Case Report

Diffuse large B-cell lymphoma presenting with gastrocolic fistula and successfully treated with R-CHOP chemotherapy

Nobushiro Nishimura1, Futoshi Iioka1✉, Hirotaka Tomimatsu2, Fusako Kusumi3, Gen Honjo4, Katsuhiro Fukutsuka5, Hitoshi Ohno1,5

1Department of Hematology, Tenri Hospital; 2Department of Radiology, Tenri Hospital; 3Department of Gastroenterology, Tenri Hospital; 4Department of Diagnostic Surgical Pathology, Tenri Hospital; 5Tenri Institute of Medical Research
*Present address: Department of General Medicine, Nara Medical University

A Taiwanese woman in her fifties presented with a feculent odor and eructation. Her white cell count was 15.56 × 10^3/µL, albumin 3.2 g/dL, lactate dehydrogenase 335 U/L, C-reactive protein 4.8 mg/dL, and soluble interleukin-2 receptor 1,398 U/mL (reference range, 145 to 519 U/mL). Computed tomography (CT) revealed a left upper quadrant tumor encompassing the greater curvature of the stomach and splenic flexure of the colon to create gastrocolic fistula, and CT colonography confirmed communication between the two luminal organs. Upper gastrointestinal endoscopy showed a submucosal tumor at the greater curvature of the stomach and the orifice of the fistula was detected at the top of the tumor. Biopsies revealed the non-germinal center B-cell–like type of diffuse large B-cell lymphoma and lymphoma cells carried the BCL6 rearrangement. She was treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy under total parenteral nutrition and achieved a complete response after 6 cycles of R-CHOP; no perforation or bleeding complications occurred during the course of treatment. To the best of our knowledge, this is the first report of DLBCL presenting with gastrocolic fistula that was successfully treated with R-CHOP chemotherapy, avoiding surgical intervention.

Keywords: gastrocolic fistula, computed tomography colonography, gastrointestinal tract lymphoma, diffuse large B-cell lymphoma, R-CHOP

INTRODUCTION

The gastrointestinal (GI) tract is the predominant site of involvement of extranodal malignant lymphoma.1 A relationship has been reported between lymphoma subtypes and anatomical sites of the GI tract: mucosa-associated lymphoid tissue lymphoma develops in the stomach in association with Helicobacter pylori infection or with the t(11;18)(q21;q21) translocation; follicular lymphoma, which is basically nodal lymphoma, may arise in the duodenum; mantle cell lymphoma occasionally presents as lymphomatous intestinal polyposis; and Burkitt lymphoma preferentially develops in the ileocecum. On the other hand, diffuse large B-cell lymphoma (DLBCL), which is the most common pathological type of GI lymphoma, develops in essentially all sites of the GI tract.1 Since...
DLBCL shows aggressive clinical behavior, a thorough work-up and the immediate initiation of treatment are required.

GI lymphoma typically presents with non-specific signs and symptoms attributable to the site of involvement. We encountered a woman with a feculent odor and eructation. Multimodal imaging studies and endoscopic investigations as well as a histopathological examination revealed that she developed DLBCL encompassing the stomach and colon to create communication between the two luminal organs, i.e. gastrocolic fistula. Her symptoms, diagnostic studies, and treatment course are described in detail herein.

CASE PRESENTATION
A Taiwanese woman in her fifties presented with a feculent odor and eructation associated with a loss of appetite as well as left hypochondrial pain. Her symptoms had begun 3 months earlier and had progressed, resulting in body weight loss of 7 kilograms. An examination showed no surface lymphadenopathy. The liver and spleen were not palpable, while tenderness was elicited by palpation of the left hypochondrial region. Her performance status was ECOG 1.

Her hemoglobin level was 11.8 g/dL, white cell count $15.56 \times 10^3/\mu L$ with 77.0% neutrophils, and platelet count $276 \times 10^3/\mu L$. Total serum protein was 6.2 g/dL, albumin 3.2 g/dL, lactate dehydrogenase (LDH) 335 U/L, aspartate aminotransferase 22 U/L, alanine aminotransferase 18 U/L, total bilirubin 0.5 mg/dL, alkaline phosphatase 194 U/L, blood urea nitrogen 10.5 mg/dL, creatinine 0.5 mg/dL, uric acid 5.0 mg/dL, and C-reactive protein 4.8 mg/dL. Her soluble interleukin-2 receptor level was 1,398 U/mL (reference range, 145 to 519 U/mL), carcinoembryonic antigen 1.6 ng/mL, and carbohydrate antigen 19-9 2.0 U/mL.

Computed tomography (CT) of the body with the administration of contrast material revealed a left upper quadrant tumor of $9 \times 7$ cm in diameter that encompassed the greater curvature of the stomach and splenic flexure of the colon to create gastrocolic fistula.

![Figure 1. Axial (top) and coronal (bottom) CT images of the body with contrast material, showing the left upper quadrant tumor. Communication between the stomach (St) and colon (C) is indicated by asterisks. The tumor extended into the spleen (Sp) and infiltrated the intercostal muscle in the left chest wall (arrowheads).](image-url)
(Figure 1). Ultrasonography showed that the tumor extended into the splenic parenchyma and left chest wall and the pancreas also appeared to be involved. 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) combined with CT disclosed strong tracer uptake in the tumor (Figure 2), and FDG-avid paraaortic and left common iliac lymph nodes were detected. We performed CT colonography using low-pressure carbon dioxide insufflation to confirm gastrocolic fistula. As shown in Figure 3, a computer-simulated endoluminal perspective of the descending colon was interrupted at the splenic flexure, which communicated with the air-filled distended stomach.

Upper GI endoscopy revealed a submucosal tumor at the greater curvature of the body of the stomach, the top of which lost the overlying mucosa and was covered with fecal material (Figure 4A). When this material was removed, whitish tumor tissues with the orifice of the fistula appeared; however, insertion of the scope through the opening was unsuccessful. Colonoscopy showed a tumor and narrowing of the lumen at a site of the proximal descending colon (Figure 4B), and air insufflation provoked feculent vomiting.

Multiple biopsy samples were obtained from the tumor protruding into the gastric lumen. They contained diffuse infiltrates of large lymphoid cells in the mucosa and beneath the muscularis mucosa (Figure 5A). Cells showed a high nuclear-cytoplasmic ratio and prominent nucleoli (Figure 5B). They were positive for CD20, CD79a, and BCL2, and negative for CD5, CD10, and BCL6, corresponding to the non-germinal center B-cell–like type of DLBCL of Hans’ algorithm. 2 CD30 was positive and Epstein-Barr virus-encoded RNAs were negative. More than 90% of cell nuclei

![Figure 2. 18F-FDG-PET/CT images showing strong tracer uptake in the left upper quadrant tumor. The maximum standardized uptake value (SUVmax) was 23.6. Anterior and lateral views of the maximum intensity projection image (left) and representative axial images of the body (right) are shown.](image-url)
DLBCL presenting with gastrocolic fistula

Method: The colon was distended with automated low-pressure carbon dioxide delivery (PROTO CO2L; Sekisui Medical Co., Ltd., Tokyo, Japan). Following an unenhanced CT series at the prone position, a contrast-enhanced CT series of the abdomen and pelvis was performed in the supine position. Imaging in the two positions minimized the likelihood of inadequate visualization because of limited colonic distention. CT colonography on the entire colorectum as well as the stomach was performed on dedicated workstations (Ziosation2, Ziosoft Inc., Tokyo, Japan).

Figure 3. CT colonography. (A) Axial images of CT in the prone (unenhanced) and supine (enhanced) positions. (B) Lucent three-dimensional air image of the colon and stomach in the prone and supine positions. Communication between the stomach and colon is indicated by an arrow.

Figure 4. Endoscopic examinations of the gastrointestinal tract. (A) Upper gastrointestinal tract endoscopy, showing a tumor protruding into the gastric lumen. The top of the tumor was covered with fecal material. (B) Colonoscopy revealed a tumor that narrowed the colonic lumen, and the lumen beyond the tumor was filled with fecal material. Biopsy of the tumor was negative. (C) After 1 cycle of R-CHOP, the stomach tumor regressed, resulting in convergence of the mucosal folds.
were positive for Ki-67 immunostaining in the most proliferative areas (Figure 5C). We subjected paraffin-embedded tissue sections to fluorescence in situ hybridization (FISH) using the BCL6 and IGH dual-color, break-apart probes. The results obtained showed cell nuclei labeled with a yellow signal and a pair of split signals by both probes, indicating rearrangements of BCL6 (Figure 6A) and IGH (Figure 6B), respectively. BCL2 and MYC rearrangements were negative.

**TREATMENT COURSE**

A surgical consultation suggested that the en...
bloc resection of the involved organs and tissues, including the fistula, was challenging, with the risks outweighing the benefits. Since a response to conventional chemotherapy for DLBCL was expected, we decided to treat the patient with standard R-CHOP chemotherapy under very close monitoring for possible complications; the regimen consisted of rituximab (375 mg/m^2 intravenously on day 2 of a 21-day cycle), cyclophosphamide (750 mg/m^2 intravenously on day 1), doxorubicin (50 mg/m^2 intravenously on day 1), vincristine (1.4 mg/m^2 intravenously on day 1), and prednisolone (100 mg on days 1 to 5); prednisolone was administered intravenously, not orally. To prevent neutropenia, pegfilgrastim was administered subcutaneously. Prior to the initiation of therapy, the patient received total parenteral nutrition, oral food intake was prohibited, and omeprazole was administered intravenously twice daily. On day 4 of the first cycle of R-CHOP, the patient developed epigastric pain; however, there was no evidence of perforation or the leakage of GI contents at the site of the tumor by CT and her symptoms quickly resolved. Upper GI endoscopy performed after 1 cycle of R-CHOP showed convergence of the mucosal folds of the stomach, suggesting regression of the underlying tumor (Figure 4C). After 3 cycles of R-CHOP, the size of the tumor

Figure 6. FISH showing BCL6 and IGH gene rearrangements in lymphoma cell nuclei. (A) FISH using the Vysis LSI BCL6 dual color, break-apart rearrangement probe, consisting of red-labeled 5′ BCL6 and green-labeled 3′ BCL6. (B) FISH using the Vysis LSI IGH dual-color, break-apart rearrangement probe, consisting of telomeric green-labeled 5′ IGH and centromeric red-labeled 3′ IGH. Both probes were purchased from Abbott Laboratories, Abbott Park, IL, USA. Tissues sections of biopsy samples were hybridized with the probes and hybridization signals were captured using a Zeiss AXIO fluorescence microscope (Carl Zeiss, Zaventem, Brussels). Pictures of DAPI, TRIC (tetramethylrhodamine B isothiocyanate), FITC (fluorescein isothiocyanate), and DAPI/TRIC/FITC triple band-pass filters are aligned. Hybridization signals are indicated by the arrowheads of their respective colors in representative nuclei.
was markedly reduced and gastrocolic fistula was no longer detectable on CT, thereby allowing for oral food intake. We confirmed a complete response by $^{18}$F-FDG-PET/CT after the completion of 6 cycles of R-CHOP (Figure 7). High-dose methotrexate was administered for the prophylaxis of central nervous system relapse. She is currently free from lymphoma relapse 2 years after the end of chemotherapy.

**DISCUSSION**

We herein described a patient with Ann Arbor stage IV and Lugano stage II$_e$ disease of DLBCL, which created gastrocolic fistula, accounting for her characteristic presenting symptoms. Lymphoma may have arisen in the peritoneal tissues adjacent to the stomach and colon, and extended to the surrounding tissues and organs. Lymphoma was classified into the high-intermediate risk category of age-adjusted International Prognostic Index scoring (i.e., stage $\geq$III and high LDH level). The treatment course was uneventful without complications and the involved organs (i.e. stomach, colon, and spleen) were preserved. To the best of our knowledge, this is the first case report of DLBCL that presented with gastrocolic fistula and was successfully treated with R-CHOP chemotherapy, avoiding surgical intervention.

Stamatakos et al. reported that gastrocolic fistula was initially described in 1755 as a complication of gastric carcinoma by Albrecht von Haller, and Douglas Firth presented the first case in the English bibliography in 1920 as a complication of gastric ulcer disease. Although gastric and transverse colon carcinomas are the two most common causes of gastrocolic fistula, this condition may develop as a complication of a

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**Figure 7.** $^{18}$F-FDG-PET/CT images after the completion of 6 cycles of R-CHOP, showing a complete metabolic response.
DLBCL presenting with gastrocolic fistula

number of benign diseases and malignant neoplasms, including gastric lymphoma. Patients with gastrocolic fistula typically present with malnutrition, visceral abdominal pain, nausea, feculent vomiting, weight loss, and diarrhea and have fecal halitosis and eructation, as observed in our case. Yin et al. previously suggested that barium enema identifies 95 to 100% cases of gastrocolic fistula; our results propose CT colonography as a substitute modality. Surgical en bloc resection of the involved organs, including fistulous tissues, has been performed for carcinoma cases, while one gastric lymphoma case underwent local resection followed by chemotherapy.

In the treatment of malignant lymphoma in the GI tract, primary GI lymphoma, or the secondary GI involvement of a disseminated disease, there is always a concern that chemotherapy may cause perforation or bleeding at the site of a tumor. A literature review revealed many sporadic case reports of GI lymphoma associated with these severe complications after chemotherapy, requiring urgent surgical intervention. In a Mayo clinic study, 92 (9%) out of 1,062 patients with GI lymphoma developed a perforation 2 to 298 days (median, 46 days) after chemotherapy. DLBCL was the most common lymphoma subtype associated with perforation (55 [59%] out of 92) and the small intestine was the most common site of perforation (59%), followed by the large intestine (22%) and stomach (16%). In a series of 73 primary gastric DLBCL patients treated with CHOP or R-CHOP, 8 (11%) bleeding and 8 (11%) gastric outlet obstruction complications occurred and 4 required surgical interventions; however, no perforation developed during the course of treatment. On the other hand, a Japanese multicenter phase II study of CHOP followed by radiotherapy for gastric DLBCL reported that none of the 52 patients enrolled developed hemorrhage or perforation, avoiding immediate surgical intervention, even though two patients underwent salvage gastrectomy for resistant or relapsed disease. Chemotherapy is currently the treatment of choice for gastric DLBCL and surgery is reserved for selected cases only.

In contrast, most patients with intestinal DLBCL undergo surgical resection followed by chemotherapy, and surgery may be associated with better survival; comparisons between patients with Lugano stage I/II intestinal DLBCL treated with surgical resection followed by chemotherapy and those treated with chemotherapy alone showed that the former had a lower relapse rate (15.3% versus 36.8%) and better 3-year overall survival rate (91% versus 62%) than the latter. On the other hand, the resection of a tumor and adjacent organs/tissues may cause immediate and long-term surgery-related morbidities and delay the initiation of chemotherapy. Thus, the decision to select surgery, chemotherapy, or both needs to be individualized according to the site and extent of the disease as well as the patient’s condition and comorbidities. In the present case, we considered surgery to be unfeasible due to the marked involvement of the surrounding organs and tissues, selected chemotherapy as the initial treatment, and successfully achieved a complete response. Nevertheless, we suggest that GI lymphoma is not treatable in the Hematology/Oncology department alone, it requires multidisciplinary management in collaboration with the Gastroenterology, Surgery, and Radiology departments.

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胃大腸瘻孔を伴う腹部腫瘤で発症し，R-CHOP 療法が奏効したびまん性大細胞型 B 細胞リンパ腫の一例

西村信城 1*, 飯岡 大 1, 富松浩隆 2, 久須美房子 3, 本庄 原 4, 福塚勝弘 5, 大野仁嗣 1,5

1 天理よろづ相談所病院 血液内科
2 天理よろづ相談所病院 放射線科
3 天理よろづ相談所病院 消化器内科
4 天理よろづ相談所病院 病理診断部
5 天理よろづ相談所 医学研究所
* 現所属：奈良県立医科大学附属病院 総合診療科

【症例】50代女性．左季肋部痛，食欲不振，糞便臭のする口臭のため受診した．【検査結果】ヘモグロビン11.8 g/dL, 白血球数15.56 × 10^3/µL, 血小板数276 × 10^3/µL, 乳酸脱水素酵素335 IU/L, アルブミン3.2 g/dL, C 反応性蛋白4.8 mg/dL, 可溶性インターロイキン2 受容体1,398 U/mL．CT で大腸脾湾曲部から脾実質内，胃内腔，左季肋部腹壁に広がる腫瘍を認め，PET 検査で同腫瘤に FDG の異常集積 (SUVmax = 23.6) を認めた．CT コロノグラフィーでは，大腸脾弯曲部から胃内へ送気 CO2 の流入を認めた．上部消化管内視鏡検査では，胃体上部大弯に粘膜下腫瘤を認め，腫瘍中央部は粘膜が欠損し便塊が付着していた．便塊を取り除くと瘻孔の入口部が観察された．病理検査では，中型から大型の腫瘤細胞の増生を認め，CD20+, CD79a+, CD5−, CD10−, BCL6− の non-germinal center B-cell–like の形質を示した．CD30+ で，Ki-67 陽性率は 90% 以上であった．BCL6 と IGH break apart probe を用いた FISH で両遺伝子の再構成を検出した．【経過】胃大腸瘻孔を合併したびまん性大細胞型 B 細胞リンパ腫 (DLBCL) と診断した．経食，プロトンポンプインヒビターの経静脈投与，中心静脈栄養を併用しながら R-CHOP 療法（リツキシマブ，サイクロフォスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロン）を 6 サイクル実施した．病変は速やかに退縮し，治療過程中に消化管穿孔や出血などの合併症を認めなかった．【考察】胃大腸瘻孔は，胃癌や大腸癌で認められることがあるが，DLBCL の報告は稀である．本症例では合併症をきたすことなく R-CHOP 療法を完遂し，外科手術を回避することができた．

キーワード：胃大腸瘻孔，CT コロノグラフィー，消化管悪性リンパ腫，びまん性大細胞型 B 細胞リンパ腫，R-CHOP 療法