Endoscopic Follow-up of 3 Cases with Gastrointestinal Tract Involvement of Mantle Cell Lymphoma

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Abstract

Gastrointestinal (GI) tract involvement of mantle cell lymphoma (MCL) presents as a variety of forms, ranging from multiple lymphomatous polyposis (MLP) to a slight mucosal change. We report 3 cases with GI tract involvement of MCL who were followed-up by endoscopy. The present study shows three new informations. MLP of the esophagus is rare, but it was observed in two of 3 patients who were extensively involved by MCL. Endoscopic follow-up in one patient suggested that lymphoma cells of MCL had invaded the lamina propria to submucosal layer before MLP developed. Two of the 3 cases showed a favorable clinical course with single-agent rituximab therapy.

Key words: mantle cell lymphoma (MCL), gastrointestinal tract involvement, multiple lymphomatous polyposis (MLP), rituximab


Introduction

Mantle cell lymphoma (MCL) is a B-cell neoplasm, accounting for 3-10% of non-Hodgkin lymphomas. MCL develops in relatively elderly persons, is often diagnosed in an advanced stage, is generally resistant to chemotherapy, and has a poor prognosis, with a mean survival of 3-5 years (1). MCL is frequently associated with gastrointestinal (GI) tract involvement, which has been reported to be identified by endoscopy in 15-30% of patients with symptoms such as diarrhea (2, 3). GI tract involvement presents as a variety of lesions, ranging from the characteristic multiple lymphomatous polyposis (MLP) (4, 5) to mucosal changes that are too vague to be identified endoscopically and can only be diagnosed through biopsy (6, 7). We encountered 3 MCL cases, in whom GI tract involvement of MCL was confirmed histopathologically on biopsy during upper and lower GI tract endoscopy in our department, and whose clinical course was followed endoscopically.

Case Report

Case 1

MCL started in the submandibular and cervical lymph nodes of a man in his 70s, who achieved a complete response (CR) after THP-COP (cyclophosphamide, pirarubicin, vincristine, prednisolone) chemotherapy. However, 2 years and 7 months later, the lymphoma first recurred in the inguinal lymph nodes. At that time, X-ray and endoscopy revealed MLP lesions in the esophagus, stomach, duodenum, and sigmoid colon (Figs. 1A-E). Chemotherapy mainly with ProMACE-CytaBOM (cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate, prednisolone) was effective, and the MLP lesions disappeared. After 5 years, discrete, elevated lesions were observed in the duodenum and sigmoid colon. Their biopsy led to a pathological diagnosis of a second recurrence of MCL, but the patient achieved remission again after single-agent rituximab (RTX) therapy. Thereafter, the patient showed repeated recurrences and remissions until 13 years.
Figure 1. (Case 1) (A) X-ray of the esophagus. (B)-(E) Upper GI tract endoscopy. MLP lesions in the middle to lower esophagus (A, B), greater curvature of the gastric body (C), gastric antrum (D), and duodenal bulb (E).

after the onset of MCL, and died of its exacerbation.

Case 2
A man in his 40s, with splenomegaly, cervical lymphadenopathy, and leukocytosis with abnormal lymphoid cells, was initially diagnosed with chronic lymphoid leukemia (CLL), and followed-up without treatment. About 1 year later, endoscopy revealed diffuse thickening of the mucosal folds along the greater curvature of the gastric body and expansion of an area of whitish, rough-surfaced mucosa of the duodenal bulb (Figs. 2A, 2B). The terminal ileum showed multiple small elevations resembling lymphoid follicular hyperplasia, and the recto-sigmoid colon displayed slight changes in vascular transparency (Figs. 2C, 2D). Their biopsy revealed the neoplastic proliferation of small- to medium-sized lymphoid cells which were positive for CD20, CD5, and Cyclin D1 (Figs. 3A-D), leading to a final diagnosis of MCL rather than CLL. Single-agent RTX induction therapy, in place of anticancer drugs, resulted in the resolution of the GI tract lesions and a hematological CR. Thereafter, the patient underwent repeated maintenance therapy with RTX. Currently, 4 years and 9 months after induction therapy, he remains free of recurrence.

Case 3
A woman in her 60s presented with axillary and inguinal lymphadenopathy. Lymph node biopsy showed that lymphoma cells were negative for CD5, but positive for CD20 and Cyclin D1, leading to a pathological diagnosis of CD5-negative MCL. RTX and THP-COP chemotherapy induced a transient CR, but the MCL recurred in the submandibular lymph nodes and thyroid 3 months later. Endoscopy revealed typical MLP lesions in the esophagus and stomach, which had not been observed at the onset of MCL, as well as ulcer scar-like lesions in the duodenum and slight changes in color tone in the recto-sigmoid colon (Figs. 4A, 4B). Biopsy of these lesions led to a diagnosis of GI tract involvement of MCL. RTX and THP-COP therapy and salvage therapy with cladribine were administered again, but induced no response. MLP lesions became manifest in the duodenum and recto-sigmoid colon (Figs. 4C, 4D), ultimately resulting in the death of the patient 1 year and 9 months after the onset of MCL.

Discussion
The term “MLP” of the GI tract was introduced in 1961 by Cornes to describe malignant lymphoma that presented as multiple polyposis affecting long segments of the GI tract (8). The subsequent accumulation of cases involving the analysis of cell surface marker and gene rearrangement led to the conclusion that most cases of MLP represent MCL (4, 5). However, other studies reported that follicular (9), MALT (10), and T-cell (11) lymphomas presented as
MLP. Whether the cause of MLP is MCL or not, most MLP invariably involves the stomach and the more anal parts of the GI tract. MLP rarely occurs in the esophagus except in an unusual case of extensive involvement of the GI tract including the esophagus (12). In 2 of our 3 patients, MLP was observed in the esophagus by endoscopy.

On the other hand, GI tract involvement of MCL does not necessarily present as MLP. Recently, Romaguera et al identified GI tract involvement of MCL through biopsy in 43% and 88% of the upper and lower GI tracts, respectively, in the absence of clear endoscopic abnormalities (6). Tamura et al reported a case of MCL in which only slight mucosal changes were observed (7). Similarly, the recto-sigmoid colonic lesions in our Cases 2 and 3 [Figs. 2(D), 4(B)] showed no prominent mucosal changes, but biopsy identified GI tract involvement of MCL. Later, in Case 3, when the patient became refractory to chemotherapy, MLP lesions became manifest. Much of the pathogenesis of MLP remains unknown. However, the clinical course in Case 3 suggests that, before the establishment of MLP lesions, MCL cells diffusely invade the lamina propria to submucosa, and the lymphoma cells proliferate to develop into MLP over time.

Recently, a new prognostic index for advanced-stage MCL (MCL international prognostic index, MIPI) using a combination of 4 factors (age, performance status, LDH, and WBC count) was proposed, classifying the prognosis into 3 groups according to the MIPI score (13). Thus, our 3 cases were scored as 5.5 (<5.7), and classified as belonging to a low-risk group. CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisolone) for MCL is not very effective, and MCL, despite being indolent lymphoma, previously carried a poor prognosis (14). Many recent studies have supported the effectiveness of chemotherapy with RTX (15), hyper-CVAD therapy (16), and high-dose chemotherapy with autologous peripheral blood stem cell transplantation (PBSCT) (17). Our 3 patients were treated with RTX, and 2 of them responded to single-agent RTX: it contributed to long-term survival in Case 1 and recurrence-free survival in Case 2. Single-agent RTX showed moderate activity in MCL (response rate, 37-38%; CR rate, 14-16%) (18). It appears that the number of patients who are well-controlled by treatment with single-agent RTX for GI tract involvement of MCL, as in our 2 cases, is limited (7). The 2 cases followed a favorable clinical course, probably because they belonged to a low-risk group according to the MIPI score. In Case 2, a CR has been maintained on repeated RTX maintenance therapy without the use of potent chemotherapy such as hyper-CVAD and PBSCT. A consensus has been reached on the efficacy of RTX maintenance therapy for follicular lymphoma (19), but it is unknown as for MCL. Further studies in more patients are needed.
Figure 3. (Case 2) Histopathological appearances. Hematoxylin and Eosin staining showing the neoplastic proliferation of lymphoma cells in the submucosa (A). Positive staining for CD20 (B), CD5 (C), and Cyclin D1 (D).

Figure 4. (Case 3) Upper (A, C) and lower (B, D) GI tract endoscopy (D, after dye spray). Ulcer scar-like changes in the duodenal bulb (A). Slight changes in color tone in the recto-sigmoid colon (B). These subtle lesions changed into MLP lesions after treatment (C, D).
References


