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Histological, immunohistological and autopsy findings in lymphogranulomatosis X (including angio-immunoblastic lymphadenopathy)

H. Knecht, E.-W. Schwarze, and K. Lennert

Lymph Node Registry, Institute of Pathology, Christian Albrecht University, D-2300 Kiel, Federal Republic of Germany

Summary. 172 cases of lymphogranulomatosis X (LgX) were studied by light microscopy. In 53 cases immunohistological techniques for detecting intracytoplasmic immunoglobulins were applied. In the lymph nodes of all cases the nodal architecture was found to be effaced. Active germinal centres were absent, and there was a generalized, markedly increased proliferation of epithelioid venules. A polymorphic infiltrate was present in all cases. It was dominated by immunoblasts in 14%, by plasma cells in 16%, by epithelioid cells in 23% and by lymphocytes in 6% of the cases. In the remaining 41% of the cases no special type of cell predominated (mixed cell type of LgX). The clusters of clear cells present in some cases with immunoblastic predominance did not stain for intracytoplasmic immunoglobulins; in contrast, the basophilic immunoblasts exhibited a polyclonal Ig pattern. In some of the cases with lymphocytic predominance most of the lymphocytes showed abundant cytoplasm with azurophil granules.

Transformation into malignant lymphoma was proven at autopsy in 5 of 38 cases (13.2%). Malignant transformation (biopsy and autopsy material) was confirmed in a total of 11 of 172 cases (6.4%) and suspected in an additional 7%. Among the malignant lymphomas were one immunologically proven B-immunoblastic lymphoma, one peripheral T cell lymphoma and 5 cases of Hodgkin's disease. An association between LgX and carcinoma was histologically verified in 7 cases. 26 cases with active germinal centres and 11 cases with only locally pronounced vascularization but with histological and cytological changes that were otherwise similar to LgX were designated as hyperimmune reactions (HR). These cases had a significantly better prognosis. Two cases that presented as HR with active germinal centres later developed into LgX. It is suggested that the disappearance of active germinal centres is important in the pathogenesis of LgX. The possibility that

Offprint requests to: K. Lennert at the above address

this may correspond morphologically to an alteration of different components of the T-cell system is discussed.

Key words: Lymphogranulomatosis X – (Angio)-immunoblastic lymphadenopathy – Immunohistology – Malignant transformation – Prognostic factors

Introduction

Lymphogranulomatosis X (LgX) (Lennert 1973; Lennert and Mohri 1974), which closely resembles and includes "immunoblastic lymphadenopathy" (Lukes and Tindle 1975; 1978) and "angioimmunoblastic lymphadenopathy" (Frizzera et al. 1974; 1975), is a clinicopathological syndrome characterized by generalized lymphadenopathy, hepato/splenomegaly, fever and quantitative changes in serum protein levels (Radaszkiewicz and Lennert 1975; Cullen et al. 1979). As early as 1954 Forster and Moeschlin reported one case that obviously belonged to this disorder. The first European report on a small series of this syndrome was given by Flandrin et al. (1972).

Histologically LgX is characterized by three typical changes in the affected lymph nodes: 1) effacement of the nodal architecture, 2) absence of active germinal centres and 3) generalized and markedly increased proliferation of epithelioid venules (Lennert et al. 1979). The cytology is always polymorphic, but one particular type of cell may predominate (Lennert et al. 1979). Hence five subtypes have been distinguished: type I, immunoblastic predominance; type II, plasma-cell predominance; type III, mixed cell type (no predominating cell type); type IV, epithelioid cell predominance; type V, lymphocytic predominance.

LgX is thought to be one of the most important prelymphomas (Lukes and Tindle 1975; Nathwani et al. 1978; Lennert et al. 1979). Evolution into malignant lymphoma occurs in more than 30% of the cases, according to Nathwani et al. (1978), although Lennert et al. (1979) give a figure of 6–13%. These differences are due largely to the varying definitions of malignant lymphoma.

Detailed information on onset of disease, clinical behaviour, malignant transformation and electron microscopic findings in LgX have been reported elsewhere (Lennert et al. 1979, Knecht and Lennert 1981 a, b, c).

This report deals with the histological, immunohistological and postmortem findings in LgX and compares them with an LgX-like lymph node lesion showing mostly active germinal centres. This kind of lymph node lesion, which is associated with a more favourable clinical course, is designated as a hyperimmune reaction (HR).

Material and methods

Lymph node samples from 172 patients with LgX and 37 patients with HR were examined histologically. In all cases 4 μ sections were stained with Giemsa, haematoxylin and eosin (H&E), periodic acid Schiff (PAS) and silver impregnation (Gomori). A second lymph node

biopsy was examined in 46 patients, a third in 15 patients and a fourth in 5 patients. Imprints of lymph nodes from 15 patients were also investigated.

Immunohistological stainings to detect intracytoplasmic immunoglobulin (Ig) and lysozyme were performed in 53 cases of LgX and 7 cases of HR by a modification of the PAP method of Sternberger et al. (1970). Dilutions of primary antisera were 1:200 for κ and λ, 1:100 for IgG, IgM and IgA and 1:50 for lysozyme. Negative controls were performed by replacing the specific antisera with normal rabbit serum and Tris-saline. The linking antiserum (sheep anti-rabbit) was furnished by Dr. H. Stein. All other antisera used were products of DAKO Immunoglobulins Ltd, Copenhagen, Denmark.

Bone marrow and *spleen biopsies* were investigated histologically in 6 cases each, liver biopsies in 7, and skin specimens in 4 cases.

Autopsy material was available for examination in 22 cases (21 cases of LgX and 1 case of HR), and in 19 additional cases (17 cases of LgX and 2 cases of HR) autopsy reports were available.

Results

Histopathology

In 172 cases in which polymorphic cellular infiltrates were found in the lymph nodes, the nodal architecture was totally effaced, active germinal centres were absent, and a generalized proliferation of epithelioid venules was found (Fig. 1). Thus these cases fulfill the diagnostic criteria for LgX. In contrast, 37 cases differed from LgX in that active germinal centres were found (26 cases) or there was only locally pronounced vascular proliferation (11 cases). Additionally they showed areas in which the nodal architecture

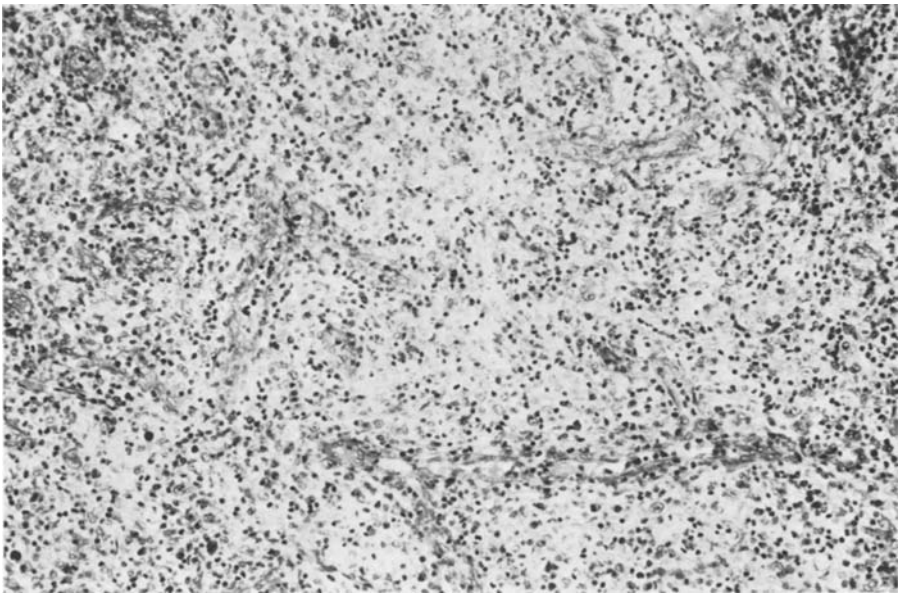

Fig. 1. Lymphogranulomatosis X. The lymph node architecture is effaced, no residual active germinal centres are found and a proliferation of epithelioid venules can be seen. Even at a low magnification the polymorphic cytology of the infiltrate is recognizable. PAS $\times 140$

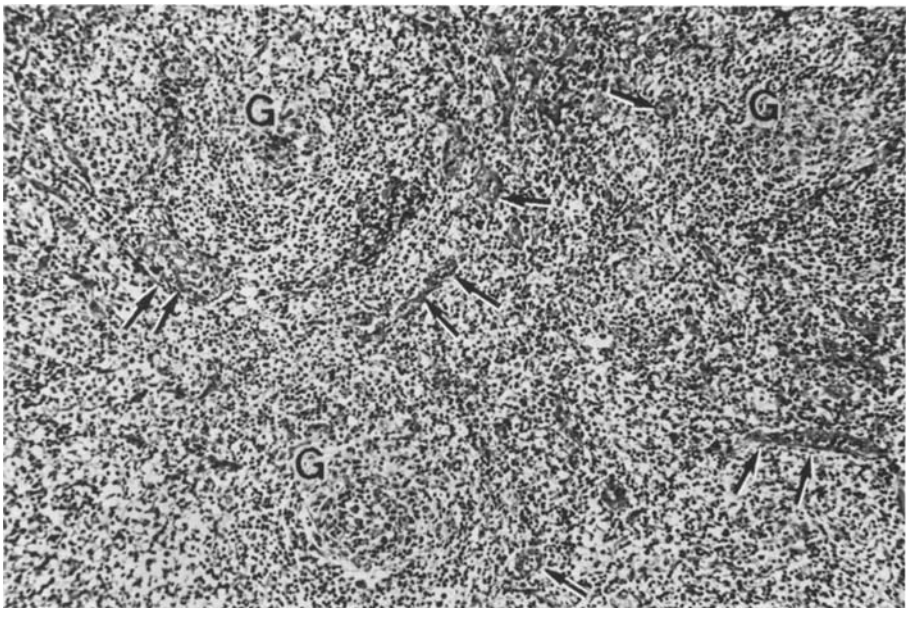

Fig. 2. Lymph node with changes classified as a hyperimmune reaction (*HR*). The architecture of the lymph node is still preserved. Active germinal centres (*G*) and expanded paracortical areas showing vascular proliferation (*arrows*) can be detected. PAS ×100

Table 1. Histological alterations in lymph nodes in LgX ($n=172$) and HR ($n=37$)

	LgX (%)	HR (%)
Residual sinuses	19	51
Capsular infiltration (immunoblasts, plasma cells, lymphocytes)	65	30
Capsular destruction by infiltrates	26	5
Pronounced capsular vascularization	24	11
Thickening of arteriolar walls	21	15
PAS positive intercellular space	49	24
Increase in number of reticulin fibres	20	32
Focal necrotic areas	5	5
Lymphocytes within walls of epithelioid venules	37	49
Lymphocytes arranged in rows around epithelioid venules	33	35
Eosinophilia (moderate to pronounced)	34	32
Mast cell (moderately elevated number)	24	24

was preserved. They were considered to be "hyperimmune reactions" (HR) (Fig. 2).

Apart from the histological particularities of LgX and HR, several alterations are present in both at variable frequency (Table 1).

Progression from HR with active germinal centres to LgX of the plasma cell predominance type was observed twice in later biopsies. It was characterized by the disappearance of active germinal centres and increased vascular-

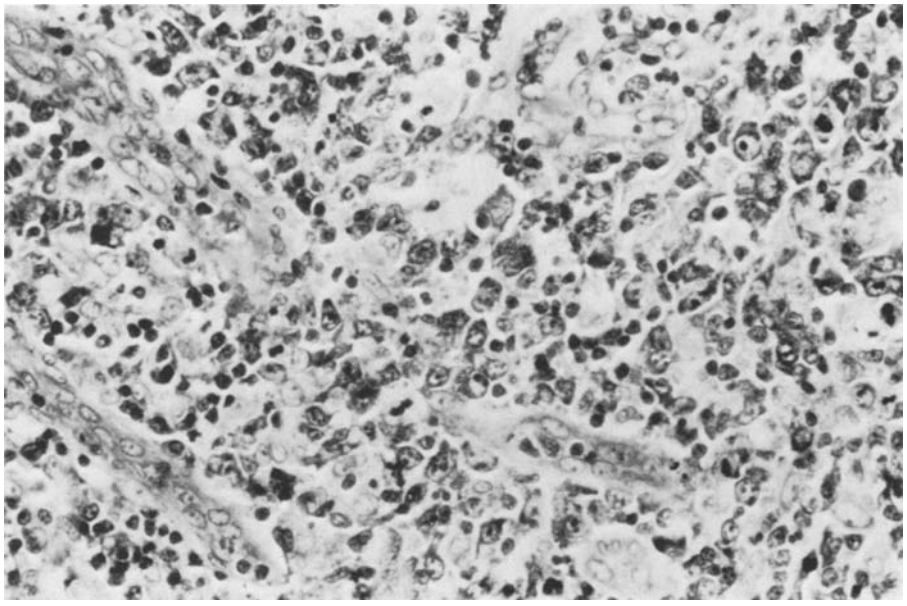

Fig. 3. Immunoblastic type of LgX. Among the infiltrating cells numerous immunoblasts with prominent nucleoli and intensely basophilic cytoplasm can be recognized. Giemsa × 320

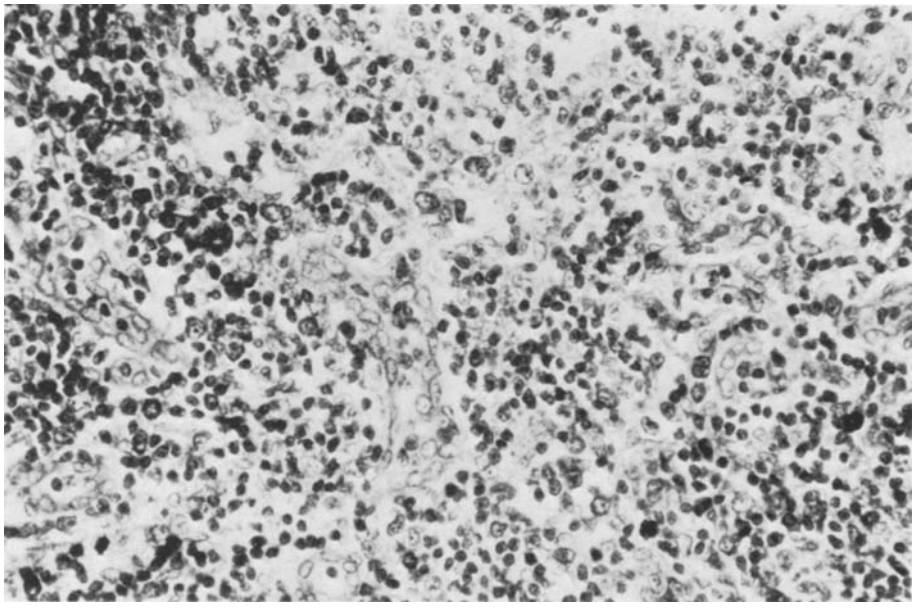

Fig. 4. Lymphocytic type of LgX. Most of the infiltrating cells are lymphocytes, often with polymorphic nuclei. A few immunoblasts and plasma cells are also present. Giemsa × 320

Table 2. Histological findings in the different types of LgX

	Type of LgX				
	I	II	III	IV	V
	($n=24$) %	($n=28$) %	($n=70$) %	($n=37$) %	($n=11$) %
Capsular destruction due to infiltration	*38*	21	27	26	9
PAS positive intercellular spaces	33	*75*	51	44	27
Burnt out germinal centres	25	21	19	3	0

Table 3. Cytological findings in the different types of LgX

Type of cell	Type of LgX				
	I	II	III	IV	V
	($n=24$) %	($n=28$) %	($n=70$) %	($n=37$) %	($n=11$) %
Clear cells	*42*	11	4	0	9
Eosinophilia (moderate to pronounced)	13	18	*51*	28	36
Mast cells (moderately elevated number)	13	7	34	23	27
Multinucleated plasma cells	0	*11*	4	0	0
Multinucleated histiocytes	0	0	6	*8*	0

isation. In one case it occurred after a period of 2 $^1/_2$ years, in the other after a few months.

It was possible to divide the 172 cases of LgX into different types on the basis of the different components of the cellular infiltrates. Although the infiltrate was polymorphic in all cases, it was dominated by one specific type of cell in about 60% of the cases. Immunoblasts prevailed in 24 cases (Fig. 3), plasma cells in 28 cases, epithelioid cells in 39 cases and lymphocytes in 11 cases (Fig. 4). The histological alterations (listed in Table 1) did not vary much between the different types of LgX, except for the destruction of the capsule by infiltrates, the PAS positivity in the intercellular spaces and the occurrence of burnt out germinal centres (Table 2).

Of particular interest were the immunoblasts, especially in the immunoblastic type of LgX. In addition to the typical B cell-derived immunoblasts with basophilic cytoplasm, there were unusual looking blast cells with abundant pale cytoplasm. The nuclei of these so-called "clear cells" displayed finely dispersed chromatin and one, or up to several small to medium-sized nucleoli. In four cases of the immunoblastic type of LgX the clear cells formed clusters or small islands. Though mainly found in the cases with immunoblastic predominance, they were also identified in other forms of

Table 4. Immunohistological findings in LgX and HR

LgX	*n*	Immunostaining for				Monoclonal areas	Clusters of clear cells without immunostaining	Monoclonality at later biopsy
		κ/λ	γ	μ	α			
I	11	11	7	7	5	0	4	–
II	13	13	13	13	12	1 κ	0	1 γ/λ
III	15	15	14	14	13	0	0	–
IV	11	11	10	8	7	0	0	–
V	3	3	3	3	1	0	0	–
HR	7	7	6	7	6	0	0	–

LgX (Table 3). Further cytological particularities of the different forms of LgX are shown in Table 3.

Mitotic activity was highest in LgX type I (25 ± 16 mitotic figures per ten fields) and lowest in type V (9 ± 8 mitotic figures per ten fields). Occasional atypical mitotic figures (tri/tetrapolar) were identified in one case of the immunoblastic type, two cases of the plasma cell type and two cases of the mixed cell type of LgX.

Immunohistology

Seven of 11 cases with immunoblastic predominance (Table 4) exhibited a polyclonal pattern (Fig. 5) with blast cells that were positive for κ and λ and also stained positively for heavy chains (γ, μ and α in 5 cases, γ and μ in 2 cases). In 4 cases only a few blast cells showed a positive reaction for κ and λ chains. The blast cells with clear cytoplasm, which were occasionally arranged in clusters, did not stain for cytoplasmic Ig.

All 13 cases of the plasma cell predominance type exhibited a polyclonal pattern at first biopsy: in 12 cases κ/λ, γ, μ and α chains, in 1 case κ/λ, γ and μ chains. In 1 case, however, there were remnants of subcapsular sinuses infiltrated by blast cells and plasma cells that stained only for κ light chains (Fig. 6). Three cases later developed monoclonal gammopathy (clinical diagnosis). In 1 case malignant progression to immunoblastic lymphoma of the type γ/λ (Fig. 7) was proven by immunohistological staining of a third biopsy performed after a 3 month interval and later confirmed at autopsy.

A polyclonal pattern was also found in the 15 cases of the mixed cell type. 13 cases were positive for κ/λ, γ, μ and α, 1 case for κ/λ, γ and μ chains. In 1 case only a few κ and λ positive cells were observed. The average number of positive plasma cells and immunoblasts was considerably lower than that seen in LgX types I and II.

In 10 of the 11 cases with epithelioid cell predominance many epithelioid cells and macrophages stained strongly for lysozyme. κ/λ light chains and γ, μ and α chains were regularly detected in 7 cases. In 4 cases only a few

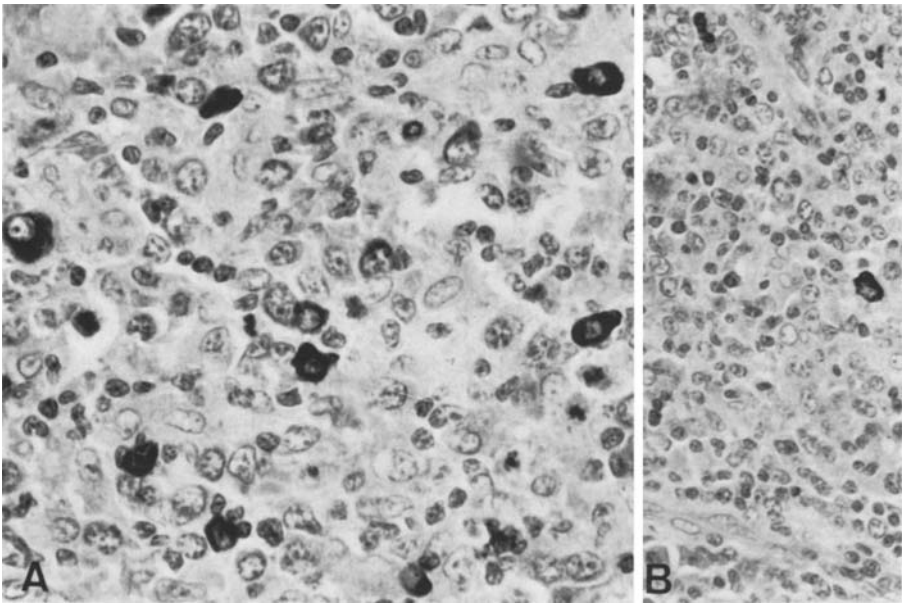

Fig. 5a, b. Immunoblastic type of LgX. **a** Many of the infiltrating cells are immunoblasts and plasmablasts. Numerous immunoblasts showing positive immunostaining for IgM are seen. (Most of the remaining immunoblasts stained for IgG). ×440. **b** Same case. Only occasional immunoblasts and plasma cells stained for IgA, as seen at a lower magnification. ×250

cells stained for intracytoplasmic Ig; κ/λ, γ and μ chains could be detected in 1 case and κ/λ and γ chains in 2 cases. In 1 case no heavy chains could be detected.

The 3 cases of the lymphocytic predominance type contained a few plasma cells that were positive for κ/λ light chains. Occasionally γ and μ positive cells were present. Cells positive for α occurred in only one case.

Six of the 7 HR cases examined immunohistologically showed a polyclonal pattern (κ/λ, γ, μ and α). In one case a few plasma cells only stained for κ/λ and μ.

Autopsy findings including malignant transformation

Generalized lymph node involvement was identified at autopsy in 86.8% of the cases (Table 5) and splenic alterations (mainly polymorphic cellular infiltrate, vascular proliferation and pronounced fibrosis) were present in 76.3%. In a few cases anaemic splenic infarctions could be identified. Splenic enlargement was generally a prominent feature; the mean weight of 20 spleens, on which precise data were available, amounted to 663 ± 364 g. Liver involvement was found in 36.8% of the cases. In addition to infiltrates of lymphocytes and plasma cells in a preferentially periportal location, fibrosis and necrosis of liver tissue was occasionally seen. Bone marrow infiltrates similar to those in lymph nodes were detected in 34.2% of the cases. Isomorphic infiltrates were identified once each in the choroid plexus, the

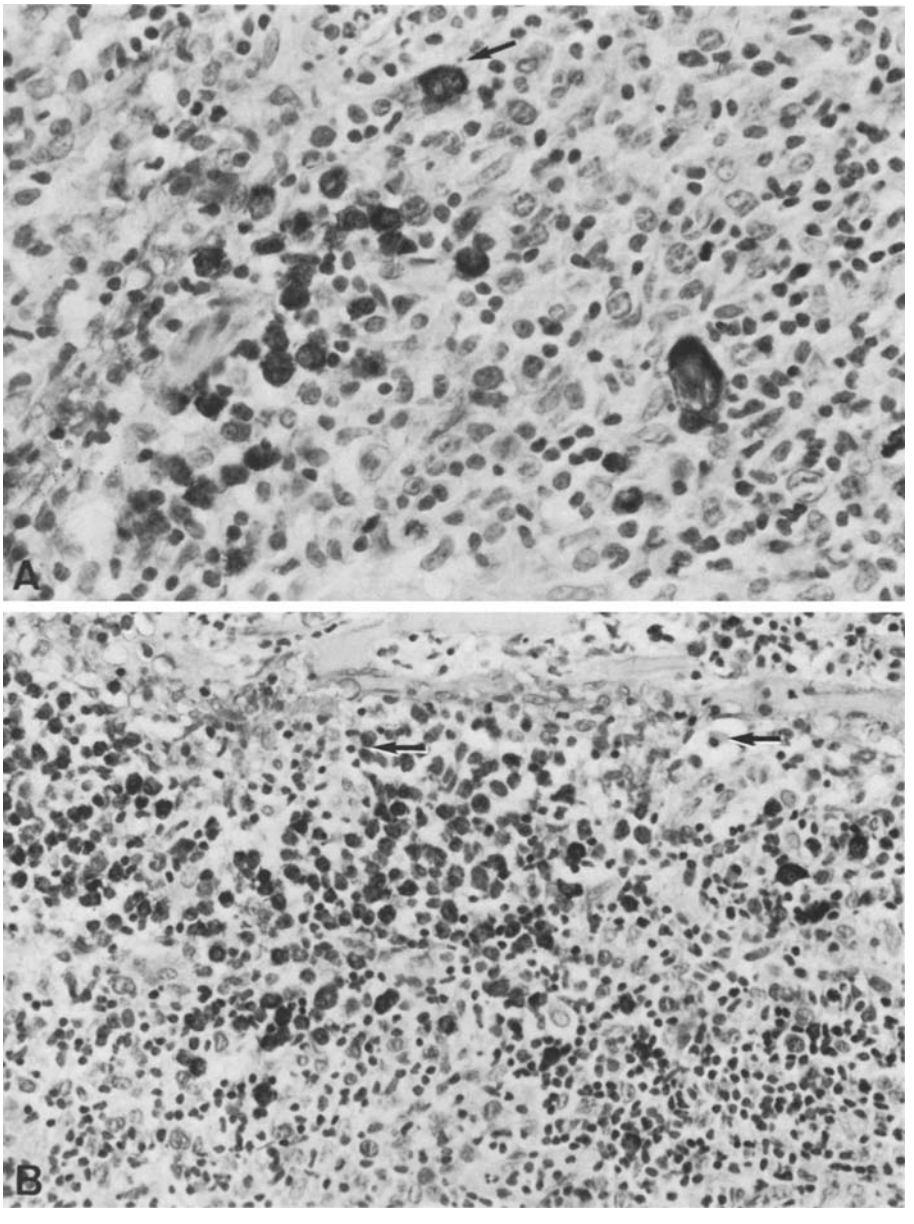

Fig. 6a, b. Plasma cell type of LgX exhibiting areas of monotypic infiltration. **a** Cluster of plasma cells showing staining for κ light chains. Note a binucleated plasma cell (*arrow*) at the top and a single atypical immunoblast at the right, also positive for κ light chains. $\times 400$. **b** same case. Infiltration of a residual sinus by a monotypic population of plasmacytes, which stained only for κ light chains. A very few plasma cells (*arrows*) lacking immunostaining for κ light chains are identifiable. These cells obviously do not belong to the monotypic clone. $\times 350$

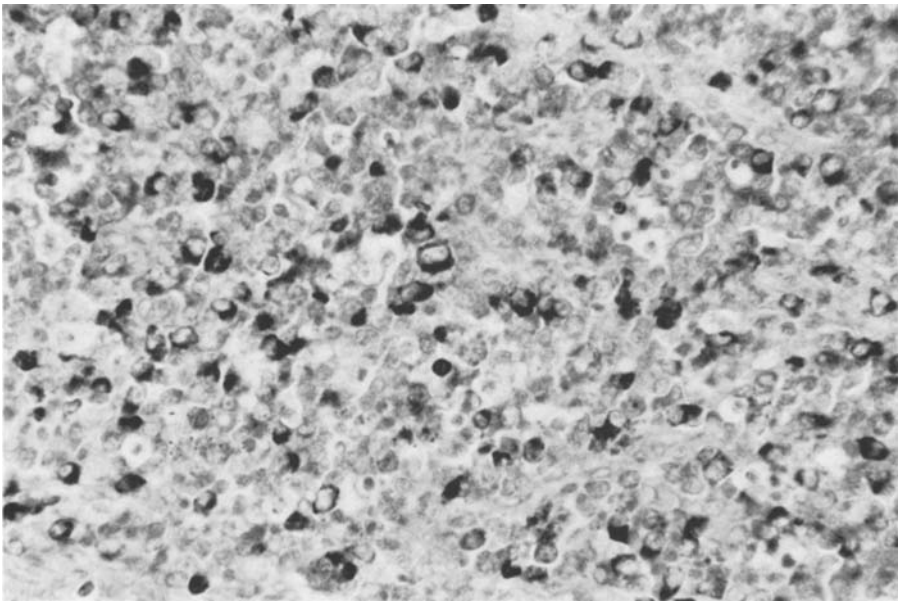

Fig. 7. Malignant transformation of LgX into B-immunoblastic lymphoma of the type IgG/λ. Numerous tumour cells exhibit strong positivity for IgG. ×350

Table 5. Autopsy findings in LgX ($n=38$)

Type of LgX (lymph node biopsy)	n	Organ involvement										Diagnosis		
		Lymph nodes												
		localized	generalized	Spleen	Liver	Bone marrow	Tonsils	Lungs	Kidneys	Skin	Stomach/small intestine	LgX	Malignant lymphoma	Carcinoma
I	4	0	4	4	2	1	1	0	0	0	0	4	0	1
II	9	0	9	9	5	5	0	1	2	0	2	8	1[a]	1
III	16	2	14	11	6	6	3	3	1	2	0	14	2[b]	1
IV	5	2	3	2	1	1	0	1	0	0	0	4	2[c]	0
V	4	1	3	3	0	0	0	0	1	0	1	3	1[d]	1
I–V	38	5	33	29	14	13	4	5	4	2	3	33	5	4

[a] B-immunoblastic lymphoma
[b] One immunoblastic lymphoma, 1 Hodgkin's disease, nodular sclerosis type
[c] Immunoblastic lymphoma (in one case localized in the stomach)
[d] Hodgkin's disease, nodular sclerosis type

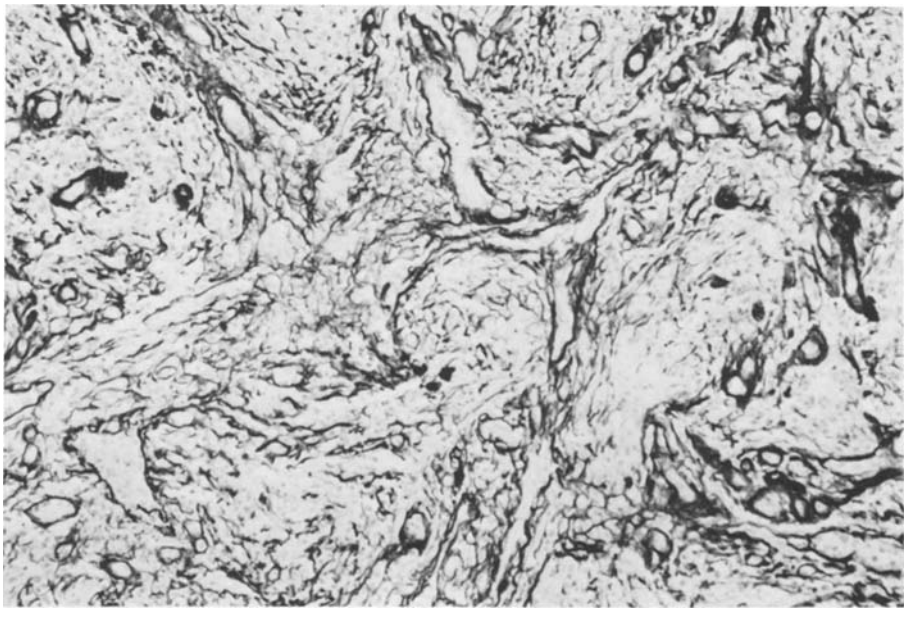

Fig. 8. Survey of a burnet out lymph node at autopsy. Prominent vascular proliferation, but also a considerable amount of reticulin fibres, are detectable. Gomori ×100

dura mater, the larynx and the submandibular gland. At autopsy the differences seen in the cellular infiltrate of LgX in biopsies (viz.: predominance of one special type of cell) diminished or could no longer be detected. In most cases, regardless of therapy, burnt out lymph nodes with prominent increase of small vessels and fibers were visible (Fig. 8). In 2 cases of the plasma cell type of LgX, however, plasma cell predominance was still present.

Five of 38 cases with the initial diagnosis of LgX (13.2%) showed histologically proven malignant lymphoma at autopsy (Table 5). In five additional cases malignant transformation was suspected on the basis of the macroscopic appearance, but this was not verified histologically. In the plasma cell predominance type there was 1 case that subsequently developed into immunoblastic lymphoma. Repeated biopsies had already shown that the initially polytypic pattern (κ/λ, γ, μ, α) had become restricted to a monotypic one (γ/λ) (Fig. 7). In one case of the mixed cell type a second biopsy had also revealed the presence of Hodgkin's disease of the nodular sclerosis type (Fig. 9). In 2 cases of the epithelioid cell type, immunoblastic lymphoma was detected at autopsy. In 1 case it involved the lymph nodes, as is usual, but in the other it was detectable only in the stomach.

In addition to the malignant lymphomas identified or suspected at autopsy, repeated biopsies also gave proof of malignant transformation. In 1 case of LgX type III a peripheral T cell lymphoma developed. It showed a somewhat pleomorphic proliferation of medium-sized lymphoid cells (more than 90% neoplastic T cells) in the lymph nodes. In 3 further cases

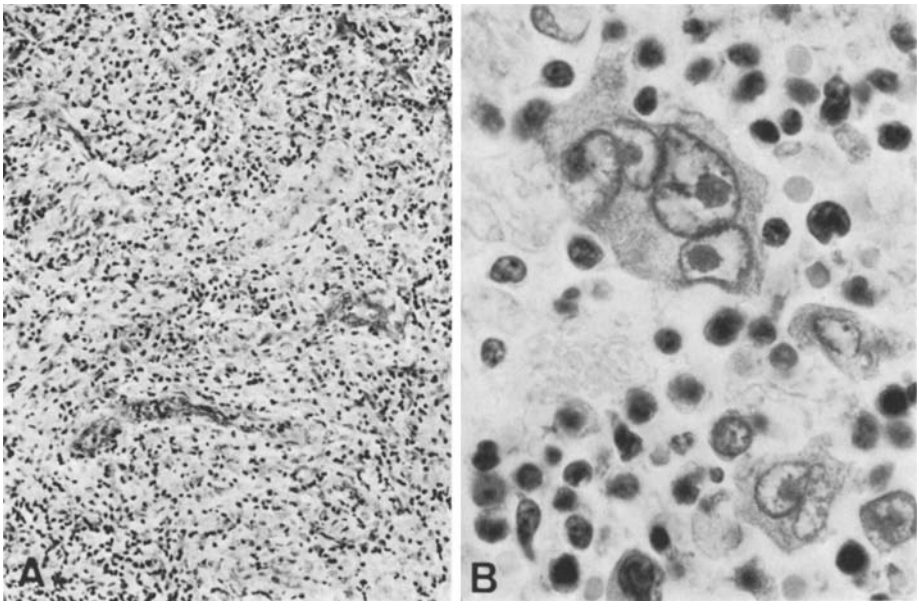

Fig. 9a, b. Malignant transformation of LgX. **a** LgX of the mixed cell type is present. Numerous vessels can be recognized. No signs of Hodgkin's disease are visible. Giemsa ×130. **b** Same case at autopsy (one year after biopsy): Hodgkin's disease is present. Typical Sternberg-Reed cells are seen. Giemsa ×800

of LgX type III Hodgkin's disease was identified in a later biopsy. Two of these belonged to the mixed cellularity type and 1 to the nodular sclerosis type of Hodgkin's disease. One of the cases that showed the mixed cellularity type of Hodgkin's disease at second biopsy later showed the characteristics of so-called Lennert's lymphoma at third biopsy. In 2 cases of the epithelioid cell type of LgX immunoblastic lymphoma was present in lymph nodes at second biopsy and in 1 case of this type it was detected in stomach tissue after surgical removal (the surrounding lymph nodes still exhibited the picture of LgX). In 2 further cases (LgX type III and V) the second biopsy showed Hodgkin's disease (mixed cellularity and lymphocytic predominance, respectively), but the third biopsy again displayed the initial pattern of LgX.

In 4 cases of LgX autopsy also revealed the presence of carcinoma (cervix uteri, prostate, rectum and kidney). In 3 cases carcinoma (stomach, cervix uteri and thyroid) was diagnosed by biopsy. In 4 additional cases the diagnosis of a malignant tumour (malignant gastric tumour in 3 cases and bronchial neoplasm in 1) was established by clinical methods.

Prognosis of LgX and HR

There is a significant difference ($p < 0.001$ by X^2 test) between the survival rates in cases of LgX and those in cases of HR. Of 172 patients with the diagnosis LgX 55.8% died within the first year and 80.4% within 5 years

Table 6. Survival of patients with the different histological types of LgX

Type of LgX	*n*	$1\ ^1/_2$ year survival	3-year survival
Immunoblastic	24	20.0%	5.6%
Plasma cell	28	18.0%	9.6%
Mixed cell	70	44.8%	21.5%
Epithelioid cell	39	42.7%	39.8%
Lymphocytic	11	18.1%	0%

after the histological diagnosis was established. In contrast, only 8.1% of the patients with lymph node lesions classified as HR had died after 1 year and after 5 years 78.4% were still alive. In the cases of LgX the prognosis was influenced by the composition of the cellular infiltrate, irrespective of therapy (Table 6).

Discussion

Histological differences between lymphogranulomatosis X (LgX), angioimmunoblastic lymphadenopathy (AIL) and immunoblastic lymphadenopathy (IL)

The occurrence of burnt out germinal centres, reported in AIL by Frizzera et al. (1974 and 1975) and Nathwani et al. (1978), is also consistent with the diagnosis of LgX. However, their presence is not compatible with the definition of IL (Lukes and Tindle 1978). Furthermore, in IL the intercellular spaces in the affected lymph nodes have to be PAS positive and the lymph nodes are described as hypocellular and lymphocyte depleted, whereas none of these features is necessary for the diagnosis of either LgX or AIL. LgX differs from AIL in that it also includes a few cases in which the infiltrates are still polymorphic but dominated by lymphocytes.

Possible significance of the absence of active germinal centres

Of particular interest is the fact that a few cases presenting initially as HR with active germinal centres evolve into AIL (Thabaut et al. 1979; Tosi et al. 1979) or LgX within a few months or years (Knecht and Lennert 1981 a, b). Analogous changes in the lymph node architecture are observed in the course of spontaneous autoimmune disease in New Zealand Black mice (Gindhart and Greenspan 1980). Dissociation or loss of germinal centres is also seen in murine spleens after antigenic stimulation (Congdon and Makinodan 1961, Hanna 1965), but in a normally responding immune system this is followed by germinal centre recovery and hyperplasia (Hanna et al. 1966). Germinal centre formation depends on the integrity of the T-cell system (Jacobson et al. 1974) and T cells are located predominantly in the light zones of reactive germinal centres (Stein et al. 1980). Most of these cells are helper T cells (Poppema et al. 1981) and their total proportion of germinal centre cells in reactive follicles is about 20% (Dvoretsky et al.

1982). A numerical and functional decrease in T cells in AIL has been shown by a number of authors (Bensa et al. 1976; Ellegaard and Boesen 1976; Palutke et al. 1976; Kosmidis et al. 1978; Neiman et al. 1978; Rice et al. 1982). In view of these data it seems likely that at least in the few cases of LgX preceded by follicular hyperplasia the dissociation of active germinal centres without a tendency towards germinal centre recovery (as demonstrated by repeated biopsies) may correspond morphologically to a deterioration of T-cell functions. Impaired T-cell function could also be implicated in the formation of burnt out germinal centres, whereas the HR with active germinal centres might reflect a still intact T-cell system.

Cytological classification of LgX: a possible link to the pathogenesis

The classification of LgX into five cytologically defined types may be of some interest with regard to the complex appearance of this disorder. In many cases of the immunoblastic type of LgX the immunoblasts are easily identified as B immunoblasts. There are, however, several cases that are dominated by large cells with a clear cytoplasm, first described in LgX by Suchi (1974). In one case of LgX (Knecht and Lennert 1981c) and one case of AIL (Klayman et al. 1981) these "clear cells" could be identified as T blast cells. Jones et al. (1978) reported two cases of AIL in which the lymph node infiltrates were dominated by T cells. This was associated histologically with blast cell proliferation. Shimoyama et al. (1979) described eight cases of "immunoblastic lymphadenopathy-like T-cell lymphoma" and Watanabe et al. (1980) five cases of "adult T-cell lymphoma with hypergammaglobulinaemia". The neoplastic cells of these lymphomas belonged to the suppressor/cytotoxic (OKT 8) phenotype (Shimoyama et al. 1982). In our cases of LgX with numerous clear cells no immunological typing of subpopulations of lymph node T cells was done, but it is likely that some of these cases belong to the "T-cell lymphomas of the IL-like type". In such cases vascular proliferation and polymorphic cellular infiltrate may suggest AIL, whereas immunological typing reveals predominance of a malignant (homogeneous) T-cell population (Brouet et al. 1984).

Some cases of "*Lennert's lymphoma*" (Lennert and Mestdagh 1968; Dorfman and Warnke 1974; Noel et al. 1979) bear a striking *resemblance to the epithelioid cell type of LgX*. In these cases a correct diagnosis is unfortunately not possible with conventional morphological methods. In the future detailed immunohistological analyses need to be performed in order to establish possible diagnostic differences.

The lymphocytic predominance type of LgX is of particular interest in that the large granular lymphocytes observed in some of these cases (Lennert and Knecht 1981) correspond light microscopically and ultrastructurally (Knecht and Lennert 1981c) to the T cells in acute infectious mononucleosis (McKenna et al. 1977), which were recently identified as suppressor T cells (Tosato et al. 1979; Reinherz et al. 1980; De Waele et al. 1981).

In normally immunoreactive individuals recovery from acute infectious mononucleosis is associated with a return to normal T-cell function (Rein-

herz et al. 1980). Abnormal activation as suppressor T cells, however, may account for some immunodeficiency syndromes, such as acquired agammaglobulinaemia (Reinherz et al. 1979b) and chronic graft-versus-host-reactions (Reinherz et al. 1979a), states known to be complicated by severe infections. In acquired immune deficiency syndrome (AIDS) (Gottlieb et al. 1981) inverted helper/suppressor T cell ratios have been demonstrated (Kornfeld et al. 1982, Guarda et al. 1983) and numerous T cells of the suppressor/cytotoxic type have been reported in B-cell areas of lymph nodes (Modlin et al. 1983). At onset of the disease the lymph nodes exhibit prominent follicular hyperplasia, whereas in a later phase of the disease "burnt out" germinal centres and prominent vascularisation are observed (Brynes et al. 1983; own observations).

An anology with the hyperplasia of the T areas in LgX is obvious. Repeated infections and short course of illness were also the impressive clinical features of the patients affected with the lymphocytic predominance type of LgX. In view of these similarities it is possible that abnormal suppressor T cell activity may have a pathogenetic function in LgX, especially in the lymphocytic type.

However, abundant proliferation of polyclonal plasma cells, associated with significant hypergammaglobulinaemia, as observed in the plasma cell type of LgX, might be due to a lack of suppressor cell activity. This has been shown to be present in cases of AIL with massive plasma cell infiltration (Bluming et al. 1979). Impaired suppressor cell function in AIL, followed by Ig overproduction, was also suggested by Skibin et al. (1980). In three cases of LgX with plasma cell predominance an elevated titer of anti-EBV antibody was present, possibly a secondary effect of plasma cell proliferation facilitated by impaired T-cell control of B-lymphocytes (Bornkamm et al. 1976; Dumont et al. 1979).

Immunohistology

The results of ths study corroborate the findings of previous reports (Flandrin 1978; Jones et al. 1978; Nathwani et al. 1978) that in LgX, as in AIL, the initial cellular proliferation is of polyclonal nature. In one case of the plasma cell type of LgX it was possible to prove immunohistologically on repeated biopsies that an initially polyclonal proliferation (κ, λ, γ, μ, α) progressed into a malignant lymphoma of the immunoblastic type (γ/λ). Monoclonal evolution was also observed in a case of AIL in which repeated biopsies were immunostained (Boros et al. 1981). In another case of the plasma cell type with a polyclonal pattern it was possible to identify areas with morphologically atypical plasma cells that stained only for κ chains. The identification of such cells in a few residual sinuses supports the hypothesis that a malignant lymphoma that was initially localized in another lymph node was disseminated to the lymph node under investigation. Thus it is easy to understand that the appearance of a monoclonal protein may escape immunohistological verification if the malignant proliferation is still localized.

Malignant Transformation including autopsy findings

In AIL clusters of immunoblasts and clear cells are already considered to be proof of malignancy by Nathwani et al. (1978) whereas in our series most of such cases were diagnosed as the immunoblastic type of LgX. In view of this different histological definition, the high rate of malignant transformation (more than 30%) observed in AIL is not surprising when compared with that in LgX, where subsequent malignant lymphoma was proven in 6.4% and suspected in an additional 7% of the cases. As is also shown in this study malignant transformation into both B-cell lymphomas (Fisher et al. 1976, Nathwani et al. 1978) and T-cell lymphomas (Habeshaw et al. 1979, Polkowska-Kulesza et al. 1981, Rubinstein and Dauber 1983) occurs. Evolution into Hodgkin's disease (HD) was also observed (Yataganas et al. 1977; Schnaidt et al. 1980). In our series HD was shown to have developed in five cases with the initial diagnosis of LgX: in two cases the diagnosis was established by autopsy, in three cases by biopsy. However, two additional cases showed LgX at first biopsy, HD at second and LgX again at third biopsy. This sequence points to the diagnostic problem encountered in LgX with evolution into HD. If the biopsy appearances of HD are not confirmed by a further biopsy or by autopsy, then the presence of a peripheral T-cell lymphoma with Sternberg-Reed-like cells can not be reliably ruled out. In this type of lymphoma a considerable T-cell pleomorphism with Sternberg-Reed-like forms is known to occur (Lennert 1981; Brouet et al. 1984).

Chromosomal abnormalities in LgX and AIL were reported by several authors (Volk et al. 1975; Hossfeld et al. 1976; Krmpotic et al. 1978; Goedde-Salz et al. 1981). Kaneko et al. (1982) emphasized that, although the histological appearance is still benign, some cases of AIL exhibit clonal and nonclonal aberrations that indicate their neoplastic nature. To what extent there is a real discrepancy between cytogenetic results and the histological appearance of LgX needs to be determined by analysing a large number of cases. Additional cytogenetic studies on LgX are also of major clinical importance for therapeutic reasons, since cases with a normal chromosome pattern (Goedde-Saltz 1983) justify a less aggressive treatment (corticoids). In cases with chromosomal aberrations, however, especially in combination with a rapid clinical course, a more rigourous therapeutic regimen (cytotoxic agents) is reasonable.

The results of this study confirm previous observations (Frizzera et al. 1975, Radaszkiewicz and Lennert 1975, Pangalis et al. 1978, Cullen et al. 1979) of multiorgan involvement and of pronounced lymph node fibrosis at autopsy, regardless of therapy. In a few cases, however, as seen in two cases of the plasmacytic type of LgX, prominent plasmacytic and immunoblastic proliferation may persist (Frizzera et al. 1975; Bluming et al. 1979; Cullen et al. 1979). These two different histological patterns, both without signs of malignant transformation, might again result from varying activity of the T-cell system. Fibrosis and cellular depletion might be related to helper T cell deficiency, or suppressor T cell activation, while impressive

plasmacytic and immunoblastic proliferation might be attributable to loss of suppressor T cell activity.

Cibull et al. (1977) reported a case of AIL associated with carcinoma of the pancreas and Tosi et al. (1979) a case complicated by Kaposi's sarcoma. In the present series carcinoma was identified in addition to LgX in 4 of the 38 autopsies (10.5%). Whether this coincidence is merely fortuitous or might be a result of decreased immune surveillance needs to be clarified by studying further series.

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