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Immunohistological study of skin involvement in Kikuchi's disease

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Summary. Five patients with histiocytic necrotizing lymphadenitis (Kikuchi's disease) with erythematus or popular skin lesions were studied. All patients healed naturally within a few months like the patients with no skin involvement. Histological findings for the skin lesions mimicked cutaneous malignant lymphoma. The infiltrated mononuclear cells usually demonstrated positive reactions for Ki-M1p (20–63%), lysozymes (13–54%), MT-1 (18–64%), UCHL-1 (22–39%) and LN2 (17–36%). OPD-4 and L26 positive cells were few in number. These results suggest that the infiltrated cells in a Kikuchi's disease skin lesion are composed of the same components as the affected lesion in the lymph node.

Key words: Histiocytic necrotizing lymphadenitis – Kikuchi's disease – Skin involvement – Plasmacytoid monocyte

Introduction

Histiocytic necrotizing lymphadenitis (HNL) is a relatively common reactive lesion of the lymph nodes in Japan and is readily mistaken for malignant lymphoma. The disease was first reported in 1972 as lymphadenitis with focal proliferation of reticular cells accompanying much nuclear debris and numerous histiocytes (Kikuchi 1972). Since then many cases have been reported in Japan (Fujimoto et al. 1972; Kikuchi et al. 1977, 1984, 1990; Fujimori et al. 1981). Recently, reports of the same lesion have appeared in Europe, the United States, and Asia (Ali and Horton 1985; Chamulak et al. 1990; Pileri et al. 1982; Chan and Saw 1983; Turner et al. 1983). Patients with cutaneous involvement have been observed occasionally and the cutaneous lesion alone was difficult to differentiate from cutaneous lymphoma upon histological diagnosis. Kuo (1990) has described clinical and histological findings in the cutaneous from of Kikuchi's disease. In this study, we describe more detailed clinical and immunohistological results, using the monoclonal antibodies of five patients with cutaneous Kikuchi's disease and we summarize the clinical and laboratory findings with and without cutaneous involvement.

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Materials and methods

Five patients with Kikuchi's disease including skin involvement were selected from the records of the Department of Pathology, Fukuoka University, Japan. Skin and lymph node specimens were removed and fixed in formalin or B-5 solution, embedded in paraffin, and stained with hematoxylin-eosin, periodic acid-Schiff, silver

Table 1. Specificities of monoclonal antibodies used in the present study

Antibody	Antigen recognized: distribution	Source
OPD-4	CD4: helper/inducer T cell	Dakopatts
MT-1	CD43: T cell, monocyte, granulocyte, macrophage	Biotest Seralc
UCHL-1	CD45RO: T cell, myeloid cell, macrophage	Dakopatts
Kp-1	CD68: histiocyte, macrophage	Dakopatts
LN2	CD74: anti-HLA-DR	Biotest Seralc
Lysozyme	Macrophage, granulocyte	Dakopatts
Ki-M1p[a]	Plasmacytoid monocyte, macrophage, histiocyte	Kiel University
L26	CD20: pan B cell	Dakopatts

[a] Ki-M1p was provided by Prof. M.R. Parwaresch, Department of Pathology, Kiel University

Table 2. Clinical findings in Kikuchi's disease

Case	Age (years)	Sex	Fever (°C)	Skin rash		Lymphadenopathy	Course
				Pattern	Distribution		
1	15	M	40	Papule single	Head	Neck	Healed
2	19	F	40	Erythema generalized	General	Generalized	Healed
3	20	M	40	Erythema generalized	Face, extremities	Neck, inguinal	Healed
4	26	M	40	Erythema multiple	Face	Neck, inguinal	Healed
5	29	M	39	Erythema generalized	Face, neck, chest	Generalized	Healed

Table 3. Labolatory data of Kikuchi's disease

Case	WBC (mm^3)	LDH elevated	GOT elevated	GPT elevated	ESR (mm)	Elevation of serum titer
1	5600	+	+	+	ND	No
2	ND	ND	ND	ND	ND	No
3	6800	+	−	−	7	EBNA
4	3000	+	+	−	54	No
5	2300	+	+	+	ND	EBVCA-IgG, Toxoplasma-IgG

ND: not done. LDH: lactic dehydrogenase. GOT: glutamic oxaloacetic transaminase. *GPT:* glutamic pyruvic transaminase. ESR: erythrocyte sedimentation rate. *EBNA:* Epstein-Barr nuclear antigen. EBVCA: Epstein-Barr viral capsid antigen

impregnation for reticulin fibers, and naphthol AS-dichloracetate esterase for neutrophils. In addition, immunohistological staining (as shown in Table 1) was performed, using the alkaline phosphatase-conjugated avidin-biotin complex method (Nanba et al. 1987). To examine the positive cells for antibodies, slides were photographed and developed into enlarged color prints. The distribution density of immunoreactive cells was measured by manual counting in the photographs. The number of positive cells per 100 cells counted was recorded in three fields for each case. We also compared clinical and laboratory data of patients with skin involvement to those without skin involvement.

Results

Clinical and laboratory data

Table 2 summarizes the main clinical findings for the five patients examined (one female and four males, ranging in age from 15 to 29 years, mean of 21.8 years). Two patients demonstrated general lymphadenopathy, and three had swelling of the neck lymph nodes; one of the latter also showed inguinal lymphadenopathy. Four of the five patients had erythema resembling a drug-induced eruption on the face; three of them showed an extensive distribution on the body surface. One patient (case 1) was different from the others; an elevated papule with a slightly reddish smooth surface on its head was diagnosed as lymphocytoma cutis macroscopically. Fever over 39° C was found in all five patients; the fever was gone within a few months in all cases. Table 3 summarizes the main laboratory findings. Elevation of LDH was seen in all four patients, GOT elevation in three of four, and GPT elevation in two of four. Leukocytopenia under 4000/mm^3 was present in two of four patients. We compared laboratory findings of 246 Kikuchi's disease patients with and without skin rashes (summarized in Table 4). High fever over 39° C and elevation of LDH, GOT, and GPT were common in the group with skin rashes.

Table 4. Clinical and Raboratory findings of Kikuchi's disease

	Skin involvement	No skin involvement
No. of cases	48	198
Age (mean) (yr.o.)	6–53 (22)	3–60 (27)
Male/female	1.3	1.5
Tender	36/48 (75%)	120/198 (61%)
* Fever elevation (> 39° C)	20/48 (42%)	34/198 (17%)
WBC > 10000/mL	2/46 (4%)	0/124 (0%)
WBC < 4000/mL	31/46 (67%)	67/124 (54%)
Atypical Lyn. (%)	11/46 (24%)	24/124 (19%)
* Elevation of GOT	17/48 (35%)	13/198 (7%)
* Elevation of GPT	14/48 (29%)	13/198 (7%)
* Elevation of LDH	32/48 (67%)	48/198 (24%)
* ESR > 10 mm	32/39 (82%)	60/95 (63%)
Positive for CRP	19/42 (45%)	34/105 (32%)

Histopathology and immunohistochemistry

Skin biopsy specimens showed patchy infiltrates of mononuclear cells around the vessels in the superficial and middermis in all cases (Fig. 1 A). The infiltrated cells were composed of large or medium-sized lymphoid cells with indented or oval nuclei, fine chromatin and indistinct nucleoli, foamy histiocytes, and some necrobiotic cells (Fig. 1 B). Histiocytes with nuclear debris in the

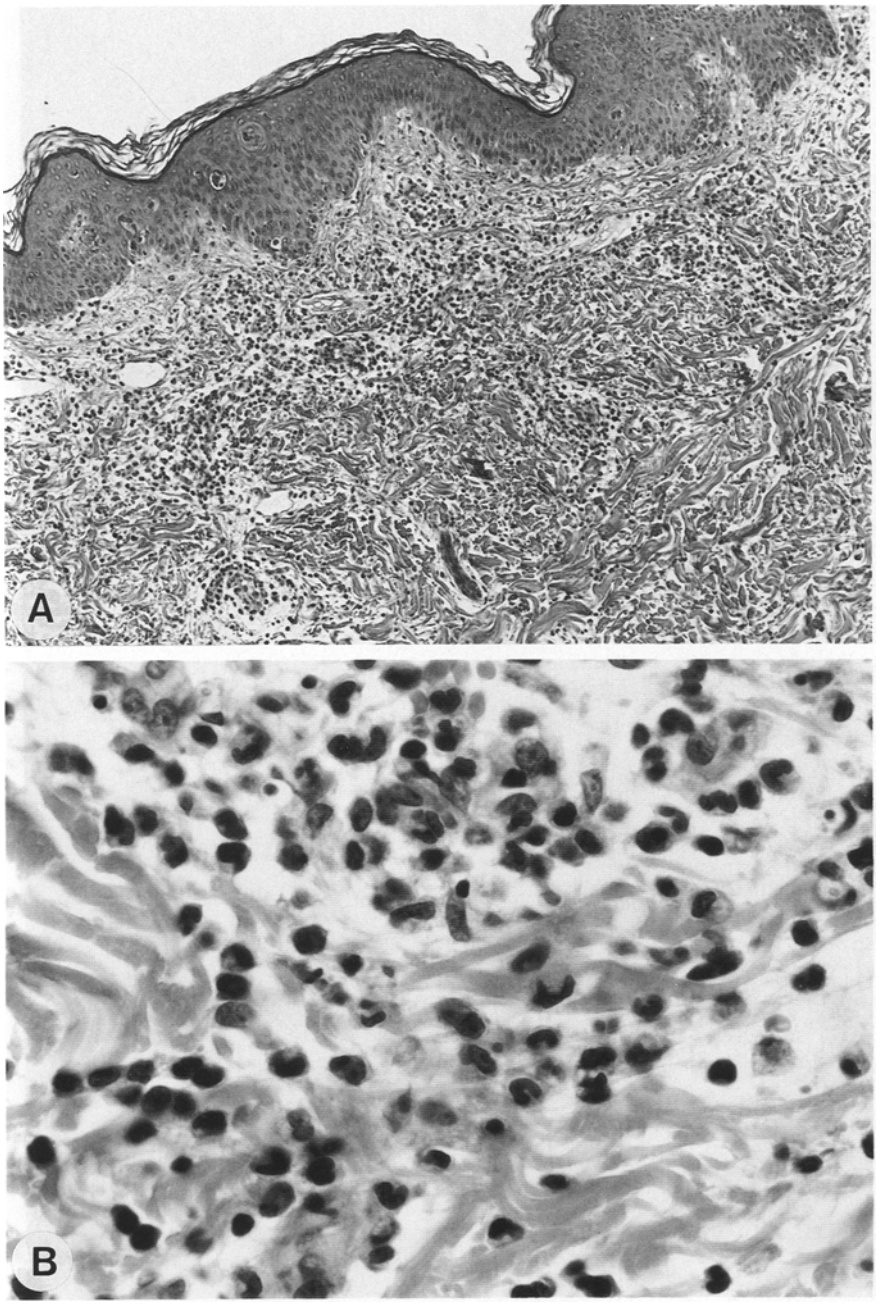

Fig. 1 A. Low magnification of skin biopsy specimen (case 2) shows patchy cellular infiltrates in the dermis. H&E, ×40. **B** High magnification of A shows many mononuclear cells with oval or irregular nuclei. Some contain phagocytic materials within their cytoplasm

Table 5. Results of Immunohistological studies

Case	Marker (%)[a]							
	UCHL-1	MT-1	OPD-4	Kp-1	Lysozyme	Ki-M1p	LN2	L26
1	31	42	17	23	13	20	36	28
2	37	33[b]	8	ND	22	47	17	1
3	39	ND	10	34	35	46	31	1
4	23	18[b]	1[b]	ND	ND	23	28	1
5	22	64	2	ND	54	63	18	6

[a] Positive rate (%) = number of positive cells/100 cells
ND = not done
[b] Inadequate for immunostaining

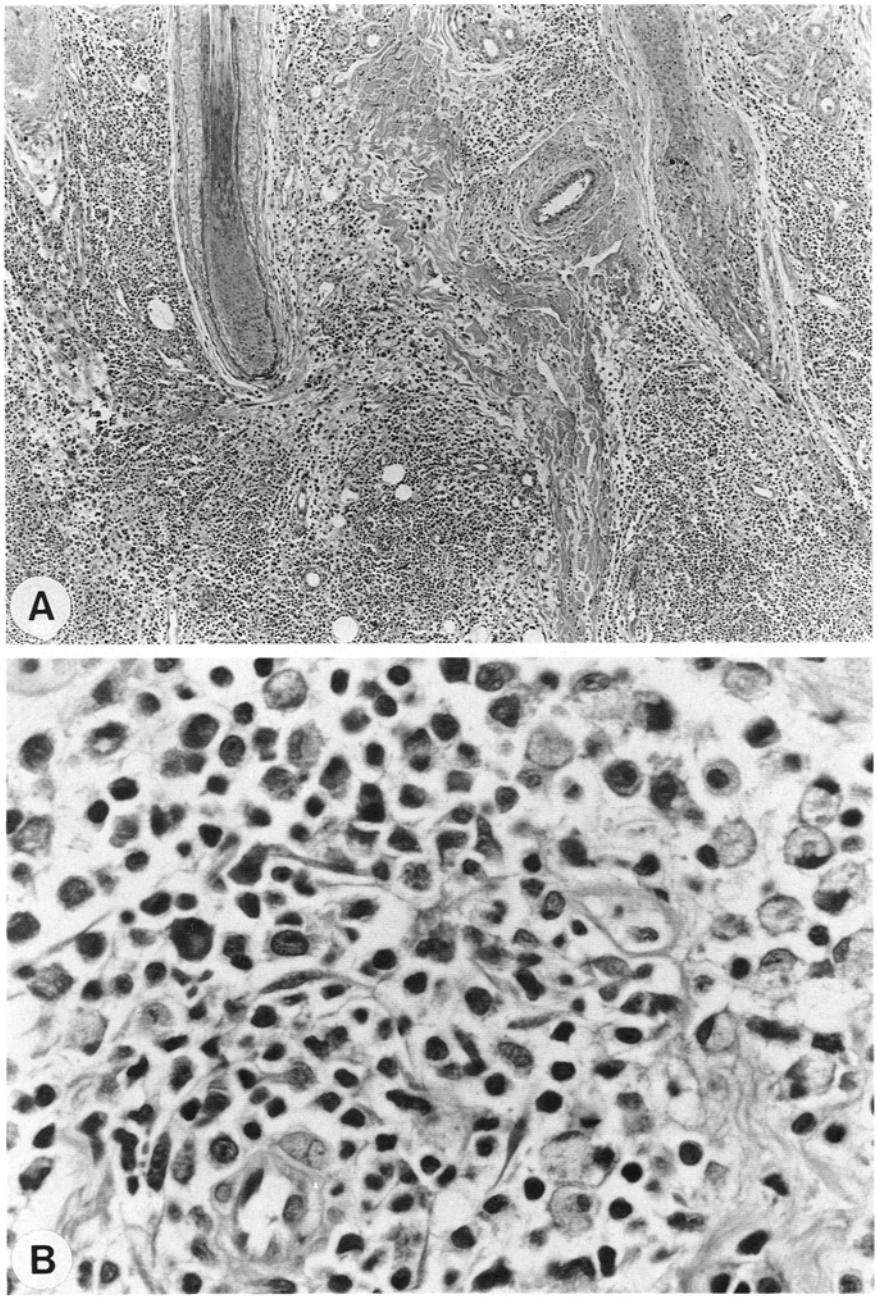

Fig. 2A. Low magnification. Numerous monocytoid cells diffuse infiltrate in the dermis. H&E, ×40. **B** High magnification of **B** shows a proliferation of numerous monocytoid cells with oval nuclei and some foamy histiocytes. H&E, ×350

cytoplasm were scattered, but no hemophagocytosis was observed. Mitotic features were few in number in these sections. Table 5 summarizes immunohistochemical findings for the skin lesions. In three of five cases, over 40% of the cells were positive for ki-M1p (Fig. 3A) which was a higher rate than that of lysozyme- (Fig. 3B) and Kp-1-positive cells. Histologically, the Ki-M1p-positive cells were composed mainly of large round or oval cells with slightly irregular or oval nuclei and abundant pale cytoplasm and medium-sized cells with oval or indented nuclei, fine chromatin, and scanty cytoplasm. UCHL-1 (Fig. 3D) positive cells comprised about 30% of the infiltrated cells, and were mainly small lymphocytes. MT-1 (Fig. 3C) positivity was higher than that of UCHL-1 in good stained specimens and the MT-1-positive cells were small nuclear lymphocytes as well as medium-sized or large lymphocytes with oval nuclei. Some of the MT-1-positive cells were positive for OPD-4, but these had small nuclei. L26 (pan B-cell marker) positive cells were few in number. A few medium-sized to large lymphoid cells were positive for LN-2 in the cytoplasm. Case 1 was again different: A papule on the head showed infiltration of small lymphoid cells with oval nuclei and monocytoid cell with abundant cytoplasm and indented nuclei (Fig. 2A, B); these infiltrated cells included many of UCHL-1-, MT-1-positive T-cells and L26-positive B-cells. Ki-M1p-positive cells were fewer than in the other patients.

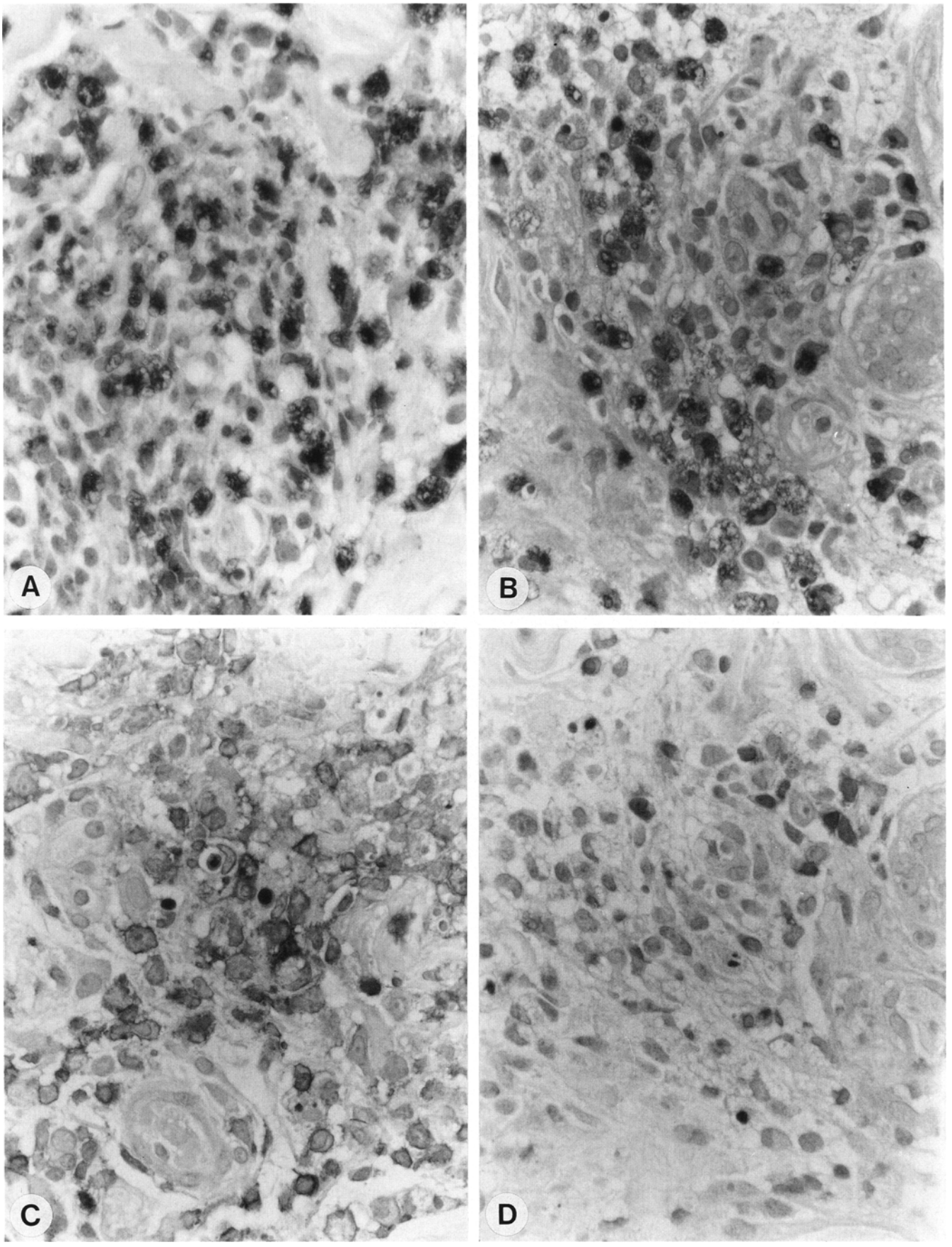

Fig. 3A. Most infiltrated cells are positive for Ki-M1p and these positive cells have abundant cytoplasm, but Ki-M1p-positive medium-sized cells with oval nuclei and scanty cytoplasm are also found. Ki-M1p, ×350. **B** Numerous lysozyme-positive cells are recognized. These cells have oval or mild irregular nuclei and abundant cytoplasm. Lysozyme, ×350. **C** Large to medium-sized cells with oval nuclei are positive for MT-1. MT-1, ×350. **D** UCHL-1-positive cells are fewer than MT-1-positive cells and most have smaller nuclei than those of MT-1-positive cells. UCHL-1, ×350

Discussion

Kikuchi's disease (HNL) was first reported in 1972 by Kikuchi as a lymphadenitis with focal proliferation of reticular cells accompanied by nuclear debris and numerous phagocytes. Fujimoto et al. (1972) reported the same findings independently shortly after. The characteristic clinical findings are localized lymphadenopathy on the neck, leukopenia, fever, skin rash, and natural healing within several months (Kikuchi et al. 1990). The disease primarily affects young adult women. Protozoa or microorganisms such as Toxoplasma gondii (Kikuchi 1978), Epstein-Barr virus (Takada et al. 1980), Ersinia enterocolitica (Feller et al. 1983), or human herpesvirus-6 (HHV-6) (Eizuru et al. 1989) were suspected as causative agents. Suspicion of viral infection was intensified by; elevated serum concentrations of 2′-5′-oligoadenylate acetate synthetase in the early stage (Kikuchi et al. 1990, Sumiyoshi et al. 1991a); tubuloreticular structures in lymphocytes, histiocytes, and vascular endothelial cells (Imamura et al. 1982; Eimoto et al. 1983); and numerous interferon-alpha-possessing cells in the affected areas (Sumiyoshi et al. 1991b). Histologically, the lesion shows a focal infiltration of transformed lymphocytes and histiocytes with nuclear debris. Necrotic changes were also emphasized in some cases. Little or no infiltration of plasma cells and neutrophils was noted (Kikuchi et al. 1986; Turner et al. 1983). Recently, Facchetti et al. (1989) and Chamulak et al. (1990) have reported another type of cell, plasmacytoid monocytes, found in varying numbers in cases of HNL.

Immunohistologically, the plasmacytoid monocytes were positive for MT-1 (CD43), Kp-1 (CD68), CD4, LN1 (CD75w), LN2 (CD74), Ki-M6, Ki-M7, HLA-DR, and Mac387, and negative for CD2, CD3, CD5, CD8, lysozyme, alpha-1-ACT, and UCHL-1 (Facchetti et al. 1988, 1989; Hornny et al. 1989; Lennert and Remmele 1958; Müller-Hermelink et al. 1973; Brado and Müller 1990). Plasmacytoid monocytes have been recognized in other forms of lymphadenitis (Facchetti et al. 1988), non-Hodgkin's lymphoma (Müller-Hermelink et al. 1983), and Hodgkins disease (Facchetti et al. in press). Additionally, plasmacytoid monocytes have been recognized in lymphoid hyperplasia of the skin (Eckert and Schmid 1989) and in Jessner's lymphocytic infiltration of the skin (Facchetti et al. 1990a).

In Kikuchi's disease, 30% of the cases demonstrated skin rashes (Kikuchi et al. 1990), and sometimes differentiation from skin invasion of malignant lymphoma was difficult on histology (Kuo 1990). Kuo (1990) reported one case of HNL diagnosed as a diffuse, large-cell-type malignant lymphoma by skin biopsy. In his report the infiltrated cells were mainly positive for lysozyme and Kp-1. Facchetti et al. (1990b) reported that the plasmacytoid monocyte infiltrates occurred in the skin lesion similarly to the affected foci of the lymph nodes in Kikuchi's disease. Our immunohistological study revealed that the infiltrated cells comprised mainly lysozyme- and Kp-1-positive histiocytes and transformed T cells. There were some medium-sized cells positive for Ki-M1p and MT-1 in these infiltrated cells but we did not corroborate the findings of Facchetti et al. (1990b) because the foci of plasmacytoid monocytes were not found also and LN2-positive cells were few in number. According to Kuo's (1990) report, the patient with HNL had involvement of extranodal sites, and progress of clinical signs was more severe than in patients without extranodal sites such as a fatal case of multicentric Kikuchi's HNL reported by Chan et al. (1989). All our patients recovered with no recurrence despite high fever, elevated LDH, and frequent elevation of GOT, as well as generalized lymphadenopathy. We compared clinical and laboratory findings in Kikuchi's disease patients with and without skin rashes in 246 cases from our records from 1978 to 1991 (Table 4). Kikuchi's disease patients with skin manifestations demonstrated a higher rate of high fever (over 39° C), and a greater elevation of GOT, GPT, ESR, and LDH. In our study the patient who had skin rashes had more severe clinical features. Kikuchi's disease usually affects the lymph nodes but in some patients the same lesions occur in the skin (rashes or erythema). On histology, the lesions resembled malignant lymphoma, but the cell components were different. Clinical and laboratory findings that suggest an inflammatory process are very important for differentiation from malignant lymphoma.

References

Ali MH, Horton LWL (1985) Necrotizing lymphadenitis without gralocytic infiltration (Kikuchi's disease). J Clin Pathol 38:1252–1257

Brado B, Müller P (1990) The plasmacytoid T cell or plasmacytoid monocyte – a sessile lymphoid cell with unique immunophenotype and unknown function, still awaiting lineage affiliation. In: Reaction Patterns of the Lymph Node. Springer, Berlin Heidelberg New York Tokyo, pp 179–192

Chamulak GA, Brynes RK, Nathwani BN (1990) Kikuchi-Fujimoto disease mimicking malignant lymphoma. Am J Surg Pathol 14:514–523

Chan JKC, Saw D (1983) Histiocytic necrotizing lymphadenitis (Kikuchi's disease). A clinicopathologic study of 9 cases. Pathology 18:22–28

Chan JKC, Wong K-C, Ng C-S (1989) A fatal case of multicentric Kikuchi's histiocytic necrotizing lymphadenitis. Cancer 63:1856–1862

Eckert F, Schmid U (1989) Identification of plasmacytoid T cells in lymphoid hyperplasia of the skin. Arch Dermatol 125:1518–1524

Eimoto T, Kikuchi M, Mitui T (1983) Histiocytic necrotizing lymphadenitis. An ultrastructural study in comparison with other types of lymphadenitis. Acta Pathol Jpn 22:863–879

Eizuru Y, Minematu T, Minamishima Y, Kikuchi M, Yamanishi K, Takahashi M, Kurata T (1989) Human herpesvirus 6 in lymph node. Lancet 1:40

Facchetti F, De Wolf-Peeters C, van den Oord JJ, Desmet VJ (1988) Plasmacytoid T-cells: A cell population normally present in the reactive lymph node: An immunohistological and electron-microscopic study. Human Pathol 19:1085–1092

Facchetti F, De Wolf-Peeters C, van den Oord JJ, De Vos R, Desmet VJ (1989) Plasmacytoid monocytes (so-called plasmacytoid T-cells) in Kikuchi's lymphadenitis. Am J Clin Pathol 92:42–50

Facchetti F, Boden G, De Wolf-Peeters C, Vandaele R, Degreef H, Desmet VJ (1990a) Plasmacytoid monocytes in Jessner's lymphocytic infiltration of the skin. Am J Dermatopathol 12:363–369

Facchetti F, Marocolo D, Morassi ML, Villanacci V, Grigolato PG (1990b) Cutaneous Kikuchi's Disease. Am J Surg Pathol 14:514–523

Facchetti F, De Wolf-Peeters C, van den Oord JJ, De Vos R, Desmet VJ (in press) Plasmacytoid monocytes (so called plasmacytoid T-cells) in Hodgkin's disease

Feller AC, Lennert K, Stein H, Bruhn HD, Wuthe HH (1983) Immunohistology and etiology of histiocytic necrotizing lymphadenitis: Report of three instructive cases. Histopathology 7:825–839

Fujimoto Y, Kojima Y, Yamaguti K (1972) Cervical subacute necrotizing lympadenitis. Naika 30:920–927 (in Japanese)

Fujimori F, Shioda K, Sussman EB, Miura M, Katayama I (1981) Subacute necrotizing lymphadenitis. A clinicopathologic study. Acta Pathol Jpn 31:791–797

Hornny HP, Feller AC, Horst HA, Lennert K (1989) Immunohistology of plasmacytoid T cells: Marker analysis indicates a unique phenotype of this enigmatic cells. Human Pathol 92:42–50

Imamura M, Ueno H, Masuura A, Kamiyama H, Suzuki T, Kikuchi K, Onoe T (1982) An ultrastructural study of subacute necrotizing lymphadenitis. Am J Pathol 107:292–299

Kikuchi M (1972) Lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytes: A clinicopathological study. Acta Haematol Jpn 35:379–380

Kikuchi M, Yoshizumi M, Nakamura H (1977) Necrotizing lymphadenitis: Possible acute toxoplasmic infection. Virchows Arch [A] 376:247–253

Kikuchi M (1978) Lymphadenopathy due to toxoplasmic infection and anticonvulsant. Recent Adv RES Res 18:97–124

Kikuchi M, Takeshita M, Tashiro K, Mitui T, Eimoto T, Okamura S (1986) Immunohistological study of histiocytic necrotizing lymphadenitis. Virchow Arch [A] 409:299–311

Kikuchi M, Takeshita M, Eimoto T, Iwasaki H, Minamishima Y, Maeda Y (1990) Histiocytic necrotizing lymphadenitis: Clinicopathologic, immunologic, and HLA typing study. In: Hanaoka M, Kadin ME, Mikata A. Cytogenetics (eds). Field and wood. New York, pp 251–257

Kuo T (1990) Cutane manifestation of Kikuchi's histiocytic necrotizing lymphadenitis. Am J Surg Pathol 14:872–876

Lennert K, Remmele W (1958) Untersuchungen an lymphoblaten und lymphzyten. Acta Haematol (Basel) 19:99–113

Müller-Hermelink HK, Kaizerling E, Lennert K (1973) Pseudofollikulare nester von plasmazellen (eines besonderen type) in der paracortikulalen pulpa menschlicher Lymphknoten. Virchows Arch [B] 14:47–56

Müller-Hermelink HK, Steinman G, Stein H, Lennert K (1983) Malignant lymphoma of plasmacytoid T-cells: Morphologic and immunologic studies characterizing a special type of T-cell. Am J Surg Pathol 7:849–862

Nanba K, Aoki J, Sasaki N (1987) A new enzyme immunohistochemical technique using alkaline phosphatase-labeled avidin and new fuchsin. Pathol Clin Med 5:333–339

Pileri S, Kikuchi M, Helbron K, Lennert K (1982) Histiocytic necrotizing lymphadenitis without granulocytic infiltration. Virchows Arch [A] 395:257–271

Sumiyoshi Y, Kikuchi M, Ohshima K, Takeshita M, Masuda Y (1991a) 2′–5′ oligoadenylate synthetase in histiocytic necrotizing lymphadenitis. Igaku Aumi 157:607–608 (in Japanese)

Sumiyoshi Y, Kikuchi M, Ohshima K, Takeshita M, Masuda Y (1991b) Interferon alpha in Kikuchi's disease. Virchows Arch [B] 61:201–207

Takada K, Iwanaga M, Toyono O, Mikuni C, Maekawa I, Kawamura T, Miyake T (1980) Elevated antibody titers to Epstein-Barr virus in subacute necrotizing lymphadenitis. Igaku Ayumi 112:194–196 (in Japanese)

Turner RR, Martin J, Dorfman RF (1983) Necrotizing lymphadenitis: A study of 30 cases. Am J Surg Pathol 7:115–123