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Peripheral T-cell Lymphomas of the Intestine

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Twenty-seven cases of primary peripheral T-cell lymphomas of the intestine (PTLI) were investigated. Seven patients had histories of malabsorption. The most frequent symptoms at presentation were weight loss, abdominal pain, and acute abdomen. The jejunum was the most common site of lymphoma and multifocal disease was found in 72% of the cases. Twenty-two patients (92%) presented with localized disease confined to the intestine and abdominal lymph nodes, only two patients had generalized disease. According to the pattern of lymphoma infiltration and the morphology of the uninvolved small intestinal mucosa, 21 cases were separated histologically into three categories; 1) enteropathy-associated T-cell lymphoma (EATCL, n = 9) showing predominant intramucosal lymphoma spread and villous atrophy of uninvolved mucosa with high density of intraepithelial lymphocytes (IEL), 2) EATCL-like lymphoma without enteropathy (EATCL-LLWE, n = 5) but with an infiltration pattern similar to EATCL, and 3) T-cell lymphoma without features of EATCL (Non-EATCL, n = 7). Distinctive features of EATCL were the high incidence of malabsorption states, multifocal intestinal disease in all cases, and the high frequency of intestinal recurrences. On frozen sections four of eight PTLI showed the phenotype $CD3^+CD4^-CD8^-HML\text{-}1^+$, which is also expressed on a small subset of normal IEL. The morphologic and immunomorphologic findings suggest that the majority of PTLI is derived from mucosal T lymphocytes. This derivation may be responsible for certain biologic features, such as the preferential spread to and relapse of PTLI at small intestinal sites. (Am J Pathol 1992, 141:1361–1371)

The gastrointestinal tract (GIT) is the most common site of primary extranodal non-Hodgkin's lymphoma (NHL).[1] Malignant lymphomas arising in the GIT are supposed to derive from the lymphoid system of the mucosa-associated lymphoid tissue (MALT), particularly of the gut-associated lymphoid tissue (GALT).[2–5] The principal categories of primary gastrointestinal lymphomas are listed in a classification proposed recently by Isaacson and co-workers.[6] The vast majority of these tumors are of B-cell origin.[7–10] Cases previously diagnosed as malignant histiocytosis of the intestine[11] were shown to be of T-cell origin,[12,13] and another highly suggestive candidate for T-cell neoplasia was introduced as malignant lymphoma with eosinophilia of the GIT.[14]

The development of small intestinal malignant lymphomas is a rare but well-documented complication of celiac disease and most of these tumors were classified as malignant histiocytosis.[11,15] Villous atrophy adjacent to or even well separated from the lymphoma may also occur in patients without evidence of celiac disease.[16] The coincidence of intestinal T-cell lymphoma with villous atrophy of the jejunal mucosa prompted O'Farrelly and co-workers to coin the term "enteropathy-associated T-cell lymphoma."[17]

This study concentrates on the most prominent clinicopathologic findings of 27 patients with primary peripheral T-cell lymphomas of the intestine (PTLI). Morphologic and immunomorphologic similarities between the T-cell compartment of the GALT and intestinal T-cell neoplasia are demonstrated and discussed.

Materials and Methods

Patient Population

Between January 1974 and December 1990, a total number of 518 primary NHLs of the GIT was listed consecutively in the files of the Department of Pathology, University of Vienna. Twenty-seven (5.2%) cases were diagnosed as PTLI and are the subject of this study. By definition, these patients had a predominant intestinal lesion that had been the cause of their presentation. Three

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previous publications included case material derived from 11 of the 27 patients; all 11 cases were part of a large study of gastrointestinal NHL,[8] which primarily focused on clinical aspects of B-cell tumors and did not include detailed discussion of clinicopathologic correlations of PTLI as presented herein; two cases were part of a clinicopathologic study of peripheral T-cell lymphomas,[18] and six cases were included in an immunomorphologic study of nodal and gastrointestinal NHL, which concentrated exclusively on the expression of the human peripheral lymph-node homing receptor LECAM-1 (LAM-1).[19] In 20 cases (74%) tissue was referred to our department from outside pathologists. Diagnoses were established on the basis of surgical specimens in 24 patients, on endoscopic biopsy specimens in two, and at autopsy in one patient.

Clinical Data

Medical records were reviewed for the patients' history, type, and duration of symptoms at initial presentation, physical examinations, clinical and laboratory investigations, and type of treatment. Reports of surgical operations were examined with regard to tumor site, abdominal lymph node status, spleen and liver, and to the aspect of the peritoneal sheet. Follow-up was obtained via clinical records, attending physicians, or autopsy files.

Tumor Staging

Stages of disease were assigned according to an adaptation of the Ann Arbor staging system for extranodal lymphomas[20] and its modification by Musshoff, respectively.[21]

Gross Pathology and Tissue Preparation

Resected parts of the gut were evaluated concerning site and unifocal versus multifocal tumor involvement. Specimens were fixed in 8% phosphate-buffered formalin, pH 7.4, embedded in paraffin and stained with H&E, Giemsa, Gomori's reticulin, and periodic acid Schiff (PAS). Bone marrow biopsies were done in 14 cases (Jamshidi), embedded in methyl-metacrylate without decalcification, and routinely stained. Bone marrow aspiration was done in all cases; bone marrow smears for review were available in 12 cases. Imprint smears were not prepared. No electron microscopic studies were done.

Histology and Lymphoma Classification

Histologically, the pattern of lymphoma infiltration was studied with special emphasis on the relationship between lymphoma spread and intestinal mucosa. The uninvolved mucosa was investigated for the presence of villous atrophy, which was graded in mild-moderate-severe. The number of normal-appearing intraepithelial lymphocytes (IEL)/100 enterocytes was assessed by counting IEL along 10 villi on Giemsa-stained sections taken from the histologically uninvolved resection margins of surgical specimens. According to Ferguson,[22] counts ranging from 9–39 IEL/100 enterocytes were considered normal and more than 40 increased. The lymphomas were classified according to the Updated Kiel Classification.[23] Independent of morphology, lymphomas were categorized as enteropathy-associated T-cell lymphomas (EATCL) if the uninvolved jejunal mucosa distant from the tumor(s) showed at least moderate villous atrophy and an increase of normal appearing IEL.

Tests for antibodies to adult T-cell leukemia virus-associated antigen HTLV-1 were not done.

Immunohistochemistry

Immunostaining of both paraffin (27 cases) and frozen sections (8 cases) was done using a sensitive three-step immunoperoxidase technique.[24] The panels of antibodies used are listed in Table 1. In selected cases of predominant intraepithelial lymphoma spread, a double staining technique was used on paraffin sections to optimize the visualization of neoplastic lymphoid cells and enterocytes. Staining for the broad cytokeratin antibody KL1 was obtained by the APAAP immunoalkaline phosphatase labeling procedure, which was followed by the immunoperoxidase method using the polyclonal anti-CD3 antiserum.

Statistical Analysis

Survival was calculated from the date of diagnosis to the date of last follow-up or death using the method of Kaplan and Meier. Survival data were compared by the appropriate test according to Breslow.

Results

Medical Histories

Seven patients had histories of malabsorption ranging from 0.5 to 10 years (median, 3 years), clinically charac-

Table 1. *Antibodies Reactive on Frozen and Paraffin Sections*

Monoclonal antibody	CD	Predominant reactivity pattern	Source
Frozen sections			
Leu-1	5	T cells, B-cell subset	BD
Leu-2a	8	T subset	BD
Leu-3a	4	T subset, macrophages	BD
Leu-4	3	T cells	BD
Leu-5	2	T cells	BD
8H8	7	T cells	IT
OKT6	1a	Cortical thymocytes	OP
βF1		TCR β-chain	TS
TCRδ-1		Invariant epitope of TCR δ-chain	TS
δ-TCS1		Variable epitope of TCR δ-chain	TS
B1	20	B cells	CI
B2	21	B cells	CI
B4	19	B cells	CI
My7	13	Granulocytes, monocytes	CI
My9	33	Myeloid progenitor cells	CI
HLA-DR		MHC class II antigen	BD
TAC	25	Activated T and B cells	BD
Ki-1	30	Activated T and B cells	D
Leu-7	57	NK cells, T-cell subset	BD
Leu-15	11b	NK cells, monocytes, granulocytes	BD
HML-1		Human intraepithelial lymphocytes	IT
Leu-8		Peripheral lymph node homing receptor (LECAM-1)	BD
Ki-67		Proliferating cells	DP
Paraffin sections			
LCA	45	Hematopoietic cells	DP
UCHL1	45RO	T cells	DP
MT1	43	T cells	BS
Leu-22	43	T cells	BD
MB1	45RA	B cells	BS
MB2		B cells	BS
L 26	20	B cells	DP
Leu-M1	15	Granulocytes	BD
Ber-H2	30	Activated T and B cells	DP
EMA		Epithelial cells	DP
KL 1		Epithelial cells	IT
Polyclonal antibody			
CD3	3	T cells	DP
Kappa, lambda		B cells	B
Lysozyme		Monocytes, granulocytes, macrophages	DP

BD, Becton Dickinson, Mountain View, CA; IT, Immunotech, Marseille, France; OP, Ortho Pharmaceutical Corporation, Raritan, NJ; TS, T-cell Sciences, Cambridge, MA; CI, Coulter Immunology, Hialeah, FL; D, Dianova, Hamburg, FRG; DP, Dakopatts, Copenhagen, Denmark; BS, Biosciences, Emmenbrücke, Switzerland; B, Behring, Marburg, FRG.

terized by chronic diarrhea and steatorrhea (stool weight ≥ 250 g/day), weight loss, and serum albumin ≤ 3g/dl. Before the diagnosis of PTLI, peroral jejunal biopsies were done in four of these patients showing classical features consistent with celiac disease in three of them and moderate villous atrophy in the remaining case. Histologically unremarkable IEL were increased in all four biopsies without any evidence of lymphoproliferative disease. Only one patient, however, had gluten-sensitive enteropathy, whereas two patients did not respond to gluten-free diet. Another patient was diagnosed as having dermatitis herpetiformis Duhring, and in three cases idiopathic chronic diarrhea was reported.

Two patients suffered from Crohn's disease-like inflammatory bowel disease for 5 and 10 years, respectively. Elevated platelet counts were detected in two other patients 2 and 4 months before the diagnosis of PTLI. One of these patients experienced venous thrombosis. One patient underwent hemicolectomy for colonic adenocarcinoma 6 months before PTLI was diagnosed.

The medical history of the remaining patients was unremarkable.

Clinical Presentation

The median age of the 27 patients was 56 years, ranging from 22 to 82 years. Fourteen patients were males and 13 were females. The majority of patients presented with a short history of abdominal pain and weight loss. Rapid weight loss (10 to 30 pounds during the last 3 months)

was reported in 11 patients. Symptoms such as diarrhea, nausea, fever, constipation, vomiting, and night sweat were evident less frequently. Eleven patients had acute abdominal emergencies due to spontaneous perforation (eight cases) and acute obstruction of the small bowel (three cases).

Abnormal Laboratory Findings (n = 21)

Eight patients (38%) presented with leukocytosis (WBC $> 11.0 \times 10^9$/L) ranging from 12.0×10^9/L to 21.0×10^9/L. Lymphocytosis was not observed. Two patients had eosinophilia with counts of 9.5×10^9/L (45% of 21×10^9/L) and 4.2×10^9/L (32% of 13×10^9/L), respectively. The former count was from a patient with malignant lymphoma with eosinophilia of the GIT. Anemia (Hb < 12.0 g/dL) was found in six patients (29%) and thrombocytosis (platelets $> 450 \times 10^9$/L) was found in four (19%) patients. The serum lactate dehydrogenase level was increased in one patient only.

Intestinal Tumor Sites and Staging

The topographic distribution of intestinal lymphoma manifestations is shown in Table 2. The jejunum was the most common site of lymphoma, either alone or in combination with other (gastro-) intestinal manifestations. Gross examination at laparatomy showed multifocal intestinal lymphoma involvement in 18 of 25 patients (72%).

Staging work-up included resection of infiltrated bowel in 24 patients, and 1 patient was staged at autopsy. Two patients were not staged.

In 8 patients, the disease was confined to the small intestine without demonstrable lymph node involvement (stage I). In 15 patients, either adjacent (stage II_1; n = 9) or further abdominal lymph nodes were involved (stage II_2; n = 6). Two patients had generalized disease (stage IV), one of them (the autopsy case) showed multifocal intestinal disease and involvement of mesenteric lymph nodes, myocardium, and adrenal gland. The other patient had multiple jejunal tumors and involvement of lung and liver.

Table 2. *Histologically Documented Intestinal Sites of PTLI at Diagnosis (n = 27)*

Sites	Number of cases (%)
Jejunum	9 (33)
Jejunum and ileum	6 (22)
Small intestine	5 (19)
Duodenum, jejunum, and stomach	2 (7)
Duodenum, jejunum, and ileum	1 (4)
Jejunum, ileum, and colon	1 (4)
Ileum	1 (4)
Rectum (Bx)*	1 (4)
Colon, sigma, and rectum (Bx)*	1 (4)

* Endoscopic biopsy.

Histology

According to the Updated Kiel Classification,[23] 17 lymphomas were classified as pleomorphic, medium and large cell type, and 6 as pleomorphic, small cell type. Four immunoblastic lymphomas were composed of monomorphic medium to large cells with pale cytoplasm and round, vesicular nuclei with solitary, centrally located nucleoli. Cytoplasmic azurophilic granules were not seen. In three cases, the lymphoma infiltration was associated with massive tissue eosinophilia, which exceeded 100 eosinophils per high power field.

Detailed histologic analysis was done on small bowel resection specimens in 21 cases. The median length of the resected bowel segment(s) per case was 36.5 cm and ranged from 8 to 270 cm. According to the pattern of lymphoma infiltration and the morphology of the uninvolved mucosa 21 cases could be separated into three categories (Figure 1): 1) EATCL; 2) EATCL—like lymphoma without enteropathy (EATCL-LLWE), but with an infiltration pattern resembling EATCL; and 3) T-cell lym-

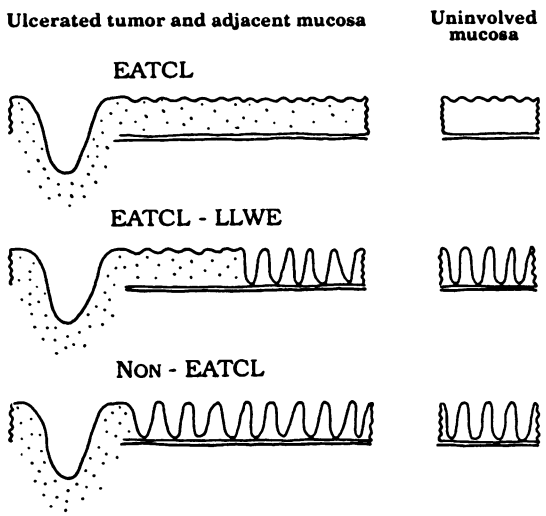

Figure 1. *Schematic illustration showing the micromorphologic features of the three categories of primary peripheral T-cell lymphomas of the intestine. In EATCL, the lymphoma infiltration (stippled area) spreads within an atrophic mucosa, even far distant from the deeply invasive lymphoma. The uninvolved mucosa is atrophic. In EATCL-LLWE, the intramucosal lymphoma spread is limited to the tumor margins, the uninvolved mucosa is unremarkable. In non-EATCL, the lymphoma infiltration is strictly confined to the ulcerated lesion, the uninvolved mucosa is unremarkable.*

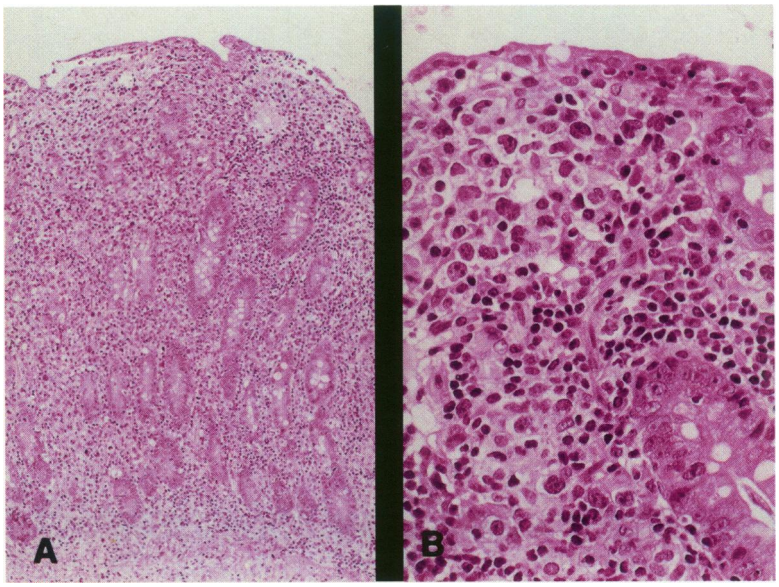

Figure 2. **A:** *Diffuse infiltration of severely atrophic jejunal mucosa by EATCL (H&E, ×105).* **B:** *Higher magnification shows focal accumulation of large atypical lymphoid cells just below the flattened surface epithelium (H&E, ×419).*

phoma without enteropathy and without features of EATCL (Non-EATCL).

There was no relationship between lymphoma morphology and belonging to one of these three groups. The remaining six cases were excluded for the following reasons: 1) in two cases only endoscopic biopsies were available, 2) due to autolytic changes the uninvolved mucosa could not be analyzed thoroughly in the autopsy case, and 3), in the remaining three cases the resection specimens were too small to allow critical analysis of the uninvolved mucosa.

Enteropathy-associated T-cell Lymphoma (EATCL, n = 9)

By definition, all of these nine cases showed villous atrophy and an increase of normal appearing IEL distant from the tumor(s). In addition, crypt hyperplasia and a dense plasmacytic infiltrate of the lamina propria was present. Multifocal lymphoma involvement was found in every case. At least one lesion each showed broad, sometimes fissuring ulceration and infiltration beyond the muscularis propria leading to thickening of the bowel wall. Adjacent to and even well away from tumorous lesions there were band-like lymphoma infiltrates which exclusively spread within a moderately or severely atrophic mucosa. The atypical lymphoid cells accumulated in the lamina propia and showed focal and/or diffuse invasion and destruction of overlying epithelium (Figure 2). Most frequently, the enterocytes of the upper and intermediate villous regions or in cases of severe villous atrophy, the epithelium of the upper parts of the elongated crypts, were the preferential targets of lymphoma cell attack (Figure 3A). In four cases, intraepithelial accumulations of atypical lymphoid cells were noticed (Figure 3B). Occasionally, deeper regions and crypt bases were additionally affected showing flattening and necrosis of enterocytes as well as intraluminal accumulations of granulocytes and cellular debris resembling crypt abscesses. In three cases, microscopic foci of intramucosal lymphoma involvement were found (Figure 4).

The atypical lymphoid cells in EATCL, classified as pleomorphic T-cell lymphoma of medium and large cell type or as immunoblastic lymphoma, differed markedly from the IEL in the uninvolved jejunal mucosa by their larger size and nuclear morphology. The atypical lymphoid cells of the two cases classified as pleomorphic T-cell lymphoma of small cell type were only slightly larger than the IEL of the uninvolved mucosa, but the nuclei were somehow more pleomorphic with often multiple indentations.

EATCL-like Lymphoma Without Enteropathy (EATCL-LLWE, n = 5)

These cases exhibited no obvious enteropathy of the mucosa uninvolved by lymphomatous infiltration. Multifocal disease was found in four and unifocal involvement in one case. At the tumor margins band-like lymphoma involvement was present within an atrophic mucosa. However, this pattern of spread was absent distant from the main tumor masses where microscopic intramucosal lymphoma foci occurred in two cases. Invasion and destruction of epithelial structures by the atypical lymphoid cells was less pronounced than in EATCL and affected solely basal crypt areas. Crypt abscesses were absent in four cases and rarely observed in one case.

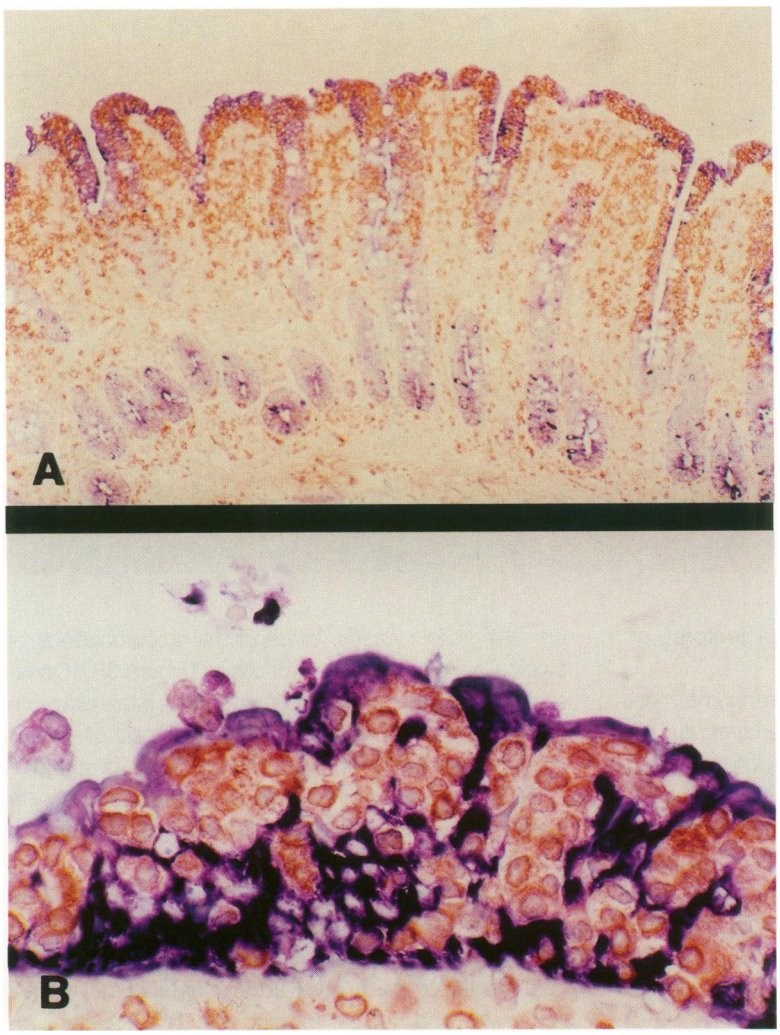

Figure 3. *Intramucosal and intraepithelial spread of jejunal EATCL.* **A:** *Brown-stained CD3-positive lymphoid cells infiltrate the blue-stained KL1-positive epithelium and upper parts of atrophic mucosa. Deeper portions of lamina propria and deeper crypt areas contain only a few scattered CD3-positive cells (APAAP/immunoperoxidase double staining technique, ×105).* **B:** *Intraepithelial accumulations of CD3-positive atypical lymphoid cells resembling "Pautrier's microabscesses" (APAAP/immunoperoxidase double staining technique, ×628).*

T-cell Lymphoma Without Enteropathy and Without Features of EATCL (Non-EATCL, n = 7)

The main feature of these cases was the sharp border between the deeply infiltrating, ulcerating tumors and the nearly unaffected intestinal mucosa at the tumor margins. Besides an inconspicuous increase of IEL (not exceeding 20 IEL/100 enterocytes) and a moderately dense mixed inflammatory infiltrate of the lamina propria the mucosa at the tumor margins was unremarkable. Multifocal involvement was found in four and unifocal disease in three cases. Enteropathy, prominent invasion, and destruction of epithelium by atypical lymphoid cells, crypt abscesses, and microscopic lymphoma foci were absent.

Concerning the seven patients with histories of malabsorption, four were classified as EATCL, one patient as Non-EATCL, and two cases were not classified.

Immunomorphologic Findings

On paraffin sections the atypical lymphoid cells stained either for UCHL1 (24 of 27 cases) or MT1 (20 of 27 cases) or both (17 of 27 cases). Leu 22 showed an identical staining pattern as MT1, but stained stronger in four cases. Reactivity for CD3 was found in 20 of 23 lymphomas tested. Three of 27 cases stained for both MB1 and MB2 but no lymphoma was positive for L26 or expressed kappa or lambda light chains. In four pleomorphic lymphomas of medium and large cell type, the majority of the large cell population stained for Ber-H2. Except two of these cases all lymphomas expressed LCA. No reactivity was present for EMA, Leu M1, and lysozyme.

The results of immunologic phenotyping on frozen sections are shown in Table 3. All eight cases were positive for CD3 and CD7, and negative for delta-gene products, CD25, Leu 8, CD57, CD11b, or all the B-cell and myelomonocytic antigens tested. One lymphoma was

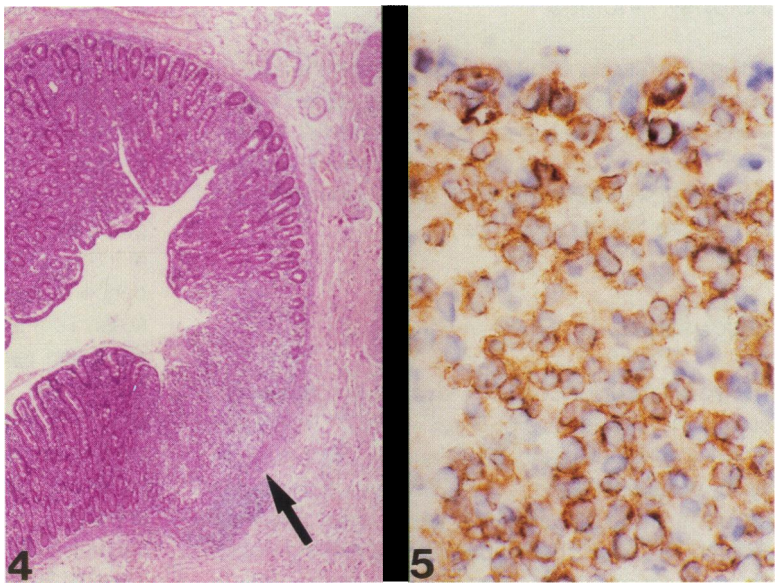

Figure 4. *Microscopic intramucosal lymphoma focus (arrow) in a case of EATCL (H&E, ×42).*
Figure 5. *Immunostaining for HML-1 in a case of primary peripheral T-cell lymphoma of the jejunum (Immunoperoxidase technique on frozen section, ×628).*

HLA-DR positive. A rather uniform phenotype was found in four cases that were positive for CD3, CD7, and HML-1, and negative for both CD4 and CD8 with variable expression of CD2 (two of four cases) and βF1 (one of four cases). Immunostaining of atypical lymphoid cells for HML-1 is shown in Figure 5. Two cases showed a $CD4^-CD8^+$ phenotype with divergent expression of HML-1, and one case each was $CD4^+CD8^-HML\text{-}1^-$ and $CD4^-CD8^-HML\text{-}1^-$, respectively. The median percentage of Ki-67-reactive cells was 55% (range, 30–80%).

Therapy, Response, and Survival

Of the 27 patients, 24 underwent bowel resection at the time of initial diagnostic laparatomy. Fourteen patients were treated with multiagent chemotherapy, only seven of them finished the complete course, and one patient was treated with local radiotherapy only. Except for surgical intervention, ten patients were not intensively treated.

Six patients (stage I, n = 4; stage II, n = 1; not staged, n = 1) who had all received chemotherapy achieved a complete remission (CR); four are alive without disease at 14, 16, 25, and 58 months, respectively. The remaining two patients relapsed at small intestinal sites; one is currently free of disease for 60 months, and the other patient experienced a second relapse and died of malnutrition 56 months after diagnosis.

The response to chemotherapy was regarded as unevaluable in seven patients who did not finish the complete course due to their bad condition and/or because they refused further treatment.

In general, eight of twenty-six patients (31%) relapsed within 1.5 to 12 months (median, 5 months); seven of them relapsed at small intestinal sites, and one patient developed an ulcerative lesion at the hard palate 6 weeks after initial diagnosis.

Twenty of 27 patients died, 17 of them within 6 months after diagnosis. The overall median survival was 4 months. The median survival of patients with stage I disease was significantly longer than for patients with stage II and IV disease ($P = 0.035$).

Table 3. *Immunophenotypes of 8 Peripheral T-cell Lymphomas of the Intestine*

Category	CD3	CD7	CD4	CD8	βF1	TCRδ-1 δ-TCS1	HML-1	CD2	CD5	HLA-DR
EATCL	+	+	−	−	−	−/−	+	+	−	−
EATCL	+	+	−	−	−	−/−	+	−	−	−
EATCL	+	+	−	+	−	−/−	−	+	−	−
EATCL-LLWE	+	+	−	−	−	−/−	+	+	−	−
EATCL-LLWE	+	+	+	−	+	−/−	−	+	+	−
EATCL-LLWE	+	+	−	−	+	−/−	+	−	−	−
Non-EATCL	+	+	−	+	+	−/−	+	−	−	+
Not classified	+	+	−	−	−	−/−	−	+	−	−

Autopsy Findings

Autopsies were done in 17 cases. The most frequent diagnoses made at autopsy are summarized in Table 4. Generalized disease was found in six cases with involvement of spleen, lung, liver, adrenal gland, and myocard. Bone marrow involvement was histologically verified in 1 of 11 cases tested.

Discussion

The majority of extranodal non-Hodgkin's lymphomas occurs in the GIT[1] and is of B-cell origin.[7–10] Peripheral T-cell lymphomas, although frequently presenting as strictly extranodal disease of the skin and upper aerodigestive tract, rarely affect the GIT at initial presentation.[18,25–30] Those PTL that primarily develop in the GIT, however, almost exclusively arise in the small bowel and may be associated with malabsorption.[16] Lymphoma may develop in a patient with long-standing celiac disease[17] or manifest as a progressive deterioration in a patient who has recently been diagnosed or suspected to have celiac disease.[16] The majority of patients in this series and also in others, however, showed no clinical or histologic evidence of enteropathy.[14,31]

The most common symptoms at initial presentation were weight loss, abdominal pain, and acute abdomen due to perforation and/or acute obstruction of the small bowel. An intriguing feature at presentation was the marked discrepancy between the bad condition of the patients and the inconspicuous laboratory findings. Mild to moderate anemia was found in less than one-third of the patients, whereas leukocytopenia or thrombocytopenia were never detected, and the lactate dehydrogenase level was increased in one patient only. These findings contrast with those obtained from studies of non-intestinal, non-cutaneous PTL and may probably be due to the advanced stages of disease observed thereof.[18,28–30] Staging work-up in 25 cases manifested only two PTLI as generalized disease but none of them demonstrated peripheral or mediastinal lymphadenopathy. Understaging cannot be excluded in four patients who died shortly after the staging procedures and showed generalized disease at autopsy. In this small group of patients the only case with documented bone marrow involvement was found. Thus, PTLI presented as a localized disease in the vast majority of cases either with or without involvement of mesenteric or further abdominal lymph nodes. The preferential site of PTLI was the small intestine and the upper parts of the jejunum in particular. Since in five cases the definite tumor location at the small intestine was not specified, the overall incidence of jejunal involvement ranged somewhere between 70% and 90% of the cases. The true incidence may even reach 100% because the two patients with colonic and rectal disease underwent endoscopic biopsy only and were suspected of having small intestinal involvement also. The high rate of spontaneous small bowel perforation, the predominance of jejunal disease, and the high incidence of multifocal bowel involvement separates PTLI from the most common Western types of intestinal B-cell lymphomas.[32–34]

Table 4. *Autopsy Findings in 17 Cases of Peripheral T-cell Lymphomas of the Intestine*

Lymphoma involvement	n
None	4
Small intestine ± mesenterical LN*	7
Generalized	6
Cachexia	8
Intestinal perforation, peritonitis	7
Septic complications	6

* LN, lymph nodes.

According to the Updated Kiel Classification,[23] 21 PTLI were classified as large cell lymphomas, that is, as pleomorphic medium and large cell type and immunoblastic type, respectively. The six remaining lymphomas were diagnosed as pleomorphic PTL of small cell type. No PTLI was classified as large cell anaplastic (Ki-1+) lymphoma, which is in agreement with the experience that this lymphoma type rarely occurs in the intestine.[35–37] Although cytoplasmic azurophilic granules were not observed, their presence cannot be excluded since this feature has been demonstrated in some PTLI but is hardly appreciated on routinely processed tissue sections.[38–40]

Detailed histopathologic analysis in 21 cases of small bowel resection specimens allowed delineation of three lymphoma categories, which differed with respect to the pattern of lymphoma infiltration and the presence of enteropathy of the uninvolved mucosa. In EATCL, the intramucosal spread distant from the main tumor masses was a constant finding and accompanied by the epitheliotropic infiltration of villous tips and upper crypt areas with occasional preservation of the basal crypt enterocytes. The density of the atypical intraepithelial lymphoid cell component varied but was pronounced in four cases with formation of Pautrier-like microabscesses, as previously described.[38] Small subepithelial collections of atypical large cells, identical to the early lesions portrayed by Isaacson,[41] were exclusively found in some EATCL. In cases of EATCL-LLWE the aforementioned morphologic features, such as intramucosal lymphoma spread and epitheliotropism, were less pronounced and confined to the tumor margins. In non-EATCL these features were absent and on morphologic grounds, the destruction of the overlying mucosa seemed to be the consequence of a submucosal lymphoma expansion.

Table 5. *Immunologic Phenotypes of Peripheral T-cell Lymphomas of the Intestine: A Review of the Literature*

Authors	n	Phenotype	Enteropathy
Foucar et al[38]	1	$CD3^+CD4^-CD8^+$	No
Spencer et al[43]	8	$CD3^{+/-}CD4^-CD8^-HML\text{-}1^+$	Yes
Kanavaros et al[39]	1	$CD3^+CD4^-CD8^+$	No
Stein et al[44]	1	$CD3^+CD4^-CD8^+HML\text{-}1^+$	Yes
Pallesen et al[45]	1	$CD3^+CD4^-CD8^-HML\text{-}1^+$	Yes
Longacre et al[40]	1	$CD3^+CD4^+CD8^-$	No
Laszewski et al[9]	1	$CD3^+CD4^-CD8^+$	Yes
Own cases	4	$CD3^+CD4^-CD8^-HML\text{-}1^+$	Yes/No*
	2	$CD3^+CD4^-CD8^+HML\text{-}1^{+/-}$	Yes/No†
	1	$CD3^+CD4^+CD8^-HML\text{-}1^-$	No
	1	$CD3^+CD4^-CD8^-HML\text{-}1^-$	Not stated

* Enteropathy present in two cases.
† Enteropathy present in one case.

Belonging to the EATCL category strongly correlated with the incidence of malabsorption states, multifocal disease at presentation, and with the high frequency of recurrent disease during course. All nine patients with EATCL had multiple lymphoma involvement and all six of those who survived more than 2 months relapsed. Five patients relapsed at small intestinal sites, two of them even experienced a second relapse at these sites. Only one patient relapsed at an extraintestinal site, namely at the hard palate. Although multifocal disease was also observed in four of five patients with EATCL-LLWE and in four of seven patients with non-EATCL, recurrent disease was only diagnosed in one non-EATCL patient and in one case that was not categorized due to lack of adequate tissue.

It has been shown that more than 95% of normal human small intestinal IEL and 40% of lamina propria T cells express a membrane antigen defined by the monoclonal antibody HML-1.[42] Moreover, the expression of HML-1 seemed to be specific for EATCL, suggesting that these tumors are derived from mucosal T cells, particularly from the intraepithelial T-cell component.[43,44] Subsequent studies, however, demonstrated HML-1 to be also reactive with a variety of extraintestinal non-Hodgkin's lymphomas,[45–48] and unreactive in a few cases of EATCL.[45] Intraepithelial T lymphocytes are a phenotypically heterogeneous population with 75%–85% IEL expressing the $CD3^+CD4^-CD8^+$ phenotype, less than 10% are $CD3^+CD4^+CD8^-$,[49] and 6.5% are $CD3^+CD7^+CD4^-CD8^-$.[50] Review of our own cases and those reported (Table 5) showed that among a total of 22 PTLI (enteropathy associated, n = 14; without enteropathy, n = 7; enteropathy not stated, n = 1) 14 expressed the $CD3^{+/-}CD4^-CD8^-$ phenotype, two were $CD3^+CD4^+CD8^-$ and six $CD3^+CD4^-CD8^+$, respectively.[9,13,38–40,43–45] The phenotype of the 14 EATCL was either $CD3^{+/-}CD4^-CD8^-$ (n = 11) or $CD3^+CD4^-CD8^+$ (n = 3) but in no case $CD3^+CD4^+CD8^-$, whereas the PTLI without enteropathy showed the $CD3^+CD4^-CD8^-$ profile in only two cases and were $CD3^+CD4^+CD8^-$ or $CD3^+CD4^-CD8^+$ in two and three cases, respectively. These findings suggest that the majority of EATCL display the $HML\text{-}1^+CD3^+CD4^-CD8^-$ phenotype and are derived from this small IEL subset. Furthermore, we speculate that PTLI may also originate from lamina propria T cells, eventually from those with the $HML\text{-}1^{+/-}$ $CD3^+CD4^+CD8^-$ phenotype. The derivation of PTLI from mucosal T cells could explain that most PTLI remain localized within the GALT, although dissemination occurs.

The derivation from IEL may be responsible for the high incidence of small intestinal recurrences found in EATCL. The organ-specific biologic behavior of PTLI implies homing of lymphoid cells to the small intestine and requires certain not completely elucidated interactions between surface molecules and recognition sites on mucosal high endothelial venules.[51] The LECAM-1(LAM-1) antigen has been shown to represent the human equivalent of the murine peripheral lymph node homing receptor MEL-14[52] and to be identical to the Leu-8 antigen.[53] The complete loss of Leu-8 in all eight PTLI of this study (which includes the six PTLI of Pals et al[19]), which is in contrast with the frequent Leu-8 expression found in nodal PTL,[19] might influence the preferential spread to and relapse of PTLI at intestinal sites.

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References

1. Freeman C, Berg JW, Cutler SJ: Occurrence and prognosis of extranodal lymphomas. Cancer 1972, 29:252–260
2. Isaacson PG, Wright DH: Malignant lymphomas of mucosa-

associated lymphoid tissue. A distinctive type of B-cell lymphoma. Cancer 1983, 52:1410–1416
3. Isaacson PG, Wright DH: Extranodal malignant lymphoma arising from mucosa-associated lymphoid tissue. Cancer 1984, 53:2515–2524
4. Isaacson PG, Spencer J: Malignant lymphoma of mucosa-associated lymphoid tissue. Histopathology 1987, 11:445–462
5. Van der Valk P, Lindeman J, Meijer CJLM: Non-Hodgkin's lymphomas of the gastrointestinal tract: A review with special reference to the gut-associated lymphoid tissue. Digestive Pathology Diseases, Chapter 5. New York, Appleton Century Croft, 1988, pp 105–119
6. Isaacson PG, Spencer J, Wright DH: Classifying primary gut lymphomas. Lancet 1988, ii:1148–1149
7. Grody WW, Weiss LM, Warnke RA, Magidson JG, He E, Lewin KS: Gastrointestinal lymphomas. Immunohistochemical studies on the cell of origin. Am J Surg Pathol 1985, 9:328–337
8. Radaszkiewicz T, Dragosics B, Bauer P: Gastrointestinal malignant lymphomas of the mucosa-associated lymphoid tissue: factors relevant to prognosis. Gastroenterology 1992, 102:1628–1638
9. Laszewski MJ, Kamat D, Kemp JD, Goeken JA, Mitras FA, Platz CE, Dick FR: Immunophenotypic and genotypic characterization of primary non-Hodgkin's lymphoma of the gastrointestinal tract. Mod Pathol 1990, 3:423–428
10. Wolf BC, Martin AW, Ree HJ, Banks PM, Smith S, Neiman RS: Non-Hodgkin's lymphomas of the gastrointestinal tract. An evaluation of paraffin section immunostaining. Am J Clin Pathol 1990, 93:233–239
11. Isaacson PG, Wright DH: Malignant histiocytosis of the intestine. Its relationship to malabsorption and ulcerative jejunitis. Hum Pathol 1978, 9:661–677
12. Isaacson PG, Spencer J, Connolly CE, Pollock DJ, Stein H, O'Connor NTJ, Bevan DH, Kirkham N, Wainscoat JS, Mason DY: Malignant histiocytosis of the intestine: A T-cell lymphoma. Lancet 1985, ii:688–691
13. Salter DM, Krajewski AS, Dewar AE: Immunophenotype analysis of malignant histiocytosis of the intestine. J Clin Pathol 1986, 39:8–15
14. Shepherd NA, Blackshaw AJ, Hall PA, Bostad L, Coates PJ, Lowe DG, Levison DA, Morson BC, Stansfeld AG: Malignant lymphoma with eosinophilia of the gastrointestinal tract. Histopathology 1987, 11:115–130
15. Swinson CM, Slavin G, Coles EC, Booth CC: Coeliac disease and malignancy. Lancet 1983, i:111–115
16. Isaacson P, Wright DH: Intestinal lymphoma associated with malabsorption. Lancet 1987, i:67–70
17. O'Farelly C, Feighery C, O'Brian DS, Stevens F, Connolly CE, McCarthy C, Weir DG: Humoral response to wheat protein in patients with coeliac disease and enteropathy associated T cell lymphoma. Br Med J 1986, 293:908–910
18. Chott A, Augustin I, Wrba F, Hanak H, Öhlinger W, Radaszkiewicz T: Peripheral T-cell lymphomas: A clinicopathologic study of 75 cases. Hum Pathol 1990, 21:1117–1125
19. Pals ST, Meijer CJLM, Radaszkiewicz T: Expression of the human peripheral lymph node homing receptor (LECAM-1) in nodal and gastrointestinal non-Hodgkin's lymphomas. Leukemia 1991, 5:628–631
20. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M: Report of the committee on Hodgkin's disease staging classification. Cancer Res 1971, 31:1860–1861
21. Musshoff K: Klinische Stadieneinteilung der nicht-Hodgkin Lymphome. Strahlentherapie 1977, 153:218–221
22. Ferguson A, Murray D: Quantitation of intraepithelial lymphocytes in human jejunum. Gut 1971, 12:988–994
23. Stansfeld AG, Diebold J, Kapancy Y, Kelenyi G, Lennert K, Mioduszewska O, Noel H, Rilke F, Sundstrom C, Van Unnik JAM, Wright DH: Updated Kiel classification for lymphomas. Lancet 1988, i:292–293
24. Stein H, Gerdes J, Schwab U, Lemke H, Mason DY, Ziegler A Schienle W, Diehl V: Identification of Hodgkin and Sternberg-Reed cells as a unique cell type derived from a newly detected small-cell population. Int J Cancer 1982, 30:445–459
25. Jaffe ES: Pathologic and clinical spectrum of post-thymic T-cell malignancies. Cancer Invest 1984, 2:413–426
26. Horning SJ, Weiss LM, Crabtree GS, Warnke RA: Clinical and phenotypic diversity of T cell lymphomas. Blood 1986, 67:1578–1582
27. Weis JW, Winter MW, Phyliky RL, Banks PM: Peripheral T-cell lymphomas: Histologic, immunohistologic, and clinical characterization. Mayo Clin Proc 1986, 61:411–426
28. Weisenburger DD, Linder J, Armitage JO: Peripheral T-cell lymphoma: A clinicopathologic study of 42 cases. Hematol Oncol 1987, 5:175–187
29. Armitage JO, Greer JP, Levine AM, Weisenburger DD, Formenti SC, Bast M, Conley S, Pierson J, Linder J, Cousar JB, Nathwani BN: Peripheral T-cell lymphoma. Cancer 1989, 63:158–163
30. Pinkus GS, O'Hara CJ, Said JW: Peripheral/post-thymic T-cell lymphomas: A spectrum of disease. Clinical, pathologic, and immunologic features of 78 cases. Cancer 1990, 65:971–998
31. Domizio P, Owen R, Shepherd NA, Norton AJ: Primary small bowel lymphoma: A clinicopathological study of 110 cases. J Pathol 1991, 163:169A
32. Dragosics B, Bauer P, Radaszkiewicz T: Primary gastrointestinal non-Hodgkin's lymphomas. A retrospective clinicopathologic study of 150 cases. Cancer 1985, 55:1060–1073
33. Cooper BT, Read AE: Small intestinal lymphoma. World J Surg 1985, 9:930–937
34. Al-Mondhiry H: Primary lymphomas of the small intestine. East-west contrast. Am J Hematol 1986, 22:89–105
35. Chan JKC, Ng CS, Hui PK, Leung TW, Lo ESF, Lau WH, Mc Guire LJ: Anaplastic large cell Ki-1 lymphoma. Delineation of two morphological types. Histopathology 1989, 15:11–34
36. Chott A, Kaserer K, Augustin I, Vesely M, Heinz R, Oehlinger W, Hanak H, Radaszkiewicz T: Ki-1-positive large cell lymphoma. A clinicopathologic study of 41 cases. Am J Surg Pathol 1990, 14:439–448
37. Greer JP, Kinney MC, Collins RD, Salhany KE, Wolff SN, Hainsworth SD, Flexner JM, Stein RS: Clinical features of 31

patients with Ki-1 anaplastic large cell lymphoma. J Clin Oncol 1991, 9:539–547

38. Foucar K, Foucar E, Mitros F, Clamon G, Goeken J, Crossett J: Epitheliotropic lymphoma of the small bowel. Report of a fatal case with cytotoxic/suppressor T-cell immunotype. Cancer 1984, 54:54–60
39. Kanavaros P, Lavergne A, Galian A, Boivin P, Fourmesteaux AR, Priollet BC, Flandrin G, Hautefeuille P: A primary immunoblastic T malignant lymphoma of the small bowel, with azurophilic cytoplasmic granules. Am J Surg Pathol 1988, 12:641–647
40. Longacre TA, Listrom MB, Spigel JH, Willman CL, Dressler L, Clark D: Aggressive jejunal lymphoma of large granular lymphocytes. Immunohistochemical, ultrastructural, molecular, and DNA content analysis. Am J Clin Pathol 1990, 93: 124–132
41. Isaacson P: Malignant histiocytosis of the intestine: The early histological lesion. Gut 1980, 21:381–386
42. Cerf-Bensussan N, Jarry A, Brousse N, Lisowska-Grospierre B, Guy-Grand D, Griscelli C: A monoclonal antibody (HML-1) defining a novel membrane molecule present on human intestinal lymphocytes. Eur J Immunol 1987, 17: 1279–1285
43. Spencer J, Cerf-Bensussan N, Jarry A, Brousse N, Guy-Grand D, Krajewski AS, Isaacson PG: Enteropathy-associated T-cell lymphoma (malignant histiocytosis of the intestine) is recognized by a monoclonal antibody (HML-1) that defines a membrane molecule on human mucosal lymphocytes. Am J Pathol 1988, 132:1–5
44. Stein H, Dienemann D, Sperling M, Zeitz M, Riecken EO: Identification of a T cell lymphoma category derived from intestinal-mucosa-associated T cells. Lancet 1988, ii:1053–1054
45. Pallesen G, Hamilton-Dutoit SJ: Monoclonal antibody (HML-1) labelling of T-cell lymphomas. Lancet 1989, i:223
46. Sperling M, Kaudewitz P, Braun-Falco O, Stein H: Reactivity of T cells in mycosis fungoides exhibiting marked epidermotropism with the monoclonal antibody HML-1 that defines a membrane molecule on human mucosal lymphcytes. Am J Pathol 1989, 134:955–960
47. Möller P, Mielke B, Moldenhauer G: Monoclonal antibody HML-1, a marker for intraepithelial T cells and lymphomas derived thereof, also recognizes hairy cell leukemia and some B-cell lymphomas. Am J Pathol 1990, 136:509–512
48. Falini B, Flenghi L, Fagioli M, Pelicci PG, Stein H, Bigerna B, Pileri S, Martelli MF: Expression of the intestinal T-lymphocyte associated molecule HML-1: analysis of 75 non-Hodgkin's lymphomas and description of the first HML-1 positive lymphoblastic tumor. Histopathology 1991, 18:421–426
49. Mowat AM: Human intraepithelial lymphocytes. Springer Semin Immunopathol 1990, 12:165–190
50. Spencer J, MacDonald TT, Diss TC, Walker-Smith JA, Ciclitira PJ, Isaacson PG: Changes in intraepithelial lymphocyte subpopulations in coeliac disease and enteropathy associated T cell lymphoma (malignant histiocytosis of the intestine). Gut 1989, 30:339–346
51. Jalkanen S: Lymphocyte homing to the gut. Springer Semin Immunopathol 1990, 12:153–164
52. Tedder TF, Isaacs CM, Ernst TJ, Demetri GD, Adler DA, Disteche CM: Isolation and chromosomal localization of cDNA encoding a novel human lymphocyte cell surface molecule LAM-1: homology with the mouse lymphocyte homing receptor and other human adhesion proteins. J Exp Med 1989, 170:123–133
53. Tedder TF, Penta AC, Levine HB, Freedman AS: Expression of the human leukocyte adhesion molecule, LAM-1. Identity with the TQ1 and Leu-8 differentiation antigens. J Immunol 1990, 144:532–540