

[CASE REPORT]

Protein-losing Enteropathy Complicated with Primary Intestinal Follicular Lymphoma

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Abstract:

Protein-losing enteropathy (PLE) is a rare syndrome characterized by hypoproteinemia due to gastrointestinal (GI) protein loss. Primary intestinal follicular lymphoma (PIFL), a specific variant of follicular lymphoma with essential only GI involvement, has not been reported as an etiology of PLE. We herein report a case of PLE complicated with PIFL that was successfully treated with rituximab, resulting in rapid improvement of PLE and a complete response of PIFL. Macroscopic findings of ulcerative lesions with diffuse involvement, which were precisely described by capsule and double-balloon enteroscopy at the diagnosis, also improved following the treatment. This case provides a clue suggesting factors that promote PLE in PIFL.

Key words: protein-losing enteropathy, primary intestinal follicular lymphoma, rituximab

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Introduction

Protein-losing enteropathy (PLE) is a rare syndrome characterized by hypoproteinemia due to gastrointestinal (GI) protein loss, which results in edema, ascites, and pleural effusion (1). Various disorders triggering gastrointestinal erosion, increased central venous pressure, or mesenteric lymphatic obstruction can play a role in the etiology of PLE, including lymphoma.

Duodenal-type follicular lymphoma (D-FL), a synonym for primary intestinal follicular lymphoma (PIFL) and previously referred to as primary GI follicular lymphoma (GI-FL), is a new designation for a specific variant of follicular lymphoma (FL) with clinical and biological features distinct from those of systemic nodal FL, according to the Revised 4th edition of the World Health Organization (WHO) classification (2). Although GI tract involvement is relatively common, accounting for 30% to 40% of primary extra-nodal lymphoma, GI-FL is reportedly quite rare, accounting for

1.0% to 3.6% of GI-NHL (3) and not reported with PLE. Among patients with FL, only two cases with PLE have been reported (4, 5), and both showed mesenteric and paraaortic lymphadenopathy, suggesting mesenteric lymphatic obstruction as a major cause of PLE. However, while GI involvement is an essential component of PIFL, PLE is a rare complication of PIFL.

We herein report a case of PLE complicated with PIFL and treated with rituximab monotherapy, which resulted in rapid improvement of PLE and a complete response of PIFL.

Case Report

A 72-year-old man was referred to the hematology department with a diagnosis of duodenal FL (Grade 1-2), as revealed by esophagogastroduodenoscopy during a medical checkup. Map-like erosion surrounded by tiny whitish nodules in the mucosa was observed in the second portion of the duodenum (Fig. 1A). Pathological findings were compat-

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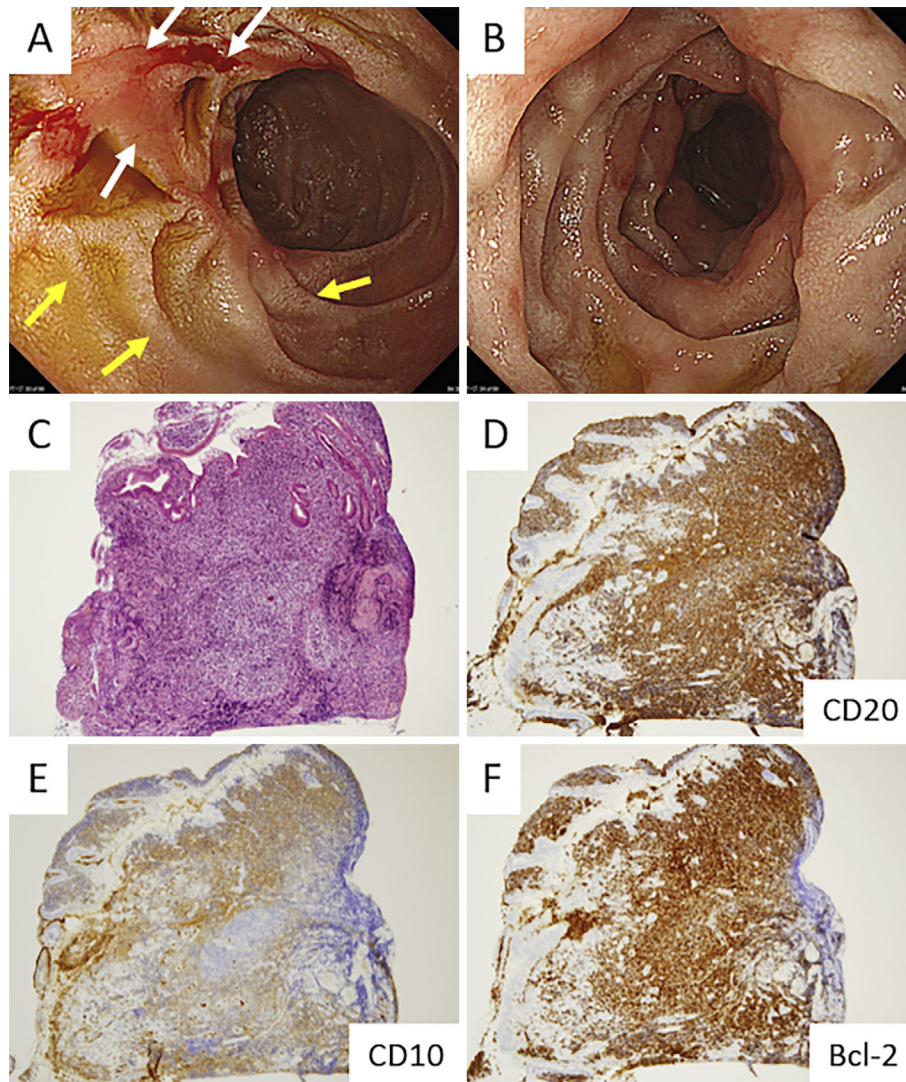


Figure 1. Map-like erosion (white arrows) surrounded by tiny whitish nodules (yellow arrows) in the mucosa was observed in the second portion of the duodenum (A). The duodenal mucosa was diffusely and circumferentially covered with tiny whitish nodules, and multiple round erosions were also observed (B). Histopathology of the duodenum showed proliferation of small lymphoid cells; immunohistochemical staining showing HE, CD20, CD10 and Bcl-2 staining (magnification, $\times 40$) (C-F).

ible with FL, including closely spaced small lymphoid cells with CD20, CD10, and Bcl-2 positivity (Fig. 1B-F).

A physical examination revealed edema of the lower legs, and a laboratory examination showed hypoproteinemia and hypoalbuminemia, in addition to iron deficiency anemia (IDA) (Table). Enhanced computed tomography showed a few small mesenteric lymphadenopathies with a long diameter < 15 mm but no other nodal or extra-nodal involvement (Fig. 2A). 18-fluorodeoxyglucose positron emission tomography (FDG-PET) showed an increased uptake of FDG [maximum standardized uptake value (SUV_{max}): 8.91] in the second and third portion of the duodenum and jejunum (Fig. 2B). Capsule enteroscopy (CE) and double-balloon enteroscopy (DBE) showed near-circumferential tiny whitish nodules with skipped low foveation, erosions, and ulcers at the jejunum and ileum, suggesting diffuse lymphoma involving the small intestine and microscopic GI bleeding leading

to IDA (Fig. 3A, B). The histological diagnosis of FL in the ileum was confirmed by DBE (Fig. 3C). The lymphatic ducts were not obviously dilated by D2-40 staining, suggesting that lymphatic obstruction was unlikely as an etiology of PLE (Fig. 3C).

Technetium-99 m-human serum albumin (Tc-99 m-HSA) scintigraphy showed diffuse exudation of labeled albumin from the abdominal cavity at 4 hours after injection and movement to the colon at 24 hours after injection, directly demonstrating protein loss from the GI tract (Fig. 3D). PLE due to PIFL was finally diagnosed.

We diagnosed the patient with intestinal FL of stage I (6). For clinical improvement of PLE and IDA, weekly rituximab monotherapy was administered. After initiation of rituximab monotherapy, the serum protein and albumin levels were rapidly increased and finally normalized (Fig. 4). Lower leg edema and body weight gain were also relieved.

Table. Laboratory Data on Admission.

| Periipheral blood | | Biochemistry | | | |
|-------------------|------------------------------|--------------|------------|-------------------|------------------|
| WBC | 4,590 / μ L | TP | 3.9 g/dL | s-Fe | 26 μ g/dL |
| Neut. | 58.8 % | Alb | 2.1 g/dL | TIBC | 261 μ g/dL |
| Lymph. | 31.4 % | T-Bil | 0.4 mg/dL | UIBC | 235 μ g/dL |
| Mono. | 7.4 % | D.Bil | 0.1 mg/dL | Ferritin | <10 ng/dL |
| Eosino. | 1.7 % | AMY | 57 U/L | | |
| Baso. | 0.7 % | AST | 19 U/L | TSH | 1.64 μ IU/mL |
| RBC | 421 $\times 10^4$ / μ L | ALT | 12 U/L | F-T4 | 0.9 ng/dL |
| Hb | 10.3 g/dL | LDH | 186 U/L | | |
| MCV | 79.1 fL | ALP | 159 U/L | β 2-MG | 2.2 mg/L |
| MCH | 24.5 pg | γ GTP | 10 U/L | s-IL-2R | 576 U/mL |
| MCHC | 30.9 g/dL | ChE | 86 U/L | | |
| Plt | 30.0 $\times 10^4$ / μ L | BUN | 18.7 mg/dL | IgG | 425 mg/dL |
| | | CRE | 0.76 mg/dL | IgA | 78 mg/dL |
| | | UA | 5.6 mg/dL | IgM | 41 mg/dL |
| | | Glu | 170 mg/dL | | |
| | | TG | 76 mg/dL | | |
| | | T-CHO | 156 mg/dL | | |
| | | Na | 145 mEq/L | Urinalysis | |
| | | K | 4.3 mEq/L | Protein | (+/-) |
| | | Cl | 108 mEq/L | Ocult blood | (-) |
| | | Ca | 7.4 mg/dL | | |
| | | IP | 3.6 mg/dL | | |

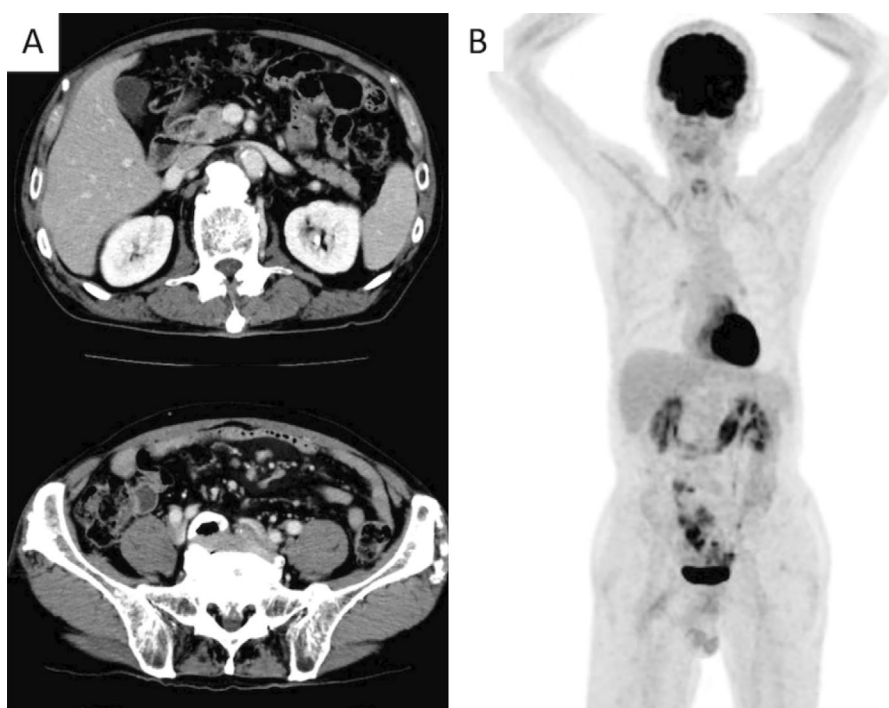


Figure 2. Small mesenteric lymphadenopathy on enhanced computed tomography (A). The intense uptake of 18-fluorodeoxyglucose (FDG) in the second and third portion of the duodenum and jejunum at the initial diagnosis on FDG-PET in maximum intensity projection mode (MIP) (B).

IDA also recovered and never relapsed following rituximab monotherapy. Esophagogastroduodenoscopy and CE performed after six cycles of rituximab showed endoscopic improvement with the disappearance of mucosal whitish nodules and ulcers on whole intestinal lesions (Fig. 5A, B).

DBE after completion of one month of eight cycles rituximab monotherapy showed no endoscopic evidence of FL in the intestine (Fig. 5C). Pathological complete response (CR) was confirmed by a random biopsy of the small intestine. Tc-99 m-HSA scintigraphy showed no exudation of labeled

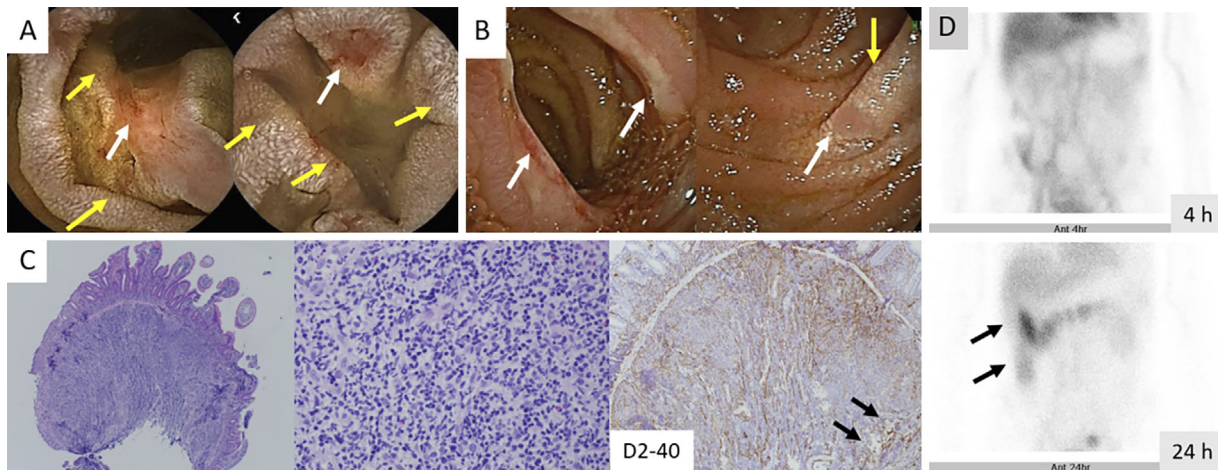


Figure 3. Capsule enteroscopy (A) and double-balloon enteroscopy (B) at the diagnosis. Erosions and ulcers (white arrows) were surrounded by tiny whitish nodules (yellow arrows). Histopathology of the ileum: immunohistochemical staining showing Hematoxylin and Eosin staining (magnification, $\times 40$ and $\times 400$) and D2-40 staining ($\times 100$). D2-40 is expressed in lymphatic endothelial cells (black arrows) and follicular dendritic cells (C). Technetium-99m-human serum albumin scintigraphy at the diagnosis (D). Labeled albumin was observed diffusely exuding at 4 hours after injection and moving to the colon at 24 hours after injection (black arrows).

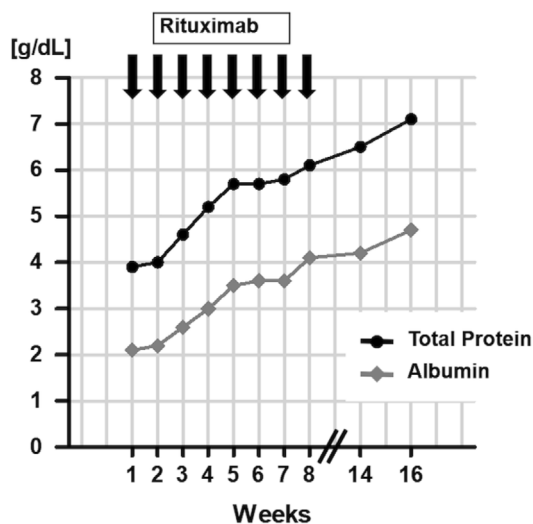


Figure 4. Clinical course with serum total protein and albumin levels.

albumin to the intestine, confirming complete remission of PLE (Fig. 5D).

Discussion

Accurate estimates of the frequency of PLE in PIFL are not available. A literature review by Yamamoto et al. found hypoalbuminemia was present in only 2 of 150 GI-FL cases (1.3%) (3). In both cases, PLE was not definitively diagnosed by Tc-99 m-HSA scintigraphy or alpha-1 antitrypsin clearance (7, 8). Regarding FL, only two cases with PLE have been reported (4, 5). One case had duodenal involvement diagnosed by a biopsy, but mesenteric and paraaortic lymphadenopathy were also observed, and abnormal find-

ings of the GI mucosa were not observed (4). The other was a systemic nodal FL case without GI involvement, caused by mesenteric lymphatic obstruction due to mesenteric and paraaortic lymphadenopathy (5). Thus, our report is the first case of PLE accompanied by PIFL diagnosed both endoscopically and histologically.

In a study of 125 PIFL cases, the most commonly involved lesion site was the duodenal second portion (81%), followed by the jejunum (40%), and 85% of cases with duodenal second portion involvement also had jejunal or ileal involvement (9). Simple involvement of the small intestine is not considered to be a promoting factor for PLE. With respect to macroscopic findings, ulcerative lesions are reported in only 5% of cases, and diffuse involvement is also rare (2%), with the most common macroscopic type being multiple nodules and polypoid lesions (92%) (10). The ulcerative lesion with diffuse involvement in our case was an atypical finding for PIFL and was hypothesized to be a promoting factor triggering PLE in PIFL. Indeed, one GI-FL case with hypoalbuminemia showed IDA, suggesting microscopic gastrointestinal bleeding from an intestinal ulcer or erosion (7), and the other showed diffuse involvement and ulceration (8).

DBE is superior to CT and FDG-PET for diagnosing PIFL (11). Given the high incidence of jejunal or ileal involvement, an evaluation of the whole small intestine by CE and/or DBE should be considered essential for elucidating the relationship between clinical features, such as PLE, and macroscopic findings as well as the area of involvement.

In cases of symptomatic PIFL such as PLE, rituximab monotherapy is a reasonable choice for attaining symptomatic improvement and circumventing potential adverse events of multi-agent chemotherapies, such as rituximab-based bendamustine or CHOP. PIFL is considered to have

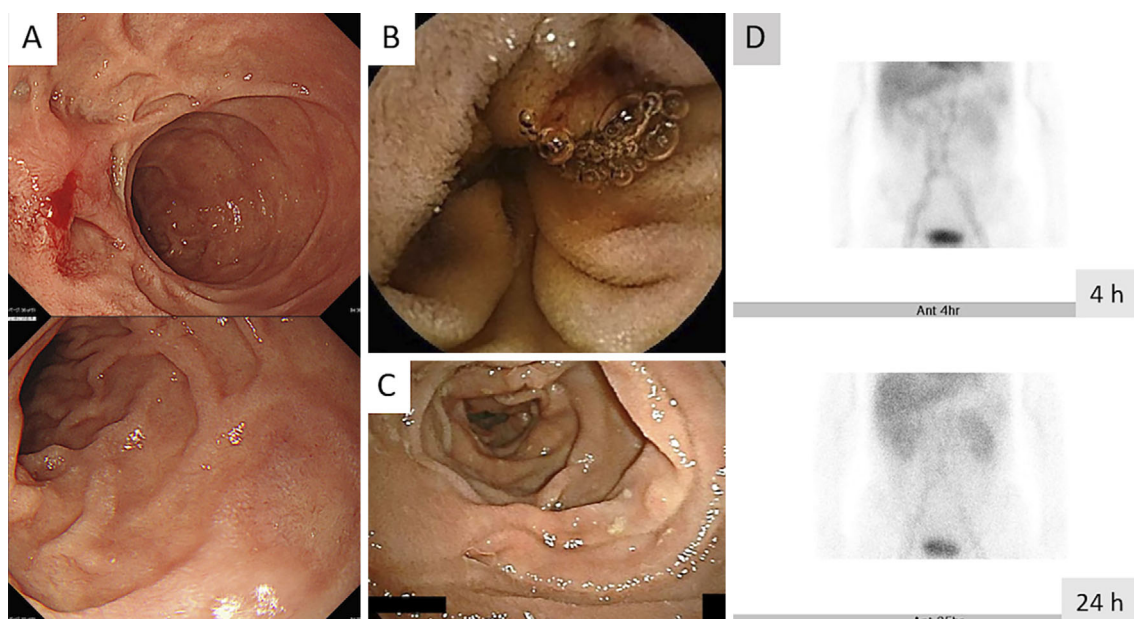


Figure 5. Esophagogastroduodenoscopy (A) and capsule enteroscopy (B) at the midpoint of rituximab treatment. Double-balloon enteroscopy after completing eight cycles of rituximab monotherapy (C). Technetium-99m-human serum albumin scintigraphy after completion of rituximab monotherapy (D).

an excellent long-term survival with a low risk of progression to disseminated nodal disease, even with the watch-and-wait approach (2). PIFL has shown high chemosensitivity to rituximab monotherapy or rituximab-based combination chemotherapy, such as R-CHOP or R-bendamustine. Schmatz et al. reported an 80% CR rate (n=5) following rituximab monotherapy for PIFL (12). Takata et al. also reported a 5-year overall survival of 92% for rituximab monotherapy, compared with 97% for R-CHOP or R-CHOP-like treatment (9).

In conclusion, PLE is a very rare complication of PIFL. The precise evaluation of macroscopic abnormalities and area of involvement within the entire small intestine by CE and DBE is useful for elucidating the endoscopic features. For the treatment of symptomatic PIFL, rituximab monotherapy may be a promising option, resulting in a sufficient clinical response and acceptable tolerability.

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

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