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Atypical Mucosa-Associated Lymphoid Tissue Lymphoma in the
Transverse Colon Associated with Macroglobulinemia
(マクログロブリン血症を伴った横行結腸の非定型粘膜関連リンパ組織リンパ腫)

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**Atypical mucosa-associated lymphoid tissue lymphoma in the transverse colon
associated with macroglobulinemia**

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Short title: Atypical MALT lymphoma in transverse colon

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 for 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 have 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 originated from MALT and 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 the cases that primarily occurred in the transverse colon should be extremely rare and only few other cases were reported [1-3].

Waldenström's macroglobulinemia is a condition that monoclonal immunoglobulin (Ig) M is observed in serum. Although malignant lymphoma accompanying macroglobulinemia might sometimes be observed, MALT lymphoma complicated by Waldenström's macroglobulinemia should be 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 female 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 2160 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 in our hospital, a solid tumor approximately 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 2974.9 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 2750.0 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 supraclavian 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 high intensity in comparison to muscles in 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 there should be the limitation for the diagnosis of lymphoma by the biopsy from the mucosa, the indications of endoscopic mucosal resection was discussed at first but we had to give up because of the high risk of massive bleeding. Therefore, we had to perform extensive biopsies because relatively much amounts of samples should be needed for the diagnosis of lymphoma including southern blotting analysis as well as pathological examinations. Biopsies were performed from 3 different locations of transverse colon and 10 repeated biopsied specimens were obtained from the same point of the middle of the transverse colon for southern blotting. Bleeding occurred by biopsy could be stopped using thrombin spreading. 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 C μ 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 (**Fig. 4**). These findings were strongly observed at the mesenteric side. Double ballon enteroscopy was performed by 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_A. Apparently, the main lesion was thought to be transverse colon, so

that this case should be considered as MALT lymphoma primarily occurred from 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 1000 mg/day, PSL 60 mg/day x 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 resolved and the mucosal surface appeared regular with translucent vessels by colonoscopy (**Fig. 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 transverse colon. MALT lymphoma is the low-grade NHL which is originating from MALT and 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 the cases that primarily occurred in the transverse colon should be extremely 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 as reflecting the disease activity; however, macroglobulinemia should be rarely observed in MALT lymphoma and there are only few reports on those connections [4-6], so that it has still not been clarified if the presence and the value of IgM might correlate with disease activity or patients' prognosis. Interestingly, a similar case has previously been 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 just similar to our case, although the pathological diagnosis was small lymphocytic NHL of B-cell origin based on 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 previous reported cases did not have any lesions in 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 correlate with disease activity, further investigation is needed concerning the clinical significance of serum CA125 in lymphoma [10, 11].

Concerning the treatment of colonic MALT lymphoma, no standardized treatment has not been established. Successful treatment of colonic MALT lymphoma by the eradication of *Helicobacter Pylori* (*H. pylori*) even in the cases that *H. pylori* was negative was previously reported [12], and the reason for the regression of the lesion was speculated as 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 much tumor volume in the patient's transverse colon and 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 conserve

the transverse colon without resection. Therefore, we chose R-CHOP rather than eradication or surgical resection for this case. Chemotherapy was successfully and immediately regress the lesion and the subsequent radiation for the residual lesion leaded to long period of CR, so that these treatments might be the suitable treatment for the cases of colonic MALT lymphoma with wide range of the lesions and the needs of 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. in submission). Accordingly, there should be a possibility that AFI is considered to be 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 macroglobulinemia. The findings of the main lesion were quite atypical. In this case, in addition to classical procedures AFI were considered to

be useful tools for the diagnosis and follow-up of the lymphoma involvement in transverse colon.

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Figure legends

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.

Figure 3.

Pathological findings of the biopsied sample from the colonoscopy. (A) Medium or large sized lymphocyte-like cells with cleaved nuclei had diffusely infiltrated between normal glands. A lymphoepithelial lesion was also observed (B). Immunostaining showed that tumor cells were positive for (C) CD20.

Figure 4.

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

Figure 5.

Colonoscopic findings of the transverse colon after treatment. (A) The edema of the mucosa of the transverse colon was improved and the surface of mucosa looked regular with normal translucency of the vessels. (B) The irregularity of the mucosa surface was improved, as revealed by observation with indigocarmine dye spray. (C) Autofluorescence imaging displayed a green color, which reflected the presence of a normal mucosa at the corresponding site. (D) Endoscopic ultrasonography showed

that the wall of the transverse colon was still thickened but was improved in comparison to the findings observed prior to treatment.

A**B**







