HIV disorders of the brain; pathology and pathogenesis

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1. ABSTRACT

Infection with HIV-1 has spread exponentially in recent years to reach alarming proportions. It is estimated that more than 33 million adults and 1.3 million children are infected worldwide. Approximately 16,000 new cases are diagnosed every day and almost 3 million people die every year from AIDS, making it the fourth leading cause of death in the world. Since the introduction of highly active anti-retroviral therapy (HAART) in the mid 1990s, the morbidity and mortality associated with HIV-1 infection has significantly decreased and AIDS has become a chronic disorder. However, neuropathological conditions associated with AIDS are still present in approximately 70 to 90% of patients and can be the result of HIV itself or of opportunistic infections. Here we briefly review the pathology and pathophysiology of AIDS-Encephalopathy, of some of the significant opportunistic infections affecting the brain in the context of AIDS, including Progressive Multifocal Leukoencephalopathy (PML) a demyelinating disease caused by the human neurotropic JC virus, Toxoplasmosis, Cryptococcosis and of primary CNS lymphoma, a brain malignancy frequently associated with HIV-1 infection, all of them considered AIDS defining conditions.
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2. HIV-ENCEPHALOPATHY

2.1. Definition

Acquired immunodeficiency syndrome (AIDS) is the name given to the disease caused by infection with the human immunodeficiency virus 1 (HIV-1), a lentivirus of the Retroviridae family. Approximately 30% of patients with AIDS will develop a variety of cognitive and motor symptoms, generally late in the course of HIV infection, known collectively as AIDS-dementia complex or HIV-1 Associated Cognitive-Motor Complex (1). HIV encephalopathy is the initial manifestation of AIDS in approximately 3% of the patients, and autopsy reports show that up to 90% of infected individuals have histopathological changes compatible with the disease.

2.2. HIV-1 Structure

Although lentiviruses have been known for a long time, HIV-1 was first isolated in 1983 from a patient with lymphadenopathy (2). Like other retroviruses HIV-1 is single-stranded RNA enveloped virus of approximately 100 nm in diameter. The HIV-1 genome is composed of two identical copies of RNA, surrounded by a nucleocapsid. The nucleocapsid is a lipid bilayer rich in envelope glycoproteins. Like other lentiviruses, the HIV-1 genome encodes for structural proteins, such as group specific antigens (Gag), which contains information for the nucleocapsid protein p24 and other internal non-glycosylated proteins, envelope proteins (Env), and enzymatic proteins responsible for reverse transcription and integration (Pol) and viral protease (Pro) (3, 4). However, the genome of HIV-1 is more complex and encodes for 6 other proteins. Vif or viral infectivity factor, essential for macrophage infectivity (5), Tat, a transactivator of RNA synthesis, required for viral replication (6), Vpr, a particle-associated regulatory protein (7), Rev, a regulator of splicing and RNA transport, Nef, a homodimer which has been controversially been associated with viral gene expression and that causes downregulation of CD4 (8), and Vpu, a protein important for virus assembly and release.

2.3. Histopathology

Gross examination of the brain in cases of AIDS Encephalopathy is disappointingly unremarkable. In some cases mild cerebral atrophy, of less that 200 g can be found. The atrophy is characterized by enlarged sulci and slight dilation of the ventricular system (hydrocephalus ex vacuo).

Histologically, HIV Encephalopathy is characterized by a subacute encephalitis, with chronic inflammatory infiltrates in close proximity to blood vessels, accompanied by parenchymal microglial nodules and the hallmark of the disease, giant multinucleated cells, which are result of the fusion of macrophages (9, 10). In some cases this vasculitis causes scattered small infarcts in the brain parenchyma, in which reactive astrocytes proliferate (11). Neuronal loss has been described consistently in the cortex of patients with HIV-encephalopathy (12, 13). Figure 1 illustrates the histological characteristics of HIV-Encephalitis.
2.4 Clinical Manifestations

The first exposure of the brain to HIV-1 occurs shortly after systemic infection and results in a usually asymptomatic infection, although in some cases signs of mild encephalitides have been reported (14). The onset of AIDS dementia complex is generally insidious and the signs and symptoms are compatible with a subcortical dementia. In early stages the clinical spectrum include poor concentration, confusion, recent memory loss, fatigue and apathy, which may be misdiagnosed as depression (15). In later stages, more specific cognitive changes develop including personality and behavioral changes, motor impairments, including tremor, weakness, appearance of release reflexes and even ataxia (16, 17). Although the prognosis of patients diagnosed with AIDS-dementia complex has improved after the introduction of HAART therapy, the survival remains poor, ranging from 1 to 3 years.

2.5. Physiopathology

HIV-1 crosses the blood-brain barrier and invades the brain shortly after systemic infection (18). The mechanism of entry involves endothelial pinocytosis through binding of viral gp120 to endothelial cell surface glycoproteins (19). HIV-1 is most likely carried by cells in traffic to the brain, infected monocytes in particular, in what is known as the ‘Trojan Horse’ hypothesis (20, 21). In support of this model, several studies have demonstrated the presence of HIV-1 in macrophages located in the Virchow-Robin space by in situ hybridization and immunohistochemistry (22, 23). Microglial cells may become subsequently infected and along with perivascular macrophages may act as viral reservoirs (24, 25). Viral-envelope proteins expressed in the surface of infected macrophages appear to be responsible for the fusion of HIV-1 infected macrophages to result in the formation of giant multinucleated cells, the hallmark cells of HIV-encephalitis (26). Viral production seem to be limited to these phenotype of cells, since infection of astrocytes have been demonstrated, does not lead to a significant viral replication (27, 28).

The mechanism of neuropathogenesis is not clearly understood, as there is no evidence of HIV-1 infection in neurons. It is possible that neuronal injury occurs as a consequence of the inflammatory process or of direct exposure to HIV proteins released by infected cells, such as gp120, Tat and Vpr, which have been shown to have a toxic effect in vitro (29, 30, 31). In addition, gp120 has been shown to cause neuronal damage through an indirect mechanism involving activation of the TNF-α / Caspase cascade of proteins (32). Several studies have also shown the toxic effects of nitric oxide secreted by HIV-1 infected macrophages (33, 34). Another non-exclusive model involves the activation of several cytokines, which results in potentiation of the inflammatory response and in neural damage (35, 36). Interestingly, the degree of inflammatory response and neuronal damage does not always correlate with the severity of the clinical symptomatology (37, 38).

3. PROGRESSIVE MULTIFOCAL LEUKEENCEPHALOPATHY

3.1. Definition

Progressive Multifocal Leukenencephalopathy (PML) is a sub-acute and fatal demyelinating disease of the CNS, caused by the opportunistic neurotropic virus JCV and seen almost exclusively in patients with immunosuppressive conditions. Before the AIDS pandemic in the early 1980s, PML was a medical curiosity, associated mainly with leukemias and lymphomas or as a complication of chemotherapy for cancer treatment and immunosuppressive therapies in transplant patients. However, recent epidemiological reports indicate that up to 10% of patients with AIDS will develop PML and that 85% of patients with PML are HIV-1 positive. In fact PML is so frequently seen in patients infected by HIV-1, that it is considered an AIDS defining condition (39, 40).

PML is a relatively new disease, originally described by Åström and Richardson in 1958 (41), who also first suggested the possibility of an infectious organism as the etiological agent (42), theory that was later confirmed with the discovery of small viral particles in the nuclei of infected cells (43, 44, 45, 46). The next step in the characterization of PML as an infectious disease came with the cultivation and isolation of the virus in a fetal glial cell culture of spongioblasts (47). Finally, experimental animal models aimed to reproduce the demyelinating diseaseyielded surprising results, as rodents and primates intracerebrally inoculated with JCV developed several varieties of brain tumors, leading to the discovery of the oncogenic potential of the virus (48, 49, 50, 51, 52).

3.2. JC Virus Biological Considerations

JCV is a member of the polyomavirus family of DNA viruses, which also includes BK virus, the causative agent of polyomavirus nephropathy (PVN) and the thoroughly studied Simian Virus 40 (SV40). JC Virus is widely spread among the human population, with approximately 85% of adults world wide exhibiting JCV specific hemagglutination antibodies (53, 54). Infection with the virus is usually sub-clinical and occurs in early childhood (55). JCV has not been implicated in disease in healthy individuals and in fact, the virus has been recovered from the urine of pregnant women and renal transplant patients, indicating productive infection, without any overt signs of disease (56, 57). The virus is presumed to remain latent, until it reactivates under immunosuppressive conditions to result in PML. Based on the multifocal nature of the demyelinating lesions it is likely that the virus reaches the brain by hematogenous spread, perhaps carried by white blood cells. Infection of B-lymphocytes with JCV has been demonstrated in patients with PML, so these cells are likely to act as a carrier for the virus (58, 59). JCV exhibits very limited tissue specificity; the virus can replicate most efficiently in primary human fetal glial cells, but is well established that the virus remains latent in the kidney, and more recently several studies support its ability to replicate in B lymphocytes (60). However, due to the species specificity of the DNA polymerase, JCV can only replicate in primates, and humans are thought to represent the natural viral host (61).

3.3. JC Virus Structure

JCV is a small (38-40 nm in diameter) non-enveloped virus the genome of which consists of a closed, circular, double stranded DNA enclosed by an icosahedral
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capsid. The prototype strain of JCV, Mad-1, contains 5,130 nucleotides (61) and can be functionally divided into three regions, an early coding region and a late coding region divided by a regulatory (non-coding) region. The control region encodes the viral origin of DNA replication and is the strain that has been isolated from PML, Mad-1, contains a bi-directional promoter composed of two 98 base pair repeats which controls transcription, compared to the archetype strain, CV, which only contains one 98 bp repeat with two insertions of 23 and 68 bp respectively and which is found in latent state in the kidney. Early and late transcription proceeds in opposite directions around the circular DNA. The viral early region encodes the viral regulatory proteins, large and small T-Antigens, and is transcribed before DNA replication, whereas the viral late region encodes for the structural capsid proteins VP-1, VP-2 and VP-3 as well as the small accessory product, Agnoprotein, and is transcribed after DNA replication (61). VP1 is the most abundant protein of the capsid, representing approximately 80% of the virion components, which consists of 360 copies of VP1 arranged in 72 pentamers (62).

3.4. Histopathology

From the pathological point of view, PML is characterized by extensive areas of demyelination in the sub-cortical white matter of the brain, due to the infection and cytolytic destruction of oligodendrocytes, the myelin producing cells of the central nervous system. Although these demyelinated plaques are more frequently seen in the sub-cortical areas of the frontal, parietal and temporal lobes, they can also be found in the white matter any part of the brain, including the basal ganglia, cerebellum and brainstem and in extreme cases the spinal cord (63). In neuroimaging studies, PML usually appears as multiple foci of hyper-intense areas affecting the sub-cortical white matter. In gross examination a demyelination plaque is yellow, of soft consistency, irregular borders and can show small foci of cavitation, which eventually become confluent as the disease progresses. Histologically, the characteristic features of PML are multiple plaques of myelin loss, containing multiple enlarged bizarre reactive astrocytes, which are often atypical, multinucleated and have multiple large processes, and enlarged oligodendrocytes, harboring prominent eosinophilic intranuclear inclusion bodies (64, 65). These inclusion bodies are the result of the viral replication as corroborated by electron microscopy studies, which have consistently revealed the presence of icosahedral viral particles. Other histological characteristics include perivascular cuffing of lymphocytes, microglial nodules and foamy macrophages whose function is to phagocytose the myelin lipidic debris accumulated after the lysis of oligodendrocytes. Figure 2 depicts the anatomic and histopathological features of PML.

3.5. Clinical Manifestations

The clinical signs and symptoms depend on the location of the demyelinated lesions and they include headache, motor alterations, visual impairments, sensory loss, cognitive alterations and in the late phase of the disease, dementia. Since the most frequently affected location is the frontal lobe, cognitive and motor dysfunction are the predominant symptoms (66). Despite significant advances in antiretroviral therapy, thus far, no effective treatment has been developed and PML remains a fatal disease with a poor survival, which ranges from 4 to 6 months after the onset of symptoms (67).

3.6. Physiopathology

The lytic cycle of JCV starts with a direct association between VP1 molecules in the viral capsid and N-linked glycoproteins bearing specific linkages of sialic acid in glial cells, particularly oligodendrocytes (68, 69). Recent evidence has indicated a role for the 5HT2A serotonin receptor in JCV entry (70). After an endocytosis process, viral particles are disassembled and uncoated DNA enters the nuclear compartment, where early transcription proceeds (71). DNA replication occurs with production of approximately 200,000 viral copies. Once DNA replication begins, the infection enters the late phase, where T-Antigen represses the transcription of early genes and stimulates the late genes. Viral capsids are synthetized in the cytoplasm and re-enter the nuclei to assemble with viral DNA, explaining the presence of eosinophilic inclusion bodies in the nuclei of oligodendrocytes.

The significantly higher incidence of PML in patients with AIDS than in patients with any other immunosuppressive conditions, suggests that the presence of HIV-1 in the brain participates, directly or indirectly, in the pathogenesis of this disease (72). One likely candidate to orchestrate the molecular events involved in the activation of JCV is the HIV-1 transactivator protein Tat, a 14 kD protein transcribed early in the HIV-1 infection cycle and important for transcription and replication through interaction with the HIV-1 LTR (73, 74, 75). It has been demonstrated that Tat has the capacity of being secreted by HIV-1 infected cells, such as macrophages, microglial cells and astrocytes and absorbed by neighboring non-infected cells (64, 76) suggesting that reactivation of JCV may not require co-infection of oligodendrocytes by both viruses. Once inside oligodendrocytes, Tat has the ability to bind to specific sequences within the JCV control region, to result in enhancement of JCV promoter transcription and enhancement of viral DNA replication as demonstrated in vitro (77, 78). An alternate, but not exclusive mechanism of JCV promoter activation mediated by Tat, may include stimulation of several cytokines, including TGF-β1, which binds to the TGF-β1 Receptor of JCV infected oligodendrocytes, which results in transactivation of the JCV promoter by Smad 3 and Smad 4 (64). In both cases, the transactivation of the JCV promoter by HIV-1 Tat in oligodendrocytes will result in active viral replication, lytic destruction and eventually the development of PML.

4. CRYPTOCOCOSIS

4.1 Definition

Cryptococcal meningitis (CM) is another opportunistic infection of the CNS caused by the encapsulated yeast Cryptococcus neoformans. As well as other opportunistic infections, the incidence of CM has increased since the AIDS epidemic (79). CM is the most
Figure 2. Histopathological Features of Progressive Multifocal Leukoencephalopathy. Axial MRI of the brain showing the characteristic hyper-intense areas located in the sub-cortical white matter of the frontal lobe (Panel A). Coronal section of the same case, at the level of the frontal lobe demonstrating extensive lytic lesions in the sub-cortical white matter particularly prominent in the right olfactory gyrus (Panel B). Low magnification view of the white matter of a case of PML reveals extensive areas of myelin loss (Panel C, Hematoxylin & Eosin, original magnification x100). The demyelinated areas are highlighted with a special stain for myelin (Panel D, Luxol Fast Blue, original magnification x100). Higher magnification of the demyelinated plaques shows the characteristic cells of PML, giant reactive astrocytes with bizarre atypical nuclei (Panel E, Hematoxylin & Eosin, original magnification x1000), and enlarged oligodendrocytes harboring intranuclear eosinophilic inclusion bodies (Panel F, Hematoxylin & Eosin, original magnification x400). Immunohistochemistry for the JCV capsid protein VP-1 shows robust reactivity in the nuclei of infected oligodendrocytes, demonstrating productive infection (Panel G, original magnification x200). The intranuclear inclusion bodies in oligodendrocytes are composed of numerous icosahedral viral particles as demonstrated by electron microscopy (Panel H).
common fungal infection developed by HIV-1 infected patients and is the third most frequent neurological complication in patients with AIDS. In fact, CM is the initial manifestation of HIV-1 infection in approximately 40% of the patients (80), and 5 to 10% of HIV-1 infected patients will develop CM. Based on these statistics, CM is considered and AIDS defining condition (81). Cryptococcosis can also affect, with a significantly lower incidence, patients with sarcoidosis, lymphoproliferative disorders and individuals undergoing immunosuppressive therapies (80). The incidence of cryptococcal meningitis seems to be particularly common in Southeast Asia (82, 83) and Southern and East Africa (84).

4.2. Cryptococcus neoformans Structure

Cryptococcus neoformans, first described simultaneously in the late eighteen hundreds, in isolates from peach juice in Italy and from a tibial lesion of a patient in Germany (85, 86), belongs to the group of fungi known as Basidiomycete. Morphologically it is a spherical yeast, of 5 to 10 µm in diameter, with an external polysaccharide capsule, which is the major factor for virulence (79). Two varieties of Cryptococcus have been described, neoformans and gattii (79, 87). From the neoformans variety three major capsule serotypes are recognized: A, D, and AD; serotype A is the most commonly isolated in AIDS patients (79). The pathogenicity of Cryptococcus requires the presence of a capsule, the temperature of 37°C and the production of phenol oxidase (88, 89).

The main component of the capsule is the Capsular Polysaccharide (CPS), a long, non-branch polymer with monosaccharide branches of xylose and glucuronic acid (glucuronoxylomannan or GXM) (90). The presence of GXM is important, as it has been shown to inhibit both phagocytosis and production of antibodies against Cryptococcus (87). Other proteins, not necessarily related to the GXM but present in the capsule, have also been shown to decrease leukocyte migration (91). Virulence has not been correlated with the amount or length of the capsular polysaccharide (92), however, recent studies have shown that organ invasion by Cryptococcus was associated not only with changes in the cryptococcal capsule structure and cell size, but also with the characteristics of the organs infected, specially the integrity of the blood-brain barrier (93). In addition, Cryptococcus also produces a unique phenol oxidase enzyme, which has the ability to convert a variety of substrates, including catecholamines, into melanin (94, 95), characteristic that may be responsible for the neurotropism of this organism, which has a marked affinity for the brain and the adrenal glands (87, 96). Melanin, can function also as an antioxidant, which may protect Cryptococcus from oxidative host defenses (97, 98).

4.3. Histopathology

At gross examination, the brain shows chronic meningitis affecting the basal leptomeninges, which are opaque and thickened. Sections of the brain reveal a gelatinous grayish material within the subarachnoid space and multiple sometime confluent small cysts within the parenchyma, which are especially prominent in the basal ganglia in the distribution of the lenticulostrate arteries and are the characteristic lesion of cryptococcal infection (99). As the infection spreads the perivascular space (Virchow-Robin) may become distended, filled with this same mucoid, gelatinous material originated from the cryptococcal capsule (100, 101). Larger collections of these same structures are known as gelatinous pseudocysts, more common in adults and rare in children (102).

Histologically, the cystic lesions in the basal ganglia consist of aggregates of organisms confined to the Virchow-Robin spaces, which are enlarged. There is minimal or absent inflammation, however, in rare cases, a granulomatous inflammatory reaction, referred as a “cryptococcoma” can be seen surrounding the microorganisms (103). In tissue sections, the Cryptococcus appears as a spherical, encapsulated structure, which is surrounded by large empty spaces result of the abundant mucoid material secreted by the yeasts. The capsule of Cryptococcus can be visualized more clearly with special staining methods and silver impregnations, such as Gomori methenamine and Grocott, periodic acid-Schiff (PAS) and mucicarmine (87). In patients with AIDS there seem to be a variability in the size of the microorganisms. Figure 3, Panels A, B and C, illustrates the macroscopic and microscopic lesions of cryptococcosis.

4.4. Clinical Manifestations

Cryptococcal meningitis in AIDS patients usually presents with headache, fever, malaise, and altered mental status over several weeks (79). Meningeal symptoms such as neck rigidity and Kerning’ sign however, are not always present. Focal neurological signs and seizures are present in approximately 10% of patients (80). The onset and duration of CM is variable. The duration of symptoms and signs may be shorter in AIDS patients because of poor inflammatory response. Mortality from HIV-associated CM is relatively high, accounting for approximately 10-30% of the cases, mainly as a complication of raised intracranial pressure (104).

4.5. Physiopathology

Cryptococcus neoformans is an environmental saprophyte that can be found in the soil and in the manure of certain types of birds. The pathogenesis of cryptococcosis is determined by three main factors: the status of the host immune system, the virulence of the strain, and the size of the inoculum (87). The human infection is an accidental event in the life cycle of the organism. It is acquired through the respiratory tract from inhalation of aerosolized particles present in soil and habitats of birds, particularly pigeons (105, 106), where it can remain latent in the immunocompetent host, or spread into the bloodstream if alveolar macrophage function is impaired, as is the case in HIV-infected patients, finally reaching the brain. The mechanism by which Cryptococcus crosses the blood-brain barrier has been recently elucidated and it involves alteration of tight junctions in endothelial cells (107, 108). Once in the perivascular space, the fungi can be located extracellulary or inside phagolysosomes in macrophages, where it has the ability to survive and
replicate (109). Finally, after intracellular replication, the microorganism accumulates in vesicles and produces the mucoid substance, leading to permeabilization of the phagolysosomal membrane and cytotoxicity of macrophages (110).

5. TOXOPLASMOSIS

5.1. Definition

Toxoplasmosis is a disease caused by the coccidian Toxoplasma Gondii, an intracellular parasite with world-wide distribution. Infection with Toxoplasma results in a wide variety of conditions, ranging from asymptomatic infections in immunocompetent individuals to fatal acute encephalitis in HIV-1 infected patients. In addition Toxoplasma causes blindness and mental retardation in congenitally infected children. Serological studies have detected antibodies for Toxoplasma in approximately 30 to 40% of adults in Europe and North America and up to 80% in undeveloped countries (111), indication of latent infection. However, the incidence of encephalitis for Toxoplasma has dramatically increased in recent years, mainly due to the pandemic of AIDS, after which toxoplasmosis has become the most common opportunistic infection involving the brain (112, 113). In approximately 95% of patients infected with HIV-1, encephalitis is believed to be the result of reactivation of a chronic latent infection, due to the loss of cellular immune response (114, 115).

5.2. Toxoplasma godii Structure

Toxoplasma gondii is a ubiquitous intracellular protozoan, member of the family Apicomplexa, which also includes Plasmodium, the etiological agents of malaria. The discovery of Toxoplasma was made in 1908 at the Pasteur Institute in Tunisia, in the spleen and liver of a small rodent called the gondi (116). The first report of human involvement came a decade later, from a case of congenital toxoplasmosis in Prague (117).

The life cycle of Toxoplasma consists of two important phases, tachyzoites and oocysts. Tachyzoites are shaped as a crescent moon, with a conical anterior end and a rounded posterior end, and measure 2 by 6 μm. Ultrastructurally, they are intricate organisms composed by a central nucleus surrounded by numerous organelles and inclusion bodies and delimited by an outer cover or pellicle. The organelles include apical and polar rings, conoid, rhoptries, micronemes, micro pore, mitochondria, endoplasmic reticulum, Golgi apparatus, ribosomes, rough and smooth endoplasmic reticulum, dense granules, and a membrane-bound organelle, also termed apicoplast (118, 119, 120). The outer cover consists of three membranes, an external plasmalemma and two close inner membranes (121). Polar rings are thickenings of the inner membrane complex at the anterior end of the tachyzoite, which encircle a cylindrical, truncated cone called the conoid. Between the anterior end and the nucleus, there are 8 to 10 club-shaped organelles called rhoptries (122), which constitute excretory structures and contain proteolytic enzymes (123, 124). Micronemes are rod-like structures, present mostly at the anterior end of the parasite. The function of these structures is not fully understood but is likely associated with penetration of host cells and creation of an intracellular environment permissible for the growth and development of the parasite. On the other hand, oocysts vary in size and bradyzoite contents; young tissue cysts may be as small as 5 μm in diameter and contain only two bradyzoites, while older cyst measure from 70 to 100 μm and may contain hundreds of organisms (125).

5.3. Histopathology

On gross examination, the characteristic lesions of AIDS-related toxoplasmosis are multiple foci of necrosis. The lesions are usually focal, variable in size but generally large, of irregular borders and can affect any part of the brain, with strong predilection for the basal ganglia and brainstem. Necrotic and hemorrhagic areas are frequent (126, 127). The multifocal nature of the necrotic lesions suggests that although encephalitis might be the result of reactivation of a latent infection, the parasite reaches the brain through hematogenous dissemination. Histologically, acute lesions differ from chronic abscesses. Acute lesions are poorly circumscribed and contain necrotic and hemorrhagic areas with scanted inflammatory cells and abundant intracellular tachyzoites and parenchymal oocysts. Chronic lesions developed after treatment, are conformed by well-demarcated cysts with microglial nodules and macrophages in the adjacent brain parenchyma, where parasites are difficult to find (128). Figure 3, Panels D, E and F, depicts the radiological, macroscopic and histological features of toxoplasmosis.

5.4. Clinical Manifestations

The clinical signs and symptoms depend on the location of the lesions. General symptoms include headache, fever, motor deficits, behavioral changes, lethargy and coma, while more focal neurological conditions include hemiparesias, aphasia, convulsive crisis, ataxia, visual field defects and extrapyramidal signs, which once more, reflect the multifocal nature of the lesions (129, 115).

5.5. Physiopathology

Members of the cat family are the definitive hosts of Toxoplasma, while humans and other mammals constitute intermediate hosts. Infection can be contracted by ingestion parasites in either of three different stages of the Toxoplasma life cycle, oocysts, tachyzoites or tissue cysts. The infectious cycle begins with ingestion of tissue cysts in undercooked or raw meat from chronically infected intermediary hosts, such as chicken, pork, goat or sheep, or by ingestion of food or water contaminated with cat feces containing oocysts (130, 131). Domestic cats constitute the major source of contamination, as they can excrete as many as 100 million oocysts per day. Surprisingly, only approximately 1% of the cat population is found to be shedding infectious oocysts (132). These cysts are highly infectious and resilient, as they have the ability of remaining viable in the soil for several years. Once the oocysts reach the stomach, the acid gastric secretions will dissolve the cyst membrane, liberating bradyzoites, which enter intestinal epithelial cells and transform into rapidly dividing tachyzoites. The parasites eventually rupture the
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Figure 3. Opportunistic Infections Associated with AIDS. Coronal section of the brain in a case of Cryptococcosis demonstrates the characteristic cystic lesions, some of them confluent in the right Putamen (Panel A). Histologically, Cryptococcus neoformans is found confined to the Virchow-Robin space, which is dilated due to the microorganism and its mucoid secretion (Panel B, Mucicarmine, original magnification x100). Special staining methods reveal the structure of Cryptococcus, which is spherical, surrounded by an external capsule (Panel C, PAS, Insert, Grocott, both images original magnification x1000). MRI of the brain reveals an extensive lesion involving the right basal ganglia and corpus callosum in a case of Toxoplasmosis (Panel D). A coronal section of the brain in the same case demonstrates a large, irregularly shaped necro-hemorrhagic lesion, involving the basal ganglia and extending into the subcortical white matter (Panel E). Toxoplasma gondii can be found in tissue sections as intracellular tachyzoites in neurons and glial cells (Panel F, Hematoxylin & Eosin), and large oocysts with no inflammatory reaction surrounding them (Insert, both images, original magnification x1000).

host cells and disseminate to other organs, including the lymphatic tissue, myocardium, skeletal muscle, retina and brain, where the cycle starts over. This acute stage is followed by a chronic condition characterized by formation of tissue cysts containing slowly replicating bradyzoites (133).

6. PRIMARY CNS LYMPHOMAS

6.1 Definition

Primary Central Nervous System Lymphoma (PCNSL) is a malignant tumor of lymphocytes arising in the CNS in the absence of tumor outside the CNS. PCNSL is the second most common neoplasm in HIV-1 infected individuals behind Kaposi’s sarcoma, and the first intracranial tumor, representing approximately 20% of all lymphomas in patients with AIDS (134, 135). Epidemiological studies have shown that the incidence of primary CNS lymphoma is 3600-fold greater in AIDS patients than in the general population (136, 137), with approximately 2 to 12% of all AIDS patients developing CNS lymphomas (138). Based on these statistics, primary CNS lymphoma is another entity considered as an AIDS defining condition.

6.2. Histopathology

In contrast with systemic lymphomas infiltrating the brain, which present as leptomeningeal infiltrates, primary CNS lymphomas in the context of AIDS arises in the brain parenchyma. On gross examination CNS lymphomas present either as a single or multiple lesions, and are located in any part of the neuroaxis, with predilection for the cerebral hemispheres particularly the frontal lobe, the basal ganglia and periventricular regions, and the corpus callosum (139). Other locations include the brainstem, the cerebellum and the spinal cord. Approximately 25 to 50% of CNS lymphomas present as multiple masses. In general the tumors are grey-tan, yellowish, of firm and granular consistency, and poorly defined margins. Areas of hemorrhage and necrosis are frequent, especially in patients with AIDS. As mentioned above, the necrotic areas found in AIDS associated primary CNS lymphomas are similar to the ones present in encephalitis for toxoplasmosis, making this a differential diagnosis.

The characteristic histological pattern of primary CNS lymphomas is an angiocentricity of neoplastic cells, which are arranged forming perivascular cuffs in a concentric manner. Deposits of reticulin fibers around blood vessels are responsible for the concentric pattern observed in CNS lymphomas. In early stages, neoplastic cells are confined to the Virchow-Robin space, contained by the reticulin network, but later they diffusely invade the adjacent brain parenchyma. All primary CNS lymphomas grow in a diffuse pattern and no cases of follicular pattern have been described (140, 141). Unlike the complex and
Figure 4. Histopathological Features of Primary CNS Lymphomas. MRI of the brain in a case of primary CNS lymphoma reveals a large necrotic mass involving the right basal ganglia and producing significant brain edema (Panel A). A coronal section of the brain demonstrates a large infiltrating mass that affects the basal ganglia, including the caudate nucleus, the putamen and globus pallidus. The tumor is friable, granular and exhibits areas of necrosis and focal hemorrhage (Panel B). A low power magnification view of the tumor shows abundant neoplastic lymphocytes arranged in a concentric perivascular pattern that diffusely infiltrate the brain parenchyma (Panel C Hematoxylin & Eosin, original magnification x400). Robust cytoplasmic immunolabeling for CD-20 reveals the B-lymphocyte nature of the tumor (Panel D, original magnification x400). Immunohistochemistry for the Epstein-Barr latent membrane protein (LMP) reveals widely expression by neoplastic lymphocytes (Panel E, original magnification x400). The JCV early protein T-Antigen has been found in the nuclei of neoplastic lymphocytes by immunohistochemistry (Panel F, original magnification x1000). Double labeling immunofluorescence for LMP (Panel G, fluorescein) and T-Antigen (Panel H, rhodamin) demonstrates co-localization of both proteins in the majority of neoplastic cells (Panel I). Panels G, H and I original magnification x1000.

heterogeneous systemic lymphomas, primary CNS lymphomas are a homogeneous group of tumors, with approximately 98% expressing B-cell markers, such as CD20 and CD79a, and exhibit immunoglobulin gene rearrangements, which confirms their monoclonal nature (142). Only in rare and sporadic occasions T-cell lymphomas have been described in the context of HIV-1 infection (143). Figure 4 illustrates the spectrum of radiological, anatomic and histological characteristics of primary CNS lymphomas, including the association of Epstein-Barr virus and JCV.

6.3. Clinical Manifestations

Although primary CNS lymphomas can affect all ages, with a peak in the seventh decade of life, immunocompromised patients develop these malignancies at an earlier age, with the peak incidence at age 38. As is the case with other brain lesions associated with AIDS, the clinical signs and symptoms of primary CNS lymphomas are not specific and depend on the location of the tumors. The most common symptoms and signs include headache and seizures, focal neurological deficits, and psychiatric disorders. Unlike their systemic counterparts, B-cell lymphomas originating in the CNS have a poor prognosis with a median survival of only 3 months after diagnosis (144).

6.4. Physiopathology

The pathogenesis and cell of origin in primary CNS lymphomas is still subject of controversy. Two
The etiology of primary CNS lymphomas also remains unclear. The Epstein-Barr virus (EBV) appears to play a significant role in the development of primary CNS lymphomas, particularly in HIV-1 infected patients, as molecular studies have demonstrated the presence of EBV genomic sequences in approximately 95% of immunosuppressed individuals, compared to only in about 5% of immunocompetent patients (147, 148, 149). Reinforcing this notion, in vitro experiments have demonstrated the ability of EBV to immortalize B cells in culture, and suggest the role of the viral Latent Membrane Protein (LMP) in the oncogenic process (150). The mechanism of malignant transformation involves LMP protection from apoptosis via Bcl-2 and NFκB pathways, providing EBV with a suitable environment for viral replication and latency (151, 152). Recent studies have implicated the previously described JCV. DNA sequences and expression of viral proteins have been detected in cases of primary CNS lymphoma (153). This is not surprising considering the well-established oncogenic potential of the virus, which has been detected in lymphocytes, most likely in a latent state (154, 155). In support of this theory, severe chromosomal damage has been detected in lymphocytes harboring JCV infection, and the presence of JCV infection seems to disrupt proper DNA repair machinery (156). Interestingly, the mechanism of malignant transformation exerted by both EBV and JCV involves the expression of viral proteins, LMP and T-Antigen respectively, which have the ability to bind, sequester and inactivate tumor suppressors p53 and pRb, leading to dysregulation of the cell cycle and uncontrolled proliferation (157, 158, 159, 160). Reactivation of viral promoters under immunosuppressive conditions may be responsible for the cascade of events leading to malignant transformation and to the development of primary CNS lymphomas.

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8. REFERENCES

Neuropathology of HIV-1 infection and associated conditions

52. Zu Rheim GM, & Varakis JN: Perinatal induction of medulloblastomas in Syrian golden hamsters by a human...
Neuropathology of HIV-1 infection and associated conditions

85. Sanfelice F: Contributo alla morfologia e biologia dei blastomiceti che si sviluppano nei succhi di alcuni frutti. Ann Igien 4: 463-495 (1894)


Neuropathology of HIV-1 infection and associated conditions


150. Cesarman E: Epstein-Barr virus (EBV) and lymphomagenesis. Front Biosci 7: e58-65 (2002)


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