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CASE REPORT

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Centrocytic-like lymphoma associated with localized amyloidosis of the large intestine

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Abstract A case of low-grade centrocytic-like (CCL) B-cell lymphoma involving the large intestine, the regional lymph nodes and the spleen is reported. In the large intestine the lymphomatous infiltrate was restricted to sites of intense antigenic stimulation (diverticula, appendix, ileo-caecal valve) and was associated with marked plasma cell differentiation and massive amyloid deposits. The immunophenotype was CD20, CD21, CD45RA/MB1/MT2, CD68, CD45 related/Ki-B3 and HLA-DR positive, and MB2, DBA.44 reactive regarding the CCL cell lymphoma subpopulation; and IgG-λ positive regarding its plasma cell fraction.

Key words Large intestine · Centrocytic-like lymphoma Localized amyloidosis

Introduction

The low-grade B-cell lymphoma of mucous membrane associated lymphoid tissue (MALT) most commonly occurs as a primary gastric tumour. It rarely arises in the intestine, at least in Western countries. This type of lymphoma is usually composed of centrocyte-like (CCL) or monocytoid cells, with frequent plasma cell differentiation [8]. We report here a case of CCL cell lymphoma involving the large intestine and the spleen, with peculiar morphological features: in the large intestine the lymphoma showed marked plasma cell differentiation and pseudotumour localized amyloidosis at sites including diverticula of the bowel wall, appendix and ileo-caecal valve.

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Case report

The patient was a 71-year-old man admitted to hospital because of abdominal pain. Both X-ray examination and colonoscopy demonstrated stenosis of the sigmoid colon and a polypoid, apparently ulcerated lesion at the ileo-caecal valve. Biopsies taken from the polypoid lesion yielded the diagnosis of an amyloid deposit. However, the preoperative clinical diagnosis was "cancer of the caecum plus inflammatory lesion (Crohn's disease?) of the sigma". A right colectomy plus sigmoid resection and splenectomy was performed.

The gross specimen revealed the presence of multiple nodules of the bowel wall, in the sigmoid and ascending colon. On the luminal surface, the nodules were visible as slight elevations covered by normal mucosa with a small orifice in the centre. On sectioning, the nodules ranged from 1 to 3 cm in diameter, were localized in the pericolic adipose tissue or inside the muscular wall, and appeared as haemorrhagic, firm tissue containing a diverticular sac of the mucosa (Fig. 1a, b). In the sigmoid colon, purulent collections were also present in the fat. The polypoid lesion of the ileo-caecal valve was made up of the same haemorrhagic tissue, mainly occupying the submucosa. The appendix was markedly swollen. The spleen weighed 1200 g and showed diffuse micronodularity on the cut surface.

A histological diagnosis of low-grade lymphoma with localized amyloidosis was made. The staging was negative for lymphomatous localization in other organs of the MALT system or elsewhere. Postoperatively, the patient received chemotherapy. Twenty-four months after surgery he is well and free of disease.

Materials and methods

The surgical specimen was fixed in 10% buffered formalin for 72 h. Tissue samples were taken, processed for routine histology and embedded in paraffin. Five micrometre-thick sections were cut and stained with haematoxylin and eosin, periodic acid-Schiff, Giemsa, silver Gomori, Congo red (with and without $KMnO_4$; [16]) and thioflavin T. Other paraffin sections were employed for immunohistochemistry, which was performed with the panel of antibodies listed in Table 1.

Results

Microscopic examination confirmed the presence of multiple diverticula, which were numerous in the si-

Table 1 Antibodies used for immunohistochemistry (*M* monoclonal, *P* polyclonal)

Antibody	M/P	Source	Method	Predominant reactivity/cluster
L26	M	Dakopatts	ABC[a]	CD20
Anti-CD3	P	Dakopatts	PAP[b]	CD3
1F8	M	Dakopatts	APAAP[c]	CD21
MHM.6	M	Dakopatts	APAAP	CD23
KP-1	M	Dakopatts	APAAP	CD68
DBA.4	M	Dakopatts	APAAP	B cells[d]
DFT-1	M	Dakopatts	APAAP	CD43
Anti-κ, λ	P	Dakopatts	ABD	Ig light chain
Anti-α, μ, γ	P	Dakopatts	ABC	Ig heavy chain
Anti-amyloid A component	M	Dakopatts	ABC	
Anti-amyloid P component	P	Dakopatts	PAP	
MB1	M	Biotest Diagnostic	ABC	CD45 RA
MB2	M	Biotest Diagnostic	ABC	B cells[e]
MT1	M	Biotest Diagnostic	ABC	CD43
MT2	M	Biotest Diagnostic	ABC	CD45RA
LN1	M	Biotest Diagnostic	ABC	Cdw75
LN2	M	Biotest Diagnostic	ABC	CD74
LN3	M	Biotest Diagnostic	ABC	HLA-DR (Ia) rel.antigen
Ki-B3	M	Courtesy of Prof. Parwaresch, Kiel, Germany	APAAP	CD45 rel.antigen
MIB-1	M	Immunotech	ABC	Ki67

[a] Streptavidin-biotin-peroxidase complex [7]
[b] Peroxidase-anti-peroxidase [15]
[c] Alkaline phosphatase-anti-alkaline phosphatase [4]
[d] Al Saati et al. [1]
[e] Poppema et al. [14]

gmoid, with purulent inflammation and peritonitis. The wall of the diverticula, as well as the polypoid lesion of the ileo-caecal valve and the appendix, contained amyloid deposits (Fig. 1b). The amyloid often involved the wall of medium-sized vessels, with associated rupture and haemorrhage (Fig. 1c). Congo Red staining was also positive after $KMnO_4$ treatment; immunostaining for the A component was negative. The amyloid was associated with a plasma cell infiltrate which showed λ light chain and γ heavy chain restriction. The amyloid deposit was often massive, so that the cellular component was obscured (Fig. 1c).

An accurate examination of the bowel revealed the presence of small diverticula in which the deposit of amyloid was minimal, the cellular infiltrate being prominent (Fig. 1b). In these areas plasma cells with Ig chain restriction were located near the luminal surface; in the deeper part of the mucosa a lymphocytic infiltrate was present, composed of cells whose morphology fitted in with CCL or monocytoid cells. Residual follicles were also visible, with invasion by CCL cells. Small aggregates of CCL or monocytoid cells were rarely found in the colonic mucosa and submucosa far from the diverticula. Lymphoepithelial lesions were infrequent (Fig. 2a).

The pericolic lymph nodes showed expansion of the marginal zone by CCL cells. The spleen was entirely occupied by a nodular infiltrate consisting of sheets of CCL or monocytoid cells (Fig. 2b).

We were unable to demonstrate Ig chain restriction in the CCL cells. These cells showed strong and diffuse positivity with the antibodies L26/CD20, 1F8/CD21, MB1/CD45RA, MB2 and MT2/CD45RA. Furthermore, 15–20% of them stained with KP1/CD68 (dot-like positivity), Ki-B3/CD45-related, DBA.44 and LN3/HLA-DR. However, the lymphomatous elements turned out to be negative with MT1/CD43, DFT1/CD43, MHM-6/CD23, CD3, LN1/CDw75 and LN2/CD74. No follicular dendritic cells (FDCs) were detected within the neoplastic population, while they formed scattered tight clusters corresponding to residual germinal centres.

Nuclear MB1/Ki67 immunoreactivity was found in a very low proportion of the lymphomatous elements (1.7%).

Discussion

The case we describe is the first example of MALT lymphoma associated with massive amyloid deposition. Strictly speaking, the diagnosis of MALT lymphoma might be denied because of the involvement of the spleen. However, using more flexible criteria [8], we can regard the spleen as being secondarily involved by a colonic lymphoma which is becoming disseminated.

The diagnosis of MALT lymphoma is based on both morphological and immunophenotypic findings. In particular, the latter allow clear-cut distinction from immunocytoma (Ic) and mantle-cell centrocytic lymphoma (MCL) of the gastrointestinal tract (lymphomatous polyposis), which represent the two entities to be considered as far as the differential diagnosis is concerned (Table 2). Ic, which is sometimes associated with amyloidosis, usually carries the CD23 and CD43 molecules. MCL, which can show cytological similarities to MALT lymphomas, is CD43 positive in most (if not all) cases and usually lacks CD21, CD68 and the DBA.44-recognized antigen. Furthermore, it is characterized by a loose meshwork of FDCs. The present case differs from the above-mentioned tumours, as it expresses the CD21 antigen, and to

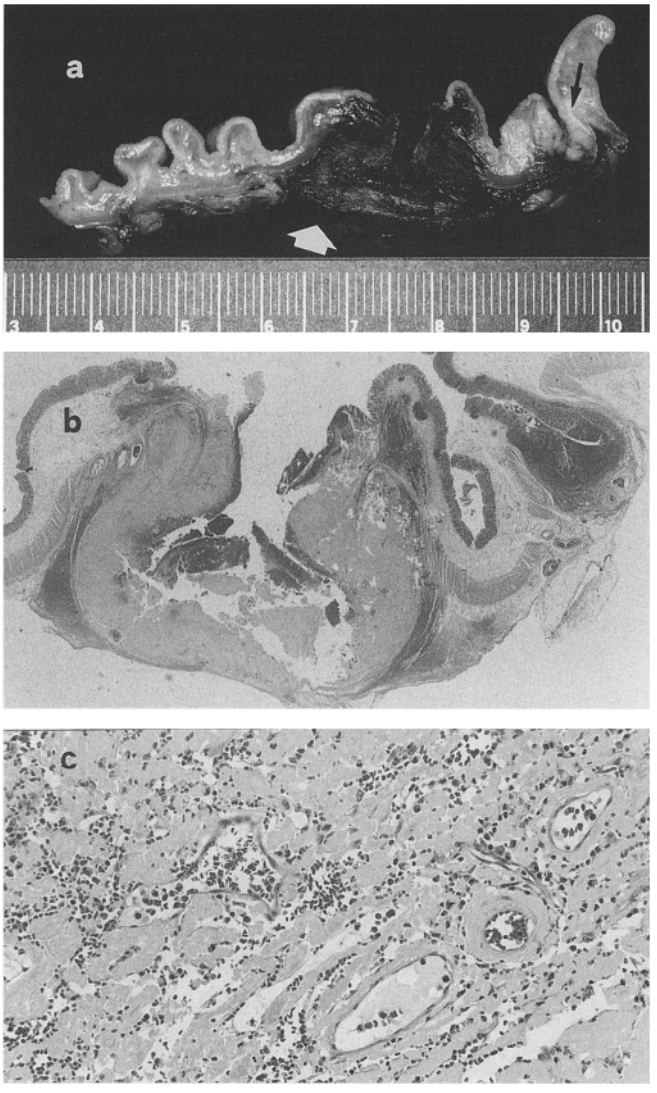

Fig. 1 **a** Gross specimen from the ascending colon. On the cut surface two diverticula can be observed. The larger (*white arrowhead*) has a thickened, haemorrhagic wall. The smaller (*black arrow*) shows nodular aggregates of whitish tissue. **b** Histological section of the same area. The diverticular wall is substituted by homogeneous pink tissue. The smaller diverticulum shows the presence of a lymphoid infiltrate. (H & E, ×3). **c** In the greater diverticulum there is a massive amyloid deposit, clearly visible around blood vessels and obscuring the cellular infiltrate, mainly composed of plasma cells. Extravasation of erythrocytes is also found. H & E, ×100

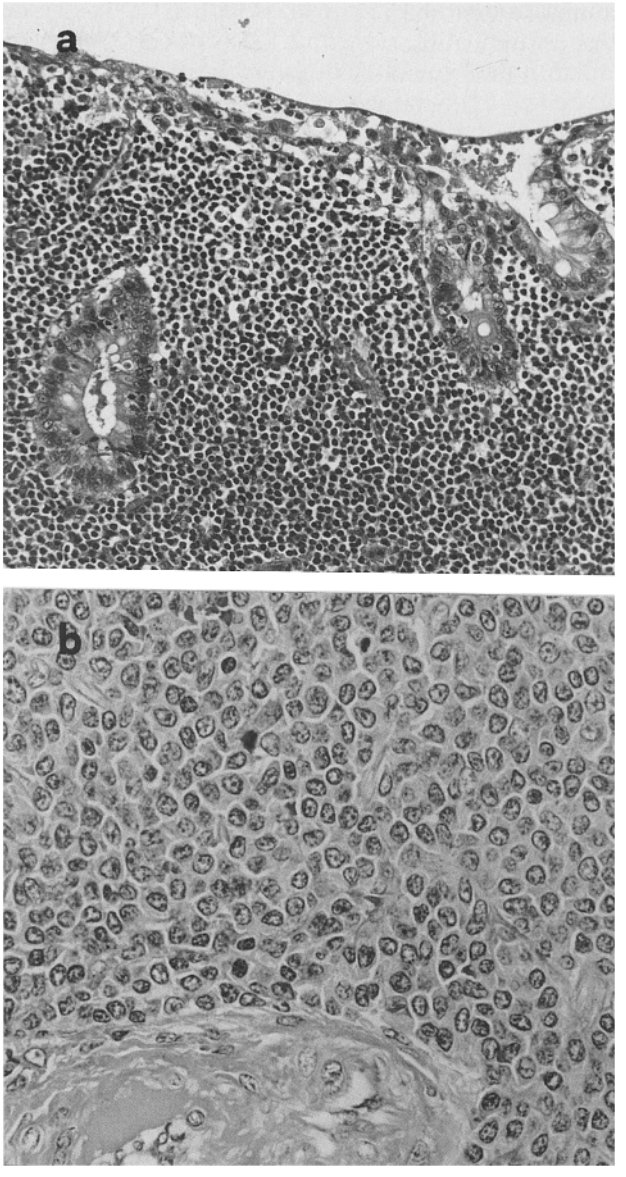

Fig. 2 **a** The lymphoid infiltrate of the colonic mucosa is composed of monotonous monocytoid cells with production of lymphoepithelial lesions. H & E, ×100. **b** White pulp of the spleen. The arteriole is surrounded by lymphomatous infiltrate composed of cells showing an irregularly shaped nucleus and pale cytoplasm, consistent with a centrocyte-like appearance. H & E, ×630

Table 2 Comparison of the phenotypic profiles reported in MALT lymphoma, immunocytoma and mantle cell/centrocytic lymphoma, and that observed in this case

	MALT lymphoma	Immunocytoma	Centrocytic lymphoma	Our case
CD21/1F8	+	–	–	+ (100%)
CD23/MHM.6	–	+	–	–
CD43/DFT-1	–/+	+/–	+	–
CD68/KP-1	+/–	–	–	+ (20%)
CD45 rel./Ki-B3	+	+/–	+	+ (20%)
DBA.44	–/+	–	–	+ (15%)
Meshwork of FDCs	–	–	Loose	–

a minor extent the CD45-related/Ki-B3, CD68 (the dot-like positivity observed with KP-1 is in our opinion very similar to the "granular" positivity described by Lennert and Feller [12], with the Ki-M1p antibody) and DBA.44 molecules, and it is not stained by the MHM-6/CD23 and MT1/DFT1/CD43 antibodies. Moreover, it evokes no FDC deposition. Positivity for Ki-B3, KP-1 and DBA.44 is observed in a percentage of cells (15–20%) lower than that usually expected in MALT lymphomas [5, 6]: however, this finding might be due to the prolonged formalin fixation, which can cause varying degrees of antigen masking [3].

In the present case the lymphomatous infiltration of the large intestine showed marked plasma cell differentiation with overproduction of λ-IgG leading to localized amyloidosis. Plasma cell differentiation is reported to be present to a variable degree in approximately one-third of low-grade B-cell lymphoma of MALT, and may be so extreme as to suggest a diagnosis of plasmacytoma [8]. Unlike systemic amyloidosis, the presence of localized amyloidosis is rarely found in B-cell lymphomas. To our knowledge, it is well documented only in extramedullary plasmacytoma and immunocytomas [2, 13], and rarely in other MALT lymphomas arising in the lung [17] or in ocular adnexa [11].

We observed plasma cell differentiation and amyloid deposits in the large intestine, but not in the spleen or lymph nodes. Moreover, this particular aspect was strictly confined to the diverticula, ileo-caecal valve and appendix, which in our view are sites where the lymphoid cells are directly and chronically stimulated by alimentary antigens. This observation is in agreement with the possible role of immune-mediated mechanisms in the pathogenesis of MALT lymphomas, which has been proposed for the immunoproliferative small intestine disease (IPSID), autoimmune diseases such as Hashimoto's thyroiditis of Sjögren's syndrome, and follicular gastritis associated with *Helicobacter pylori* [10].

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