Virchows Archiv A Pathol Anat (1991) 418:215–223

Virchows Archiv A
Pathological Anatomy and Histopathology

Necrotizing lymphadenitis: a clinicopathological and immunohistochemical study of four familial cases and five recurrent cases

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Received May 25, 1990 / Accepted October 2, 1990

Summary. We report the clinicopathological and immunohistological findings of nine cases of necrotizing lymphadenitis, consisting of four cases of familial infection and five cases of recurrence. Fever, cervical lymphadenopathy, leucopenia and swelling of the tonsils are characteristic clinical findings. Morphological features of the lymph nodes include the presence of immunoblasts, plasmacytoid T cells, histiocytes and macrophages, the latter with phagocytized nuclear debris derived from degenerated lymphocytes. However, granulocytes are generally absent. Ultrastructurally, tubuloreticular structures are observed not only in lymphoid cells, but in vascular endothelial cells. Immunological studies of peripheral blood using monoclonal antibodies disclose that CD 8^+ (Leu $2a^+$: suppressor/cytotoxic) cells predominate at the onset, but they gradually decrease with the clinical course and the ratio of CD 4^+:CD 8^+ (helper:suppressor) increases as the disease progresses. However, in the affected lymph nodes, CD 4^+ (Leu $2a^+$: helper/inducer) cells often increase with the clinical progression, but the ratio of CD 4^+:CD 8^+ in the lymph nodes does not correlate with clinical progression. In addition, Ki-67^+CD 8^+ cells are more often seen than Ki-67^+CD 4^+ cells. It is suggested that necrotizing lymphadenitis is an infectious disease in which CD 4^+ cells are disrupted and CD 8^+ cells undergo transformation to blastoid cells. This results in a change in the ratio of T subsets.

Key words: Necrotizing lymphadenitis – Recurrence – Immunohistochemistry – T subset

Introduction

Necrotizing lymphadenitis (NEL) is a disease entity which was originally described in Japan in the early 1970s (Fujimoto et al. 1972; Kikuchi et al. 1972; Wakasa et al. 1973). Although it is assumed to be an infectious disease, there have been few reports describing familial occurrence or the recurrence in the same case. Recently, we experienced nine cases of NEL comprising four cases of familial infection and five with recurrence and have examined these cases electron microscopically and immunohistologically.

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Materials and methods

Four cases showed familial occurrence and five cases were recurrent (Tables 1, 2).

The tissue samples were divided into three, one part being fixed in 10% formalin for routine diagnosis, the second in 4% periodate-lysine-paraformaldehyde (PLP) for immunohistochemical analysis, and the third in 2.5% glutaraldehyde for conventional electron microscopy. For light microscopy, paraffin-embedded serial sections were cut (2 μm) and stained with haematoxylin and eosin (H & E), Giemsa, periodic acid-Schiff (PAS), methyl green-pyronin, silver impregnation and elastica-Masson. PLP-fixed tissue (cases 1, 2 and 5) were snap-frozen in OCT compound (Miles, Elkhart Ind.) and stored at −80° C until use for immunohistochemistry. Fresh frozen tissue sections were cut (4 μm) on a cryostat and air-dried for 30 min.

Immunohistochemistry was performed on paraffin and frozen sections with use of the avidin biotin-peroxidase complex (ABC) technique (Hsu et al. 1981). The specificity and sources of the monoclonal and polyclonal antibodies are reported in Table 3. For immunoelectron microscopic observation, frozen sections were processed in the same way, applying monoclonal antibodies such as CD 4 and CD 8. After immunoperoxidase staining, sections were fixed in 2.5% glutaraldehyde for 1 h at 4° C, post-fixed in 1.0% OsO_4 for 30 min at 4° C, and embedded in Epon 812. Ultrathin sections were stained with lead citrate for 2 min and observed with a JEM 100 CX electron microscope. Double immunostaining (Ki-67 and CD 4 or CD 8) was performed by using both the ABC method and the peroxidase-antiperoxidase (PAP) method modified for immunohistochemistry as described previously (Hsu et al. 1982). In brief, 4-chloro-1-naphthol, which yields a dark blue colour, was used as the double immunostaining chromogenic substrate in the modified PAP method, after the ABC method. Negative controls for immunohistochemistry and immunoelectron microscopy were obtained by omission of the primary antibody and substitution with phosphate buffered saline (PBS).

Table 1. Clinical features of four cases of familial infection and five cases of recurrence of necrotizing lymphadenitis

Case no.	Age/sex	CC	Site of lymphadenopathy	Size	Complication	Recurrence (follow-up period)	
Familial cases							
1	21/M	Fever LA	Cervical, bilateral Inguinal, right	l	Tonsillar swelling	+	Case 5
2	23/M	Fever LA	Cervical, bilateral Axillary, right Inguinal, right	r	Aphta of oral mucosa	−	
3	16/F	LA	Cervical, right	l	Tonsillar swelling	−	
4	50/M	Fever LA	Cervical, left	a t b t	Angina pectoris Tonsillar swelling	−	
Recurrent cases							
5	23/M	Fever LA	Cervical, left	l	Gastric erosion Tonsillar swelling	+	(2 years 7 months)
6	26/M	Fever LA	Cervical, right Axillary, bilateral Inguinal, right	a r b r	Tonsillar swelling Hepatosplenomegaly (3 FB)	+	(8 years)
7	36/F	Fever Malaise LA	Cervical, right Supraclavicular, right	l	(−)	+	(10 years)
8	25/F	Fever LA	Cervical, right Axillary, bilateral Inguinal, right	a l b l	Tonsillar swelling	+	(8 years)
9	23/M	Fever Malaise LA	Cervical, bilateral	a r b l c l	Skin rash	+	(3 years)

CC, Chief complaint; LA, lymphadenopathy; l, little finger tip size; r, rice size; t, thumb tip size; a, first biopsy; b, second biopsy; c, third biopsy; FB, finger breadth. Cases 1 and 2 are male siblings.
Cases 3 and 4 are father and daughter. Case 5 is the recurrence of case 1

Table 2. Peripheral white blood cell and T cell subset of nine cases

Case no.	Peripheral blood and T subset (%)					Days after the onset of symptoms
	WBC (lymphocytes) /mm^3		CD 5	CD 4/CD 8		
1	3700	(2183)[a]	74	34/50	(0.68)	7
	3100		85.8	40.3/45.1	(1.12)	10
	9700					21
2	4700		58	30/33	(0.91)	7
	3400	(2244)[a]				17
3	6400		61.7	43.7/19.5	(2.2)	14
	3200					111
4	4700		73.2	47.4/28.9	(1.65)	9
	11600		76.4	45.6/29.9	(1.52)	22
	8200					38
5	4700	(2256)[a]	60.6	33.2/34.2	(0.97)	9
6	6400		ND	ND ND		18
7	4600	(1978)[a]	ND	ND ND		2
8	2500	(1400)[a]	ND	ND ND		12
9	2900		ND	ND ND		[b]

[a] Number of lymphocytes; [b] unclear; ND, not done

For the estimation of the number of positive cells, a square, cross-hatched grid mounted in a 10× microscope eyepiece was used to count at the 20× objective lens. The number of cells for CD 4, CD 8, Ki-67 and CD 4, and Ki-67 and CD 8 per 100 cells counted was recorded in three counts for each region of the specimen in each case. Analysis of T subset in peripheral blood was also performed (cases 1–5) by using flow cytometry.

For conventional electron microscopy, specimens from the lymph nodes were fixed in 2.5% glutaraldehyde, post-fixed in 1% OsO_4 and embedded in Epon 812. Ultrathin sections prepared by an ultramicrotome (LKB Bromma, Sweden) were stained with uranyl acetate and lead citrate, and examined with a JEM 100 CX electron microscope at 100 kV.

Results

The clinical findings are summarized in Tables 1 and 2. There were six males and three females. The age of the patients at the time of excision ranged from 16 to 50 years old (average of 27 years). All patients visited the doctor several times for common cold-like symptoms with fever, general malaise and lymphadenopathy. Cervical lymph nodes were usually involved; tonsillar swelling (cases 1, 3–6, 8), skin rash (case 9) and hepatosplenomegaly (case 6) were also observed. The white blood cell count at the initial stage was generally below 5000/mm^3, except in cases 3 and 6. Antibiotics produced no response.

Case 1 and 2 are male siblings. Case 2 was affected 2 weeks after the onset of case 1 and showed similar symptoms. Case 1 was admitted in 1978 for lymphadenopathy suspicious of infectious mononucleosis. Case 1 recurred twice at 2 years 7 months and 10 years after the first onset.

Cases 3 and 4 are daughter and father. Case 4 was affected about 2 months after the onset in case 3. The lymphadenopathy of case 4 appeared during admission for angina pectoris and hypertension.

Table 3. Specificities of monoclonal antibodies used in this study.

Antibody	Specificity	Source
LCA	CD 45; leucocyte common antigen	Dakopatts
B1	CD 20; pan-B cells	Coulter Immunology
L 26	Majority of B cells	Dakopatts
Leu 1	CD 5; pan-T cells, small proportion of normal B cells	Becton-Dickinson
Leu 2a	CD 8; cytotoxic/ suppressor T cells	Becton-Dickinson
Leu 3a	CD 4; helper/ inducer T cells	Becton-Dickinson
Leu 4	CD 3; pan-T cells	Becton-Dickinson
Leu 6	CD 1; interdigitating reticulum cells, Langerhans cells and cortical thymocytes	Becton-Dickinson
Leu 7	Natural killer cells	Becton-Dickinson
UCHL-1	Peripheral T cells	Dakopatts
HLA DR	B cell lineage cells, macrophages, activated T cells	Dakopatts
Ki-67	Proliferation-associated nuclear antigen	Dakopatts
S-100	Interdigitating reticulum cells, Langerhans cells, melanocytes	Dakopatts
Lysozyme	Histiocytic cells, neutrophilic granulocytes and monocytes/macrophages	Dakopatts
α_1-anti-trypsin	Histiocytic cells, neutrophilic granulocytes and monocytes/ macrophages	Dakopatts

Cases 5–9 recurred at 2 years 7 months, 8 years, 10 years, 8 years and 3 years after the initial onsets. In these cases, symptoms were similar to those of the early stage of NEL. The affected lymph nodes also showed histological features characteristic of NEL. In cases 6 and 7, lymphadenopathy with pain was observed.

The surgically removed lymph nodes, up to 0.5 cm in size, are smooth with a soft and fragile consistency. On the cut surface irregular yellowish white foci are seen.

The histopathological findings are shown in Table 4. Several cases show periadenitis with capsular thickening (cases 4, 6–9). The lesions appear mainly in the paracortical area where the depletion of lymphocytes is marked. Lymph follicles remain sporadically in the lesion (cases 4, 7–9). Morphological features of the involved lymph nodes include the presence of immunoblasts, plasmacytoid T cells, histiocytes and macrophages, the latter with phagocytized nuclear debris mainly derived from degenerated lymphocytes. No granulocytes and no evidence of bacteria are present in the lesion (Figs. 1 a, b, 2).

The cell components differ from case to case. Several cases contain fibrin thrombi within the coagulation necrotic area, and the vascular wall in the coagulation necrosis shows degenerative change (cases 3 and 9) (Fig. 3). However, there is no evidence of angiitis.

The lymph node rebiopsy from case 4, obtained on the 22nd day after the initial onset of symptoms, showed partial coagulation necrosis, neovasularization and numerous lymph follicles near the necrotic lesion. Case 7 had repeated recurrences four times during 10 years. Biopsies were performed each time and showed typical features of NEL on three occasions. S-100 protein$^+$ cells increased in the dermatopathic lesions despite the lack of a skin rash (cases 2, 4–6 and 9). Lysozyme and α_1-antitrypsin reacted with macrophages in the lesion. Ultrastructurally, a similar cell population was seen as with the light microscope. Tubuloreticular structures are of-

Table 4. Histopathological finding in nine cases

Case no.	Periadenitis	Germinal centre	Blastoid cell	Macrophages	Lymphocytes depletion	Coagulation necrosis	Fibrinoid thrombus	Postcapillary venules	Silver depletion	Other findings
1	±	+	+	+++	++	−	−	−	−	−
2	+	−	++	+++	++	−	−	±	+	Dermatopathic lesion
3	−	−	±	+	+++	+++ Diffuse	++	−	+	−
4	+	+	++	++	+++	+	+	+	−	Dermatopathic
	±	++	±	+	++	++	+	+++	−	lesion
5	±	−	+	++	++	−	−	−	+	Dermatopathic lesion
6	+	−	±	++	++	−	−	±	−	Foam cell
	+	−	++	++	+++	++	+	−	−	Dermatopathic lesion
7	+	+	+	++	+	−	±	++	+	−
8	+	++	±	++	+	+++	++	−	+	−
	++	+	++	++	+	++	++	−	+	
9	−	−	+	++	++	+++	+	−	−	Dermatopathic
	±	++	+	++	++	+++	+	−	−	lesion
	±	+	++	++	+	+	−	−	−	Capsular thickening

Reactivity is graded follows: −, none; ±, most negative; +, weak; ++, moderate; +++, strong

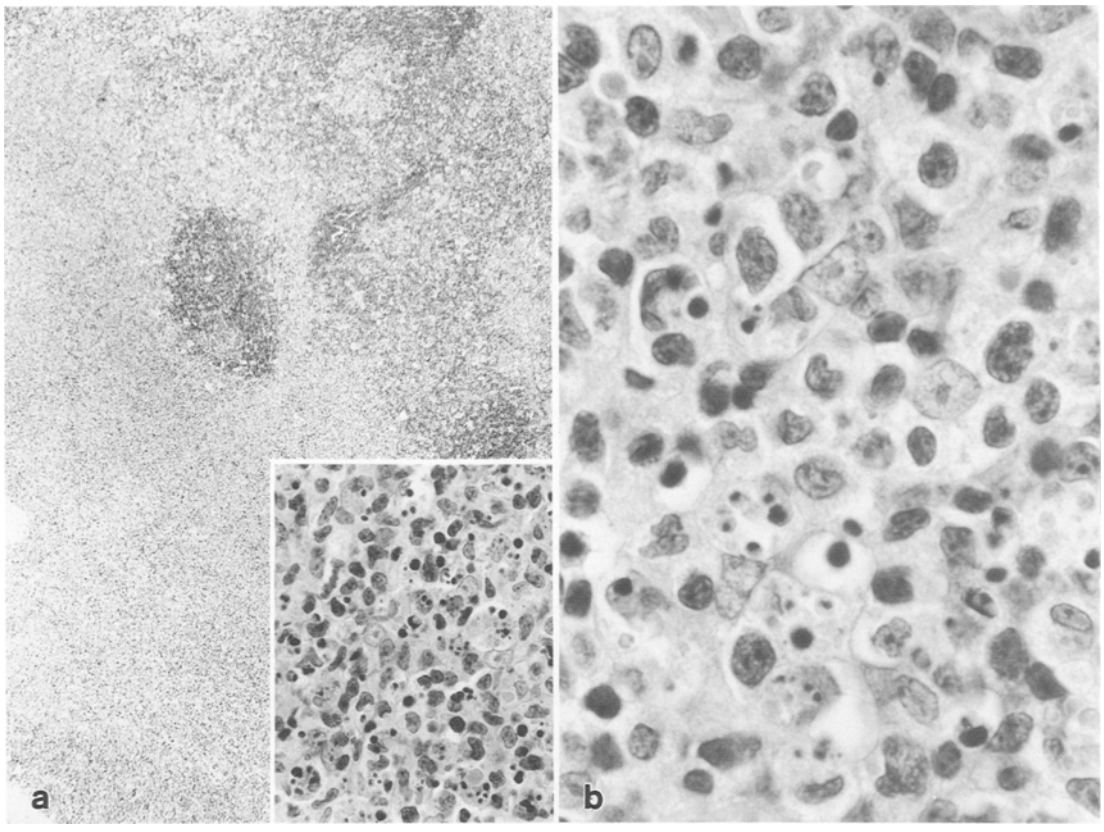

Fig. 1. **a** Major lesions of necrotizing lymphadenitis (NEL) correspond to the clear zone of the paracortical area of the affected lymph node. Dark, island-like zone is aggregation of small lymphocytes (case 1). ×22, *inset* ×132. **b** Magnification of **a**. Many blastoid cells, macrophages, phagocytizing degenerated lymphocytic cell debris and non-phagocytic histiocytic cells are major components. ×330

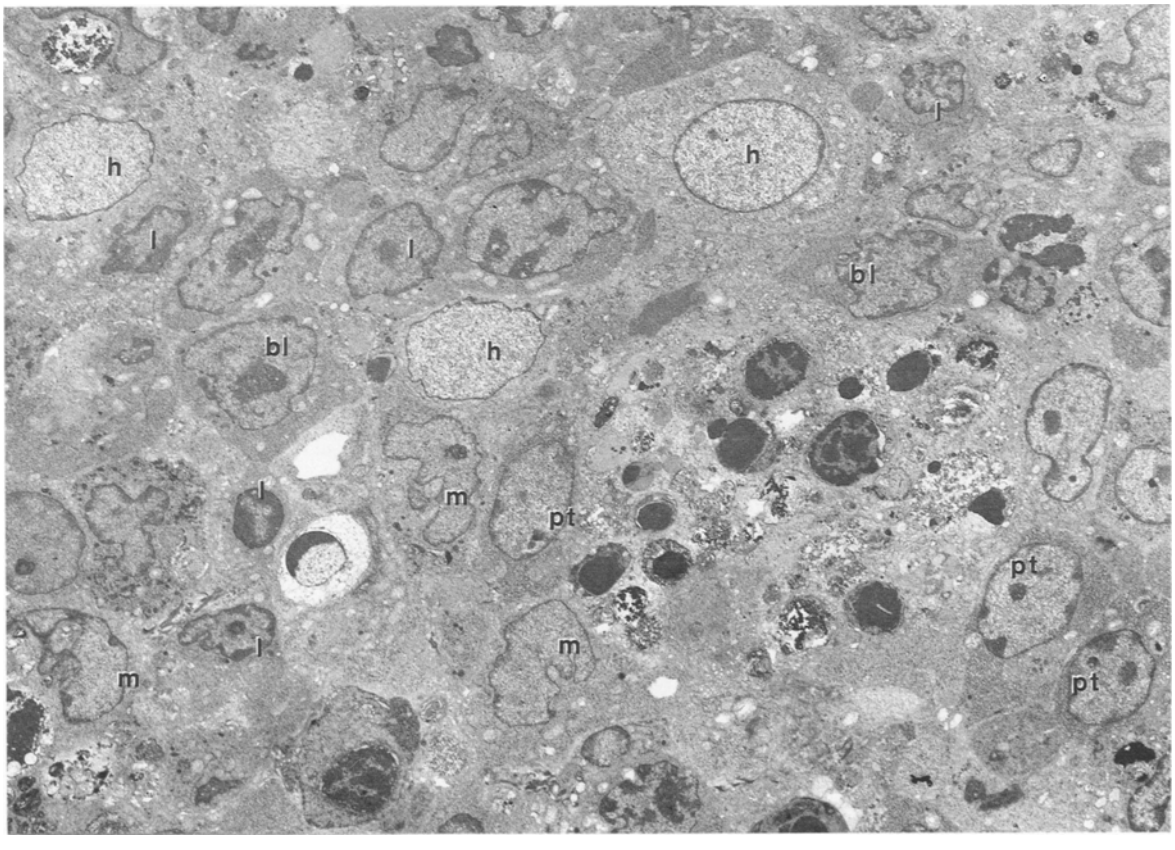

Fig. 2. Characteristic features of NEL including many blastoid cells (*bl*), histiocytic cells (*h*), plasmacytoid T cells (*pt*), lymphocytes (*l*) and macrophages (*m*) phagocytizing lymphocytes (case 5). ×2300

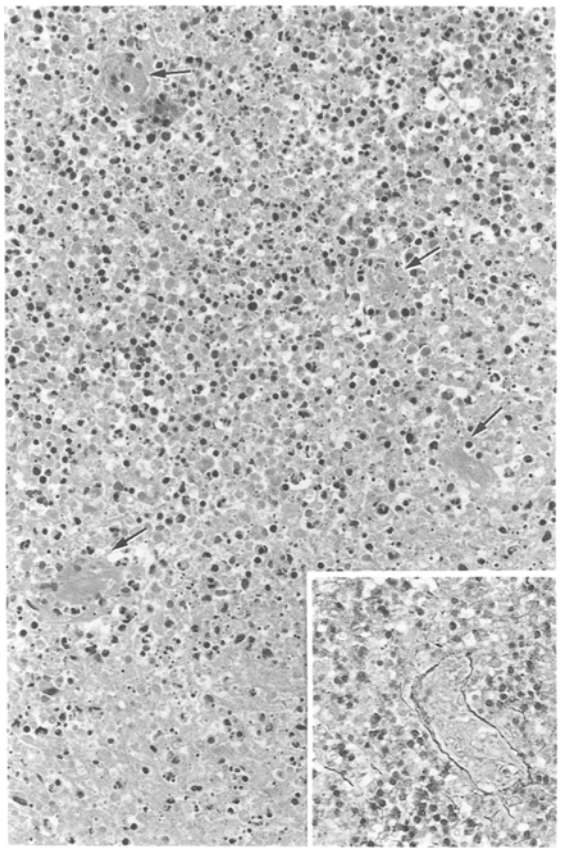

Fig. 3. Fibrin thrombi (⇒) within the coagulation necrosis. *Inset*: Poorly developed silver impregnation of vessel wall within the coagulation necrosis of affected lymph nodes (case 3). ×44, *inset* ×109

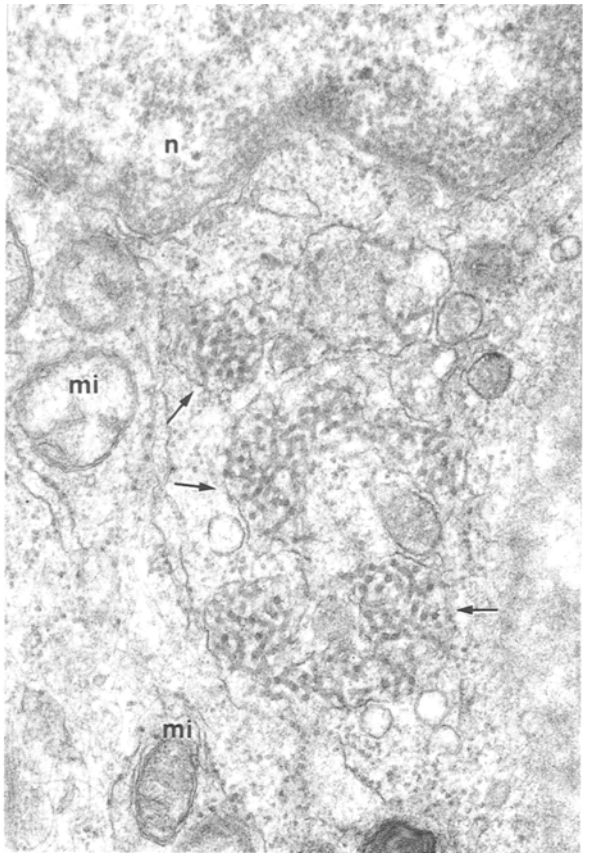

Fig. 4. Tubuloreticular structure (⇒) in lymphocyte. Bead-like structures filling endoplasmic reticulum space. *n*, Nucleus of lymphocyte; *mi*, mitochondria. ×44800

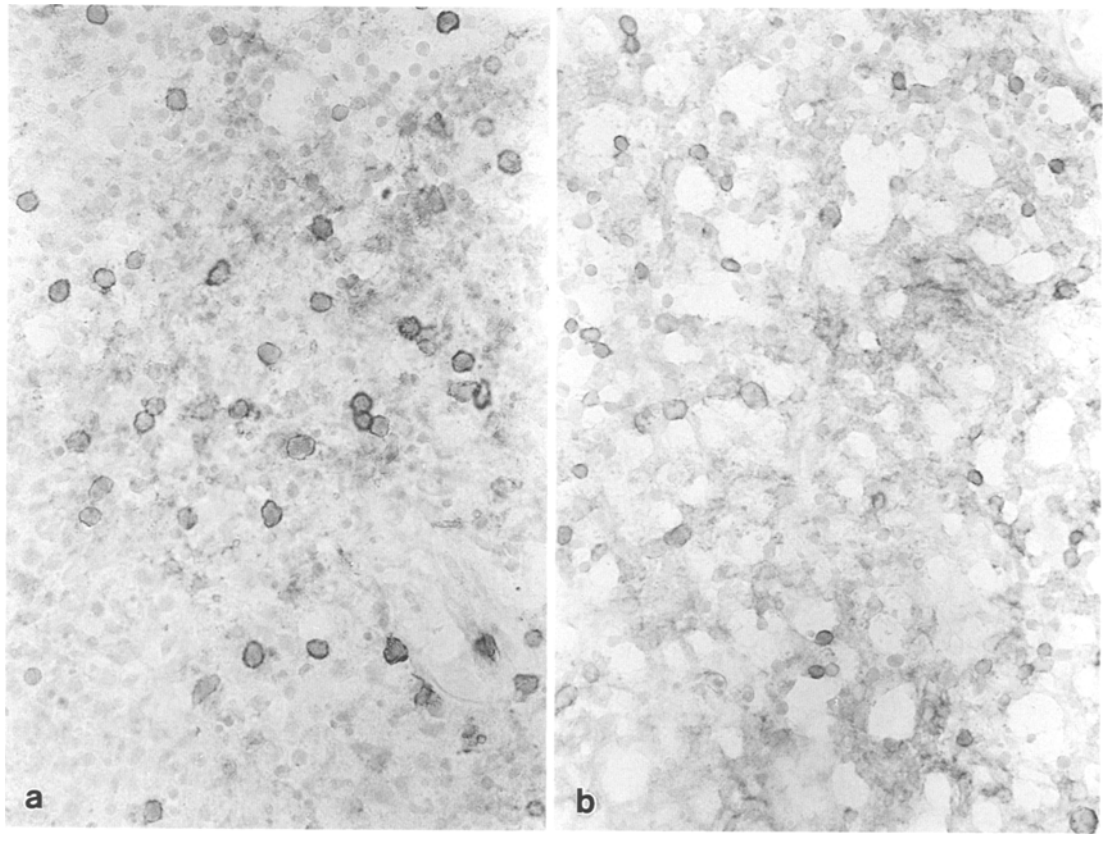

Fig. 5. **a** CD 8^+ (Leu $2a^+$) cells in focus. The number of the positive cells is less than in the paracortical area (case 5). ×132. **b** CD 4^+ (Leu $3a^+$) cells in focus. The positive cells are rare and fewer in number than CD 8^+ cells (case 5). ×132

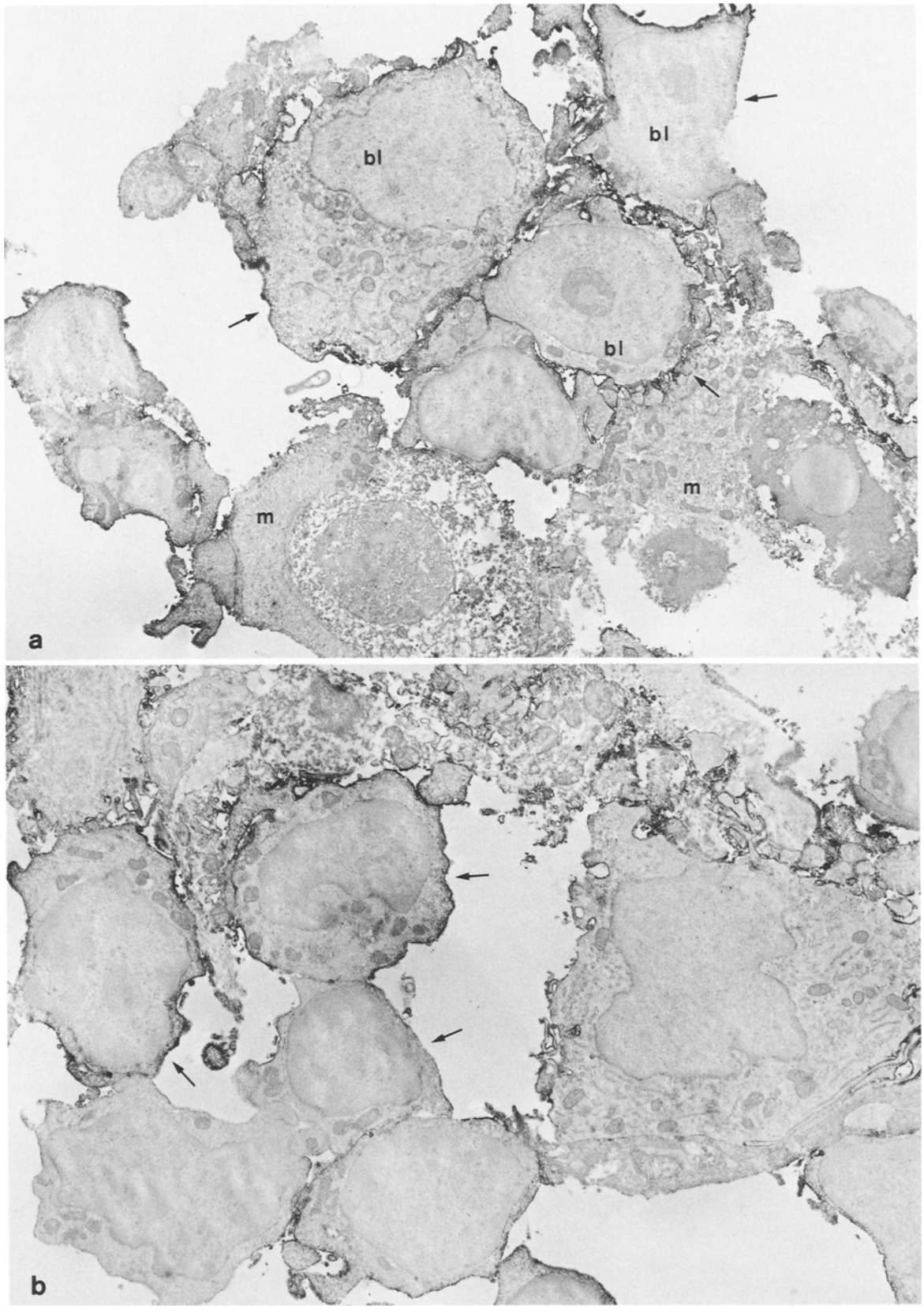

Fig. 6. **a** CD 8^+ (Leu $2a^+$) cells (⇒). CD 8^+ granules are seen along the cytoplasmic processes of the cell. These cells, corresponding to blastoid cells (*bl*), are larger than those of CD 4^+ cells (case 5). *m*, Macrophage, ×4900. **b** CD 4^+ cells (⇒) with indented nuclei are smaller than CD 8^+ cells (case 5). ×6200

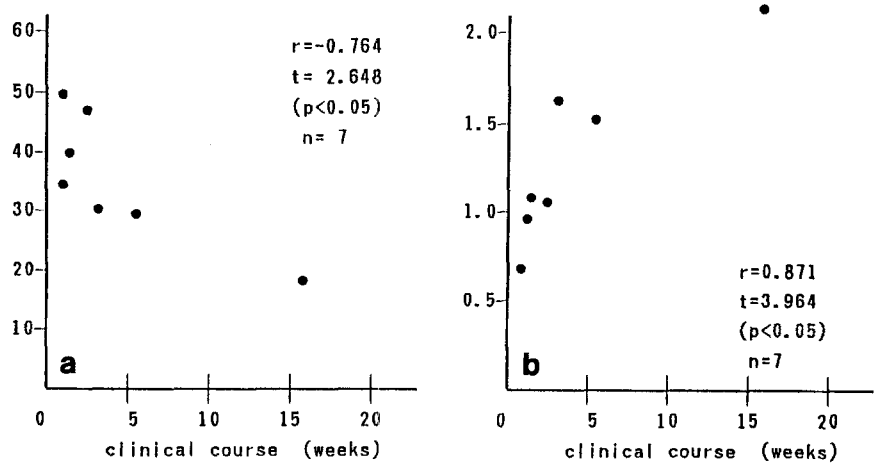

Fig. 7. **a** Correlation between clinical course and CD 8^+ cells, and **b** the CD 4^+:CD 8^+ ratio

ten observed, not only in the lymphoid cells, but in the histiocytes and vascular endothelial cells (Fig. 4).

The lymph nodes in cases 1, 2 and 5 were examined with monoclonal antibodies and showed that CD 8^+ cells are more abundant than CD 4^+ cells during the early stage of the disease (Fig. 5a, b). CD 8^+ cells, which clearly correspond to immunoblasts, have large round nuclei. CD 4^+ cells have smaller nuclei than those of CD 8^+ cells (Fig. 6a, b). In the affected lymph nodes, CD 4^+ cells often increase as the disease progresses, but the clinical course and the ratio of CD 4^+:CD 8^+ in lymph nodes does not correlate with that of peripheral blood. Immunoblasts, which react with UCHL-1 (MT-1) but rarely with L-26, are located more at the periphery of the lesions rather than centrally. Ki-67^+ cells are observed in a small number, but Ki-67^+CD 8^+ cells (mean 7.69%) are likely to be present in larger numbers than Ki-67^+CD 4^+ cells (mean 4.07%).

Peripheral blood T cell subset analysis from cases 1–5 disclosed that CD 8^+ cells were more numerous than CD 4^+ cells in the early stage of the disease, and that CD 8^+ cells gradually decreased with clinical progression (negative correlation, $r = -0.764$, $P < 0.05$). The ratio of CD 4^+:CD 8^+ in peripheral blood of cases 3 and 4 revealed normal values. Case 5, which is a recurrence in case 1, showed leucopenia (4700/mm^3) and a low CD 4^+:CD 8^+ ratio (0.91). Statistical analysis showed that the ratio of CD 4^+:CD 8^+ increased with clinical course (positive correlation, $r = 0.871$, $P < 0.05$) (Table 2, Fig. 7).

Discussion

NEL is a reactive process, described under different names by Japanese pathologists in the early 1970s (Fujimoto et al. 1972; Kikuchi 1972; Wakasa et al. 1973). Recently, this type of lymphadenitis has also been reported in America and Europe (Feller et al. 1982; Pileri et al. 1982; Turner et al. 1983; Ali et al. 1985; Rivano et al. 1987; Dorfman et al. 1987; Facchetti et al. 1989; Chamulak et al. 1990). In Japan, NEL is observed more frequently in the northern area; however, no characteristic seasonal occurrence has been noted. In general, the disease affects young females more than males, mainly from the 3rd or 4th decades onwards. The patients complain of common cold-like symptoms with fever, lymphadenopathy of the cervical region and leucopenia in the early stages. The symptoms seldom respond to antibiotics; however, steroid and anti-inflammatory drugs are relatively effective (Wakasa et al. 1982; Kikuchi et al. 1983; Asano et al. 1985, 1987, 1990).

Although a number of papers on NEL have been published, cases showing familial occurrence and recurrences in the same individual are infrequent (Tanaka et al. 1983; Hanaoka 1985; Mitsuya et al. 1986; Fukuda et al. 1987; Asano et al. 1987, 1990; Katayama et al. 1988). In this paper, four familial and five recurrent cases are reported. In almost all of the recurrent cases the symptoms were similar to those of the early stages of the disease. An occasional finding of tonsillar swelling, hepatosplenomegaly and change of T subset in peripheral blood suggests that the disease is a systemic disorder rather than a simple disorder of the lymph nodes.

Histopathological features of the lymph nodes are similar in non-familial and non-recurrent cases. It should be emphasized that granulocytes are absent in spite of the presence of necrotic foci (Wakasa et al. 1982; Asano et al. 1985, 1987, 1990; Rivano et al. 1987; Facchetti et al. 1989; Chamulak et al. 1990). The role of the plasmacytoid T cells is still unclear but the cells may play a role in the T-cell-mediated immune response (Feller et al. 1983; Facchetti et al. 1988).

In the familial cases, it is possible that case 2 was infected by case 1, as described in other reports (Hanaoka 1985; Fukuda et al. 1987; Asano et al. 1987; Katayama et al. 1988). A similar relationship may be considered between cases 3 and 4, although other family members have not been affected. Elucidation of the mode of infection of the disease is difficult.

It is postulated that CD 4^+ cells are primarily affected by agents resulting in their degeneration and depletion in the early stages of the disease and possibly in the recurrent state. The damaged lymphocytes are subsequently phagocytized by macrophages. However, CD 4^+ cells gradually increase, while CD 8^+ cells gradually decrease with an increase of the CD 4^+:CD 8^+ ratio, similar to what is seen in peripheral blood (Rivano

et al. 1987; Asano et al. 1987, 1990). Blast transformation of T cells into immunoblasts occurs in the lesions (Rivano et al. 1987; Asano et al. 1987, 1990) and these immunoblasts, corresponding to CD 8^+ cells, may be stimulated by causative agents (Asano et al. 1990). In our study, Ki-67^+CD 8^+ cells generally predominate (rather than Ki-67^+CD 4^+ cells) and the Ki-67^+CD 4^+:Ki-67^+CD 8^+ ratio does not correlate with the course of the illness. Chamulak et al. (1990) considered these immunoblasts to be of B cell origin because of staining with L 26 and LN1; we demonstrated neither clusters of monocytoid B cells nor of B immunoblasts within the foci of NEL.

The pathogenesis of NEL is still obscure, but it seems to be associated with viruses, antibiotics are ineffective (Asano et al. 1987, 1990); no granulocytes appear in the lesion (Pileri et al. 1982; Turner et al. 1983); there is a frequent appearance of tubuloreticular structures (Imamura et al. 1982; Asano et al. 1987, 1990); and elevation of the 2′–5′ oligoadenylic acid synthesizing enzyme which induces α-interferon is found (Takeshita et al. 1986). These viruses may be Epstein-Barr (Takada et al. 1980), rubella (Kikuchi et al. 1983), paramyxo- (Imamura et al. 1981), parainfluenza (Sakuma et al. 1983; Asano et al. 1985) or human herpes simplex virus-6 (Feller et al. 1983; Minamishima 1990). NEL may be caused by *Toxoplasma* (Kikuchi 1977) or *Yersinia enterocolitica* (Feller et al. 1983).

There are several diseases which must be differentiated from NEL. These include malignant lymphoma (Kikuchi et al. 1983; Rivano et al. 1987; Chamulak et al. 1990), cat-scratch disease (Wakasa et al. 1982), tularaemia (Wakasa et al. 1982), *Yersinia enterocolitica* (Feller et al. 1983), infectious mononucleosis (Kikuchi et al. 1983), toxoplasmosis (Kikuchi et al. 1977), lymphadenitis accompanying systemic lupus erythematosus (Wakasa et al. 1982; Kikuchi et al. 1983), tuberculosis (Nieman 1990) and influenza (Kikuchi et al. 1983). Precise clinicopathological and immunohistochemical analysis gives useful information in understanding the disease.

Acknowledgement. This study was supported in part by a Grant-in-Aid from the Ministry of Education, Science and Culture of Japan (nos. 60304049 and 63304035).

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