Virus-Cell Interaction in Oligodendroglia, Astroglia and Phagocyte in Progressive Multifocal Leukoencephalopathy

An Electron Microscopic Study* **

Itaru Watanabe and Sheldon H. Preskorn

Department of Pathology and Oncology, University of Kansas College of Medical Sciences and Hospital, Kansas City, Kansas 66103
and Veterans Administration Hospital, Kansas City, Missouri 64128, U.S.A.

Summary. A 46-year-old female, with an 11 year history of malignant lymphoreticular disease, developed a neurological illness clinically manifested by a focal mass lesion in the left frontal lobe. In biopsied tissue, immunofluorescence study revealed the presence of JC antigen in the glial cells. Histologically, the lesion was characteristic of PML consisting of focal necrosis in the subcortical white matter, numerous fat laden macrophages and marked hypertrophy of oligodendrocytes and astrocytes. By electron microscopy, hypertrophic astrocytes contained intranuclear viral particles consistent with papova virions and aggregates of intracytoplasmic viral particles consisting of a single to several virions tightly surrounded by a single membrane. The membrane appeared to have been derived from that of the cellular vesicles. Fusion of the virus-associated membrane to the astroglial plasmalemma occurred when the virions appeared to shift towards extracellular space. The virion-containing astrocytes showed cytoplasmic “fibrillar hypertrophy” similar to the characteristic gigantic astroglia of PML. This fact would provide an additional evidence that these gigantic cells, although lacking identifiable viral structures, were the result of anaplastic transformation by JC virus. Many virus-bearing astroglia were noted to be in the early stage of cellular necrosis, or “edematous degeneration”. This further indicates that the JC virus is capable of inducing both lytic and abortive astroglial infections. Many oligodendroglia were hypertrophic due to the presence of intranuclear viral particles and markedly increased numbers of microtubules and free ribosomes in the cytoplasm. Membrane-bound intracytoplasmic viral particles were also noted in the oligodendroglia. Some fat laden macrophages contained large intracytoplasmic viral bodies, presumably originating from phagocytized virus-bearing cells.

* This paper was presented in part at the 33rd Annual Meeting of Electron Microscopy Society of America, Las Vegas, August, 1975 (Abstract by Preskorn et al., 1975).
** Supported in part by Veterans Administration Research Project, U.S.A. No. 9242-01.
Key words: Progressive multifocal leukoencephalopathy — J. C. virus — Papova virus — Demyelinating disease — Viral encephalitis.

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a subacute viral disease of the central white matter, occurring often in patients with extensive neoplastic disorders of lymph nodes. The causative agent has recently been isolated by Padgett et al. (1971) and identified as a new member of the human papova virus group, the JC virus. Although a virus strain related to simian virus 40 (SV40) has also been isolated in a few patients with PML (Weiner et al., 1972), the JC type has been demonstrated in a far larger number of cases (Narayan et al., 1973; Field et al., 1974). PML was originally described in 1958 by Åström, Mancall and Richardson, who noted, by light microscopy, hypertrophic oligodendroglias with intranuclear inclusion and gigantic astroglia in the multiple, minute demyelinating lesions. By electron microscopy, ZuRhein and Chou (1965) and Silverman and Rubinstein (1965) first identified the intranuclear inclusion bodies as consisting of thousands of papova-type viral particles. Since then, their ultrastructural observations have been confirmed in many case reports (Vanderhaeghen and Perier, 1965; Dolman et al., 1967; Ikuta, 1967; Muller and Watanabe, 1967; Woodhouse et al., 1967; ZuRhein, 1967; Tomiyasu, 1968; ZuRhein, 1969; Morecki and Porro, 1970; Cancilla, 1971; Kanshepolsky et al., 1971; Lyon et al., 1971; Manz et al., 1971; Åström, 1972; Knight et al., 1972; Krempien et al., 1972; Navarro et al., 1972; Shirabe et al., 1972; Brun et al., 1973; Castaigne et al., 1973; Tarsey et al., 1973; Hadfield et al., 1974; Kepes et al., 1975). It has been established that the cells containing papova virus particles are mostly oligodendroglias. Some virus-containing astrocytes and probable microglial cells have also been reported (ZuRhein and Chou, 1968; ZuRhein, 1969). In the majority of these reports, however, examination was performed on autopsy brains in which ultrastructural components of the glia cells were markedly altered by autolysis; therefore, it has been difficult to study virus-cell interaction at ultrastructural level, although not impossible.

The purpose of this paper is to present cytopathological aspects of brain biopsy material from a patient with PML. An optimal fixation of the tissue and a high population of virus-containing glial cells in the lesion permitted us to carry out a detailed ultrastructural study of the viral propagation and the cellular reaction in the oligodendroglia, astroglia and macrophages.

CLINICAL SUMMARY

This 46-year-old white female had an 11 year history of malignant lymphoreticular disease which started as Hodgkin's disease in 1963 and progressed to chronic lymphocytic leukemia in 1969. Since the onset of the illness, she had been treated at the University of Kansas Medical Center. She had been normal neurologically until April, 1974, when she became unable to write, type or drive a car due to intellectual deterioration. In August of