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Case Report

Trousseau's Syndrome with Advanced Neuroendocrine Carcinoma of Colon: A Case Report

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Keywords
Neuroendocrine carcinoma · Colon · Chemotherapy · Trousseau's syndrome · Cerebral infarction

Abstract
Here, we present a 69-year-old female with advanced neuroendocrine carcinoma (NEC) of colon with multiple liver, bone, and kidney metastases who developed Trousseau's syndrome. The patient received etoposide plus cisplatin (EP) as the first-line therapy; however, after single administration of EP, she developed the severe lower-limb edema and EP was considered to be intolerable. Etoposide plus carboplatin was administered as the second-line therapy and after 3 cycles of administration, the progressive disease (PD) was confirmed and 5-fluorouracil + leucovorin + irinotecan (FOLFIRI) plus ramucirumab was administered as the third-line therapy. However, PD was confirmed after 3 cycles of the therapy, and she was to receive the best supportive care and was hospitalized in our hospital. Four weeks after hospitalization, mild impaired consciousness and dysarthria were observed. Blood tests showed coagulation abnormalities including elevation of plasma fibrin/fibrinogen degradation products (FDPs) and D-dimer levels, and the diffusion-weighted image of magnetic resonance imaging (MRI) of the head showed multiple cerebral infarcts. She was diagnosed with Trousseau's syndrome due to the progression of NEC and intravenous unfractionated heparin was administered as anticoagulant therapy. After the administration of heparin, plasma FDP and D-dimer levels decreased; however, due to the progression of NEC, the patient died 6 weeks after hospitalization. This is the first report of NEC of the colon that developed Trousseau's syndrome.

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Introduction

Neuroendocrine carcinoma (NEC) is a subtype of neuroendocrine neoplasm (NEN) derived from neuroendocrine cells with a poor differentiation. NEC is a rare cancer that accounts for about 10% of NEN cases and for less than 1% of colorectal carcinomas. Immunohistochemical staining for neuroendocrine markers, including synaptophysin, chromogranin A, and NCAM/CD56, as well as pathological examinations including differentiation, mitotic figure, and Ki67 index, are used for the diagnosis of NEC [1, 2]. NEC generally shows a rapid growth and early metastases. Systemic chemotherapy is administered for advanced cases and the therapeutic effects have been reported in several regimens as follows: irinotecan plus cisplatin (IP), etoposide plus cisplatin (EP)/carboplatin, 5-fluorouracil + leucovorin + irinotecan (FOLFIRI), and 5-fluorouracil + leucovorin + oxaliplatin (FOLFOX) [3, 4]. Recently, the combination therapy of chemotherapy and ramucirumab, anti-vascular endothelial growth factor receptor 2 (VEGFR2) antibody, or immune checkpoint inhibitor, has been reported to be promising for advanced NEC [5, 6]. However, the prognosis of advanced NEC remains poor. The relationship between malignant tumors and a hypercoagulable state has been reported. Tumor cells activate coagulation through cancer procoagulant, tumor cell surface tissue factor, plasminogen activator, and plasminogen activator inhibitor-1 [7]. Trousseau's syndrome is recognized as the thrombosis induced by hypercoagulable state or disseminated intravascular coagulation (DIC), which is associated with malignancies. Trousseau's syndrome is commonly observed in patients with lung, gastrointestinal, and gynecologic advanced adenocarcinoma; however the relationship between Trousseau's syndrome and NEC is unknown [7, 8]. To the best of our knowledge, there is no previous report of Trousseau's syndrome in NEC of colon. We report a case of Trousseau's syndrome that developed after the progression of NEC of colon.

Case Presentation

A 69-year-old female was admitted to a local hospital complaining of abdominal discomfort in December 2021. Abdominal ultrasonography showed multiple diffuse space occupying lesions with a maximum diameter of 10.5 cm in the liver, and contrast-enhanced computed tomography (CT) also showed multiple lesions of liver, both kidneys, and cecum (Fig. 1a–c). Colonoscopy showed an excavated lesion in the cecum (Fig. 1d) and a biopsy was performed. She was suspected to have advanced colorectal cancer and was referred to our hospital. A pathological examination of biopsy samples of the cecum showed atypical epithelial cells showing a solid pattern of proliferation. Immunohistochemically, tumor cells were positive for CAM5.2, synaptophysin, and CD56, and negative for chromogranin A and CDX2 (Fig. 2), and she was diagnosed with advanced NEC of colon. She had no history of other malignant tumor, cerebral infarction, arrhythmia, or hypertension. The general condition was Eastern Corporative Oncology Group Performance Status (ECOG PS) 1. Physical examination showed a palpable right hypochondrial mass and abdominal tenderness; however, no edema of limbs was observed. Blood tests showed elevated plasma levels of FDP and D-dimer (36.5 μg/mL and 17.5 μg/mL, respectively); however, PT% and the plasma fibrinogen level were within normal limits. Elevated serum levels of tumor markers including CEA, CA19-9, and NSE (41.3 ng/mL, 1,945.1 U/mL, and 582 ng/mL, respectively) were observed, while plasma ProGRP level was within normal limits (33.9 pg/mL). EP (etoposide 100 mg/m^2 day1–3, cisplatin 80 mg/m^2 day1, 3-week cycle) was administered as the first-line chemotherapy for advanced NEC of the cecum in December 2021; however, after single administration of EP, she developed grade 3 lower-limb edema according to Common Terminology

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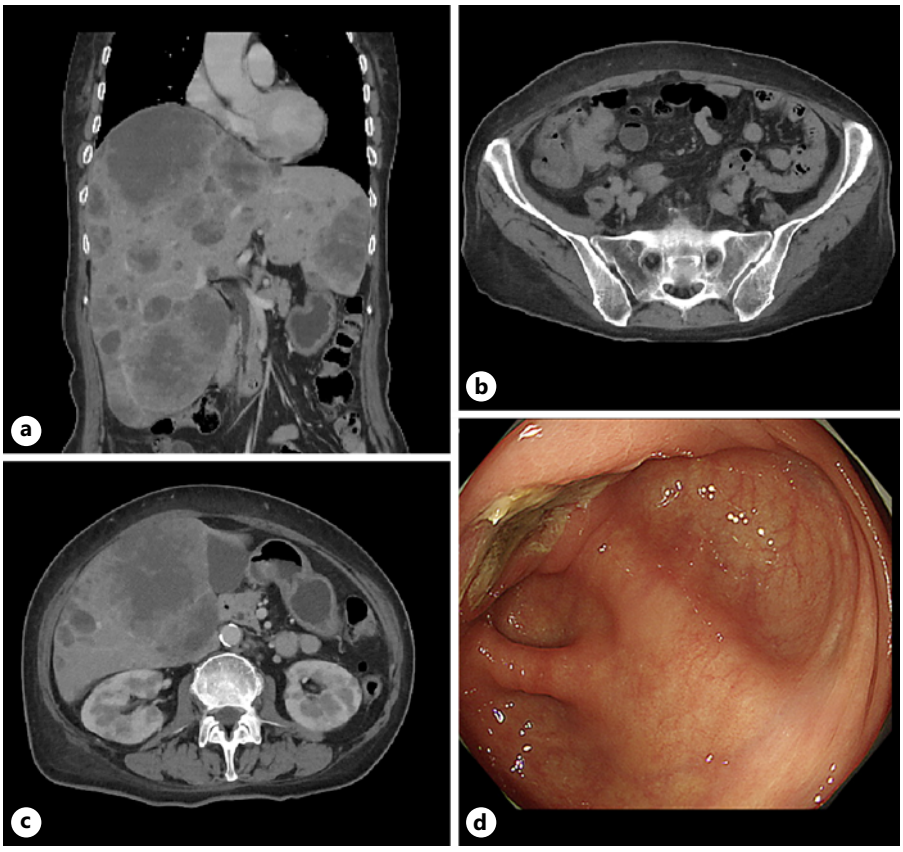

Fig. 1. Contrast-enhanced CT and colonoscopy images prior to the administration of chemotherapy. Multiple lesions of liver (**a**), cecum (**b**), and kidney (**c**) are shown. Colonoscopy showed an excavated lesion in the cecum (**d**).

Criteria for Adverse Events v5.0 due to the infusion load and had difficulty in the daily life. EP was considered to be intolerable. The lower-limb edema improved after withdrawal of EP and oral administration of diuretics including spironolactone and furosemide. EC (etoposide 100 mg/m^2 day1–3, carboplatin AUC 5 mg/mL/min day1, 3-week cycle) was administered as the second-line therapy. After 3 cycles of EC, PD was confirmed by CT and FOLFIRI plus ramucirumab was administered as the third-line therapy. However, gradual progression of general malaise and worsening of PS were observed. CT after 3 cycles of the therapy showed new multiple bone metastases of the vertebrae, and PD was confirmed in April 2022. As her general condition got worsened (ECOG PS 3), it was considered to be difficult to continue chemotherapy. She was hospitalized in our hospital for the best supportive care. Her general condition got worsened (ECOG PS 4); however, there was no finding of dehydration or arrhythmia including atrial fibrillation on electrocardiogram. Four weeks after hospitalization, she developed mild impaired consciousness (Glasgow Coma Scale; E4V4M6) and had slurred speech. The diffusion-weighted image of MRI of the head showed multiple small infarcts in cerebral cortex and white matter (Fig. 3). Blood tests showed coagulation abnormalities (FDP 44.8 μg/mL, D-dimer 22.7 μg/mL, APTT 72.4 s, PT% 59.7%, AT-III 40%, fibrinogen 155.3 mg/dL, platelets 98,000/μL). According to the International Society on Thrombosis and Haemostasis's DIC diagnostic criteria (ISTH criteria), score was 5 points, and she was diagnosed with DIC. Transthoracic echocardiography showed no evidence of

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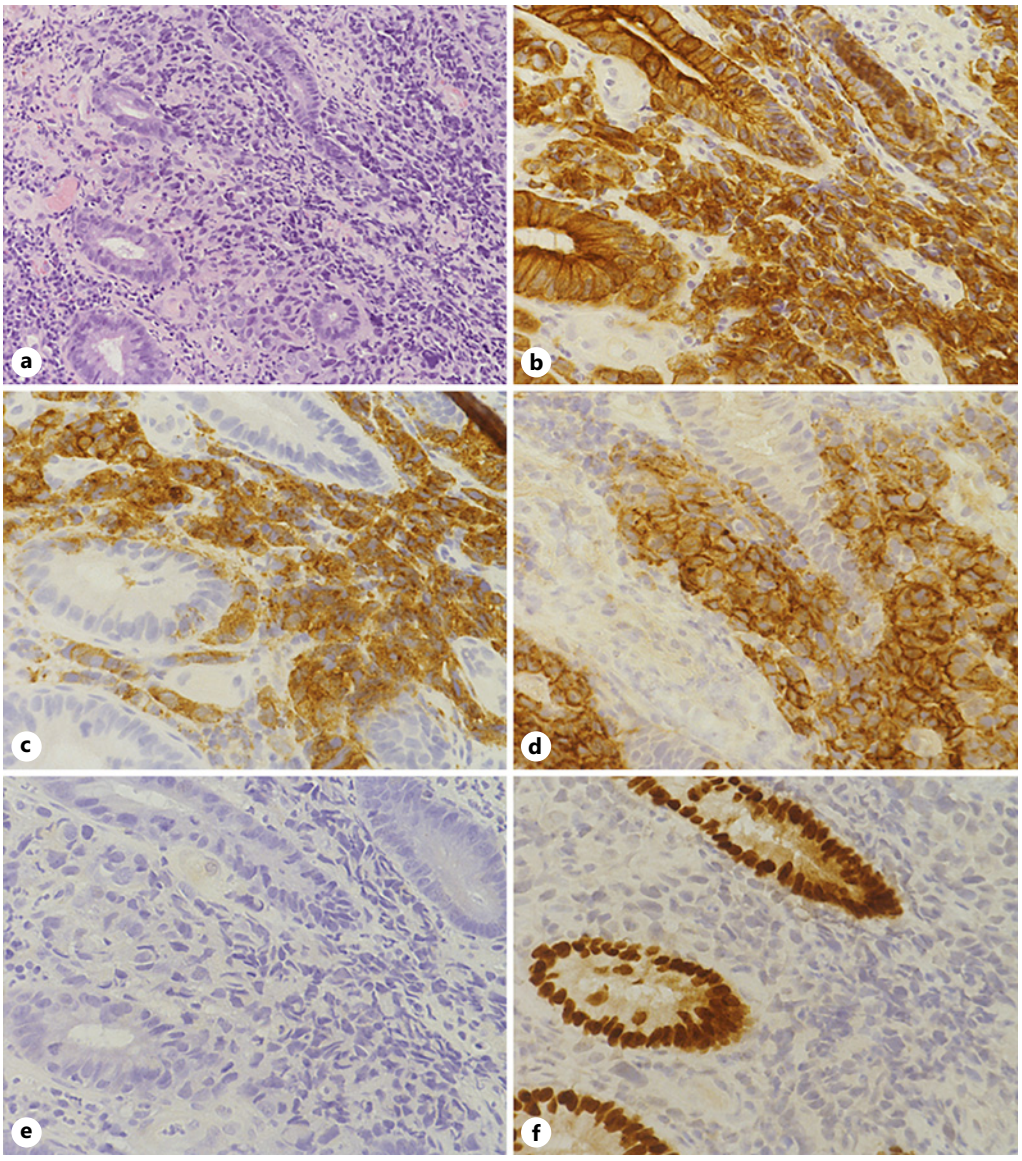

Fig. 2. a Histopathological examination of the biopsy from the lesion of cecum showed atypical epithelial cells showing a solid pattern of proliferation. Immunohistochemically, tumor cells were positive for CAM5.2 (**b**), synaptophysin (**c**), and CD56 (**d**) and negative for chromogranin A (**e**) and CDX2 (**f**).

intracardiac thrombosis or arrhythmia. Blood tests showed no serum sugar or electrolyte abnormalities that would cause impaired consciousness. According to these results, she was diagnosed with Trousseau's syndrome, and anticoagulant therapy with intravenous unfractionated heparin (10,000 U/day) was administered. Two days after the administration of heparin, plasma levels of FDP and D-dimer decreased (28.2 μg/mL and 12.5 μg/mL, respectively), suggesting the treatment effect of anticoagulant therapy. No other neurological symptom had developed; however, her complaint of abdominal discomfort got stronger, and physical examination showed an increase in the right hypochondrial mass, suggesting the disease progression. The patient died 6 weeks after hospitalization due to the progression of NEC.

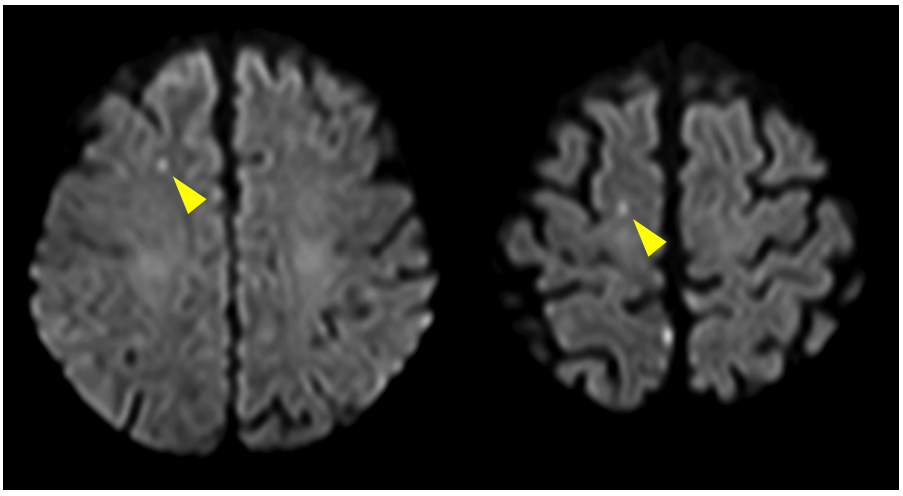

Fig. 3. The diffusion-weighted image of MRI of the head showed multiple small infarcts in the brain. Yellow allows indicate the lesions.

Discussion

This case was diagnosed with Trousseau's syndrome based on the findings of malignant tumor, DIC, and thrombosis. Transthoracic echocardiography showed no intracardiac thrombosis or vegetation, and the cardiogenic cerebral embolism was ruled out. Trousseau's syndrome is the cancer-related thrombosis, and about 10% of all thrombotic events are arterial thrombosis, which have been observed in cerebral arteries and upper and lower limb arteries [9]. The case report of Trousseau's syndrome in NEC was searched using PubMed, Scopus, CiNii, and J-STAGE from inception to November 2022 using the search terms "neuroendocrine carcinoma" and "Trousseau's syndrome", and one case report of Trousseau's syndrome with advanced NEC of esophagus was found [10]. Anticoagulant therapy with low-molecular-weight heparin (LMWH) or unfractionated heparin has been reported to be effective for Trousseau's syndrome [9]; however, it has also been reported that significant recurrence of thrombosis occurs due to the discontinuation of heparin, making it difficult to discontinue anticoagulant therapy and long-term administration might be required [11]. Direct oral anticoagulants (DOACs) including rivaroxaban, apixaban, and edoxaban have been reported to be promising for the management and prevention of thromboembolism [12] and can be administered orally without the need for PT-INR monitoring. A previous systematic review and meta-analysis that compared DOAC with LMWH for cancer-associated venous thromboembolism (VTE) showed that DOAC was associated with the lower risk of recurrent VTE and the higher risk of major bleeding compared with LMWH; however, these results were not statistically significant [13]. Khorana score is used to classify the risk of developing cancer-associated VTE [14] and this case was classified into the low-risk group, making it difficult to predict the onset of thromboembolism. However, it has been reported that Trousseau's syndrome is commonly observed in patients with advanced malignancies [9]; early administration of anticoagulants including heparin or DOAC for cases with advanced malignancies might be desirable. Adenocarcinomas have also been reported as a risk factor for cancer-related thrombosis which is considered to be caused by mucin secretion from adenocarcinoma [15]. NEC has been reported to coexist with adenocarcinoma and the tumor with different component of NEC and adenocarcinoma is defined as

mixed neuroendocrine-non-neuroendocrine neoplasm in the 2019 WHO classification. This case was pathologically diagnosed as NEC; however, elevated serum tumor markers of adenocarcinoma (CEA and CA19-9) as well as serum neuroendocrine markers were observed, suggesting the coexistence of the adenocarcinoma component outside the scope of biopsy, which might have contributed to the risk of thrombosis.

In this case, the cerebral infarcts occurred approximately 1 month after the last dose of ramucirumab. It has been reported that the half-life of ramucirumab in the blood is approximately 1 week, suggesting sufficient drug clearance of ramucirumab. Anti-VEGF antibodies, including bevacizumab, have been reported to be associated with the increased risk of thromboembolic events; however, ramucirumab, anti-VEGFR2 antibody, has not increased the risk of thromboembolic events in a meta-analysis of safety data from six randomized, placebo-controlled trials with ramucirumab [16]. In this study, arterial thromboembolic events were observed in 1.4% of ramucirumab arm and 1.8% in the control arm. And venous thromboembolic events were observed in 3.9% of ramucirumab arm and 5.2% in the control arm. These results also suggest that advanced cancer itself is the risk factor for thromboembolic events, supporting the anticoagulant therapy for patients with advanced cancer. Trousseau's syndrome may not be a rare disease; however, Trousseau's syndrome also occurs in a rare disease, NEC, and the risk of thrombosis should always be considered in advanced cases. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material at https://doi.org/10.1159/000530927.

Conclusion

In summary, we report the first case of NEC of the colon that developed Trousseau's syndrome after the disease progression. Early administration of anticoagulants including heparin or DOAC for cases with advanced malignancies might be desirable for preventing the cancer-related thrombosis including Trousseau's syndrome.

Acknowledgments

The authors are grateful to the patient for participating in this case report.

Statement of Ethics

Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

E.B. has received lecture fee from Ono Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, Merk, Sanofi, MSD, Eisai, and Daiichi-Sankyo. E.B. received research funding from Taiho Pharmaceutical, Chugai Pharmaceutical, and Eli Lilly. All the other authors have no conflict of interest.

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Author Contributions

H.O., E.B., and T.H. contributed to the design of the report and drafted the manuscript. T.T. and K.M. critically revised the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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