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Malignant lymphoma with a high content of epithelioid histiocytes (so-called Lennert's Lymphoma)

Immunocytochemical and ultrastructural observations

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Summary. The clinicopathological findings of four cases of an uncommon form of non-Hodgkin's lymphoma called malignant lymphoma with a high content of epithelioid histiocytes (MLHH) are described. In each case the peroxidase antiperoxidase technique was used for detecting cytoplasmic immunoglobulins (CIg) in the diagnostic lymphoid tissue. In one case (patient 1), IgG and IgM heavy chains and kappa light chain were detected in 30 to 40 percent of the atypical lymphoid cells. This result suggests that the proliferating B lymphocytes in this patient with MLHH are neoplastic rather than reactive in nature. We were unable to identify CIg in the proliferating lymphoid cells of the other three patients.

Our case when coupled with others reported in the literature suggest that the morphologic features of MLHH (so-called Lennert's lymphoma) can be associated with a neoplastic proliferation of either T or B lymphocytes.

The ultrastructural findings of one case are presented.

Key words: Non-Hodgkin's lymphoma – Lennert's lymphoma – Epithelioid histiocyte – Cytoplasmic immunoglobulins – Ultrastructure of Lennert's lymphoma

The name "Lennert's lymphoma" has been applied to a rare form of malignant lymphoproliferative disorder characterized by a high content of epithelioid histiocytes. In the course of a cytological investigation of Hodgkin's disease and Piringer's (Toxoplasmic) lymphadenitis in

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1952, Lennert noticed 3 cases in which small focal accumulations of epithelioid cells completely destroyed the lymph node architecture and the patients died within a relatively short period of time (Lennert 1981). Lennert considered the disease to be a variant of Hodgkin's disease and called it "epithelioid cellular lymphogranulomatosis". Lennert and Mestdagh (1968) studied 50 cases of "lymphogranulomatosis" (Hodgkin's disease) with a constantly high content of epithelioid histiocytes and they separated a particular form characterized by massive infiltrations of focally aggregated epithelioid histiocytes, paucity to absence of typical Reed Sternberg cells., frequent plasma cells and lack of fibrosis. They proposed the name "epithelioid cell lymphogranulomatosis" and they believed it was a variant of Hodgkin's disease. Subsequently Lennert et al. (1975) included this lesion within the non-Hodgkin's lymphomas, referring to it as "lymphoepithelioid cellular lymphoma".

It later became clear that the histopathological features described by Lennert and Mestdagh (1968) may occur in a variety of neoplastic and nonneoplastic lymphoid disorders, including non-Hodgkin's lymphoma, Hodgkin's disease, immunoblastic lymphadenopathy and unclassified abnormal immune responses. Burke and Butler (1976) and Kim et al. (1978) described two series of cases with histologic features similar to those reported by Lennert and Mestdagh (1968) under the disignation "malignant lymphoma with a high content of epithelioid histiocytes" (MLHH). They defined certain morphological criteria that would separate MLHH from other lymphoid lesions. Klein et al. (1977) and Delsol et al. (1978) pointed out that "Lennert's lymphoma" might not be a neoplasm but an abnormal immune reaction with similarities to angioimmunoblastic lymphadenopathy as well as a T cell proliferation. A recent review by Kim et al. (1980) concluded that non-Hodgkin's lymphoma with a multifocal epithelioid histiocytic reaction previously included in the heterogenous group called "Lennert's lymphoma", appears to be a distinct clinicopathological entity.

Uncertainty still exits, however, as to the morphological criteria, origin of the proliferating cells and natural history of MLHH. In this study we report on four patients of MLHH with immunocytochemical study of all cases and ultrastructural observations in one of the patients.

Materials and Methods

One or both of the authors was/were directly involved with surgical or autopsy material from cases 1, 2 and 4. Case 3 was obtained from the files of Presbyterian-University Hospital. Previous and subsequent surgical pathology material from all four cases were reviewed. Where indicated, paraffin blocks from referring hospitals were obtained and special stains performed. Clinical information was obtained from individual patient charts and from attending physicians.

The surgical pathology specimens were processed in the following manner. Sections for light microscopy were fixed in 10% formalin. These sections and those obtained from paraffin blocks from referring hospitals were stained with hematoxylin and eosin (H&E), periodic acid-Schiff reagent (PAS) with and without diastase, and methyl green pyronin (MGP) with and without ribonuclease. Representative formalin fixed paraffin embedded sections were immuno-stained using the peroxidase anti-peroxidase (PAP) technique (Sternberger 1979). Monospecific antisera to IgG, IgA, IgM, kappa and lambda light chains and lysozyme were employed. All antibodies used were commercially available from DAKO (Accurate Chemical and Scientific Co., Hicksville, NY USA).

Substitution of the primary antibody by tris-buffered saline solution and tissue from known cases of reactive and neoplastic lymphoproliferative disorders were simultaneously used as controls. Sections for electron microscopy from case 1 were obtained from two consecutive surgical specimens; the radical neck lymph node dissection (June 1980) and the axillary node biopsy (December 1980). The first specimen was initially fixed in 10% buffered formalin. Samples of this tissue were subsequently minced, washed thoroughly in 0.1 M Sorensen's phosphate buffer and post fixed in 1% OsO_4 (osmium tetroxide). After alcohol dehydration, they were embedded in Epon®-Araldite®. Portions of the axillary node were initially fixed in 2% glutaraldehyde and processed for electron microscopy. Thin sections were examined and photographed with a Phillips 200® electron microscope.

Results

Clinical and pathologic observations

The clinical data and stage of the disease at presentation are summarized in Table 1. Cervical lymphadenopathy was the chief complaint in all cases; in two, it was asymptomatic (Patients 1 and 4) and in the remaining two, it was associated with sore throat (Patient 2) and with fatigue, generalized lymphadenopathy and weight loss (Patient 3). The survival was from 17 to 72 months, with 2 patients presently alive, one with evidence of disease. One patient died 17 months after the initial diagnosis of MLHH, Residual MLHH type of lymphoma was found at autopsy and the cause of death was heart failure due to Loffler's endocarditis associated with blood eosinophilia. The second patient died with disseminated lymphoma 18 months after the initial diagnosis, no autopsy was done. The histopathological findings in the pretreatment lymph node biopsies are described in Table 2.

Table 1. Malignant lymphoma with high content of epithelioid histiocytes: Clinical information, stage of disease, treatment and survival

Patient	Age/sex/race	Stage of disease at presentation	Treatment	Survival
1	76/F/W	IA	RT[a], COP[b]	18 months, died with disease
2	61/F/W	IA	COPP[c], MOPP[d], RT[a]	72 months, alive with enlarged right cervical lymph node and splenomegaly
3	80/M/W	IIB	COP[b], COPP[c]	24 months, alive with no evidence of disease
4	56/F/W	IA	COP[b], C-MPP[e], Ch[f]	17 months, died with lymphoma. Cause of death: Loffler's endocarditis

[a] RT = Radiotheraphy
[b] COP = Cyclophosphamide, vincristine and prednisone
[c] COPP = Cyclophosphamide, vincristine, procarbazine and prednisone
[d] MOPP = Nitrogen mustard, vincristine, procarbazine and prednisone
[e] C-MPP = Cyclophosphamide, nitrogen mustard, procarbazine and prednisone
[f] Ch = Chlorambucil

Table 2. Malignant lymphoma with high content of epithelioid histiocytes. Histopathological findings in pretreatment lymph nodes

Patient	Architecture	Cellular morphology	Number of Mitoses per HPF	Necrosis and fibrosis	Vascular proliferation
1	Effaced, diffuse pattern. Extracapsular extension	Cells vary in size from small lymphocytes to large lymphoid cells and immunoblasts. Nuclei are mostly round to oval. Large number of epithelioid histiocytes in diffuse pattern. Rare plasma cells, neutrophils and eosinophils	2–6	Absent	Mild
2[a]	Same	Predominance of medium size lymphoid cells with round to oval nuclei and scanty cytoplasm. Small clusters of epithelioid histiocytes. Moderate number of plasma cells, neutrophils and rare eosinophils	0–2	Absent	Mild
3	Same	Same as patient 1. Moderate number of plasma cells. Mild number of eosinophils and neutrophils	0–2	Focally present	Mild
4	Same, involvement of capsule. No extracapsular extension	Same as patient 1. Numerous plasma cells	1–3	Absent	Moderate

[a] Second cervical lymph node biopsy, December 1976

Patient 1 underwent a left radical neck dissection and partial parotidectomy after a previous cervical lymph node biopsy was misdiagnosed as undifferentiated carcinoma. MLHH (so-called Lennert's lymphoma) was present in 26 of 31 left cervical lymph nodes (Fig. 1). Tonsillar involvement was present only in patient 2. A second left axillary lymph node biopsy in patient 3, one year after the initial diagnosis of MLHH, revealed a diffuse malignant lymphoma, mixed cell type, but without the component of epithelioid histiocytes.

Immunohistochemistry

Selected sections from the surgical specimens obtained from the four patients were stained by an immunoperoxidase method (Sternberger 1979). Cytoplasmic immunoglobulins, including the heavy chains of IgG and IgM and

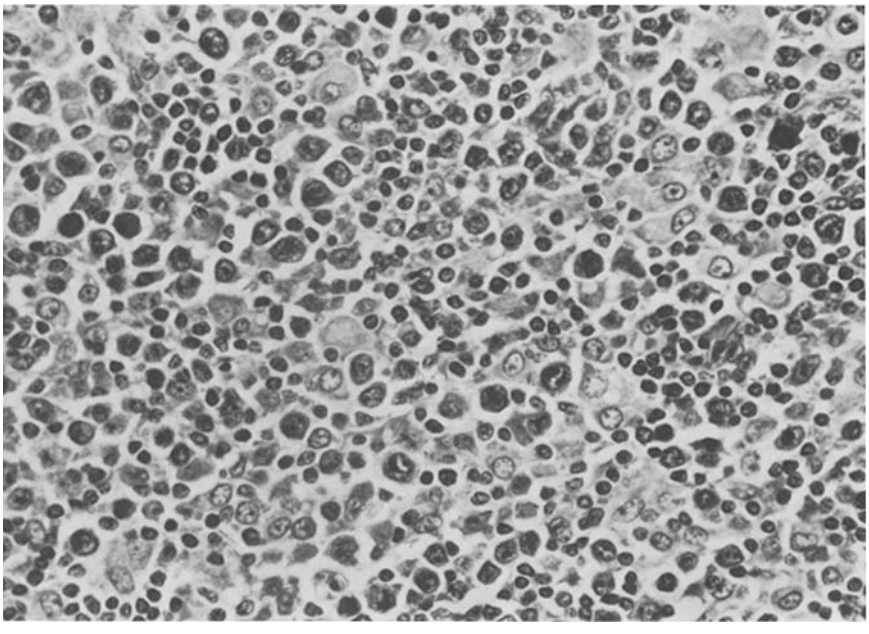

Fig. 1. Lymph node with a diffuse polymorphous infiltrate composed of epithelioid histiocytes, immunoblasts and irregular lymphocytes. Hematoxylin and eosin × 370

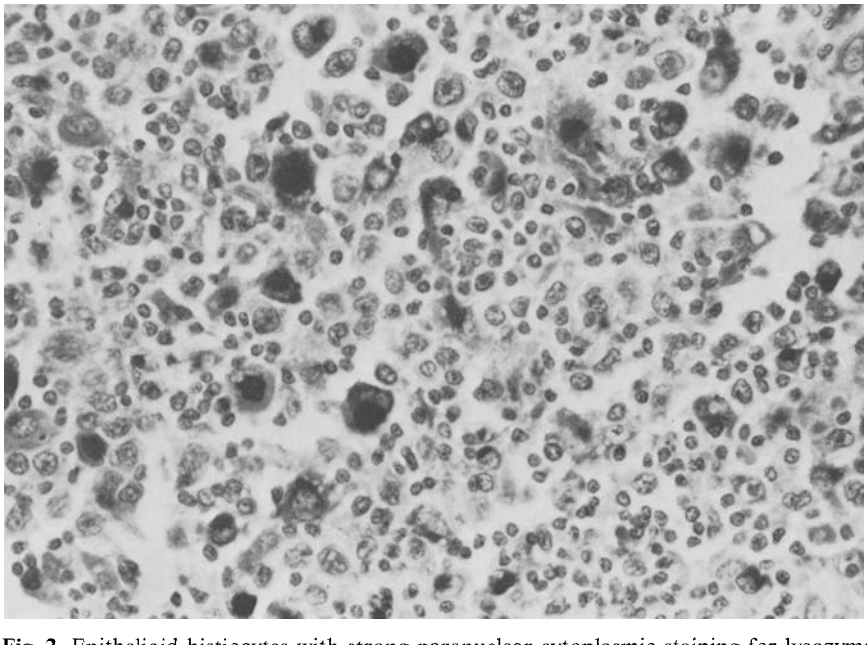

Fig. 2. Epithelioid histiocytes with strong paranuclear cytoplasmic staining for lysozyme. Immunoperoxidase × 370

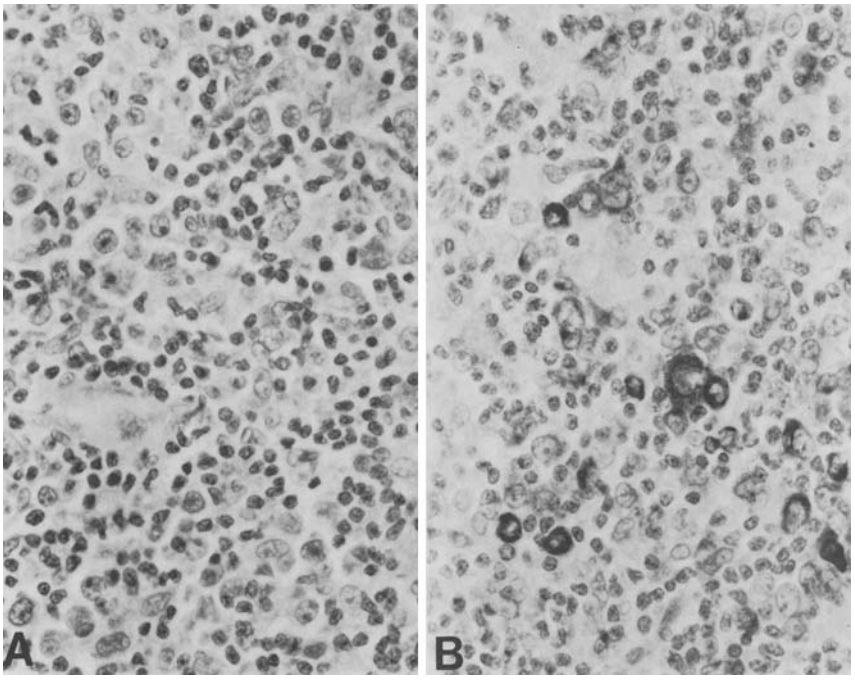

Fig. 3A, B. Malignant lymphoma with high content of epithelioid histiocytes showing **A** absence of staining for lambda light chain, and **B** cytoplasmic staining of atypical lymphoid cells with antiserum against Kappa light chain. Immunoperoxidase × 400

Kappa light chain were detected in 30–40% of the large atypical lymphoid cells in the axillary lymph node biopsy from patient 1. Antiserum to IgA and lambda light chain failed to stain the tumor cells (Fig. 3). Scattered mature plasma cells showed variable staining for all the immunoglobulins and both light chains. Sections from the cervical lymph nodes obtained from the radical neck dissection of patient 1 (pretreatment tissue) revealed similar findings than the axillary lymph node, though the proportion of stained cells was reduced to about 10%. No cytoplasmic immunoglobulins were detected in the proliferating lymphoid cells of the pathologic specimens from patients 2, 3 and 4. Only mature plasma cells stained in a polyclonal pattern. Immunoperoxidase staining for lysozyme (muramidase) showed in every case mild diffuse cytoplasmic staining of the epithelioid histiocytes with accentuation of the paranuclear regions (Fig. 2). Antiserum to lysozyme also stained scattered polymorphonuclear leukocytes and eosinophils.

Electron microscopy

Ultrastructural study was performed in the cervical lymph nodes and axillary lymph node of patient 1 and it confirmed the findings by light microscopy. Three distinct cell populations were identified by electron microscopy

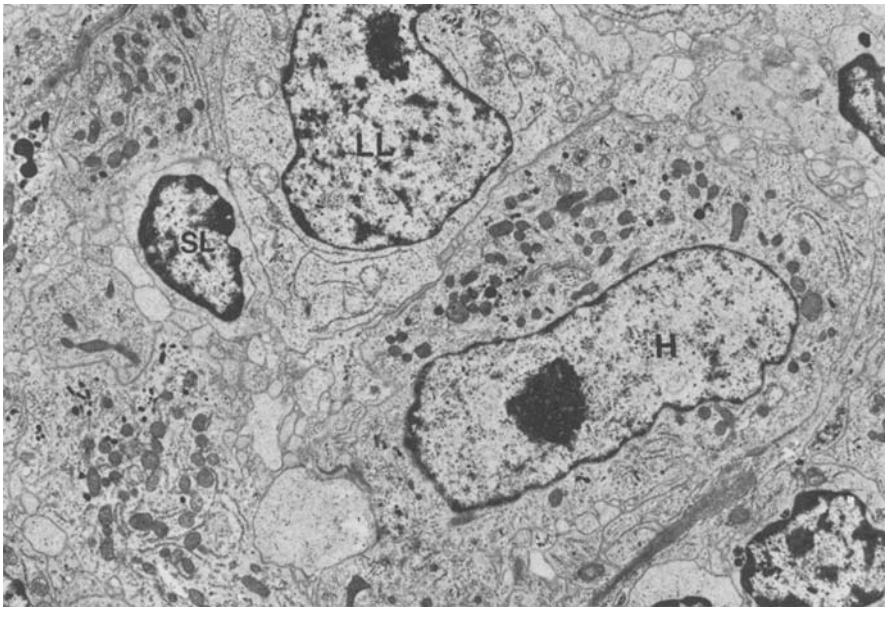

Fig. 4. Electron micrograph of involved axillary lamph node (patient 1) showing 3 main cellular types: (*H*) large histiocyte with elongated nucleus, prominent nucleolus and abundant cytoplasm containing numerous mitochondria, lysosomes, smooth and rough endoplasmic reticulum and a well developed Golgi apparatus; (*LL*) transformed lymphocyte with large nucleus and eccentric necleolus and cytoplasm containing strands of rough endoplasmic reticulum and few mitochondria, (*SL*) small to medium size lymphocyte (× 5,700)

(Fig. 4). The first cell type was a small to medium size lymphocyte with round dense nucleus containing coarse chromatin and occasional small nucleolus. The cytoplasm was scant and contained very few organelles. The second cellular component was a large lymphoid cell with round to slightly irregular nucleus, fine chromatin pattern and one to two prominent round to oval nucleoli. The cytoplasm of these cells was more abundant and contained numerous polyribosomes, few long strands of undilated rough endoplasmic reticulum and scattered mitochondria. A variant of these large lymphoid cells had features of immunoblasts and it was characterized by increased amount of rough endoplasmic reticulum and more prominent nucleoli. The third cell type was a large macrophage with abundant cytoplasm and irregular plasma membrane due to the presence of cell processes in intimate contact with the surrounding lymphoid cells. The nucleus of the macrophages was round to oval, often eccentric in location and contained fine chromatin and at least one well defined nucleolus. The cytoplasm showed a well developed golgi apparatus, numerous mitochondria, moderate amount of smooth and rough endoplasmic reticulum and many electron dense bodies of lysosomal nature. Occasional cells with intermediate features between lymphoid cells and macrophages were observed.

Discussion

The precise classification of MLHH (so-called Lennert's lymphoma) within the spectrum of lymphoproliferative disorders remains to be established. It was originally thought to be a variant of Hodgkin's disease, which tends to occur in older persons without sex predilection and with a relatively frequent tonsillar involvement (Lennert and Mestdagh 1968). Lennert et al. (1975) subsequently separated this lesions and came to view it as a non-Hodgkin's lymphoma, calling it lymphoepithelioid cellular lymphoma. Since then multiple cases and five series have been reported (Bednar 1979; Burke and Butler 1976; Hayes and Robertson 1979; Kim et al. 1978 and 1980). Numerous terminologies have been used to describe "Lennert's lymphoma" (Bednar 1979; Burke and Butler 1976; Dorfman 1975; Kim et al. 1978 and 1980; Lennert and Mestdagh 1968; Lennert et al. 1975; Robb-Smith 1976; The Lancet (editorial) 1976; Tindle 1977) which explains why many physicians are unfamiliar with this lesion. Even the term "lymphoma" has been questioned, and the suggestion has been made than „Lennert's lymphoma" may be an immune aberration of T cell origin rather than a neoplasm (Delsol et al. 1978; Klein et al. 1977).

A T lymphocyte origin has been implicated in the majority of previously reported cases (Delsol et al. 1978; Klein et al. 1977; Palutke et al. 1978; Tindle 1977). However, a B lymphocyte origin has also been proposed (Bednar 1979; Kim et al. 1980; Miller et al. 1979; Mikata et al. 1979; Watanabe et al. 1981).

In one of our cases (patient 1), two consecutive lymph node specimens contained a monoclonal population of atypical lymphoid cells bearing cytoplasmic IgG and IgM heavy chains and Kappa light chain. Although uncommon, the production of more than a single class of light and/or heavy chains by neoplastic lymphoid cells of a single clone has been well documented (Choi and Wong 1981; Pangalis et al. 1981). This result indicates that this case, which fit the morphologic criteria for MLHH as defined by Burke and Butler (1976) and Kim et al. (1978) represents a neoplastic proliferation of B lymphocyte origin. We were unable to detect cytoplasmic immunoglobulins in the specimens of the other 3 patients by the PAP method on paraffin embedded material. The negative PAP reaction in these cases may be due to inactivation of the antigenic reactivity of CIg during fixation and processing of the tissue. An alternative explanation is that the proliferating lymphoid cells are of T cell origin. Unfortunately, unfixed tissue was unavailable for performing studies of T cell markers. However, a T cell origin of the proliferating lymphoid cells has been demonstrated in some cases of MMLH (Delsol et al. 1978; Palutke et al. 1978 and 1980; Tindle 1977). Therefore, we believe that neoplastic proliferations of either B or T cell lymphocyte origin can manifest the morphologic features of MLHH. The nature of the epithelioid histiocytes remains to be elucidated. While most reports describe these cells as benign in appearance and suggest a reactive role (Kim et al. 1980), in some of our cases there appeared to be focal histiocytic dysplasia characterized by nuclear irregularity, increased nucleocytoplasmic

ratio and nucleolar prominence. Focal nuclear atypicality of the epithelioid histiocytes was also reported by Bednar (1979) and a case of "Lennert's lymphoma" terminating as malignant histiocytosis has been described (Economopoulos et al. 1979). These findings raise the question of a neoplastic potential for the epithelioid histiocytes. Ultrastructurally, however, these cells do not differ from reactive macrophages seen in other non neoplastic disorders.

MLHH can be distinguished histologically from angioimmunoblastic lymphadenopathy and Hodgkin's disease. Morphologic criteria that help to differentiate the above mentioned lesions have been described by Burke and Butler (1976) and Kim et al. (1978).

In our cases we excluded the diagnosis of Hodgkin's deseases on the basis of the absence of Reed-Sternberg cells and by the presence of atypical lymphoid cells. Angioimmunoblastic lymphadenopathy was ruled out by the atypia of the proliferating lymphoid cells and the lack of a prominent arborizing vascularity of the stroma and absence of amorphous intercellular material. Electron microscopy appears to have a very limited value in the differentiation between these lymphoproliferative disorders. In one of our cases, the ultrastructural study confirmed the light microscopic findings and demonstrated three different main types of cells in MLHH (Fig. 4).

Since MLHH is an uncommon type of lymphoid malignancy, pathologists are in general unfamiliar with this lesion. In three of our patient's, the definitive diagnosis was made only after consultation with an experienced hematopathologist. The lymph node biopsy of the other patient (Case 1) was initially misdiagnosed as undifferentiated carcinoma. The subsequent left radical neck dissection showed MLHH involving 26 of 31 cervical lymph nodes.

In conclusion, we believe that MLHH (so-called Lennert's lymphoma) represents a variant of non-Hodgkin's lymphoma, most commonly of a "mixed" cell type by virtue of the polymorphism of its proliferating lymphoid cells and characterized by a prominent epithelioid histiocytic cell component. The morphologic features of this lymphoma can be associated with a neoplastic proliferation of either T or B cell lymphocytes. We describe four cases of MLHH, one of which was associated with a monoclonal proliferation of B cell origin as demonstrated by the presence of CIg in the proliferating lymphoid cells.

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