Successful treatment of mucosa-associated lymphoid tissue lymphoma in a patient with gastric and rectal lesions with metachronous and ectopic development

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Abstract

A 75-year-old female, who had an abnormal stomach x-ray finding, was admitted to the hospital for further examination and therapy. Upper GI endoscopy showed reddish and swollen folds on the greater curvature of the gastric body and a biopsy was of this lesion revealed malignant lymphoma (small cell type or mucosa-associated lymphoid tissue (MALT) lymphoma suspected). The patient was infected with Helicobacter pylori (H. pylori), however, in response to the patient’s wishes, a total gastrectomy, omentectomy and splenectomy were performed and the histological diagnosis was gastric MALT lymphoma. Two courses of CHOP therapy (cyclophosphamide (CPM) 750 mg/m²/day, day 1, adriamycin (ADM) 50 mg/m²/day, day 1, vincristine sulfate (VCR) 1.4 mg/m²/day, day 1, prednisolone 100 mg/body, day 1-5) were administered as adjuvant chemotherapy. A colonoscopic examination performed about 4.5 yr after the operation revealed rectal submucosal tumors and the histological diagnosis was MALT lymphoma (Figure 3 A,B) with a slight invasion of the tumor was the muscularis propria. The depth of greatest invasion and monoclonal proliferation were confirmed (figure not shown). A Positive IgG-rearrangement and monoclonal proliferation were confirmed (figure not shown). The background mucosa of the stomach was positive for an H. pylori infection in a retrospective pathological examination. We did not perform any chromosomal study at that time. Very recently, we performed the FISH assay to evaluate the translocation of t(11;18) in formalin fixed tissues of gastric and colonc tumors, however, we could not perform any proper examination on this translocation because the tumor tissues with formalin fixation were in bad condition. A computed tomography (CT) scan of the chest, abdomen

and pelvic lesion demonstrated no swollen lymph nodes. Although there were several options for treatment, the patient and her family requested that the lesion be treated surgically. A total gastrectomy, omentectomy and splenectomy (D2 resection of regional lymph nodes and Roux-en-Y gastrojejunostomy) were thus performed in November 1995 (Figure 2 A, B). The histopathological diagnosis was MALT lymphoma (Figure 3 A,B) with a slight invasion into the spleen. Lymphoepithelial lesion (LEL), positive immunoreactivity for CD20 (L26) and CD79a, and negative immunoreactivity for cyclin D1 and CD5 were observed (figure not shown). A Positive IgG-rearrangement and monoclonal proliferation were confirmed (figure not shown). The depth of greatest invasion of the tumor was the muscularis propria. No metastatic lymph nodes and no vestigial remnant of the tumor were seen. Therefore, the patient was diagnosed as stageIE by Ann Arbor classification,10 as stageHE1 by Lugano International classification11 and as stageH1 by Blackledge Staging System.12 Two courses of CHOP therapy (cyclophosphamide (CPM) 750 mg/m²/day, day 1, adriamycin (ADM) 50 mg/m²/day, day 1, vincristine sulfate (VCR) 1.4 mg/m²/day, day 1, prednisolone 100 mg/body, day 1-5) were administered as an adjuvant chemotherapy, beginning December 11, 1995. Afterward, the patient was followed as an out-

Introduction

Mucosa-associated lymphoid tissue (MALT) lymphoma is a lymphoma derived from B-cells originating from the marginal zone of the MALT in an extra-nodal organ in the presence of chronic inflammations in the gastrointestinal tract, thyroid gland, salivary gland, lung and so on.1,2 Many cases of MALT lymphoma of the stomach have been reported to date in association with an Helicobacter pylori (H. pylori) infection, however, the development of MALT lymphoma in the colon and rectum without the apparent etiology such as an H. pylori infection is comparably rare. Anecdotal reports in which MALT lymphomas develop metachronously in the same or different organs have been reported to date.3,8 In the present case, a focal resection was performed for MALT lymphoma developed metachronously and ectopically in the rectum 3 years after a total gastrectomy for gastric MALT lymphoma followed by 2 courses of adjuvant chemotherapy. MALT lymphomas developed repeatedly in the rectal lesion, however, these were focally resected repeatedly and no recurrence has occurred over the past two years. This report presents a very rare case of successfully treated MALT lymphomas that developed metachronously and ectopically in gastric and rectal lesions.

Case Report

A 75-year-old woman showed an abnormality in the findings of barium X-ray screening for gastric cancer and was transferred to our hospital (Medical Hospital, The Nippon Dental University School of Life Dentistry at Niigata) for further examination and therapy in October 1995. Upper GI endoscopy revealed swollen giant folds of the body (Figure 1A, 1B). A biopsy was performed and malignant lymphoma suspected. The background mucosa of the stomach was positive for an H. pylori infection in a retrospective pathological examination. We did not perform any chromosomal study at that time. Very recently, we performed the FISH assay to evaluate the translocation of t(11;18) in formalin fixed tissues of gastric and colon tumors, however, we could not perform any proper examination on this translocation because the tumor tissues with formalin fixation were in bad condition. A computed tomography (CT) scan of the chest, abdomen

and pelvic lesion demonstrated no swollen lymph nodes. Although there were several options for treatment, the patient and her family requested that the lesion be treated surgically. A total gastrectomy, omentectomy and splenectomy (D2 resection of regional lymph nodes and Roux-en-Y gastrojejunostomy) were thus performed in November 1995 (Figure 2 A, B). The histopathological diagnosis was MALT lymphoma (Figure 3 A,B) with a slight invasion into the spleen. Lymphoepithelial lesion (LEL), positive immunoreactivity for CD20 (L26) and CD79a, and negative immunoreactivity for cyclin D1 and CD5 were observed (figure not shown). A Positive IgG-rearrangement and monoclonal proliferation were confirmed (figure not shown). The depth of greatest invasion of the tumor was the muscularis propria. No metastatic lymph nodes and no vestigial remnant of the tumor were seen. Therefore, the patient was diagnosed as stageIE by Ann Arbor classification,10 as stageHE1 by Lugano International classification11 and as stageH1 by Blackledge Staging System.12 Two courses of CHOP therapy (cyclophosphamide (CPM) 750 mg/m²/day, day 1, adriamycin (ADM) 50 mg/m²/day, day 1, vincristine sulfate (VCR) 1.4 mg/m²/day, day 1, prednisolone 100 mg/body, day 1-5) were administered as an adjuvant chemotherapy, beginning December 11, 1995. Afterward, the patient was followed as an out-
A colonoscopic examination in May, 1999 showed two rectal submucosal tumors (SMT), 2 cm or less in diameter (Figure 4 A,B). A biopsy was performed and malignant lymphoma was suspected. A trans-anal focal resection of the tumor was performed in May, 1999. The histopathological diagnosis was MALT lymphoma which was similar to the gastric lesion which had been resected previously (Figure 3 C,D). Lymphoepithelial lesion (LEL), positive immunoreactivity for CD20 (L26) and CD79a, and negative one for cyclin D1 and CD5 were observed (figure not shown). Colonoscopy in February, 2003 showed a rectal SMT (figure not shown) and the biopsy specimens were diagnosed as lymphoid hyperplasia. Trans-anal focal resection of the tumor was performed in March, 2003. The histopathological diagnosis also suggested lymphoid hyperplasia but could not be diagnosed as an apparent lymphoma. Afterward, colonoscopy performed in May, 2006 again revealed SMT-like lesions (figure not shown). A biopsy was performed and the pathological diagnosis was malignant lymphoma as with the previously resected tumors. A trans-anal focal resection was again performed in June, 2006. The pathological diagnosis was MALT lymphoma, which strongly correlated with the pathological findings of the tumor resected in May, 1999 and in March, 2003, however, the malignant cells of the tumor resected in June, 2006 were characterized by well differentiated plasma cells (figure not shown). The patient is currently being followed as an outpatient without additional adjuvant chemotherapy, however, the patient shows no sign of recurrence of MALT lymphoma and her serum IL2-recepter levels remain within the normal limits.

Discussion

MALT lymphoma is a low grade malignant B-cell lymphoma that develops from mucosa-associated lymphoid tissue (MALT). The concept of MALT lymphoma was first introduced by Isaacson et al. The pathological features of MALT lymphoma are as follows: i) lymphoma cells with faint, bright and abundant cell body (clear cells), and mildly pinched-off nuclei (Centrocyte-like cells: CCLCs); ii) a diffuse proliferation in the marginal zone of monocy-
Case Report

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Case Report

Revuo Medicina identified only 3 cases\(^7-9\) of rare. A literature search of Japana Centra

metachronous development of MALT lymphoma and other lymphoma types) are very

lymphoma cases (including the cases with

MEDLINE found only 4 cases\(^3-6\) of metachro-

nous MALT lymphoma cases (Key words: MALT lymphoma, metachronous). No cases of MALT lymphomas that develop metachronously and ectopically in gastric and rectal lesions have been reported and this present case seems to be the first reported to date.

There are various macroscopic forms of MALT lymphoma. Most gastric MALT lymphoma show surface-accrative lesions with growing progression in the mucosa because the mucosal invasive type accounts for many of the gastric MALT lymphoma cases. In contrast, because colonic MALT lymphomas are likely to progress mainly in the submucosal layers, most colonic MALT lymphomas appear to be a macroscopic form of submucosal tumor (SMT).\(^14,18\) In the present case, the gastric lesion showed swollen and reddish folds on the greater curvature and the colonic lesion showed a flat elevation like a SMT. These macroscopic forms were characteristic of MALT lymphoma as described above.

MALT lymphomas also show characteristic chromosomal and genetic features. Most MALT lymphomas have API2/MALT1 chimeric DNA resulting from a translocation of t(11;18).\(^20,21\) These chromosomal changes are recognized in about 50% of all MALT lymphomas and in 10-20% of all gastric MALT lymphomas.\(^22\) Additional chromosomal changes include tri-

some 3\(^2\) and t(1;14) with a translocation of the Bcl10-gene.\(^23\) Many of the MALT lymphoma cases with the t(11;18) translocation are resistant to eradication of \(H.\) pylori and show multiorgan involvement,\(^24,25\) although, there is little or no concern of their developing malignan
t potential. However, several previous reports indicate that, in most MALT lymphoma patients with multiple organ involvement, the multiple lesions consisted of an identical

clonal.\(^27-29\) Iwano et al. reported that most API2-MALT1-positive gastric MALT lymphomas with multiple lesions or multiple organ involvement appear to originate from a single lesion and disseminate to other lesions or organs.\(^29\) In the present case, the presence of t(11;18), API2-MALT1 fusion transcripts and the monoclonal-

ity of CDR3 was not determined, partly because there was no frozen sample of the tumor lesions. Therefore, it is impossible to deter-

mine whether the primary lesion metastasized to the rectum or whether the MALT lymphomas developed metachronously from the background so common in the gastric and rectal lesions. In the current case, the rectal MALT lymphoma developed about 3 and a half years after the operation for gastric MALT lymphoma. The incidence of metastasis from a gastric lesion to the rectum is very low, with respect to the metastatic pathway. The background factors common to gastric and rectal lesions are not known nor is the association between the infection and the inflammation caused from the infection or other factors. However, anecdotal reports have indicated that antibiotics were effective for treating colonic MALT lymphoma regardless of the presence of an \(H.\) pylori infection in the gastric lesion.\(^30,31\) These reports suggested the possibility of a correlation between colonic MALT lymphoma development and colonic bacteria.

In contrast, Grünberger et al. reported that 16 patients with extra-gastric MALT lymphoma and positive \(H.\) pylori infection in the gastric lesion underwent eradication before the initia-

tion of definitive treatment with extra-gastric MALT lymphoma and none of these 16 patients showed regression of the lymphoma.\(^23\) This

Figure 4. (A)(B) Colonoscopic findings on 13 May 1999, about 3 and a half years after the first operation for gastric MALT lymphoma, showed two SMT-like lesions in the rectum. The biopsy specimens indicated that the lesions were suspected to be malignant lymphomas.
nodes and the invasion into the spleen, thus two courses of CHOP therapy were added as adjuvant chemotherapy, however, rectal MALT lymphomas thereafter developed metachronously and repeatedly. Anecdotal reports on the effectiveness of eradication for colonic MALT lymphomas have been published and eradication therapy could have been administered, however, because the patient and her family requested a surgical operation, we judged that the advantages due to a preservation of a quality of life by not performing a colostomy were therefore greater than the disadvantages due to a relapse after a focal resection and thus selected a trans-anal focal resection of the tumor. It was strongly suggested that MALT lymphomas are likely to develop due to some background factor common in the stomach and rectum.

These common factors in the stomach and rectum are unknown, however, because several cases in which eradication therapy were effective, have been reported to be an internationally accepted standard therapy for the limited type of gastric MALT lymphoma. In particular, in those cases with positive H. pylori infections, eradication of the infection has been shown to improve the cure rate from 80% to 90%. Even if the patients are negative for H. pylori infections, eradication is advantageous in the cases positive for H. heilmani or false-negative for H. pylori infections, however, most cases negative for H. pylori infections have the API2/MALT1 transcripts produced by the translocation of t(11;18),2 reveal multiorgan involvements and show no effect of H. pylori eradication.

A salvage operation is the standard therapy for patients who do not respond to eradication, however, radiation therapy,36,37 administration of CHOP therapy,35 single drug therapy with cyclophosphamide,39 cladribine,40 etc. and Rituximab (anti-CD20 antibody)41-43 are other selected forms of treatment.

No therapy has been established for colonic MALT lymphoma. Anecdotal reports have described effective eradication for colonic MALT lymphoma as with gastric lesions, regardless of H. pylori infection status in the stomach,1,13,44,45 and it would seem appropriate to perform eradication therapy because it involves simple oral therapy for 7 days. However, it has been reported that eradication therapy was not effective for extra-gastric MALT lymphoma in one study36 and there are a number of questions of its therapeutic effect. Surgical resection is the most frequent therapeutic procedure for rectal MALT lymphoma in Japan. Further more, CHOP therapy and oral cyclophosphamide,39 etc, or Rituximab etc. are used as they are with gastric MALT lymphoma.

In the present case, eradication seems appropriate to the initially selected therapeutic procedure, because the patient was positive for H. pylori infection. Ho wever, in 1995, when the correlations between MALT lymphoma and H. pylori were initially reported, the patient and her family strongly requested a surgical resection. Therefore, a total gastrectomy was performed. The pathological examination suggested the involvement of the regional lymph

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