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Granzyme B Immunoreactivity in T/natural Killer Cell Lymphomas

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Granzyme B is one of the serine proteases expressed in natural killer (NK) cells and activated cytotoxic T-lymphocytes. To evaluate the usefulness of granzyme B immunoreactivity in the diagnosis of T/NK-cell lymphoma, we studied 69 cases of lymphomas occurring in the upper aerodigestive tract by paraffin-section immunohistochemistry using a commercially available monoclonal antibody to granzyme B (GrB-7). All 19 cases of T/NK-cell lymphomas defined by the expression of CD56 (NHK-1) and one or both T-cell markers (polyclonal CD3 and CD45RO) expressed granular cytoplasmic granzyme B immunoreactivity. Two out of 9 cases of T-cell lymphomas showing no CD56 expression demonstrated strong granzyme B immunoreactivity. No tumor cells among 39 cases of B-cell diffuse large cell lymphomas and 2 cases of null cell diffuse large cell lymphomas were immunoreactive for granzyme B, however a few scattered granzyme B-positive reactive small lymphoid cells were consistently observed. Based on its sensitivity in this study as well as its reactivity in routinely processed tissue sections, even without heat-induced epitope retrieval technique, monoclonal antibody to granzyme B (GrB-7) can be applied as a useful marker in the diagnosis of T/NK-cell lymphomas in conjunction with CD56.

Key Words: T/NK-cell lymphomas, granzyme B, immunohistochemistry

Nasal T/NK (natural killer)-cell lymphoma (Chan *et al.* 1994; Jaffe *et al.* 1996) is a newly-proposed diagnostic term for a distinct type of lymphoma which has been previously called lymphomatoid granulomatosis (Liebow *et al.* 1972), polymorphic reticulosis (de Remee *et al.* 1978), midline malignant reticulosis (Kassel *et al.* 1969), and angiocentric immunoproliferative lesion (Jaffe *et al.* 1989). It is a mid-facial-destructive or mass-forming lesion common among Asians and is characterized by angiocentric infiltration of polymorphic atypical lymphoid cells, extensive necrosis, radiosensitivity and high association with Epstein-Barr virus. The cases showing proliferation of many large atypical cells can be easily diagnosed as malignant, however those composed of small to medium sized tumor cells lacking clear cytologic atypia may cause great diagnostic difficulties, especially in small biopsy specimens.

For the verification of the T/NK-cell nature of this tumor, the expression of CD56 has been regarded as the most useful marker (Chan *et al.* 1994; Macon *et al.* 1996) and now its expression can be detected immunohistochemically in routinely processed tissue sections using heat-induced epitope retrieval tech-

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niques (Tsang *et al.* 1996; Tomita *et al.* 1997). Granzyme B is one of the serine proteases identified in the cytoplasmic granules of NK-cells and activated cytotoxic T-lymphocytes (CTLs) (Hameed *et al.* 1988; Krähenbühl *et al.* 1988; Poe *et al.* 1988). Actually, granzyme might be a better marker for T/NK-cell lesions than other conventional NK-cell markers, such as CD16 and CD56, since NK cells may show a loss of surface markers after activation (Tak *et al.* 1994).

In this study we investigated the expression pattern of granzyme B immunoreactivity in 69 cases of lymphomas occurring in the upper aerodigestive tract to evaluate the diagnostic usefulness of this marker in the identification of neoplastic T/NK-cells in routinely processed tissue sections.

MATERIALS AND METHODS

Case selection

Sixty-nine cases of lymphomas of the upper aerodigestive tract biopsied between 1986 and 1995 were retrieved from the surgical pathology files of the Department of Pathology, Yonsei University College of Medicine, Seoul, Korea. Some of the cases were included in the previous study on Epstein Barr virus expression in lymphoproliferative diseases in the sino-nasal region (Tomita *et al.* 1997). All cases were fixed in 10% formalin before conventional tissue processing and paraffin embedded. Hematoxylin-eosin stained sections of 4μm thickness generated from formalin-fixed, paraffin-embedded material were reviewed in each case.

Immunohistochemistry

Paraffin sections were used for immunohistochemical staining with the streptavidin-biotin peroxidase technique (Universal LSAB kit, Dako, Carpinteria, CA, USA). The antibody panel for each case included CD20 (L26, mouse monoclonal, Dako), CD3 (CD3, ε chain, rabbit polyclonal, Dako), CD45RO (UCHL-1, mouse monoclonal, Dako), CD56 (NKH-1, mouse monoclonal, Zymed Laboratories Inc., South San Francisco, CA, USA), granzyme B (GrB-7, mouse monoclonal, Monosan, Uden, Netherlands). Sections were preheated by microwaving (800W) in 0.01M sodium citrate buffer (pH 6.0) for 24 minutes and 12 minutes for immunostaining with CD56 and CD3, respectively. The peroxidase reaction was visualized using DAB chromogen (Zymed Laboratories Inc.). The T/NK-cell nature of the tumor was defined as the presence of NK-cell specific antigen (CD56) and one or both T-cell specific antigens (CD3, CD45RO) on at least 25% of the tumor cell population. Results of immunostaining to CD56 and granzyme B were evaluated semiquantitatively according to the number of tumor cells showing immunoreactivity as follows: −, <25% positive; +, 25 to 50% positive; ++, 51~75% positive; +++, 76 to 100% positive.

RESULTS

The clinical, histopathologic and immunophenotypic findings of the 69 cases are summarized in Table1 & 2. The patients (20 women, 49 men) ranged in age from 2 years to 87 years (mean 50.5 years). Among the 69 cases of lymphomas of the upper aerodigestive tract, 39 were of B-cell lineage (CD20+, CD3-, CD45RO-, CD56-) , 19 were of T/NK-cell lineage (CD56+, CD45RO+, CD3+, CD20-: 11 cases, and CD56+, CD45RO-, CD3+, CD20-: 8 cases), and 9 were of T cell lineage (CD56-, CD45RO+, CD3+, CD20-: 6 cases and CD56-, CD45RO+, CD3-, CD20-: 1 case, and CD56-, CD45RO-, CD3+, CD20-: 2 cases). Two cases composed of a diffuse sheet of large pleomorphic cells did not express any markers. All 39 cases of B-cell lymphomas were diffuse large cell type. The tonsils were the most common site of presentation (34 cases), followed by the nasal cavity and the paranasal sinus (19 cases). Among 34 cases presented in the tonsils, 27 cases (79.4%) were B-cell lymphomas whereas only 10.5% (2/19 cases) of the lymphomas presented in the nasal cavity and paranasal sinuses were B-cell lymphomas.

T/NK-cell lymphomas defined by the expression of CD56 in general showed sheets of variable-sized atypical lymphoid cells in a mixture of inflammatory cells, necrosis and angiocentricity (Fig. 1). Three cases of T/NK-cell lymphomas (case 15, 16, 32) were

Table 1. Clinical findings, pathologic diagnosis and immunophenotypes of the studied cases

Case no.	Surgical no.	Sex	Age	Site	Pathologic Dx.	L26	CD3	UCHL1	CD56	Gran-B
1	87~4692	M	30	Nasal cavity	T/NK cell L	N	P	N	P	P
2	87~8285	M	28	Tonsil	DL, B-cell	P	N	N	N	N
3	87~12066	F	71	Nasal cavity	DL, T-cell	N	P	N	N	P
4	87~14588	M	58	Nasopharynx	DL, B-cell	P	N	N	N	N
5	88~855	F	57	Tonsil	DL, B-cell	P	N	N	N	N
6	88~1491	M	50	Tonsil	DL, B-cell	P	N	N	N	N
7	88~2137	F	50	Tonsil	DL, B-cell	P	N	N	N	N
8	88~4529	M	46	Nasal cavity	T/NK cell L	N	P	N	P	P
9	88~9790	M	67	Pharynx	DL, B-cell	P	N	N	N	N
10	88~10987	F	83	Tongue	DL, B-cell	P	N	N	N	N
11	88~13883	M	58	Tonsil	DL, B-cell	P	N	N	N	N
12	88~14639	F	30	Nasal cavity	T/NK cell L	N	P	P	P	P
13	89~702	M	68	Nasal cavity	T/NK cell L	N	P	N	P	P
14	89~2174	M	45	Nasal cavity	DL, T-cell	N	P	N	N	N
15	89~6313	M	70	Nasal cavity	T/NK cell L	N	P	P	P	P
16	89~6324	M	28	Nasal cavity	T/NK cell L	N	P	N	P	P
17	89~7113	M	12	Nasal cavity	DL, B-cell	P	N	N	N	N
18	89~7186	F	48	Tonsil	DL, B-cell	P	N	N	N	N
19	89~7871	M	65	Tonsil	DL, B-cell	P	N	N	N	N
20	89~7984	M	31	Tonsil	DL, B-cell	P	N	N	N	N
21	89~13555	F	26	Nasopharynx	DL, B-cell	P	N	N	N	N
22	89~13642	M	61	Tonsil	DL, B-cell	P	N	N	N	N
23	89~14259	M	60	Nasopharynx	DL, B-cell	P	N	N	N	N
24	89~14325	F	72	Palate	DL, B-cell	P	N	N	N	N
25	90~1392	M	50	Oral Cavity	DL, B-cell	P	N	N	N	N
26	90~1455	M	66	Nasopharynx	DL, B-cell	P	N	N	N	N
27	90~10308	F	6	Tonsil	DL, B-cell	P	N	N	N	N
28	90~10569	F	63	Tonsil	DL, B-cell	P	N	N	N	N
29	90~13510	F	12	Nasal cavity	T/NK cell L	N	P	P	P	P
30	90~14876	F	49	Tonsil	DL, T-cell	N	N	P	N	N
31	91~32	F	46	Tonsil	DL, B-cell	P	N	N	N	N
32	91~2144	M	56	Nasal cavity	T/NK cell L	N	P	N	P	P
33	91~2150	M	35	Nasal cavity	T/NK cell L	N	P	N	P	P
34	91~7839	M	72	Tonsil	DL, B-cell	P	N	N	N	N
35	91~16307	M	33	Tonsil	DL, B-cell	P	N	N	N	N
36	91~16632	M	66	Nasal cavity	T/NK cell L	N	P	P	P	P
37	92~1099	F	35	Tonsil	DL, null-cell	N	N	N	N	N
38	92~1828	F	63	Tonsil	DL, B-cell	P	N	N	N	N
39	92~6985	M	73	Nasal cavity	T/NK cell L	N	P	N	P	P
40	92~7165	M	76	Tonsil	DL, B-cell	P	N	N	N	N
41	92~11696	M	31	Tonsil	DL, B-cell	P	N	N	N	N
42	92~13580	M	68	Tonsil	DL, B-cell	P	N	N	N	N
43	92~16336	M	60	Tongue	DL, B-cell	P	N	N	N	N
44	92~16364	M	62	Tonsil	DL, B-cell	P	N	N	N	N
45	92~16776	M	60	Nasal cavity	DL, T-cell	N	P	P	N	N
46	92~16870	M	29	Tonsil	DL, B-cell	P	N	N	N	N
47	92~17127	M	62	Nasopharynx	DL, B-cell	P	N	N	N	N
48	93~72	M	57	Nasal cavity	T/NK cell L	N	P	P	P	P
49	93~2587	F	77	Pharynx	DL, T-cell	N	P	P	N	N
50	93~3092	M	29	Pharynx	T/NK cell L	N	P	P	P	P
51	93~3364	F	58	Tonsil	DL, B-cell	P	N	N	N	N
52	93~3549	M	38	Tongue	DL, T-cell	N	P	P	N	N
53	93~4912	M	33	Tonsil	DL, T-cell	N	P	P	N	N

Table 1. Continued

Case no.	Surgical no.	Sex	Age	Site	Pathologic Dx.	L26	CD3	UCHL1	CD56	Gran-B
54	93~7081	F	33	Nasal cavity	T/NK cellL	N	P	P	P	P
55	93~8945	F	47	Nasopharynx	T/NK cell L	N	P	N	P	P
56	93~10459	M	53	Tonsil	DL, B-cell	P	N	N	N	N
57	93~13730	M	29	Tonsil	T/NK cell L	N	P	P	P	P
58	93~17062	M	60	Tonsil	DL, B-cell	P	N	N	N	N
59	93~17460	M	70	Tonsil	DL, B-cell	P	N	N	N	N
60	93~19437	M	64	Tonsil	DL, T-cell	N	P	P	N	P
61	94~3412	M	69	Nasalca vity	T/NK cell L	N	P	P	P	P
62	94~3662	M	41	Pharynx	T/NK cell L	N	P	P	P	P
63	94~12127	M	87	Tonsil	DL, B-cell	P	N	N	N	N
64	94~12252	M	50	Tonsil	DL, B-cell	P	N	N	N	N
65	94~12737	M	49	Tonsil	DL, B-cell	P	N	N	N	N
66	94~15311	M	15	Tonsil	DL, T-cell	N	P	P	N	N
67	94~15787	M	71	Palate	T/NK cell L	N	P	P	P	P
68	94~16882	M	66	Tonsil	DL, null-cell	N	N	N	N	N
69	94~17076	M	2	Paranasal sinus	DL, B-cell	P	N	N	N	N

M: male, F: female, DL: diffuse large cell lymphoma, NK: natural killer, L: lymphoma, Gran-B: granzyme B, P: positive, N: negative

Table 2. Distribution of lymphoma according to the cell type and site

	Nasal cavity (No.)	Nasopharynx (No.)	Paranasal sinus (No.)	Pharynx (No.)	Oral cavity (No.)	Tonsil (No.)	Total No.
DL, B-cell	1	5	1	1	4	27	39
DL, T-cell	3	.	.	1	1	4	9
DL, null-cell	.	.	.	.	.	2	2
T/NK cell L	14	1	.	2	1	1	19
Total No.	18	6	1	4	6	34	69

DL: diffuse large cell lymphoma, NK: natural killer, L: lymphoma

composed of a relatively pure population of large cells and tumor cells were outnumbered by mixed inflammatory cells in 3 cases (case 50, 55, 62), thus showing typical histologic features of polymorphic reticulosis. Nine cases of T-cell lymphomas showed similar histologic findings to T/NK-cell lymphoma. So we could not predict the T/NK-cell phenotype from the morphologic findings alone.

Granzyme B immunoreactive tumor cells showed diffuse granular cytoplasmic staining or paranuclear dot-like immunoreactivity (Fig. 2). Reactive histiocytes or neutrophils around the necrotic areas did not show intracytoplasmic granular immunoreactivity and background staining was not noted even within necrotic areas. Granzyme B immunoreactivity over 25% of the tumor cells was identified in all T/NK-cell lymphomas (19 cases) and 2 of 9 cases of T-cell lymphomas (Table 3). In 17 cases of T/NK-cell lymphoma, the number of granzyme B-positive tumor cells was similar to CD56-positive cells. However, there were 2 cases (case 48, 62) showing some difference in the staining intensity between CD56 and granzyme B (Table 3). We did not find a case of B-cell or null-cell lymphomas showing granzyme B immunoreactive tumor cells, but a few scattered granzyme B-positive reactive small lymphocytes were consistently identified and they usually outnumbered CD56-positive reactive cells (Fig. 3).

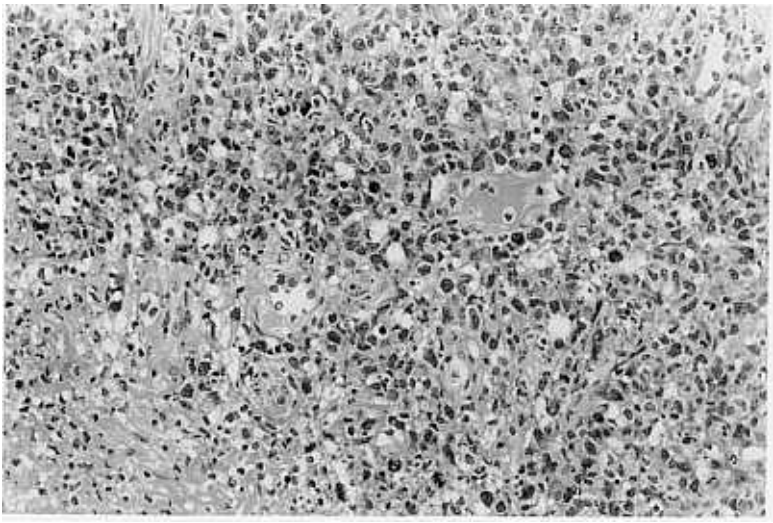

Fig. 1. T/NK-cell lymphoma showing angiocentric proliferation of medium and large atypical lymphoid cells mixed with inflammatory cells and focal necrosis.

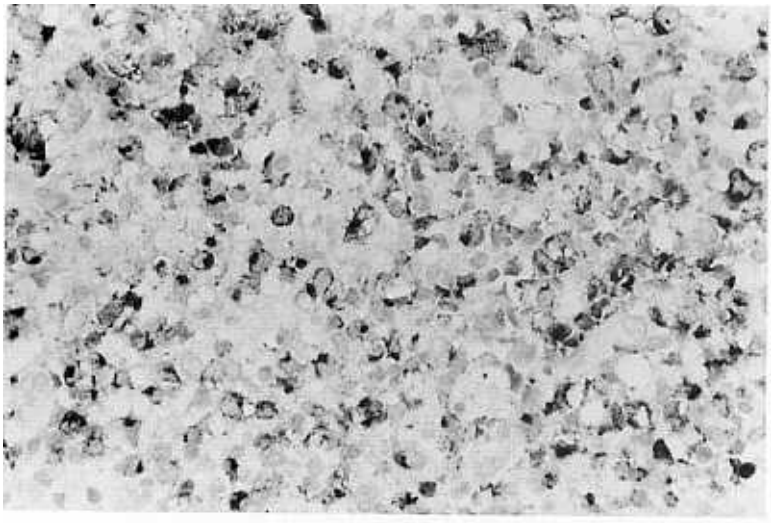

Fig. 2. Immunohistochemical staining for granzyme B in T/NK-cell lymphoma showing intracytoplasmic granular or dot-like paranuclear staining.

DISCUSSION

The results of this study demonstrate that the commercially monoclonal antibody to granzyme B (GrB-7) can be used as a useful marker for the identification of T/NK-cell lymphomas. The recently-proposed term 'nasal T/NK-cell lymphoma' emphasizes the immunophenotype of tumor cells and the predilection site of this tumor and verification of the T/NK-cell nature of the tumor cells by immunophenotyping study is essential for the diagnosis. Monoclonal antibodies to CD56 (Lippman *et al.* 1987;

Table 3. Comparison of granzyme B immunoreactivity with CD56 immunoreactivity

Case number	Biopsied site	Pathologic diagnosis	CD56 immunoreactivity	Granzyme B immunoreactivity
1	Nasal cavity	T/NK cell lymphoma	+++	+++
3	Nasal cavity	Diffuse large, T-cell	−	+++
8	Nasal cavity	T/NK cell lymphoma	++	++
12	Nasal cavity	T/NK cell lymphoma	+++	+++
13	Nasal cavity	T/NK cell lymphoma	+++	+++
15	Nasal cavity	T/NK cell lymphoma	+++	+++
16	Nasal cavity	T/NK cell lymphoma	+++	+++
29	Nasal cavity	T/NK cell lymphoma	+++	+++
32	Nasal cavity	T/NK cell lymphoma	+++	+++
33	Nasal cavity	T/NK cell lymphoma	+++	+++
36	Nasal cavity	T/NK cell lymphoma	+++	+++
39	Nasal cavity	T/NK cell lymphoma	+++	+++
48	Nasal cavity	T/NK cell lymphoma	+++	++
50	Pharynx	T/NK cell lymphoma	++	++
54	Nasal cavity	T/NK cell lymphoma	+++	+++
55	Nasopharynx	T/NK cell lymphoma	+	+
57	Tonsil	T/NK cell lymphoma	+++	+++
60	Tonsil	Diffuse large, T-cell	−	+++
61	Nasal cavity	T/NK cell lymphoma	+++	+++
62	Pharynx	T/NK cell lymphoma	++	+++
67	Palate	T/NK cell lymphoma	+++	+++

−: <25% positive, +: 25 to 50% positive, ++: 51~75% positive, +++: 76 to 100% positive

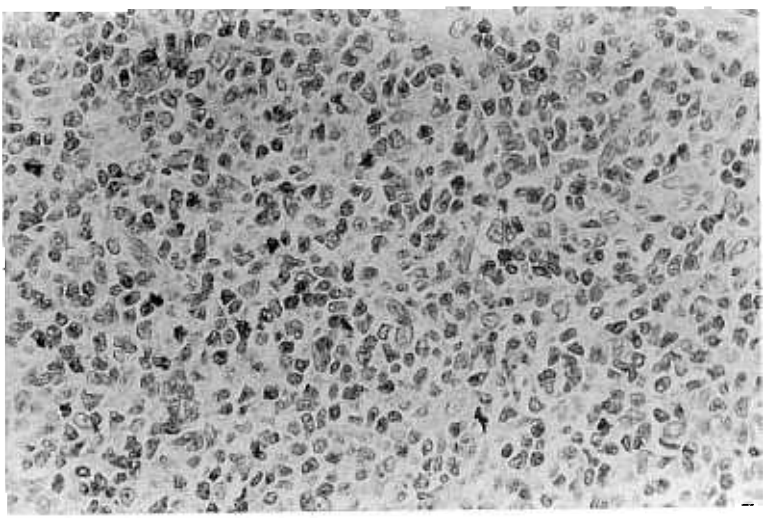

Fig. 3. B-cell diffuse large cell lymphoma showing a few scattered granzyme B-positive small reactive cells.

Ng *et al.* 1987; Chan *et al.* 1993; Kanavaros *et al.* 1993; Tsang *et al.* 1996; Tomita *et al.* 1997) have been mainly used for this purpose in conjunction with some T-cell markers, such as CD2 and polyclonal CD3 (Chan *et al.* 1993; van Gorp *et al.* 1994; Tomita *et al.* 1997). Interestingly it usually does not

show cell surface CD3 expression (Chan *et al.* 1993) and T-cell receptor chain gene rearrangement (Weiss *et al.* 1988; Medeiros *et al.* 1991) while intracytoplasmic CD3 detected by polyclonal CD3 antibody and CD2 are expressed in a high proportion of cases (Chan *et al.* 1993).

CD56 is one of the family of cellular adhesion molecules associated with neural cells (N-CAM) (Schubert *et al.* 1989), which is mainly expressed in NK-cells, neural/neuroendocrine tissues and their corresponding tumors. Although various hematologic and non-hematologic tumors have been reported to be occasionally stained with CD56 (van Camp *et al.* 1990; Jin *et al.* 1991; Mechtersheimer *et al.* 1991; Kern *et al.* 1992), CD56 has been regarded as a useful and sensitive marker for NK-cells. It was initially applied only to fresh, frozen-tissue sections but the recent development of the heat-induced antigen retrieval technique has made it possible to detect CD56 reliably even in routinely processed tissue sections (Tsang *et al.* 1996; Tomita *et al.* 1997). However, CD56 immunostaining using paraffin-embedded tissue sections is not easy and requires meticulous technique.

Granzyme B is one of the serine proteases identified in the cytoplasmic granules of NK-cells and activated CTLs and is considered to be involved in cell-mediated cytolysis with perforin (Hameed *et al.* 1988; Krähenbül *et al.* 1988; Poe *et al.* 1988; Griffiths and Mueller, 1991; Krähenbühl and Tschopp, 1991). NK-cells are the major subset of lymphoid cells expressing granzymes in normal lymphoid tissue (Kummer *et al.* 1995), and the synthesis of both granzyme A and B proteins was reported to be strongly up-regulated in both NK-cells and CTLs after stimulation with IL-2 (Liu *et al.* 1989; Salcedo *et al.* 1993) or autonomously in malignant T-cells (Simon *et al.* 1987). Moreover, a recent report demonstrated that there was a loss of conventional NK-cell markers, such as CD56, after the activation of NK-cells (Tak *et al.* 1994). So granzyme B might be used as a more sensitive marker for the detection of T/NK-cell lesions than CD56. There have been only two studies (de Bruin *et al.* 1994: Ng *et al.* 1996) evaluating the expression of granzyme B in lymphoid neoplasms and their results were similar to those of our study. However, it is difficult to compare the results because they used a different type of antibody (Gr B9) and one study was done on frozen tissue sections. In this study, we compared the intensity of granzyme B and CD56 immunostaining. Most cases showed comparable staining intensity and only 2 cases expressed minor differences. However, 2 cases of T-cell lymphoma without CD56 immunoreactivity showed intense immunostaining to granzyme B. We thought of them as T/NK-cell lymphomas showing no immunoreactivity to CD56 for technical factors, but we could not exclude the possibility that they are peripheral T-cell lymphomas of CTL lineage. So the results of our study indicate that the sensitivity of the commercially available monoclonal antibody to granzyme B (GrB-7) we used is at least as sensitive as monoclonal antibody to CD56 for the detection of T/NK-cell neoplasms. Considering that monoclonal antibody to granzyme B (GrB-7) can be used in paraffin-embedded tissue sections without heat-induced antigen retrieval technique, it seems to be a better marker for the diagnosis of T/NK-cell lymphomas. Two recent studies on perforin and TIA-1 expression in lymphoid neoplasms also addressed the idea that these cytotoxic granule-associated proteins were excellent markers for the detection of T/NK-cell neoplasms as granzyme B (Mori *et al.* 1996; Felgar *et al.* 1997).

All B-cell and null-cell lymphomas showed a few scattered granzyme B-positive small lymphocytes and they outnumbered CD56-positive small lymphoid cells. A rare granzyme B-or CD56-positive reactive small lymphoid cells are present in various lymphoid organs and most of them are NK-cells (Kummer *et al.* 1995). However in some reactive lesions, such as infectious mononucleosis and subacute necrotizing lympadenitis, fairly large numbers of NK-cells or CTLs could be observed (Oudejans *et al.* 1996; Takakuwa *et al.* 1996). Some of the monoclonal antibodies to granzyme, such as Gr B9 used in the study by de Bruin *et al.* (1994), might show cross-reactivity with neutrophils (Kummer *et al.*, 1995) and granzyme B transcripts were detected in mast cells and macrophage cell lines (Brunet *et al.* 1987). So in this study we interpreted cases as granzyme B or CD56 immunoreactive only when more than 25% of the tumor cells demonstrated immunoreactivity. However, both markers demonstrated clear immunostaining and neither reactive inflammatory cells nor necrotic foci showed any immunore-

activity. Therefore, we believe that the diffuse expression of granzyme B in lymphoproliferative lesions strongly supports the diagnosis of T/NK-cell lymphomas as the strong expression of CD56 and EBER1 (Tsang *et al.* 1996) and could be used as a supportive diagnostic criteria of malignancy in lesions lacking clear cytologic atypia.

In conclusion, granzyme B immunoreactivity can be used as a useful diagnostic marker for the identification of neoplastic T/NK cells in paraffin embedded tissue sections together with CD56.

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