Atypical Mucosa-Associated Lymphoid Tissue Lymphoma in the Transverse Colon Associated with Macroglobulinemia

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Abstract

We herein present a quite atypical case of primary gastrointestinal mucosa-associated lymphoid tissue (MALT) lymphoma in the transverse colon. Computed tomography and endoscopic ultrasonography revealed diffuse thickening of the wall, and colonoscopy showed a white-colored mucosa with reduced superficial vessels in the entire transverse colon. The lesion was diagnosed as MALT lymphoma by pathological examination of the biopsied specimen. Secondary macroglobulinemia of IgM-κ type was also found in the present case. After chemotherapy and radiation, the lesions in the transverse colon improved and the patient has been in good condition without any evidence of recurrence for more than 1 year.

Key words: mucosa-associated lymphoid tissue (MALT) lymphoma, transverse colon; macroglobulinemia, IgM, CA125, auto-fluorescent imaging (AFI)


Introduction

Mucosa-associated lymphoid tissue (MALT) lymphoma, which originates from MALT, is now classified as an extranodal marginal zone B-cell lymphoma of MALT type according to World Health Organization (WHO) classification. MALT lymphoma frequently originates in the stomach and intestine, while cases that primarily occurred in the transverse colon are extremely rare; only a few cases have been reported (1-3).

Waldenström’s macroglobulinemia is a condition whereby monoclonal immunoglobulin (Ig) M is observed in the serum. Although malignant lymphoma accompanying macroglobulinemia is sometimes observed, MALT lymphoma complicated by Waldenström’s macroglobulinemia is rare.

We herein present an atypical case of primary gastrointestinal MALT lymphoma in the transverse colon that displayed atypical endoscopic and computed tomography (CT) images and was associated with secondary macroglobulinemia of IgM-κ type.

Case Report

A 54-year-old Japanese woman experienced abdominal distension that persisted for 2 months. She subsequently felt abdominal pain and consulted a physician.

The physician detected a palpable tumor in her abdomen. CT and ultrasonography (US) imaging revealed diffuse thickening of the wall of the transverse colon, and she was consequently admitted to the hospital. She did not have any remarkable past or family medical history. Laboratory data on admission showed a high IgM value of 2,160 mg/dL, and immunoelectrophoresis revealed M-proteinemia of IgM-κ type. The physician could not make a final diagnosis, and she was referred to our hospital.

Upon admission to our hospital, a solid tumor approxi-
 intimately 10 cm in size was palpable in her abdomen. Laboratory data on admission showed a WBC count of 6.34×10^9/L and a platelet count of 223×10^9/L. The hemoglobin concentration was 107 g/L, with MCV 84.5 fl and MCHC 27.6%, indicating slight normocytic anemia. Biochemical data showed a high total protein level of 8.2 g/dL. Immunoglobulin levels were determined to be IgG 622.0 mg/dL, IgA 80.6 mg/dL, and IgM 2,974.9 mg/dL (normal range: 48-199 mg/dL), and M-protein of IgM-κ type was detected by immunoelectrophoresis. Among the tumor markers, the soluble interleukin-2 receptor (sIL-2R) level was 2,750.0 IU/mL (normal range: 220-530 U/mL) and the CA125 level was 433 U/mL (normal range: 0-28 U/mL). Other tumor markers, such as CEA, CA19-9, AFP, PIVKA-II, SCC, NSE, were negative.

Whole body CT with contrast enhancement detected diffuse and extreme thickening of the wall of the transverse colon (Fig. 1A). Homogenous, relatively strong enhancement and vessel augmentation were observed in the thickened wall. Peritoneal thickening, an increased density of fat tissue, and ascites were also detected. The right supravclavian lymph node and several lymph nodes in the pelvic space showed evidence of swelling, but the sizes of those lesions were approximately 10 mm. Magnetic resonance imaging (MRI) of the abdomen was also performed, and revealed that the diffuse thickening of the transverse colon showed a high intensity in comparison to muscles on both T1- (Fig. 1B) and T2-weighted images. Both CT and MRI indicated that the lumen was relatively preserved despite the great thickening of the colon wall, implying that the tumor was soft.

Total colonoscopy was then performed. The entire transverse colon displayed white-colored mucosa with reduced superficial vessels. Although there was no obvious ulceration, the wall of the transverse colon was edematous and the translucency of the vessels had disappeared. The surface of the mucosa was fragile and bled easily on contact (Fig. 2A). Indigocarmine dye spray detected mucosal irregularity (Fig. 2B). Auto-fluorescent imaging (AFI) revealed a magenta area at the corresponding region, which suggested a reduced auto-fluorescence intensity emitted from the lesion (Fig. 2C). Endoscopic ultrasonography (EUS) revealed thickening of the submucosa and muscularis propria with calcified vessels, which indicated that these abnormal findings were caused by submucosal alterations due to lymphoma or phlebosclerotic colitis (Fig. 2D). The main lesions seemed to be in the submucosa and muscularis propria and while the diagnosis of lymphoma should not be easy to determine based on the biopsy from the mucosa, the indications of endoscopic mucosal resection were discussed at first but we had to give up due to the high risk of massive bleeding. Therefore, it was necessary to perform extensive biopsies as relatively large amounts of samples are necessary for the diagnosis of lymphoma including southern blotting analysis as well as pathological examinations. Biopsies were performed from 3 different locations of the transverse colon; 10 repeated biopsied specimens were obtained from the same point of the middle of the transverse colon for southern blotting. Bleeding due to the biopsy procedure could be stopped by spraying of thrombin. The pathological findings of biopsied specimens showed that medium or large sized lymphocyte-like cells with cleaved nuclei were diffusely infiltrated between normal glands (Fig. 3A). A lymphoepithelial lesion (LEL) was also observed (Fig. 3B). CD20 (Fig. 3C) and IgM were positive, and CD3, CD5, CD10, cyclin D1, bcl-2 were negative by immunostaining. Southern blot analysis from a biopsied sample revealed immunoglobulin H-chain Cμ and JH rearrangements, which indicated that the tumor cells produced IgM-κ protein. In light of the findings by immunostaining, the presence of LEL, and the presence of diffusely infiltrating cells, follicular lymphoma and mantle cell lymphoma were excluded, and the patient was eventually diagnosed to have extranodal marginal zone lymphoma of MALT type.

A barium enema revealed the disappearance of the haustra and the irregularity of the surface of the entire transverse colon.

Figure 1. (A) Computed tomography showed diffuse thickening of the wall of the transverse colon. Homogenous and relatively strong enhancement was observed, and the vessel augmentation was clearly observed in the thickened wall. (B) T1-weighted magnetic resonance imaging revealed that the diffuse thickened wall of the transverse colon displayed high intensity compared to muscles.
Figure 2. Colonoscopic findings of the transverse colon before treatment. (A) The wall of the transverse colon was edematous and the translucency of the vessels had disappeared. In addition, the surface of the mucosa was irregularly nodular. (B) Indigocarmine dye spray emphasized the irregularity of the mucosal surface. (C) Auto fluorescent imaging displayed the lesion as magenta, which reflected the decreased amount of autofluorescence emitted from the lesion. (D) Endoscopic ultrasonography indicated the thickening of the submucosa and muscularis propria.

colon (Fig. 4). These findings were strongly observed at the mesenteric side. Double balloon enteroscopy was performed via an oral approach, but no abnormal findings were observed in the small intestine. A bone marrow aspiration was also performed and revealed no obvious infiltration of tumor cells into the bone marrow.

Because the entire transverse colon was involved, and the right supraclavian and intrapelvic lymph nodes were suspected to be involved, the clinical staging was thought to be IV. Apparently, the main lesion was thought to be transverse colon, and thus this case was considered as MALT lymphoma primarily occurring from the transverse colon. The patient was treated with chemotherapy. She received R-CHOP regimen (rituximab 500 mg/day, ADR 70 mg/day, VCR 1.4 mg/day, CPA 1,000 mg/day, PSL 60 mg/day ×5 days). Her symptoms and the abdominal tumor showed a dramatic improvement. The IgM, IL-2R, and CA125 levels were also observed to gradually decrease. After 6 courses of chemotherapy, her symptoms completely disappeared and the aforementioned serum markers dropped to within normal ranges. Because immunoglobulin H-chain rearrangement was detected by southern blot analysis on a biopsy of the transverse colon after completion of chemotherapy, radiation therapy of 20 Gy was then performed on the entire transverse colon. After radiation, no obvious lymphoma cells were observed and H-chain rearrangement was negative on biopsied specimens obtained by colonoscopy, so that complete remission (CR) was thought to be finally achieved. The mucosal edema in the transverse colon was resolved and the mucosal surface appeared regular with translucent vessels by colonoscopy (Figs. 5A, 5B). AFI revealed no reduction of autofluorescence in the corresponding area (Fig. 5C). EUS demonstrated that the wall of the transverse colon was still thickened but was quite improved compared to the findings observed prior to treatment (Fig. 5D). A pathological examination of biopsy specimens detected no obvious tumor cells. She has been in good condition without any evidence of recurrence more than 1 year after the completion of chemotherapy.

Discussion

We have reported a case of MALT lymphoma characterized by diffuse and extreme thickening of the wall of the transverse colon. MALT lymphoma is the low-grade NHL which originates from MALT and is now classified by the WHO as an extranodal marginal zone B-cell lymphoma of MALT type. Like other types of NHL, MALT lymphoma frequently originates in the stomach and intestine while cases that primarily occur in the transverse colon are ex-
tremely rare. Several cases of MALT lymphoma of the transverse colon have been reported before; the endoscopic and imaging patterns were not uniform (1-3). For example, the morphological features are characterized as a flat elevation with nodular formation (2, 3). However, the present case revealed diffuse and extreme thickening of the wall of the transverse colon. This finding was quite different from those in previously reported cases of MALT lymphoma in the large intestine. The pathological examination revealed diffuse infiltration of lymphoma cells and EUS findings also detected a diffusely thickened submucosal layer and muscularis propria. This suggests that MALT lymphoma initiating in the transverse colon may diffusely infiltrate to the intestinal wall.

Characteristically, macroglobulinemia was observed in the present case and the value of IgM changed, reflecting the disease activity; however, macroglobulinemia is rarely observed in MALT lymphoma and there are only few reports on those connections (4-6), and thus it has still not been clarified whether or not the presence and the value of IgM correlate with disease activity or prognosis. Interestingly, a similar case was previously reported from the point of view of the combination of malignant lymphoma and macroglobulinemia (7). That case displayed the entire diffuse thickening of the wall of transverse colon and showed macroglobulinemia with M-protein of IgM-κ type similar to the present case, although the pathological diagnosis was small lymphocytic NHL of B-cell origin based on a working formulation (8) that was different from our case. Therefore, our case was considered to be the first case of primary MALT lymphoma of the transverse colon with macroglobulinemia because the previous reported cases did not have any lesions in the transverse colon (4-6). Malignant lymphoma associated with macroglobulinemia of IgM-κ type may exhibit diffusely infiltrated progression regardless of the histological type, however, further epidemiological and biological analyses with a sufficient number of malignant
lymphoma cases are expected to clarify the clinical characteristics and progression mechanisms of MALT or other types of lymphomas in the large intestine.

Our case also showed a high serum level of CA125, which seemed to reflect the disease activity in this case. Serum CA125 has been reported to be elevated in lymphoma, although lymphoma cells do not secrete CA125 (9). Some reports stated that CA125 levels appear to be correlated with disease activity, further investigation on the clinical significance of serum CA125 in lymphoma is needed (10, 11).

Concerning the treatment of colonic MALT lymphoma, no standardized treatment has been established. Successful treatment of colonic MALT lymphoma by the eradication of Helicobacter pylori (H. pylori) has been reported even in the cases where H. pylori was negative (12), and the reason for the regression of the lesion was speculated to be the elimination of pathogenic bacteria other than H. pylori by antibiotics. In fact, similar to the relationship between gastric MALT lymphoma and H. pylori, the pathogenesis of intestinal, orbital and cutaneous MALT lymphoma are thought to involve infection by Campylobacter jejuni (13), Chlamydia psittaci (14) and Borrelia burgdorferi (15), respectively. In the present case, the indication of the eradication therapy was discussed at first, but there seemed to be a large tumor volume in the patient’s transverse colon and the high serum level of IgM should have been reduced immediately. Surgical resection of the lesion was also discussed, but the extent of the lesion was not clear and chemotherapy might preserve the transverse colon without resection. Therefore, we chose R-CHOP rather than eradication or surgical resection for this case. Chemotherapy successfully and immediately brought about regression of the lesion and the subsequent radiation for the residual lesion lead to a long period of CR; therefore, these treatments might be suitable treatment for cases of colonic MALT lymphoma with a wide range of lesions and needs for immediate improvements.

Another characteristic point of this case is the colonoscopic figures obtained by AFI (16): a homogeneous magenta color prior to treatment, and the image changed to green after the treatment with chemotherapy and radiation. This color change may reflect the diminished population of lymphoma cells. We have demonstrated that AFI detected intestinal lymphoma as magenta area and the fluorescence captured by AFI was inversely proportional to the density of lymphoma cell (Ueno et al. data unpublished). Accordingly, there should be the possibility that AFI is considered as a useful procedure for both the differential diagnosis and follow-up studies in lymphoma treatment.

In conclusion, we herein presented a case of primary MALT lymphoma of the transverse colon with macroglobu-
linemia. The findings of the main lesion were quite atypical. In this case, in addition to the classical procedures, AFI was considered to be a useful tool for the diagnosis and follow-up of the lymphoma involvement in the transverse colon.

References