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CASE REPORT

Histiocytic and T-cell Rich B-Cell Lymphoma (TCRBCL) of the Stomach+

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Although stomach is a frequent site of extranodal lymphomas, histiocyte-rich TCRBCL has not yet been described there. Even histology of repeated gastrobiopsies of this uncommon, diffuse, large B-cell lymphoma may be inconclusive and partial gastrectomy cannot be avoided. It is only immunohistology (CD20, CD43, CD68) of the paraffin blocks from the resection specimen that can lead to the final diagnosis of intermediate grade malignant lymphoma. (Pathology Oncology Research Vol 3, No 3, 219–223, 1997)

Key words: B-cell lymphoma, gastric lymphoma, extranodal lymphoma, T-cell rich B-cell lymphoma, histiocyte-rich lymphoma, gastroscopy

Introduction

In contrast to Hodgkin's disease prominent reactive cell infiltration is uncommon in non-Hodgkin's lymphoma. Occasionally, however, a large subpopulation of non neoplastic cells overlaps the sparse tumour cells in these lymphomas[30]. Such a tumour, i.e. an extranodal T-cell rich B-cell lymphoma (TCRBCL), or to be more precise, its histiocytic variant in the stomach is presented in the following.

Methods

Immunohistochemistry was carried out by indirect method, visualistion by streptavidin and biotinylated enzyme kit. Appropriate normal tissues were used as positive controls and normal serum instead of immune serum as negative control. Sera are listed in *Table 1*.

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Case report

A 77 year old woman was suffering from abdominal pain connected with meal for half a year. *Gastroscopy* revealed an ulcerated, apparently malignant lesion two months previously, but histology was negative in another hospital. She lost 12 kg weight. Gastroscopy in our hospital showed that the antrum was circularly narrowed. The mucosa was rigid, with ventral ulceration. The pylorus was hard to access. *Histology-1:* From five tissue fragments, regular glands appeared in two mucosa fragments. The glandular lumina were dispersed. The three other fragments consisted only of granulation tissue with lymphocytes, plasmocytes and capillaries. The endothelial lining in vessels was swollen. The largest fragment contained some muscle fibres and connective tissue referring to a chronic process. The sample was Helicobacter pylori negative, and showed no signs of malignancy. Diagnosis: Giant chronic ulcer of elderly people. *Roentgenogram*: The oral part of the antrum was of finger's-breadth covered with rough, and uneven mucosa. The prepyloric part of the antrum was expandable, but the mucosa remained polypoid. The pylorus and the bulbus were free. At surgery the cavity of the stomach was found to be enlarged, antrum was fistful, and its thickened wall formed bottleneck lumen. A tumor reach-

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***Table 1.* Primary antibodies in the phenotypic analysis of TCRBCL**

Cluster of differentiation/ Antigen	*Antibody/ clone*	*Source and dilution*	*Major specificity*	*Stained cells in 5 fields of sights (in % of all cells)*
CD45	2B11+PD7/26	BioGenex, 1:40	all leucocytes	70–98
CD43	MT1	BioGenex, 1:40	T cells	65–95
CD45RO	UCHL1	DAKO A/S, 1:50	T cells	60–90
CD20 (MB2)	L26	BioGenex, 1:40	B cells	5–15
CD77	BLA-36	BioGenex, 1:40	B follicular cells	1–2
CD30 (Ki1)	BerH2	DAKO A/S, 1:5	activated lymphocytes, R-S cells	<1
Bcl-2	N19	Santacruz Biotechnology, 1:40	t(14;18) translocation protein	2–50
EMA	E29	BioGenex, 1:40	R-S cells	neg
CD15	C3D-1	DAKO, 1:50	R-S cells	neg
CD68	KP1	DAKO A/S, 1:30	macrophage	20–40
Lysosyme	polyclonal	Cambridge Res Lab, 1:1	macrophage	10–30
Alpha-1-antitrypsin	polyclonal	BioGenex, 1:20	macrophage	neg
IgG	GG-5	BioGenex, 1:40	heavy chain of IgG	neg
IgM	polyclonal	BioGenex, 1:1	heavy chain of IgM	<1
κ light chain	L1C1	BioGenex, 1:40	kappa light chain	<1
λ light chain	HP6054	BioGenex, 1:100	lambda light chain	neg

ing to the serosa was palpable and was accompanied by enlarged lymph nodes along the curvature minor. *Operation specimen:* the antral wall of the resected stomach (12x6 cm) was circularly thickened to 5-15 mm between 2-6 cm from the surgical line. There were some erosions of 2 mm in diameter. The enlarged lymph nodes (diameter 5 mm or less) were palpable in the subserosa of the curvature minor.

Histology-2 and immunohistology – Conventional histology on paraffin sections showed predominantly small lymphocytes and few eosinophils arranged in a diffuse pattern among the superficial glands *(Fig. 1)*. These lymphocytes exhibited minimal atypia and were CD43 and UCHL-1 (CD45RO) positive *(Table 1.)*. Blood vessels with thick endothelial lining were present adjacent to the erosions. At the level of the muscularis mucosae, the picture was less monotonous. It appeared vaguely nodular or diffuse. No eosinophils but numerous reactive histiocytes were admixed with the small T lymphocytes. In some microscopic fields, about 40% of the cells stained positively with CD68 *(Fig. 2)* or lysozyme. No granulomas or clusters of histiocytes were seen. Here atypical, large tumor cells were sparsely interspersed with numerous small lymphocytes and histiocytes *(Fig. 3)*. These large cells were EMA and CD15 negative, CD20, BLA36, bcl-2 positive and very rarely CD30 positive. Distinct surface IgM kappa positive monoclonality was detected in this B-cell population. Some of these large immunoblast- and centroblast-like cells possessed nuclei with slight to marked irregularities and sometimes with foldings, whereas the nucleoli were small to moderately large. Therefore, these cells resembled the L+H variants of Reed-Sternberg-cells *(Fig. 3)*. Lymph nodes were free from alterations, therefore the tumor is supposed to be of extranodal - gastric – origin. L+H elements apparently pointed to Hodgkin's disease. However the number of L+H elements was low and diagnostic Reed-Sternberg cells were com-

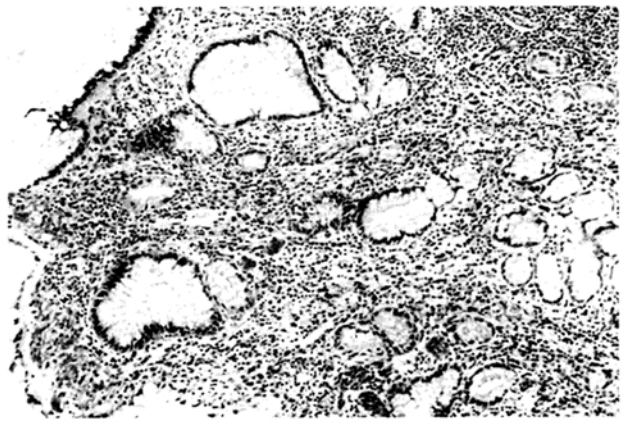

Figure 1. *Superficial part of gastric mucosa with small lymphocytes only, without atypical cells, x40*

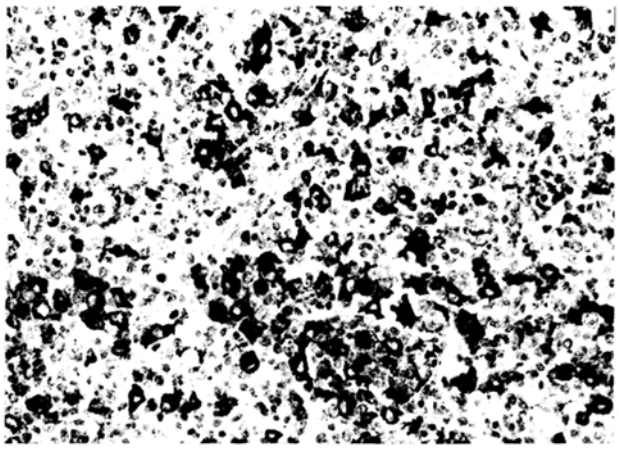

Figure 2. In the deep part of mucosa among large number of CD68 positive histiocytes numerous pleomorphic tumor cells, x200

pletely absent (EMA and CD15 negativity). T-lymphocytes occurred in great numbers, whereas B-lymphocytes were rare but with monotypic immunoglobulin light chain restriction. These findings favour the diagnosis of TCRBCL over Hodgkin's disease. The very rare CD30 positivity raised the possibility of anaplastic large B-cell lymphoma (ALCL). Only few tumor cells (see *Table 1*) and some histiocytes showed CD30 positivity, and cohesive growth pattern of CD30 positive cells was missed: large cells singly interspersed in the reactive background were CD30 negative, sometimes with fine κ monoclonality. All these facts exclude the ALCL and render probable TCRBCL (*Table 2*). In conclusion: a morphologically uncommon type of diffuse large B-cell lymphoma was diagnosed: a *histiocytic variant of TCRBCL as an extranodal, gastric lymphoma.*

Clinical course: Postoperatively at the intensive care unit, circulation was improved and pneumonia cured (a thick discharge was sucked off from the bronchi). Normal bowel function returned after purgation. She returned to the surgery on the 6th day and is symptomless at present, one and a half years after operation.

Table 2. Differential diagnosis of TCRBCL by immunostaining of large cells

antibodies	*a*	*b*	*c*	*d*	*e*
CD3 (T-cell)	–	–	–	+/–	+
CD15 (Reed-Sternberg)	–	+	–	–	–
CD20 (L26, B-cell)	+	+/–	+	+/–	–
CD30 (Ki1, anaplastic T,0)	–	+	–	+	–
CD43 (T-cell)	–	–/+	+	–/+	+
CD45 (LCA)	+	–	+	+/–	+
CD68 (macrophage)	–	–	–	–	–
CD79a (mbl, B-cell)	+	+/–	+	–	–
EMA	–/+	–	+	+/–	–
T-cell genom rearrangement	–	–	–	+/–	+
Ig gene rearrangement	+/–	+/–	+	–	–
Monoclonal Ig expression	+/–	–	+	–	–

a. T-cell rich B-cell lymphoma (TCRBCL); *b.* Hodgkin's disease;[4,17] *c.* Lymphocyte predominant Hodgkin's disease;[4,17,27] *d.* Anaplastic large cell ly (ALCL[23]); *e.* Peripheral T-cell ly (PTCL[7,25])

Discussion

In 1984 Jaffe and coworkers[15], and in 1985, Mirchandani et al.[18] described B-cell lymphomas that mimicked the morphologic appearance of peripheral T-cell lymphomas. Ramsay et colleagues[24] introduced the term T-cell rich B-cell lymphoma (TCRBCL) to classify such cases. In 1989, Scarpa et al[26] demonstrated the clonal rearrangement of immunoglobulin genes that proves the B-cell origin of such tumors.

Lymphoma makes up only 8% of all gastric neoplasms, but its incidence is growing[9]. Nearly 80% of these are primaries. Although the stomach is the most common site of origin of extranodal lymphomas (*24%* of which arise there[10]), TCRBCL has not yet been mentioned as a primary gastric malignancy.[6,10,20,25] This is not surprising as the upper limit of its frequency may be 1% of all non-Hodgkin's lymphomas[1,8], indicating that TCRBCL is rare.

The relationship of TCRBCL to other forms of B-cell lymphomas remains to be determined. Some cases of interfollicular or T zone lymphoma may represent early TCRBCL. There is evidence to suggest that some cases of TCRBCL are of follicular center cell origin (bcl-2 gene

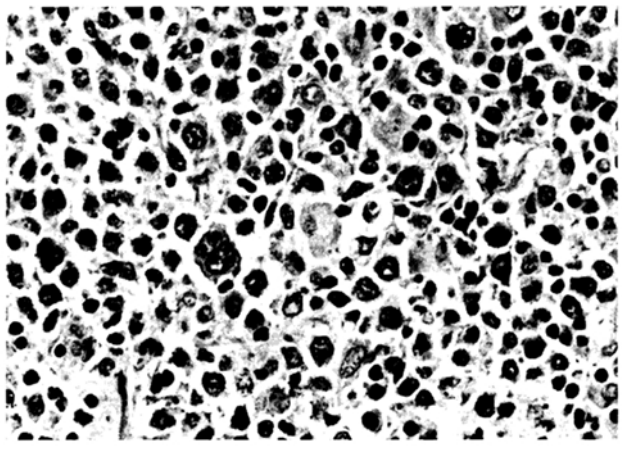

Figure 3. Sparse atypical B cells among small lymphocytes and histiocytes in deep part of tumor, x300

breakpoints, bcl-2 gene rearrangement and t(14:18) translocations). Cleaved cells and broken up remnants of partial nodularity, even neoplastic follicles were noticed in some early TCRBCL cases.[1,4,28] This partial nodularity characterizes our case too in some fields of the tumour. Postmortem histology of TCRBCL sometimes showed diffuse sheets of large B-cells without significant T-cell content[3,8,24]. Not only a similarity but a possible connection between TCRBCL and lymphocyte rich Hodgkin's disease were supposed[3,4,27]. It remains to be shown whether transformation of MALT lymphoma to TCRBCL takes place or not.[14a,b,31] The possibility emerges that TCRBCL represents, beside de novo tumor, a transitory stage of an unusual type of diffuse, large B-cell lymphoma derived from different entities, or from nodular lymphocyte predominant Hodgkin's disease, or from lymphomas of follicular center cell origin[4].

There is no accepted upper limit for the number of nonneoplastic cells - it may vary from 50 to 95%. It is difficult to ascertain if these nontumorous cells are normal residual elements or parts of the host response to the tumor. The existence of extranodal TCRBCL - as ours - supports the second possibility. Histiocytes are described as an additional component apart from T lymphocytes of the non tumorous background. Their proportion was prominent in our case. Therefore, although the term TCRBCL has been generally accepted, a more exact designation for this peculiar lymphoma variety would be T-cell rich and histiocyte rich B-cell lymphoma.[2,5,15,16,27] Whatever much "reactive cells" are, the clinical course is rather similar, i.e. aggressive, corresponding to intermediate grade lymphoma. Cases of apparent follicular center cell origin, as ours, may have more favorable prognosis[1,18].

It seems clear that the nosology of TCRBCL in the context of lymphoma classification requires further refinement. Most earlier cases were diagnosed either as Hodgkin's disease or T cell lymphoma,[24] or as a malignant histiocytic lymphoma[3,10] Probably, there is a spectrum of TCRBCL. The subclassification of these B cell tumours is possible according to the subpopulation of nonneoplastic cells: histiocytic, lympho-histiocytic and the small lymphocytic reactive T cells.[2,3,5] Some authors[2,3,5] claim that nothing but the histiocyte-rich subgroup – including our lymphoma – represents a morphologic and clinicopathologic entity. Our case is however in an early clinical stage as contrasted with the other ones reported so far. At present all these diffuse lymphomas – which morphologically appear to be mixed lymphomas – have been reclassified as diffuse large cell lymphomas.[1,5,7,21,26] TCRBCL is also not a new clinicopathological entity, either, but a peculiar presentation of a large B-cell lymphoma in REAL classification.[11]

Diagnosis of TCRBCL has *therapeutic* significance. TCRBCL is an intermediate grade B cell lymphoma which needs more effective chemotherapy than Hodgkin's disease does.[1,8,17,24] Paraffin embedded blocks, with their better capacity to preserve morphology, are essential for correct diagnosis. The accuracy of gastric malignant lymphoma diagnosis on endoscopic specimen ranges between 52% and 80%.[2,25] Demonstration of clonality may work well only in 20% of cases. Using in situ hybridization and polymerase chain reaction (PCR) the results are slightly better.[12,13] Demonstration of B-cell clonality, however, may not be successful because of the sparsity of neoplastic cells.[1,3,17,21,24]

Therefore, some authors do not consider B-cell clonality to be an essential diagnostic criterion in TCRBCL. Cytogenetically, the presence of 14q32 chromosome aberration and 1q duplication in TCRBCL may help diagnosis[28]. Differential diagnosis of TCRBCL by immunostaining is outlined in *Table 2*. As diagnosis is usually not definitive on the small gastric biopsy , a partial gastrectomy cannot be avoided which is a therapeutic intervention in a limited (Stage I) case as ours. Our endoscopic sample did not contain tumour cells. Strip biopsy was mentioned as a better method than the conventional forceps biopsy.[19]

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