Yonsei Medical Journal
Vol. 26, No. 1, 1985

Subacute Necrotizing Lymphadenitis:

I. Histopathologic Study

Young Hyeh Koh, M.D.[1] In Joon Choi, M.D., and Yoo Bock Lee, M.D.

Since 1972, a unique lymphadenitis called "subacute necrotizing lymphadenitis" has been described in much Japanese literatures and in a few English articles. Although this condition is accepted as a new entity in Japan, it is not yet accepted in other countries. Occasionally, we have encountered lymph node biopsies which showed histologic pictures of subacute necrotizing lymphadenitis with clinical impressions of malignant lymphoma. As an initial step to investigating the etiology of this disease, the common clinicopathologic features in 24 cases of subacute necrotizing lymphadenitis were studied. The lesion frequently developed in the cervical lymph node of young women, causing simple enlargement of the lymph node and was accompanied occasionally by fever or pain. The duration of symptoms was within one month and seasonal distribution was not remarkable. In laboratory tests, WBC count was below 4000/mm³ in 8 cases and Widal test was negative in all 4 cases examined. Microscopically, the characteristic finding was the wide area of patch or confluent necrosis associated with numerous karyorrhectic nuclear dust and surrounded by diffuse infiltration of immunoblastic or activated histiocytoid cells. No appreciable increase in plasma cells or neutrophilic infiltration was noted.

Key Words: Sebucute necrotizing lymphadenitis (SNL), Pseudolymphomatous hyperplasia, necrosis, Nuclear debris, Immunoblast and histiocytoid cells

Since 1972 when Kikuchi *et al.* described a case of unique lymphadenitis called "subacute necrotizing lymphadenitis" (SNL) which had developed in the cervical lymph node of a young woman, approximately 380 cases have been reported in Japanese literatures. Terminology used to describe this phenomenum include; necrotizing lymphadenitis, necrotizing histiocytic lymphadenitis, phagocytic necrotizing lymphadenitis, focal histiocytic necrotizing lymphadenitis and pseudolymphomatous hyperplasia in lymph node.

Because of characteristic clinicopathologic features, subacute necrotizing lymphadenitis is well recognized in Japan as a distinct entity causing enlargement of the lymph node, but it is not recognized in other countries. Although Ebstein-Barr virus or Toxoplasma have been proposed as causative agents, the etiology remains unclear. Some investigators thought it was a kind of hyperimmune lymphadenitis.

Clinically, subacute necrotizing lymphadenitis presents as a cervical lymphadenopathy in young women and histologically shows focal necrosis surrounded by proliferating lymphoreticular cells.

The purpose of this paper is to report our experience on common clinico-histopathologic features of 24 patient with SNL as an initial step to investigating the etiology and pathogenesis of this condition.

MATERIALS AND METHODS

We reviewed 170 lymph node biopsies from January, 1979, to September, 1983, as lymphadenitis or necrotizing lymphadenitis in surgical pathology files at Yonsei University College of medicine, Severance Hospital. The cases associated with malignant lymphoma, suppuration with infiltration of neutrophils and infarct of lymph node were excluded. The 24 cases selected for this study showed only histologic features of SNL.

We reviewed all available clinical data. For histologic examination, hematoxylin-eosin stain, periodic-acid-Schiff stain, methyl-green pyronin stain and Giemsa stain were applied to all the paraffin sections.

Department of Pathology, College of Medicine, Yonsei University, Seoul, Korea

Present address; Instructor in Pathology, Hanyang University College of Medicine, Seoul, Korea[1]

Reprint request to Department of Pathology, Yonsei University College of Medicine (Chairman, In Joon Choi, M.D.).

RESULTS

Clinical data

Age, sex and seasonal distribution: Ages of the patients ranged from 1 month to 63 year old with a median value of 28, the majority (54%) belonging to the third decade. Females were affected more often than males. There were 20 females and 4 males with the female to male ratio of 5 to 1. Seasonal distribution of occurrence was not remarkable. But they developed more often in March and October, 6 and 4 cases respectively, as compared to other months.

Signs and symptoms: *Among 20 cases in which* clinical symptoms were recorded, all cases (100%) showed enlargement of a lymph node and this was accompanied by pain in 4 cases (20%) and fever in 5 cases (25%). Among 11 cases in which symptom duration was recorded, 5 cases (45%) were less than 10 days and 4 cases (36%) were less than 1 month. Among 24 cases, the site of lymphadenopathy was confined to the cervical lymph node in 19 cases (79%). The other 2 cases involved multifocally axillary, inguinal and cervical lymph nodes. The mesenteric lymph node was involved in 2 cases. The size of the lymph node after fixation in formalin solution was usually small to moderate. Thirteen cases were less than 1 cm and 1 case was between 1 and 2 cm.

Laboratory findings: Among 8 cases in which WBC was available, leukocytopenia less than 4000/mm³ was noted in six cases. Erythrocyte sedimentation rate was elevated in two out of three cases. Among cases where serologic tests were performed, Widal test was negative in all four cases and LE cell test was negative in one case.

Treatment and clinical course: All cases were not treated except antibiotic medicated 2 cases. Follow up study was possible in 15 cases, and among them 4 cases complained of recurrent lymphadeopathy. Rebiopsy was performed in 1 case and revealed the same histologic features of SNL.

Pathologic findings: All the cases showed partial or focal effacement of the normal nodal architecture with proliferation of mononuclear cells composed of large lymphoid and histiocytoid cells. On these backgrounds, focal or confluent necrosis was present and abundant karyorrhetic debris was scattered. Twenty-four cases were divided into three groups according to degree of necrosis and proliferation of mononuclear cells. Six cases were included in the first group characterized by extensive necrosis in area of more than a half of a lymph node with minimal proliferation of mononuclear cells.

Fig. 1. The lymph nodes show focal and multiple necrosis at cortex and paracortex. (H & E, ×100)

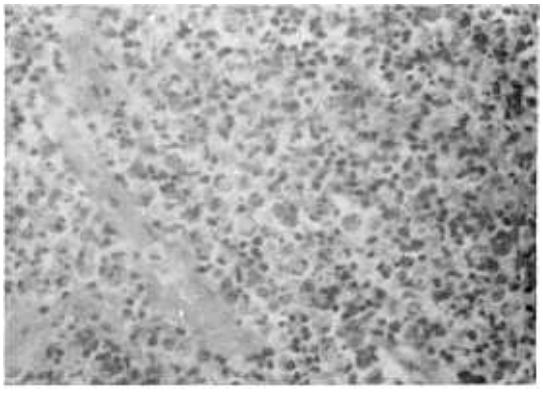

Fig. 2. The high power view of necrotic area showing numerous karyorrhectic nuclear debris. (H & E, ×400)

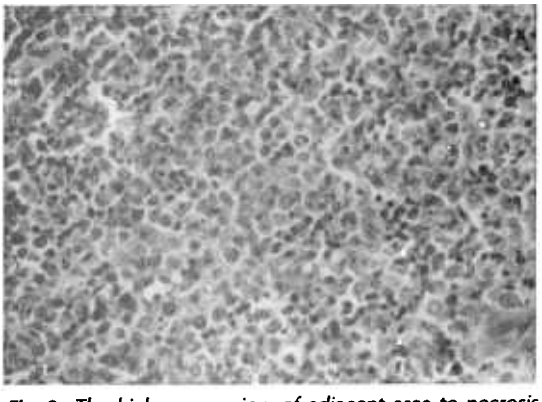

Fig. 3 The high power view of adjacent area to necrosis showing proiferation of immunoblasts and histiocytoid cells with frequent mitosis and active phagocytosis. (H & E, ×400)

The second group containing 13 cases showed typical histologic findings of SNL described in the

Table 1. Clinical findings in 24 cases of subacute necrotizing lymphadenitis

1. Age incidence: median age 28 yrs			
1 Mo - 9 yrs	2		
10 yrs - 19 yrs.	2		
20 yrs - 29 yrs.	13		
30 yrs - 39 yrs	4		
40 yrs - 49 yrs.	0		
50 yrs - 59 yrs.	2		
60 yrs - 63 yrs.	1		
2. Sex ratio. M:F = 4:20			
3. Symptom duration			
10 day ↓	5/11		
1 Mo ↓	4/11		
3 Mo ↓	1/11		
6 Mo ↓	1/11		
4. Seasonal distribution			
Jan.	2	July	2
Feb.	1	Aug.	2
Mar.	6	Sept.	2
Apr.	0	Oct.	4
May	1	Nov.	1
Jun.	2	Dec.	1
5. Lymphadenopathy			
Site – Cervical	19		
Axilla	1		
Mesentery	2		
Multiple	2		
Size – 1 cm ↓	13		
1 - 2 cm	10		
2 cm ↑	1		
Pain	4/20		
Fever	5/20		
6. Laboratory findings			
Leukopenia (<4000/mm³)	6/8		
ESR elevated (>20 mm/hr)	2/3		
Widal negative	4/4		
7. Treatment			
None	22		
Antibiotics	2		

Table 2. Morphologic pattern

I. Extensive necrosis with minimum cellular proliferation	6/24
II. Focal necrosis with nodular proliferation of mononuclear cells	13/24
III. Nodular proliferation of mononuclear cells with nuclear debris and phagocytosis	5/24

Table 3. Histopathologic features

Extent of lymph node involvement		
	entire	8/24
	partial	10/24
	focal	6/24
Extent of necrosis	confluant	6/24
	focal	13/24
	none	5/24
Germinal center		8/24
Mottled pattern		22/24
Capsular infiltration of large mononuclear cells		12/24
Karyorrhectic nuclear debris		24/24
Large mononuclear cell proliferation with frequent mitosis		24/24
Scarcity of plasma cell & absence of neutrophils		24/24

literature. These included focal necrosis in area less than a half of a lymph node and surrounded by a wide zone of proliferating mononuclear cells.

The third group showed extensive proliferation of mononuclear cells without evident focus of necrosis. Karyorrhectic debris was diffusely scattered. Five cases were included in this group

Necrosis was distributed throughout the cortex and paracortex in 13 cases; in 5 cases it was limited to the cortex and in 6 cases it was limited to the paracortical zone. In the necrotic area, phagocytoses of nuclear dust and deposition of fibrin were frequently noted but fibrinoid necrosis was not observed. Residual normal lymphoid tissue showed a mottled pattern in 22 cases. This finding was especially prominent in 12 cases. Germinal center was observed in 8 cases. The sinus was generally intact and not distended. The capsule of the lymph node was infiltrated by histiocytes and small lymphocytes in 12 cases.

DISCUSSION

In 1972, Kikuchi reported a case of lymphadenopathy which had developed in the cervical lymph node of a young woman, with histologic findings of focal proliferation of lymphoreticualr cells with abundant karyorrhectic material and active phagocytosis. At about the same time, Fujimoto reported a similar case and described is as "cervical subacute necrotizing lymphadenitis."

Characteristically, this lesion affects the young

adult. The cervical lymph node is most frequently involved and a few cases of systemic involvement have also been reported. Pain and fever frequently accompany it. This is invariably a benign process which resolves spontaneously within 2-4 weeks.

In addition to the common clinical features described in the literature, our 24 cases manifested relatively frequent leukopenia. But widal test was negative. After biopsy, all cases except 4 resolved spontaneously. Histologically, this condition was characterized by proliferation of lymphoreticular cells, a variable degree of necrosis, scarcity of plasma cells and absence of neutrophils.

Because of the proliferation of large mononuclear cells, differential diagnoses from other benign or malignant lymphadenopathy are important. Among these, malignant lymphoma with necrosis can be differentiated by monomorphous proliferation of neoplastic lymphoid cells completely effacing the normal lymphoid architecture. Lymphadenopathy in SLE is characterized by hematoxylin bodies scattered in the necrotic zone or perivascular area with more plasma cells, neutrophils and less phagocytic activity and nuclear dust than in SNL.

Toxoplasmosis shows clusters of epithelioid cells which are not found in SNL. Infectious mononucleosis is different from SNL in the presence of diffusely scattered immunoblasts with visible focus of necrosis. Among other benign lymphadenopathy with necrosis, catscratch-disease shows granulomatous lesion accompanied by abundant neutrophils. Necrosis by venous thrombosis is different from SNL in that many neutrophilic infiltrates with presence of thrombus in the perinodal vein. But these diseases cannot be easily differentiated. Diagnosis of SNL may be possible only after complete exclusion of other diseases. In all but 6 cases, proliferation of lymphoreticular cells was prominent but malignant lymphoma was easily excluded. Nests of epithelioid cells or infiltrates composed of plasma cells or neutrophils were not observed.

Although the etiology of SNL is still unclear, a lymphadenitis may be caused by a virus because in some patients diagnosed as SNL a high antibody titer to the Toxoplasma or Ebstein-Barr virus was noted. In some cases, toxin was suggested as a causing agent, but efforts to segregate the virus or other causative agents failed.

Because this lesion begins in the paracortical zone and shows findings similar to that of viral lymphadenopathy, the possibility of preceding viral infection as part of its etiology has been considered. Recently, a tubulo-reticular structure was found by ultrastructural study in the cytoplasm of lymphocyte or histiocytes in SNL. This structure had been reported in autoimmune disease, malignancy and viral infection. They were especially found in the glomerular endothelial cells and peripheral lymphocytes of patients with SLE. With this supportive evidence, SNL was thought to be a kind of autoimmunity and to have originated from a self-limited host reaction against the lymphocytes infected with some lymphocytotrophic virus.

The mechanism of necrosis is obscure. Some authors have proposed that this lesion might originate from necrosis of histiocytes because the proliferating mononuclear cells surrounding the necrosis have lysozyme in their cytoplasm. But a recent ultrastructural study indicated that these histiocytoid cells are ultrastructurally different from mature histiocytes and that transitional forms between the immunoblasts and histiocytoid cells were present. So the cells comprising this lesion are thought to be activated lymphocytes or immunoblasts. By immunohistochemical study, Turner determined that cells comprising this lesion are made up of an admixture of monocytes/macrophage and cytotoxic/suppressor T-lymphocytes. So necrosis in SNL might originate from cytotoxic T-lymphocytes induced by virus or other antigenic stimuli with reactive proliferation of lymphoid tissue.

We concluded that the 24 cases reviewed belonged to discrete entity of SNL recognized by a very typical clinical course and homogenous histologic findings. *For investigating the etiology and pathogenesis of this lesion, further clinical study and stepwise pathologic and immunologic planning would be valuable.*

REFERENCES

Campbell JAH: *Cat-scratch disease. In pathology annual, Vol 12, S.C. Sommers, Ed. Appleton-Century-Crofts, New York, 1977. pp. 277-292*

Dorfman RF, Warnke R: *Lymphadenopathy simulating the malignant lymphomas. Hum Pathol 5:519-550, 1974*

Fujimori T, Shioda K, Sussman EB, Miura M, Katayama I: *Subacute necrotizing lymphadenitis: A clinicopathologic study. Acta Pathol Jpn. 31:791-797, 1981*

Fujimoto Y, Kojima Y, Yamaguchi K: *Cervical subacute necrotizing lymphadenitis (in Japanese). Naika 30:920-927, 1972 (cited by Turner)*

Grimley PM, Schaff Z: *Significance of tubuloreticular inclusions in pathology of human diseases. Pathobiol Annu 6:221-257, 1976*

Imamura M, Ueno H, Matsuura A, Kamiya H. Suzuki T, Kikuchi

K, Oeno T: *An ultrastructural study of subacute necrotizing lymphadenitis. Am J Pathol 107:292-299, 1982*

Ioachim HL: *Lymph node biopsy. JB. Lippincott Company, Philadelphia, 1982, pp. 42-96*

Kikuchi M, Iwakaki H, Mitsui T: *Clinicopathologic study on histiocytic necrotizing Lymphadenitis (so called necrotizing lymphadenitis) (in Japan). J Jan Soc RES 20:Suppl 11-12, 1980*

Kikuchi M: *Lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytosis: A clinicopathologic study (in Japanese). Nippon Ketseuki Gakki Zasshi 35:379-380, 1972 (cited by Pileri)*

Kikuchi M: *Lymphadenopathy due to toxoplasmic infection and anticonvulsant. Recent Adv RES Res 18:97-123, 1978*

Kikuchi M, Uryu Y: *Phagocytic necrotizing lymphadenitis (in Japanese). Medical bulletin of Fukuoka University 3:321-322, 1976*

Kikuchi M, Yoshizumi T, Nakamura H: *Necrotizing lymphadenitis: Possible toxoplasmic infection: Case report. Virchows Arch (Path Anat) 376:247-253, 1977*

Michaeleck H: *Pseudolymphomatous hyperplasia in lymph nodes (Report of 9 cases). Trans Soc pathol Japan 66:209-210, 1977*

Norton WL: *Endothelial inclusions in active lesions of systemic lupus erythematosus. J Lab Clin Med 74:369-379, 1969*

Pileri S, Kikuchi M, Helbron D, Lennert K: *Histocytic necrotizing lymphadenitis without granulocytic infiltration. Virchows Arch (Patho Anat) 395:257-271, 1982*

Shimamine T, Mori S, Itoyama S: *Diagnostic points on biopsied lymph node of malignant lymphoma and allied disorders (in Japan). Nippon Rinsho 32:1197-1202, 1974 (cited by Pileri)*

Takada K, Iwanaga M, Osato T, Mikuni C, Maekawa I, Kawamura K, Miyake T: *Anti-EB virus titer in patient with subacute necrotizing lymphadenitis. Prog Med 112:194-196, 1980 (in Japanese)*

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

Wakasa H, Kimura N, Takahashi T: *Necrotizing lymphadenitis (in Japanese). Nippon Rinsho 33:1938-1943, 1975 (cited by Pileri)*

Wakasa H, Takahashi H, Kimura N: *Necrotizing lymphadenitis. Recent Adv RES Res 18:85-96, 1978*

Yamaguchi K, Shimamine T: *Cervical subacute necrotizing lymphadenitis (in Japanese). J Jpn Soc RES 20: Suppl 1-10, 1980.*