Journal of Korean Medical Science
Vol 6, No. 1, 55-61, March 1991

Necrotizing Lymphadenitis
—A Clinico-Pathologic Study of 36 Cases with Immunohistochemical Analysis—

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Thirty-six cases of necrotizing lymphadenitis——including 33 cases of unknown etiology, 1 typhoid lymphadenopathy, and 2 cases of suspicious lupus lymphadenopathy——were clinico-pathologically reviewed and analyzed with immunostaining for s-100 and lysozyme. All cases histologically showed architectural effacement by paracortical lesions composed of nuclear karyorrhexis and mononuclear cell proliferation. Immunohistochemical study revealed proliferation of lysozyme-positive macrophages in the necrotizing areas and an increase in the number of s-100-positive cells in the uninvolved paracortical areas. This observation suggests that necrotizing lymphadenitis may be a common morphologic expression of a T cell-mediated hyperimmune condition induced by diverse etiologies.

Key Words : *Necrotizing lymphadenitis, Subacute necrotizing lymphadenitis, Immunohistochemistry, S-100 protein, Lysozyme, T cell*

INTRODUCTION

Necrotizing lymphadenitis has been studied most often in Japan since its first description as "lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytes" by M. Kikuchi in 1972. Many authors have regarded it as a relatively specific disease entity of unknown etiology because of the characteristic clinical and histopathologic features. The patients are usually young women with cervical lymphadenopathy of 2 to 3 months' duration, with or without fever. The lymphadenopathy resolves spontaneously, and the involved lymph nodes histologically show focal, rather well-circumscribed paracortical necrotizing lesions with abundant karyorrhectic nuclear debris and mononuclear cell proliferation. The differential diagnoses include malignant lymphoma, cat-scratch disease, lymphogranuloma venereum, systemic lupus erythematosus, mesenteric lymphadenitis due to yersinia enterocolitica, and other lymphadenopathies associated with bacterial infection. Recently we experienced 36 cases diagnosed as necrotizing lymphadenitis, 3 of which later were clarified as lymphadenitides of specific etiologic entities. A clinico-pathologic review and immunohistochemical study for S—100 protein and lysozyme in this series of cases were performed to un-

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This study is supported in part by a Seoul National University Hospital Clinical Research Grant (1985)

derstand the pathogenesis of this lesion and to examine whether any differences exist in the immunohistochemical reactions between the cases of unknown etiology and the others.

MATERIALS AND METHODS

Thirty-six cases diagnosed as necrotizing lymphadenitis or subacute necrotizing lymphadenitis were selected from the files of the Department of Pathology, Seoul National University Hospital, from 1980 through 1987. Tuberculosis cases and malignant lesions initially diagnosed as necrotizing lymphadenitis were excluded. Clinical histories and histopathologic materials of these cases were reviewed. For immunohistochemical study, the biotin-streptavidin (BSA) method was used. Steps for blocking of endogenous peroxidase activity and nonspecific antibody binding were processed as usual. As primary antibodies, rabbit polyclonal anti-human S−100 protein and anti-human lysozyme antibodies were applied for 40 minutes. Aminoethyl carbazole (AEC) was used as chromogen-substrate. Primary antibodies and BSA kits were purchased from Biogenex Laboratory (Calif., USA).

RESULTS

1. Clinical data

The ages of the 36 patients ranged from 13 to 43, with 78% in the 3rd or 4th decades. Females were more frequently encountered than males in a ratio of 3 : 1. The chief manifestations were cervical lymphadenopathy only in 28 and cervical lymphadenopathy with fever in 8. General malaise, anorexia, headache, or myalgia were present in a few patients. The durations of the symptoms were variable, ranging from 1 week to 20 years. Cervical lymphadenopathy was solitary in 22 and multiple in 14 cases and usually non-tender. Four patients had previous episodes of cervical lymphadenopathy 2 to 3 years ago. Splenomegaly was noted in one case. White blood cell (WBC) counts, checked in 23 cases, ranged from 1800 to 8300 /mm^3, and 10 cases counted under 4000/mm^3. A 20−year−old female patient was readmitted due to persistent fever and proved to be positive for Salmonella typhi on repeated blood cultures. A 32−year−old female with lymphadenopathy of the longest (20 years) duration turned out to have a long history of facial skin lesions of which histologic diagnosis was discoid lupus erythematosus. However, a further diagnostic work-up including

Table 1 . Summary of Clinical Data

Diagnosis	Sex	Age	Clinical Manifestation (No.of Cases)	Laboratory Data
Necrotizing lymphadenitis of unknown etiology (33)	F(24) M(9)	13−43 (mean 27)	*Single(21) or multiple(12) cervical lymphadenopathy for 1 wk−10 yrs *fever (6) *Malaise (3) *Anorexia (21) *Headache (1) *Splenomegaly (1) *Recurrence (4)	WBC 1800−8300 CRP(+) (3) Heterophile Ab (+) (1) Widal H 640 (1) Old Tb (3)
Suspicious lupus lymphadenopathy (2) pathy (2)	F(2)	21, 32	*Single or multiple cervical lymphadenopathy for 7&20 yrs *Skin lesion (1) *Hyperthyroidism& myalgia (1)	WBC 2600 (1) ASO>200 (+)
Typhoid fever (1)	F	20	*Multiple cervical lymphadenopathy for 3 wks *Fever& headache for 1 wk	WBC 2100 Blood culture (+) for S. typhi

laboratory tests was not done. Another problem case of a 21−year−old female showed a long history of repeated fever, arthralgia, myalgia, lymphadenopathy, and hyperthyroidism. A certain type of connective tissue disease was strongly suspected, but related laboratory tests revealed only positive ASO (>200) and CRP. None except these 3 patients harbored any specific etiological factor. The remaining remarkable laboratory findings included positive CRP in 3, weakly positive RA factor in 2, positive heterophile antibody in 1, Widal titer H 640 in 1, and old tuberculous lesions on chest x-ray in 3 patients. The clinical findings of all the cases are summarized in Table 1.

2. Histologic findings

Lymph nodes in thirty-three cases of unknown etiology showed focal (4 cases), partial (15 cases), or near total (14 cases) effacement of normal architecture by variable degree of paracortical necrotic areas with mononuclear cell proliferation. The necrosis was often extensive with scanty cellular elements but usually composed of nuclear karyorrhexis and phagocytosis rather than complete cell death. The degree of phagocytosis was also variable : severe in 7, moderate in 17, and mild in 9 cases. The proliferating cells largely consisted of histiocytes. Small areas of epithelioid histiocyte collections were observed in 5 cases. Another important cellular component was the immunoblast, and marked immunoblastic proliferation was noted in 8 cases (Fig.1). Remaining non-necrotic areas showed effaced follicles in most, but occasionally preserved lymphoid follicles were seen in 10 cases. In the medulla, starry-sky-like histiocytic proliferation was common (20 cases), and remarkable sinus dilatation and immunoblastic proliferation were noted in 3 and 1 case, respectively. Blood vessel (post-capillary venule) proliferation was usually associated. The histology of typhoid and suspicious lupus lymphadenopathy was virtually the same as those cases of unknown etiology. In the typhoid lymphadenopathy case, the necrosis was extensive with histiocytic proliferation and active phagocytosis. The non-necrotic protion revealed no residual follicles. The cases of suspicious lupus lymphadenopathy also showed multifocal or extensive necrotizing lesions of the same nature without demonstrable neutrophilic infiltration. The uninvolved areas contained a few preserved follicles with mild sinus histiocytosis. Minor histological variations are summarized in Table 2.

3. Immunohistochemical findings

Thirty-three cases were subjected to immunostaining for S−100 protein and lysozyme. The staining patterns were characteristic. In most cases, lysozyme-positive histiocytes were heavily aggrega-

Table 2. Summary of Minor Histological Variations.

Features	Unknown Etiology	Suspicious Lupus (No. of Cases)	Typhoid Fever
Extent of necrosis			
Extensive	14	1	1
Partial	10		
Focal	4		
Multifocal	5	1	
Cellular proliferation			
Minimal	3	1	
Histiocytes	17		1
Histiocytes& immunoblasts	8		
Histiocytes& epithelioid cells	5	1	
Phagocytosis			
Severe	7		1
Moderate	17		
Mild	9	2	
Non-necrotic portion			
Starry-sky pattern	20		
Sinus histiocytosis	3	1	1
Preserved follicles	10	1	

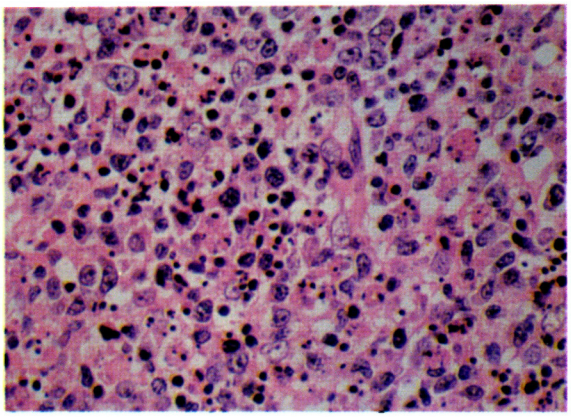

Fig. 1. Necrotizing area consisting of karyorrhectic nuclear debris, phagocytizing macrophages, and atypical immunoblasts (H&E, ×200).

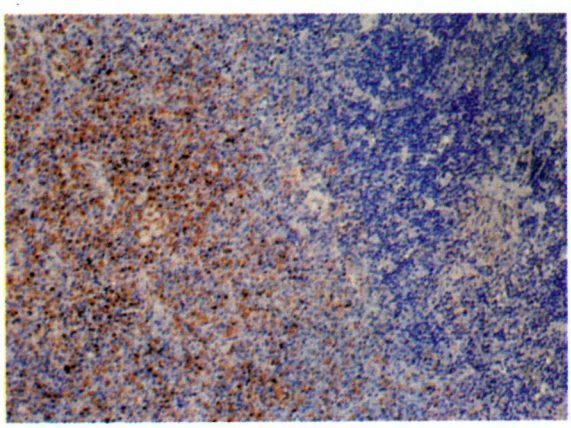

Fig. 2. Aggregated lysozyme-positive histiocytes in the necrotizing area (Immunostaining, ×40).

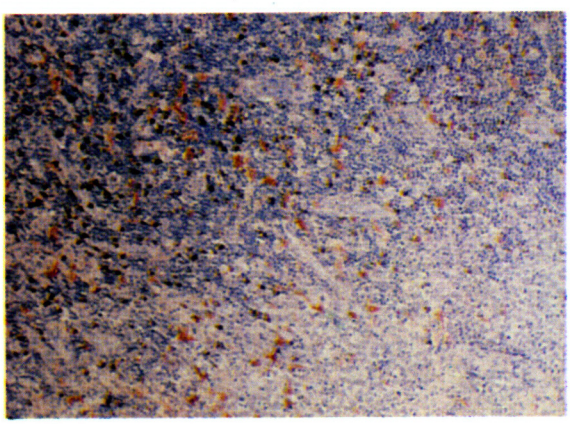

Fig. 3. Increased S−100−positive cells in non-necrotic paracortical portions (Immunostaining, ×40).

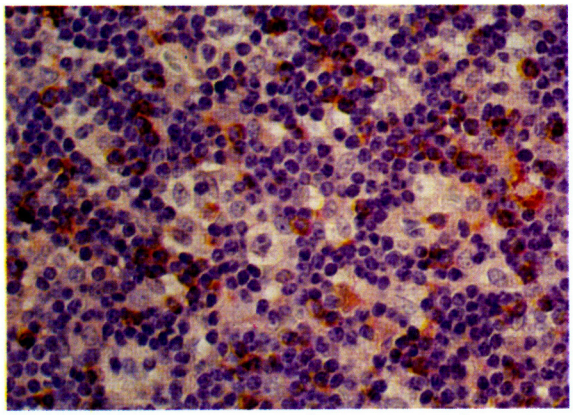

Fig. 4. A number of S−100−positive lymphocytes, possibly activated T cells, were noted in non-necrotic areas (Immunostaing, ×200).

ted in the necrotic zone, especially at the periphery (Fig.2). Non-necrotic paracortical areas showed an increase in S−100 protein-positive cells which were diffusely scattered or occasionally aggregated (Fig.3). A few lysozyme-positive cells were observed in this non-necrotic zone in half of the cases. Most of the paracortical S−100 protein-positive cells were large and polygonal, representing the T zone histiocytes, but often small with round nuclei and narrow cytoplasmic rims, possibly representing a kind of lymphocytes (Fig.4). The case of typhoid fever showed increased lysozyme-positive cells throughout the lymphnode. The cases of suspicious lupus lymphadenopathy also showed lysozyme-positive cells mainly in the necrotic zone and S−100 protein-positive cells nearby.

DISCUSSION

A group of lymphadenopathies reported in Japan as "lymphadenitis showing reticulum cell hyperplasia with nuclear debris and phagocytes" (Kikuchi, 1972), "cervical subacute necrotizing lymphadenitis" (Fujimoto et al., 1972), "necrotizing lymphadenitis" (Wakasa et al., 1975 & 1978), "phagocytic necrotizing lymphadenitis" (Kikuchi& Uryu, 1976), and "histiocytic necrotizing lymphadenitis" (kikuchi et al., 1980& 1986) represent a disease entity having characteristic clinico-pathologic features. Recently many compatible cases have been encountered in Korea (Koh et al., 1985) and elsewhere over the world (Dorfman, 1988 ; Pileri et al., 1982 ; Turner et al., 1983). Typical cases of necrotizing lymphadenitis are clinically characteri-

zed as self-limited cervical lymphadenopathies of subacute course in young females with or without fever or leukopenia. occasional cases of axillary, inguinal, mediastinal, abdominal, and generalized lymph node involvement have been reported (Imamura et al., 1982 ; Koh et al., 1985 ; Pileri et al., 1982 ; Wakasa et al., 1975 & 1978), but cervical lymphadenopathy is the rule. Female preponderance was common in many series, but a male predominance was also reported (Chan & Saw, 1986 ; Kikuchi et al., 1986). Thirty-three cases in this study showed similar clinical settings to the other reports, but longer symptom durations (up to 10 years).

Histologically, the lymph nodes showed paracortical necrotizing lesions with karyorrhexis, phagocytosis, and histiocytic proliferation, along with diffuse effacement of the nodal architectrue. Wakasa et al. (1978) divided the morphologic characteristics of necrotizing lymphadenitis into 3 patterns, but it was difficult to classify the patterns of the present cases clearly. The proliferating cells in the necrotic zones in most cases were phagocytizing histiocytes which stained positive for lysozyme on immunohistochemistry but included large atypical immunoblastic cells in 8 cases. Many authors described that these large lymphocytes were transformed T cells, which showed markers for cytotoxic/suppressor cells (Asano et al., 1987 ; Rivano et al., 1987 ; Turner et al., 1983), helper/inducer cells (Feller et al., 1983), or their mixtures (Kikuchi et al., 1986 ; Unger et al., 1987).

The nodular configuration of mononuclear cell proliferation and the presence of large blastoid cells with prominent nucleoli and frequent mitotic figures can lead to a misdiagnosis of malignant lymphoma. Conversely, the erroneous interpretation of the cases of malignant lymphoma or leukemic infiltration as necrotizing lymphadenitides accounts for the overemphasis on the atypism of mononuclear cell components of necrotizing lymphadenitis. It should be kept in mind that atypical mononuclear cell proliferation in subacute necrotizing lymphadenitis is restricted in the well-demarcated areas of necrotic background and admixed with histiocytic cells.

In portions of the lymph nodes spared by necrosis, a few residual follicles, histiocytosis of starry-sky pattern, and postcapillary venular proliferation were the most common findings. The same features have previously been described (Imamura et al., 1982 ; Kikuchi et al., 1986 ; Koh et al., 1985 ; Pileri et al., 1982 ; Unger et al., 1987), and Pileri et al. (1982) suspected that numerous cells scattered in mottled appearance among the small lymphocytes were interdigitating reticulum cells because of their negative reaction to lysozyme. These cells proved to be positive for S−100 protein in this study, possibly representing the antigen-presenting cells of the T zones.

The lymph nodes in some infectious diseases or systemic lupus erythematosus may show the features of necrotizing lymphadenitis. As a differential point, the absence of neutrophils, plasma cells, and Hematoxylin bodies in the latter has been emphasized (Dorfman, 1987 ; Pileri et al., 1982 ; Turner et al., 1983 ; Unger et al., 1987), however, the cases of typhoid and suspicious lupus lymphadenopathy in this series were so similar to the histologic and immunohistochemical features of those of unknown etiology that a differential diagnosis seemed impossible without clinical information. No other examples of necrotizing lymphadenitis with Salmonella infection have been documented so far.

The etiology of necrotizing lymphadenitis is still unclear. A viral etiology has long been suspected. A few cases with positive serum antibodies to Ebstein-Barr virus (Kikuchi et al., 1986 ; Rivano et al., 1987 ; Shirakusa et al., 1988), varicella (Kikuchi et al., 1986), cytomegalovirus (Kikuchi et al., 1986), and human immunodeficiency virus (Dorfman, 1987) were reported, but no viral particles have been identified ultrastructurally. Instead, many authors found intracytoplasmic tubuloreticular structures, which had been noticed within the endothelial cells or lymphocytes of patients with SLE or SLE-related diseases, within the immunoblasts, endothelial cells, and histiocytes in necrotizing lymphadenitis (Asano et al., 1987 ; Imamura et al., 1982 ; Shirakusa et al., 1988), suggesting that the lesion might reflect a SLE-like autommune condition. Dorfman and Berry (1988) observed that two patients who initially had histiocytic necrotizing lymphadenitis developed SLE and proposed that this disease might be a "forme fruste" of SLE. Elevated titers to Yersinia enterocolitica (Feller et al., 1983 ; Rivano et al., 1987) and Toxoplasma (Kikuchi et al., 1977, 1978 & 1986) were reported in several cases but have not been consistently demonstrated.

A great similarity of necrotizing lymphadenitis to the lupus lymphadenopathy, and the presence

of sporadic cases with serum titers to various microorganisms render the etiology of the disease obscure. But the consistent histologic and immunohistochemical features including characteristic paracortial T zone involvement, T cell and histiocyte proliferation in the necrotic areas, and the activation of T zone reticulum cells highly suggest a common pathogenesis by a T cell-mediated cellular immunity. It can be considered that this lesion may be a morphologic expression, rather than a distinct pathogenetic entity, of altered T cell-mediated cellular immunity induced by certain antigenic stimulation, which may be autoimmune, viral, bacterial, or protozoal. The natural history of necrotizing lymphadenitis was self-limited in most cases, but recently a mortality has been reported (Chan et al., 1989).

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