoperative morbidities after surgical management, likely contributed to this patient's favorable outcome.

Despite the rarity of gallbladder carcinoma with secondary Trousseau syndrome, its poor prognosis after curative resection indicates that we must strive to improve the surgical outcomes of this disease. More epidemiological and pathological data are required to determine the appropriate surgical indications in this situation.

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