PRIMARY LYMPHOMA OF THE CENTRAL NERVOUS SYSTEM

A clinical-pathological and immunohistochemical study of ten autopsy cases

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ABSTRACT - *Context:* Primary central nervous system lymphomas (PCNSL) are a rare subgroup of lymphomas generally associated with HIV and EBV.   *Objective:* To study ten autopsy cases of PCNSL, to describe the neuropathological findings, to characterize the phenotype of the neoplastic cells, to detect EBV in the lesion and to compare the findings with the clinical and laboratory data of the patients.   *Method:* The clinical, histological and immunohistochemical data of ten cases of PCNSL, eight cases from patients with AIDS, identified among 265 autopsies of these patients were analyzed.   *Results:* Seven patients were males and the mean age was 40.9 years. The most frequent symptomatology was focal neurologic deficit (70%). Six patients presented with only one lesion. Histologically, densely cellular and polymorphous neoplasms with angiocentrism were observed, in 90% of cases. An association with other diseases was observed in four cases. Most patients had diffuse large B cell non-Hodgkin's lymphoma. EBV was detected by immuno-histochemistry in only one case. The lack of detection of the virus might have been due to the long time of fixation of the brain which might have inactivate epitopes therefore compromising the testing. *Conclusion:* In the present series, PCNSL presented with focal symptoms, with unifocal or multifocal lesions, with a predominant B-cell CD20 positive phenotype, rarely associated with EBV.

KEY WORDS: primary central nervous system lymphoma, neuropathology, immunohistochemistry, acquired immunodeficiency syndrome.

Linfoma primário do sistema nervoso central: estudo clínico-patológico e imuno-histoquímico de dez casos de necropsia

RESUMO - *Contexto:* Linfoma primário do sistema nervoso central (LP-SNC) é raro subgrupo de linfomas relacionado à AIDS, geralmente associado EBV.   *Objetivo:* Identificar os achados clínico-patológicos dos pacientes com LP-SNC. *Método:* Foram analisados dados clínicos, histológicos e imuno-histoquímicos de dez necrópsias de LP-SNC, oito deles de pacientes com AIDS, identificados entre 265 autopsias destes. *Resultados:* Sete pacientes foram masculinos e a idade média foi 40,9 anos. A sintomatologia neurológi-ca mais freqüente era focal (70%). Seis exibiram lesão única. Histologicamente, eram neoplasias densa-mente celulares e polimorfas, com angiocentrismo em 90% dos casos. Em quatro casos, houve associação com outras afecções. A maioria dos casos foi de linfoma não-Hodgkin difuso de grandes células B. A pesquisa para EBV foi positiva em um caso.   *Conclusão:* P redominaram os LP-SNC associados à AIDS, com sintoma-tologia focal, lesão em massa ou multifocal, com predominância de células B CD-20.

PALAVRAS-CHAVE: linfoma primário do sistema nervoso central, achados neuropatológicos, imuno-histo-química, síndrome da imunodeficiência adquirida.

Primary central nervous system lymphomas (PCNSL) a re a rare group of neoplasms, accounting for about 0.3 to 1.5% of all intracranial tumors and for 0.7 to 2% of lymphomas[1]. These tumors are generally asso-ciated with immunosuppression due to either the use of immunosuppressive drugs[2], human immunodefi-ciency virus (HIV) infection[3,4] or congenital disorders such as Wiskott-Aldrich syndrome[5]. PCNSL differ from extranodal lymphomas in terms of patient survival, p redisposing factors, histological subtypes and diffi-

culties in the classification according to the Working Formulation, the Kiel criteria and the revised European-American Lymphoma (REAL) system. In view of their restriction to a non-lymphoid organ, among other reasons, PCNSL have been considered a separate entity whose prognosis is generally worse than that of systemic lymphomas[6]. With the advent of AIDS and the introduction of organ transplants, the incidence of PCNSL has been increasing. These tumors currently represent an important subgroup of lymphomas[2,4]. In patients with AIDS, PCNSL are the second most common lesion with a mass effect[4] and the most frequent noninfectious cause of death[7]. The tumor represents the fourth cause of death in this group of patients[8]. PCNSL show a male/female ratio of 1.5 to 1, whereas the T subtype presents a ratio of 7:1[9]. The clinical manifestations are indistinguishable from cerebral toxoplasmosis and include loss of consciousness and focal neurologic deficits[10]. In the case of meningeal involvement, the tumor manifests as a meningeal syndrome[11,12]. Most PCNSL involve the basal nuclei or the frontal and parietal lobes, and present as homogenous mass lesions with ring-like zone of contrast enhancement and perilesional edema. The neuroimaging differential diagnosis with cerebral toxoplasmosis is difficult[10]. The lesions are multifocal, bilateral or periventricular and may extend to the subarachnoid space or ventricular cavity[13]. The macroscopic findings are variable[14]. Some tumors present as well-defined masses with a homogenous cut surface. Other lesions are poorly demarcated, diffusely infiltrating, showing areas of softening, hemorrhage and necrosis[15]. In immunocompetent patients, PCNSL are more superficial and located in the white and/or gray matter[16], or exclusively in the subarachnoid space[17].

The histopathological findings of PCNSL are similar to those of systemic non-Hodgkin's lymphomas and include densely cellular lesions comprised by atypical lymphoid cells[13] with an angiocentric pattern at the margins of the infiltrate and a rich reticulin network dissociating the vascular wall[18]. In voluminous tumors, the areas of necrosis can be extensive. Mitotic activity is high and hemorrhage is common. Neoplastic cells may invade normal adjacent structures. Therefore subependymal infiltration extending into the ventricular cavity and subarachnoid space are not uncommon[14]. The oncogenesis of PCNSL is still controversial. The site of origin of these lymphomas and the oncogenetic mechanisms are still unclear, especially because the tumor develops from and is restricted to a non-lymphoid organ without lymphatic vessels[19]. It might occur due to the development of a monoclonal proliferation from a pre-existing inflammatory lesion, similar to the mechanism underlying the origin of MALT lymphoma from *Helicobacter pylori*-induced gastritis. This hypothesis is supported by the demonstration of inflammatory lesions preceding the development of PCNSL[20,21]. Other authors suggest that non-neoplastic lymphocytes might be targeted to the CNS by a viral infection, more notably HTLV-1 or EBV, with the possible later occurrence of clonal neoplastic transformation of these cells[12]. In the case of immunodepressed patients, one may speculate that the lack of control of T cells over EBV present in patients with AIDS promotes the reactivation of EBV infection, leading to the proliferation of B cells, induction of oncogenes and gene rearrangements, and finally to the development of PCNSL[22]. Therefore in patients with AIDS, infection with EBV is suggested to be the most likely oncogenetic mechanisms since the EBV genome is found in more than 95% of these tumors and in less of 20% of PCNSL not associated with AIDS[23-25]. Herpes virus genomes such as HHV-6 or HHV-8 have been identified in some cases, suggesting that these or other herpes viruses may predispose to the development of primary lymphoma, even in immunocompetent patients[23]. HIV-infected subjects show a 60 to 100 times higher risk of developing malignant lymphoma, which represents a diagnostic criterion for AIDS[5].

Based on the above observations, we studied ten autopsy cases of PCNSL to more accurately describe the neuropathological findings and to characterize the phenotype of the neoplastic cells, to test the presence of EBV and to compare the morphological findings with the clinical and laboratory data of the patients.

METHOD

A total of 265 autopsies of patients performed at the Service of Pathological Anatomy, Department of Pathology, Antônio Pedro University Hospital, Federal University Fluminense, between 1987 and 1996 were revised and 10 cases of PCNSL were selected (3.7%).

Preparation of the material and fixation – The autopsy was complete in all cases and the CNS was fixed in 30% formalin for 21 days and then examined. The cerebral hemispheres were studied in approximately 1.0-cm thick coronal sections and in 0.5- to 1.0-cm perpendicular sections cut from the cerebral trunk and cerebellar hemispheres.

Fragments representative of the lesions were embedded in paraffin, cut into 5-μm thick sections, stained with hematoxylin-eosin and for reticulin fibers.

Table 1. Panel of antibodies.

Primary antibody	Dilution	Source	Code	Origin	Secundary antibodies	Antigen retrieval procedure
CD30	1/100	Dako	M 751	Mouse	R x M *	Trypsin
CD15	1/150	Dako	M 733	Mouse	R x M *	MW/PC*
CD3	1/200	Dako	A 0452	Rabbit	G x R***	MW/PC*
CD20	1/250	Dako	M 0755	Mouse	R x M *	MW/PC*
Kappa	1/4000	Sigma	K-4377	Mouse	R x M *	MW/PC*
Lambda	1/4000	Sigma	L-6522	Mouse	R x M *	MW/PC*
EBV	1/2500	Dako	M 0897	Mouse	R x M *	MW/PC*
CMV	1/100	Dako	M 854	Mouse	R x M *	Trypsin
GFAP	1/400	Dako	Z 0334	Rabbit	G x R***	Trypsin

*Ig Rabbit anti-Ig Mouse; **MW/PP, Microwave/Pressure chamber ; ***Ig Goat anti-Ig Rabbit.

Immunohistochemistry– 5-μm thick CNS sections were mounted on slides previously treated with 3-aminopropy-ltriethoxysilane (Sigma, A3648). After incubation in an oven at 60ºC for about 18 h, the sections were deparaffinized in xylene and hydrated in decreasing ethanol concentrations. Next, the specimens were incubated in two baths of 3% oxygenated water in methanol for 15 min each to inhibit endogenous peroxidase and washed with Tris buffer, pH 7.4. For antigen retrieval, the sections were immersed in citrate buffer, pH 6.0, and heated in a microwave oven for 5 min at maximum potency. Pressure chamber was used to CD3, CD20, CD15, KAPPA, LAMBDA e EBV antibodies. To inhibit nonspecific binding, the sections were incubated in a Tris-buffered solution of 1% skim milk (w/v) and 1% bovine serum albumin (w/v) in a humid chamber for 1 h at room temperature. Next, the sections were incubated over-night in a humid chamber at 4°C with the following primary antibodies: rabbit anti-human CD3 polyclonal (Dako, A 0452, diluted 1/200), mouse anti-human CD20 monoclon-al (Dako, M 0755, diluted 1/250), mouse anti-human CD15 (Dako, M 733, diluted 1/150), mouse anti-human Kappa monoclonal (Sigma, K-4377, diluted 1/4000), mouse anti-human Lambda monoclonal (Sigma, L-6522, diluted 1/4000), and mouse anti-EBV monoclonal (Dako, M 0897, diluted 1/2500).

For the anti-CD30, anti-CMV and anti-GFAP antibodies, the sections were trypsinized, nonspecific binding of the antibodies was blocked and the specimens were incubat-ed in a humid chamber at 37°C with the following primary antibodies: mouse anti-human CD30 monoclonal antibody (Dako, M 751, diluted 1/100), mouse anti-CMV monoclon-al antibody (Dako, M 854, diluted 1/100), and rabbit anti-GFAP polyclonal antibody (Dako, Z 0334, diluted 1/400).

Next, the sections were washed three times in Tris buffer for 10 min each and incubated with the biotinylated sec-ondary antibodies: goat anti-rabbit immunoglobulins (Dako, E 432, diluted 1/200) or rabbit anti-mouse immunoglobu-lins (Dako, E 0354, diluted 1/200) for 1 h in a humid cham-ber at 37°C. The primary and secondary antibodies were diluted in Tris-buffered 1% bovine serum albumin (w/v). After three washes in Tris buffer for 10 min each, the sec-tions were incubated with the streptavidin-biotin-peroxi-dase complex (Dako, K 0377) for 45 min in a humid cham-ber at room temperature, washed again three times in Tris buffer, and the peroxidase reaction was developed with diaminobenzidine (Sigma, 5637) and oxygenated water. The sections were counterstained with Mayer's hematoxylin. The antibodies used are shown in Table 1.

RESULTS

General clinical data and laboratory exams – The gender, age, risk behavior, clinical data and comple-mentary exams of the patients are summarized in Ta-ble 2. Seven patients were males and three were females, with age ranging from 24 to 64 years (mean ±standard deviation: 40.9±11.8 years). Neurological signs or symptoms were observed in all but one case, with a predominance of focal neurological deficit in seven patients. The time between the discovery of HIV positivity and the diagnosis of PCNSL ranged from 6 months to 3 years.

Gross findings – Brown-grayish, poorly demarcat-ed lesions with areas of necrosis, comprised by soft, fleshy to friable tissue, were identified in the basal nuclei (Fig 1) and thalamus of six, in the cerebral trunk of four, in the cerebellar hemisphere of three, and in the cortex and corpus callosum of two pa-tients. Multiple lesions were observed in six cases, with the number of lesions ranging from 2 to 4. In three cases, only one lesion was identified.

In one case, the gross findings differed from those observed in other cases. The tumor lesion was char-acterized by a whitish color and homogenous surfa-ce with a fish-flesh appearance, and involved struc-tures of the midline and deep gray matter, extend-ing to the corpus callosum and adjacent white mat-ter (Fig 2). Another case was characterized by the enlargement of the nerve roots and cranial nerves, and opacity of the leptomeninges. Analysis of the

Table 2. Identification, clinical data, risk behavior and complementary exams of 10 autopsy cases of CNS primary lymphoma diag-nosed.

| Case	Age (Y/O)	Gender	Risk behavior	HIV	Time of evolution (months)	Clinical data	Neurological signs
1 N87-297	64	F	Hemotransfusion	+	10	Loss weight, fever, diarrhea, hemorrhage	Focal neurologic deficit, convulsion, coma
2 N88-422	35	M	NE	+	NE	Loss weight, fever, diarrhea, pulmonary infection	No neurological signs.
3 N89-009	46	M	Promiscuous	+	12	Loss weight, fever, diarrhea, pneumocystosis	Paraplegy, dysfunction of sphincter
4 N89-224	28	M	NE	+	12	Loss weight, fever, diarrhea, pneumocystosis, Kaposi's sarcoma	Meningeal syndrome, coma
5 N91-013	38	M	NE	+	8	Loss weight, fever, diarrhea, pneumocystosis	Focal neurologic deficit, meningeal syndrome
6 N91-113	42	M	Hemotransfusion Homosexualism	+	13	Loss weight, fever, diarrhea, pulmonary infection, Kaposi's sarcom	Focal neurologic deficit
7 N93-041	24	M	Hemotransfusion	+	24	Loss weight, fever, diarrhea,pneumocystosis, digestive hemorrhage	Focal neurologic deficit, convulsion
8 N95-163	33	F	Hemotransfusion Promiscuous	+	36	Loss weight, fever, diarrhea	Focal neurologic deficits, convulsion, headache, vomiting, meningeal syndrome, coma
9 N95-205	50	M	–	–	4	–	Focal neurologic deficit, headache, vomiting, cerebellar syndrome
10 N96-326	49	F	–	–	4	–	Focal neurologic deficit, paraplegy, vomiting, pain in inferior extremities, visual hallucinations, dysfunction of sphincter

NE, not especificated; +, positive; –, absent/negative.
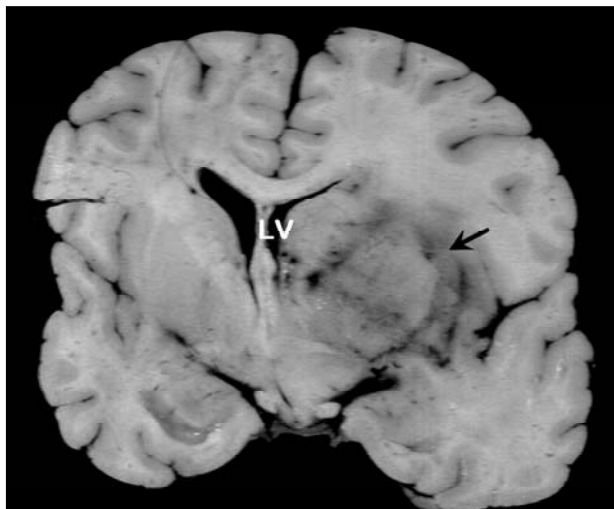
Fig 1. Tumoral involvement of basal nuclei (arrow), with hyper-emic halo and compression of the lateral ventricle (LV) and deviation of the central structures.
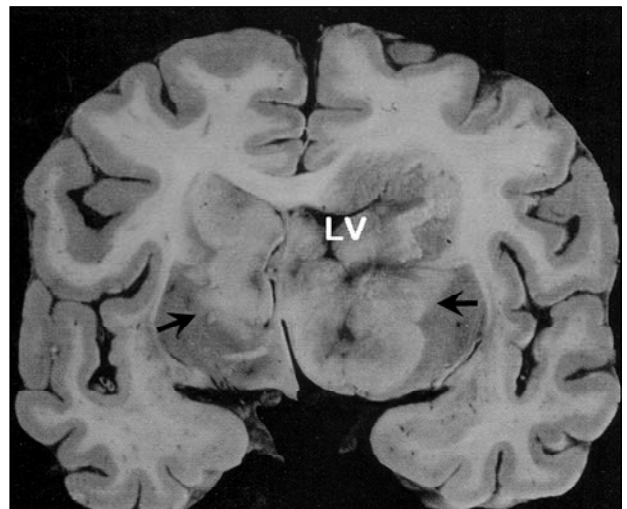

Fig 2. Bilateral tumoral masses in the basal nuclei (arrow) and the corpus callosum, with compression of the lateral ventricle.

Table 3. Gross findings at of 10 autopsy cases of CNS primary lymphomas.

Case	External exam	Nº tumoral lesions	Lobar lesion	Basal nuclei	Cerebral trunk	Cerebellar hemisphere	Size (major lesion)
1	Cortical atrophy / old infarct	3	–	1	1	1	1.5 x 1.0 cm
2	Congestion	1	1	–	–	–	< 1.0 cm
3	NL	1	–	–	–	–	< 1.0 cm
4	Oedema / cerebral hernia	2	–	1	1	–	4.0 x 3.5 cm
5	Oedema / cerebral hernia	1	–	1	–	–	6.0 x 4.0 cm
6	Cortical atrophy	2	–	2	–	–	2.0 x 2.0 cm
7	Cortical atrophy Cavitary lesion	2	2	–	–	–	2.0 x 1.5 cm
8	Cortical atrophy	4	–	–	–	2	3.0 x 2.5 cm
9	Mild oedema	4	–	2	1	1	5.0 x 4.0 cm
10*	Mild oedema	–	–	–	–	–	–

NL, no lesions; *Absence of parenchymatous lesions. Enlargement of the nerve roots and cranial nerves.
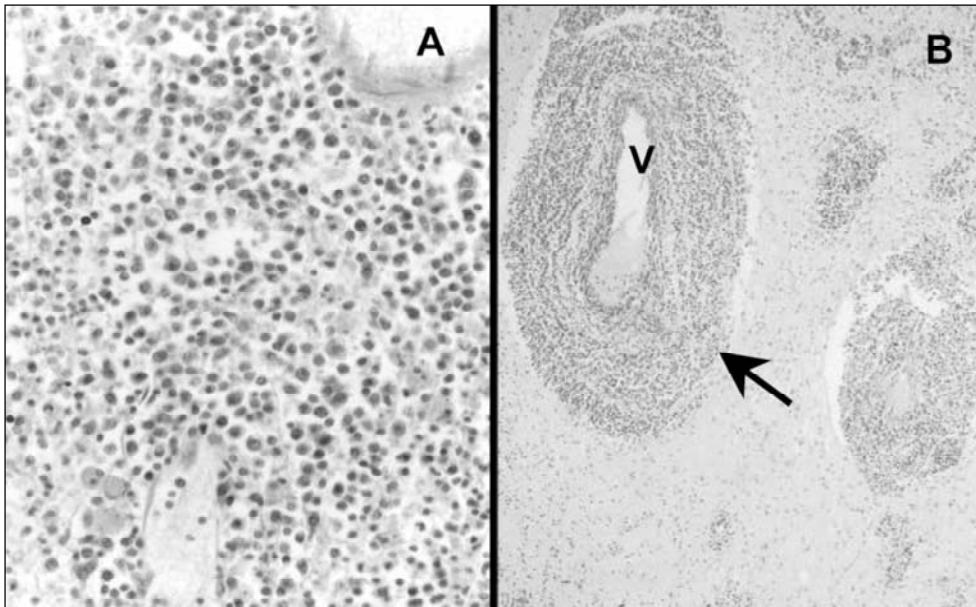

Fig 3. Histopathology of the non-Hodgkin large B-cell lymphoma. (A) Note dense sheet of typical lymphocytes (HE; 40x). (B) Angiocentric pattern (arrow; V) of the tumoral involvement (HE; 5x).

various sections did not reveal any parenchymal abnormalities.

Other important associated macroscopic findings were cortical atrophy in four cases and cerebral edema accompanied by uncal and tonsillar herniation in two (Table 3).

Microscopic findings – Microscopic examination revealed densely cellular parenchymatous lesions in nine cases (Fig 3A). These lesions were characterized by atypical lymphoid cells, a central area of necrosis and an angiocentric pattern at the periphery of the infiltrate (Fig 3B), with a rich reticulin network dis-

sociating the vascular wall. Only one case did not present the angiocentric arrangement.

In most cases, infiltration was diffuse and consisted of a polymorphic infiltrate comprised predominantly by large, sometimes bi- or multinucleated, immunoblast-like cells containing large, pleomorphic, vesicular nuclei, clearly visible nucleoli and scarce cytoplasm. The mitotic count was high. In two cases the cellular infiltration was made up by small lymphoid cells with inconspicuous mitotic activity. Plasma cell differentiation was also observed in one case (Table 4).

Gliosis was identified in all cases, especially at the

Table 4. *Classification and histopathologic findings at of 10 autopsy cases of CNS primary limphoma.*

Case	Classification (REAL)	Necrosis	Angiocentric pattern	Subependimal infiltration	Associated infections
1	Lymphoplasmacytic NHL (low grade)	Yes	Yes	Yes	No
2	Diffuse large cell NHL	Yes	Yes	No	Cryptococcosis HIV-E
3	Diffuse large cell NHL	Yes	Yes	No	No
4	Diffuse large B-cell NHL	Yes	Yes	Yes	HIV-E
5	Diffuse large cell NHL	Yes	Yes	Yes	No
6	Diffuse large B-cell NHL	Yes	Yes	Yes	No
7	Diffuse large B-cell NHL	Yes	Yes	Yes	CMV-E Treated toxoplasmosis
8	Diffuse large B-cell NHL	Yes	Yes	Yes	CMV-E
9	B-lymphoblast precursor NHL	No	No	Yes	No
10	Peripheral T-cell NHL not otherwise specified	No	Yes	No	No

NHL, non-Hodgkin's lymphoma; HIV, human immunodeficiency virus; CMV, cytomegalovirus; E, encephalitis.
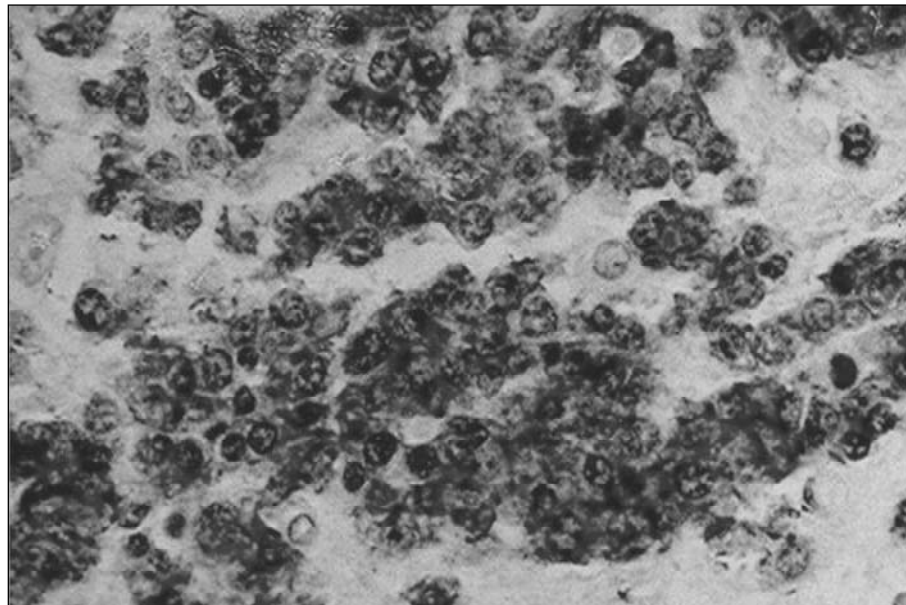

Fig 4. *Immunoreactivity of the neoplastic lymphoid cells for CD20. Note strong membrane pattern of positivity (IHC; 40x).*

periphery of the tumoral mass, and reactive astrocy-tes were eventually observed within the tumor tissue.

Associated disorders – Opportunistic infections were observed in six cases: HIV-encephalitis (n=2), CMV - encephalitis (n=2), cerebral toxoplasmosis (n=1) and cerebral cryptococcosis (n=1) (Table 4).

Immunohistochemical findings – All cases but one showed a B phenotype (CD20 positive); the remaining case, from a HIV negative patient, was positive for T-lymphocytes (CD3 positive). In addition, just one case was CD30 positive and one case EBV positive (Fig 4).

According to the REAL classification[26], three cases were classified as diffuse large B-cell non-Hodgkin's lymphoma, one case as lymphoplasmacytic non-Hodgkin's lymphoma, one case as B-lymphoblast precursor non-Hodgkin's lymphoma, and one case as peripheral T-cell non-Hodgkin's lymphoma, not otherwise specified. The three cases, in which no immunohistochemistry could be performed, were classified as probably diffuse large B-cell lymphoma.

DISCUSSION

In the present study, all tumors were only identified in the CNS, in agreement with the criteria for the diagnosis of PCNSL which require that no lymphomas are detected in organs other than the CNS or posterior region of the retina at the onset of neurological symptoms[11,14]. By definition, extranodal lymphomas are recognized as lymphoid tumors arising from lymphoid cell-containing sites other than the lymph nodes[27].

Macroscopically, the lesions were similar to those of toxoplasmosis, a finding also reported by Cirilo and Rosenblum[15]. Similarly, neuroimaging does not permit a differential diagnosis with cerebral toxoplasmosis[4] and other methods are necessary for diagnosis conclusion[28]. Thus, in the present study, the diagnosis of PCNSL was made only by microscopy.

In the present study, immunohistochemistry for EBV revealed only one positive case in an AIDS patient. The lack of detection of the virus might have been due to the long time of fixation of the brain which might have inactivate epitopes therefore compromising the testing.

Association with other CNS disorders was a frequent finding in the present series. It might be speculated as proposed by Aderson et al.[20] and Aozasa et al.[21] that the presence of HIV- or CMV-induced encephalitis is responsible for B-cell hyperreactivity.

PCNSL continue to be a challenge in terms of their morphology and oncogenesis. Molecular studies of oncogenes and suppressor genes are still inconclusive. These lymphomas develop in non-lymphoid organs without lymphatic vessels, and as such represent one of the main areas of neuro-oncological research.

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