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OPPORTUNISTIC INFECTIONS OF THE CENTRAL NERVOUS SYSTEM IN THE COURSE OF ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS).
Morphological analysis of 172 cases

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A neuropathological analysis of 172 cases of AIDS in adults was carried out, to determine the occurrence and nature of the opportunistic infections of the central nervous system (CNS). The material comprised 155 cases of men, and 17 women. Mean age of patients was 38 years. Collection under study originated from the period between 1987 and 1997.

Opportunistic infections were present in 57.5 percent of cases being in 38.4 percent the only pathological process, whereas in 19.1 percent they coexisted with HIV-dependent pathology or with neoplastic growth.

Cytomegalovirus infection (22.7%), toxoplasmosis (16.3%), cryptococcosis (8.1%) and progressive multifocal leukoencephalopathy (9.3%) were the most common opportunistic infections of CNS. The remaining viral (herpetic encephalitis, tick-borne encephalitis and herpes zoster multifocal encephalitis), bacterial (lues, metastatic encephalitis connected with heart valvular changes) and fungal (candidiasis) infections were present only in single cases. It is worth mentioning 3 cases of brain aspergillosis and 5 cases of leptomeningeal tuberculosis.

Great morphological variability in the most common opportunistic infections found in our material (cytomegaly, toxoplasmosis, cryptococcosis and PML) was the most striking phenomenon. Neuropathological abnormalities in cases of toxoplasmosis and cryptococcosis revealed remarkable dependence on clinical medication used. Cases of PML were characterized by strong variances of the type and intensity of demyelination, ranging from disseminated foci of various size to diffuse complete myelin loss in the white matter involving uni- or bilaterally cerebral or cerebellar hemispheres. The coexistence of opportunistic infections with HIV-dependent cerebral pathology or other types of opportunistic processes was a very characteristic feature. Concomitance of HIV-dependent pathology with viral opportunistic processes was common. The frequency of this concomitance and more severe HIV-dependent pathology in cases with other viral cerebral infections may suggest pathogenetic interaction of viral infections. Cerebral tuberculosis was less frequent as compared with other neuropathological collections, especially those from the United States. However, it seems worth mentioning that 3 of 5 cases occurred in the last year of observation.

Key words: *AIDS, opportunistic infections, neuropathology*

The very characteristic feature of the acquired immune deficiency syndrome (AIDS) consists in appearance of clinical manifestations of one or several concomitant opportunistic infections (Skotnicki, Kornaszewski, 1988). In the case of AIDS this phenomenon is much more frequent as compared with other both inborn and acquired immune deficiences. By definitions opportunistic infections comprise the group of diseases which manifest clinically exclusively in people with disturbed immune reactivity and in most of the cases they are due to the microorganisms preexisting in the latent forms being totally neutral to healthy organism. Most of the adult human population shows features of peracted asymptomatic infection with various pathogenes, the limited virulency of which result from normally functioning immune homeostasis. Under conditions of its damage, both first contact with pathogenic agent and/or reactivation of latent preexisting infection result in the development of full-blown clinical syndrome. The clinical course of opportunistic infections in patients with AIDS is usually atypical, severe, longlasting and frequently recurrent; their clinical manifestations depend both on the biology of infectious agent and even more so on the degree of the immune deficiency (Levy et al. 1988, Skotnicki, Kornaszewski, 1988).

Opportunistic infections of the central nervous system (CNS) represent frequent complication in AIDS and are the most common causes of focal neurological symptoms. They appear usually in advanced periods of AIDS and are accompanying severe insufficiency of cellular immunoreactivity. Opportunistic infections are caused by different organisms: viruses, bacteria, fungi and protozoa. Frequency of different infections varies to a great

extent. In the pediatric autopsy material the percentage of opportunistic infections is relatively low and usually does not exceed 14% (Kozłowski et al. 1993, Wrzołek et al. 1995), while in adult material it reaches in some collections even 60% (Lang et al. 1989, Chimelli et al. 1992). In addition to the age-dependence (pediatric *versus* adult cases) the incidence of various kinds of opportunistic infections reflects geographic, epidemiologic and socio-economic conditions and probably risk-group prevalence in various populations (Rosenblum et al. 1988, Martinez et al. 1995). Very illustrative in that respect is data obtained in different regions of the United States, including New York, Los Angeles, San Francisco and Miami areas in which incidence of toxoplasmosis ranged from 6- to 30%, and that of CMV from 2 to 26% (Moskwitz et al. 1984, Levy et al. 1985, Anders et al. 1986, Petito et al. 1986).

The most common opportunistic infections are cytomegalovirus (CMV) encephalitis, toxoplasmosis, cryptococcosis and progressive multifocal leukoencephalopathy (PML). Opportunistic infections caused by other pathogenes are rather sporadic and they occur in a relatively low percentage of cases, with striking variations in various neuropathological collections.

Despite considerable differences in frequency of the CNS opportunistic infections in different collections they surpass in a significant way specific HIV-dependent brain pathology, in most of the collections not exceeding 20%, with the highest values of 38% presented in Budka's et al. (1987) material.

Material and methods

The pathomorphological analysis was performed on 172 brains from patients, who died in 1987-1997 in the course of AIDS. The 161 patients were diagnosed and treated in the Infectious Diseases Wolski Hospital in Warsaw and autopsied in the Laboratory of Morbid Anatomy of the same hospital (Dr Zdzisław Kamiński) and 11 cases in some infectious diseases departments outside of Warsaw. The material included 155 males and 17 females, aged 23-64 years (mean 38.5).

Formalin-fixed brains were obtained for neuropathological evaluation. In none of the cases spinal cord was available for the study. The fixed brains were weighed and cut in the coronal plane. Cutting of brain stem was performed in the same way. In some cases small fragments of the subbulbar spinal cord were also taken for examination.

For histopathologic study tissue blocks were taken routinely from the left cerebral hemisphere (frontal, central, parietal, occipital and temporal regions, hippocampus, basal ganglia and diencephalon), as well as midbrain, pons, medulla and left cerebellar hemisphere. In cases of focal changes visible at the brain cutting additional blocks were taken from all abnormal areas. The tissue blocks were processed for paraffin embedding. Tissue sections were stained with hematoxylin-eosin, and with Heidenhain's method. Depending on the results of preliminary examination, additional stainings were performed (some histological methods, silver impregnations, histochemical and immunohistochemical reactions).

Results

The total number of cases with opportunistic infections and cases with HIV-specific brain pathology are presented in Table 1. It shows that in the entire group of 172 examinated cases, opportunistic infections were found in 99 cases (57.5%), while HIV-specific abnormalities were seen in only 59 cases (34.1%). In 27 of them they coexisted with opportunistic infections.

Table 1. Opportunistic infections and HIV-specific changes in the central nervous system in the material of 172 investigated AIDS cases

Year	Number of cases	Opportunistic infections	HIV-specific changes	Opportunistic infections and HIV-pathology or/and malignancy
1987	2	1	1	0
1988	0	0	0	0
1989	7	2	2	0
1990	12	6	2	3
1991	9	5	1	1
1992	12	6	1	2
1993	17	7	2	2
1994	15	5	5	4
1995	25	5	3	10
1996	31	12	6	7
1997	42	17	9	4
	172	66	32	33*

*Opportunistic infections + HIV-pathology   – 21 cases
Opportunistic infections + HIV-pathology + malignancies– 6 cases
Opportunistic infections + malignancies   – 6 cases

Table 2 presents appearance of opportunistic infections in different age-groups of patients. The largest age-group in our material was that between 30 and 40 years. No age dependence on the appearance and development of the opportunistic infections was found.

Table 3 comprises specification of opportunistic infections found in the total group of examined cases. It clearly demonstrates that the most common cause of opportunistic infections in our material was

Table 2. Classification of verified AIDS cases according to age taking into account frequency of opportunistic infections

Age group (years)	Verified AIDS cases		Cases with opportunistic infections	
	number	percent	number	percent
20 – 29	26	15.8	16	9.8
30 – 39	69	42.1	38	23.2
40 – 49	49	29.9	33	20.1
50 – 59	16	9.8	8	4.9
over 60	4	2.4	2	1.2
Total	164*		97**	

* 8 cases without clinical data are omitted
** 2 cases without clinical data are excluded.

CMV (39 cases). Toxoplasmosis took the second place in frequency (28 cases). Relatively common were cryptococcosis (14 cases) and PML (16 cases). In 3 cases aspergillosis was diagnosed. The remaining neuropathologically diagnosed opportunistic infections were rather uncommon except tuberculosis appearing in 5 cases. Viral infections represented by leukoencephalopathy connected with herpes zoster infection, necrotizing encephalitis of herpetic origin and tick-borne encephalitis were diagnosed in one case each. So were bacterial infections taking the form of cerebral syphilis, with dominant vascular pathology and metastatic encephalitis connected with fulminant heart valve process. In 3 cases lymphocytic leptomengitis of unknown origin was diagnosed. Four cases in which both histopathological and immunohistochemical examinations did not determine etiological diagnosis were described as micronodular encephalitis.

Table 3. Opportunistic cerebral infections found in 172 AIDS cases

Diagnosis	Number of cases	Percent
Viral infections		
CMV infection	39	22.8
PML	16	9.3
Herpes zoster encephalitis	1	0.58
Acute necrotizing encephalitis	1	0.58
Acute tick-borne encephalitis	1	0.58
Fungal infections		
Cryptococcosis	14	8.1
Aspergillosis	3	1.7
Candidiasis	1	0.58
Parasitic infections		
Toxoplasmosis	28	16.3
Bacterial infections		
Tuberculosis	5	2.9
Lues	1	0.58
Metastatic encephalitis	1	0.58
Others		
Micronodular encephalitis	4	2.3
Lymphocytic leptomeningitis	3	1.7

The most typical feature of our collection was coexistence of several pathological processes in the same cases. Appearance of only one opportunistic infection, without any other accompanying pathological processes (neoplastic or HIV-related) was found in 56 cases. In the remaining 43 cases coexistence of several opportunistic infections (10 cases), opportunistic infections with HIV-specific changes (21 cases), and in some cases opportunistic infection with neoplastic process (6 cases), or opportunistic infection, HIV-specific pathology and proliferative neoplastic process (6 cases) were revealed.

CMV infection was the only independent process in 15 cases, in a further 6 it coexisted with other opportunistic infections. In 11 cases CMV infection coexisted with HIV-specific pathology or both HIV-specific changes and other opportunistic infections. In 7 cases CMV infection was accompanied by malignant lymphoma of the CNS alone or concomitant with HIV-specific abnormality or other type of opportunistic infections. Toxoplasmosis was the only pathological process in 8 cases, in a further 7 it was accompanied by other opportunistic infection. In the remaining 13 cases it accompanied HIV-specific brain pathology, in 4 cases as an only pathological process while in the remaining ones concomitant with different types of opportunistic processess and/or neoplastic proliferation. PML was the only pathological process in 7 cases, while in another 4 it was concomitant with other opportunistic infections. In 5 cases PML coexisted with HIV-specific pathology, among which 4 were connected with additional opportunistic diseases and/or neoplastic growth. Cryptococcosis was the only neuropathological abnormality in 7 cases, in another 4 it was accompanying HIV-specific pathology; in 1 case it was connected with another opportunistic infection and in a further 2 additionally with lymphomatous proliferation.

Neuropathological expression of already mentioned opportunistic infections (CMV, PML, toxoplasmosis, cryptococcosis) showed remarkable variations in different cases as far as topography, structure and extension of tissue abnormalities were concerned.

Infection with CMV was manifested most often in the form of nodular encephalitis (30 cases) with appearance of relatively well delimited microglial nodules spread over all CNS structures with an obvious preponderance of grey formations. They were most common in the subcortical structures and brain stem. Their frequency varied from case to case. In a relatively small proportion of nodules typical cytomegalic cells were present (Fig. 1a). Their appearance was a decisive diagnostic element. Micronodular changes were present in practically all cases of CMV infection, being in most of them (over
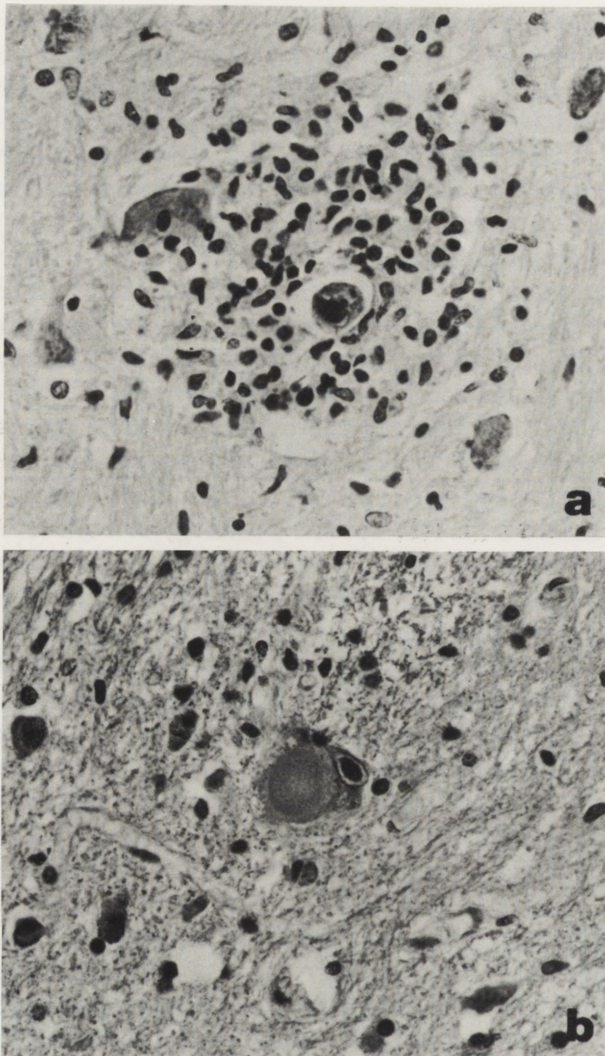
Fig. 1. Cytomegaly. a) Microglial nodule with centrally located typical basophilic intranuclear inclusion body. HE, ×400. b) Cytomegalic cell with "owl eye" intranuclear inclusion lying free in the unchanged tissue. HE, ×400

75%) its only exponent. Isolated CMV cells lying loosely in totally unchanged tissue without any inflammatory or glial reaction were relatively frequent (Fig. 1b). In about 25% of cases the neuropathological picture of the infection was dominated by necrotizing ependymal inflammatory process involving relatively extensively periventricular areas (Fig. 2). Varying in size focal necroses localized usually in corticosubcortical junctions and in subpial grey formations were also present. They were seen in the cerebellum (Fig. 3), brain stem, mostly in medulla, and in subbulbar spinal cord. The latter showed usually a topographic contact with spaces containing cerebrospinal fluid. The necrotic areas were frequently covered with numerous CMV cells characterized by appearance of both intranuclear and abundant cytoplasmic inclusions. Participation of hematogenic inflammatory reaction was usually scarce. In one of the cases there was diffuse involvement of the optic nerves, optic chiasm and optic tracts; this concerned a case with intravitally diagnosed bilateral cytomegalic retinitis. Involvement of leptomeninges and radices of the cranial nerves, although present, was not a frequent feature. An extensive accumulation of CMV cells within granular layer of cerebellar cortex, evoking no tissue reaction should be considered as a rarity.

Parasitic infections with *toxoplasma gondii* revealed also remarkable variability as far its neuropathological expression was concerned. This variability reflected on one hand different stages of evolution of the pathological process, and on the other its different dynamics, and also resulted from pharmacological treatment, applied in some cases, especially those observed in more recent years. Single toxoplasmic cysts spread freely in the brain
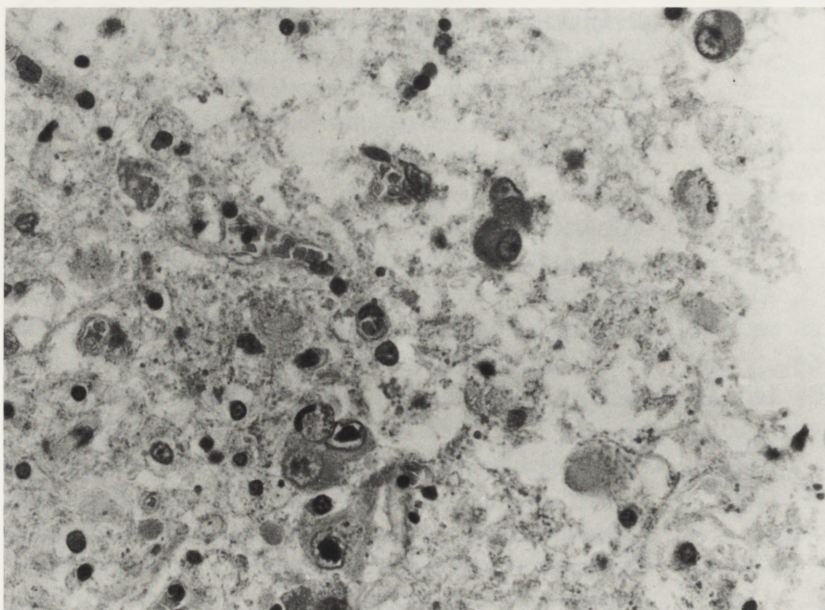

Fig. 2. Cytomegaly. Periventricular necrosis destroing totally ependymal layer with numerous cytomegalic cells. HE, ×200

Fig. 3. Cytomegaly. Large necrotic focus involving dentate nucleus and neighboring cerebellar white matter. HE, ×40

tissue with no inflammatory and glial reaction were relatively rare. So were micronodules, localized mostly in grey matter structures. They were fundamental feature of the so-called micronodular toxoplasmic encephalitis (Fig. 4a). The characteristic element of micronodules consisted in appearance either in their centre or in their direct vicinity of
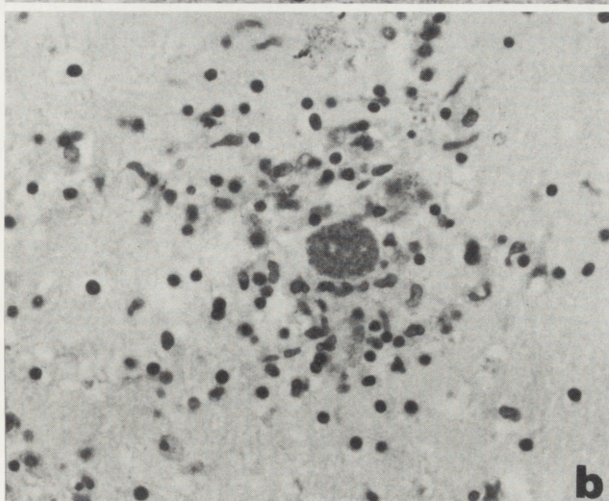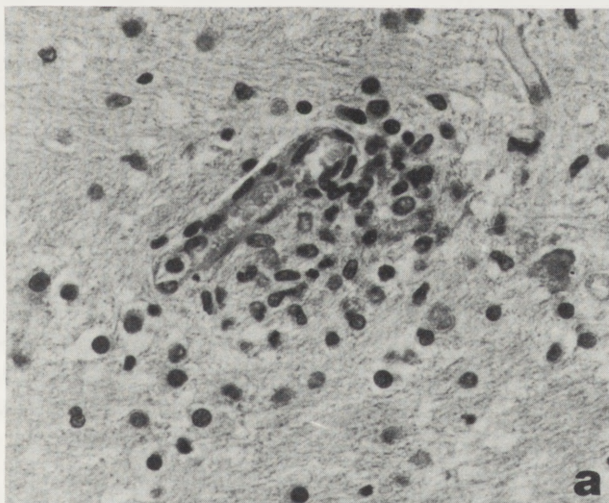

Fig. 4. Toxoplasmosis. a) Perivascular micronodule composed of histiocytic and microglial cells. HE, ×400, b) Microglial nodule lying on slightly rarefied tissue with centrally located parasitic cyst. HE, ×400
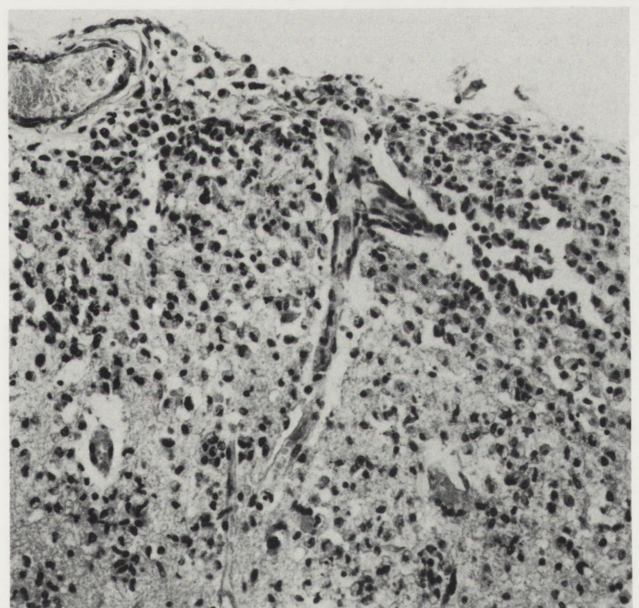
Fig. 5. Toxoplasmosis. Subpial necrosis covered with activated microglial cells with some admixture of hematogenic elements. HE, ×100

encapsulated forms of the microorganism and presence of small micronecrosis occupying the central part of the nodule (Fig. 4b). The more common feature, especially in the early period of our observation, was diffuse necrotizing inflammation at different stages of tissue disintegration, leading to full necrosis (Fig. 5). Their foci, usually confluent were characterized by appearance of varying in intensity inflammatory process and remarkable accumulation of encapsulated microorganisms and
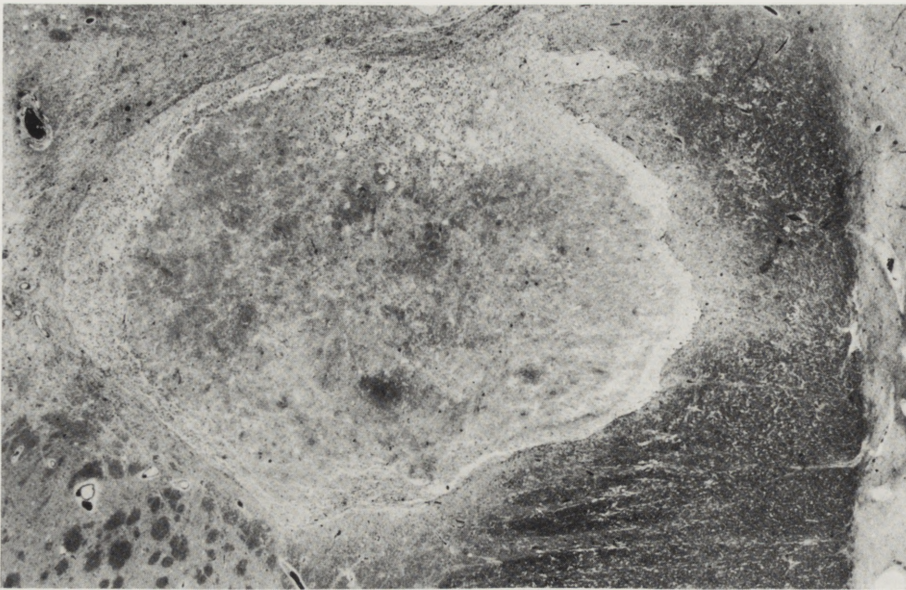
Fig. 6. Toxoplasmosis. Sharply delineated encapsulated abscess located in the basal ganglia. Heidenhain, ×10
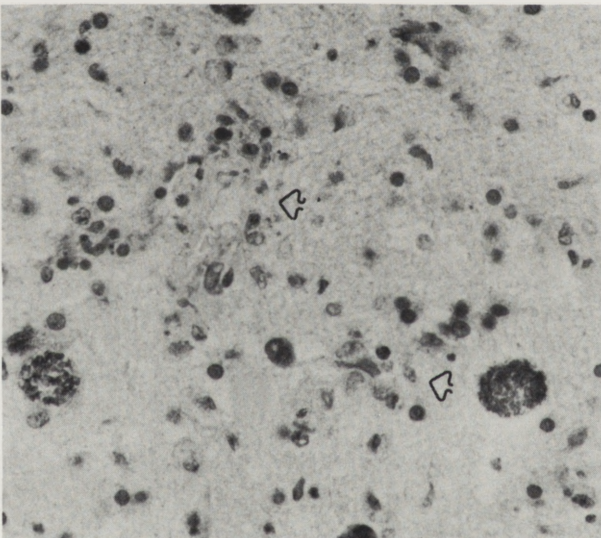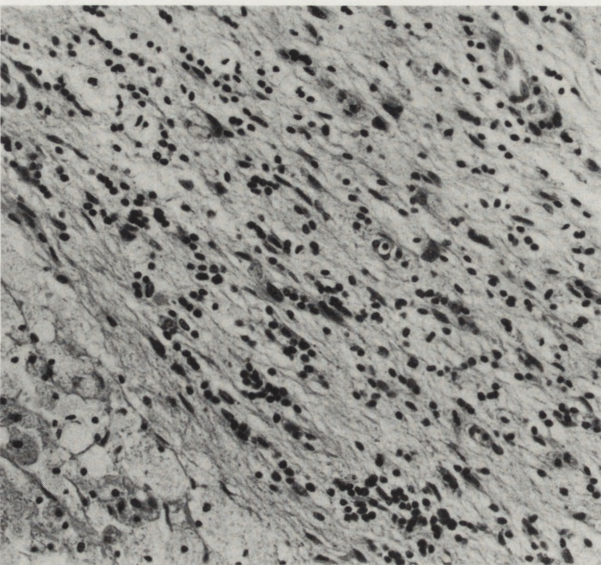

Fig. 7. Toxoplasmosis. Surroundings of fresh abscess with numerous parasitic cysts. Some free lying tachyzoites (arrows) are seen. Immunostaining for *Toxoplasma*. PAP method, ×400

spread free tachyzoites. The so-called toxoplasmic abcesses, taking the form of varying in size and advancement foci of tissue destruction, were the most common and characteristic feature. They were localized most often in the cerebral hemispheres with a preponderance of the basal ganglia (Fig. 6). In the early stages they were not sharply delimited from the surrounding tissue and filled with masses of coagulative necrosis. On their periphery numerous cysts and free tachyzoites were present (Fig. 7). Severely edematous tissue with proliferative glial reaction was seen already at this stage of the process. At the stage of organization, necrotic foci were sharply delineated from the surroundings by accumulation of macrophages and typical granulomatous tissue. Here and there some cysts and free tachyzoites could be found in this area. Very often periphery of abscesses and less frequent their central part contained granular calcium deposits. Surrounding nerve tissue in addition to edematous changes revealed severe neuronal loss and degeneration of the remaining nerve cells. Some of them were calcified. Infrequently small and midsized blood vessels surrounded by hematogenous infiltration were present. Chronic toxoplasmic abscess, typical for treated cases took the form of cavernous foci filled with macrophages and surrounded by fibrous connective tissue and hypertrophied astrocytes (Fig. 8). Encapsulated forms and free tachyzoites were hardly seen.

Fig. 8. Toxoplasmosis. Fibrous capsule of an old abscess. In the lower corner a field of densely packed macrophages from the central part of abscess is seen. HE, ×200

Cryptococcosis of the brain took two main patho-morphological forms. First, less common, was manifested as a productive granulomatous inflammatory process, with the presence of typical epithelioid and giant cells, with some lymphocytic component (Fig. 9). The most characteristic feature consisted in dense accumulation within granulomatous tissue of typical fungal cells, most of which were surrounded by PAS-positive envelopes (Fig. 10).
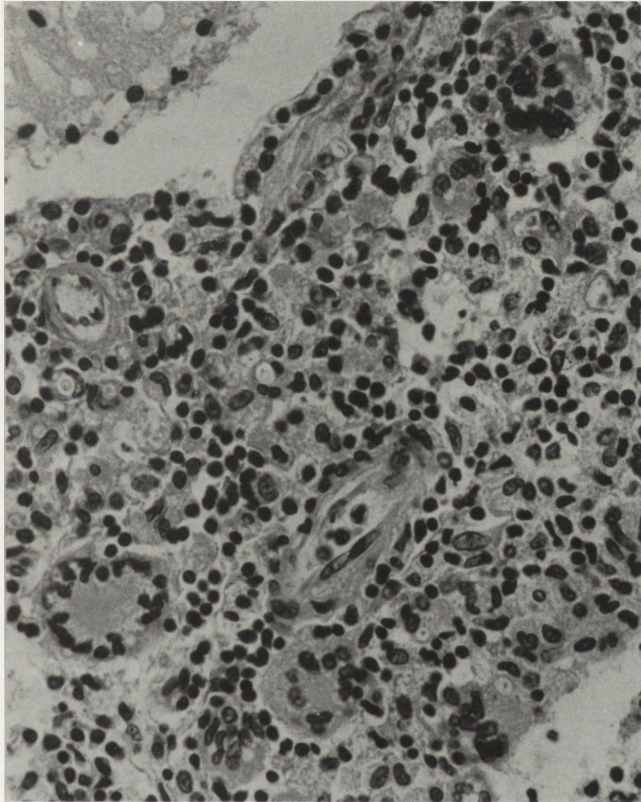

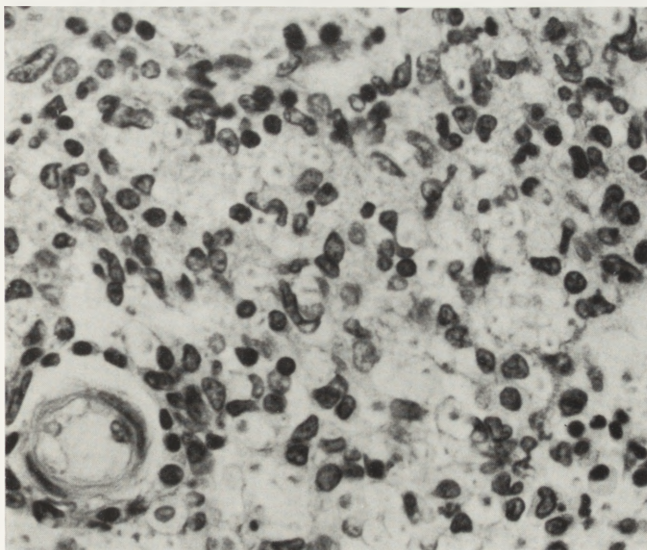**Fig. 9.** Cryptococcosis. Granulomatous leptomeningitis with epithelioid and multinuclear giant cells. HE, ×400

Fig. 10. Cryptococcosis. Fragment of granulomatous leptomeningitis with fungal colonies with characteristic mucopolysaccharide capsules. HE, ×400

The fungal cells were also visible within cytoplasm of giant cells. This type of changes was most characteristic for leptomeningeal involvement although they penetrated along perivascular spaces into cerebral parenchyma. The second type of cryptococcosis took the form of numerous, confluencing, varying in size and density multicystic formations surrounded by tissue showing no cellular reaction of either hematogenic or glial nature. In cases of extensive accumulation of these structures, particular caves were separated from each other by thin strings of atrophic brain tissue. The caves were either empty or contained some amount of microorganisms (Fig. 11) surrounded by sharply-limiting birefringent membranes with typical radially arranged spines. This type of changes was most commonly localized within cerebral cortex and basal ganglia, although they were seen also in the cerebral white matter, brain stem and cerebellum. They were present also in the leptomeninges, forming bulbous distensions of the subarachnoid space, penetrating along the perivascular spaces into the brain parenchyma. In some cases cryptococci were accumulated not only in distended perivascular spaces but also within vascular lumina. In four cases cystic changes localized within cerebral hemispheres (Fig. 12) with
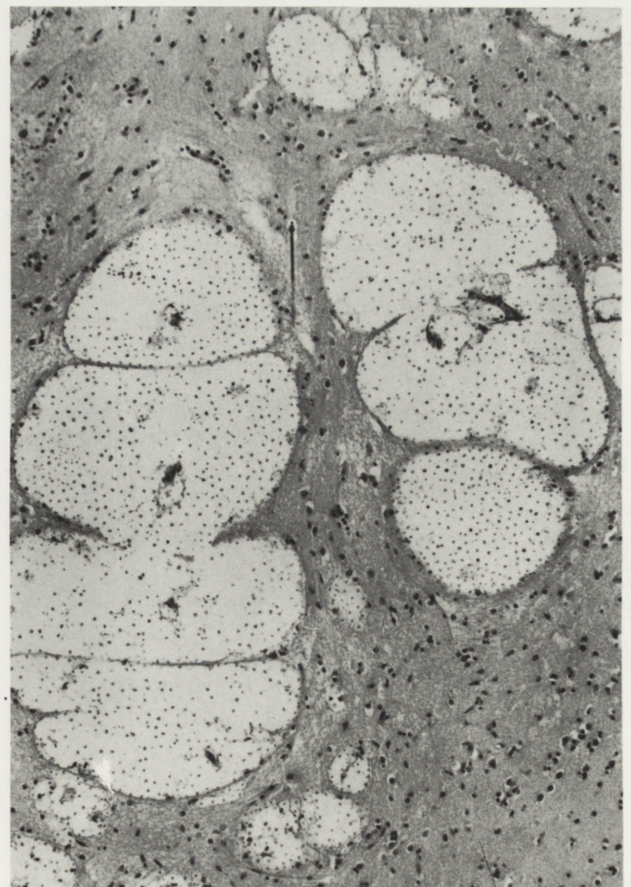

Fig. 11. Cryptococcosis. Severe tissue cavitation. Caves lumina are filled with cryptococcal microorganisms. HE, ×100
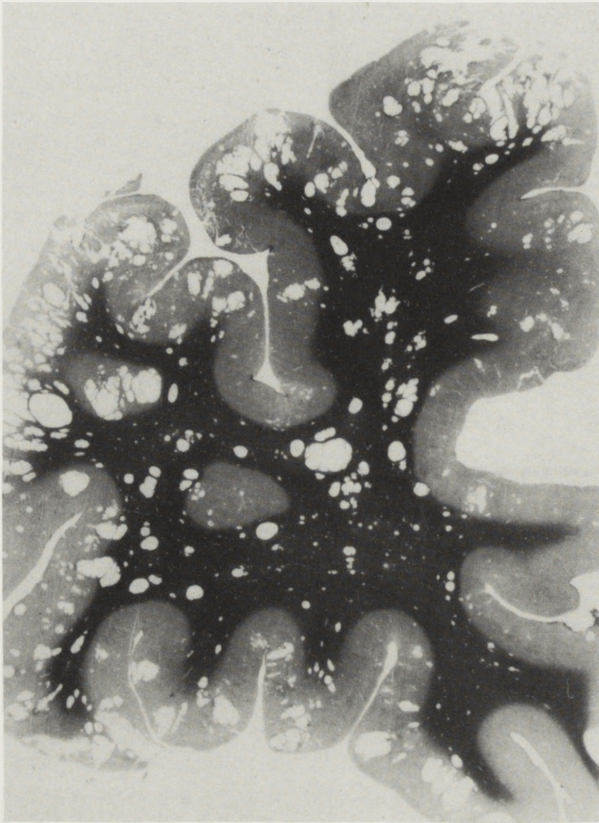
Fig. 12. Cryptococcosis. Severe tissue cavitation involving both cerebral cortex and subcortical white matter. Heidenhain, ×10

process. Demyelination ranged from small limited foci of myelin pallor spread in various brain structures (Fig. 13) to large, confluent fields of full demyelination of the white matter of the cerebral hemispheres, either bi- or unilaterally, involving basal ganglia and cerebral cortex as well as that of the brain stem formations and cerebellum. In some cases diffuse demyelination of the cerebellar white matter was very extensive involving practically both hemispheres (Fig. 14). In some instances in the fields
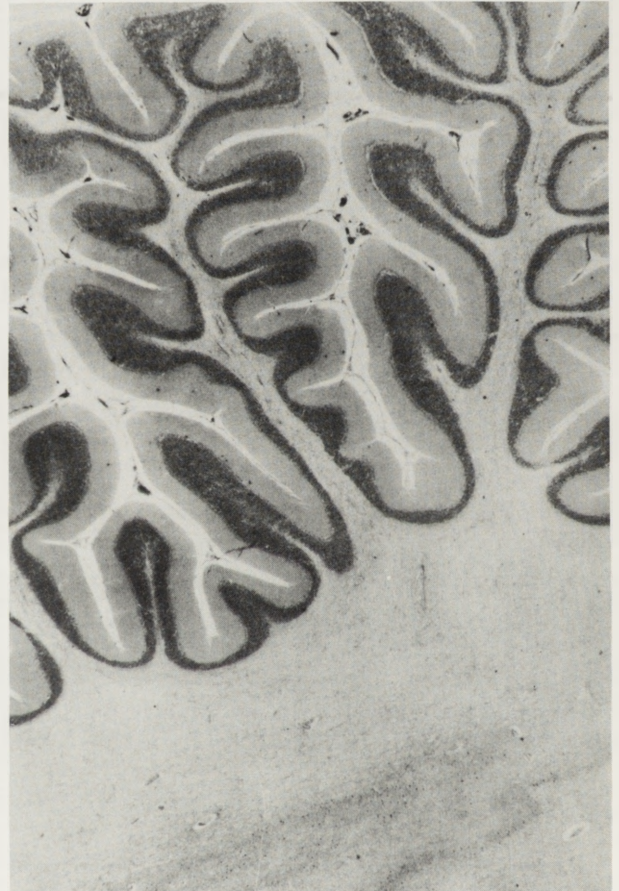
an evident preponderance of basal ganglia were so prominent and extensive that pathological diagnosis was done already on gross examination. Pathology of treated cases differed in lack of evident inflammatory infiltrations and great reduction of microorganisms.

In the material with PML the most striking differences of the neuropathological picture consisted in intensity and extension of the pathological

Fig. 14. PML. Cerebellar white matter totally devoid of myelin. Heidenhain, ×10
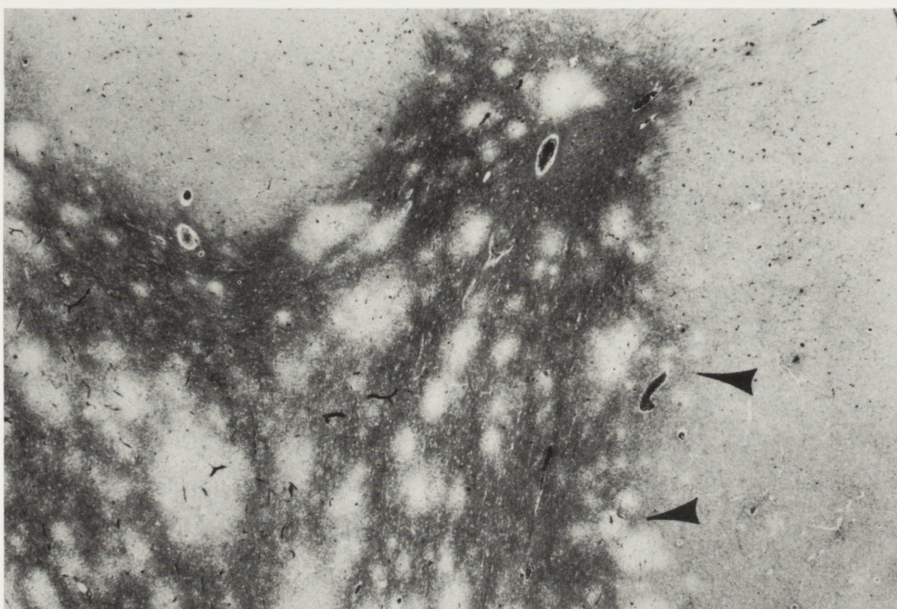

Fig. 13. PML. Innumerable confluencing demyelination foci within the white matter of cerebral hemisphere; some of them are visible in the cerebral cortex (arrows). Heidenhain, ×10

of most advanced demyelination severe tissue disintegration, leading to its cavitation, was present. Typical neuropathological exponents of glial involvement in the form of enlarged oligodendroglial nuclei, very often with intranuclear inclusions (Fig. 15) and abnormal hypertrophied astrocytes with hyperchromatic "bizarre" nuclei were very numerous (Fig. 16). Oligodendrocytes were mostly localized on the periphery of the lesions and in grey matter formations, while astrocytes with blastomatous nuclei were typical for the "burn out" and severely damaged tissue areas where they accompanied macrophages, covering densely both demyelinated as well as disintegrated fields. In the demyelinated areas and in their vicinity some blood vessels showed presence of lymphocytic cuffs (Fig. 15). Small "fresh" demyelinating areas spread over the CNS did not show as a rule any astrocytic abnormalities, they contained some proportion of pathologically changed oligodendroglial nuclei.

Three cases of cerebral aspergillosis* seem to be worth mentioning due to their unusual appearance among opportunistic infections in the course of AIDS. In one case, concomitant with CMV infection a large isolated abscess localized in the right frontal lobe was present. Wide ring of granuloma-

* Presented at the X Conference of Polish Association of Neuropathologists. Warsaw, May 15-17, 1996 (Zelman IB, Mossakowski MJ, 1996).
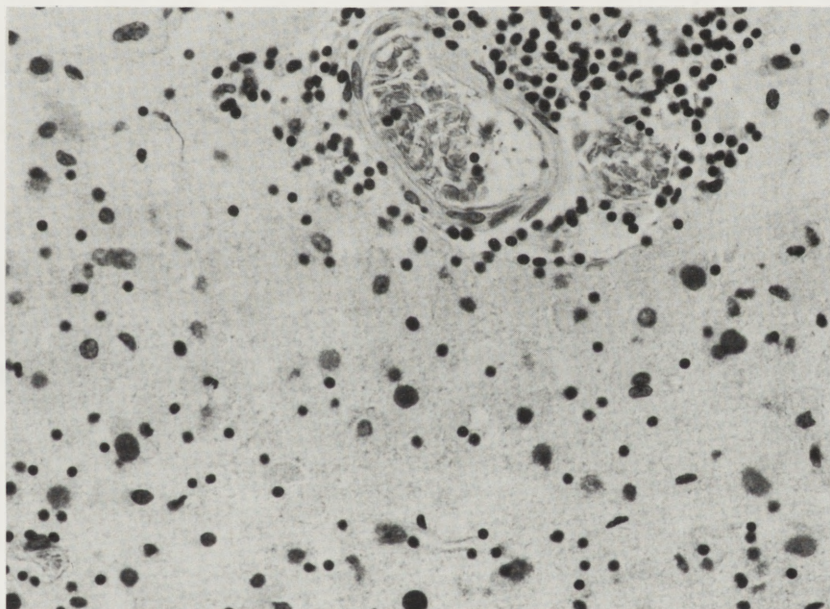

Fig. 15. PML. Numerous enlarged hyperchromatic, homogenously stained oligodendroglial nuclei spread in the demyelinated white matter. HE, ×400
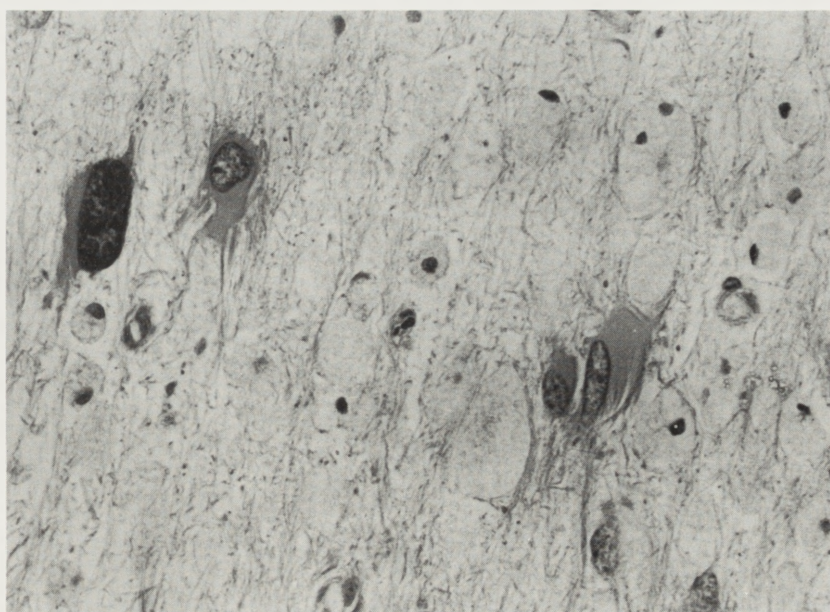

Fig. 16. PML. Demyelinated white matter densely covered by macrophages. Abnormal hypertrophied bizarre astrocytes are seen, some of them with "blastomatous" nuclei. HE, ×400

tous tissue surrounding abscess contained numerous cytomegalic cells. The abscess contained very rich fungal colonies (Fig. 17). In the second case in which aspergillosis was accompanying HIV-specific cerebral process and CMV infection, the fungal changes were limited to bilateral gyri recti and neighboring orbital gyri and their leptomeninges. Optic nerves and their chiasm were also involved. Topography of changes suggested penetration of the infection from nasal sinuses to the leptomeninges and then their spread into the brain tissue. In the third case concomitant with pulmonary aspergillosis the pathological changes were generalized and took the form of numerous necrotic-inflammatory foci spread in the brain and cerebellum. Their pathomorphological structure differed extensively, depending on their localization, evolution stage and the way of spreading: hematogenic or *via* cerebrospinal fluid. The pathological feature common for all three cases consisted in thrombotic-inflammatory process with abundant colonies of aspergillus present within vascular lumina and walls as well as in the surrounding tissue (Fig. 18). No giant cells of Langhans type considered to be a typical component of aspergillosis without HIV-infection were seen within inflammatory granulomatous tissue. Fungal infections were complemented by one case of cerebral candidiasis manifested by leptomeningeal process with severe ventricular wall involvement.

Cerebral tuberculosis in all 5 cases was characterized by leptomeningeal involvement of different intensity in the form of granulomatous inflammatory process (Fig. 19) with numerous multinuclear giant cells of Langhans type (Fig. 20) In one case severe involvement of the larger leptomeningeal vessels with consecutive vasogenic parenchymal changes was present. In three cases leptomeningeal process was accompanied by parenchymal tuberculomas localized in the pons, cerebellum and frontal lobe white matter. In all cases pathological diagnosis was confirmed by visualization of *mycobacterium tuberculosis* (Fig. 21).

Fig. 17. Aspergillosis. Dense colony of fungi located in the necrotic tissue HE, × 200
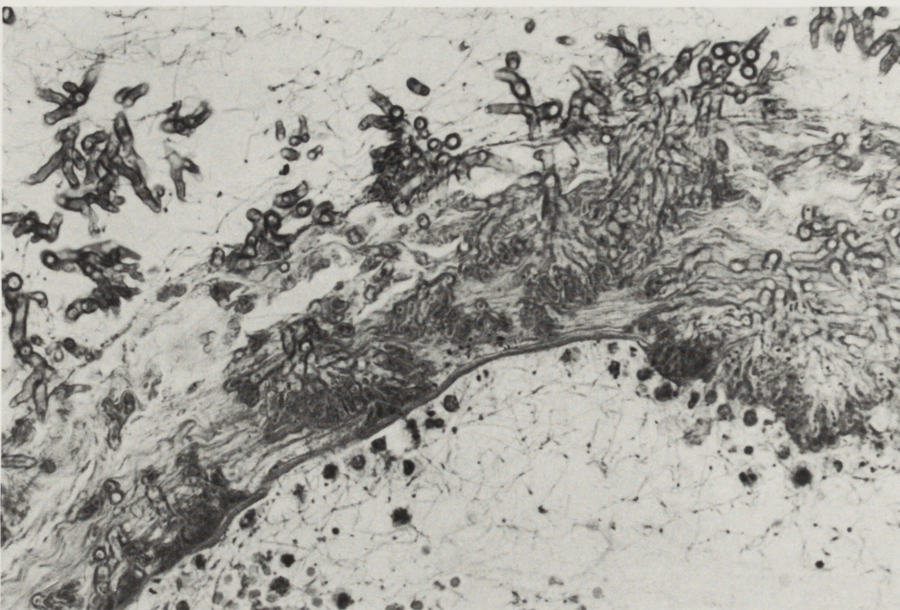

Fig. 18. Aspergillosis. Fungal colonies within the blood vessel wall, protruding into its lumen. Fungi are also spread in the perivascular tissue of choroid plexus. Heidenhain, × 400
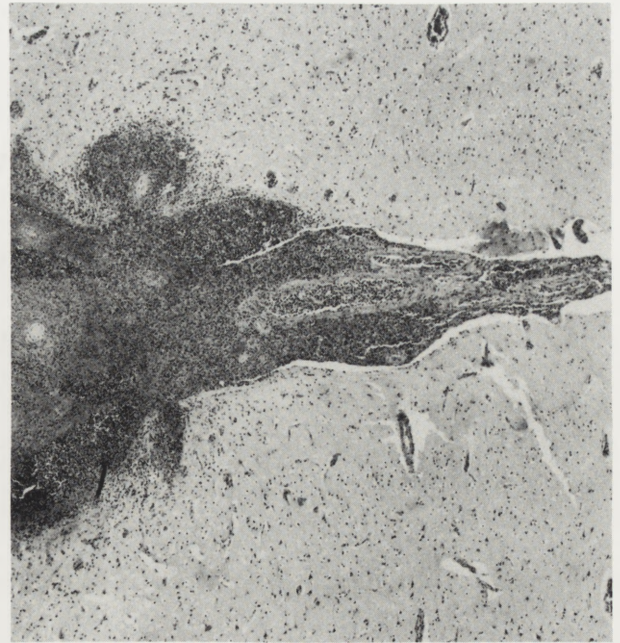
Fig. 19. Tuberculosis. Severe inflammatory infiltration of the leptomeninges invading neighboring cerebral cortex. Large perivascular infiltration (arrow). HE, ×40
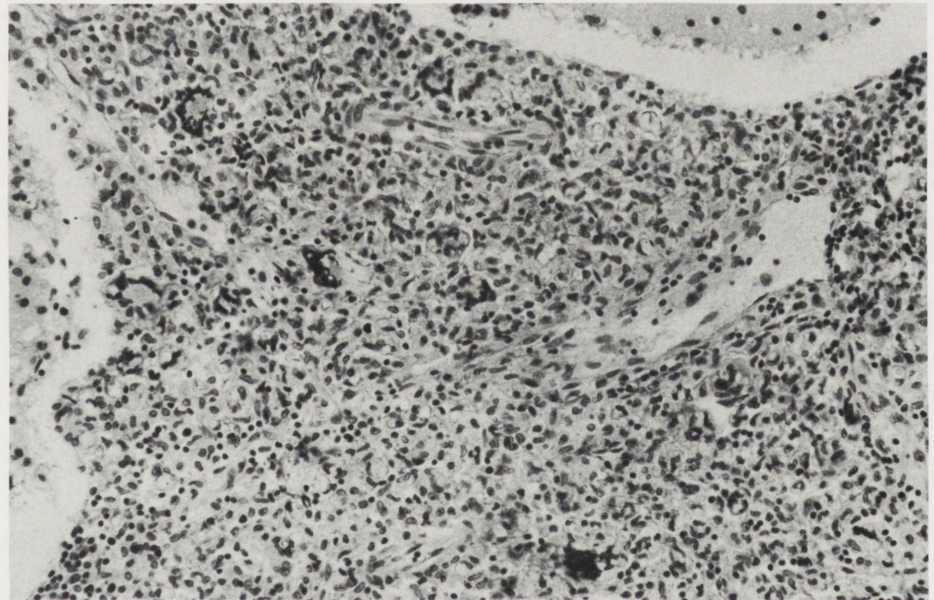

Fig. 20. Tuberculosis. Massive granulomatous inflammation of the leptomeninges with numerous multinuclear giant cells of Langhans type. HE, ×200
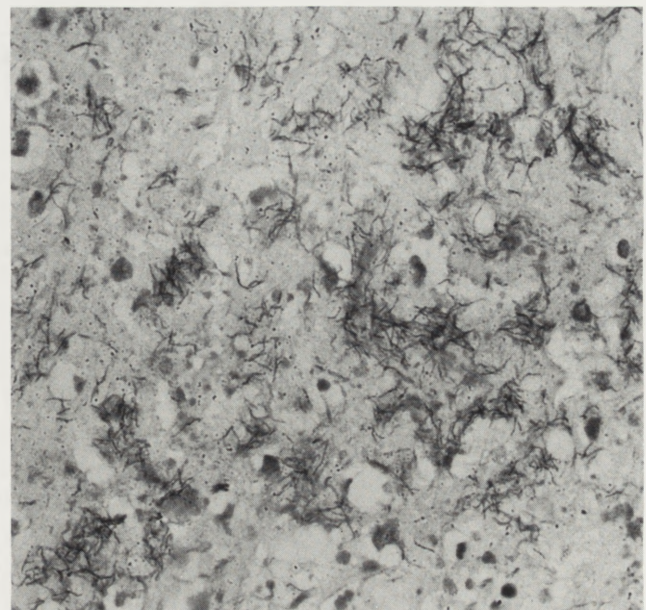

Fig. 21. Tuberculosis. Abundant colonies of acid-fast bacilli within leptomeningeal infiltration. Ziehl-Neelsen, ×600
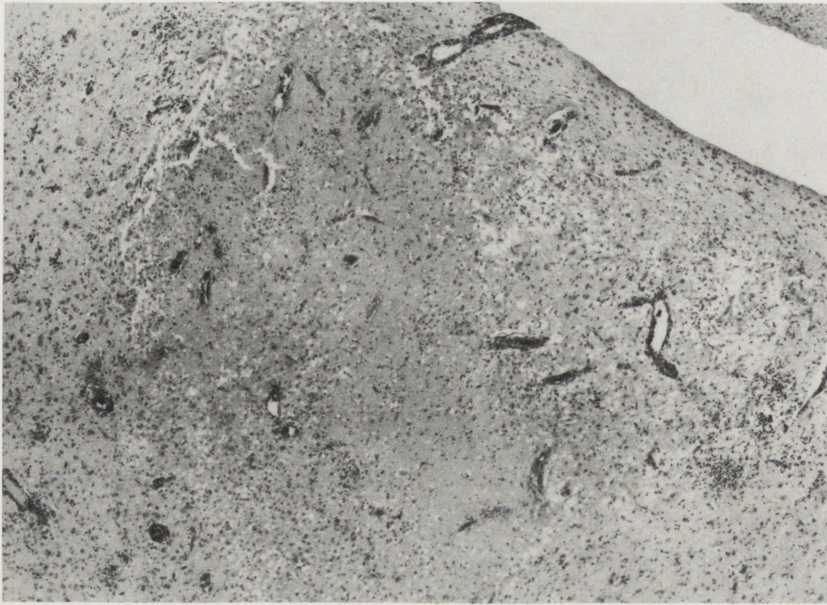
Fig. 22. Herpetic encephalitis. Inflammatory necrosis of the apical portion of the temporal lobe. Note numerous perivascular cuffs both in the necrotic area and its surroundings. HE, × 40

The most representative of rare viral infections were herpetic necrotizing encephalitis, with typical involvement of limbic system structures by inflammatory necroses (Fig. 22) with numerous perivascular hemorrhages and abundant intranuclear inclusions, both in neuronal and glial populations (Fig. 23a,b) and tick-borne encephalitis with typical histopathology.

Fig. 23. Herpetic encephalitis. Intranuclear basophilic inclusion bodies in nerve (a) and glial (b) cells. HE, × 600

Discussion

Neuropathological study of 172 brains of adult patients with AIDS, who died in 1987-1997 revealed a large spectrum of opportunistic infections, leading in many cases to extensive damage of the CNS. Opportunistic infections were found in 99 cases (57%), overwhelming highly incidence of HIV-specific processes present in 34% of the material under study.

Most of the analyses, originating from European and non-European countries indicate that opportunistic infections prevailed among CNS alterations in adult patients with AIDS (Petito et al. 1986, Budka et al. 1987, Chimelli et al. 1992, Martinez et al. 1995, Rosemberg et al. 1996, Mossakowski, Zelman 1997 and others). Frequency of their occurrence ranged usually within the limits of 46-64% of cases and was relatively comparable with our data. A low percentage of the CNS opportunistic infections in the material presented by Budka et al. (1987) amounting to only 46% is worth noting. Much higher differences, concerned incidence of HIV-related brain abnormalities, especially comparing European data and those from other part of the world; this in Lang's et al. (1989) studies amounted only 16%, in Budka et al. (1986) – 38% and in Berlin collection, presented by Martinez et al. (1995) – 35.5%. Brasilian data amounted to only 10% and 17%, respectively, in Chimelli's et al. (1992) and Rosemberg's et al. (1996) material. The most constant positions in all analyses are taken by CMV infection, toxoplasmosis, PML and cryptococcosis, with significant differences concerning their frequency in different collections (Tab. 4). Other infections both viral, bacterial, protozoan and fungal are rare or very rare, and noted only in some collections.
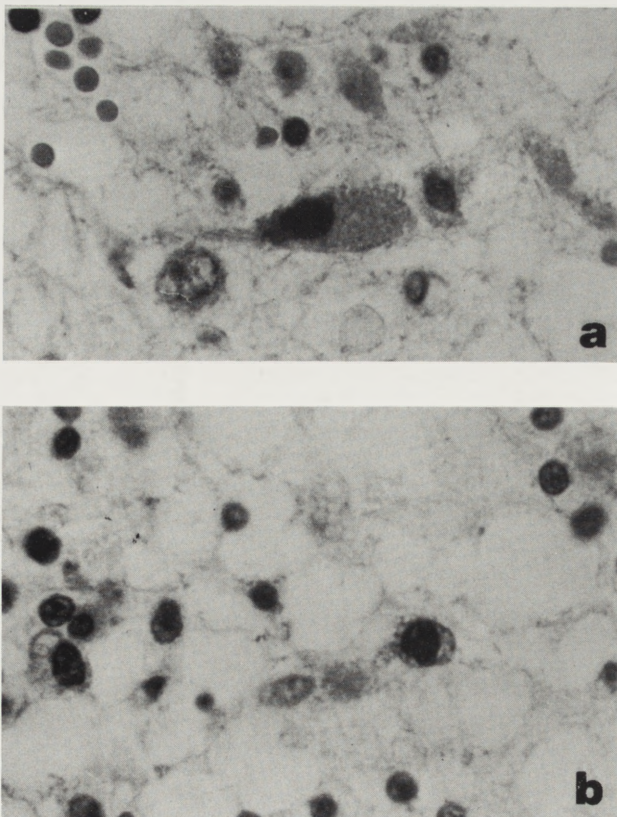
In Polish material among CNS opportunistic infections in AIDS first position is taken by CMV infection (39/172 – 23%). In other collections frequency of cases with neuropathological expression of CMV infection is generally lower and ranged from 2 to 26 percent (Table 4). These values could be

Table 4. Comparison of incidence of some opportunistic infections in AIDS in own material with literature data

Area	No of cases	CMV %	Toxoplasmosis %	Cryptococcosis %	PML %
Austria/Italy (Budka et al.1987)	100	18	17	9	5
Switzerland (Lang et al.1989)	135	10	26	4	7
Berlin (Martinez et al.1995)	200	13	34	2	8
Brasil (Chimelli et al.1992)	252	8	34	13	1
(Rosemberg et al.1996)	481	6	31	13	2
USA – New York (Petito et al. 1986)	153	26	11	3	2
USA – San Francisco (Levy et al.1985)	128	2	14	13	2
USA-Los Angeles (Anders et al.1986)	89	16	6	12	7
Poland	172	23	16	8	9

The percentages have been rounded up to the complete numbers.

lowered by the fact of a rather low frequency of typical CMV cells within microglial nodules, being in great proportion the only neuropathological exponent of the infection. According to Morgello et al. (1987) typical CMV cells are visible in about 6.5% nodules. Basing on a retrospective analysis of 235 cases autopsied in Vienna during 1984-1994, Setinek et al. (1995) are stressing systematic increase of cases with cerebral CMV infection in AIDS patients: in 1994 it was the most common opportunistic infection, reaching a value of 37%. A similar tendency was noticed in our material, this being probably linked with an extended duration of patients survival. It is worth noting that the above mentioned authors did not find any significant differences between patients treated with Ganciclovir and/or Foscanet and those who were not treated with any drugs.

A relatively low percentage of cases of the cerebral CMV infection, both in our material and in collections of other authors, revealed periventicular necrotizing process. Some authors found in periventricular necrotizing inflammatory foci exponents of coinfection of CMV with herpes simplex virus (HSV), confirmed by immunohistochemical studies (Morgello et al. 1987, Gray et al. 1988, 1993, Lang et al. 1989, Vago et al. 1996). Vago et al. (1996) using both immunohistochemistry and PCR reaction

analysed 82 cases with periventricular CMV infection and/or necrotic foci localized in areas far away from the ventricular system, showing presence of HSV1/2 in 16% of cases. In none of these cases histological exponents of HSV infection were present. This suggests that coinfection of both viruses can lead to exacerbation of tissue alterations. It has been also suggested that in the pathomechanism of cerebral CMV infection in the course of AIDS an important role may be played by synergetic action of HIV and CMV on the cellular level (Nelson et al. 1988, Skolnik et al. 1988, Belec et al. 1990, Fiala et al. 1993). This hypothesis was based on the presence of both viruses in giant multinuclear cells, found in immunohistochemical and electron microscopic studies (Belec et al. 1990, Gray 1993). This was also supported by *in vitro* observations indicating an increase of productivity of CMV in the presence of HIV and enhancement of HIV replication in the presence of CMV (Skolnik et al. 1988).

PML was the second opportunistic infection of viral etiology relatively common in our material. It appeared in 9.35% of cases. In the majority of other collections diagnosed cases of PML ranged from 1 to 8 percent (Tab. 4). In our series only in 5 of total of 16 PML cases it was related to HIV-specific abnormalities. No dependence of this coinfection on the neuropathological picture of the process connected with JC virus (JCV) infection was found. It is a general assumption that in most of the cases PML develops as a result of reactivation of a latent infection persistent within CNS. It seems, however, that this mechanism concerns more often extracerebral body organs, first of all kidneys, from where JCV reaches CNS *via* blood circulation (Major, Ault 1995). Hematogenic pathway of the infection may be also suggested by frequent perivascular location of early PML changes as well as predilection of their accumulation in corticosubcortical junction area. *In vitro* studies revealed reciprocally positive interaction between viruses HIV and JCV. As PML in most of the cases is connected with severe inflammatory-macrophagic reaction one can assume its influence on the development of HIV-specific changes by penetration into the CNS monocytes/macrophages latently infected with HIV. Without final determination of the above presented hypothesis concerning reciprocal interaction of both viruses, it is well established that appearance of HIV within the pathological foci of PML is relatively common (Rhodes et al. 1988, Aksamit et al. 1990, Einsiedel et al. 1993). Their concomitance within the same cellular elements was not found. Comparative studies of PML in patients with and without AIDS showed relatively small differences in their neuropathology, expressed by a greater tendency to tissue

disintegration and more abundant aggregation of JCV-infected oligodendrocytes in the brains of patients with HIV infection (Aksamit et al. 1990, Schmidbauer et al. 1990). Recently Adle-Biasette et al. (1996) described a case of rabies in a 42-year-old male, clinically asymptomatic HIV-carrier. The most striking feature of neuropathology of the case consisted in relatively slight inflammatory reaction and abundance of Negri bodies, indicating increased replication of rabies virus. This could be referred directly to the damage of CD4 lymphocytic population, influencing in a decisive way pathogenicity of rabies virus.

Herpes simplex encephalitis in its classical form of acute necrotizing encephalitis, as found in our material, was sporadically described in the literature (Rhodes 1988, Lang et al. 1989, Gray 1993) contrary to this tick-borne encephalitis in the course of AIDS to the best of our knowledge has not been yet presented.

Varicella zoster virus (VZV) infection observed in one of our cases, was also sporadically described by other authors. Gray et al. (1994) basing on the analysis of their own 11 cases, suplemented by 11 cases from the literature had described several neuropathological types of the process in addition to most common multifocal necrotizing leukoencephalitis. Those were ependymitis, vasculopathy of parenchymal and leptomeningeal blood vessels, focal myelitis and acute myeloradiculitis. Lack of spinal cords in our material excludes by definition diagnosis of the two latter forms. None of the above described types of the cerebral pathology was found in our case, which was characterized by widespread disseminated foci of perivascular demyelination similar to the so-called allergic encephalitis.

Protozoan infection with *toxoplasma gondii* takes the second position in our collection as far as frequency of opportunistic infections is concerned, whereas in most of the other collections it occupied the first place (Tab. 4). Variability of its neuropathological expression in the course of AIDS, elaborated in details in selected collections (Gray et al. 1989, Navia et al. 1989, Arent et al. 1991, Strittmatter et al. 1992) found its exact conformity in our material. Variability of the intensity of inflammatory reaction, extensiveness of necrotic changes and abundance of microorganisms accumulation in the brain tissue depend on the host immunological state. However, it is worth underlining that in our collection nearly 50 percent of cases of toxoplasmosis were concomitant with HIV-specific pathology. Perhaps, similarly as in case of PML they could be initiated or facilitated by penetration into the brain of HIV-infected monocytes/marcrophages.

Cryptococcosis is the most common fungal opportunistic infection accompanying AIDS (Chuck et al. 1989), observed postmortem with an incidence rate of 2-13% in adult patients (Tab. 4). In our collection frequency of cryptococcic infection was relatively high as compared with the material from other European countries. This seems important from the clinical stand point due to relatively easy intravital diagnosis of the disease in cerebrospinal fluid examination and possibility of its effective pharmacological treatment.

Tuberculosis in our material was found in 5 cases. In two of them leptomeningeal pathology was accompanied by massive involvement of meningeal and parenchymal blood vessels, with consecutive vasogenic tissue damage, in further three occurrence of small parenchymal and meningeal tuberculomas was very striking feature. The American data indicates a remarkable increase of tuberculosis among HIV-infected population. An increase of extrapulmonary tuberculosis in AIDS cases and appearance of tuberculomatous abscesses and tuberculomas in the brain has been noticed (Barnes et al. 1991). This tendency is not so much reflected in our AIDS-material despite a significant increase of turbeculosis incidence in general population. It is worth mentioning, however, that three of 5 cases with cerebral tuberculosis appeared in the last year (1997) of our studies.

Zakażenia oportunistyczne ośrodkowego układu nerwowego w przebiegu nabytej niewydolności immunologicznej (AIDS)

Streszczenie

Przeprowadzono anaiizę neuropatologiczną 172 przypadków AIDS pod kątem występowania i charakterystyki zakażeń oportunistycznych oun, stanowiących najczęstszą przyczynę ogniskowych zespołów neurologicznych. Materiał obejmował 155 przypadków dorosłych mężczyzn i 17 dorosłych kobiet. Średnia wieku wynosiła 38,5 lat. Kolekcja stanowiąca przedmiot analizy obejmowała przypadki zgromadzone w latach 1987-1997.

Zakażenia oportunistyczne obecne były w 57,5% przypadków i stanowiły w 38,4% wyłączny proces patologiczny, a w 19,1% współistniejący ze zmianami zależnymi od zakażenia HIV lub rozrostami nowotworowymi. Najczęstszymi zespołami patologicznymi były zakażenia wirusem cytomegalii (22,7%), pierwotniakiem *toxoplasma gondii* (16,3%) oraz postępująca wieloogniskowa leukoencefalopatia (9,3%)i kryptokokoza (8,1%). Pozostałe

zakażenia wirusowe (herpetyczne zapalenie mózgu, kleszczowe zapalenie mózgu i wieloogniskowa encefalopatia związana z zakażeniem wirusem herpes-zoster), bakteryjne (kiła, zapalenie przerzutowe związane z ropnymi zmianami zastawkowymi) oraz grzybicze (kandydoza) dotyczyły pojedynczych przypadków. Na odrębną uwagę zasługuje obecność 3 przypadków aspergilozy i 5 przypadków gruźlicy oponowo-mózgowej, której w 3 przypadkach towarzyszyły gruźliczaki parenchymalne.

Cechą zmienną obrazu neuropatologicznego czterech najpospolitszych zakażeń oportunistycznych (cytomegalia, toksoplazmoza, PML i kryptokokoza) było bardzo znaczne zróżnicowanie ich postaci morfologicznych. Zespoły patomorfologiczne toksoplazmozy i kryptokokozy wykazywały odrębności obrazu w zależności od klinicznego leczenia preparatami ukierunkowanymi na właściwe patogeny. Przypadki PML znamionowało znaczne zróżnicowanie charakteru i nasilenia demielinizacji od typowych rozsianych ognisk do rozlanej demielinizacji obejmującej jedno- lub obustronnie istotę białą półkul mózgu lub móżdżku.

Cechą zmienną przedstawionego materiału było zarówno współistnienie zakażeń oportunistycznych z wykładnikami infekcji HIV jak i różnych typów procesów oportunistycznych. Zwraca uwagę częste skojarzenie infekcji HIV z wirusowymi zakażeniami oportunistycznymi. Wymieszanie zmian HIV-zależnych z wykładnikami infekcji wirusowych innego typu oraz znaczne nasilenie patologii HIV-zależnej w tych razach może sugerować patogenetyczną interakcję zakażeń wirusowych. Gruźlica oun w naszym materiale występowała rzadziej niż w innych zbiorach neuropatologicznych, zwłaszcza amerykańskich. Na uwagę zasługuje jednak fakt, że większość przypadków infekcji tbc przypada na ostatni rok obserwacji.

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