

Progressive Multifocal Leukoencephalopathy (PML) in A Japanese Patient with Acquired Immunodeficiency Syndrome (AIDS): A Case Report

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Abstract: We report an autopsy case of progressive multifocal leukoencephalopathy (PML) of a 40 year-old Japanese male with acquired immunodeficiency syndrome (AIDS). Since he was diagnosed as hemophilia A at the age of 15 years, he had been treated with factor VIII concentrates. When he was 35 years old, the antibody against human immunodeficiency virus (HIV) was found to be positive. Four years later he was pointed out left hemiparesis. *Pneumocystis carinii* organisms were detected and he was diagnosed as AIDS at the age of 40 years. During his admission multiple lesions were demonstrated in the cerebral white matter by MRI and CT scan and suspected to be PML. Dyspnea aggravated rapidly and he died from respiratory failure. Autopsy examination revealed multiple necrotic foci in the cerebral white matter, which showed characteristic histological features to be confirmed as PML, namely, multiple demyelinating foci with enlarged and bizarre astrocytes, hypertrophied oligodendrocytes with intranuclear inclusion bodies and numerous lipid-laden macrophages.

Key words: Progressive multifocal leukoencephalopathy (PML), Acquired immunodeficiency syndrome (AIDS), Oligodendrocyte, Histopathology

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a fatal demyelinating disease of the central nervous system (CNS) due to an opportunistic virus infection of glial cells (Åström *et al.*, 1958; Richardson, 1961; ZuRhein, 1969; Richardson, 1970; Walker, 1978; Nagashima *et al.*, 1982; Greenlee, 1989). It is now well known that PML is an opportunistic papova virus infection, mainly caused by JC virus (JCV) infection, of the CNS in the immunologically deficient host (Padgett *et al.*, 1971; Nagashima *et al.*, 1982; Walker, 1985; Greenlee, 1989). More than 60% cases among 230 PML patients showed immunosuppression

due to an underlying lymphoproliferative disease, malignant neoplasms and chronic inflammatory diseases (Brook and Walker, 1984). Since acquired immunodeficiency syndrome (AIDS) was recognized in 1981 (CDC, 1982), many cases of PML have been described in association with AIDS in the U.S.A. (Holman *et al.*, 1991). However, in Japan, few cases of PML in patient with AIDS have been reported (Japan AIDS association, 1993). We present and discuss the morphological features of an autopsy case of PML in a Japanese patient with AIDS.

CLINICAL SUMMARY

Since the patient was diagnosed as hemophilia A at the age of 15 years in 1965 after the examination of spontaneous intraabdominal hemorrhage, he had been treated with factor VIII concentrates. HIV antibody was found to be positive and the CD4 to CD8 ratio of T-lymphocyte (CD4/CD8) showed 0.7 in 1985. After he was infected with herpes zoster virus in mid 1989, dry cough and exertional dyspnea occurred, respiratory failure progressed gradually and also he was pointed out left hemiparesis. When he was admitted to the hospital, *Pneumocystis carinii* organisms were detected by broncho-alveolar lavage (BAL) examination and he was diagnosed as AIDS in late 1989. During his admission, his CD4/CD8 decreased to 0.1 and his left hemiparesis progressed gradually. MRI and CT scan demonstrated multiple lesions mainly in the subcortical areas of the right cerebral hemisphere, suspected to be PML (Photo. 1). In spite of intensive chemotherapy against *Pneumocystis carinii* pneumonia (PCP), respiratory failure progressed rapidly and he died at the age of 40 years in early 1990.

AUTOPSY FINDINGS

GROSS FINDINGS: Postmortem examination was performed two and half hours after death. The brain, weighing 1420g, showed externally normal appearance. On cut surface there were multiple necrotic foci with confluent, gray and gelatinous appearance, measuring up to 2cm in diam., in the cerebral white matter, mainly in the subcortical areas (Photo. 2). Although the lesions were present mainly in the upper half of the right frontal, superior frontal, precentral, postcentral and parietal lobes, multiple pinhead-sized foci were scattered in the right temporal, left parietal and left temporal lobes. The left and right lung, weighing 1570g and 1130g respectively, showed diffuse consolidation with loss of alveolar architectures on cut surface. The generalized lymph nodes showed slight enlargement.

HISTOLOGICAL FINDINGS: The necrotic lesions of the cerebral white matter were demyelinating foci which showed totally devoid of myelin sheaths (Photo. 3). In the lesions, there were numerous lipid-laden of foamy cell macrophages, pleomorphic astrocytes with enlarged, bizarre and hyperchromatic nuclei, hypertrophied glial cells and lack of inflammatory cells (Photo. 4 and 5). The hypertrophied glial cells with abnormally large nuclei which contain full type intranuclear inclusion bodies and stained homogeneously basophilic with hematoxylin-eosin, were scattered mainly in the periphery or outside of the

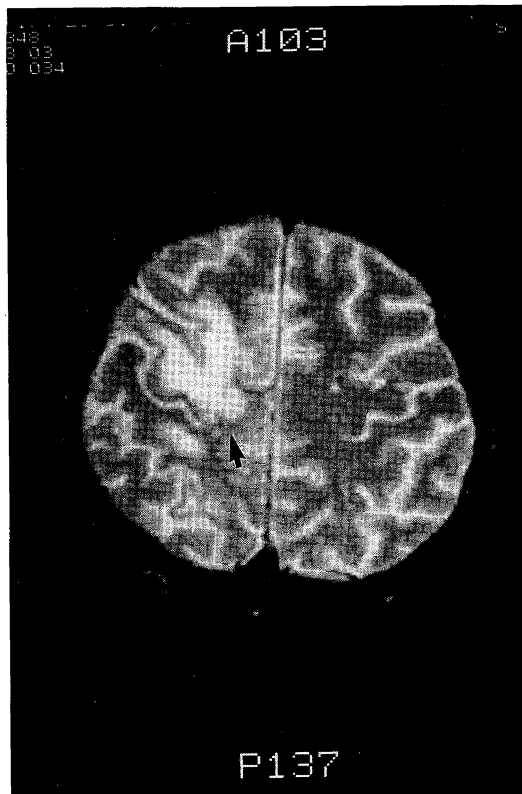


Photo. 1. Cerebral MRI demonstrates a confluent lesion in the right subcortical area (arrow).



Photo. 2. Confluent, gray and gelatinous necrotic lesions in the right cerebral white matter (arrows).

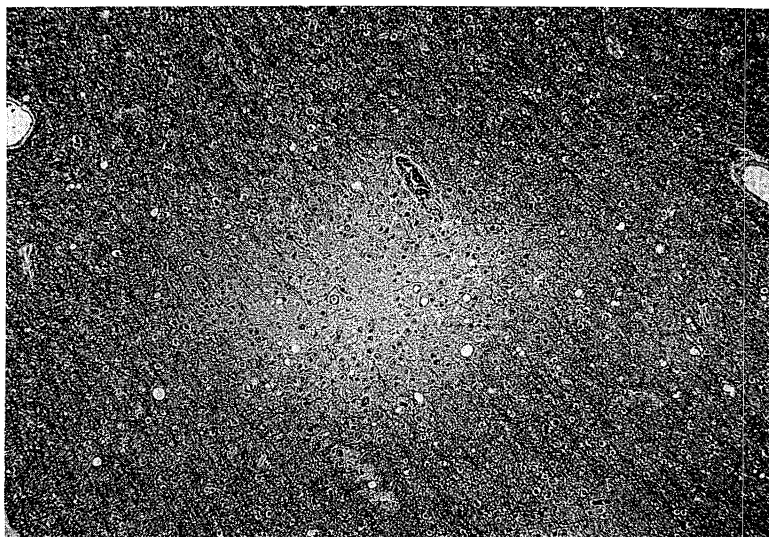


Photo. 3. A pinhead-sized lesion shows demyelination and devoid of myelin sheaths (Klüver-Barrera, $\times 40$).

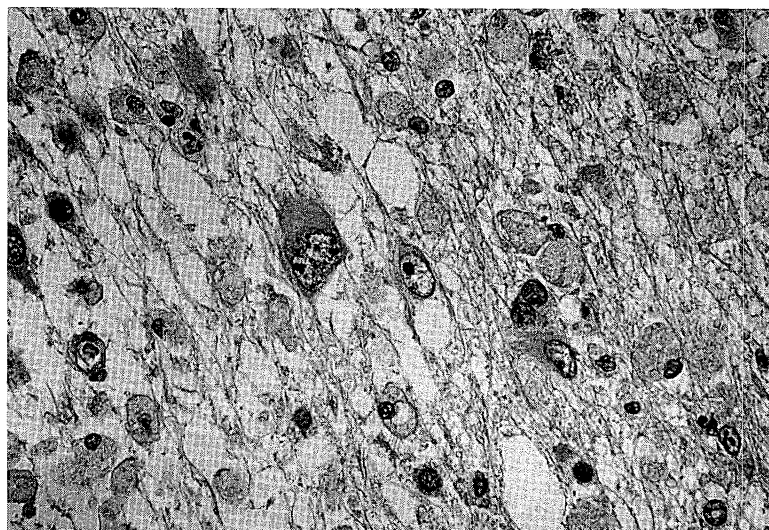


Photo. 4. A pleomorphic astrocyte with an enlarged and bizarre nucleus (HE, $\times 200$).

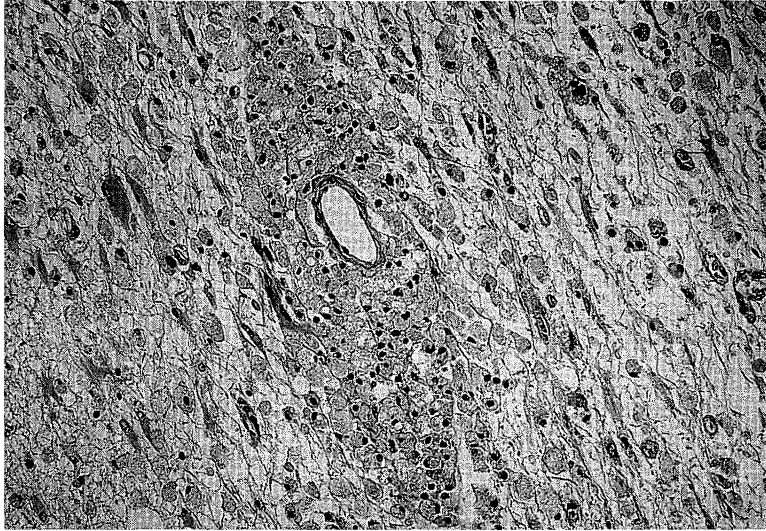


Photo. 5. Numerous lipid-laden or foamy cell macrophages in a perivascular space and necrotic area (HE, $\times 100$).

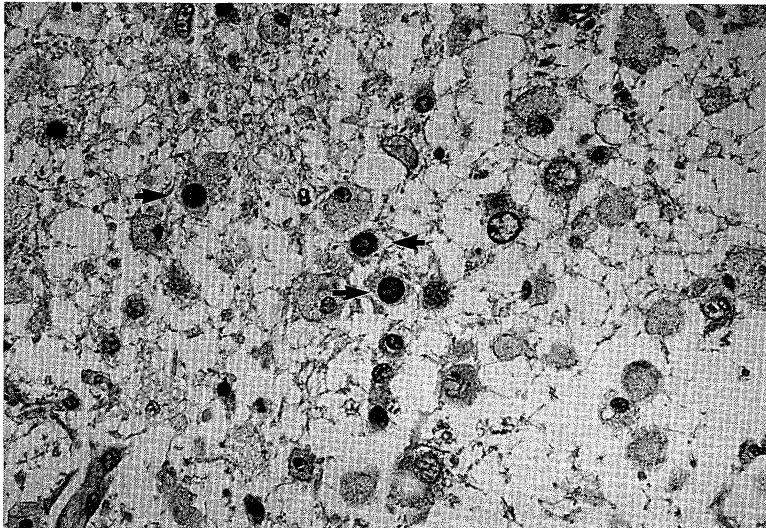


Photo. 6. Hypertrophied oligodendrocytes with abnormally large nuclei which contain full type intranuclear inclusion bodies (arrows) (HE, $\times 200$).

demyelinated necrotic areas (Photo. 6). These glial cells were not stained immunohistochemically by glial fibrillary acidic protein (GFAP), which is a marker of the astrocyte, therefore, the infected cells were recognized as oligodendrocytes.

Numerous degenerated *Pneumocystis carinii* organisms in foamy, fibrinous and poorly cellular exudate filled the alveolar cavities of the both lungs.

The lymph nodes showed depletion of lymphocytes, extensive vascular proliferation, perivascular fibrosis, several multinucleated giant cells with grape-like cluster of nuclei and no follicle formations (burnt-out node).

DISCUSSION

Since AIDS was first recognized in 1981 (CDC, 1982), the immune defects of this disease have been manifested by multiple opportunistic infections and/or by the development of uncommon malignant neoplasms in not one organ but practically all the tissues and organs of the human body (Pitchenik *et al.*, 1983). It has been estimated that up to 50% in patient with AIDS will develop neurological symptoms and as many as 90% will have neurological change at autopsy (Hall *et al.*, 1991). These include not only HIV encephalopathy and malignant cerebral neoplasms but also opportunistic cerebral infections such as toxoplasmosis, cytomegalovirus (CMV) encephalitis, cryptococcosis, mycobacteriosis, papova virus or herpes virus infections (Vieira *et al.*, 1983; Pitchenik *et al.*, 1983).

PML, a subacute, progressive and fatal demyelinating disease of the CNS, is commonly seen as a complication of immunocompromised diseases such as lymphoproliferative diseases, malignant neoplasms and chronic inflammatory diseases among the old age peoples (Brook and Walker, 1984). Nowadays, the numbers of cases of PML have been reported in association with AIDS and have become increasingly prevalent, mainly affecting young generations, and it can no longer be regarded as an extremely rare disease (Holman *et al.*, 1991). The incidence of PML in patients with AIDS is 0.72% in the U. S. A. (CDC, 1990). The causative agent of PML is a DNA virus called JCV, which belongs to the family of papovaviruses (Padgett *et al.*, 1971). The primary infection of JCV probably occurs in childhood and remains latent, possibly in the CNS, until conditions of deficient immunity permit its reactivation (Padgett and Walker, 1983). Other Papovaviruses may be also human pathogens: SV-40 virus has been detected in several cases of PML (Kuchelmeister *et al.*, 1993). In Japan, few cases of PML in patient with AIDS have been reported (Japan AIDS association, 1993).

Although we could not perform the ultrastructural examination and could not detect the causative agent, our gross and microscopical findings are characteristic to be diagnosed as PML (Nagashima *et al.*, 1982; Ioachim, 1989).

In conclusion, we report an autopsy case of PML in a Japanese patient with AIDS and further studies at the molecular level are required to determine the mechanisms involved in the characteristic leukoencephalopathy of this disease.

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