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【 CASE REPORT 】

Choledochoduodenal Fistula during Chemotherapy with Brentuximab Vedotin for Methotrexate-associated Lymphoproliferative Disorder

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Abstract:
We herein report a patient with a history of rheumatoid arthritis treated with methotrexate, which caused methotrexate-associated lymphoproliferative disorder and obstructive jaundice due to an enlarged lymph node. The obstructive jaundice was treated with endoscopic biliary stenting. A histopathological examination revealed features of Hodgkin's lymphoma, and chemotherapy with brentuximab vedotin was administered. Cholangiography and duodenoscopy after four rounds of chemotherapy revealed a choledochoduodenal fistula that developed in response to chemotherapy. It should be noted that, in cases of lymphoma infiltrating the gastrointestinal wall, fistulae can occur because of rapid regression due to regimens comprising monoclonal antibodies, such as rituximab and brentuximab vedotin.

Key words: choledochoduodenal fistula, methotrexate-associated lymphoproliferative disorder, rheumatoid arthritis, brentuximab vedotin

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Introduction

Choledochoduodenal fistula (CDF) is a relatively rare condition involving an abnormal communication between the common bile duct (CBD) and duodenum. The most common etiologies of CDF are duodenal ulcer, carcinoma of the duodenum or bile duct, and iatrogenic injury due to a self-expandable metallic stent (1-6). However, CDFs associated with lymphoma treatment are rare.

We herein report a rare case of CDF that occurred during chemotherapy with brentuximab vedotin for methotrexate-associated lymphoproliferative disorder (MTX-LPD).

Case Report

An 83-year-old man was admitted to our hospital to undergo cholangiography. He had a history of rheumatoid arthritis and had been taking methotrexate (MTX, 8 mg per week) for six years. After developing multiple lymphadenopathy 11 months earlier, he was diagnosed with MTX-LPD, prompting the immediate withdrawal of MTX. Subsequently, his multiple lymphadenopathy partially resolved. However, he developed obstructive jaundice 2 months later because of a 40-mm mass adjacent to the CBD. Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) demonstrated the uptake of ^{18}F-FDG by the mass (Fig. 1). A histopathological examination of the mass obtained via an endoscopic ultrasonography-guided fine-needle aspiration biopsy showed atypical lymphocytic infiltration. An immunohistological analysis was difficult because of the insufficient volume of the sample.

The obstructive jaundice was treated with percutaneous transhepatic biliary drainage and endoscopic biliary stenting, and four rounds of chemotherapy with rituximab were administered. However, his multiple lymphadenopathy did not improve. Therefore, an excisional biopsy of the left supraclavicular lymph node was performed. A histopathologi-

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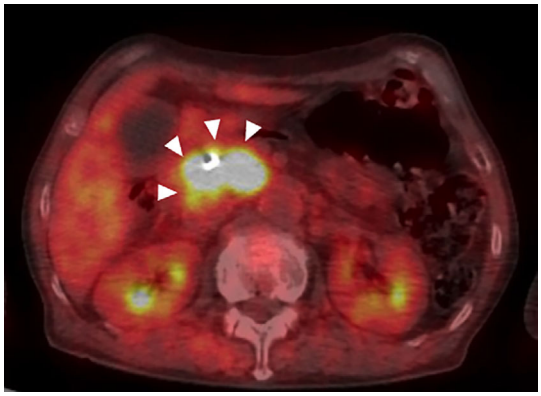

Figure 1. **Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography scan showing the uptake of ^{18}F-FDG by the mass, adjacent to the common bile duct (white arrowheads).**

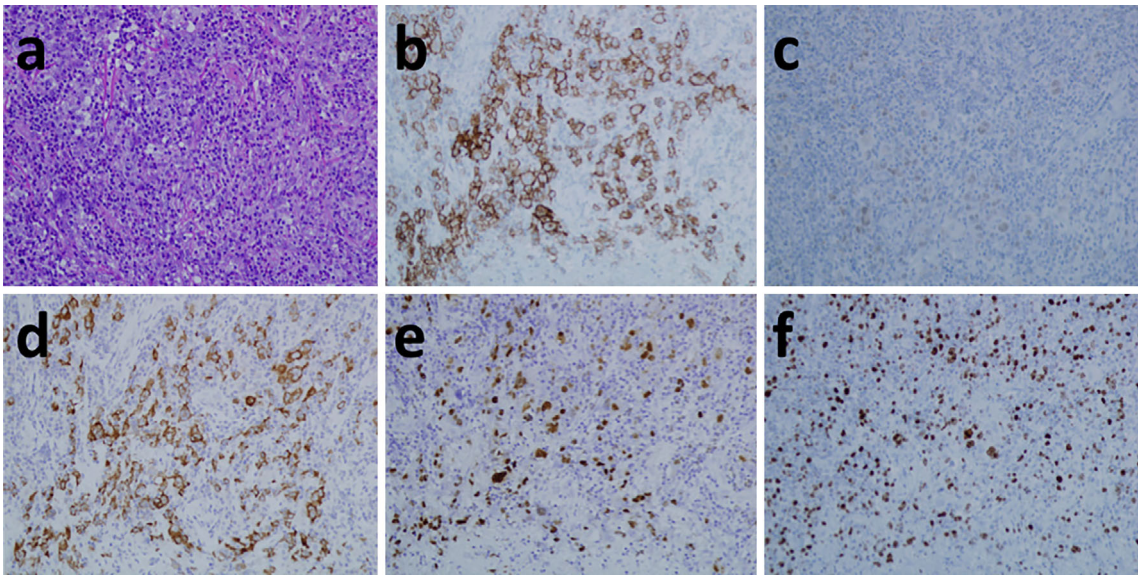

Figure 2. **(a) A histopathologic examination of the resected the left supraclavicular lymph node (Hematoxylin and Eosin staining, ×200). (b-f) Immunohistochemistry findings of the lymph node. The neoplastic cells are positive for CD30 (b), PAX-5 (c), IMP3 (d), EBER (e), and Ki-67 (f), which is consistent with methotrexate-associated lymphoproliferative disorder with Hodgkin's lymphoma-like features (×200).**

cal analysis revealed Reed-Sternberg cells with immunohistological positivity for CD30, PAX5, IMP3, EBER, and Ki-67 (Fig. 2). He was therefore diagnosed with MTX-LPD with Hodgkin's lymphoma-like features, and rituximab was switched to brentuximab vedotin (Adcetris®, Takeda Pharmaceutical, Tokyo, Japan), an antibody-drug conjugate directed against CD30. ^{18}F-FDG-PET after four rounds of chemotherapy with brentuximab vedotin revealed a markedly reduced mass (Fig. 3). Therefore, removal of the biliary drainage tubes was planned.

Percutaneous transhepatic cholangiography showed outflow of the contrast dye from the CBD to the duodenum (Fig. 4a). Duodenoscopy revealed the exposure of the side wall of the stent, indicating a CDF due to the response to chemotherapy (Fig. 4b). Drainage tubes were removed because the bile was thought to smoothly flow through the CDF. After removal of the tubes, obstructive jaundice did not recur, and the patient was discharged on day 14 of hospitalization. Two additional rounds of chemotherapy with brentuximab vedotin were administered at an outpatient clinic.

One month after discharge, the patient visited the emergency department of our hospital with a chief complaint of melena. Emergent gastroduodenoscopy revealed no active bleeding. However, the accumulation of blood was found in the duodenum, and hemorrhaging from the fistula was highly suspected (Fig. 5a). Angiography did not identify active contrast medium extravasation (Fig. 5b). However, contrast-enhanced computed tomography (CT) suggested that the gastroduodenal artery (GDA), which was adjacent to the fistula, was the source of the bleeding (Fig. 5c). Therefore, transcatheter arterial embolization (TAE) using seven

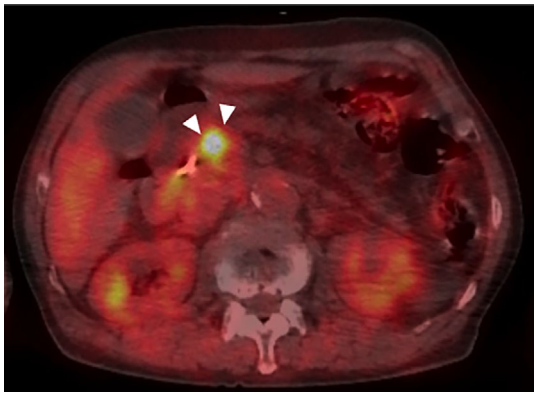

Figure 3. **Fluorine-18-fluorodeoxyglucose positron emission tomography findings after four rounds of chemotherapy with brentuximab vedotin revealing a markedly reduced mass (white arrowheads).**

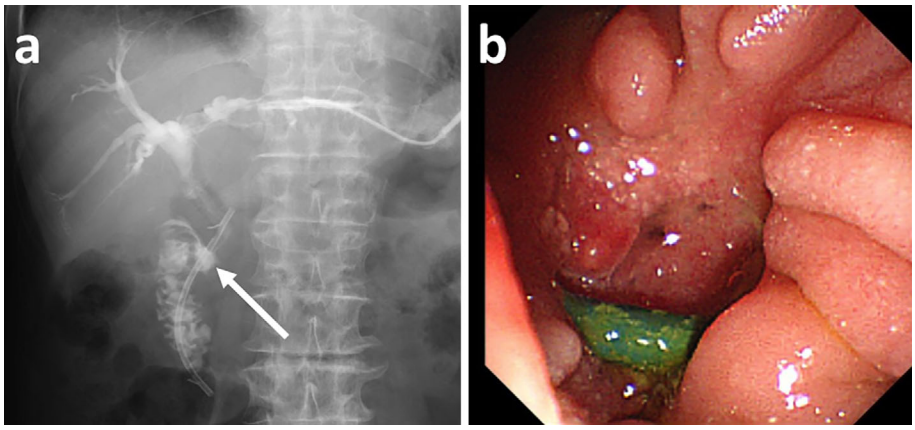

Figure 4. **(a) Percutaneous transhepatic cholangiography showing outflow of the contrast dye from the common bile duct to the duodenum (white arrow). (b) Duodenoscopy revealing the exposure of the side wall of the stent, indicating a choledochoduodenal fistula.**

coils for the GDA was performed to prevent re-bleeding. Angiography after TAE confirmed the complete occlusion of the GDA (Fig. 5d). The patient recovered and was discharged 15 days after TAE. ^{18}F-FDG-PET one month after TAE revealed the progression of MTX-LPD, including re-enlargement of the mass adjacent to the CBD (Fig. 6). Therefore, brentuximab vedotin was switched to nivolumab (Opdivo®, Ono Pharmaceutical, Osaka, Japan), an anti-programmed death-1 receptor antibody and three rounds of chemotherapy with nivolumab were administered.

The patient was admitted to the emergency department again with hematemesis. The last course of chemotherapy with nivolumab was administered 13 days before presentation. Blood transfusion and emergent CT were planned; however, he suddenly developed hemorrhagic shock after massive hematemesis followed by asystole and expired despite resuscitative efforts. An autopsy revealed enlarged lymph nodes infiltrating the duodenal wall and fistula formation, which were consistent with the source of bleeding.

Discussion

MTX-LPD is a rare but critical complication in patients treated with MTX. MTX-LPD is categorized as an iatrogenic immunodeficiency-associated LPD in the recent World Health Organization classification of lymphoid neoplasms. In many cases, spontaneous regression is achieved after MTX withdrawal, especially in cases of peripheral Epstein-Barr virus-DNA positivity, non-diffuse large B-cell lymphoma-type MTX-LPD, and the early recovery of the absolute lymphocyte count (7-9). However, in many cases of diffuse large B-cell lymphoma-type MTX-LPD, systemic chemotherapy is required (7, 8).

CDF involves an abnormal passage between the CBD and duodenum. The most common etiologies of CDF are duodenal ulcer, carcinoma of the duodenum or bile duct, and iatrogenic injury due to a self-expandable metallic stent (1-6). However, CDF associated with treatment of lymphoma is rare, and only one case of non-Hodgkin's lymphoma of the duodenum treated with cyclophosphamide, vincristine, hydrocortisone, and doxorubicin has been reported (10). In

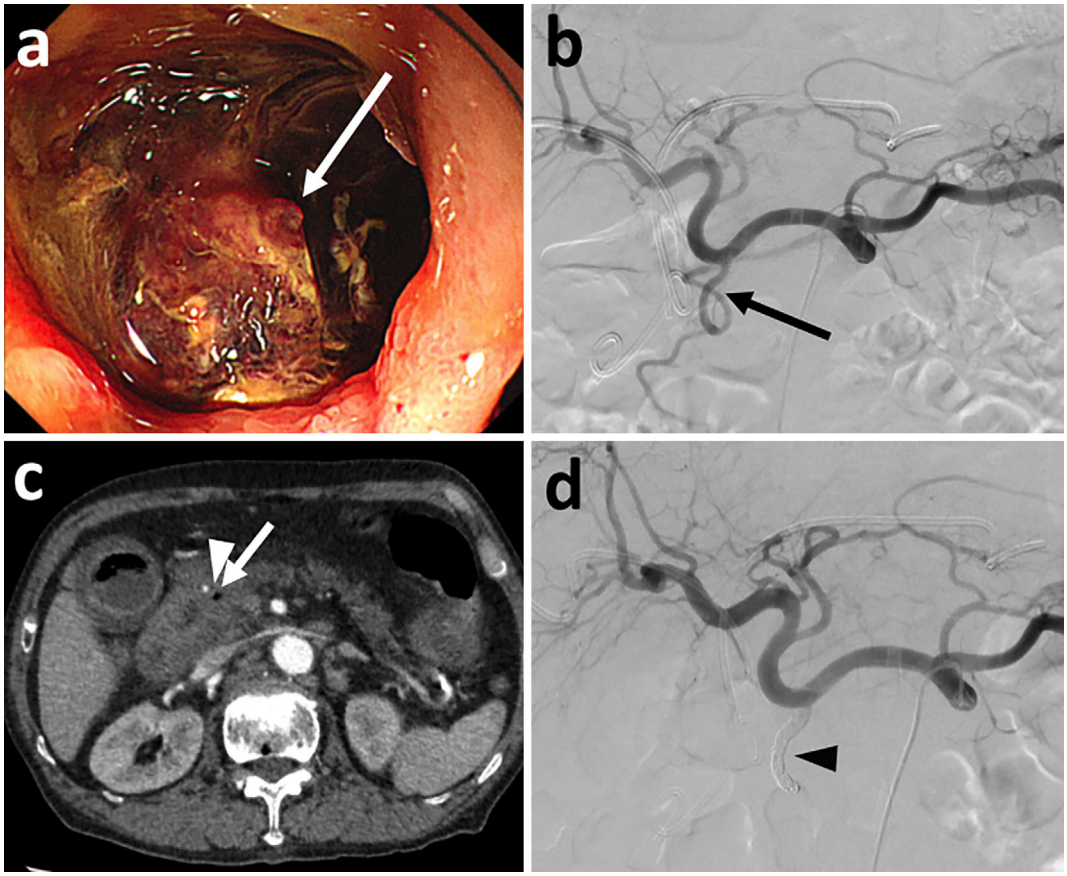

Figure 5. **(a) Duodenoscopy revealing a visible vessel in the fistula, which was suspected to be the source of bleeding (white arrow). (b) The angiogram did not identify active contrast medium extravasation from the gastroduodenal artery (GDA, black arrow). (c) A contrast-enhanced tomography scan showing that the GDA (white arrowhead) was adjacent to the fistula (white arrow), suggesting that the GDA was the source of bleeding. (d) An angiogram after embolization confirming the complete occlusion of the GDA (black arrowhead).**

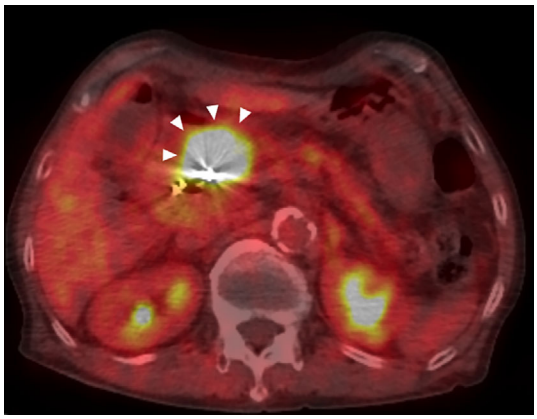

Figure 6. **Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography findings showing re-enlargement and the uptake of ^{18}F-FDG by the mass adjacent to the common bile duct (white arrowheads).**

cases of lymphoma infiltrating the gastrointestinal wall, gastrointestinal fistulae can occur as a result of rapid regression due to systemic chemotherapy. Regimens comprising monoclonal antibodies, such as rituximab and brentuximab vedotin, can lead to an increased incidence of fistula formation due to the potency of the treatment (11). In the present case, the rapid regression of an enlarged lymph node adjacent to both the duodenal wall and CBD was thought to have resulted in CDF formation and the first instance of hemorrhaging. The association between re-bleeding and the effect of nivolumab was unknown because the therapeutic effect of nivolumab was not assessed until the patient had died of

hemorrhagic shock. However, based on the autopsy findings, the effect of nivolumab was suspected to have been relatively slight at that moment, and the second episode of hemorrhaging was likely caused by tumor progression.

In conclusion, it should be noted that, in cases of lymphoma infiltrating the duodenal wall, the development of CDF or even of fatal hemorrhaging can occur after chemotherapy, especially with regimens containing monoclonal antibodies, such as rituximab and brentuximab vedotin.

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

References

1. Wong WM, Hu WH, Lai KC. Images of interest. Hepatobiliary and pancreatic: Choledochoduodenal fistula secondary to duodenal ulcer disease. J Gastroenterol Hepatol **19**: 829, 2004.
2. B S B, Kar A, Dutta M, et al. A case of choledochoduodenal fistula - an unusual case report. Clin Case Rep **5**: 1462-1464, 2017.
3. Lin CT, Hsu KF, Yu JC, et al. Choledochoduodenal fistula caused by cholangiocarcinoma of the distal common bile duct. Endoscopy **41**: E319-E320, 2009.
4. Williamson JB, Draganov PV. Choledochoduodenal fistula after biliary metallic stent placement for pancreatic cancer. Dig Endosc **26**: 292, 2014.
5. Ogawa T, Horaguchi J, Fujita N. Patent choledochoduodenal fistula created by endosonography-guided biliary drainage after migration of a metallic stent. Dig Endosc **25**: 84-85, 2013.
6. Chaudhari D, Saleem A, Murthy R, et al. Choledochoduodenal fistula after biliary placement of a self-expanding metallic stent for palliation of pancreatic cancer. Endoscopy **45**: E77, 2013.
7. Ichikawa A, Arakawa F, Kiyasu J, et al. Methotrexate/iatrogenic lymphoproliferative disorders in rheumatoid arthritis: histology, Epstein-Barr virus, and clonality are important predictors of disease progression and regression. Eur J Haematol **91**: 20-28, 2013.
8. Gion Y, Iwaki N, Takata K, et al. Clinicopathological analysis of methotrexate-associated lymphoproliferative disorders: comparison of diffuse large B-cell lymphoma and classical Hodgkin lymphoma types. Cancer Sci **108**: 1271-1280, 2017.
9. Takanashi S, Aisa Y, Ito C, et al. Clinical characteristics of methotrexate-associated lymphoproliferative disorders: relationship between absolute lymphocyte count recovery and spontaneous regression. Rheumatol Int **37**: 1629-1633, 2017.
10. Scott J, Spencer JA, MacLennan KA. Choledochoduodenal fistula complicating non-Hodgkin's lymphoma of the duodenum during chemotherapy. Clin Radiol **56**: 508-510, 2001.
11. Palmowski M, Zechmann C, Satzl S, et al. Large gastrosplenic fistula after effective treatment of abdominal diffuse large-B-cell lymphoma. Ann Hematol **87**: 337-338, 2008.