

Comparative neuropathology of human (HIV) and simian (SIV) immunodeficiency virus infections in man and macaque monkeys

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meningiomas,¹³ and the angioproliferation associated with meningio-angiomatosis may be demonstrated with FVIII-RA.¹⁴

In the past three years, we have applied a variety of neural and non-neural markers to formalin-fixed, paraffin embedded CNS tumours. The most reproducible immunostaining patterns have been cytokeratin for choroid plexus papilloma; GFAP, S-100 and/or cytokeratin for ependymoma; vimentin and/or cytokeratin for meningioma; cytokeratin for thoracolumbar spinal cord blastoma; GFAP for gliomas; and NSE and NF for neuroepithelial neoplasms.

There is considerable variability in the specificity of commercially available polyclonal or monoclonal antisera and, therefore, in their diagnostic value. For instance, GFAP and synaptophysin have an exquisite specificity for cells of the astrocytic and neuronal series, respectively. On the other hand, NSE and S-100 are less specific in their distribution and, therefore, of limited diagnostic value. Also, due to the limited studies that have been carried out with CNS tumours in animals, immunohistochemical results should be carefully interpreted. Lack of staining may be due to fixation or methodological factors, rather than the absence of antigen in neoplastic cells.^{1,2,6} The aim of immunohistochemistry is to obtain consistent and highly sensitive results, essential for the confident evaluation of results. The choice of immunohistochemical methods, the inclusion of appropriately selected positive and negative controls, and the implementation of controlled procedures such as optimal incubation times and temperature, dilutions of primary antibody, and requirements for pretreatment of sections with proteases, should be carefully evaluated.

Classification of neoplasms can provide an important estimate of biologic behavior and patient prognosis, and routine histopathology remains the cornerstone of such classification. However, in some instances reliance on morphology alone may be insufficient. Immunohistochemistry have become a powerful research and diagnostic tool in human neurooncology, but its relative value in the diagnosis of primary CNS neoplasms in veterinary medicine is yet to be determined.

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COMPARATIVE NEUROPATHOLOGY OF HUMAN (HIV) AND SIMIAN (SIV) IMMUNODEFICIENCY VIRUS INFECTIONS IN MAN AND MACAQUE MONKEYS

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The human immunodeficiency virus (HIV) has been etiologically associated with the acquired immune deficiency syndrome (AIDS) in man.^{1,2} Involvement of the central nervous system (CNS) by HIV accounts for a significant proportion of the morbidity and mortality associated with HIV infection and AIDS. At necropsy, approximately 75% of HIV patients will have CNS abnormalities caused by opportunistic infections or neoplasms, or as a direct consequence of HIV infection.³ The simian immunodeficiency virus (SIV) induces in susceptible macaque monkeys an immunosuppressive disease which shares common clinical, pathological, and immunological features with AIDS. It is characterized by depletion of the CD4-bearing helper/inducer subset of T lymphocytes, interference with cell mediated immunity, impaired resistance to opportunistic infections, progressive multisystem disease including meningoencephalitis, cachexia, and death.⁴

We have analyzed the comparative neuropathology of late stage disease in 140 adult and 16 pediatric HIV cases from the AFIP AIDS Registry, and acute and late stage disease in approximately 20 young macaque monkeys experimentally infected with several SIV strains. Opportunistic infections constitute the most common finding in adult

HIV patients, with more than 50% of cases in our series presenting with one or more reactivation infections.^{5,6} A necrotizing encephalitis due to *Toxoplasma gondii* was the most common infectious complication. Reactivation of viral infections due to cytomegalovirus (CMV) and JC virus (a papovavirus) were also commonly seen. CMV can produce in HIV patients a necrotizing ventriculo-encephalitis, polyradiculomyelitis, or a subacute encephalitis, and JC virus is the etiologic agent of progressive multifocal leukoencephalopathy (PML).⁶ Opportunistic infections caused by other viruses, protozoa, fungi or bacteria were less commonly seen. Cytomegalovirus reactivation was the main opportunistic infection present in one HIV child with ventriculo-encephalitis and the only CNS infection in one SIV monkey with ganglioradiculitis.

Primary CNS lymphoma is the most common CNS malignancy in HIV patients⁷ and was present in our series in 5% of adult HIV patients. Microscopically, it appears as multifocal necrotic masses which are composed of neoplastic B lymphocytes. Although it has been reported in HIV-infected children, it was not present in either children or monkeys in our study.

Over 25% of human patients in our series had evidence of a dementing process during life. Pathologically, when infections or neo-

plasms were excluded, these patients had microscopic evidence of a subacute encephalitis.^{5,8} SIV also causes a subacute meningoencephalomyelitis which is characterized by randomly distributed, perivascular collections of macrophages, glial cells, and multinucleated giant (syncytial) cells throughout the neuraxis.^{9,10} During early stages of SIV-CNS infection, leptomenigeal lesions predominated; in more advanced stages the lesions were mainly parenchymal. Both early and advanced lesions in HIV-CNS infection were parenchymal with minimal involvement of the leptomeninges. Numerous investigators have demonstrated the presence of HIV and SIV proteins and genome in syncytial and other mononuclear cells.^{11,12} Infected cells have been immunophenotyped to a monocytic lineage and the presence of virions in monocytes has been demonstrated by electron microscopy,^{8,12} although neuroglia and endothelium have also been incriminated. In our material, SIV proteins were localized in cells of monocytic lineage only.¹³ It appears from these data that both HIV and SIV cross the blood-brain barrier in a «trojan horse» fashion via infected mononuclear cells and replicate mainly within macrophages and syncytial cells infiltrating the brain parenchyma.

Vacuolar myelopathy is a thoracic spinal cord syndrome seen in adult late stage HIV-CNS disease and characterized by loss of myelin and spongy degeneration.⁶ It was not demonstrated in our animals, although it has been reported in one monkey.¹⁴ Gross cerebrocortical atrophy occurred in 30% of HIV-infected brains, but none in SIV-infected brains. Vascular calcification was seen in pediatric HIV-CNS, only.

Some features of SIV-CNS infection, notably direct lentivirus-induced lesions, resemble more closely pediatric than adult HIV-CNS encephalitis.¹⁰ Both viruses cause CNS lesions, and the extent and severity of these lesions increase with duration of infection. The differences between adult HIV and SIV-induced CNS disease may be due, among other factors, to the fact that in an experimental setting

there is no intervention to slow down or halt the progression of disease. Consequently, the lifespan of a SIV-infected monkey is by design shortened as compared to the lifespan of a HIV-infected person. In addition, considerably fewer monkeys have died of SIV infection than people infected with HIV. Despite these caveats, however, there are significant differences in HIV- and SIV-CNS pathological expression and, therefore, as the AIDS pandemic continues to take its toll, there is an urgent need to develop SIV strains with enhanced ability to cause chronic CNS clinical and pathological disease (supported in part by Grants RRO0165 and AFIP/WRAIR U941).

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SYSTEMIC SIDEROSIS AFTER PROPHYLACTIC PARENTERAL IRON ADMINISTRATION TO MUNICH MINI-PIGS WITH SPECIAL REFERENCE TO THE KIDNEYS

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When speaking of iron in connection with pigs, the first idea to arise spontaneously concerns iron deficiency anemia in suckling piglets. Perhaps one also remembers the violent myotoxic alterations after intramuscular injection of ionic iron, as it was sometimes given in former days. This report however, concerns systemic iron overload, occurring after the preventive administration of a common iron dextran compound (Myofer, Hoechst, 1 ml) usually given to mini-pigs at the breeding station during the first days of life.

Material and methods

The mini-pigs used at BAYER belong to the Troll® strain of the Munich breeding-line of miniature swine (MSM). The following results derive from histopathological investigations of 96 animals of both sexes, ageing between 5 and 12 months, and are not related to the application of test compounds. The animals were housed two to

a pen, given tap water (free choice), and fed a commercially prepared, standardized diet for mini-pigs (Altromin 8023). At the end of the study they were killed by exsanguination in deep hexobarbital-Na-anesthesia (Evipan®, Bayer) and necropsied immediately. Organs were fixed in Bouin's fluid and embedded in paraplast. Sections about 5 µm thick were stained with H & E and by the Prussian-blue reaction. Sections of the kidneys were additionally stained by PAS and the Turnbull-blue reaction, as well as the Azan method. To exclude the presence of melanin, sections were bleached with 10% hydrogen peroxide over 72 hours.

Results

The histopathological investigation revealed an accumulation of pigmented cells in a few organs. First, numerous brownish pigment deposits were observed in the livers of 94/96 animals, chiefly in the interstitial tissue at the lobular periphery, in blood-vessel walls and