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ORIGINAL PAPER

Focal Lymphoid Hyperplasia of the Terminal Ileum Presenting Mantle Zone Hyperplasia with Clear Cytoplasm. A Report of Three Cases

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Abstract We report three unusual cases of focal lymphoid hyperplasia of the ileocecal valve. The gross specimens showed thickening of the ileocecal valve. Low power magnification showed a dense lymphoid infiltrate in the mucosa and submucosa. This condition was characterized by reactive lymphoid follicles with large reactive germinal centers surrounded by a pale cuff of mantle zone lymphocytes presenting a marginal zone distribution pattern. These cells had intermediate- to- medium-sized round or slightly indented nuclei and a broad rim of clear cytoplasm. However, immunohistochemical study demonstrated that both the mantle zone lymphocytes and the pale cuff of the lymphoid cells were CD20+, sIgM+, sIgD+, CD5−, CD10−, CD23−, CD43−, Bcl-2+, Bcl-6−, CyclinD1−. The polytypic nature of these cells was demonstrated by immunohistochemistry and polymerase chain reaction. This unusual mantle cell hyperplasia with clear cytoplasm associated with focal lymphoid hyperplasia in middle-aged and elderly patients should be differentiated from the extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue type or mantle cell lymphoma showing a marginal zone distribution pattern. To avoid overdiagnosis and overtreatment, it is suggested that immunophenotypic and genotypic studies might be required, and careful attention should be paid to the morphologic examination.

Keywords Focal lymphoid hyperplasia · Terminal ileum · Mantle zone hyperplasia · MALT lymphoma · Immunohistochemistry

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Introduction

The gastrointestinal tract is a common site for lymphoproliferative disorders. Among these conditions, focal lymphoid hyperplasia in the terminal ileum (FLHTI) can be subdivided into a more common form seen in children and young adults and a rarer form seen in older patients [1, 2]. In the adult form, the lesions usually contain usually numerous reactive lymphoid follicles with active germinal centers and are easily recognized as having a non-neoplastic nature [2]. However, Rubin et al reported five cases of FLHTI demonstrating histological findings closely resembling marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type. The lesion is characterized by large reactive germinal centers and a

diffuse lymphoplasmacytic infiltrate extending deeply into the wall of the ileum [3]. Moreover, a structure resembling lymphoepithelial lesion (LEL) was also noted. We report here three cases of FLHTI containing numerous mantle cells with clear cytoplasm and the problems of differential diagnosis of MALT type lymphomas and extranodal mantle cell lymphoma showing a marginal zone distribution pattern are discussed.

Materials and Methods

All three cases were obtained from the files of the one of the authors (M.K). The tissue specimens were fixed in formalin, routinely processed and embedded in paraffin. For light microscopy, the sections were stained using hematoxylin–eosin and Giemsa. Immunohistochemistry was performed on paraffin sections using a Ventana automated (BenchMarkTM) stainer according to the manufacturer's directions. A panel of antibodies against human immunoglobulin light chain (kappa and lambda; Novocastra, Newcastle, UK), IgD (Novocastra), IgM (Dako A/S, Glostrup, Denmark), PS-1 (CD3; MBL, Nagoya, Japan), 4C7 (CD5; Novocastra), 56C6 (CD10; Novocastra), L26 (CD20; Dako), 1B12 (CD23; Novocastra), DFT-1(CD43; Novocastra), CNA.42 (anti-follicular dendritic cell antibody; Dako), SP4 (Cyclin D1; Nichirei Co., Tokyo, Japan), 124 (bcl-2; Dako), polyclonal bcl-6 (Dako) and AE1/3 (Dako) were used. The primary antibodies were replaced by normal rabbit- and mouse-serum was used as a negative control.

Using a Ventana automated (BenchMarkTM) stainer, 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.

Paraffin-embedded tissues from the biopsy specimen were prepared for polymerase chain reaction (PCR), and rearranged heavy-chain genes were amplified using the seminested PCR method as described by Wan et al [4].

Results

Clinical Findings

Clinical findings of three cases are shown in the Table 1.

The patients were 45- and 80-year-old Japanese females and a 53-year-old Japanese male.

Pathological, Immunohistochemical and Genotypic Findings

In three cases, the gross specimens showed thickening of the ileocecal valve (Fig. 1a). In case 2, there was a polypoid mass projecting into the lumen.

There were essentially similar histopathological findings in all three cases. Low power magnification showed a dense lymphoid infiltrate present in the mucosa and submucosa. The lesions contained numerous lymphoid follicles with active germinal centers. The majority of the lymphoid follicles were surrounded by a pale ring of lymphoid cells resulting in the narrowing of the interfollicular area (Fig. 1b). Some of the lymphoid follicles in all three cases showed follicular lysis (Fig. 1c). On high power-field, the pale cuffs were composed of intermediate to medium-sized lymphocytes with round or slightly indented nuclei and a broad rim of clear cytoplasm (Fig. 1d).

Immunohistochemical study demonstrated that both the mantle zone lymphocytes and the pale cuff of the lymphoid cells were CD20+, CD5−, CD10− CD23−, CD43−, Bcl-2+, Bcl-6−, CyclinD1−, sIgM+(Fig. 1e), sIgD+(Fig. 1f). Moreover, mantle zone lymphocytes and the pale cuff of the lymphoid cells showed polytipic surface immunoglobulins in the two cases evaluated (nos. 2 and 3). Follicular dendritic cells (FDCs) showed strong immunoreactivity to monoclonal antibody CNA. 42. The majority of the FDC networks showed a normal reactive pattern with the exception of a few expanded/disrupted follicles. There were no lymphoepithelial lesions (LELs) detected even by immunostaining for cytokeratin.

There were no EBER-positive lymphoid cells detected in the lesion.

Table 1 Summary of clinical findings of three cases

	Age/gender	Site	Clinical presentation	Size (cm)	Associated disease	Follow-up (months)
1[a]	45/F	Ileocecal valve	Anal bleeding	1.5	Adenocarcinoma + adenoma of the colon	3 A
2	53/M	Ileocecal valve	3 weeks abdominal pain	3.5	None	5 A
3	80/F	Ileocecal valve	General fatigue	1.5	Adenocarcinoma + adenoma of the colon, Gastric adenocarcinoma	7 A

A alive

[a] History of endometrioid adenocarcinoma of uterus

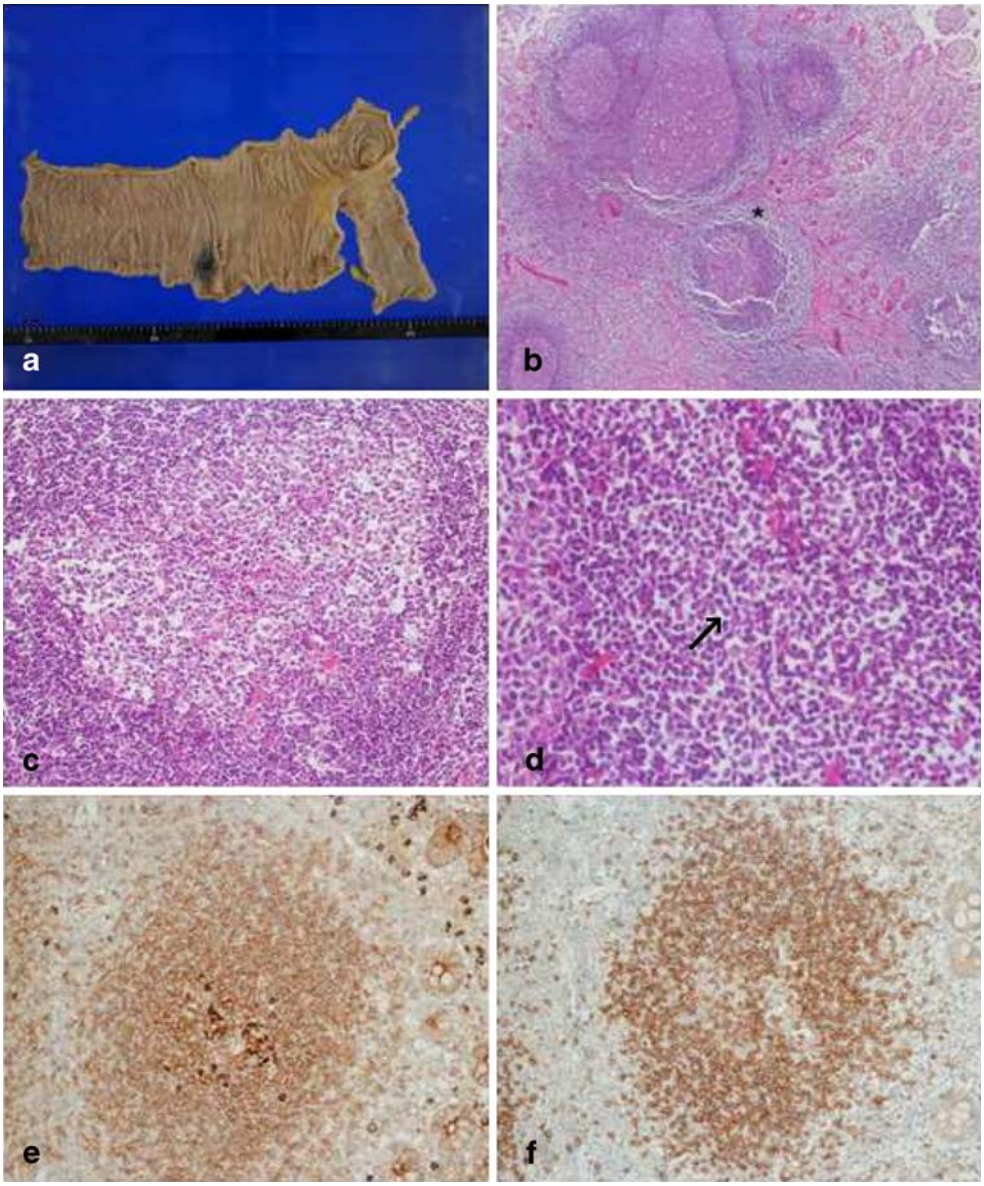

Fig. 1 **a** Resected specimen demonstrated the thickening of the ileocecal valve (case 3). **b** Low-power field of the resected specimen demonstrated lymphoid follicles with active germinal centers. The majority of the lymphoid follicles were surrounded by a pale cuff of lymphoid cells (*asterisk*). HEx10 (case 1). **c** On medium power field, a reactive lymphoid follicle showed follicular lysis with an ill-defined germinal center border. HE ×25 (case 2). **d** On higher magnification, the pale cuffs were composed of intermediate to medium-sized lymphocytes with round or slightly indented nuclei and a broad rim of clear cytoplasm and scattered large transformed lymphocytes. A few plasma cells (*arrow*) were also present. HE ×100 (case 1). On immunohistochemistry, both the mantle zone lymphocytes and the pale cuff of the lymphoid cells were sIgM+ (**e**) and sIgD+ (**f**). ×25 (case 1)

Genotypic studies with immunoglobulin heavy chain probes demonstrated only germ line bands.

Discussion

Histologically, majority of the lymphoid follicles in this lesion were surrounded by a pale cuff of mantle zone lymphocytes resembling the marginal zone distribution pattern of MALT type lymphoma [1, 2]. Recently, Hant et al. reported hyperplasia of mantle zone lymphocytes with clear cytoplasm in peripheral lymph nodes and discussed the problems of differentiating nodal marginal zone B-cell lymphoma or mantle cell lymphoma (MCL) [5]. The present three cases confirmed this observation in reactive lymphoid hyperplasia of the terminal ileum.

MALT type lymphoma presents the most important diagnostic problem. The tumor cells of MALT type lymphoma are small to medium-sized lymphocytes showing a moderate amount of clear cytoplasm, indented or round nuclei, and absent or small nucleoli (centrocyte-like cells)[1, 2]. Lymphocytes in the pale cuff showed cytologic findings similar to those of centrocyte-like cells. The lymphoid follicles showing follicular lysis also resembled colonized follicles of MALT type lymphoma [1, 2]. However, there were no LELs detected even on immunostaining for cytokeratin. Moreover, immunohistochemistry demonstrated that pale cuff of the lymphocytes were sIgD+, sIgM+, CD5−, CD43−, bcl-2+ suggesting their non-neoplastic mantle cell nature [6–8].

MCL represents another differential diagnostic problem. In approximately 5% of cases of MCL, tumor cells may

demonstrate moderate quantities of pale-staining cytoplasm [9]. Such cells may represent so-called marginal zone B-cell differentiation [9]. Moreover, extranodal MCL showing a marginal zone distribution pattern has also been reported [10]. MCL typically express B-cell antigens, CD5, CD43 and cyclinD1 [6, 9, 10]. However, immunohistochemical study demonstrated that the pale cuff of the lymphocytes were CD5−, CD43− and cyclin D1− in all three cases. Finally, in all three cases, the polytipic nature of B-cells was demonstrated by immunohistochemistry and PCR.

Although, reactive lymphoid hyperplasia in the MALT system rarely shows prominent mantle cell hyperplasia with clear cytoplasm, it is important for pathologists to be aware of this type of lesion during diagnostic practice. To avoid overdiagnosis and overtreatment, it is suggested that immunophenotypic and genotypic studies be required.

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