Immunoreactivity of B-Cell Markers (CD79a, L26) in Rare Cases of Extranodal Cytotoxic Peripheral T- (NK/T-) Cell Lymphomas

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The monoclonal antibodies L26 (CD20) and CD79a are very useful reagents for the immunohistochemical assessment of B-cell lineage in lymphoproliferative disorders. Although very few CD20-positive peripheral T-cell lymphomas (PTL) have been reported, comprehensive analyses of CD79a reactivity in extranodal PTL and NK/T-cell lymphomas have not been performed previously. This study investigated CD79a (clone JCB117) and CD20 reactivity in 94 extranodal non–B-cell lymphomas (enteropathy-type intestinal T-cell lymphoma [*n* = 52], nasal NK/T-cell lymphoma [*n* = 11], and primary cutaneous PTL [*n* = 31]) and in 17 cases of nodal PTL, unspecified. In four cases (enteropathy-type intestinal T-cell lymphoma [*n* = 3] and nasal NK/T-cell lymphoma [*n* = 1]), the majority of tumor cells stained for CD79a (all CD20 negative) and one cutaneous PTL, unspecified, was CD20 positive (CD79a negative). Extensive immunophenotyping and polymerase chain reaction–based molecular analyses revealed that all five B-cell marker–positive extranodal lymphomas had a cytotoxic phenotype and did indeed represent monoclonal peripheral T-cell proliferations. To minimize the risk of misinterpretation of lymphoma cell lineage, especially in cases of extranodal lymphoproliferative disease, we suggest the use of both CD79a and CD20 in combination with a panel of antibodies reactive to T cells, such as βF1 and CD5, and to T cells and NK cells, such as CD3, CD2, CD56, and TIA-1.

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Immunohistochemistry on paraffin-embedded sections is a valuable technique in both diagnostic and investigative pathology as it optimally combines immunoreactivity and tissue morphology. Especially in hematopathology, immunohistochemistry has become an integral part of the diagnostic workup. An increasing number of antibodies that are reactive on routinely processed tissue has contributed substantially to the understanding of hematopoietic malignancies in general and to malignant lymphomas in particular. The report on the revised European-American classification of lymphoid neoplasms includes a record of the most characteristic immunophenotype for each lymphoma entity, and the majority of antigens listed can be detected on paraffin sections by commercially available antibodies (1, 2). Some antibodies, such as those that recognize CD20 and CD79a, have gained widespread acceptance because they are considered to be largely B-lineage restricted and therefore useful for differential diagnosis of B-cell *versus* T-cell lymphoma (3–9). Although occasional examples of CD20-positive T-cell lymphomas have been reported (5, 10, 11), to our knowledge no case of CD79a-positive peripheral T-cell lymphoma (PTL) has been published. During an ongoing study on intestinal T-cell lymphomas, one of these cases showed reactivity to CD79a in a significant proportion of tumor cells. Prompted by this observation, additional cases of extranodal PTLs and NK/T-cell lymphomas were evaluated for immunoreactivity to CD79a. This report describes the histopathologic, immunophenotypic, molecular, and clinical findings of five cases, four of which were reactive to CD79a and one to CD20.

MATERIALS AND METHODS

Tissue

To study the reactivity of CD79a and CD20 in PTLs and NK/T-cell lymphomas, a total of 111 cases were retrieved from the files of the Department of Clinical Pathology, General Hospital Vienna. According to the World Health Organization (WHO) classification of neoplastic diseases of the hematopoietic and lymphoid tissues (12), they were composed of 52 cases of enteropathy-type intestinal T-cell lymphomas, 11 cases of nasal NK/T-cell lymphomas, 31 cases of primary cutaneous PTLs (mycosis fungoides [$n = 14$], PTL unspecified [$n = 7$], and CD30-positive lymphoproliferative disease [$n = 10$]), and 17 cases of nodal PTLs, unspecified. Histologic examination was done on formalin-fixed (7.5%, pH 7.4), paraffin-embedded tissue. Sections were stained with hematoxylin and eosin, periodic acid-Schiff, and Giemsa for routine histopathologic evaluation. One patient (Case 3) has been included in a previously published series on intestinal T-cell lymphomas (13).

Immunohistochemistry

Immunostaining was done using the polyclonal antibodies anti-CD3 (Dako, Copenhagen, Denmark; 1:400) and TdT (Dako; 1:20) and the monoclonal antibodies CD79a (clone JCB117; Dako; 1:25), L26 (Dako; 1:200), CD34 (Immunotech, Marseille, France; 1:100), βF1 (T-Cell Sciences, Woburn, MA; 1:10), CD1a (Novocastra, Newcastle, UK; 1:20), CD2 (Novocastra; 1:20), CD4 (Novocastra; 1:20), CD5 (Novocastra; 1:20), CD7 (Novocastra; 1:40), CD8 (Dako; 1:30), TIA-1 (Coulter, Hialeah, FL; 1:800), CD56 (Sanbio, Uden, The Netherlands; 1:200), CD57 (Becton-Dickinson, San Jose, CA; 1:10), CD30 (Dako; 1:80), EMA (Dako; 1:100), LMP1 (Dako; 1:100) and MIB-1 (Immunotech; 1:50). The monoclonal antibody Granzyme B-4 (GB-4, 1:50) was generously provided by Dr. J.A. Kummer, Department of Pathology, Free University Hospital, Amsterdam, The Netherlands. Pretreatment for unmasking of antigens was done either by digestion with 0.05% preheated protease (type XXIV; Sigma Chemical Co., St.Louis, MO) in TRIS-buffered saline for 5 min at 37° C (for βF1 and CD3), by microwaving in citrate buffer (10 mmol/L, pH 6.0) twice for 5 min each at 600 W (for CD79a, CD34, TdT, CD1a, CD7, GB-4, TIA-1, CD30, EMA, LMP1, and MIB-1), or by autoclaving at 1 bar for 20 min, followed by cooling down for 40 min (for CD2, CD4, CD5, CD8, and CD56). Application of CD34, TdT, βF1, CD3, CD4, CD5, and CD8 was followed by incubation with biotinylated goat antirabbit IgG (for TdT and CD3) or horse antimouse IgG (for CD34, βF1, CD4, CD5, and CD8) as the secondary antibody and then by peroxidase-conjugated streptavidin (Super Sensitive HRP Label; Biogenex, San Ramon, CA). Staining was developed using 3-amino-9-ethylcarbazole as the chromogen (Sigma) in the presence of H_2O_2. For the remaining antibodies, biotinylated horse antimouse IgG was used as the secondary antibody followed by Vectastain Elite ABC reagent (Vector Laboratories, Burlingame, CA) and 3,3′-diaminobenzidine as a chromogen (Fluka, Buchs, Switzerland) in the presence of H_2O_2. Nonspecific reactivity was assessed by omission of the primary antibodies. Staining of tumor cells was scored: +, more than 50% positive; ±, 20 to 50% positive; −, fewer than 20% positive; I+, individual tumor cells positive. The latter score was used for TIA-1 and GB-4 only.

EBER *In Situ* Hybridization

Fluorescein-labeled oligonucleotides complementary to Epstein-Barr virus small nuclear RNA (EBER) 1/2 were used according to the instructions of the manufacturer (PNA ISH detection kit, Dako) under RNAse-free conditions.

T- and B-cell Clonality Analyses by Polymerase Chain Reaction

For the detection of T-cell and B-cell clonality, polymerase chain reaction (PCR) techniques were used to amplify rearranged T-cell receptor (TCR) γ-chain and immunoglobulin heavy chain genes, respectively, as described (14). Genomic DNA was extracted from formalin-fixed, paraffin-embedded tissue by proteinase K digestion without detergents or EDTA according to Frank *et al.* (15). PCR products were separated on precast 6% polyacrylamide gels (Novex, San Diego, CA).

RESULTS

Identification of Five Extranodal Peripheral T-(NK/T-) Cell Lymphomas Reactive to CD79a or CD20

A total of 111 cases of various types of extranodal PTL and NK/T-cell lymphomas and a group of nodal PTL, unspecified, were studied for the immunoreactivity of the B-cell markers CD79a and CD20 on paraffin sections (Table 1). None of the 17 nodal PTL was reactive to CD79a or CD20. In contrast, 5 of the 94 extranodal lymphomas (5.3%) stained either for CD79a (enteropathy-type intestinal T-cell lymphoma [$n = 3$] and nasal NK/T-cell lymphoma [$n = 1$]) or for CD20 (primary cutaneous PTL, unspecified [$n = 1$]), indicating a mutually exclusive reactivity pattern of the two B-cell markers. The clinical presentation and follow-up, histopathology, immunologic phenotyping, and PCR-based clonality

TABLE 1. Peripheral T-Cell Lymphomas and NK/T-Cell Lymphomas Evaluated for CD79a and CD20 Immunoreactivity

Diagnosis[a]	*n*	CD79a+	CD20+
Enteropathy-type intestinal T-cell lymphoma	52	3	—
Nasal NK/T-cell lymphoma	11	1	—
Primary cutaneous PTL			
Mycosis fungoides	14	—	—
PTL, unspecified	7	—	1
CD30+ lymphoproliferative disease[b]	10	—	—
Nodal PTL, unspecified	17	—	—
Total	111	4	1

PTL, peripheral T-cell lymphomas.

[a] According to the World Health Organization classification (12).

[b] According to the EORTC classification for primary cutaneous lymphomas (27): large cell cutaneous T-cell lymphoma CD30+, anaplastic ($n = 2$); pleomorphic ($n = 8$).

analyses of these five cases are discussed in the following sections.

Clinical Findings

The clinical findings are summarized in Table 2. Two patients presented with localized cutaneous lesions (Cases 1 and 5), two patients had multiple jejunal tumors (Cases 2 and 3), and one patient had gastric and colonic lesions (Case 4). The clinical course was aggressive in all cases and characterized by progressive disease irrespective of therapeutic interventions.

Histopathology

The histopathology of each of the five lymphomas is shown in the left panel in Figure 1. The nasal and cutaneous lesions in Case 1 were histologically identical showing nonangiocentric, densely packed medium- and large-sized cells with often clear cytoplasm and moderately pleomorphic nuclei. Cases 2 and 3 had multiple jejunal tumors each composed of monomorphic small- to medium-sized cells that were of monocytoid clear cell appearance (in Case 2) or displayed lymphoplasmacytoid features with narrow, slightly basophilic cytoplasm (in Giemsa-stained sections) and inconspicuous nuclei (in Case 3). As both of these cases additionally showed prominent intraepithelial lymphoma cell accumulations resembling lymphoepithelial lesions, they strikingly mimicked low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type. The gastric and ileal lesions in Case 4 showed different histologies: the gastric lymphoma infiltrate exhibited mostly medium-sized and a few large pleomorphic cells, whereas the multiple intestinal tumors were mainly composed of anaplastic large cells (not shown). Two of the three intestinal T-cell lymphomas (Cases 2 and 4) were enteropathy associated. In Case 5, the band-like cutaneous infiltrate extended into the deep dermis and showed mild epidermotropic features without formation of Pautrier's microabscesses. As shown in Figure 1 (bottom row, left panel), the tumor cells were just slightly larger than reactive lymphocytes and contained pleomorphic, sometimes deeply indented nuclei.

Immunologic Phenotyping and Clonality Analyses

The antigen profiles of the four cases that were reactive to CD79a (Cases 1 through 4) and the CD20-positive lymphoma (Case 5) are summarized in Table 3. Some immunostains are shown in Figure 1.

Among the CD79a-positive samples of all four cases, the majority of tumor cells showed membrane and cytoplasmic staining that was only slightly weaker than in plasma cells present in ad-

TABLE 2. Clinical Findings in Five Patients with B-Cell Marker–Positive Peripheral T-Cell Lymphomas

Case	Diagnosis	Age/Sex	Presentation	Follow-Up	Survival
1	Nasal NK/T-cell lymphoma, CD79a+	77/M	Ulcerated lesion on tip of nose extending into nasal cavity	Local radiotherapy cutaneous recurrences, parapharyngeal tumor 10 mo after presentation	Died of pharyngeal hemorrhage 11 mo after diagnosis
2	Enteropathy-type intestinal T-cell lymphoma CD79a+	63/M	Jejunal tumor	6× CHOP, intestinal recurrence, perforation	Died of peritonitis 11 mo after diagnosis
3	Enteropathy-type intestinal T-cell lymphoma CD79a+	42/M	Perforated jejunal tumor	No therapy	Died of intestinal hemorrhage 1 mo after diagnosis
4	Enteropathy-type intestinal T-cell lymphoma CD79a+	45/M	Gastric and colonic ulcers	2× CHOP, small bowel obstruction	Died 3 mo after diagnosis
5	Peripheral T-cell lymphoma, unspecified CD20+	38/M	Localized indurated plaque-like cutaneous lesions at jugular fossa	4× CHOP, no response, appearance of additional skin lesions	Alive at 6 mo

CHOP, cyclophosphamide, hydroxydaunomycin, vicristine, and prednisone.

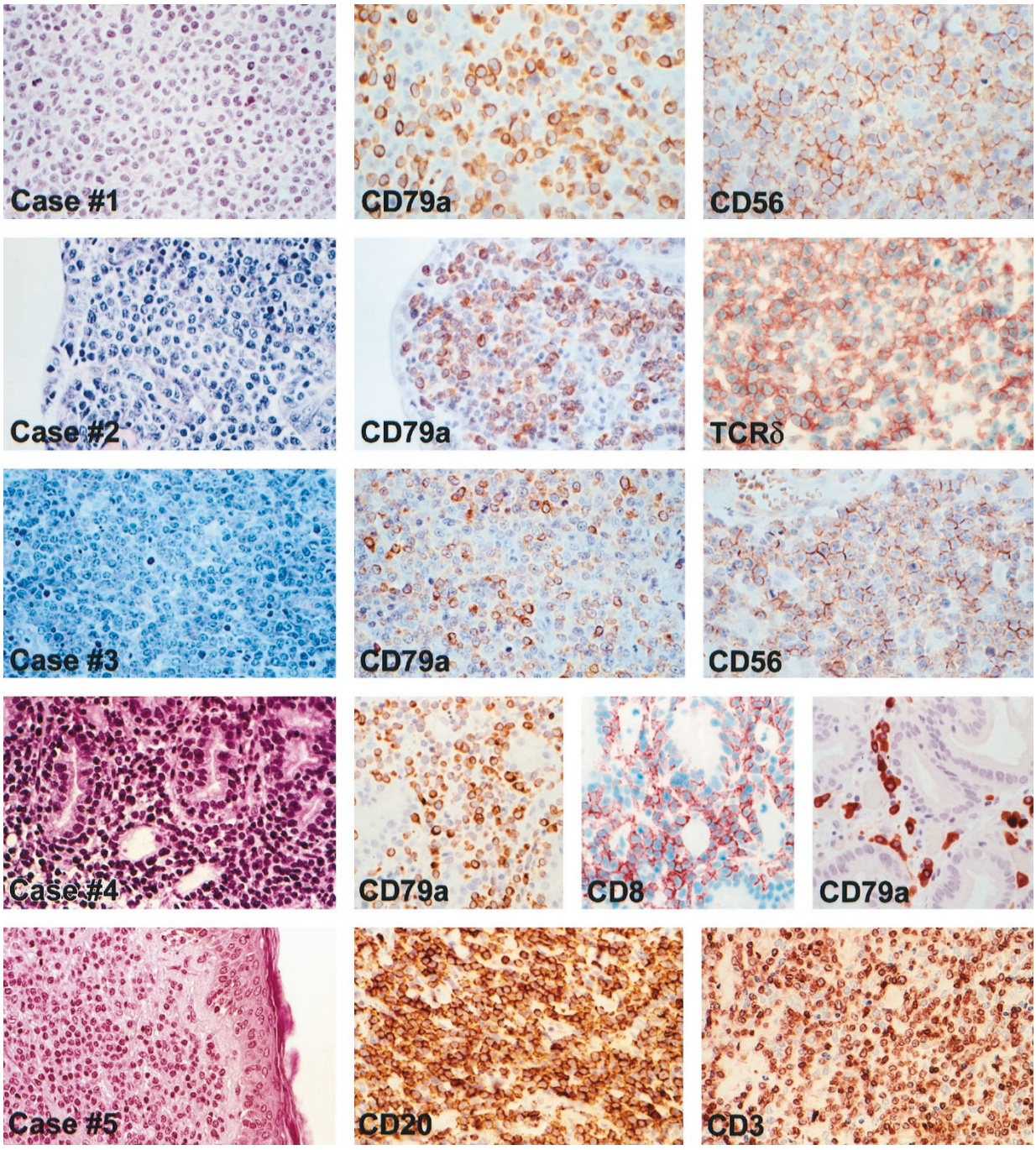

FIGURE 1. Histopathology (***left row***) and immunohistochemistry (images following to the right) of five B-cell marker (CD79a or L26) positive extranodal peripheral T-cell lymphomas (Cases 1 through 5). The CD79a-positive lymphomas are from nose (1), jejunum (2 and 3), and stomach (4). The majority of lymphoma cells show CD79a staining that is slightly weaker than on reactive plasma cells, as shown for Case 4 (***left***). The cutaneous lymphoma (Case 5) stains strongly for L26 (CD20). Hematoxylin and eosin staining in Cases 1, 4, and 5; Giemsa staining in Cases 2 and 3. All images at same magnification.

jacent tissue. The comparative plasma cell labeling, which served as a positive internal control in all cases, is shown in Case 4 (Fig. 1). In two cases (1 and 4), two biopsies each from different sites were available: the tumor cells at the nasal site (Case 1) and in the gastric biopsy (Case 4) stained for CD79a, whereas the lymphomatous tissue at the second site was negative (Table 2). As mentioned above, all four CD79a reactive lymphomas were negative for CD20.

In Case 5 a plaque-like cutaneous infiltrate extending into the deep dermis stained strongly for CD20 but was negative for CD79a. Phenotyping on frozen sections entirely confirmed the results obtained in paraffin sections and, in addition, revealed lack of reactivity to the B-cell–associated antigen CD19 (data not shown). It is interesting that the tumor cells were strongly positive with the monoclonal antibody HECA-452, which detects the cutaneous lymphocyte antigen expressed on nor-

TABLE 3. Paraffin Section Immunohistochemistry, EBER-ISH, and TCRγ/IgH Clonality Analysis of Four CD79a-Positive and One CD20-Positive Extranodal Peripheral T-Cell Lymphomas[a]

Antibody	Case 1		Case 2	Case 3	Case 4		Case 5
	Nose	Skin	Jejunum	Jejunum	Stomach	Ileum	Skin
CD79a	+	−	+	+	+	−	−
L26 (CD20)	−	−	−	−	−	−	+
βF1	+	+	βF1-/TCRδ+[b]	−	−	−	+
CD3ε/cyt.	+	+	+	+	+	+	+
CD2	−	−	−	+	+	+	−
CD5	+	+	−	−	−	−	+
CD7	+	+	+	ND	+	+	±
CD4	−	−	−	−	−	−	−
CD8	−	−	−	+	+	+	−
CD56	+	+	−	+	−	−	−
TIA-1	i+[c]	−	+	+	+	+	±
GB-4	i+	−	+	+	+	+	i+
CD30	−	−	−	−	+	+	−
EMA	−	−	−	−	ND	+	−
HECA-452	−	−	−	ND	−	−	+
MIB 1	70%	70%	80%	90%	ND	65%	15%
EBER-ISH	−	−	−	−	ND	−	−
TCRγ-PCR	+	+	+	+	+	+	+
IgH-PCR	−	−	−	−	−	−	−

ISH, *in situ* hybridization; TCRγ-PCR, T-cell receptor γ-chain gene-polymerase chain reaction; IgH-PCR, immunoglobulin heavy chain gene-polymerase chain reaction.

[a] All cases negative for CD34, TdT, CD1a, CD57, and LMP1.

[b] TCRδ staining on frozen section.

[c] i+, individual tumor cells positive.

mal/reactive cutaneous T cells and on the majority of primary cutaneous T-cell lymphomas (16, 17).

Because CD79a and L26 (CD20) are regarded as excellent markers of neoplastic B-cell proliferations, comprehensive immunophenotypic and genotypic studies were undertaken to evaluate lineage derivation and clonality of the four lymphomas that were positive for CD79a and the lymphoma that was reactive to CD20. Lack of reactivity to CD20 (in the four CD79a-positive cases) and to CD79a and CD19 (in the CD20-positive case) and to antigens expressed in precursor T- and B-cell lymphomas (CD34, TdT, CD1a) but constant expression of CD3 and proteins associated with cytotoxic granules (TIA-1, GB-4) and variable reactivity to T-cell receptor–associated antibodies (βF1 or TCRδ 1) and to T/NK-cell associated antibodies (CD2, CD7, CD56) provided strong immunophenotypic evidence of cytotoxic T- or NK/T-cell derivation. Finally, genotypic studies demonstrated monoclonal rearrangements of the T-cell receptor γ-chain genes (Fig. 2) and lack of monoclonal immunoglobulin heavy chain gene rearrangement (not shown), indicating (in combination with the immunophenotypic findings) that all five cases were indeed cytotoxic peripheral T-cell lymphomas. Bone marrow and peripheral blood samples obtained from the CD20-positive PTL (Case 5) during initial staging and peripheral blood samples at 3 and 6 months after diagnosis did not show evidence of lymphoma dissemination (Fig. 2, right panel).

EBER transcripts were undetectable in all five cases.

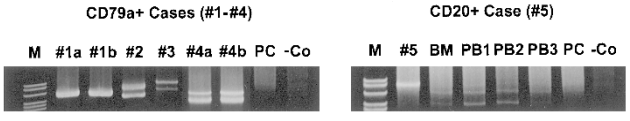

FIGURE 2. T-cell receptor γ-chain gene rearrangement of amplified genomic DNA extracted from paraffin sections of four CD79a+ (Cases 1 through 4) and one L26 (CD20)+ (Case 5) extranodal peripheral T-cell lymphomas. One or two dominant bands indicating clonal mono- or biallelic rearrangements are present in all tumor specimens. Bone marrow (BM) and peripheral blood (PB) samples of Case 5 are negative. PC, polyclonal control; -Co, negative control (no DNA added).

DISCUSSION

The monoclonal antibody CD79a (clone JCB117), which recognizes the mb-1 polypeptide of the B-cell antigen receptor complex, has been introduced as an excellent marker for B-cell neoplasms that are reactive in routinely processed tissue samples. Because all neoplasms of T-cell or nonlymphoid origin have been negative and the antibody reacted with B-cell neoplasms covering the full range of B-cell maturation, it was judged superior to other commercially available B-cell markers, such as those directed against CD20, CD38, CD45RA, CD74, and CDw75 (9). A subsequent report on a large series of lymphoblastic leukemia/lymphoma cases, however, demonstrated coexpression of CD3 and CD79a in approximately 10% of precursor T-cell lymphoblastic leukemia/lymphoma neoplasms (18), and another study found a

high frequency of CD79a expression (clone HM57) in acute promyelocytic leukemia (19).

To the best of our knowledge, no investigation has focused on the reactivity of CD79a in extranodal peripheral T-cell or NK/T-cell lymphomas. The present study was undertaken after the personal observation of a CD79-positive intestinal T-cell lymphoma (Case 3 in this series) and was stimulated additionally by the IX Meeting of the European Association for Hematopathology in Leiden (1998), at which CD79a reactivity had been noted in very few extranodal PTLs. By screening a large series of primary extranodal peripheral T-cell and NK/T-cell lymphomas, comprising the well-defined clinicopathologic entities of enteropathy-type intestinal T-cell lymphoma and nasal NK/T-cell lymphoma, as well as several subtypes of cutaneous lymphomas, four CD79-positive lymphomas that all were CD20 negative were identified: three enteropathy-type intestinal T-cell lymphomas and one nasal NK/T-cell lymphoma. Two of the enteropathy-type intestinal T-cell lymphomas (Cases 2 and 3) microscopically simulated low-grade B-cell lymphoma of MALT type. This observation has important clinical implications as enteropathy-type intestinal T-cell lymphoma is a very aggressive disease (13), whereas low-grade B-cell lymphoma of MALT type usually follows a prolonged indolent course (20). To minimize the risk of misdiagnosis, especially in small endoscopic or surgical biopsies, we suggest the use of both CD79a and CD20 in combination with a panel of antibodies that are reactive to T cells, such as βF1 and CD5, and to T cells and NK cells, such as CD3, CD2, CD56, and TIA-1.

The biology of CD79a reactivity in these non–B-cell lymphomas is not clear. Surface immunoglobulin (Ig) on B cells is noncovalently associated with the CD79 heterodimer comprising mb-1 (CD79a) and B29 (CD79b) transmembrane polypeptide chains, which both are required for the expression of surface Ig (21). Although discordant expression of Ig and CD79a (Ig-negative/CD79a-positive) occurs frequently in mediastinal large B-cell lymphomas and in a minority of follicular lymphomas (22), none of these B-cell receptor components is expressed in normal or neoplastic peripheral T cells (23). Thus, aberrant expression of CD79a seems to be very unlikely, whereas cross-reactivity with unknown epitope(s) represents a plausible explanation. The latter is underscored by the inconstant reactivity of CD79a observed in the two cases from which sequential biopsies were available (Cases 1 and 4): the initial biopsies each showed CD79a staining in the majority of the tumor cells, whereas the second biopsies clearly were negative (Table 2).

To the best of our knowledge, Case 5 of this series represents the first CD20-positive primary cutaneous T-cell lymphoma. The monoclonal antibody L26 recognizes an intracellular epitope of CD20 and has been shown to be a valuable reagent for the diagnosis of B-cell lymphomas in routinely processed tissues (3–8, 24). A few cases of CD20-positive (L26) nodal PTLs, however, have been reported (5, 10, 11). The most recent case study suggested that the CD20-positive nodal PTL evolved from neoplastic transformation of a normal subset of CD20-positive peripheral blood T cells, which argues against aberrant CD20 expression by the neoplastic T cells (11, 25). In contrast, the CD20-positive cutaneous PTL presented herein is probably derived from skin-homing T cells because of the reactivity to cutaneous lymphocyte antigen that is preferentially expressed on normal and neoplastic cutaneous T cells (16, 17). Similar to the two enteropathy-type intestinal T-cell lymphomas discussed above, the CD20-positive cutaneous PTL could easily be mistaken for low-grade B-cell lymphoma. The clinical significance of correct lineage assignment and diagnosis is emphasized again by the more aggressive behavior of the PTL as compared with low-grade cutaneous B-cell lymphomas (26, 27).

In summary, this study revealed mutually exclusive reactivity of the widely used B-cell markers CD79a or L26 in a very small proportion of extranodal cytotoxic PTLs and a case of a nasal NK/T-cell lymphoma. As our series was biased toward certain entities and did not cover the full spectrum of predominantly extranodal malignant T-cell and NK-cell neoplasms, it cannot be excluded that CD79a reactivity might also occur in other non–B-cell lymphomas, such as subcutaneous panniculitis-like T-cell lymphoma, hepatosplenic γ/δ T-cell lymphoma, and blastoid NK-cell lymphoma. To minimize the risk of misinterpretation of lymphoma cell lineage, especially in cases of extranodal lymphoproliferative disease, we suggest the use of both CD79a and L26 in combination with a panel of antibodies that are reactive to T cells, such as βF1 and CD5, and to T cells and NK cells, such as CD3, CD2, CD56, and TIA-1.

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