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PATHOMORPHOLOGICAL VARIATIONS OF THE AIDS-ASSOCIATED PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

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Pathological analysis of 20 cases of the progressive multifocal leukoencephalopathy (PML) appearing in the course of acquired immune deficiency syndrome (AIDS) is presented. PML occurred in 10% of all AIDS cases, collected in the period from 1987 to 1999. PML appeared either as the only brain pathology or accompanied HIV-related brain alterations isolated or concomitant with one or several opportunistic infections and/or neoplastic growth (malignant lymphoma). Basing on the pathomorphological picture and clinical symptomatology early, atypical and severe forms of the disease were distinguished. All of them were characterized by typical PML demyelination with oligodendroglial and astrocytic pathology. The group with early changes revealed widespread, multifocal myelin alterations of a moderate intensity with predominant oligodendroglial abnormalities and less advanced astrocytic changes. Atypical form of the disease was represented by cases with unifocal changes, although containing all key elements of PML pathology. The leading pathological feature of the severe form of the disease consisted in a particular intensity of the demyelination, resulting in tissue destruction often with its cavitation, with typical glial reaction and intense macrophage and lymphocytic infiltration. The other distinguishing feature consisted in strong topographic prevalence of the pathological process either to brain hemispheres or cerebellum.

Differences of PML pathology in the course of AIDS as compared with non-AIDS cases are discussed. Due to the relatively high frequency of cases of isolated or strongly predominant involvement of cerebellum, separation of the cerebellar form of the disease has been suggested.

Key words: *progressive multifocal leukoencephalopathy, AIDS, neuropathology, ultrastructure*

Introduction

Progressive multifocal leukoencephalopathy (PML) is a subacute demyelinating disease, which occurs almost exclusively in adults with disturbed immune reactivity mostly of the cellular type. It is caused by JC virus (JCV) from the papova group. Symptomless infection with the virus is very common in the human population. Anti JCV-antibodies are present in about 70-90 per cent of the general adult population [5]. Before the appearance of acquired immune deficiency syndrome (AIDS) pandemics, PML was a very rare clinical condition. Since the early eighties a progressive increase of PML occurrence was observed, mostly connected with AIDS [3, 11, 12]. According to epidemiological data the general number of PML cases in the United States in 1987 was four times higher than in 1978 [11]. A retrospective analysis of 205 AIDS cases with accompanying PML, who died in 1981-1984 and 1991-1994 revealed a four-fold increase of PML cases in the space of 10 years. This increase might only partially be connected with a prolonged survival time of patients and more successful treatment and prophylaxis of opportunistic diseases accompanying AIDS [12].

The frequency of PML appearance varies greatly in different neuropathological collections. For instance it seems relatively low in Brasilian material, despite the high incidence of AIDS cases [6, 18]. A low incidence rate of PML (2-3%) was also noted in almost all American centres, except Los Angeles (7%) [2]. In general, European material showed a higher number of PML cases than American [4, 14, 15, 23]. In our own collection of AIDS cases the frequency of PML amounted to 9-11 per cent [16, 23]. Davies et al. [7] presented results of the comparative international studies on brain pathomorphology from patients with AIDS, carried out in four European centres (Budapest, Edinburgh, London and Paris) based on common unified diagnostic criteria. The material studied concerned cases from the decade 1983-1993. The mean frequency of PML incidence in European centres was 4-5% (as compared with 2-3% in the United States), with the highest incidence rate

in Paris (11%). In that context PML incidence in Polish material can be considered as very high. The increased number of fatal AIDS cases was found also in our material. The first hundred cases originated between the years 1987-1995, while the second hundred was accumulated in the course of the following three and a half years [16, 23]. However, the frequency of PML in both periods did not change so significantly.

Striking differences in the extent and intensity of the demyelinating process in PML cases were noticeable at the routine neuropathological examination of brains from AIDS patients. This inclined us to perform a more detailed morphological analysis of our whole collection.

Material and methods

The studies were carried out on 20 cases of PML diagnosed post mortem in the collection of 203 brains of patients with AIDS, who died at Wolski Infectious Diseases Hospital in Warsaw (Director, Dr. A. Horban, Ph.D.) during the years 1987-1999, examined in the Department of Neuropathology Medical Research Centre, PAS. The material concerned 20 male cases, aged 28 to 64 years (mean 40.3). The PML cases with a complete neuropathological diagnosis are presented in Table 1. The formalin fixed brains, received from the Department of Morbid Anatomy, Wolski Infectious Diseases Hospital in Warsaw (Dr Z. Kamiński, PhD) were routinely autopsied and the material for histopathological examination was taken according to the protocol, described previously [16, 23], including blocks from various regions of the cerebral and cerebellar hemispheres and from different structures of the brain stem. Additional tissue blocks were taken from focal brain abnormalities and their vicinity. The tissue samples were routinely processed and embedded in paraffin. For the routine diagnostic studies brain sections were stained with haematoxylin-eosin and according to Heidenhain's or Klüver-Barrera's methods. When necessary, additional histological, histochemical and immunohistochemical methods were applied. No immunostainings for JCV and HIV were performed due to technical reasons.

In three PML cases with very extensive demyelination of the white matter in cerebral or cerebellar hemispheres the formalin fixed material from the immediate vicinity of the pathological foci was taken for electron microscopy.

Results

In 6 cases PML was the only pathological process in the brain, in another 6 it was accompanying HIV-related pathology, taking the form of either HIV-leukoencephalopathy or HIV-encephalitis; in 2 of those PML was the only accompanying process, in 4 others it was concomitant with additional opportunistic disease. In the remaining 8 cases PML co-occurred simultaneously with various opportunistic processes (Table 1).

Taking into account the above mentioned differences in the extent and severity of the demyelinating

Table 1. Progressive multifocal leukoencephalopathy in 203 AIDS cases

Case	Age (years)	Risk group	Neuropathological diagnoses
1.	31	not established	HIV-encephalitis. Cerebral cytomegaly. PML
2.	64	homosexual	Brain toxoplasmosis. PML
3.	49	homosexual	Brain toxoplasmosis. PML
4.	46	homosexual	PML
5.	41	homosexual	Brain toxoplasmosis. PML
6.	ca 40	homeless	PML
7.	59	bisexual	Temporo-occipital hemorrhagic focus. Disseminated necrotic foci. Brain malignant lymphoma. PML
8.	36	uncontrolled sex	Brain aspergillosis. PML
9.	50	bisexual	HIV-leukoencephalopathy. PML
10.	45	homosexual	HIV-encephalitis. Brain malignant lymphoma. PML
11.	35	drug addict	PML
12.	28	not established	Respiratory brain. PML
13.	42	homosexual	HIV-encephalitis. Malignant lymphoma. Brain and ocular cytomegaly. PML
14.	31	homosexual	HIV-leukoencephalopathy. Brain toxoplasmosis. PML
15.	31	drug addict	PML
16.	36	drug addict	Encephalitis metastatica. PML
17.	39	not established	PML
18.	46	not established	HIV-leukoencephalopathy. PML
19.	29	not established	Brain toxoplasmosis. Hepatic encephalopathy. PML
20.	34	drug addict	PML

process, our PML cases were arbitrarily divided into 3 groups: an early form (9 cases), atypical form (2 cases) and severe form (9 cases). In the early form of the disease, the demyelinating process was expressed as more or less numerous small, disseminated foci, situated predominantly in the cerebral hemispheres at the cortico-subcortical junction and its immediate vicinity in deep cortical layers or in deeper regions of the white matter. The PML changes in most of those cases were marginal to extensive and multifocal lesions due to other pathological processes such as a necrotizing form of toxoplasmosis or infiltrative growth of multifocal malignant lymphoma, necrotic hemorrhagic changes on the ground of generalized vascular dysplasia or anoxic-ischemic pathology of the respiratory brain type. It is worth mentioning that quite a proportion of cases included into this group originated from the early period of the AIDS epidemics in Poland, before introduction of more effective therapeutic and prophylactic menagements directed against at least some opportunistic infections, which have since almost disappeared from AIDS pathology (toxoplasmosis, CMV-infection, cryptococcosis etc). It is very easy to overlook discreet PML pathology on the grounds of the extensive tissue lesions due to other pathogenic factors. The only case of this group, which was not accompanied by other brain pathology, concerned a patient who died due to embolism of the pulmonary artery. In all these cases "blastomatous" forms of astrocytes were not a feature. Astrocytic reaction was limited to some non-specific proliferation with slight features of hypertrophy. Diagnosis was based on the appearance of characteristic oligodendroglial abnormalities expressed in the form of enlarged, homogenous, metachromatic nuclei, occurring both in the demyelination foci and at their periphery.

The atypical form of PML was represented by two cases, in which pathological process was unifocal in nature; moderate in diameter, although seen already at naked eye examination. Diffuse demyelination foci were characterized by intense tissue breakdown accompanied by all typical forms of glial pathology, involving both oligodendrocytes and astrocytes.

The third group of the pathological process, described as its severe form, concerned 9 cases, characterized by a progressive neurological symptomatology and 2-6 months survival period from the beginning of the neurological disease (Table 2). The most

Table 2. Clinical characteristics and demyelination topography in severe form of PML

Case	Age (years)	Neurological symptomatology	Survival time	Topography of severe demyelination
1.	46	Cerebellar syndrome, bulbar syndrome	4 m	Cerebellar hemispheres, pons, medulla
2.	ca 40	Right hemiplegia, aphasia	?	Cerebral hemispheres, midbrain, pons, medulla
3.	50	Right hemiparesis, dementia	6 m	Cerebral hemispheres, basal ganglia
4.	35	Left hemiplegia,	3 m	Cerebral hemispheres, cerebellum, brain stem
5.	36	Cerebellar syndrome, dysarthria	2 m	Cerebellar hemispheres, brain stem
6.	39	Cerebellar syndrome	5 m	Cerebellar hemispheres, pons
7.	46	Left hemiplegia, damage of the cranial nerves	6 m	Cerebellar hemispheres, pons
8.	29	Right hemiparesis, motor aphasia	4 m	Cerebral hemispheres
9.	34	Right hemiparesis, speech disturbances	2 m	Cerebral hemispheres, midbrain

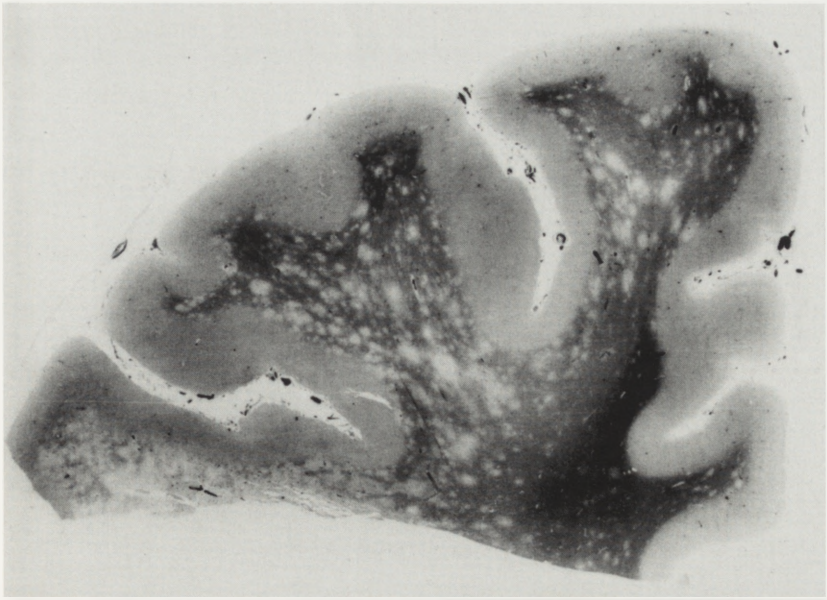

Fig. 1. Numerous demyelination foci of different size in the white matter of the cerebral gyri, involving cortico-subcortical junction and deep cortical layers. Heidenhain. Magn. glass

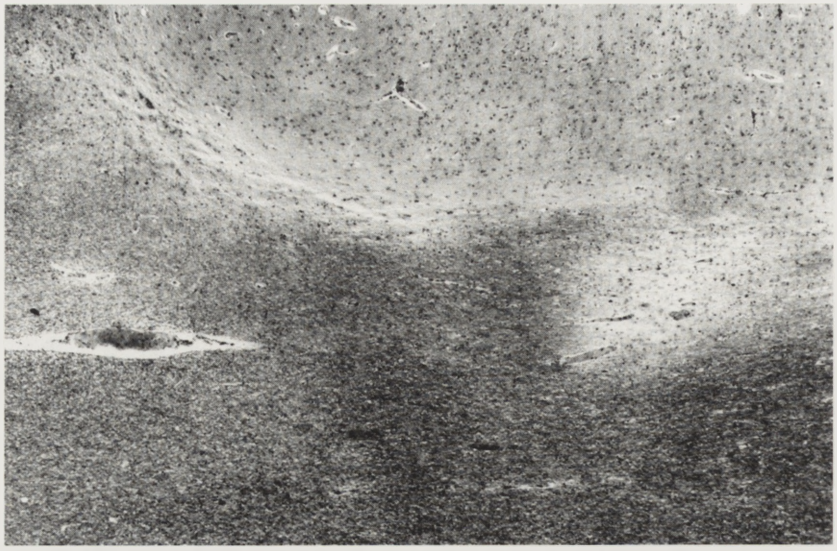

Fig. 2. Arciform demyelination in the cortico-subcortical junction. Perivascular myelin damage in deeper subcortical white matter. Heidenhain, ×40

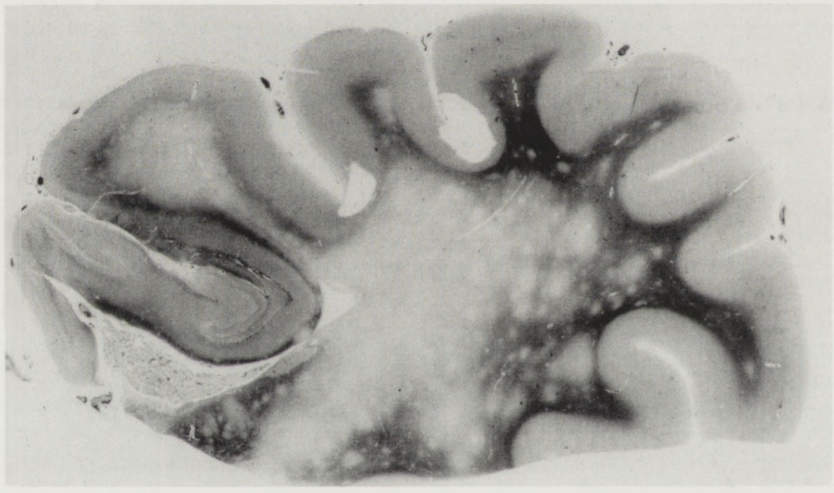

Fig. 3. Disseminated and confluent demyelination foci in the temporal lobe. Heidenhain, Magn. glass

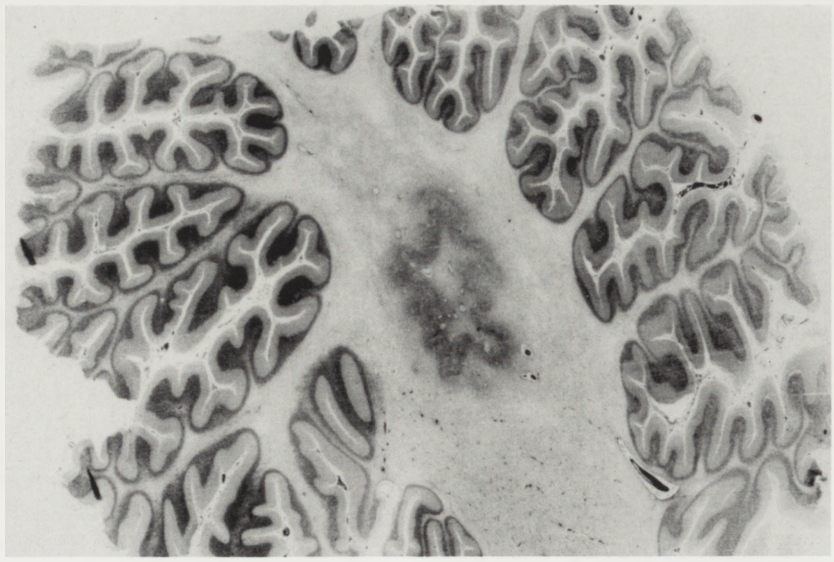

Fig. 4. Total demyelination of cerebellar white matter. Heidenhain, Magn.glass

typical pathological feature consisted in a great topographic variation of the intensity of the demyelinating process, predominantly involving the cerebral or cerebellar hemispheres.

In only one case severe demyelination was generalized, involving as well as cerebrum, brain stem and cerebellum. In 4 cases demyelination predominantly involved the white matter of the cerebellum with some patchy lesions of the brain stem structures. In only one of those slight myelin abnormalities were also seen in the cortico-subcortical junction of cerebral hemispheres. In 4 remaining cases demyelination of the cerebral white matter dominated, in 3 of which accompanying changes in the brain stem were present.

In all cases demyelination was bilateral, asymmetric and manifested various forms of focal lesions: disseminated, confluent and diffuse with total and almost total myelin destruction (Figs 1-4), very often with the whole tissue disintegration of varying intensity and extent. The degree of axonal damage was usually parallel to the intensity of myelin sheath destruction; taking the form of rarefaction of axis-cylinders and degeneration of the preserved ones. The cellular structure of demyelination foci depended on their size and advancement of myelin damage and tissue destruction. Myelin breakdown was accompanied by accumulation of macrophages, particularly intense in cases of tissue disintegration (Fig. 5). The most early abnormalities consisted in appearance of enlarged, metachromatic oligodendroglial nuclei, part of them of homogenous structure, some with evident intranuclear inclusions (Fig. 6). Parallel with the progress of demyelination the number of abnormal oligodendroglial nuclei within the foci was decreasing. They were present mostly on the periphery of demyelination. Progress of demyelination also influenced astrocytic reaction taking the form of hypertrophic astrocytes and characteristic gemistocytes of the blastomatous type (Fig. 7). The latter, due to further transformation, appeared as typical bizarre

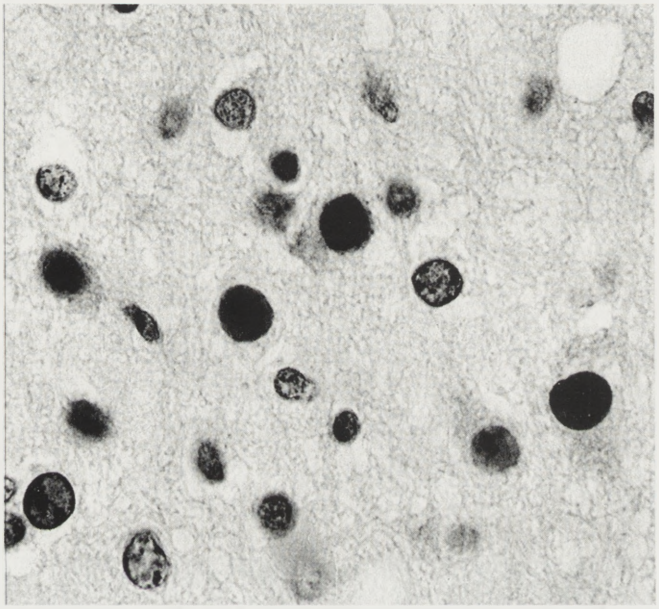

Fig. 6. Enlarged, metachromatically stained oligodendroglial nuclei in the field of myelin damage. HE, ×400

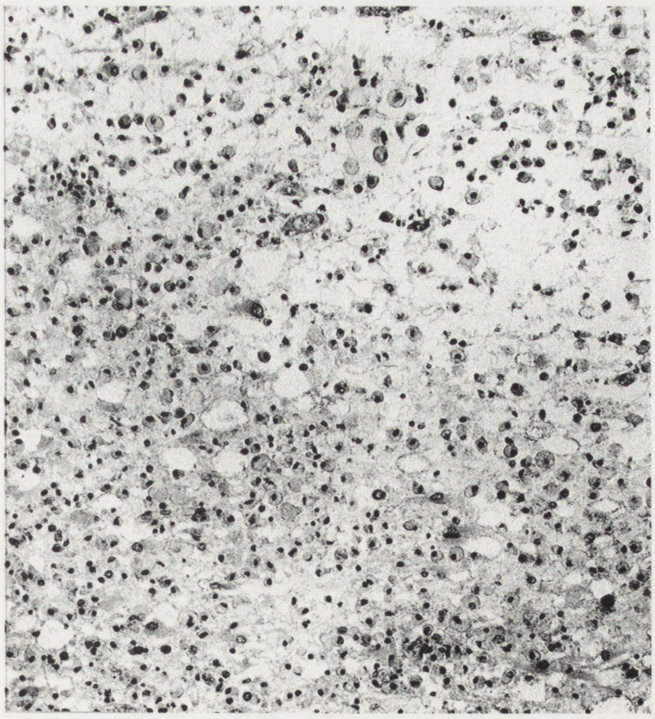

Fig. 5. Fragment of the demyelination focus with tissue breakdown in the cerebellar white matter at the stage of macrophagic infiltration. HE, ×200

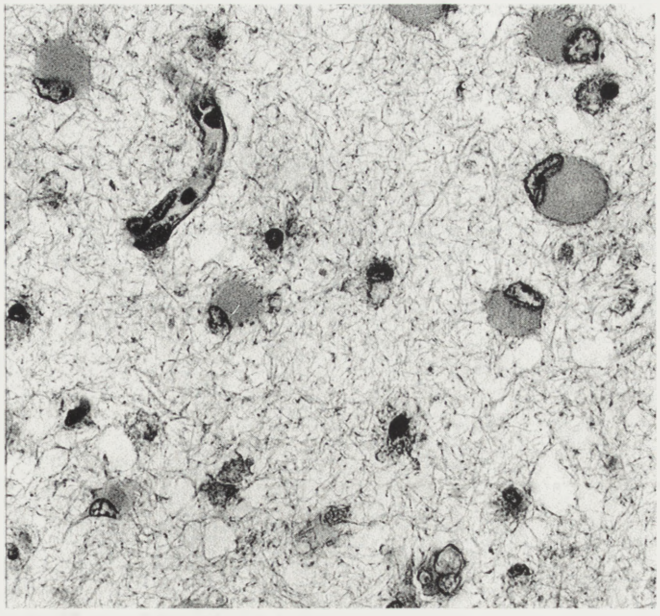

Fig. 7. Astrocytic reaction in the field of total demyelination with severe tissue destruction and spongiosis. HE, ×400

astrocytes with greatly variable morphology (Figs 8-9). They were present mostly in burned out demyelination areas characterized by relatively reduced cellular population, presence of macrophages with washed out cytoplasm or ghost macrophages and rather scanty regressive and blastomatous astrocytes (Fig. 10). That was complemented with rather intense tissue rarefaction leading to its reticular and spongy appearance (Fig. 11).

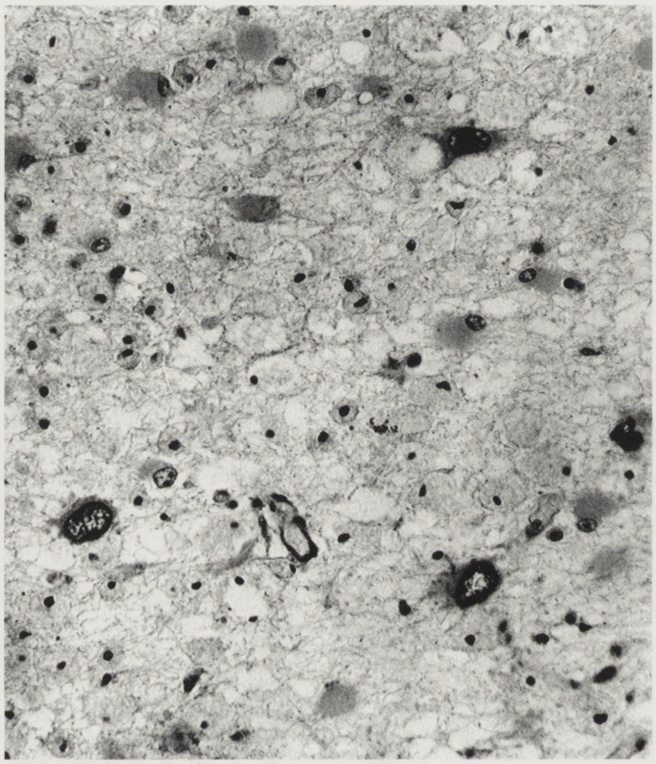

Fig. 8. Macrophages and hypertrophied astrocytes, some with blastomatous nuclei in severely damaged cerebral white matter. HE, ×200

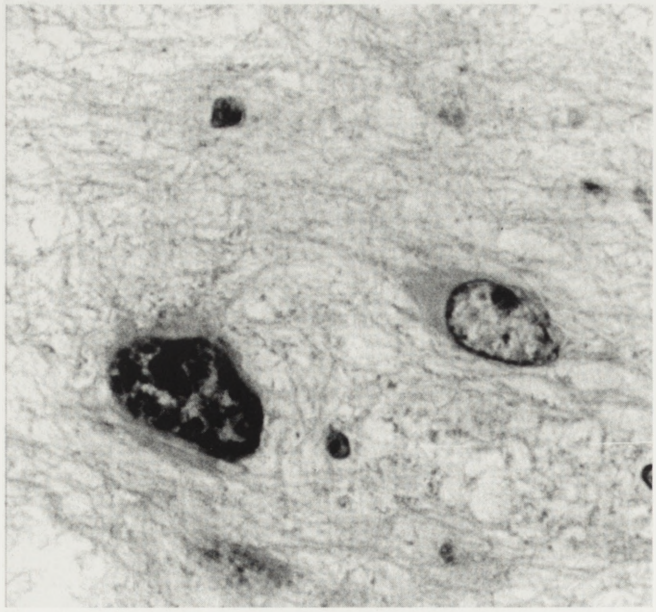

Fig. 9. Hypertrophied astrocytes with bizarre nuclei in demyelinated white matter. HE, ×400

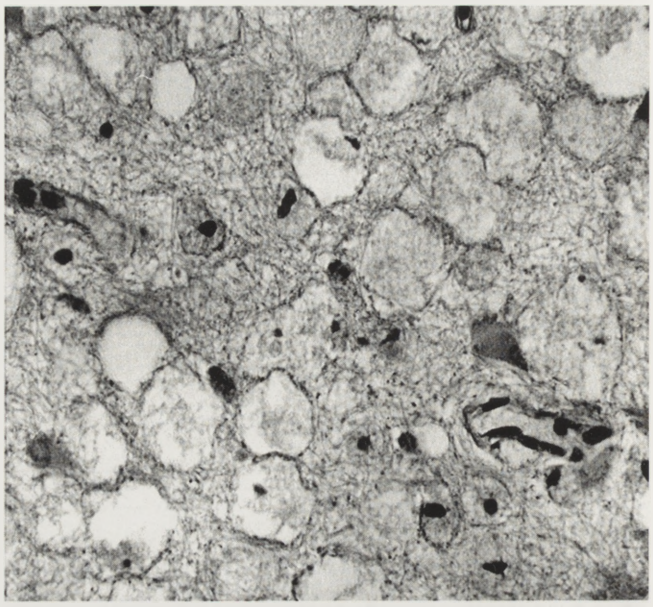

Fig. 10. Macrophages with washed out cytoplasmic content and some regressive astrocytes in the final stage of demyelination process. HE, ×400

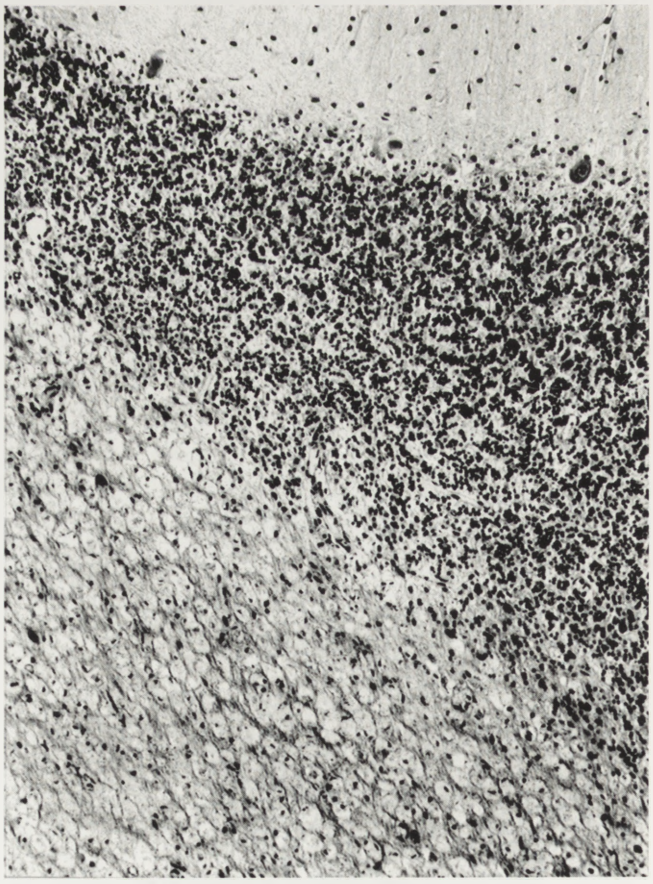

Fig. 11. Severely damaged cerebellar white matter at the final stage of demyelination. Note "reticular" appearance of the tissue background. HE, ×200

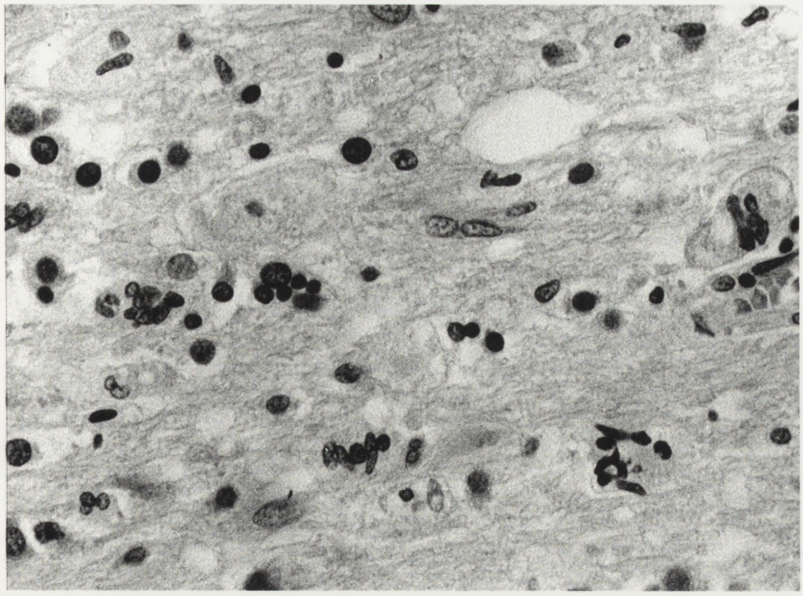

Fig. 12. Typical multinuclear giant cells (HIV type) in the demyelinated focus with abnormal oligodendroglial nuclei. HE, ×400

Typical multinuclear giant cells of HIV-type within the PML demyelination foci were found only in one case (Fig. 12). Multinuclear giant cells with appearance of giant HIV-carriers resulting from fusion of mononuclear macrophages under the influence of viral infection were also rare within demyelination foci (Fig. 13). Their identification without HIV-specific immunocytochemistry was obviously impossible.

An inflammatory reaction in the severe form of PML revealed different intensity in individual cases. As a rule, it was very intensive in the foci with total tissue disintegration. In most of the cases lymphocytic perivascular infiltrations with some admixture of plasma cells were present. Frequently inflammatory perivascular infiltrations were present both in the demyelination foci and in unchanged tissue, in which they were less intense. In 2 cases from this group the perivascular infiltrations were mild, in 5 they were intense or moderate; in the 2 remaining cases inflammatory infiltration involved vascular walls and penetrated into the surrounding tissue (Figs 14-15).

Electron microscopy in all 3 cases examined revealed abundant virions of JCV accumulated in a great proportion of enlarged oligodendroglial nuclei. Damage of nuclear membrane was also present which led to aggregation of viral particles in the perinuclear

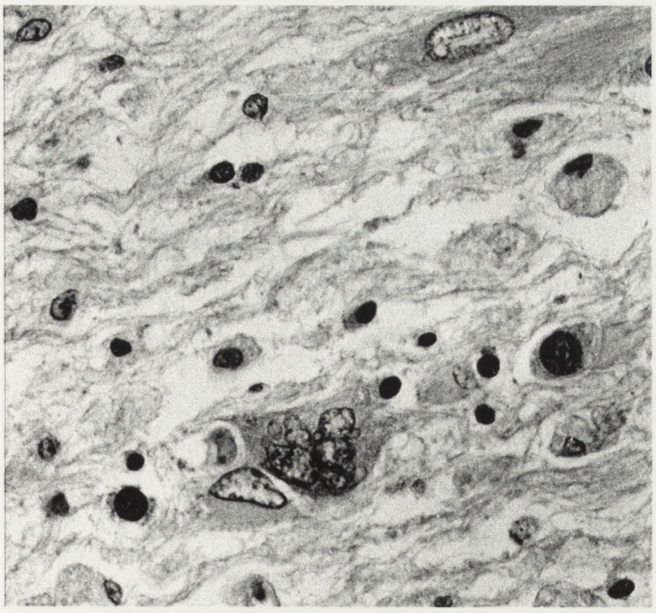

Fig. 13. The other type of multinuclear giant cell. Its structure is characteristic for cellular forms originating from fusion of mononuclear HIV-infected macrophages. HE, ×400

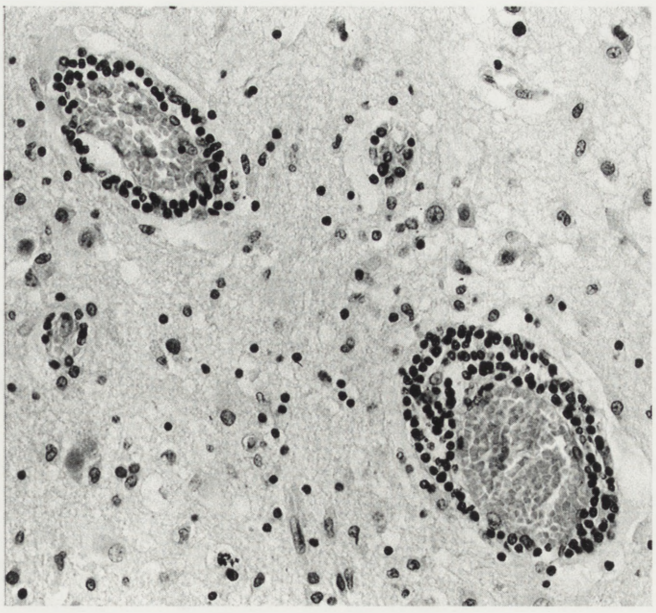

Fig. 14. Perivenular lymphocytic infiltration within demyelination focus. HE, ×200

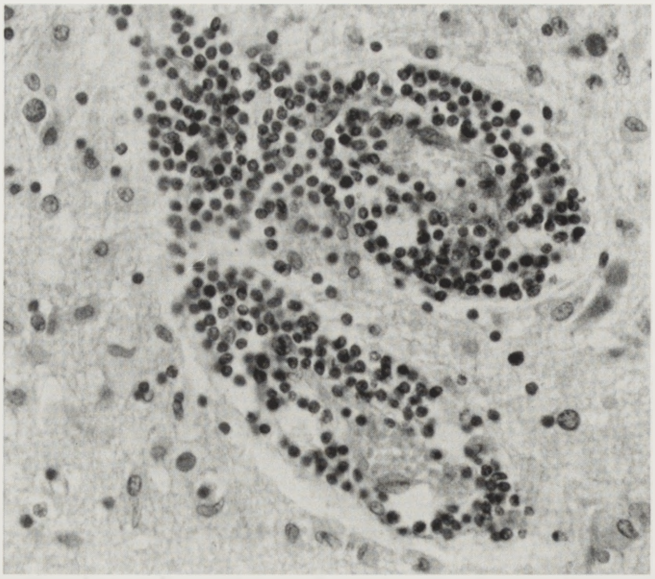

Fig. 15. Perivascular lymphocytic infiltration penetrating into the surrounding tissue. HE, ×400

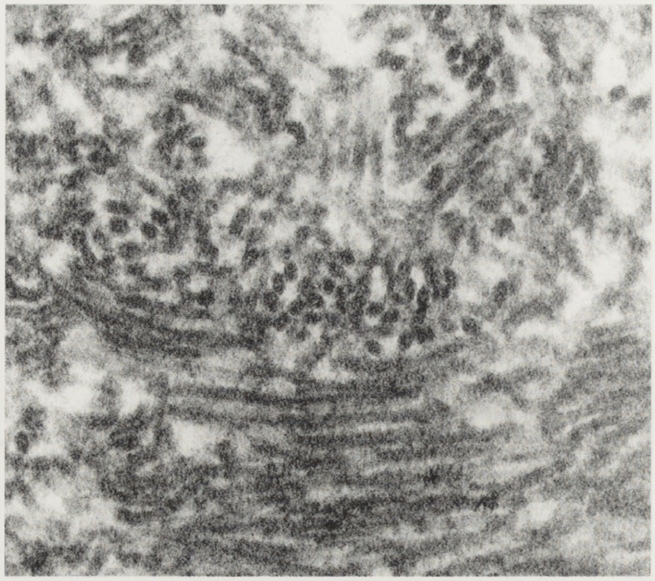

Fig. 17. Fragment of oligodendrocytic nucleus containing spherical and filamentous JCV viral profiles. EM, ×75,000

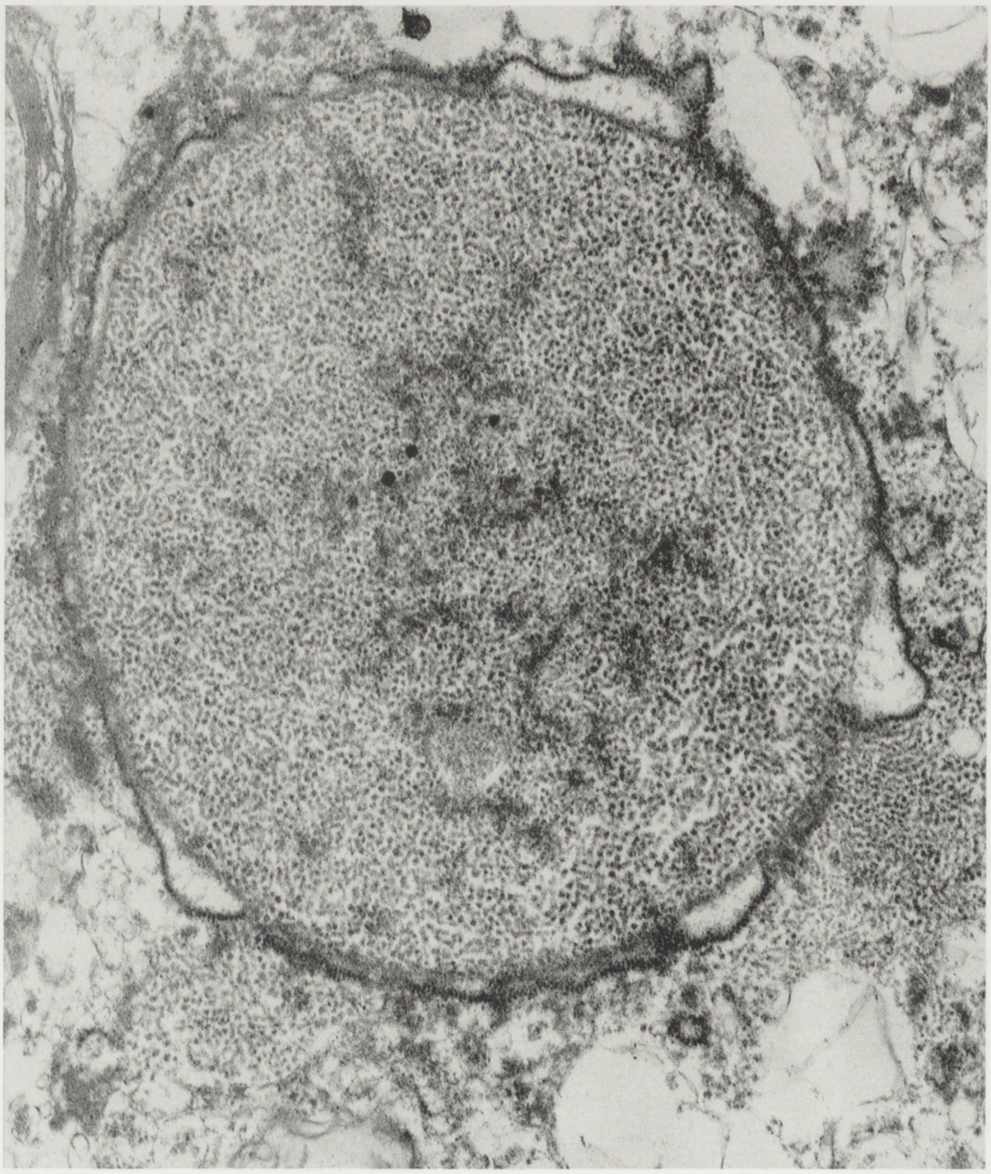

Fig. 16. Oligodendroglial nucleus filled with JCV virions. Damaged nuclear membrane and aggregation of virions within perinuclear cytoplasm. EM ×25,000

cytoplasm (Fig. 16). JCV virions most frequently were spherical in shape. Sometimes small component of filamentous viral profiles were present (Fig.17). No essential differences were noticed in electron microscopy of all 3 cases examined.

Discussion

Progressive multifocal encephalopathy is considered one of the most destructive opportunistic infections, accompanying acquired immune deficiency syndrome. In the earliest period of the AIDS epidemics in USA, Rhodes et al. [17] suggested that it represented the most severe form of this disease, though this opinion has not been commonly accepted. Scaravilli and Gray [19] were pointing out the atypical PML cases accompanying AIDS, including to this group unilateral or mildly advanced pathological changes. This category of cases was observed in the early periods of AIDS pandemics, when slight PML changes were frequently found accidentally during brain autopsy in neurologically symptomless patients. This was also the case in our material in the two first groups.

Although, PML is by definition a pathological process of the white matter, in our series involvement of the cerebral cortex and other grey matter formations was frequent in cases with extensive and diffuse demyelination of the cerebral hemispheres. It was particularly striking in a case in which neurological symptomatology appeared 3 weeks following severe head trauma, without its pathological exponents at brain autopsy. Abnormalities in the cerebral cortex manifested in the form of the involvement of deep cortical layers resulting from the penetration of diffuse white matter changes or small demyelination foci situated within cortico-subcortical junction. Small isolated primary cortical lesions were also seen in the areas remote from the dominating white matter alterations. Abnormal oligodendroglial nuclei were seen both in changed and apparently normal cortical areas. Einsiedel et al. [9] observed involvement of the cerebral cortex in half of the PML cases from their series. This has been confirmed by presence of the JCV virions in the oligodendroglial nuclei both pathologically changed and histologically normal. In general it has been stated that the proportion of infected oligodendrocytes was higher than the number of cells of this type revealing histological alterations in PML cases with and without AIDS [1, 9]. Kleihues et al. [13] found JCV antigen in some oligodendroglial nuclei located within the areas of myelin pallor in cases of HIV-dependent leukoencephalopathy. They considered their presence as an opportunistic epiphenomenon unrelated with myelin damage. There exists a hypothesis [8] that JC viruses which after primary infection remain in the latent form in kidney, nervous system or in lymphoid cells, can become activated in cases of local immune disturbances with viral replication causing no clinical symptoms. Those symptomless JCV can be transformed into the pathogenic form under the conditions of prolonged or more severe immunosuppression. The mechanism of transformation of activated viruses to the pathogenic ones remains obscure [8]. PCR analysis discovered DNA of JCV in the brain of patients without PML and HIV-infection. This indicates occurrence of latent JC viruses in brains of immunocompetent people [10].

A relatively high frequency of concomitance of PML with AIDS naturally raises a question concerning interdependence of both infections and their reciprocal influence on the pathomorphology of coexisting processes. An analysis of our cases with full-blown clinico-pathological picture of PML leads to the conclusion that despite the similarity of the general pattern of structural abnormalities observed in PML in AIDS and non-AIDS patients, there also exist some differences between them, which probably should be referred to the greater dynamics of pathological process in AIDS-cases. Though the relative value of this observation has to be remembered as the same abnormalities may also be observed in non-AIDS patients. Pathomorphological differences include greater extensiveness of demyelination and involvement of some structures and regions which in non-AIDS cases are rather spared. This includes, for instance cerebral cortex, temporal lobes, thalami and basal ganglia. Demyelination process seems to be more severe, leading quite often to lacunar tissue breakdown seen already at naked eye examination. Brain histopathology reveals more severe axonal damage, more abundant oligodendroglial abnormalities, more intense macrophage infiltration and less numerous population of blastomatous forms of astrocytes. Although Aksamit et al. [1], who performed comparative morphometric studies on abnormal oligodendroglial nuclei in 10 cases of PML accompanying AIDS and 10 non-AIDS cases, showed no significant difference between these two groups.

Occurrence of macrophages productively infected with HIV within the fields of demyelination due to JCV has been proven by numerous authors [1, 9, 20-22]. They are not frequent. Neither are multinuclear giant cells, resulting from fusion of HIV infected macrophages. The proportion of HIV infected macrophages is increasing with the extent of survival time of patients as shown by comparison of the biopsy and autopsy material in the same cases [22].

It seems very convincing that in this way PML may influence the development of productive HIV infection in the brain, similar to all other processes leading to the inflow of macrophages to the brain areas undergoing destructive lesions.

The involvement of the cerebellar white matter by the demyelinating process was found in a great proportion of PML cases. It has been described with varying frequency in several neuropathological collections [9, 14]. In most of the cases it was accompanying lesions of the cerebral hemispheres, Rhodes et al. [17] described a case of cerebellar PML, characterized by severe alteration of the cerebellar white matter with some brain stem involvement and insignificant changes in the cerebral hemispheres. The typical, most common topographic distribution of demyelination process in PML cases consist in most intense changes in the cerebrum, rarer in the brain stem and least of all in the cerebellum. The same distribution is typical for AIDS-associated PML. Our cases with predominant cerebellar abnormalities and minimal or no participation of the cerebral hemispheres represent inversion of the typical pattern. This might justify the distinction of the cerebellar form of the disease.

Acknowledgement

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