Acta Med. Okayama, 2021
Vol. 75, No. 5, pp. 625–629

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Case Report

Histologic Transformation from Follicular Lymphoma to Diffuse Large B-cell Lymphoma Detected during Colonoscopy

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A 77-year-old Japanese woman who had been treated for follicular lymphoma for 8 years developed abdominal pain and intra-abdominal lymphadenopathies. Colonoscopy revealed an elevated lesion in the rectum, which presented as two humps with erosions. A diagnosis of histologic transformation of follicular lymphoma to diffuse large B-cell lymphoma was made by endoscopic biopsy. This case underscores the importance of endoscopy examinations and biopsy of newly emerged gastrointestinal lesions for the prompt diagnosis of histologic transformation, since salvage chemotherapy must be initiated quickly in such cases.

Key words: colorectal lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, histologic transformation

Most patients with follicular lymphoma have an indolent clinical course [1, 2]. However, development of a high-grade, aggressive non-Hodgkin lymphoma occurs in some follicular lymphoma patients via a process called histologic transformation [3]. Because histologic transformation necessitates prompt initiation of treatment, the diagnosis of histologic transformation is crucial in the management of follicular lymphoma.

We herein report the case of a follicular lymphoma patient who had histologic transformation to diffuse large B-cell lymphoma (DLBCL). Of note, histologic transformation was detected during colonoscopy as a newly emerged rectal lesion. Endoscopic features of the colorectal lesions of follicular lymphoma and DLBCL are discussed later in this report.

Case Presentation

A 69-year-old Japanese woman visited her family clinic with abdominal pain. Computed tomography (CT) scanning revealed intra-abdominal and inguinal lymphadenopathies. She was referred to our hospital for further investigation and treatment. A diagnosis of follicular lymphoma (grade 1, stage IIA) was made by biopsy examination of the inguinal lymph nodes. Six cycles of cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab resulted in a decrease of the lymphadenopathies. However, tracer uptake persisted in the mesenteric lymph nodes on fluorodeoxyglucose-positron emission tomography (FDG-PET). At 71 years of age her mesenteric lymph nodes were enlarged again, and she was treated with 6 cycles of bendamustine and rituximab. Her right neck lymph nodes were still avid for FDG-PET tracer after bendamustine and rituximab treatment. Thus, rituximab monotherapy, spaced 3 to

Received February 17, 2021; accepted March 25, 2021.
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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

4 months apart, *i.e.*, rituximab maintenance, was started at 72 years of age. Colonoscopy performed at 72 years of age revealed an adenoma in the rectosigmoid junction, while there was no lymphoma involvement in the colorectum.

At 77 years of age, the patient experienced persistent abdominal pain. Physical examination revealed no abnormalities, and there was no evidence of hepatosplenomegaly or peripheral lymphadenopathy. Laboratory tests showed slightly elevated values for lactate dehydrogenase (237 U/L; normal range: 124-222 U/L), aspartate aminotransferase (38 U/L), alkaline phosphatase (394 U/L), urea nitrogen (28.1 mg/dL), creatinine (0.82 mg/dL), and uremic acid (6.6 mg/dL). Her hemoglobin, serum calcium, and soluble interleukin 2-recepter levels were within the normal ranges. Computed tomography revealed intra-abdominal lymphadenopathies (Fig. 1A) and tracer accumulation was observed on FDG-PET (Fig. 1B). Therefore, lymphoma progression was considered to be the cause of her abdominal pain.

Colonoscopy revealed an elevated lesion in the rectum, which presented as 2 humps with subepithelial tumor-like appearance (Fig. 2A). Linked color imaging observation (Fig. 2B) and indigo carmine dye spraying (Fig. 2C) emphasized the lesion's reddish color. Magnifying observation with blue laser imaging showed dilated microvessels (Fig. 2D) and erosions (Fig. 2E) on the surface. Because the colorectum had been intact on colonoscopy performed 5 years previously, we suspected the lesion to be a lymphomatous rectal involvement. A biopsy showed dense infiltration of atypical lymphoid cells of medium to large size in the interstitium (Fig. 3A). Immunostaining revealed that the lymphoid cells were positive for CD20 (Fig. 3B), CD10 (Fig. 3C), and BCL2 (Fig. 3D), and were negative for CD3 (Fig. 3E) and CD5 (Fig. 3F). Cells were diffusely

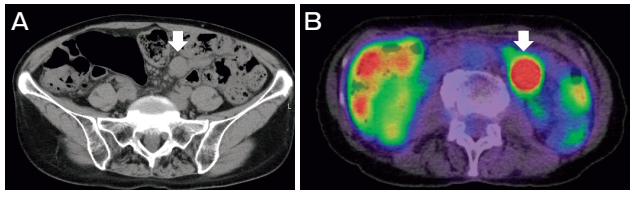

Fig. 1 Radiological images. Computed tomography revealed intra-abdominal lymphadenopathies (**A**). Fluorodeoxyglucose-positron emission tomography showed tracer accumulation in the lymph nodes (**B**).

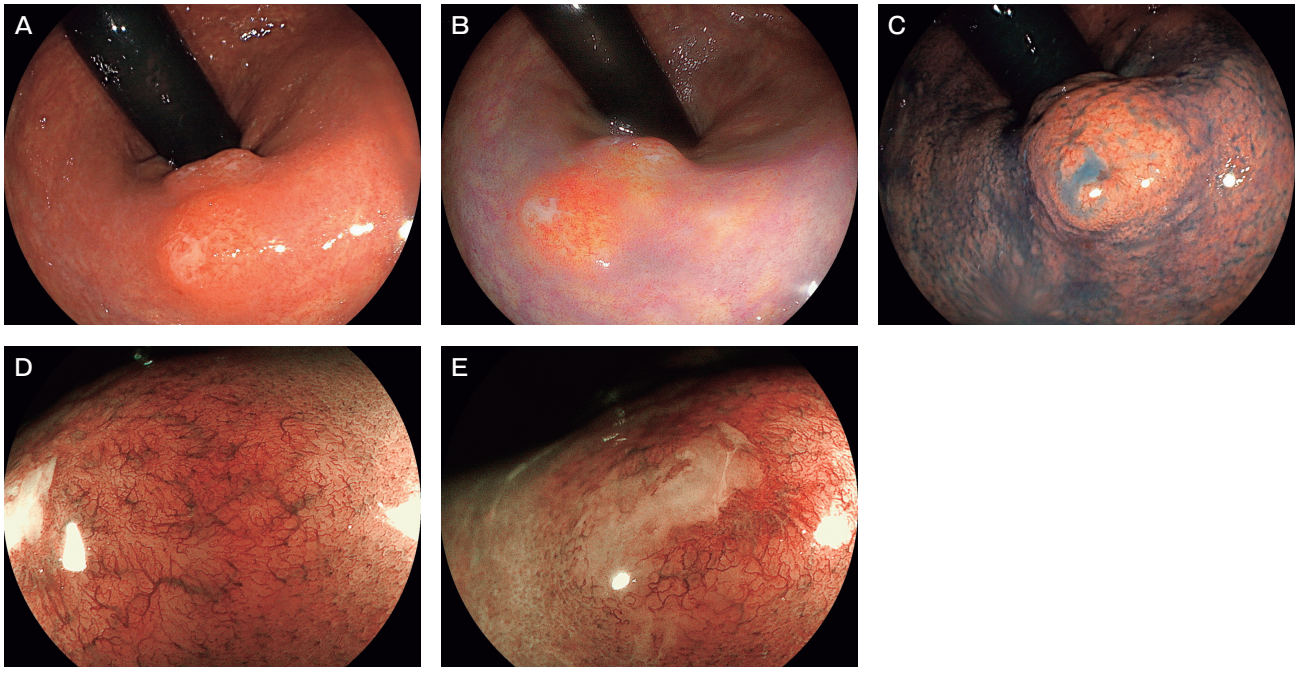

Fig. 2 Colonoscopy images. An elevated lesion is observed in the rectum (**A**). Linked color imaging observation (**B**) and indigo carmine dye spraying (**C**) emphasized the lesion's reddish color. Magnifying observation with blue laser imaging revealed dilated microvessels (**D**) and erosions (**E**).

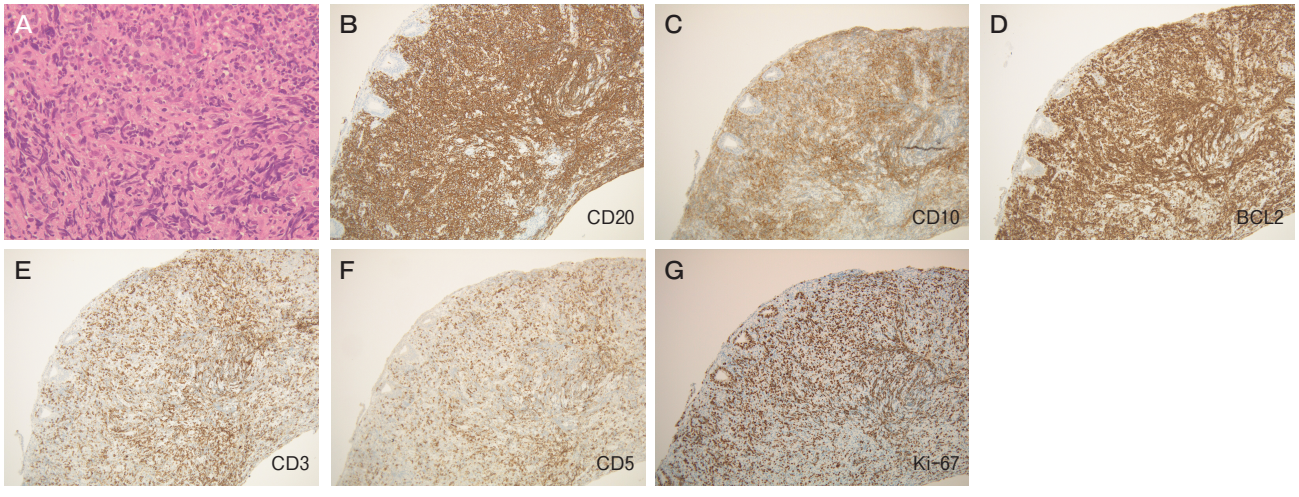

Fig. 3 Pathology images. A biopsy shows dense infiltration of atypical lymphoid cells (**A**). The lymphoid cells are positive for CD20 (**B**), CD10 (**C**), and BCL2 (**D**), and are negative for CD3 (**E**) and CD5 (**F**). Cells are diffusely positive for Ki-67 (**G**).

positive for Ki-67 (Fig. 3G). Therefore, we diagnosed the patient with histologic transformation of follicular lymphoma to DLBCL. Salvage chemotherapy with 6 cycles of bendamustine and rituximab resulted in the disappearance of metabolic tumor activity in lymphoma lesions on FDG-PET.

Discussion

In the patient presented in this case report, histologic transformation of follicular lymphoma to DLBCL occurred during maintenance therapy with rituximab. Histologic transformation is generally defined as an increase in the proportion of large cells infiltrating the lymph nodes diffusely and leading to effacement of the follicular architecture [3-5]. Clinically, DLBCL is the most commonly observed histologic transformation of follicular lymphoma. The annual incidence of histologic transformation of grade 1, 2, and 3a follicular lymphoma into an aggressive lymphoma has been estimated at 1% to 2% [6]. An open-label, multicenter, international, randomized phase III study of 2 years of rituximab maintenance after first-line immunochemotherapy (PRIMA study) revealed that rituximab maintenance provided a significant long-term progression-free survival in follicular lymphoma patients, whereas such maintenance was not associated with a difference in overall survival [7,8]. The prevalence of and time to histologic transformation were not different between patients with and without rituximab maintenance. Thus, the evolution of follicular lymphoma to a clinically aggressive lymphoma can occur even during maintenance therapy with rituximab, as observed in our patient.

In the present case, transformation to DLBCL was pathologically confirmed by endoscopic biopsy of the rectal lesion. In our earlier work, we investigated the endoscopic features of colorectal lesions in 12 patients with follicular lymphoma [9,10]. Macroscopic appearance of colorectal follicular lymphoma was classified as papular (n=4), polypoid (n=4), and flat elevated lesions (n=4). We also reviewed 8 previously reported cases in which detailed morphological characteristics of colorectal involvement with follicular lymphoma were described [11-18]. Among these cases, the macroscopic appearance of the colorectal lesions could be categorized into papular (n=1), polypoid (n=5), and flat elevated (n=1), with ulcerative tumor occurring in only one patient with grade 3a follicular lymphoma [19]. Apart from the latter exceptional case [19], no erosions or ulcers were found in the previously reported cases. Therefore, we speculate that follicular lymphoma, particularly that of grade 1-2, presents as elevated lesions without erosions or ulcers in the colorectum.

Colorectal lesions of DLBCL exhibit a diverse range of morphologies, including ulcers [20,21], large masses with or without ulceration [22-24], nodular masses [25], and colitis-like changes [26]. Maeshima *et al.* investigated the clinicopathological characteristics of 126 patients with DLBCL involving the small and

large intestines [27]. They reported that rectal lesions were observed as ulcerated (n=1, 17%), nodular (n=2, 33%), multiple polyposis (n=2, 33%), and flat elevated (n=1, 17%). Ileocecal lesions of DLBCL most frequently presented as ulcerated (n=31, 56%), followed by nodular (n=22, 39%), and flat elevated lesions (n=3, 5%). In the colon, ulcerated (n=8, 73%), nodular (n=2, 18%), and flat elevated lesions (n=1, 9%) were observed. Thus, ulcerative lesions are predominant features of DLBCL occurring in the large intestine, while follicular lymphoma lesions in the large intestine generally lack erosions or ulcers. We speculate that histologic transformation should be considered when colorectal lesions with erosions and/or ulcers emerge in patients with follicular lymphoma, as observed in the present patient.

It was also noteworthy that the rectal lesion was not detected on FDG-PET but was identified during colonoscopy. FDG-PET is generally recommended for staging of DLBCL patients because of its superior sensitivity for the detection of nodal and extra-nodal lymphoma involvement [28, 29]. However, because the tracer concentration corresponds to the regional glucose uptake, it is likely that small lesions cannot be detected. Another hypothesis is that treatment for follicular lymphoma resulted in the false-negative FDG-PET results. It has been reported that not a few patients with DLBCL show false-negative results for relapse after chemotherapy [29, 30]. Moreover, we previously investigated FDG-PET results in 41 patients with follicular lymphoma, and found that false-negative tracer uptake was detected in 24 patients (58.5%) [31]. In this context, we consider that endoscopic examinations should be performed in follicular lymphoma patients irrespective of FDG-PET results, in order to detect histologic transformation as well as lymphoma progression to the gastrointestinal tract.

In conclusion, in our patient with follicular lymphoma, histologic transformation to DLBCL was identified as a rectal lesion with erosions. Although such a manifestation is considered to be infrequent, the clinical course of our patient underscores the importance of endoscopy examinations and biopsy of newly emerged gastrointestinal lesions, particularly those with erosions, for prompt diagnosis of histologic transformation.

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