

Original Article

Histological Variety of Localized Lymphoid Hyperplasia of the Large Intestine : Histopathological, Immunohistochemical and Genotypic Findings of 16 Cases

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Previous reports emphasized that localized lymphoid hyperplasia (LLH) of the large intestine is usually histologically characterized by large lymphoid follicles with striking enlarged germinal centers, and a narrow surrounding mantle zone and marginal zone (MZ). To clarify the histological varieties of LLH of the large intestine, 16 such cases have been studied. The present study demonstrated histological diversity of the LLH of the large intestine including (i) reactive follicular hyperplasia (RFH) (n = 8), (ii) RFH with progressive transformation of the germinal center (PTGC) (n = 3), (iii) RFH with MZ hyperplasia (n = 3) and (iv) RFH with PTGC and MZ hyperplasia (n = 2). Overall histomorphological findings of the present series appear quite different from previous descriptions of LLH of the large intestine. The present study showed histological variety of the LLH of the large intestine. Moreover, LLH of the large intestine should be differentiated from extranodal marginal zone B-cell lymphoma and nodular lymphocyte predominant Hodgkin lymphoma as well as follicular lymphoma. Immunohistological studies demonstrated the reactive nature of all 16 lesions. However, three cases showing RFH demonstrated immunoglobulin heavy chain gene rearrangement by polymerase chain reaction study in 12 cases examined. It remains unclear whether these three cases showing RFH could be a sign of the prelymphomatous stage (incipient follicular lymphoma) or representing merely an exaggeration of normal B-cell clonal response in the germinal centers. [*J Clin Exp Hematopathol* 49(1) : 15-21, 2009]

Keywords: localized lymphoid hyperplasia, large intestine, histological findings, progressive transformation of the germinal center, marginal zone hyperplasia

INTRODUCTION

Prominent lymphoid tissue organized as lymphoepithelial complexes is a normal component of the mucosa and superfi-

cial submucosa of the small and large intestine.¹ Notably, the frequency of the lymphoepithelial complex is unevenly distributed and increases from the right to the left colon, being most frequently found in the rectum.¹⁻⁶ These lesions are also known as lymphoid polyps, benign lymphoid polyps, localized lymphoid hyperplasia (LLH) and rectal tonsils.²⁻⁶ However, when exuberant, the reactive lymphoid infiltrates can be difficult to distinguish from lymphoma on small biopsy specimens.²⁻⁶ Histologically, a dense lymphoid infiltrate is present in the lamina propria and submucosa. This is usually characterized by follicles with well-formed germinal centers that vary in size, often being strikingly enlarged with a narrow surrounding mantle zone.²⁻⁶ However, LLH of the large intestine appears to show histological variations. They included LLH of the rectum associated with prominent marginal zone hyperplasia or LLH demonstrating progressive transformation of the germinal center (PTGC).^{7,8} To further clarify the histological, immunohistochemical and genotypic findings of LLH of the large intestine, retrospective analysis of 16 cases of LLH large intestine was performed on polypectomy, endoscopic mucosal resection or biopsy specimens.

Received : September 9, 2008

Revised : November 25, 2008

Accepted : December 18, 2008

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MATERIALS AND METHODS

Sixteen cases were collected from a series by one of the authors (M. K.) treated between January 2002 and June 2006. Five cases (Nos. 3, 5, 7, 10 and 12) have been reported previously.^{7,8}

Tissue specimens were fixed in formalin, routinely processed and embedded in paraffin. For light microscopy, the sections were stained using hematoxylin and eosin (HE). Immunohistochemistry was performed on paraffin sections using a Ventana automated (BenchMark™) stainer according to the manufacturer's directions. A panel of antibodies against human immunoglobulin light chain (κ and λ) (Dako, Glostrup, Denmark), IgD (Novocastra, Newcastle upon Tyne, UK), IgM (Dako), CD3 (PS-1; MBL, Nagoya, Japan), CD5 (4C7; Novocastra), CD10 (56C6; Novocastra), CD15 (C3D-1; Dako), CD20 (L26; Dako), CD23 (1B12; Novocastra), CD30 (Ber-H2; Dako), CD43 (DFT-1; Dako), CD57 (NK-1; Novocastra), Cyclin D1 (SP4; Nichirei, Tokyo, Japan), bcl-2 (124; Dako) and epithelial membrane antigen (EMA) (E29; Dako) were used. Replacement of the primary antibodies by normal rabbit- and mouse-serum was

performed as a negative control.

In situ hybridization (ISH) with Epstein-Barr virus (EBV)-encoded small RNA (EBER) oligonucleotides was performed to test for the presence of EBV small RNA in formalin-fixed paraffin-embedded sections using a Ventana automated (BenchMark™) stainer. In 12 cases (Nos. 2, 3, 5-11, 13, 14 and 16), paraffin-embedded tissues from specimens were sectioned on charged slides, deparaffinized with xylene, and hydrated before being scraped into polymerase chain reaction (PCR) tubes using a single-edged razor blade. To determine clonality of *immunoglobulin heavy-chain (IgH)* genes, PCR was performed as described by Wan *et al.*⁹

A summary of the 16 cases is shown in the Table 1. The patients, 13 females and 3 males, ranging from 19 to 74 years old, had a mean age of 60 years and a median age of 65 years. Colonoscopy was conducted for the evaluation of hematochezia/rectal bleeding in 10 cases (Nos. 1, 2, 5-8, 10, 11, 13 and 14), for screening in three patients (Nos. 3, 4 and 12), for the evaluation of constipation in one (No. 9). Whether colonoscopy was performed was not described in the remaining two cases (Nos. 15 and 16). None of the patients had a diagnosis of immunodeficiency.

Table 1. Summary of the clinicopathological findings of 16 cases

Case No.	Age/ Sex	Site	Main clinical finding	Main endoscopic finding	Therapy	Follow-up (months)	Histological findings	IHC	PCR	EBER
1	19/F	Rectum	Anal bleeding	Confluence of multiple small nodules, up to 5 mm	None (biopsy only)	72, A	RFH	P	NE	-
2	45/F	Rectum	Anal bleeding	Confluence of multiple small nodules, up to 5 mm	None (biopsy only)	2, A	RFH	P	M	-**
3	46/F	Rectum	Screening	Solitary SMT ($\phi = 5$ mm)	Polypectomy	48, A	RFH with MZE*	P	P	-
4	50/F	Rectum	Screening	Solitary polyp ($\phi = 5$ mm)	Polypectomy	16, A	RFH with PTGC*	P	NE	+
5	58/F	Rectum	Anal bleeding	Solitary polyp ($\phi = 10$ mm)	Polypectomy	25, A	RFH	P	P	-
6	60/F	Cecum	Occult bleeding	Solitary polyp ($\phi = 4$ mm)	Polypectomy	10, A	RFH	P	P	-
7	64/F	Rectum	Anal bleeding	Multiple SMT (n = 30, $\phi = 6$ mm)	Polypectomy + radiotherapy	38, A	RFH with MZE*	P	P	-
8	64/F	Rectum	Anal bleeding	Solitary polyp ($\phi = 5$ mm)	Polypectomy	Lost	RFH	P	P	-
9	65/M	Rectum	Constipation	Solitary SMT ($\phi = 4$ mm)	Polypectomy	28, A	RFH with PTGC*	P	P	-
10	66/F	Rectum	Occult anal bleeding	Multiple SMT (n = 5, $\phi = 6$ mm)	Polypectomy	61, A	RFH with MZE*	P	P	-
11	69/F	Rectum	Occult anal bleeding	Multiple SMT (n = 2, $\phi = 5$ mm)	Polypectomy	60, A	RFH	P	M	-
12	71/F	Rectum	Screening	Solitary polyp ($\phi = 5$ mm)	Polypectomy	14, A	RFH with PTGC*	P	NE	+
13	71/F	Rectum	Occult anal bleeding	Multiple SMT (n = 3, $\phi = 3$ mm)	EMR	31, A	RFH	P	P	-
14	72/M	Rectum	Occult anal bleeding	Confluence of multiple small nodules, up to 5 mm	None (biopsy only)	23, A	RFH	P	M	-**
15	72/M	Rectum	Unknown	Solitary SMT ($\phi = 10$ mm)	EMR	Recent case	RFH with PTGC and MZE	P	NE	-
16	73/F	Ascending colon	Unknown	Solitary polyp ($\phi = 3$ mm)	Polypectomy	Lost	RFH with PTGC and MZE	P	P	-

SMT, submucosal tumor; EMR, endoscopic mucosal resection; A, alive; RFH, reactive follicular hyperplasia; MZE, marginal zone expansion; PTGC, progressive transformation of germinal center; IHC, immunohistochemistry; P, polyclonal; PCR, polymerase chain reaction; NE, not examined; M, monoclonal; EBER, Epstein-Barr virus-encoded small RNA; *, Presence of epithelioid cell cluster; **, EBER⁺ cells were located in the epithelial cells.

Descriptions of the endoscopic lesions were either submucosal tumors in seven cases (Nos. 3, 7, 9-11, 13 and 15) or polyps in six cases (Nos. 4-6, 8, 12 and 16). In the remaining three cases (Nos. 1, 2 and 14), the lesions were described as the confluence of multiple small nodules up to 5 mm.

One case (No. 7) was tentatively diagnosed as marginal zone B-cell lymphoma (MZBL) of mucosa associated lymphoid tissue (MALT) type, and the patient underwent radiotherapy. The remaining 15 patients did not receive any medication after colonoscopy.

Follow-up information was available in 13 patients (Nos. 1-7 and 9-14) for periods ranging from two to 72 months (mean 33 months, median 28 months). None of these 13 patients showed evidence of malignant lymphoma during the follow up period.

RESULTS

Pathological and immunohistochemical findings

Microscopically, a dense lymphoid infiltrate was present in the mucosa and submucosa (Fig. 1a). Lymphoid follicles with hyperplastic germinal centers could be identified in all 16 cases. Occasionally, hyperplastic germinal centers with ill-defined mantle zone were present (Fig. 1a). PTGC could be identified in five cases (Nos. 4, 9, 12, 15 and 16) (Fig. 1b). PTGC was characterized by enlarged but well-circumscribed follicles without clear demarcation of the germinal center and mantle zone, which contained a predominance of small lymphocytes and variable numbers of centrocytes, centroblasts and immunoblasts (Fig. 1c). A few centroblasts and immunoblasts resembling lymphocytic and/or histiocytic (L&H) Reed-Sternberg cell variants in nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) were also identified (Fig. 1c) in two lesions (No. 4 and 12). Moreover, expansion of the marginal zone (MZ) was identified in five cases (Nos. 3, 7, 10, 15 and 16) (Fig. 1d). At higher magnification, the MZ contained numerous small lymphocytes and monocytoid B-cells (MBCs) with abundant pale or clear cytoplasm, and medium indented or round nuclei with small conspicuous nucleoli accompanied by scattered large transformed lymphocytes. Scattered plasma cells and histiocytes with or without epithelioid cell features were intermingled with lymphoid cells (Fig. 1e). Small-to-medium sized clusters of epithelioid cells were also identified in four cases (Nos. 3, 4, 7, 9, 10 and 12). Typical lymphoid follicles and those showing PTGC both expressed CD20 antigen.

B-cells in the germinal centers were bcl-2⁺ (Fig. 2a) and CD10⁺ B-cells were confined strictly to the germinal centers. Immunohistochemical studies of the light-chain determinant for germinal center cells demonstrated a polytypic nature.

The majority of small lymphocytes in PTGC, which were surface IgD⁺ (Fig. 2b) and IgM⁺, CD5⁺, CD43⁺, Cyclin D1⁺,

exhibited non-neoplastic follicular mantle cells. Residual follicular center cells were usually CD10⁺ and Bcl-2⁻. Using T-cell associated antigens CD3 and CD5, it was demonstrated that the nodules in PTGC contained a few small lymphocytes either scattered or aggregated in groups of up to 10 cells. The majority of T-cells were also CD57⁺, but there were no T-cell rosettes identified around the L&H-like cells. Scattered B immunoblasts in the PTGC and interfollicular area were CD30⁺, but CD15⁻ or EMA⁻. Staining with CD23 highlighted the meshwork of the follicular dendritic cells (FDCs). The FDC meshwork showed complete disruption into clusters in PTGC.

MBCs and large transformed lymphocytes were CD20⁺, sIgD⁻, CD5⁻, CD10⁻, CD23⁻, CD43⁻ (Fig. 2c), bcl-2⁻ and cyclin D1⁻. A portion of MBCs were surface IgM⁺. MBCs and large transformed B-cells and plasma cells had polytypic immunoglobulin light chains.

There were no destructive lymphoepithelial lesions detected even by immunostaining for EMA in any of the 16 cases.

EBV findings

ISH studies demonstrated scattered EBER⁺ medium- and large-lymphoid cells and crypt epithelium in two lesions (Nos. 4 and 12) (Fig. 2d). In two lesions (Nos. 2 and 14), scattered EBER⁺ cells were identified in only crypt epithelium.

Genotypic findings

PCR analyses for IgH gene demonstrated a polyclonal pattern in nine cases (Nos. 3, 5-10, 13 and 16). However, three lesions showing RFH (Nos. 2, 11 and 14) demonstrated a clonal band on PCR assay for the IgH gene (Fig. 3). There was no clonal band on PCR assay for the IgH gene in four cases (Nos. 3, 7, 10 and 16) showing MZ expansion.

DISCUSSION

Histologically, LLH of the large intestine is usually characterized by large lymphoid follicles with active germinal centers and a narrow surrounding mantle zone.¹⁻⁶ However, the present study demonstrated the histological diversity of the LLH of the large intestine including (i) reactive follicular hyperplasia (RFH) (n = 8; Nos. 1, 2, 5, 6, 8, 11, 13 and 14), (ii) RFH with PTGC (n = 3; Nos. 4, 9 and 12), (iii) RFH with MZ hyperplasia (n = 3; Nos. 3, 7 and 10) and (iv) RFH with PTGC and MZ hyperplasia (n = 2; Nos. 15 and 16). The overall histomorphological findings of the present series appear quite different from previous descriptions regarding LLH of the large intestine.¹⁻⁶ The present study showed histological variety of LLH of the large intestine. However, the reason

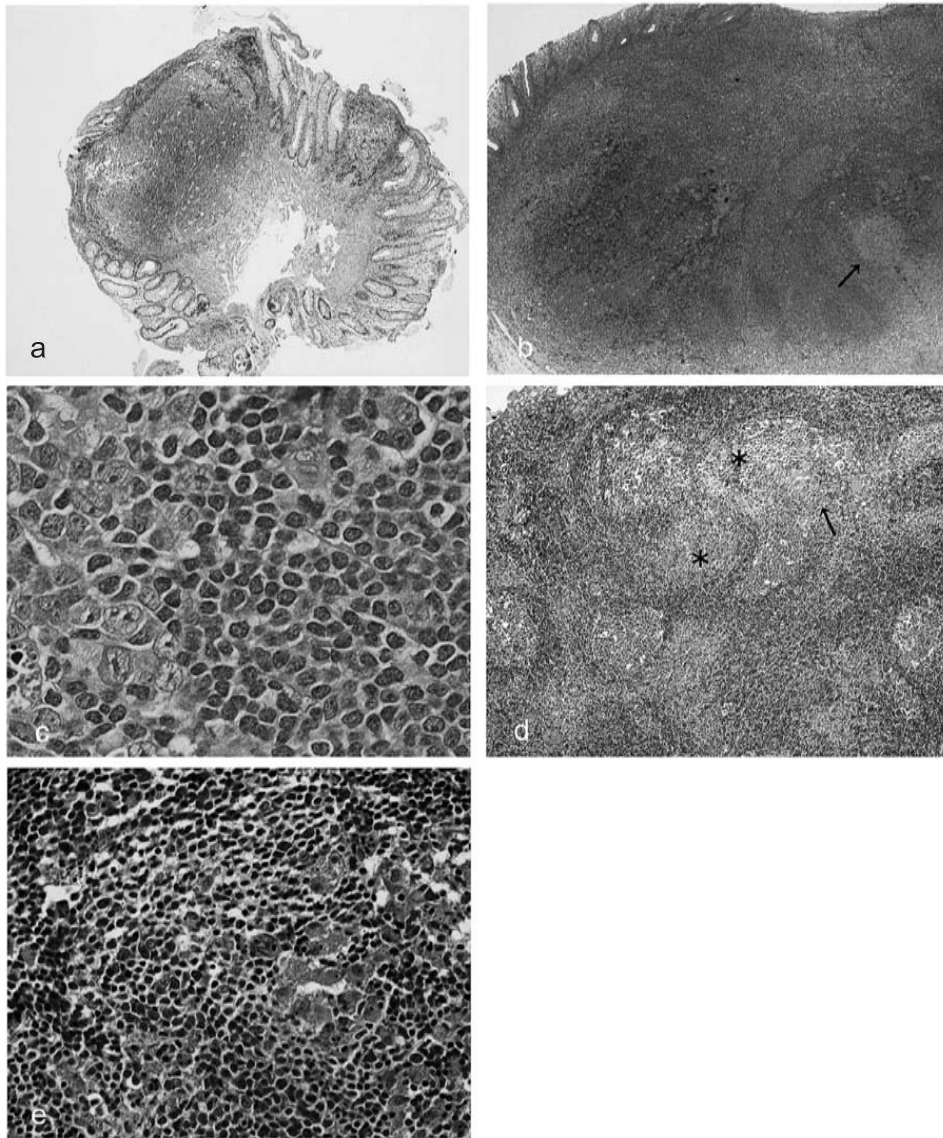


Fig. 1. Histological findings. (*1a*) Low-power field of the biopsy specimen. Note a lymphoid follicles with hyperplastic germinal centers and ill-defined mantle zone. Case 1, HE (hematoxylin and eosin), x10. (*1b*) Low-power field of the polypectomy specimen. A large progressive transformation of the germinal center (PTGC) was surrounded by secondary lymphoid follicles. Note the epithelioid cells clusters (*arrow*). Case 4, HE, x10. (*1c*) High-power field of Fig. 1b. A relatively large number of residual centrocytes, centroblasts and immunoblasts were present, in addition to the small mantle zone lymphocytes. Note a few centroblasts resembling L&H Reed-Sternberg cells. Case 12, HE, x 250. (*1d*) Low-power field of the polypectomy specimen. Lymphoid follicles with hyperplastic germinal centers and an expanded marginal zone (*). Note the epithelioid cells clusters (*arrow*). Case 7, HE, x25. (*1e*) High-power field of Fig. 1a. The marginal zone contained numerous monocytoïd B-cells and scattered large transformed lymphocytes. Histiocytes with or without epithelioid features and a few plasma cells and neutrophils were present. Case 2, HE, x100.

underlying the histological diversity of the LLH of the large intestine still remains to be determined.

PTGC was initially reported by Lennert and Müller-Hermelink¹⁰ and further studies were subsequently reported

by others. PTGC is larger than a typical germinal center and mainly composed of mantle zone lymphocytes and remnants of large germinal center cells.^{11,12} The mantle zone is obscured, and the interfollicular areas usually contain small

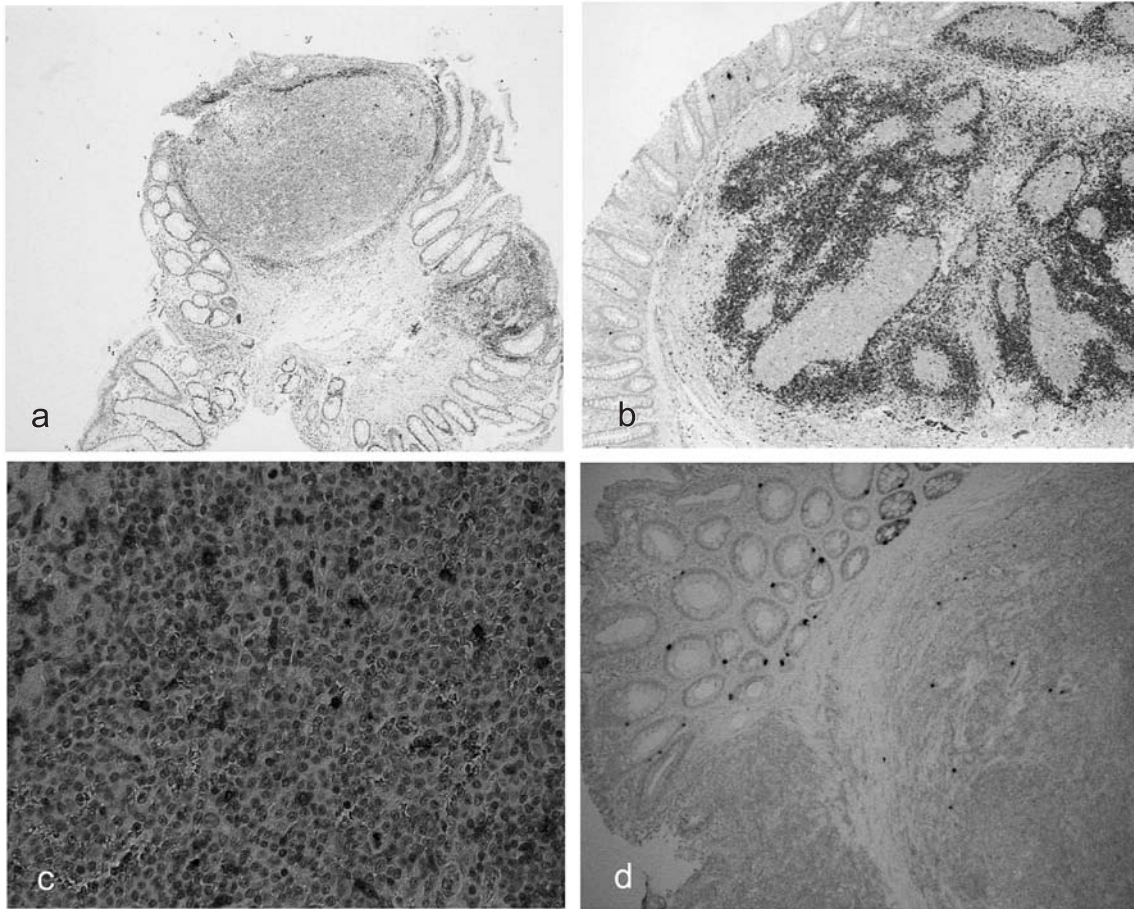


Fig. 2. Immunohistological findings. (2a) Germinal center B-cells and marginal zone B-cells were *bcl-2*⁻. Case 2. (2b) Small lymphocytes of the transformation of the germinal center (PTGC) were surface *IgD*⁺. Case 4. (2c) Residual germinal center cells of the PTGC were *CD43*⁻. Case 3. (2d) *In situ* hybridization studies demonstrated scattered EBER-positive medium- and large-lymphoid cells and crypt epithelium in the lesion. Case 4. (2a-2d) counterstained with hematoxylin, (2a, 2b, 2d) x 25, (2c) x 100.

lymphocytes and a few immunoblasts.^{11,12} PTGC usually affects peripheral lymph nodes.^{10,11} The incidence of PTGC at extranodal sites appears rarer.¹¹ However, the present study indicated that PTGC occasionally occurs in BLH of the large intestine (5 cases ; 30%).

As previously emphasized follicular lymphoma appears to be the most important diagnostic problem.¹⁻⁶ Primary follicular lymphomas arising from the large intestine appear to be rare.¹³ Primary follicular lymphoma may present as a polypoid mass.¹³ *Bcl-2* immunostain suggested the reactive nature of lymphoid follicles in our lesion.¹⁴ In follicular lymphoma, the expression of *CD10* was seen in both follicular and interfollicular areas.¹⁵ However, in all 16 lesions, *CD10* were expressed almost exclusively by the follicular center cells, which are characteristic findings of reactive follicular hyperplasia. Immunohistochemical studies of light-chain determinant for germinal center cells demonstrated a polytypic nature.

Although the immunohistochemical study suggested the reactive nature of lymphoid follicles in our series, three cases (Nos. 2, 11 and 14) showing RFH demonstrated *IgH* gene rearrangement by the PCR study. Recently, Nam-Cha *et al.* analyzed 6 florid RFH specimens using immunohistochemistry, *IgH*-PCR and microdissected PCR.¹⁶ They found that some germinal centers contained a population of plasma cells and plasmacytoid germinal center cells showing immunoglobulin light-chain restriction.¹⁶ In three cases, the monotypic germinal center cells also showed distinct *bcl-2* expression.¹⁶ Two cases demonstrated a predominant *IgH* rearrangement on a florid polyclonal background and one had an *IgH* monoclonal rearrangement by PCR.¹⁶ Nam-Cha reported that only one of the six cases developed follicular lymphoma.¹⁶ It remains unclear whether these three cases in our study (Nos. 2, 11 and 14) having *IgH* gene rearrangement could be a sign of a prelymphomatous stage (incipient follicular lymphoma)¹⁷ or whether they merely represent an exaggeration of a normal

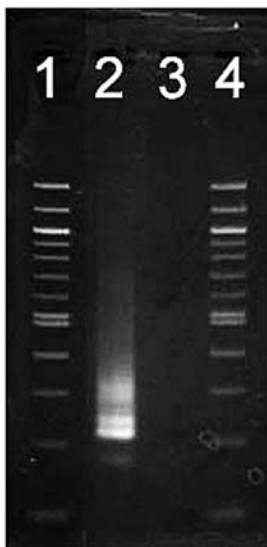


Fig. 3. PCR analysis of case 2 for clonal immunoglobulin heavy chain rearrangement. The lanes contain molecular control m (1), Case 2 (2), negative control (3), and molecular control m (4).

B-cell clonal response in the germinal center. However, our three cases showed a relatively short follow up period. To clarify this issue, further study is needed.

MZ hyperplasia were present in five (30%) of the present series. Tumor cells of the MALT type lymphoma are small-to-medium lymphocytes showing a moderate amount of clear cytoplasm, indented or round nuclei, and absent or small nucleoli (centrocyte-like cells).^{5,18} Occasionally, MALT type lymphoma shows a follicular growth pattern resulting from prominent follicular colonization.¹⁸ The colonized germinal centers were occupied by neoplastic cells with various numbers of residual follicular center cells and mantle cells. On the low power field, poorly defined follicles contained fragmented residual follicular center cells.^{11,18} The histological findings of follicular colonization appear somewhat similar to those of PTGC.¹⁸ Two of five lesions showing MZ hyperplasia also contained PTGC. Moreover, colorectal MALT type lymphoma sometimes presented as a solitary polyp or multiple polypoid lesions.^{19,20} However, there were no CD43⁺ and/or bcl-2⁺ MZ B-cells in the any of the five lesion demonstrating MZ hyperplasia.^{14,21} Immunophenotypic study demonstrated the polytypic nature of the B-lymphocytes. Moreover, there was no clonal band on PCR assay for the *IgH* gene in four cases (Nos. 3, 7, 10 and 16) showing MZ expansion examined.

Very rarely, nodular NLPHL can show extranodal localization.²² PTGC should be differentiated from NLPHL. One of the characteristic immunohistological findings of NLPHL is the presence of CD57⁺ lymphocyte rosette around the L&H Reed-Sternberg cell variants. However, there were

no CD57⁺ rosettes around the L&H-like cells in either of our cases.^{12,22} Moreover, L&H Reed-Sternberg cell variants are occasionally EMA⁺. However, there were no EMA⁺ L&H-like cells in either of our cases.^{12,22}

The etiology of LLH of the large intestine is unclear. ISH studies demonstrated scattered EBER⁺ medium- and large-lymphoid cells and crypt epithelium in two of 16 lesions. However, reactivity of lymphoid cells for EBV has been reported in lymphoid tissues from a high percentage of normal individuals.²³ To clarify this issue, further study is needed.

In conclusion, the present series demonstrated the histological diversity of the LLH of the large intestine and indicated that several types of low-grade B-cell lymphoma should be differentiated from LLH of the large intestine.

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