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Histiocytic Necrotizing Lymphadenitis Without Granulocytic Infiltration*

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Summary. Twenty-seven cases of an unusual necrotizing lymphadenitis previously described only in Japan are reported as occurring in West Germany (23 cases), Iran (1 case), Italy (1 case), Korea (1 case) and Spain (1 case). The lesion frequently develops in the cervical lymph nodes of young women. It is characterized by infiltration of the cortex and/or paracortex by large collections of proliferating histiocytes and is devoid of granulocytes. Complete or, more often, incomplete necrosis of lymphoid tissue is seen in all cases. In cases with incomplete necrosis, the histiocytes are interspersed with pyknotic cells and nuclear debris. Based on the histological findings, the term "histiocytic necrotizing lymphadenitis without granulocytic infiltration" is proposed. Lesions to be considered in a differential diagnosis are malignant histiocytic neoplasms and necrotizing lymphadenitis with granulocytic infiltration, which is seen in lupus erythematosus and bacterial infections. The aetiology of histiocytic necrotizing lymphadenitis without granulocytic infiltration is still unclear. Some clinical and histological features indicate the possibility of an underlying viral infection.

Key words: Necrotizing lymphadenitis – Histiocytic lymphadenitis – Lupus erythematosus

In 1972, one of the authors (M.K.) described an unusual "lymphadenitis showing focal reticulum cell hyperplasia, with nuclear debris and phagocytes", which was usually found in cervical lymph nodes of young women and showed an excellent prognosis. At about the same time, similar lesions were reported by Fujimoto et al. (1972) as "cervical subacute necrotizing lymphadenitis". Since

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then, about 380 examples of the lesion occurring only in Japanese patients have been published under several different names, viz.: "necrotizing lymphadenitis" (Wakasa et al. 1975, 1978; Kikuchi et al. 1977), "necrotizing histiocytic lymphadenitis" (Shimamine et al. 1974), "phagocytic necrotizing lymphadenitis" (Kikuchi and Uryu 1976), "focal histiocytic necrotizing lymphadenitis" (Kikuchi 1978) and "pseudolymphomatous hyperplasia in lymph nodes" (Michaeleck 1977). According to the observers, the lesion might be a new entity, because it shows special clinicopathological features.

Clinically, the lesion often appears as lymphadenopathy in the neck; the enlarged nodes are painful. Manifestation in sites other than the cervical region and generalized lymphadenopathy are less common. Fever and leukopenia are observed frequently. The prognosis is always excellent, and many patients recover without treatment.

Histological examination of involved lymph nodes reveals partial effacement of the architecture and the presence of foci of proliferating and infiltrating cells in the cortex and/or paracortex. The foci are composed of histiocytes interspersed with small lymphocytes, immunoblasts and only a few plasma cells. Regressive changes, such as nuclear debris or marked tissue necrosis, are always observed. Neutrophils and eosinophils have not been found in any case, with very few exceptions.

The aetiology of the lesion is still unclear. It has been suggested that some cases might be due to a toxoplasmic infection (Kikuchi et al. 1977; Kikuchi 1978), but this has not been confirmed.

The aim of the present study was to determine whether the lesion occurs outside Japan. The collection of the Lymph Node Registry in Kiel (FRG) was reviewed and was found to contain 27 examples of the lesion.

Materials and Methods

In a 10-year period (1970–1979), 164 cases of necrotizing lymphadenitis and 579 cases of hyperimmune reaction had been collected at the Lymph Node Registry. These cases were reviewed and found to include 40 cases showing lesions resembling the ones described in Japan. Paraffin blocks of formalin-fixed tissue were available in all but two cases. New sections were prepared and stained with the following methods: haematoxylin and eosin (H & E), Giemsa, periodic acid Schiff (PAS), silver impregnation (Gomori), Goldner and naphthol-AS-D-chloroacetate esterase.

Immunohistological analyses were also performed with the PAP method described by Mepham et al. (1979). Briefly, after inhibition of endogenous peroxidase activity with 0.3% H_2O_2 in methanol for 30 min, dewaxed paraffin sections were pretreated with fresh 0.1% trypsin solution in 0.4% calcium chloride (pH 7.8) at 37° C for 30 min. After two 10 min washes in PBS, the sections were incubated with non-immune swine serum (diluted 1:5) for 10 min. Antisera were then applied in the following sequence: specific rabbit antiserum, swine anti-rabbit IgG serum, rabbit PAP complexes; each of these stages lasted 30 min and was followed by a wash in PBS. Peroxidase activity was demonstrated with the 3,3′-diaminobenzidine tetrahydrochloride (Fluka 32750) reaction described by Graham and Karnovsky (1966). The sections were counterstained with haemalum and mounted with Eukitt (Kindler, Freiburg, FRG). In the present investigation, the following antisera were employed: (1) rabbit anti-human κ (Dako 10-9K2), diluted 1:300 with PBS, pH 7.4, (2) rabbit anti-human λ (Dako 10-9L2), diluted 1:300 with PBS, pH 7.4, (3) rabbit anti-human lysozyme (Dako 10-099), diluted 1:100 with PBS, pH 7.4, (4) rabbit anti-human albumin (Dako 10-001), diluted 1:100 with PBS, pH 7.4, (5) swine anti-rabbit IgG (Dako 21-090), diluted 1:50 with PBS, pH 7.4, and (6) rabbit PAP complexes (Dako Z113), diluted 1:100 with PBS, pH 7.4.

Clinical data were collected by sending a questionnaire to the physician or hospital caring for each patient at the time of biopsy.

Results

Of the 743 cases reviewed, 40 cases had been diagnosed as "lymphadenitis as described by Kikuchi". These cases showed more or less extensive infiltration of the cortex and/or paracortex by histiocytes and lymphoid cells, associated with varying degrees of necrosis. Evaluation of the content of neutrophils indicated, however, that the lesions could be divided into two groups: those with and those without granulocytic infiltration. Based on the clinical findings, it was evident that only the lesions without granulocytic infiltration corresponded to the lesion described by Kikuchi (1972 and 1978; Kikuchi and Uryu 1976; Kikuchi et al. 1977); the cases with granulocytic infiltration showed completely different clinical features.

Group of Lesions Without Granulocytic Infiltration

There were 27 cases in this group. *Histologically* (Table 1), they were characterized by partial or almost complete effacement of the lymph node architecture, which was replaced by one or several large collections of infiltrating and proliferating cells, usually located in the pulp of the cortex and/or paracortex (Fig. 1). The infiltrating and proliferating cells looked gray with Giemsa staining and were mostly histiocytes (Figs. 2, 3a and b). These cells showed phagocytic activity and a strong reaction for lysozyme (Figs. 3c and 4). They were interspersed with numerous small lymphocytes, which often showed twisted nuclei. There were also medium-sized lymphoid cells with sparse gray cytoplasm (possibly so called T-associated plasma cells), a few plasma cells and a variable number of immunoblasts, which were usually negative for both κ and λ chains.

Necrotic changes were found in all cases. These mainly consisted of pyknotic, small or medium-sized cells with oxyphilic cytoplasm and nuclear debris (Fig. 3a

Table 1. Histological findings in 27 cases of histiocytic necrotizing lymphadenitis without granulocytic infiltration

Constant findings
Focal infiltration of the cortex and/or paracortex by proliferating histiocytes interspersed with small lymphocytes, medium-sized lymphoid cells and T immunoblasts
Necrotic changes, ranging from single pyknotic cells to extensive tissue necrosis
Absence of granulocytes
Marked phagocytotic activity
Low content of plasma cells and B immunoblasts
Variable number of mitotic figures
Hyperplasia of the pulp in portions spared by necrosis
Remnants of sinuses
Facultative findings
Capsulitis and pericapsulitis (96%)
Expansion of capsule (38%)
"Immature sinus histiocytosis" (30%)
Fibrin thrombi (24%)
Small collections of foamy cells (17%)
Foci of so called T-associated plasma cells (14%)
Germinal centres (7.5%)

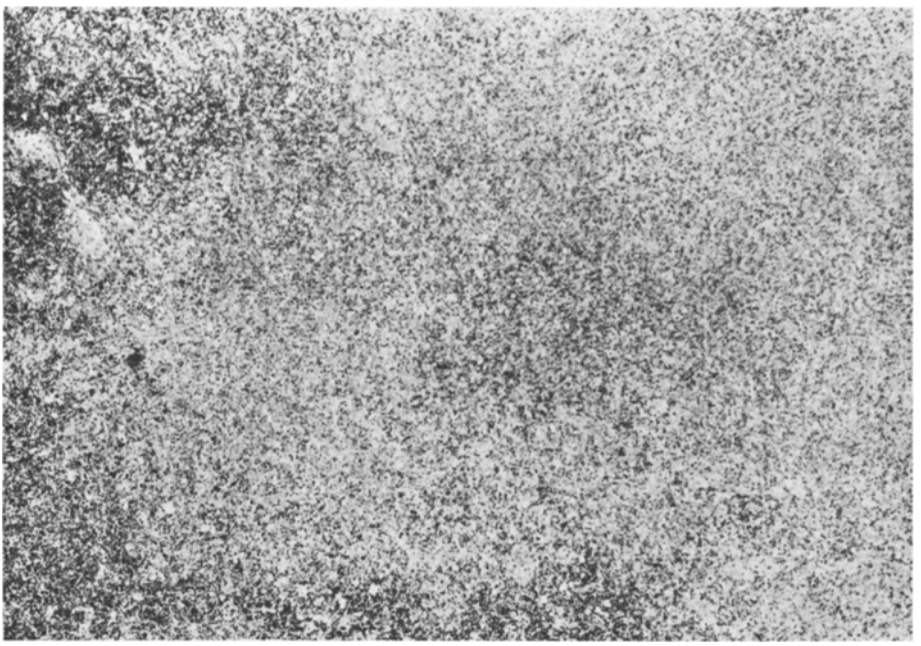


Fig. 1. Large area showing necrobiosis and many histiocytes. Giemsa × 56

and b), with or without complete tissue necrosis (Fig. 5). When examined at a low magnification, Giemsa-stained sections from the cases with more extensive tissue necrosis showed a pink area surrounded by a mass of medium-sized gray cells. In areas of incomplete necrosis, there was a marked increase in the number of small vessels and argyrophilic fibres (Fig. 6). Areas of complete necrosis contained only a few recognizable fibres. The number of mitotic figures varied from few to many; they were found mainly among the histiocytes surrounding necrotic areas, but also in parts of the pulp farther away from the necrosis. In some cases, we found occasional fibrin thrombi, rare nuclear shadows, small collections of foamy cells (Fig. 7) and foci of so-called T-associated plasma cells (Müller-Hermelink and Lennert 1978).

In portions of lymph nodes spared by necrosis, the main change was hyperplasia of the pulp, with numerous epithelioid venules and a "mottled" appearance (Fig. 8). The latter was due chiefly to the presence of numerous reticulum cells scattered among small lymphocytes. The reticulum cells were identifiable as interdigitating reticulum cells because of their negative reaction for lysozyme. Most cases showed no, or only a few residual follicles. In 2 cases, however, there were several germinal centres in the second or third phase of development (Müller-Hermelink and Lennert 1978). The sinuses were largely preserved in all cases. In eight cases, however, features of so-called immature sinus histiocytosis (Lennert 1959) could be recognized. The capsule of the lymph nodes was focally or heavily infiltrated by lymphocytes in all but one case and showed expansion in 11 cases.

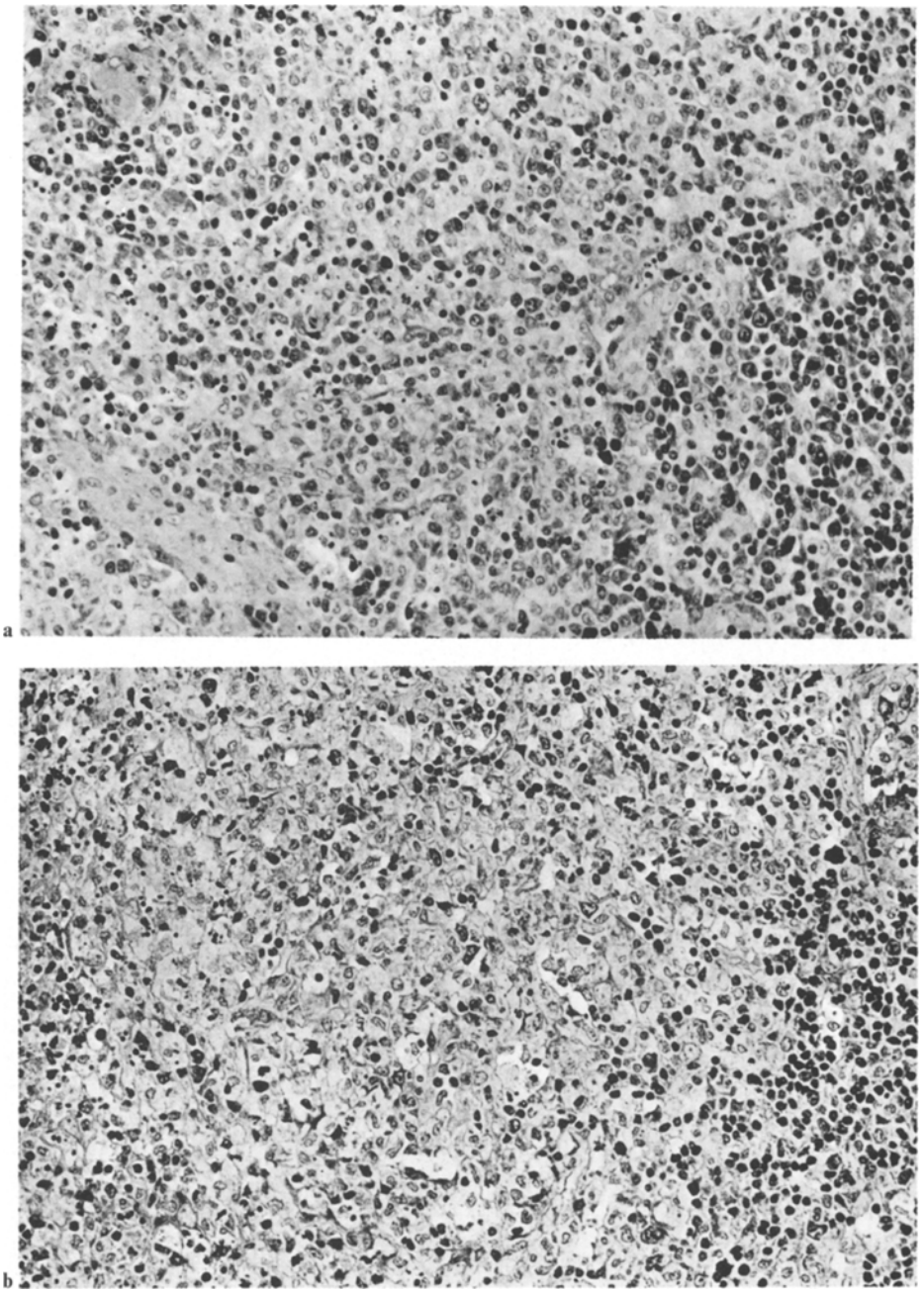


Fig. 2a, b. Two different areas of necrobiosis of the same lymph node. The adjoining lymphocyte-rich pulp is visible in the lower right corner of each photomicrograph. Giemsa ×280

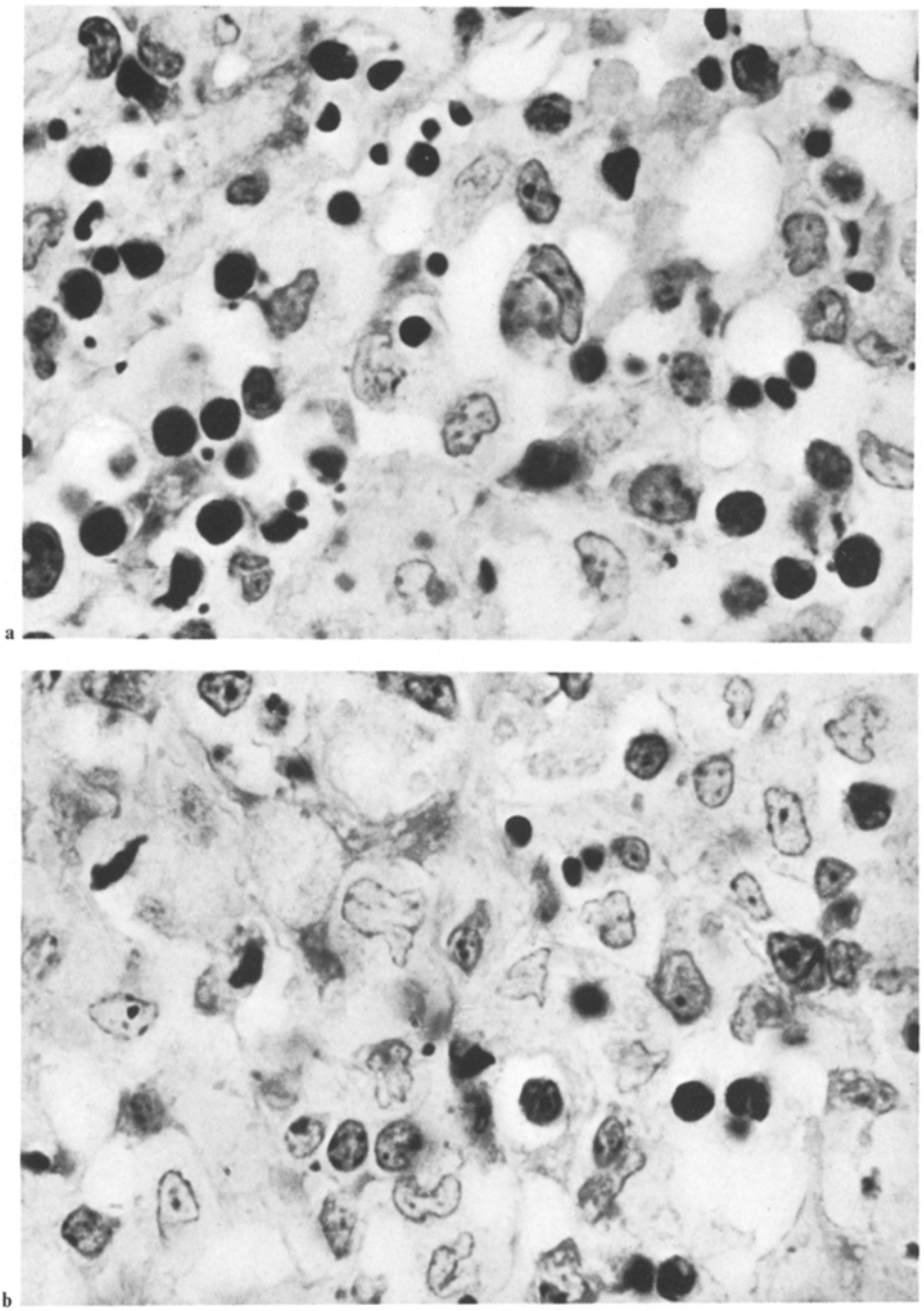
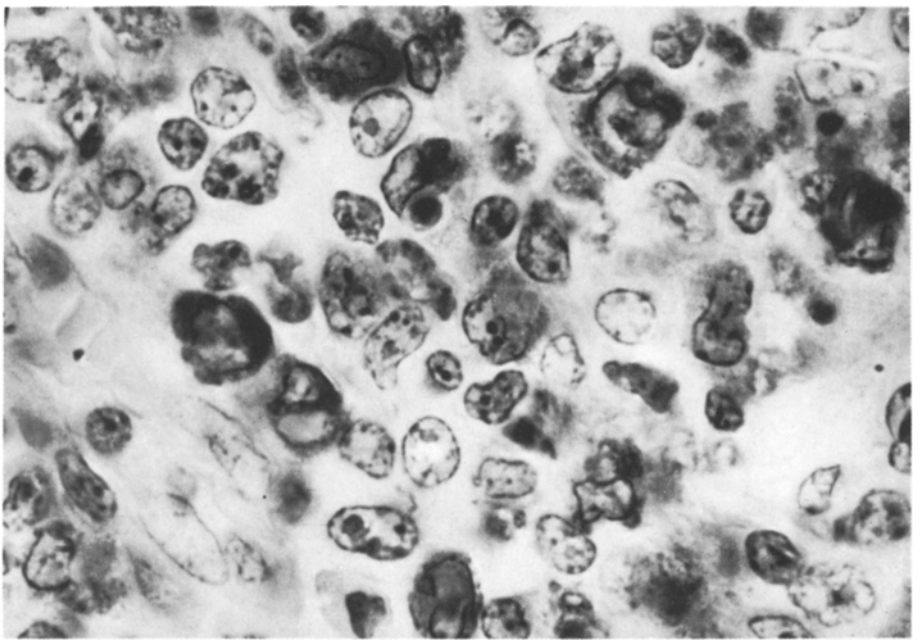


Fig. 3a–c. Three different areas of necrobiosis of the same lymph node as in Fig. 2. *a* Some histiocytes and many pyknotic cells. Giemsa ×1,350. *b* Many histiocytes and a few pyknotic cells. Giemsa ×1,350. *c* Lysozyme-positive histiocytes are intermingled with many medium-sized lymphoid cells devoid of lysozyme activity. PAP immunostaining ×1,350



c

Fig. 3c

Clinically (Table 2), the lesion presented as lymphadenopathy, usually localized in the cervical region. Most patients were young women working in small communities (schools, kindergartens, hospitals, banks, etc.). Tonsillectomy was recorded in the past medical history of 11 patients. One patient had diabetes mellitus. In another patient, the response of peripheral lymphocytes to PHA stimulation was reduced. Twenty-three patients were born and living in West Germany, one in Iran, one in Italy, one in Korea and one in Spain. Six patients showed enlargement of solitary lymph nodes at sites other than the cervical region and six showed generalized lymphadenopathy.

The enlarged nodes were reported to vary in size (bean- to plum-sized) and consistency. On palpation, they were painful in nine of 17 patients. Fever was reported in 11 of 22 cases, hepatomegaly in four of 21 and splenomegaly in two of 21. Fifteen of 21 patients showed an elevated ESR. Leukocytosis, leukopenia and elevated α_2- or γ-globulins were less common. Serological tests for toxoplasmosis and infectious mononucleosis were negative in all cases tested.

Follow-up data were available in 14 cases. The prognosis was excellent in all cases, and a majority of the patients recovered without treatment. One patient received chemo- and radiotherapy, because "histiocytic malignant lymphoma" had been diagnosed elsewhere.

Group of Lesions With Granulocytic Infiltration

Granulocytic infiltration was found in 13 cases. The clinical data are summarized in Table 3. Clinical evidence of lupus erythematosus was reported in five cases,

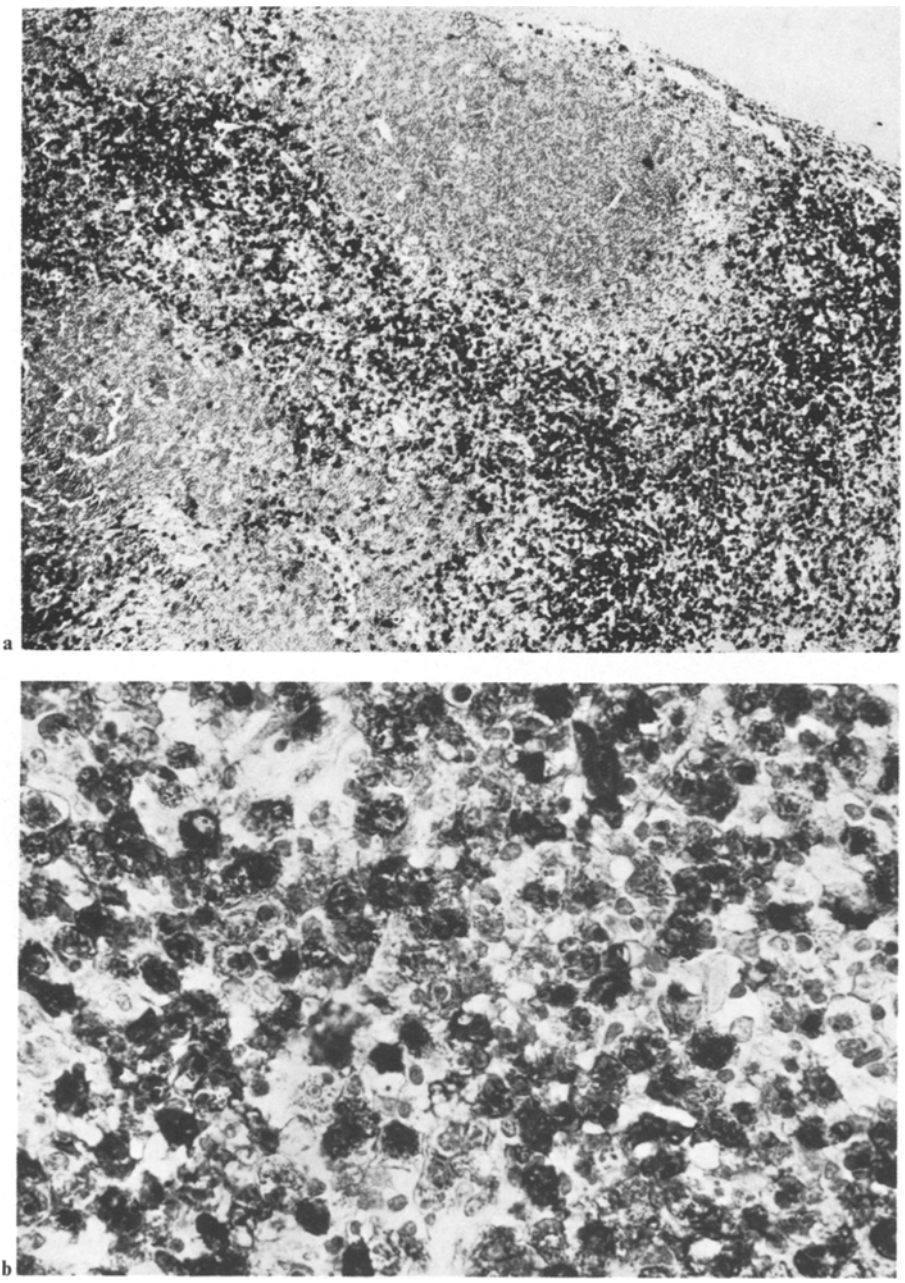


Fig. 4. **a** Large confluent areas of histiocytes in the pulp of cortex and paracortex (dark-staining cells). Remnants of the cortex and paracortex can be recognized. PAP immunostaining for lysozyme ×80. **b** Histiocytes showing a strong reaction for lysozyme. PAP immunostaining for lysozyme ×400

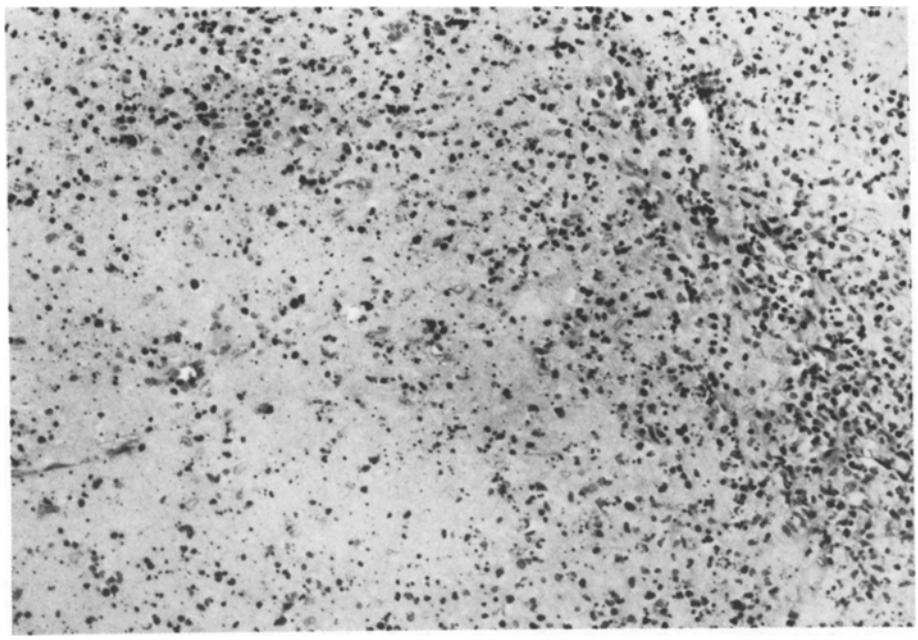


Fig. 5. Extensive tissue necrosis. Giemsa ×80

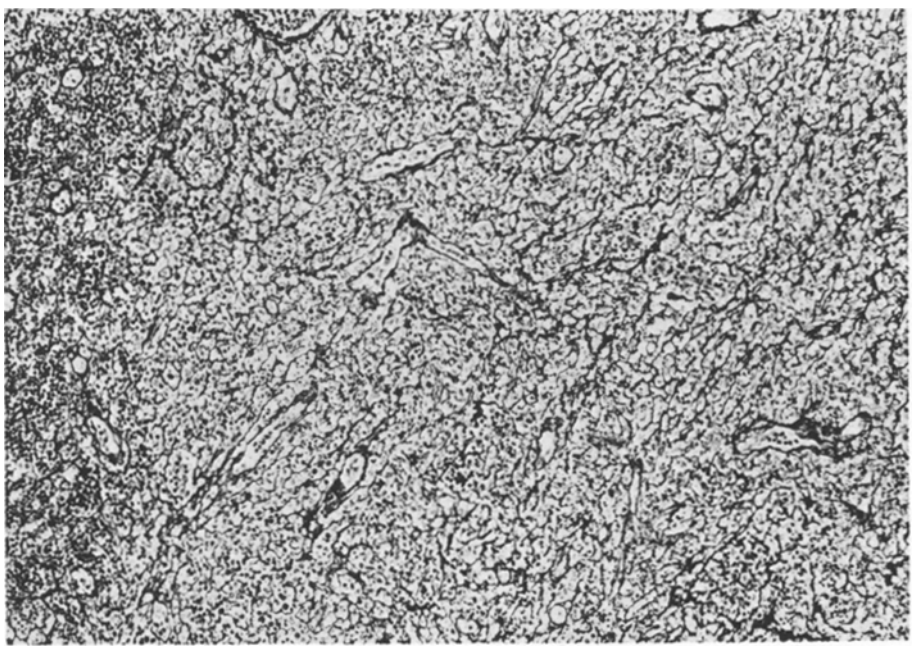


Fig. 6. The same lymph node as in Figs. 2 and 3 with silver impregnation. Many fibres and small vessels are visible. Gomori ×112

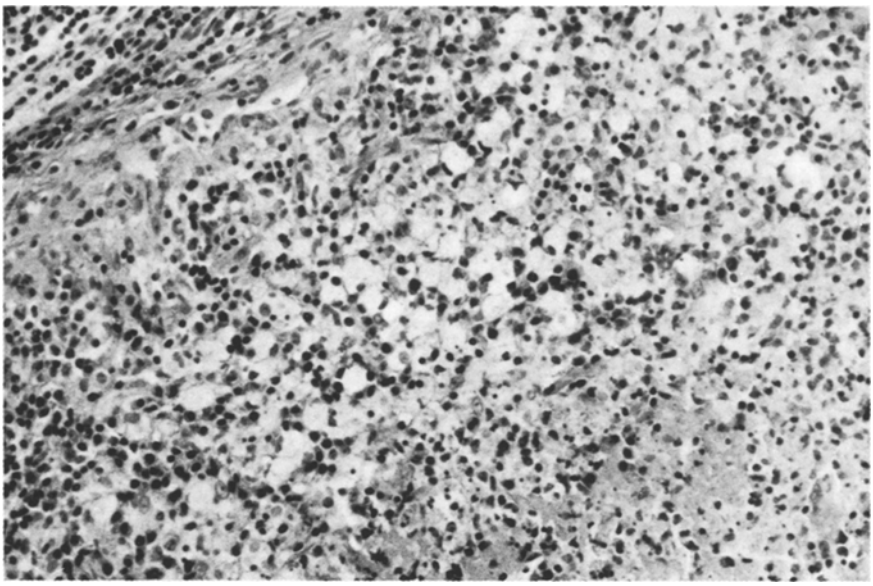


Fig. 7. Focus of foamy cells at the margin of a necrotic area. H & E ×250

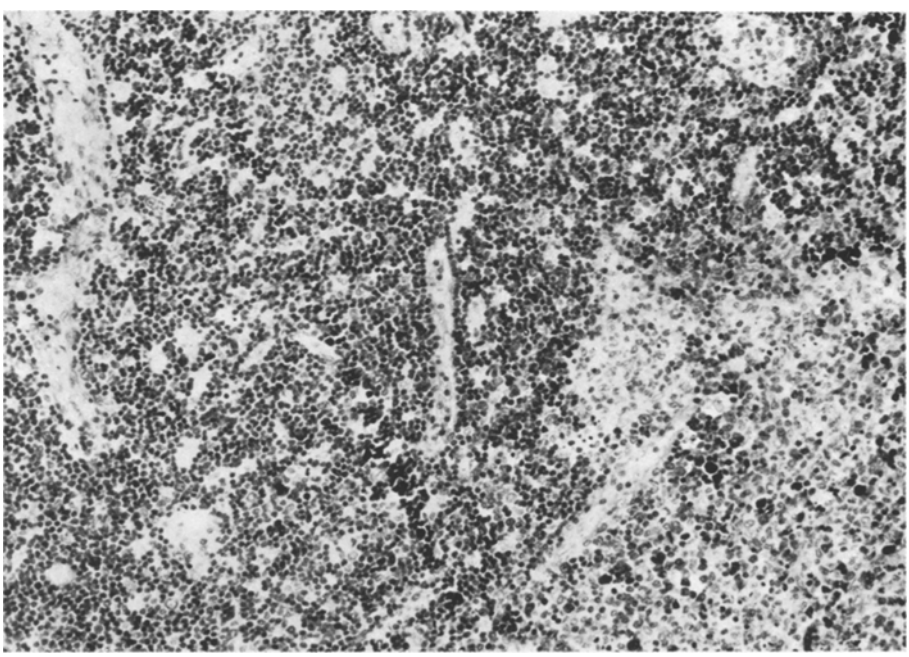


Fig. 8. The pulp next to a necrotic area shows hyperplasia with a mottled appearance and numerous epithelioid venules. The necrotic area in the lower right corner contains many histiocytes. Giemsa ×80

Table 2. Clinical findings in 27 cases of histiocytic necrotizing lymphadenitis without granulocytic infiltration

Age: range: 10–48 years, mean: 26.6 years	
Sex ratio: ♂:♀=1:2.85	
Nationality: German (23), Iranian (1), Italian (1), Korean (1), Spanish (1)	
Past medical history: Tonsillectomy was recorded in 11 cases	
Lymphadenopathy	
Site	
Cervical	10 (3 bilateral)
Axillary	3 (1 bilateral)
Inguinal	2
Cervical + axillary + supraclavicular	2
Cervical + axillary	2
Cervical + supraclavicular	1
Supraclavicular	1
Generalized	6
Size	
Bean-sized	8/21
Cherry-sized	10/21
Plum-sized	3/21
Consistency	
Hard	6/19
Medium	5/19
Soft	8/19
Pain	9/17
Signs and symptoms	
Fever	11/22
Hepatomegaly	4/21
Splenomegaly	2/21
Laboratory findings	
Leukocytosis (>10,000 WBC/μl)	1/20
Leukopenia (<4,000 WBC/μl)	5/20
ESR elevated (20–100)	15/21
α_2-Globulins elevated	6/13
γ-Globulins elevated	4/13
Serological tests	
Toxoplasmosis, negative	10/10
Mononucleosis, negative	9/10
Autoimmune disease: No evidence in any of 14 patients	
Treatment	
None	9/14
Antibiotic	4/14
Chemo- and radiotherapy	1/14
Prognosis: Data were available in 14 cases. All patients were alive and well 12–126 months after biopsy	

Table 3. Clinical findings in the group with granulocytic infiltration ($n=13$)

Case No.	Age	Sex	Site of lymphadenopathy	Other significant clinical findings
1	23	F	Generalized	Lupus erythematosus
2	24	F	Generalized	Lupus erythematosus
3	27	F	Generalized	Lupus erythematosus
4	38	M	Cervical	Lupus erythematosus
5	72	F	Axillary	Lupus erythematosus
6	22	M	Axillary	Skin abscess in the same region as lymphadenopathy
7	23	F	Generalized	Generalized bacterial disease
8	23	M	Inguinal	Skin abscess in the same region as lymphadenopathy
9	68	M	Peripancreatic	Retroperitoneal abscess 20 days after pancreatectomy
10	27	F	Axillary	High cryoglobulin titres and thrombosis of axillary vein at same site as lymphadenopathy
11	23	F	Cervical	Not available
12	26	M	Cervical	Not available
13	33	M	Generalized	Not available

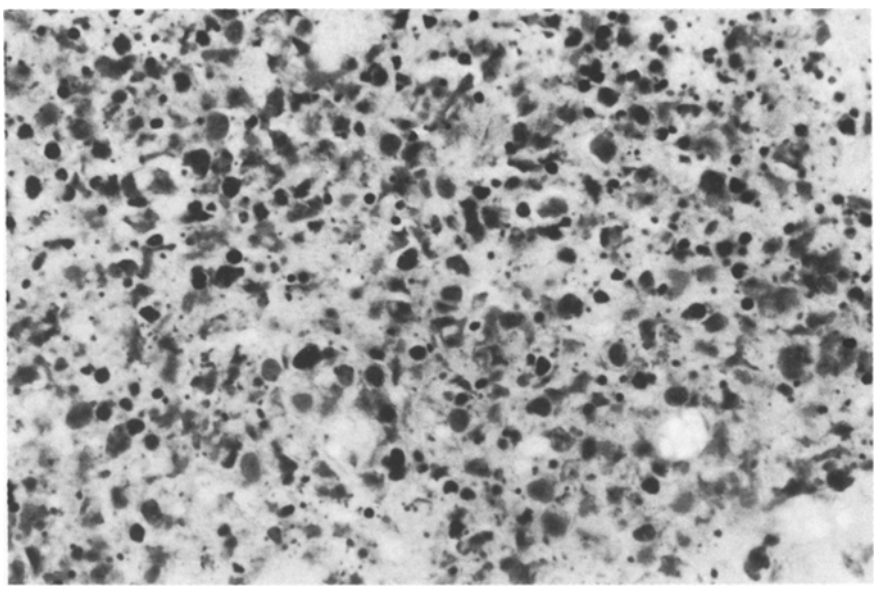


Fig. 9. Necrotizing lymphadenitis in a case with clinical evidence of lupus erythematosus. Many nuclear shadows are seen in addition to pyknotic cells and nuclear debris. Giemsa ×400

generalized or localized bacterial infections in 4 cases and venous thrombosis at the same site as lymphadenopathy in 1 case. In 3 cases, only the age, sex, and site of biopsy were known.

Histological examination revealed that the number of histiocytes and pyknotic cells and the degree of phagocytosis were much lower in these cases than in the group without granulocytic infiltration. The biopsies from the patients with lupus erythematosus showed numerous nuclear "shadows" (Fig. 9)

Table 4. Main histological criteria for differential diagnosis between histiocytic necrotizing lymphadenitis without granulocytic infiltration (HNLWG) and necrotizing lymphadenitis in lupus erythematosus and bacterial infections

	HNLWG	Lupus erythematosus	Bacterial infections
Granulocytes	−	++	++
Nuclear shadows	+/−	++	+/−
Histiocytes	++	+	+
Nuclear debris	++	+	+
Phagocytosis	++	+	+
B immunoblasts	+/−	+	++

in addition to pyknotic cells and cellular debris in the necrotic areas. The biopsies from patients with bacterial infections contained a relatively large number of immunoblasts and plasma cells, which were positive for κ and λ chains. In the case with venous thrombosis at the same site as lymphadenopathy, the lymph node biopsy revealed extensive necrosis of lymphoid tissue, capsule fibrosis, dilatation of the marginal sinus, marked sclerosis of the medullary sinus and thrombosis of the veins around the node. Two of the three cases with incomplete clinical data showed nuclear shadows like those seen in the patients with lupus erythematosus. In the third case, there was a relatively large number of B immunoblasts and plasma cells.

Discussion

Among the cases presented here, the group without granulocytic infiltration represents the first observation of the lesion described by Kikuchi (1972) outside Japan. As in the Japanese reports, a majority of the patients in the present series were young women. The lesion frequently appeared as painful lymphadenopathy in the neck. The prognosis was always excellent, and many patients recovered without treatment. It is noteworthy, however, that generalized lymphadenopathy and enlargement of solitary lymph nodes outside the cervical region were more frequent in our series than in the larger ones reported previously (Kikuchi 1978; Wakasa et al. 1978). In contrast, leukopenia and fever appeared to be somewhat less common in the present series than in Japan.

On histological examination, involved lymph nodes showed varying degrees of necrosis and infiltration by histiocytes phagocytosing necrotic cells in the cortex and/or paracortex. Neutrophils and eosinophils were not found in any case. There was only a small number of plasma cells, and reactive changes were not evident in follicles. Only 2 cases showed moderate follicular hyperplasia; we could not determine whether it was preexistent. These findings are consistent with those previously reported to be characteristic of the lesion in Japan (Fujimoto et al. 1972; Kikuchi 1972, 1978; Wakasa et al. 1975, 1978; Kikuchi and Uryu 1976; Kikuchi et al. 1977). We propose that the lesion be called "histiocytic necrotizing lymphadenitis without granulocytic infiltration", because this term meets all the prerequisites for a histological diagnosis.

The second group of lesions included in the present study demonstrates that changes similar to those observed in histiocytic necrotizing lymphadenitis without granulocytic infiltration may be found in lymph nodes of patients with other diseases, namely, lupus erythematosus and bacterial infections. In such cases, however, the differential diagnosis is easy because of the large number of granulocytes, the moderate to small number of histiocytes, the small amount of nuclear debris and the low phagocytic activity. Futhermore, in lupus erythematosus, a high number of nuclear shadows is seen and in bacterial infections, the content of B immunoblasts and plasma cells is always larger. A similar lesion was also found in a patient with venous thrombosis at the same site as lymphadenopathy. This case showed features resembling those described by Steinmann et al. (1981) in lymph nodes of rabbits after venostasis and lymphostasis. A differential diagnosis was possible, not only because of the large number of granulocytes, but also because of the presence of thrombi in the veins around the involved node, which has never been observed in histiocytic necrotizing lymphadenitis without granulocytic infiltration.

Neoplasms that must be considered in a differential diagnosis are "sarcomas of histiocytic reticulum cells" or malignant histiocytosis. In the present series, a case without granulocytic infiltration had been diagnosed elsewhere as "histiocytic malignant lymphoma". In histiocytic necrotizing lymphadenitis without granulocytic infiltration, however, the histiocytes are more polymorphic, phagocytose more cellular debris (and relatively seldom erythrocytes) and do not show any atypical features.

Definite conclusions as to the aetiology of the lesion cannot be drawn from the present study. Only 10 cases were tested serologically. Toxoplasma gondii has been suspected of being responsible for the disease (Kikuchi et al. 1977; Kikuchi 1978), but all tests for this pathogen in our present series were negative. Nevertheless, the possibility of an underlying viral infection has to be considered, because necrosis of the lymph node parenchyma, especially in the paracortical region, is not uncommon in nodes of patients with viral diseases (e.g., infectious mononucleosis, vaccinia, varicella). There have been no reports, however, of contagion of histiocytic necrotizing lymphadenitis without granulocytic infiltration from one person to another.

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