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CEREBRAL LYMPHOMAS IN AIDS.
NEUROPATHOLOGICAL STUDY

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A morphological analysis was done of 15 cases of malignant cerebral lymphomas selected from the material of 160 brains of patients, who died in the course of full-blown acquired immune deficiency syndrome (AIDS) during the period of 1987-1997. Cases with cerebral lymphomas comprised 9.4% of the whole collection. There were 13 males and 2 females in the studied group. The patients age ranged from 25 to 61 years. In 10 cases lymphomas were localized solely in the central nervous system, and in further 4 they were accompanying systemic neoplastic process. In one case lack of clinical and autopsy data did not permit classification of neoplasm to the primary or to the secondary group. In 13 cases immunophenotype of the lymphomas was characterized by immunohistochemical methods. In 11 cases neoplastic cells originated from B cells line and in 2 – from T cells line. In 10 cases lymphomas were found in macroscopic examination, in the remaining 5 cases they were disclosed at the brain histopathology.

The dynamics and extensiveness of the neoplastic process were different in particular cases. In most of them the process was multifocal and manifested in the form of diffuse proliferation, formed tumors with changing nature of their delineation and as multilayer perivascular cuffs. The characteristic feature of diffuse neoplasmatic growth was the appearance of large coagulative necroses in the central parts of tumors. Neoplastic foci were localized most often in the cerebral hemispheres (white matter, basal ganglia, periventricular regions), less frequently in the brain stem and cerebellum. In one case diffuse lymphoid growth involved selectively leptomeninges. In most of the cases leptomeningeal infiltrations accompanied large parenchymal neoplastic foci.

The most striking feature of our collection consisted in concomitance of cerebral lymphomas with HIV-specific brain pathology and/or opportunistic infections mostly of viral etiology. Their frequency was much higher than in cases of AIDS without cerebral lymphomas. Another finding which seems to be worth mentioning was the appearance of morphological exponents of various pathological processes such as for instance multinuclear giant cells, CMV inclusions within neoplastic tissue. The relatively frequent presence of numerous HIV-specific giant cells on the periphery of lymphomatous tumors suggests pathogenetic participation of immune deficiency virus in the blastomatous transformation of lymphoid cells within the central nervous system.

Key words: *AIDS, cerebral lymphomas, neuropathology, immunohistochemistry, immunophenotype of neoplastic cells*

Non-Hodgkin's malignant lymphomas, together with Kaposi's sarcoma have been officially recognized as malignancies accompanying acquired immune deficiency syndrome (AIDS) already at the beginning of the eighties, in other words at the early stages of AIDS pandemic (Centre for Disease Control, CDC, 1982) Moreover, in 1985 CDC accepted malignant lymphomas as one of the complications indicating transition from HIV-carrier stage to full-blown AIDS (in a significant proportion they precede other AIDS symptomatology) (Skotnicki, Kornaszewski 1988; So et al. 1988).

The central nervous system lymphomas have been considered as non-common neoplastic processes. According to the data from the mid seventies they amounted 0.85-1.5% of intracranial tumors and corresponded to about 1-2% of all lymphomas (Jellinger et al. 1975, Zimmerman, 1975) Epidemiological studies are indicating significant increase of lymphomas incidence in the course of the last several years. This increase concerns both population of immunocompetent peoples as well as those representing various groups with hereditary and acquired immune deficiencies. In the latter groups organ-transplant recipients, treated with immunosuppressive drugs and AIDS and pre-AIDS patiens, represent those in which frequency of cerebral lymphomas had shown the highest increase (So et al. 1986, 1988, Wilkinson et al. 1989, Grant, Isaacson 1992). According to Eby et al. (1988) incidence of lymphomas in the United States had tripled in the course of 1973-1984. DeAngelis (1991) reported that at the Sloan Kettering Memorial Cancer Institute in New York primary central nervous system lymphomas corresponded to 15.4% of all primary intracranial tumors in 1985-1990. The greater proportion concerned immuno-competent people.

Contrary to Kaposi's sarcoma, intracranial localization of which is extremely rare in AIDS, mean frequency of the brain malignat lymphomas is evaluated generally as 6 to 8 percent (Gray, 1993). It varies within a relatively large range in different neuropathological collections from 4 to 14 percent (Petito et al. 1986, Budka et al. 1987, Lang et al. 1989, Chimelli et al. 1992, Martinez et al. 1995 and others). In the collection of 100 AIDS cases from Poland, who died during 1987-1995 there were 10 cerebral lymphomas, (Mossakowski, Zelman, 1997). In most cases lymphomas occur in adult patients, although they are also found in pediatric material (Epstein et al. 1988, Dickson et al. 1990, Keohane et al. 1993, Wrzołek et al. 1995)

Collective neuropathological analyses of the cerebral lymphomas in adults are not numerous. Paper of Morgello et al. (1990), presenting neuropathological analysis of 15 cases of brain lymphomas selected from the material of 119 cases of patients who died in 1982-1987, and that of Iglesias-Rozas et al. (1991) comprising 8 lymphomas of 80 AIDS cases from Berlin, examined in the course of 1985-1989 are the most representative. This inclined us to present our own collection of the cerebral lymphomas, from patients who died in the course of AIDS.

Material and methods

The study included 15 brains in which routine histopathological examinations revealed non-Hodgkin's malignant lymphomas of the central nervous system. They were selected from the material comprising 160 brains of patients with full-blown AIDS, who died between 1987-1997. In 10 cases lymphomas were limited to the central nervous system. In another 4 cases they were accompanying systemic lymphomas. In one case lack of detailed clinical and general autopsy data did not permit us to define primary or secondary nature of the process. Fourteen cases originated from the Centre for Diagnostics and Therapy of AIDS at Wolski Infectious Diseases Hospital in Warsaw (Dr A. Horban).

Brains were received after previous fixation in the formalin, done in the Laboratory of Morbid Anatomy of Wolski Infectious Diseases Hospital (Dr Z. Kamiński). Fixed brains were weighed and cut frontally into blocks, 1 cm thick. Tissue blocks from the brain stem were 0.5 cm thick. As a rule 12 tissue sections were taken for histopathological processing. These were tissue sections including cerebral cortex and underlying white matter from the frontal, central, parietal, temporal (together with hippocampal formations) and occipital regions from the left cerebral hemisphere. Additionally, tissue sections from the left basal ganglia and diencephalic region, midbrain, pons, medulla and subbulbar cervical spinal cord as well as left cerebellar hemisphere were taken. Sections from all changed areas, including both pathological focus and its surroundings supplemented the histopathological material. The tissue blocks were processed in a standard way to paraffin. Paraffin sections, 6-8 μm thick were stained with hematoxylin and eosin and according to Heidenhain's method for the preliminary histopathological evaluation. Depending on its results additional histological, histochemical and in some cases immunohistochemical techniques were applied. In all cases with lymphomas silver impregnation for reticulin fibres was performed (Griedley's, Gomori's methods). For characterization of immunophenotype of lymphoma cells immunohistochemical reaction with monoclonal antibodies Bcell-CD20 and Tcell-CD 45 RO (Daco) were done in all cases on paraffin sections (Hsu et al. 1981).

Results

In the material comprising 160 brains from patients with verified full-blown AIDS, in 15 cases (9.4%) malignant non-Hodgkin's lymphomas were found on neuropathological examination. In 10 cases they involved the central nervous system solely. In a further 4 cases they were concomitant with the systemic lymphomatous process. Due to a lack of general pathology data one case was not classified to either the first or the second group.

Data concerning age, sex, and disease risk-groups of patients with neoplastic growth are presented in Table 1. In the examined group there were two females and thirteen males. The patients age ranged from 25 to 61 years (mean age 41.7 years). Five

Table 1. Cases with lymphomas of the central nervous system

Case No	Catologue No	Sex	Age (yrs)	Risk-group
1.	66/87	M	61	bisexual
2.	68/92	M	40	none
3.	20/93	M	no data	no data
4.	44/94	M	59	bisexual
5.	53/94	M	45	homosexual
6.	48/95	M	33	drug addict
7.	59/95	M	28	drug addict
8.	68/95	M	42	high risk sexual contacts
9.	70/95	M	36	high risk sexual contacts
10.	77/95	M	38	homosexual
11.	12/96	M	42	homosexual
12.	4/97	M	53	high risk sexual contacts
13.	44/97	F	39	drug addict
14.	69/97	M	44	none
15.	107/97	F	25	drug addict

cases concerned homo- or bisexuals, 3- people with high risk sexual contacts, and 4 – drug addicts.

Macroscopically visible brain abnormalities were found in 10 cases. In 5 of them neoplastic foci were diagnosed already at the brain cutting, in the remaining 5 nature of focal changes was established in stained sections. In 5 cases no focal changes were detected either macroscopically or microscopically, the presence of perivascular lymphomas was found at histopathology. The dynamics and aggressiveness of the proliferative process and its neuropathological expression showed remarkable variability in particular cases. Lymphoma proliferation was either uni- or multifocal, diffuse or perivascular, involving in an asymmetric way different brain structures, including leptomeninges. In one case the whole pathological process was limited to the leptomeninges of the brain base.

Parenchymal proliferation took the form of either ring-like perivascular cuffs of lymphoid cells (Fig. 1) or well formed tumor masses infiltrating widely brain tissue or showing relatively sharp, well defined borders (Fig. 2). A very characteristic feature of lymphomatous tumors consisted in appearance of large fields of coagulative necrosis, sometimes with hemorrhagic foci, occupying as a rule the central portion of the tumor masses (Fig. 3).They were surrounded by a wide ring of solid neoplastic tissue, with no histoformative tendencies (Fig. 4) or forming dense, confluent angiocentric neoplastic foci (Fig. 5). In some cases neoplastic tissue necroses formed complex systems of clefts and nests, which together with preserved perivascular neoplastic cuffs created a mosaic-like tissue pattern (Fig. 6). In the periphery of the tumor the condensed neoplastic tissue rarefied and was surrounded by a wide zone in which loosely arranged angiocentric nests of lymphoid cells, spread neoplastic cells, microglial cells, hypertrophied and gemistocytic astrocytes or even degenerating nerve cells were visible (Fig. 7).

Confined tumors involved subcortical white matter, sometimes together with neighboring cerebral cortex and periventricular areas. In the latter case choroid plexus was infiltrated (Fig. 8). They occurred also in basal ganglia, diencephalic structures and in the white matter of the cerebellum. They were rather sporadic in the brain stem formations. Confined tumors were relatively often accompanied by angiocentric proliferation not only in the direct vicinity of the main tumor masses, but also in relatively remote areas. In some cases massive leptomeningeal neoplastic proliferation was a significant accompanying feature.

Confined lymphomas appeared in 9 cases; in 5 of them they represented primary cerebral process, in 3 others they were components of the systemic pathology. In one case its nature was not defined, due to the previously mentioned lack of adequate data. In the latter case, similar to those of secondary nature, neoplastic foci were numerous, very large, marginally located with accompanying diffuse leptomeningeal infiltration.

Exclusively perivascular growth of lymphomas was present in 5 cases. Only in one case it was unifocal, in the remaining ones lymphoid perivascular infiltrations were disseminated in different brain structures. One case in this group was a part of the systemic neoplastic process. Pathomorphology of the perivascular growth of lymphomas showed remarkable variety as far as the relation of neoplastic process to the blood vessels and parenchymal brain tissue was concerned. In most cases vascular and perivascular neoplastic proliferation was accompanied by diffuse, rather slight dissemination of the lymphoid cells into the surrounding brain tissue with relatively well preserved structure (Fig. 9). Sometimes perivascular spread was very delicate and totally limited to the direct vicinity of infiltrated blood vessels (Fig. 10). Intensity of infiltration of vascular walls also revealed great differences, ranging from relatively loose distribution of neoplastic cells within the vascular wall (Fig. 10) to thick cuffs covering totally vascular wall structures, filling densely perivascular space and invading the surrounding tissue (Fig. 11). In case of thin veins, infiltrations of vascular walls and lumina filled with the thrombotic material were seen (Fig. 12).

Leptomeningeal neoplastic proliferation in most cases was diffuse, more seldom multifocal. In the latter case it was confined to the direct vicinity of formed, extensive parenchymal tumors, mostly those localized in the subcortical white matter or involving simultaneously cortex and underlying white matter. Leptomeningeal proliferation was most often limited to the *pia mater*, less frequently it filled subarachnoid space. In some cases necrotic foci within massive leptomeningeal proliferation were visible. They very seldom penetrated cerebral or cerebellar cortex *per continuitatem*, more often they invaded superficial layers of the brain parenchyma along perivascular spaces (Fig. 13).

Two cases of our collection require separate presentation. In the first one in which lymphomatous systemic process was clinically diagnosed and due to suspicion of the cerebral involvement several courses of chemotherapy were applied, neuropathology in addition to lymphomatous proliferation revealed advanced multifocal cerebral toxoplasmosis and exponents of HIV-specific process. In this case multiple foci of coagulative-colliquative necroses covered with trophozoits and numerous toxoplasmic endcysts were present practically in all structures of the

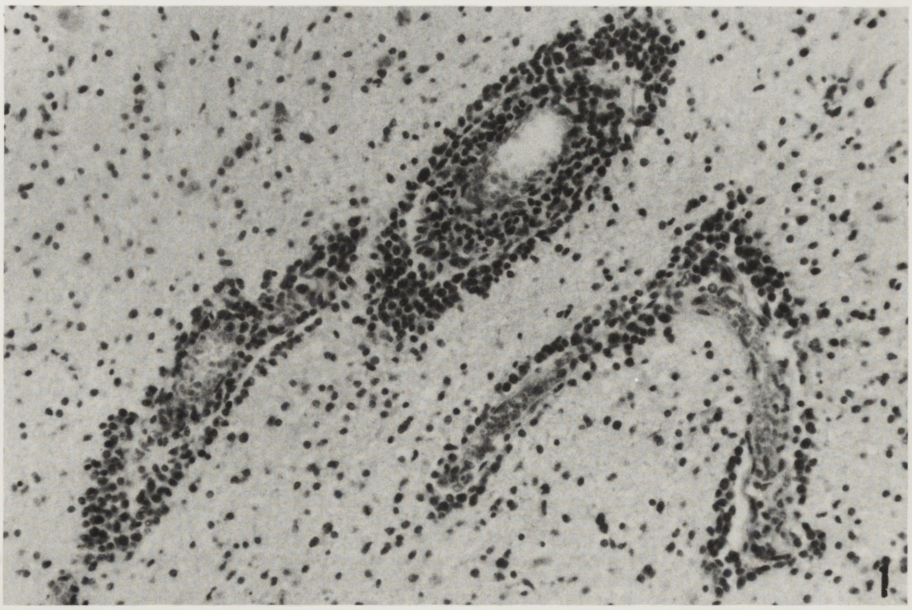

Fig. 1. Vascular and perivascular growth of neoplastic cells with some spread to the neighboring tissue. HE, ×200

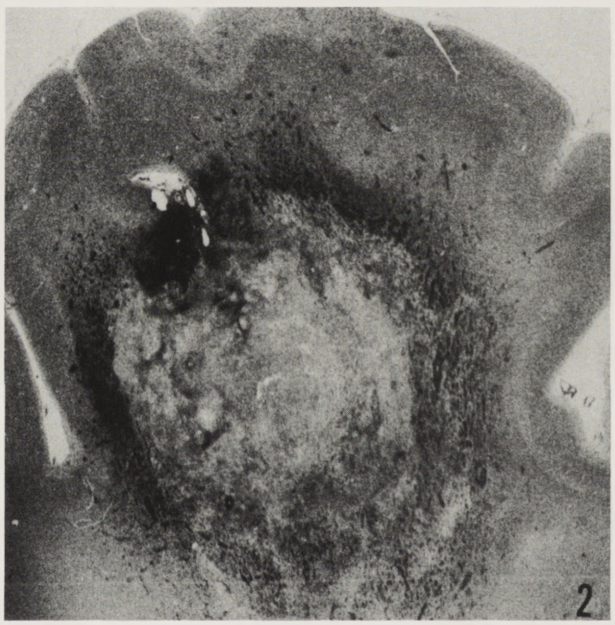

Fig. 2. Well-defined neoplastic tumor with extensive central necrosis. HE. Magn. glass, ×4

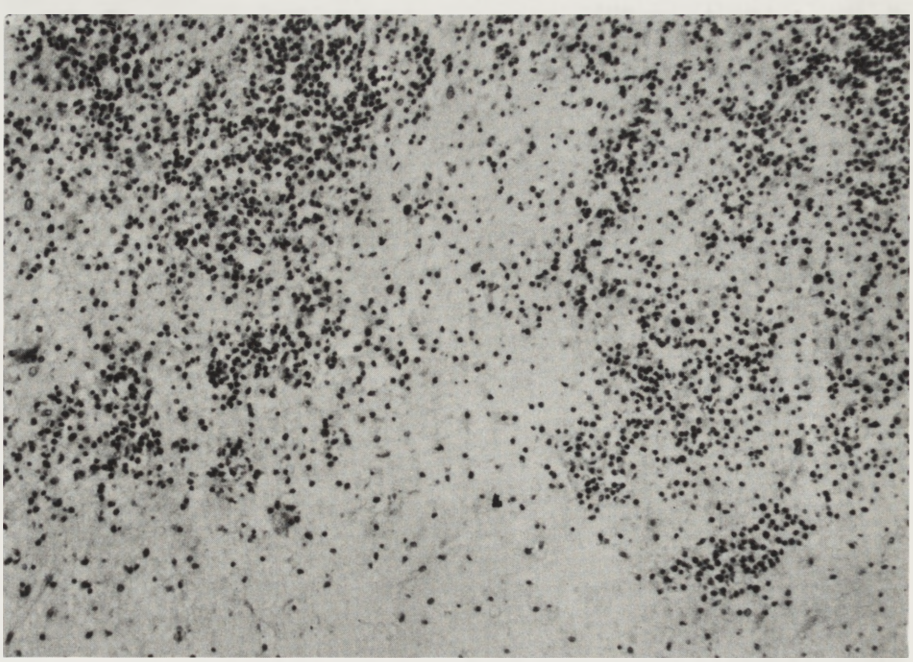

Fig. 3. Borders between preserved part of the tumor and large field of necrosis involving its central part. HE, ×150

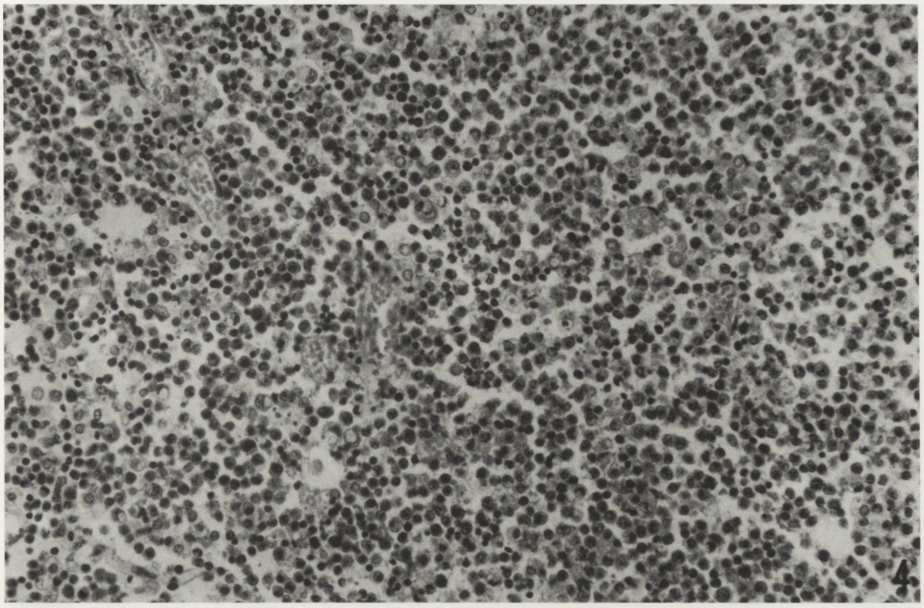

Fig. 4. Solid part of anaplastic large cell lymphoma. HE, ×200

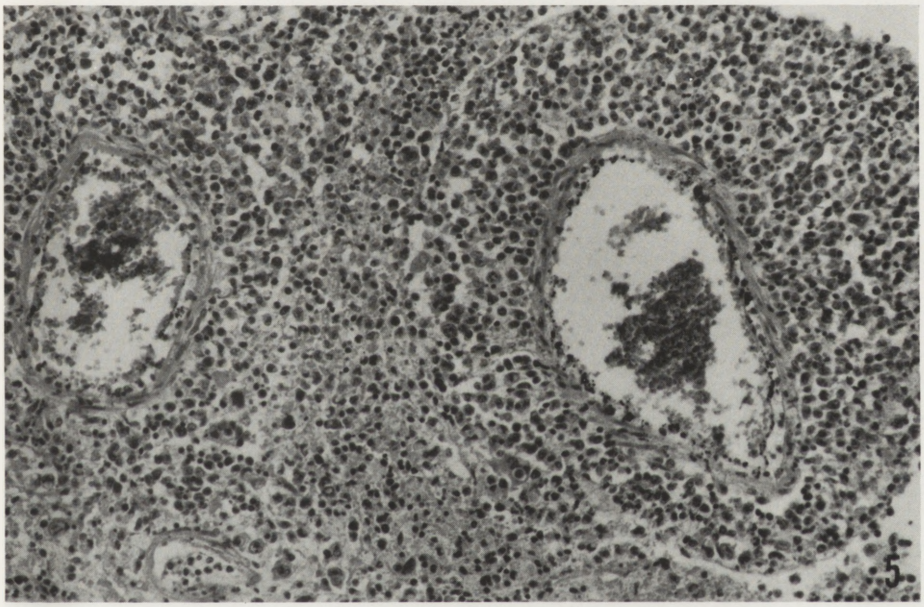

Fig. 5. Perivascular cuffs of neoplastic cells in lymphoma forming well-defined tumor. HE, ×200

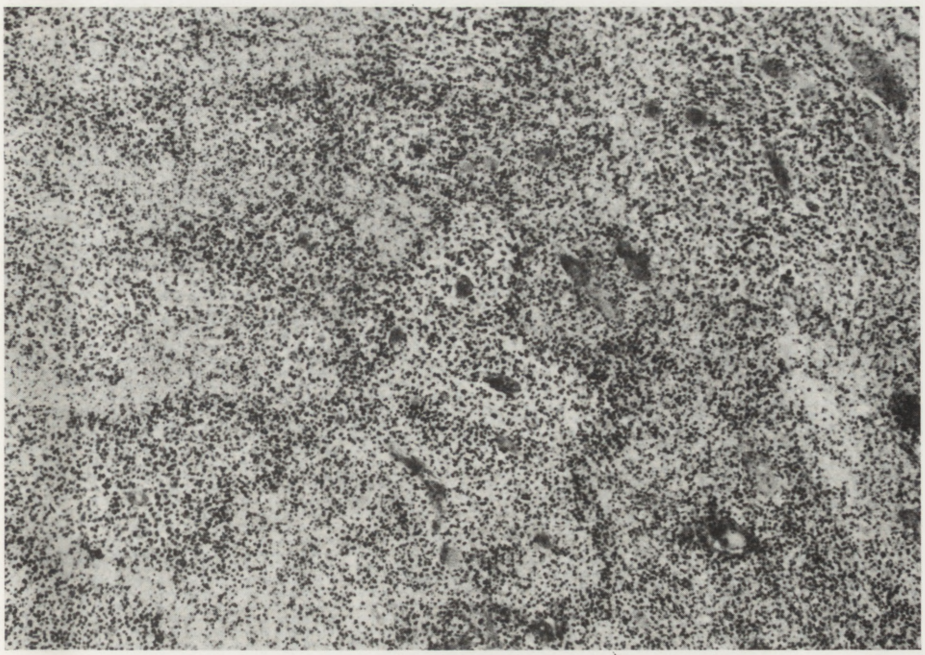

Fig. 6. Mosaic-like texture of solid lymphoma due to complex system of cleft necrotic foci. HE, ×60

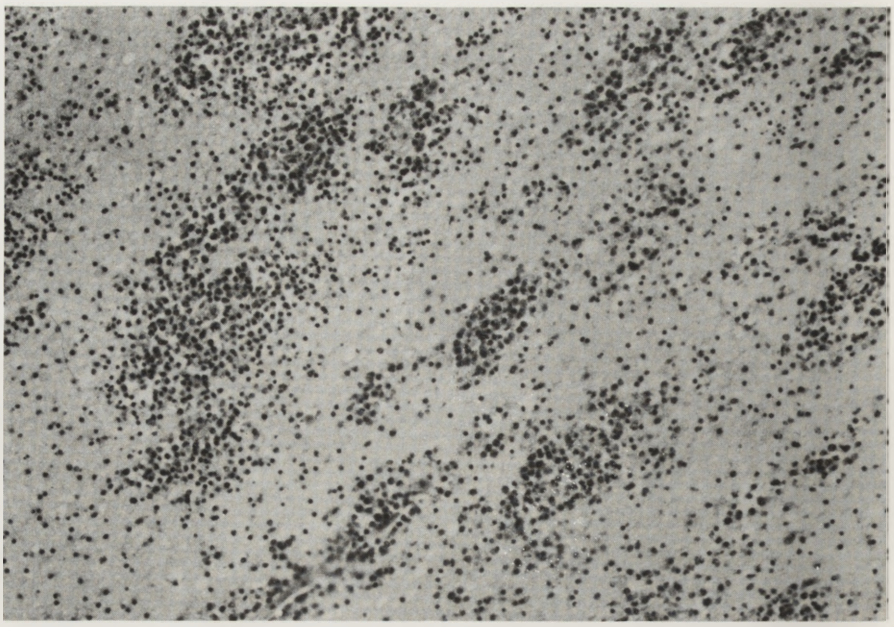

Fig. 7. Periphery of solid lymphoma with numerous perivascular neoplastic cuffs and interfascicular nests in the preserved brain tissue. HE, ×150

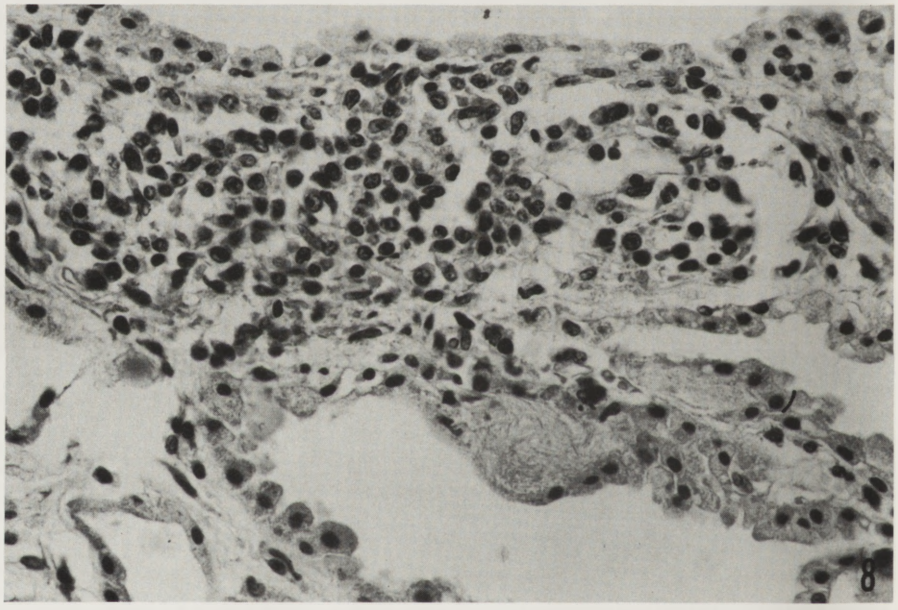

Fig. 8. Neoplastic infiltration of choroid plexus stroma. HE, ×400

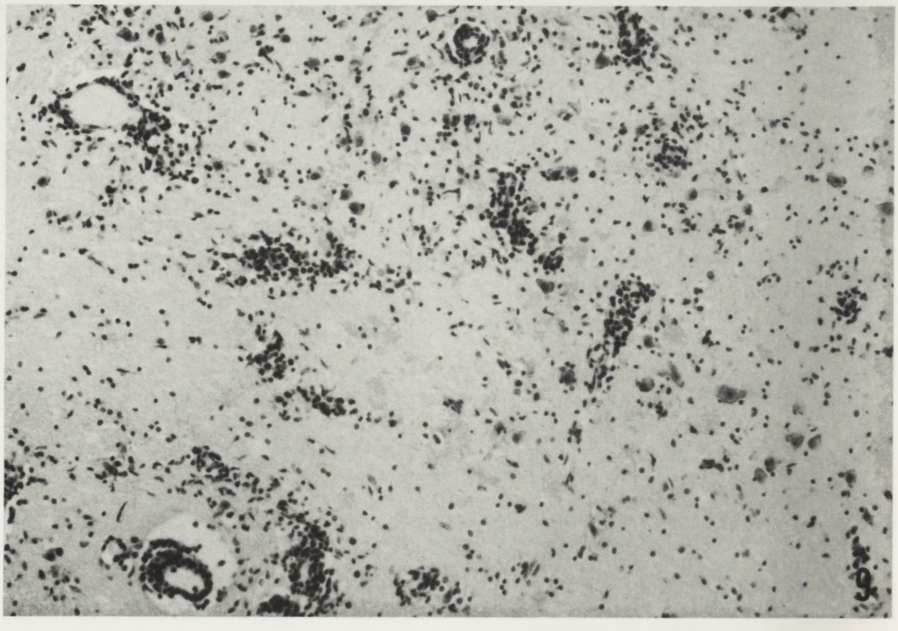

Fig. 9. Disseminated perivascular cuffs of neoplastic cells with their slight invasion into relatively well preserved nervous tissue. HE, ×100

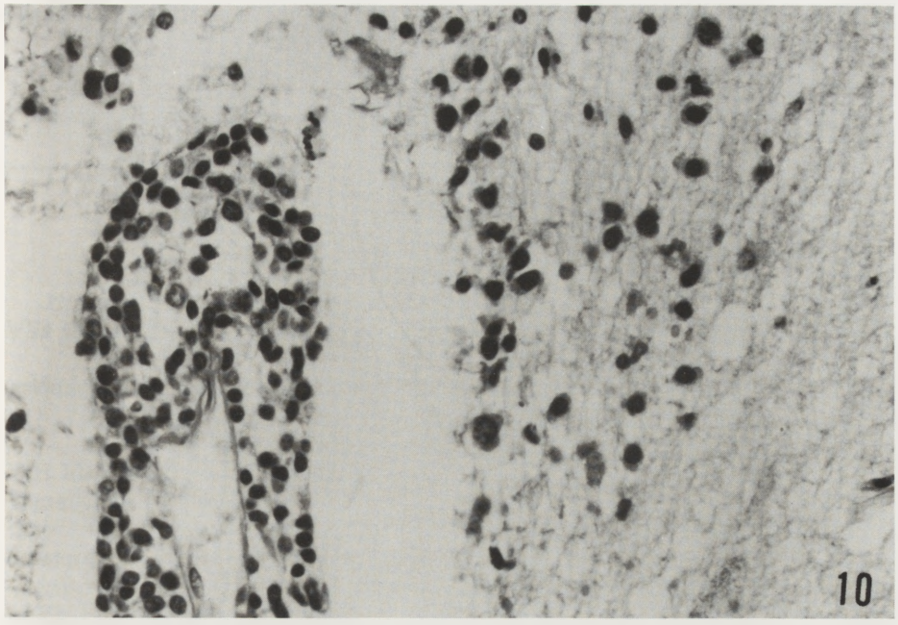

Fig. 10. Loose proliferation of neoplastic cells within the wall of cerebral vein with slight spread into neighboring tissue. HE, ×400

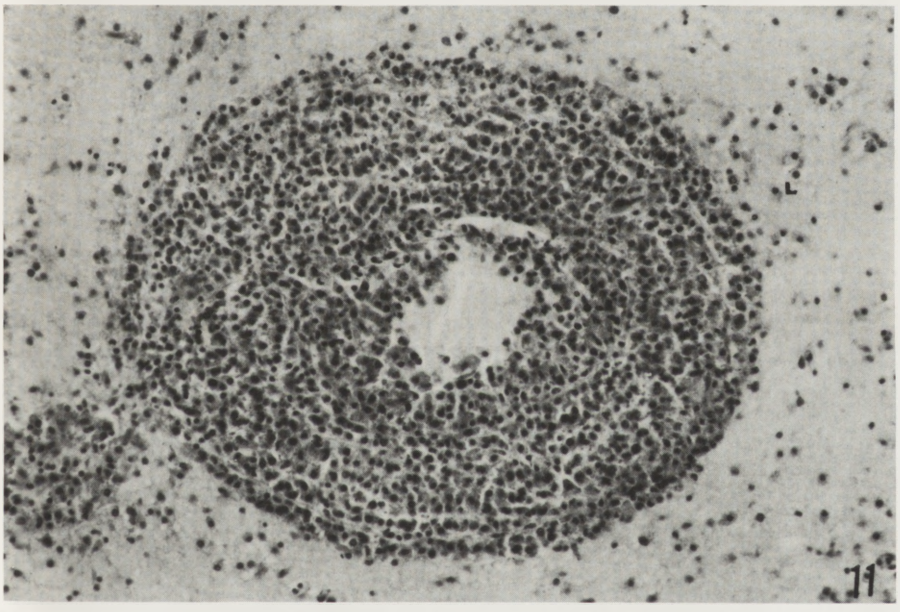

Fig. 11. Neoplastic invasion of the vascular wall and perivascular space with some loose and nodular proliferation into the surrounding cerebellar white matter. HE, ×200

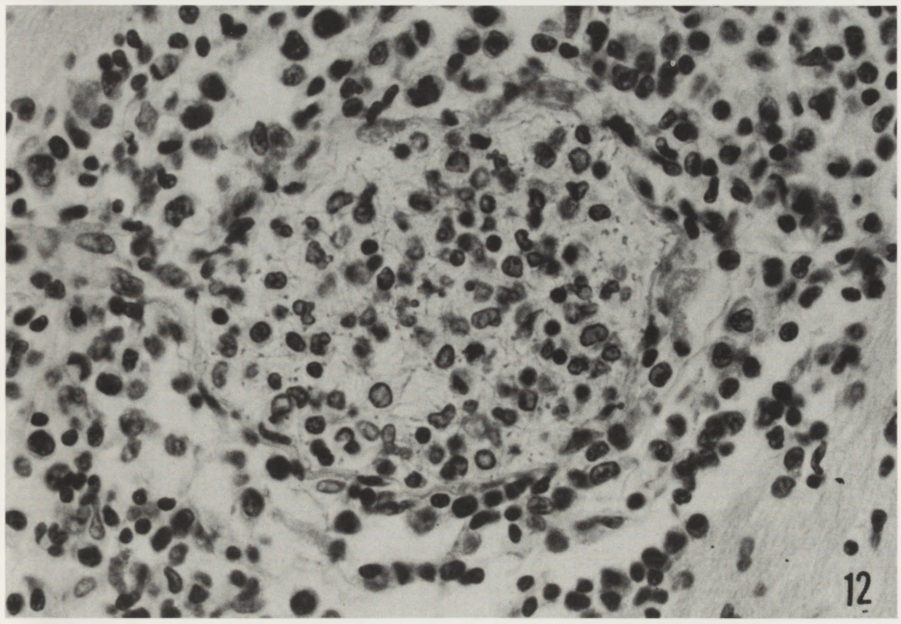

Fig. 12. Neoplastic growth within vascular wall and perivascular space invading diffusely neighboring tissue. Neoplastic cells within thrombotic tissue filling vascular lumen. HE, ×400

central nervous system. The necrotic foci were surrounded by zones of granulomatous tissue or massive infiltrates composed of lymphoid cells, which had to be differentiated between reactive and blastomatous lymphocytic proliferation. The basic question arose as to whether toxoplasmosis was involving necrotic fields of the lymphoma or primary parasitic infection evoked strong inflammatory response, leading to atypical morphology of the reactive cells. The third possibility was the coexistence of both blastomatous and inflammatory reactive processes. The neoplastic nature of the process was suggested by cellular activity, angiocentric type of cellular proliferation in brain parenchyma and leptomeninges, mitotic figures and the presence of neoplasia outside the central nervous system.

In the second case with dominating dysplastic features of the brain blood vessels, consecutive multiple vasogenic tissue abnormalities, both necrotic and hemorrhagic and exponents of diffuse intravascular coagulation (DIC), single or groups of blood vessels surrounded with wide cuffs of abnormal lymphoid cells, corresponding to lymphoma picture were found widespread within brain hemispheres. Leptomeninges showed diffuse and focal proliferation of atypical lymphoid cells. The intensity of secondary tissue abnormalities permits only diagnosis of neoplastic proliferation without its further characterization.

The typical feature of our material consisted in concomitance of different pathological processes in the same case. In two cases lymphoma was the only pathological process. In the remaining cases lymphoma was accompanied by either HIV-specific changes and/or opportunistic infections (Table 2). In 8 cases HIV-specific changes were present, being the only accompanying pathology in 2 cases, in further 3 cases concomitant with toxoplasmosis and two others with viral infections (CMV or PML). In one case HIV-specific changes co-existed with cryptococcosis and toxoplasmosis. In 4 cases lymphoma co-existed with CMV infection, in 3 of which viral process was the only accompanying pathology, in one it was concomitant with cryptococcosis. In one case lymphoma co-existed with progressive multifocal leukoencephalopathy (PML).

Another typical feature of our collection was the co-existence of the exponents of different pathological processes within the same altered tissue areas and even within the same cellular elements. For example toxoplasmic trophozoits and end-cysts were present within diffuse lymphoblastic proliferation, so were multinuclear giant HIV-specific cells within perivascular lymphoblastic cuffs. Cryptococci within leptomeningeal and perivascular lymphoblastic proliferation were a rather frequent finding, so were CMV-intranuclear inclusions within lymphoblastic cells. Not seldom was concomitance of blastomatous and reactive infiltrates within the same areas in case of lymphoma co-existing with HIV-specific process as well as accumulation of HIV-specific multinuclear giant cells in the vicinity of lymphomatous foci.

Table 2. Concomitance of lymphomas with HIV-specific changes and opportunistic cerebral infections

Case No	Catalogue No	Origin	Accompanying pathological cerebral process
1.	66/87	primary	HIV-encephalitis
2.	68/92	primary	CMV infection
3.	20/93	no data	---------
4.	44/94	primary	PML
5.	53/94	secondary	HIV-encephalitis, PML
6.	48/95	primary	HIV-encephalitis and HIV-encephalopathy
7.	59/95	secondary	HIV-encephalitis,Toxoplasmosis
8.	68/95	secondary	CMV infection
9.	70/95	secondary	HIV-encephalitis and HIV-encephalopathy, Cryprococcosis, Toxoplasmosis
10.	77/95	primary	CMV infection, Cryptococcosis
11.	12/96	primary	HIV-encephalitis, CMV infection
12.	4/97	primary	CMV infection
13.	44/97	primary	HIV-encephalitis, PML
14.	69/97	primary	----------
15.	107/97	primary	HIV-encephalitis, Toxoplasmosis

Cell morphology and degree of malignancy in particular cases were evaluated according to the principles of Updated Kiel Classification (Stansfeld et al. 1988). In 10 cases lymphomas of high grade of malignancy, in 4 cases of low grade of malignancy were classified. In one case the degree of malignancy was not established.

As presented in Table 3 the largest group of lymphomas was classified as pleomorphic malignant centroblastic lymphomas (5 cases) (Fig. 14). The next most frequent was centroblastic/cyntrocytic malignant lymphoma (3 cases) and the third was malignant lymphocytic lymphoma (2 cases) (Fig. 15). The other types of lymphomas such as malignant centrocytic lymphoma (Fig. 16), malignant immunoblastic lymphoma (Fig. 17) were represented by single cases. Due to an insufficient amount of material in one case neoplasm remained unclassified.

Among 13 cases in which immunophenotype of the neoplastic cells was determined it was stated that 11 were of B cell line (Figs 18 and 19) and 2 could be connected with T lymphocyte line (Fig. 20). The proportion of reactive lymphocytes among neoplastic cells varied to a great extent in particular cases. It ranged from 5 to 30 percent. In one case the participation of the reactive T cells was so high that

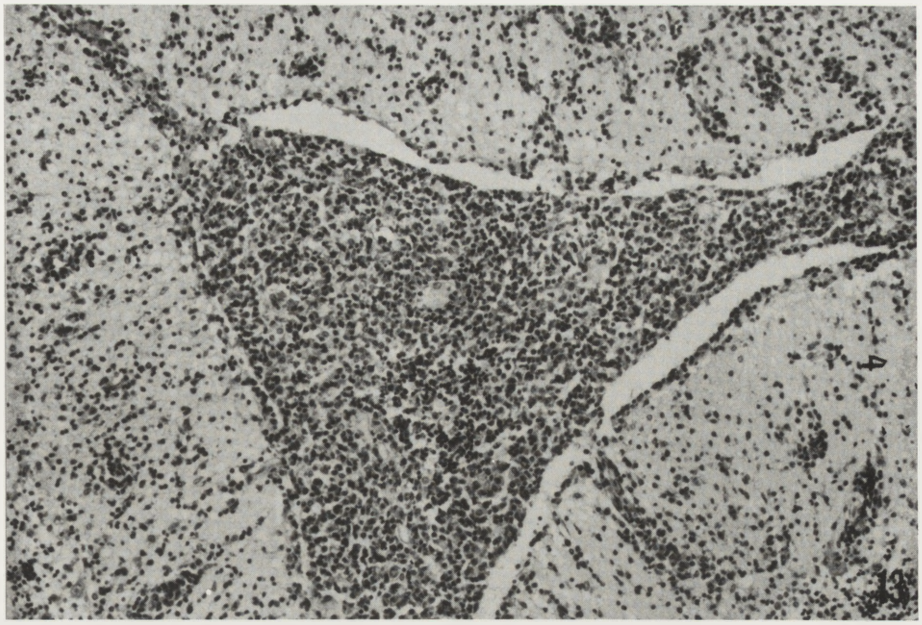

Fig. 13. Diffuse neoplastic growth within cerebellar leptomeninges. Note invasion of cerebellar cortex both *per continuitatem* and along penetrating blood vessels. HE, ×400

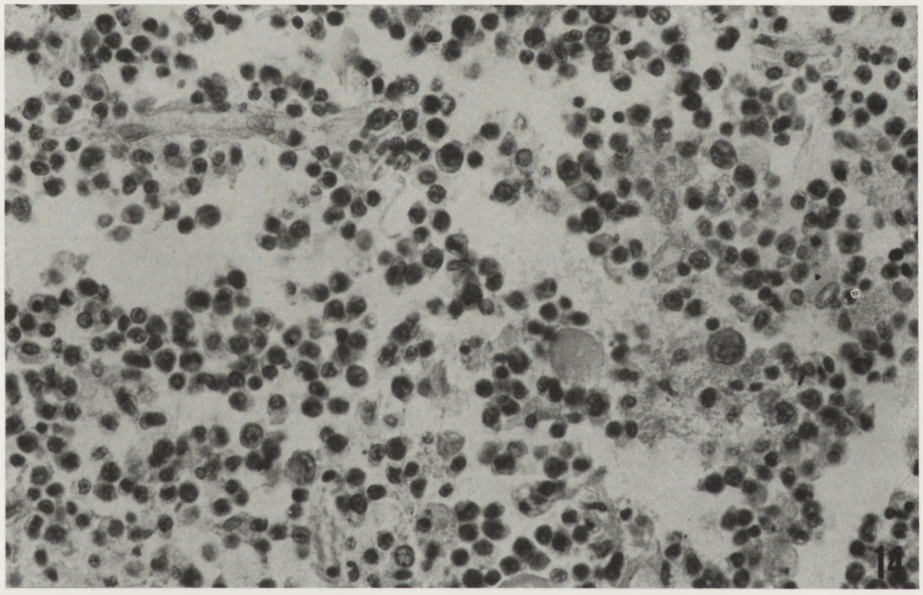

Fig. 14. Diffuse growth of pleomorphic centroblastic malignant lymphoma. HE, ×300

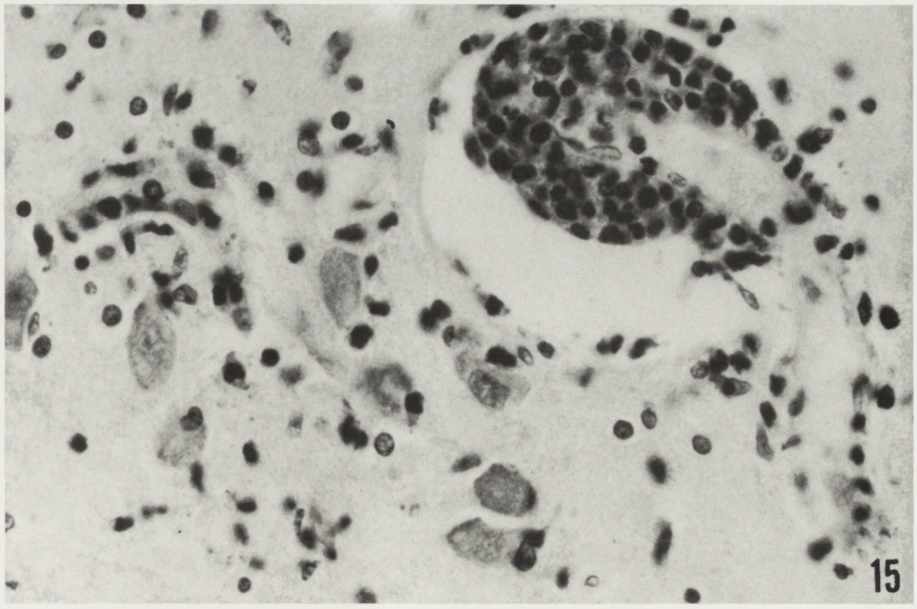

Fig. 15. Perivascular growth of lymphocytic malignant lymphoma. HE, ×400

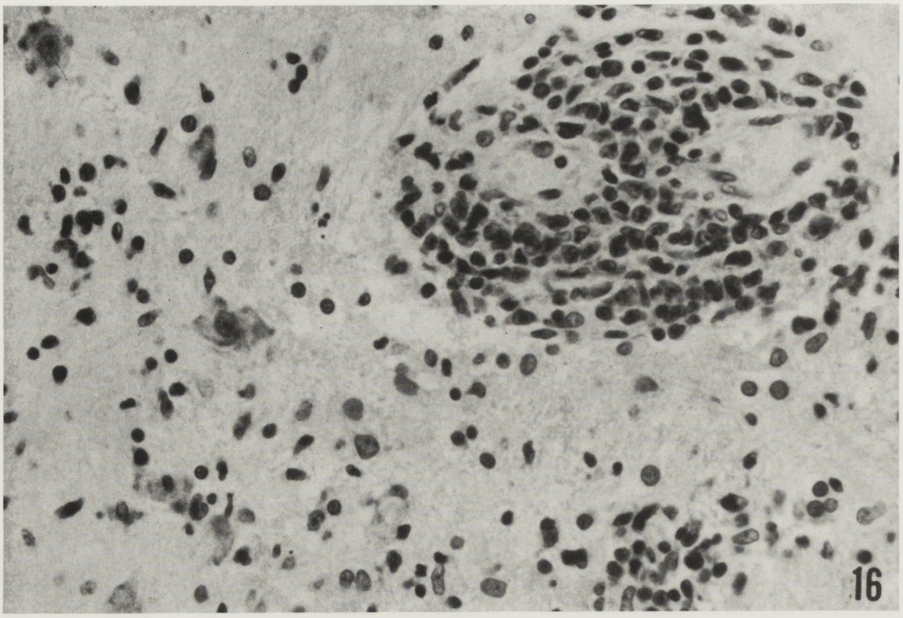

Fig. 16. Perivascular growth of centrocytic malignant lymphoma. HE, ×400

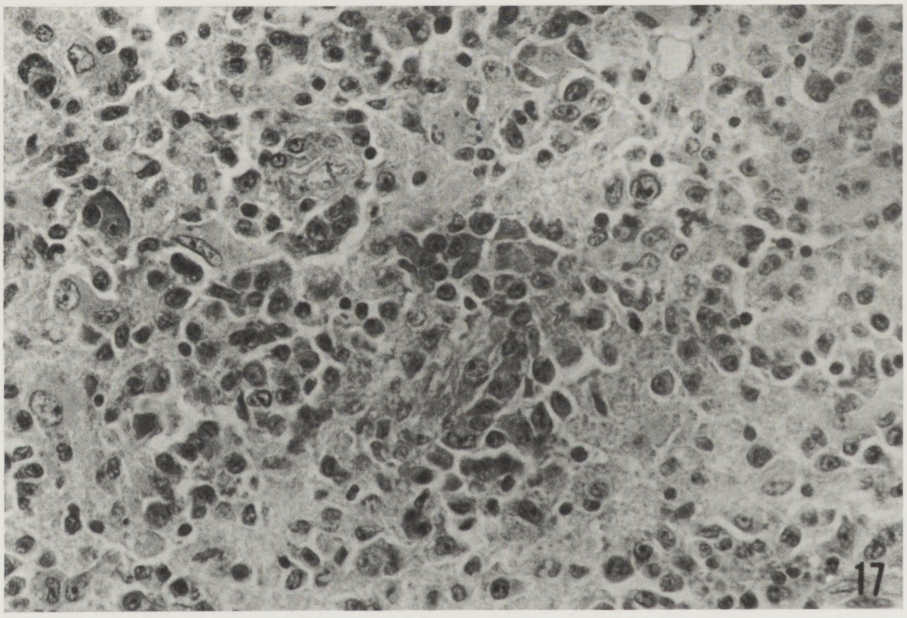

Fig. 17. Diffuse growth of immunoblastic malignant lymphoma. HE, ×400

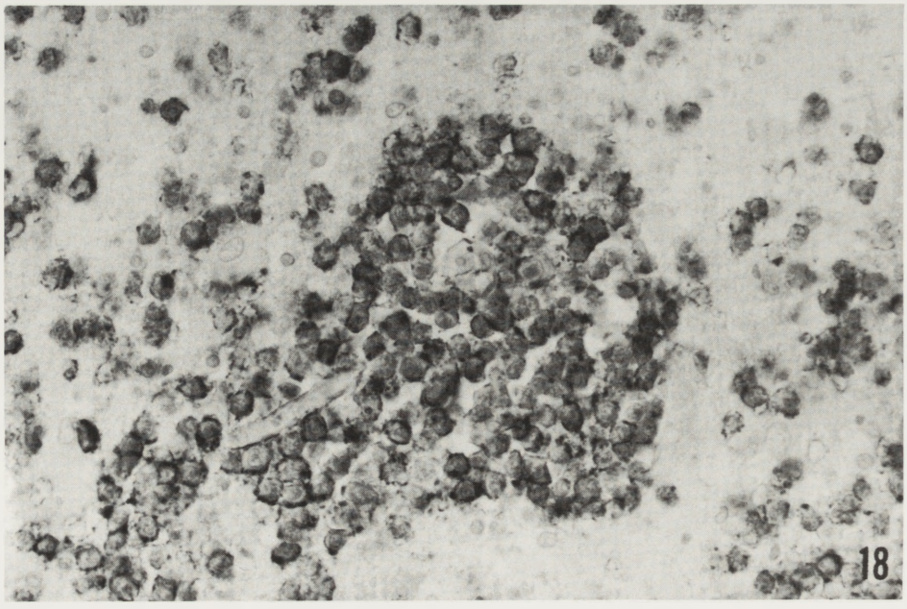

Fig. 18. B cell lymphoma. Perivascular and diffuse distribution of CD20-positive neoplastic cells. Immunocytochemistry, ×600

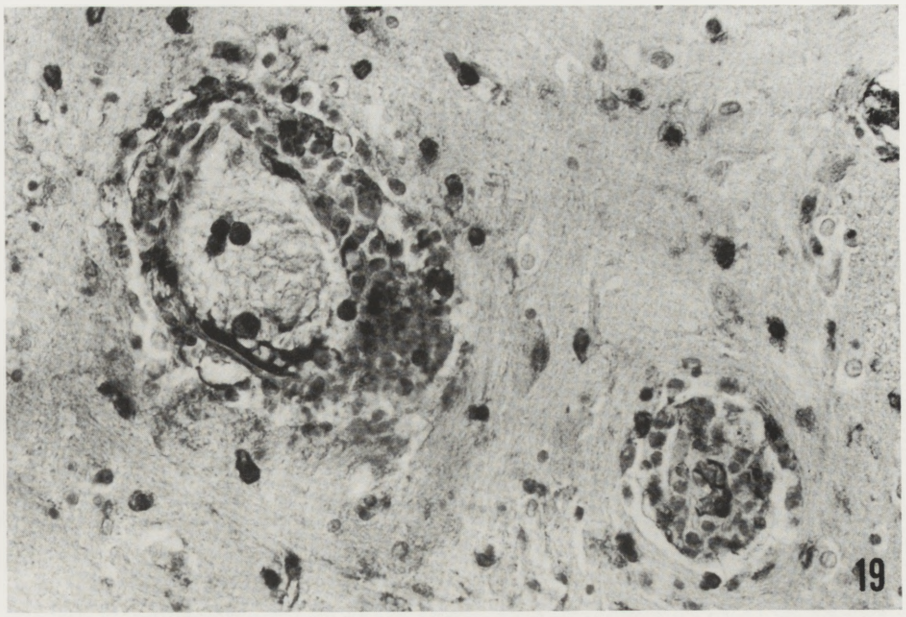

Fig. 19. B cell lymphoma. Perivascular accumulation and slight diffuse spread of CD20-positive neoplastic cells. Some admixture of negative cells is visible. Immunocytochemistry, ×400

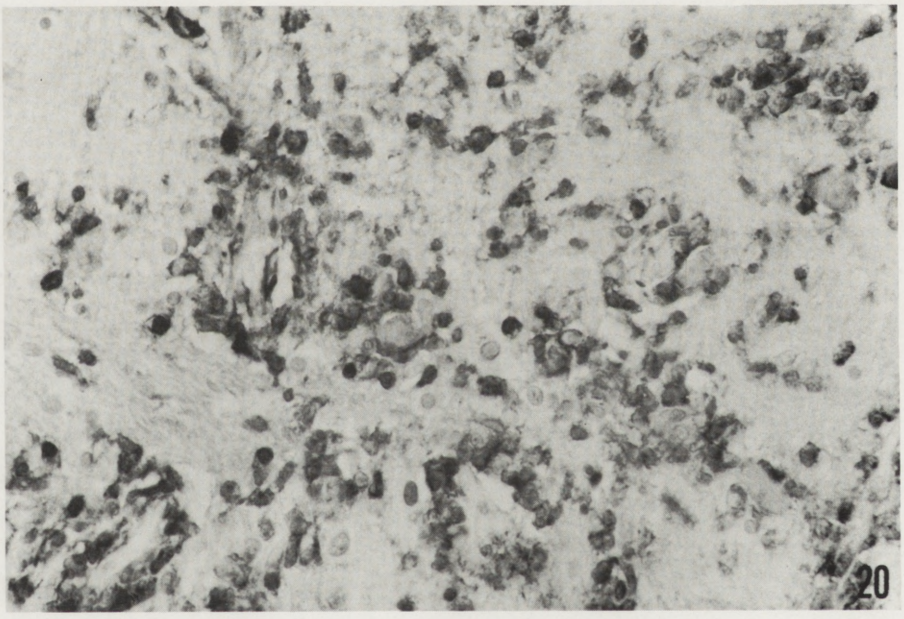

Fig. 20. T cell lymphoma. Diffuse spread of CD45RO-positive cells. Immunocytochemistry, ×400

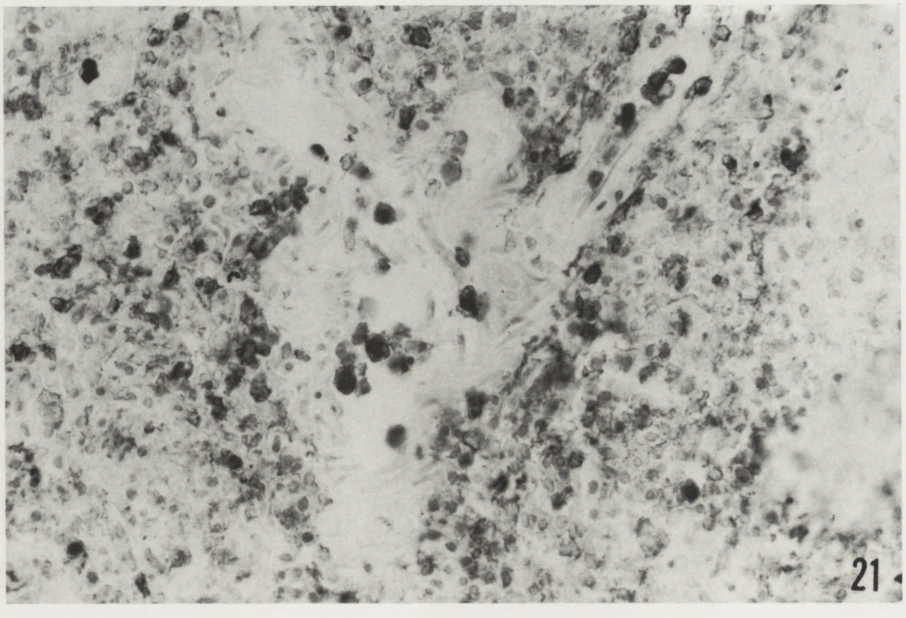

Fig. 21. T cell rich B cell lymphoma. T cells with positive CD45RO-reaction. Majority of cells correspond to immuno-negative B cells. Immunocytochemistry, ×400

Table 3. Histological diagnosis according to Updated Kiel Classification (Stansfeld et al. 1988) and immunophenotype determination

Case No	Catalogue No	Diagnosis	Malignancy	Phenotype
1.	66/87	*Lymphoma malignum immunoblasticum diffusum*	high grade	CD20(+) CD45RO(-)
2.	68/92	*Lymphoma malignum centroblasticum/centrocyticum diffusum*	high grade	CD20(+) CD45RO(-)
3.	20/93	*Lymphoma malignum centroblasticum pleomorphicum diffusum*	high grade	CD20(+) CD45RO(-)
4.	44/94	*Lymphoma malignum*	–	not studied
5.	53/94	*Lymphoma malignum pleomorphicum diffusum* (T line)	low grade	CD20(-) CD45RO(+)
6.	48/95	*Lymphoma malignum lymphocyticum diffusum* (T line)	low grade	CD20(-) CD45RO(+)
7.	59/95	*Lymphoma malignum centroblasticum/centrocyticum diffusum*	high grade	not studied
8.	68/95	*Lymphoma malignum centroblasticum pleomorphicum diffusum*	high grade	CD20(+) CD45RO(-)
9.	70/95	*Lymphoma malignum centroblasticum/centrocyticum diffusum*	high grade	CD20(+) CD45RO(-)
10.	77/95	*Lymphoma malignum lymphocyticum diffusum*	low grade	CD20(+) CD45RO(-)
11.	12/96	*Lymphoma malignum centroblasticum pleomorphicum diffusum*	high grade	CD20(+) CD45RO(-)
12.	4/97	*Lymphoma malignum centrocyticum diffusum*	low grade	CD20(+) CD45RO(-)
13.	44/97	*Lymphoma malignum centroblasticum pleomorphicum diffusum*	high grade	CD20(+) CD45RO(-)
14.	69/97	*Lymphoma malignum centroblasticum pleomorphicum diffusum*	high grade	CD20(+) CD45RO(-)
15.	107/97	*Lymphoma malignum anaplasticum magnocellulare* (B line)	high grade	CD20(+) CD45RO(-) CD30(+)- Ki-1(+)

tumor was diagnosed as *lymphoma malignum diffusum* B cell, T-cell rich (Fig. 21).

Table 4 summarizes macroscopic, histological and immunocytochemical characteristics of the material under study.

Discussion

In the collection of 160 brains, originating from adult patients with AIDS in 15 cases (9.4%) non-Hodgkin's lymphomas were found. This frequency corresponds to the lymphoma incidence described by other authors. In Budka's et al. (1987) material it amounted to 6%, in Brasil material (Chimelli et al. 1992) – 4%, in Berlin collection (Martinez et al. 1995) – 14%. Morgello et al. (1990) in New York collection found malignant lymphomas of the central nervous system in 12.6%.

In our material, similar to data presented by other authors lymphomas of primary cerebral location prevailed over secondary ones. In our collection relation between primary and secondary cerebral lymphomas was 10:4, similar to those presented by Morgello et al. (1990), in whose material of 15 malignant lymphomas of the central nervous system only 4 represented the systemic proliferative process. The only exception in this respect is the data of Lang et al. (1989) in which among 9 brain lymphomas 4 were primary and 5 secondary.

The mutual relation between cerebral and extracerebral lymphomas in the same case is not clear. Morgello et al. (1990) demonstrated morphological differences between lymphoid cells in lymphomatous foci localized in different anatomical structures. They ascribed the crucial role to establishing their mono- or polyclonal nature. In that context they are addressing the results of the experimental studies of Cleary et al. (1985), who documented that in lymphomas in cotton-topped tamarins, evoked by infection with Epstein-Barr virus (EBV), different neoplastic foci originated from different clones of B cells.

The pathogenesis of lymphoma's development does not seem to be identical in all cases and depends on the population of patients, in which the neoplasm is proliferating. In lymphomas accompanying AIDS, special attention has been turned to the possibility of the pathogenetic role of EBV in their development. This has already been suggested by Pattengale et al. (1979) and then by Hochberg et al. (1983), Hamilton-Dutoit et al. (1991), Morgello (1992) and many others. According to the results of epidemiologic studies, a very large percent of the human population is infected with EBV but posseses a relatively small proportion of lymphocytes permanently infected by this virus (Essex, 1984). Patients with AIDS, as well as those with immunosuppression primary and/or accompanying organ

Table 4. Summarized characteristics of brain lymphomas

Case No	Catalogue No	Origin	Type of growth	Distribution	Site
1.	66/87	primary cerebral, B cell	confined tumor formation	multifocal	periventricular regions of lateral, IIIrd and IVth ventricles
2.	68/92	primary cerebral, B cell	perivascular	disseminated	cerebellar and cerebral hemispheres
3.	20/93	no data, B cell	confined tumor formation	multifocal	cerebral hemispheres, brain stem, cerebellum
4.	44/94	primary cerebral, not determined	perivascular	disseminated	cerebral hemispheres
5.	53/94	systemic, T cell	perivascular	disseminated	leptomeninges, subthalamic and hippocampal regions
6.	48/95	primary cerebral, T cell	perivascular	disseminated	cerebral hemispheres: basal ganglia
7.	59/95	systemic, not studied	confined tumor formation	multifocal	cerebral hemispheres
8.	68/95	systemic, B cell	confined tumor formation	multifocal	cerebral hemispheres, thalamus, cerebellum
9.	70/95	systemic, B cell	confined tumor formation	multifocal	cerebral hemispheres: frontal and central regions
10.	77/95	primary cerebral, B cell	confined tumor formation	multifocal	cerebellum, brain stem, cerebral hemispheres: periventricular regions
11.	12/96	primary cerebral, B cell	confined tumor formation	multifocal	cerebral hemispheres: basal ganglia, thalamus
12.	4/97	primary cerebral, B cell	perivascular	unifocal	central pons
13.	44/97	primary cerebral, B cell	meningeal	diffuse	leptomeninges
14.	69/97	primary cerebral, B cell	confined tumor formation	multifocal	basal ganglia, thalamus, mesencephalon
15.	107/97	primary cerebral, B cell	confined tumor formation	multifocal	cerebral hemispheres: frontal and occipital regions

transplantation are losing control of proliferation of B cells evoked by EBV. This may condition the development of monoclonal/polyclonal lymphomas, originating from these cells (Hochberg et al. 1983, Hochberg, Miller, 1988, MacMahon et al. 1991, Vital et al. 1992).

In blood sera of AIDS-patients with lymphomas very high titres of IgG against EBV antigens as well as high titres of IgM against EBV antigens were found. This may support activation of the virus (Bantz et al. 1989, Iglesias-Rozas et al. 1991). Expression of EBV genome presented by *in situ* hybridization and/or PCR reaction was observed mostly in lymphomas from patient with deficient immune reactivity and only sporadically in those from immunocompetent patient (Bignon et al. 1991; Nakleh et al. 1991; Bashir et al. 1993).). It is accepted that c-myc translocation results in transformation and than activation of B cells which may finally undergo unlimited proliferation (Niewiadomska, Woźniak, 1997). Pathogenesis of primary brain lymphomas is in all probability different than that of the lymphomas in the same patients but developing outside the central nervous system. According to MacMahon et al. (1991) only 30-50 percent of extracerebral lymphomas reveal the presence of EBV, whereas in primary lymphomas of the central nervous system it is present practically in all cases.

In the last years some evidence was provided that in addition to EBV recently identified human herpesvirus 8 (HIV-8), formerly known as Kaposi's sarcoma associated herpes virus, may play a pathogenetic role in the development of primary CNS lymphomas (Epstein 1998).

Cornford et al. (1991) noticed the frequent appearance of macrophages and multinuclear giant HIV-specific cells in the lymphomas of the central nervous system in patients with AIDS. Our material revealed the same phenomenon. As clonal proliferation of B cells is taking place mostly in the nests of EBV replication, it seems very probable that we are dealing there with focal activation of macrophages by the infected neoplastic lymphocytes. In this way in patients with AIDS, HIV and EBV can act synergetically in the development of primary lymphomas of the central nervous system (Cornford et al. 1991, Morgello, 1992).

Proliferation of lymphomas of the central nervous system in AIDS cases is as a rule accompanied by additional pathological processes: HIV-specific syndromes and opportunistic infections mostly of viral etiology. This has been documented both in the

collective neuropathological analyses of AIDS material, and in casuistic reports as well as in overviews concerning cerebral lymphomas in the course of AIDS. It was confirmed by our observations and the results of statistical analysis of Morgello et al. (1990). This co-existence of different cerebral pathological processes with CNS lymphomas, showing a confirmed statistical significance, does not seem to be incidental, although no mutual pathogenic relations have been established yet. In the case of opportunistic viral infections possible interaction between pathogenic virus and activated EBV can be taken into consideration as postulated by Hochberg and Miller (1988). In this way viruses causing opportunistic infection(s) may play an additional pathogenic role in the development of lymphoma, arising from the cellular population originating due to clonal expansion of progenitoric cells (Hamilton-Dutoit et al. 1991). It is generally accepted that primary lymphomas of the central nervous system originate from B cells, although the number of T cells derived lymphomas of the central nervous system is increasing (Grant, Isaacson 1992; Niewiadomska, Woźniak 1997)). In our material 2 lymphomas represented the T cell line. In both cases the tumors were characterized by low degree of malignancy and relatively slight tissue destruction In our collection 10 lymphomas were classified to the group of high malignancy. A low degree of malignancy was found in 4 cases. Most authors classify around 70-80% of primary lymphomas of the central nervous system as highly malignant. Morgello et al. (1990) and Iglesias-Rozas et al. (1991) consider practically all primary cerebral lymphomas in their collection as representing high degree of malignancy. It seems that the discrepancy between our material and that of the above mentioned authors may be related, at least in part, to application of different classification criteria.

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Złośliwe chłoniaki OUN u pacjentów z AIDS

Streszczenie

Przeprowadzono analizę morfologiczną 15 przypadków złośliwych chłoniaków oun, wyselekcjonowanych spośród 160 mózgów pacjentów zmarłych w przebiegu AIDS w latach 1987-1997. Stanowiły one 9.4% całej kolekcji. W 13 przypadkach mózgi pochodziły od mężczyzn, w 2 – od kobiet. Wiek pacjentów wahał się od 25 do 61 lat. W 10 przypadkach chłoniaki oun miały charakter pierwotny, w 4 – współistniały z układowym rozrostem limfoidalnym. W 1 przypadku brak danych klinicznych i anatomopatologicznych uniemożliwiał jednoznaczne zakwalifikowanie go do grupy pierwotnych lub wtórnych chłoniaków oun. W 13 przypadkach określono immunofenotyp komórek chłoniaka: w 11 przypadkach wywodziły się one z komórek B, w 2 – z komórek T. W 10 przypadkach ogniska chłoniaka były widoczne makroskopowo, w 5 obecność chłoniaka ujawniono w trakcie badania mikroskopowego.

Dynamika i rozległość procesu nowotworowego była zróżnicowana w poszczególnych przypadkach. W większości z nich proces miał charakter wieloogniskowy i manifestował się obecnością rozlanych nacieków śródtkankowych, uformowanych guzów o różnym stopniu odgraniczenia oraz wielopokładowych nacieków okołonaczyniowych. Charakterystyczną cechą rozlanych rozrostów była obecność martwicy skrzepowej w centralnej części guza. Ogniska neoplazji znajdowano najczęściej w półkulach mózgu (istocie białej, zwojach podstawy, okolicach okołokomorowych) rzadziej w strukturach pnia mózgu i móżdżku. W jednym przypadku rozrost limfoidalny zajmował wybiórczo opony miękkie, w innych rozrost oponowy towarzyszył rozległym śródmiąższowym ogniskom nowotworowym. Znamienną cechą materiału było współwystępowanie z chłoniakami procesów HIV-swoistych i/lub zakażeń oportunistycznych, zwłaszcza o etiologii wirusowej, przewyższające jego częstość w mózgach z AIDS bez chłoniaków. Również zasługującą na uwagę cechą była obecność wykładników innych procesów patologicznych w ogniskach nowotworzenia. Stwierdzone w badanym materiale szczególnie liczne nagromadzenie HIV-swoistych komórek wielojądrzastych na obrzeżach nowotworu sugeruje możliwość patogenetycznego udziału wirusa niewydolności immunologicznej w transformacji blastomatycznej komórek limfoidalnych na terenie oun.

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