Review

Primary central nervous system lymphomas in immunocompetent patients

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Summary. Primary Central nervous system lymphoma is a rare non-Hodgkin's tumor of the brain that has been traditionally found in patients with immunodeficiency syndromes. However, there are several immuno-competent patients that have also been reported with this neoplasm. In this group of patients, the mean age of diagnosis is around 60-year old, with a very slight predominance in women. Macroscopically, most of the tumors are unique and mainly located in the supratentorial region in the proximity of the cerebrospinal fluid circulation. The typical histological pattern is a perivascular distribution of tumor cells, within a network of reticulin fibers. Even though they are usually well defined masses, it is not rare to find tumor invasion beyond the macroscopic margin. Coagulative necrosis is not as common as in immunodeficiency-related cases. Immunohistochemistry has demonstrated that most of the tumor cells are B-lymphocytes and the electron microscopic findings do not differ from those reported in systemic non-Hodgkin's lymphomas. There are several histological classifications of these tumors, some of them with recent modifications to facilitate the analysis, but unfortunately, up now with a little or no clinical significance. The diagnosis is based on the histological study of the specimen obtained mainly through a Stereotactic biopsy. The treatment is based on a combination of chemotherapy followed by radiotherapy, but the mortality rate is still high.

Key words: Brain tumor, Central nervous system, Immunohistochemistry, Non-Hodgkin's lymphoma

Introduciton

Primary central nervous system lymphoma (PCNSL) was initially described by Bailey in 1929 as perivascular sarcoma (Bailey, 1929), however it was not recognized as a distinctive nosological entity until 1974 (Henry et al., 1974). It consists in a rare form of extranodal lymphoma confined to the brain. PCNSL has been described mostly in patients with congenital or acquired immunodeficiencies, but recently, a relatively high number of cases in immunocompetent patients (ICP) have been reported. A clear difference between these two entities has to be established, because they display different pathogenic and clinical aspects, especially related to prognosis and therapeutic approach.

Clinical characteristics

PCNSL represents 1-6% of all intracranial neoplasms and 1-2% of all extranodal lymphomas (Basso and Brandes, 2002). Even though an increasing number of cases of acquired immunodeficiency syndrome (AIDS) have been reported, the global incidence of this tumor has diminished (Kadan-Lottick et al., 2002); however, a notably exception is observed in patients over 60-year old without human immunodeficiency virus (HIV) infection, where the disease has remained unchanged, suggesting that it is a different pathological entity. The mean age of diagnosis of PCNSL in ICP is 61 years (Tomlinson et al., 1995), with a male/female ratio of 1.35:1.5. Among older people, white race and male gender are associated with the greatest risk, especially for those ages 75-79 years.

There are several potential risk factors that have been reported in PCNSL in ICP, but none of them has demonstrated to be clearly related to this disease; those include the following: autoimmune conditions with or without accompanying immunosuppression, hepatitis C virus infection, HTLV I/II, and *Helicobacter pylori* infection. Besides, no genetic predisposition has been described and only 4.5% to 8% of the patients have a family history of cancer, must commonly leukemia and adenocacinoma, being this an indicator of poor prognosis (Bataille et al., 2000).

The time between the first symptom and the hospital admission is an average of 80 days. In 10 to 15% of cases, the neurological symptoms are preceded by systemic manifestations such as gastrointestinal discomfort, febrile or respiratory illness (B symptoms),

which are more frequently seen in HIV-positive cases. The clinical course depends mostly on the location of the lesion. In 60-65% of patients a unique tumor is found (Hayabuchi et al., 1999; Bühring et al., 2001); mainly located at cerebral hemispheres (31%), followed by the corpus callosum and the basal ganglia. Some authors have reported that multiplicity of lesions is a bad prognostic indicator, but this has not been found by others (Namasivayam and Teasdale, 1992). The most important clinical factors that have a negative prognosis impact are the following (Kim et al., 1996; Ferrei et al., 2003): age more than 60 years, a low performance Karnofsky scale (≤ 70), symptoms duration under four weeks, and involvement of deep regions of the brain (periventricular regions, basal ganglia, brainstem and/or cerebellum). The presence of leptomeningeal tumor is another very important factor with prognostic implication (Balmaceda et al., 1995). The incidence of this finding is reported as high as 42% of patients at diagnosis and 41% at recurrence and it can be identified by positive findings on cerebrospinal fluid (CSF) cytology, leptomeningeal or subependymal enhancement on magnetic resonance imaging (MRI), elevated serum level of lactate dehydrogenase isoenzime-5 or pathological evidence in the surgical specimens.

Imaging studies

In patients with normal immunity, PCNSL classically presents in MRI as a solitary iso or slightly hypo-intense mass on T1-weighted that shows an intense homogeneous enhancement with the gadolinium contrast (Fig. 1). The rim enhancement and hemorrhage within the tumor, findings that are relatively common on AIDS patients, are only seldom reported (Watanabe et al., 1992; Johnson et al., 1997; Erdag et al., 2001). On T2-weighted, most of the lesions appear hyperintense (Ueda et al., 1995). Some authors have reported a strong correlation between a higher degree of necrosis found on histological analyses and a hyperintensity signal on T2-weighted MRI (Johnson et al., 1997). The average size of the lesions reported is 19.9 mm (range 2-50 mm) and most of them are located in the periventricular or subcortical areas, adjacent to the CSF circulation.

Thallium[201]-based single photon emission computed tomography (SPECT) may be useful to discriminate PCNSL from gadolinium enhancing infectious lesions, because the lymphomatous nodules incorporate the radioactive contrast more intensely, and retain it for a longer time compared with inflammatory tissues. Given the high expression of somatostatin receptors shown by lymphomatous cells, indium[111]-pentetreotide scintigraphy has also been proposed as a highly sensitive study, but this is most used to identify a false complete remission of the disease after the first line of treatment (Roland et al., 1998). F[15]-deoxyglucose positron emission tomography (PET) might be also useful, because PCNSL has a very high cellular density, with an accelerated glycolitic metabolism, so this study can be used for the early detection of recurrence (Roelcke and Leenders, 1999), but the main problem is its high cost. Finally, there is a tumor marker called soluble CD27, which has been identified in the CSF of ICP with PCNSL that might also be of diagnostic utility (Murase
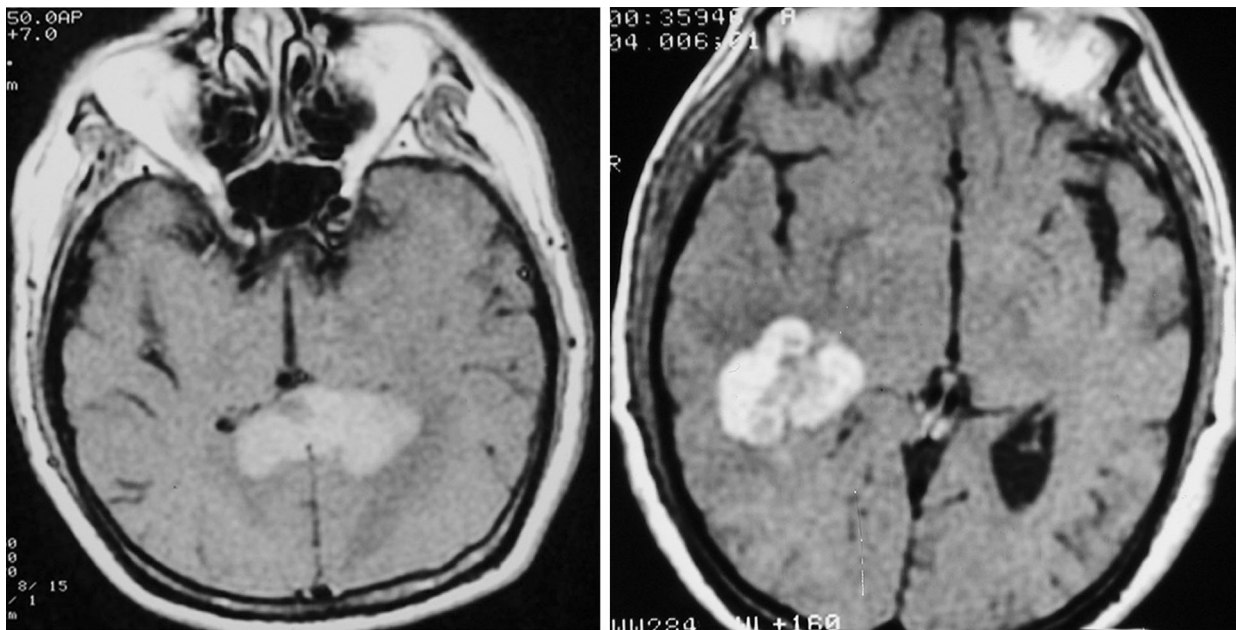
Fig. 1. Typical appearance on axial T1 weighted MRI with contrast enhancement of PCNSL in ICP. The aspect of the tumor is a solid lesion with marked homogenous enhancement in the proximity of the CSF circulation. **Left:** The lesion is located in the splenium. **Right:** The tumor is near the right ventricular atrium.

et al., 2000).

Pathogenesis and molecular biology

The central nervous system (CNS) is usually considered virtually unreachable from the immune system and so, it would not be anticipated that lymphomas could arise there as a primary site (DeAngelis, 1999). It is believed that some specific process (unknown to date) present in elderly patients, may attract peripheral blood lymphoid cells that are stimulated to proliferate locally and may undergo clonal selection. In other words, the brain of these patients lacks some regulatory mechanism of lymphoid proliferation that is normally present in peripheral tissues (Postler et al., 1999). Three hypotheses have been postulated to explain this fact (Paulus et al., 2000): 1) B-cells may be transformed at a site elsewhere in the body and then develop adhesion molecules specific for cerebral endothelium; 2) lymphoma cells may be systematically eradicated by an intact immune system, but may be relatively protected within CNS; 3) a polyclonal intracerebral inflammatory lesion may expand clonally within the brain and progress to the monoclonal neoplastic state. Besides, it is possible that intracerebral antigens or superantigens may stimulate persistence and expansion of B-cells.

Unlike AIDS-related lymphomas, PCNSL in ICP almost never correlates with Epstein-Barr virus infection (Geddes et al., 1992; Chang et al., 1993). It was reported (Jellinger and Paulus, 1995; Camilleri-Broet et al., 1998; Nozaki et al., 1998; Thompsett et al., 1999) that the BCL-6 protein is highly expressed and frequently mutated in its 5'-extremity, while BCL-2 and/or p53 are rarely expressed. Furthermore, the immunoglobulin heavy chain gene of the neoplastic clone undergoes frequent events of somatic mutations. Therefore, it is believed that this tumor originates from the subgroup of mature B-lymphocytes that, after an encounter with the antigen, normally reside and proliferate within the germinal center of secondary lymphoid organs. Molecular analyses of rearranged variable regions genes of PCNSL demonstrated clonally rearranged immunoglobulin genes with somatic mutations which were more frequent than in other lymphoma types; thus, these tumors correspond to germinal center B-cells.

Cytogenetic analyses of PCNSL in ICP showed clonal abnormalities of chromosomes 1, 6, 7, and 14, as well as translocations (1;14), (6;14), (13;18) and (14;21).

Histopathology

The pathological findings of PCNSL in ICP are very similar to those HIV-positive patients, even though they show several clinical, radiological and physiopathological differences. Macroscopically they can be found as unique or multiple lesions with a relatively well defined borders and mainly located in the proximity of the CSF. They tend to be grayish and with a granular aspect. The cut surface is yellow-white and granular, and the tumor is soft. There may be areas of focal necrosis or hemorrhage, but cystic changes are rare. Low-power microscopy demonstrates an angiocentric infiltration pattern, forming collars of tumors cells surrounding small brain vessels, with different amounts of reticulin deposits (Adams and Howatson, 1990) (Figs. 2, 3). In advanced tumors there may be a lost of the perivascular arrangement (O'Neill et al., 1987). From these perivascular cuffs, tumor cells invade neural parenchyma, either with compact cellular


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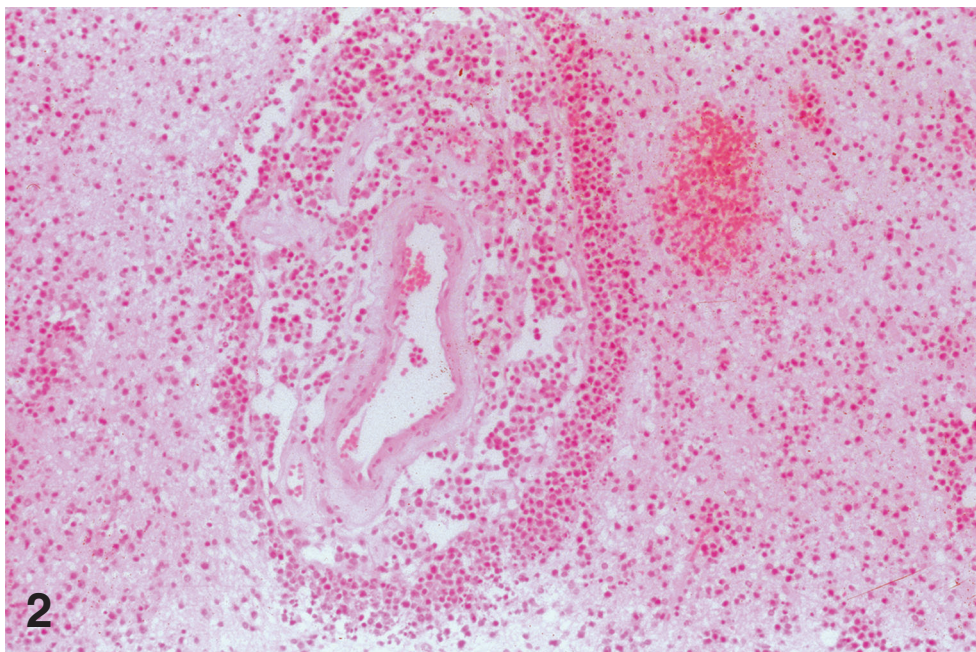
Fig. 2. The cellular arrangement shows a typical angiocentric pattern. HE, x 258

aggregates or with single diffusely infiltrating tumor cells resembling encephalitis (Fig. 4). Careful examination usually demonstrates tumor infiltration beyond the macroscopic margin. There also may be an associated astrocytic reaction accompanied by the presence of macrophages (Ashby et al., 1988) and, in contrast to gliomas and metastases, without a significant degree of endothelial proliferation, but multiplication of involved blood vessels basement membranes may be observed. When tumors become confluent, geographic necrosis may be seen, with perivascular islands of viable tumor cells surrounded of large regions of coagulative necrosis. This latter finding is most frequently reported on HIV-positive patients. The periphery of the tumor is often composed of a T-lymphocyte infiltrate with some occasional T-cells seen throughout the tumor (Murphy et al., 1989). It has been described that the presence of reactive astrocytes may be so intense, that it may mimic a low grade astocytoma (Kepes, 1987); this could explain the incorrect diagnosis on the trans-operative
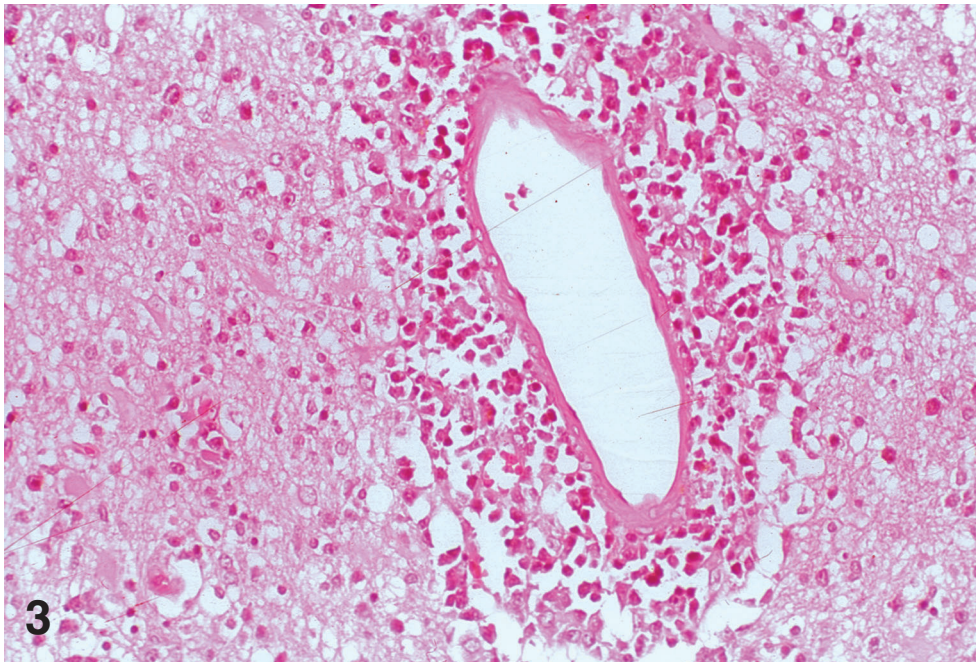
Fig. 3. Dense perivascular distribution of lymphoma cells. HE, x 280
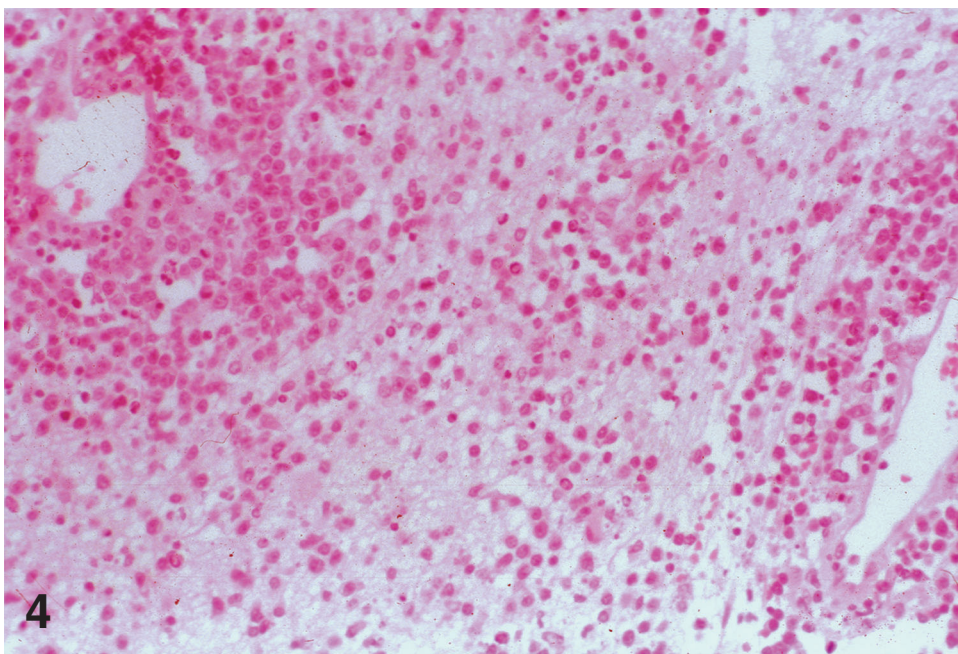
Fig. 4. From the perivascular cuffs, the tumor cells are diffusely invading the brain parenchyma. HE, x 280

pathological report. In patients who have been radiated and/or treated with chemotherapy (see below) it is not rare to find areas with demyelinative leokoencephalopathy, manifested by large areas of severe myelin loss surrounding the tumor.

High-power microscopy shows lymphoid cells with a variable appearance, some of them enlarged, with eccentrically placed nuclei, prominent nucleoli, and thick nuclear rims (Fig. 5). Tumor cells demonstrate a basophilic cytoplasm and also numerous mitoses (Yu et al., 1996) (Fig. 6). In some cases, highly anaplastic cellular changes can be found (Fig. 7).

Immunohistochemical studies are used mainly to determine the nature B/T of the tumors cells. Normally, T cells traffic in and out of the CNS, as manifest by the few lymphocytes which can be found in normal CSF, but B cells are not normally found in the CNS. Because of this, it becomes paradoxical that the great majority of PCNSLs in both HIV-positive and -negative patients show positive reaction to B-cell antibody (CD20 and
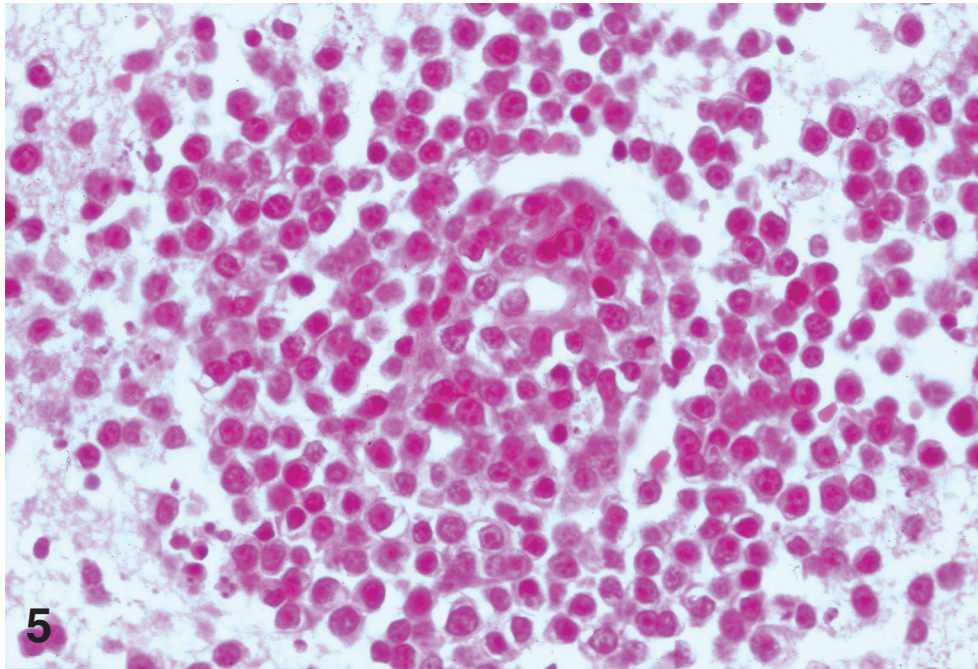
Fig. 5. Neoplastic lymphoid cells show a thick nuclear membrane, with prominent nucleoli. HE, x 320
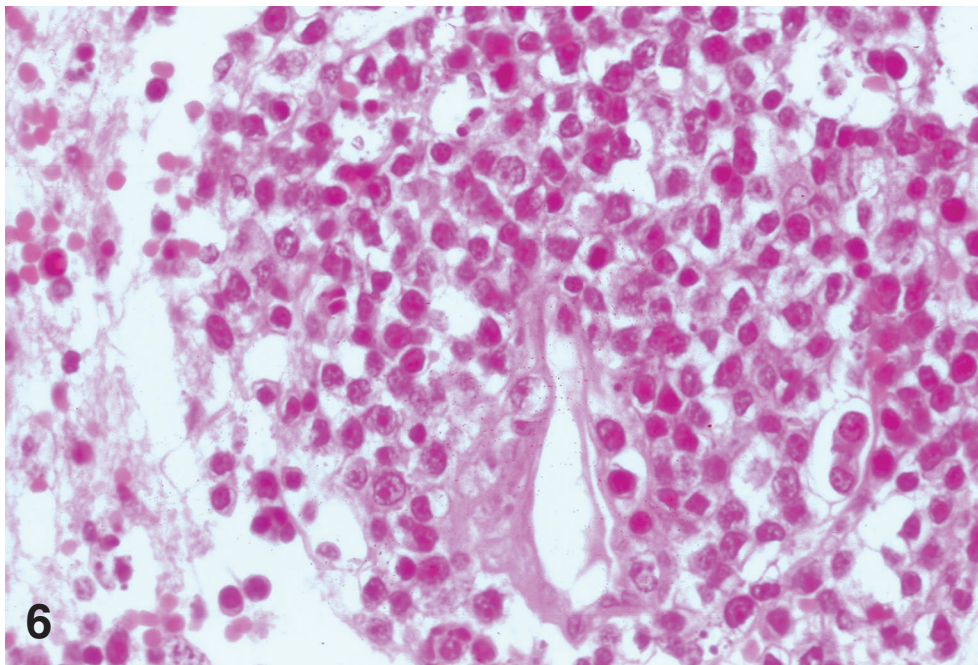

**Fig. 6.** Malignant diffuse large B-Cell lymphoma. x 320

CD79a) (Figs. 8, 9). There are several hypotheses to explain the origin of B-cell in PCNSL but not definitive data to explain their physiopathology. As it was mentioned before, B-cells may be transformed outside the CNS and thus be able to cross the normal barriers and to get into a relatively immunoprivileged environment. This mechanism would suggest that these tumor cells have special surface markers which would induce this migration to the CNS, but up to now, all the surface cellular receptors found in the cellular component of PCNSL are the same as a common non-Hodgkin's lymphoma cells (Paulus and Jellinger, 1993). On the other hand, it could be possible that the B-cells become transformed during the passage through the CNS, or even intravascularly, and then remain in the brain, causing this tumor.

T-cells (positive reaction to CD3 antibody) are found in approximately 2% (ranging from 0-9.8%) of PCNSL, and they are reported slightly higher in HIV-negative patients (Menet et al., 1997; Powari et al., 2002). The diagnosis of T-cells tumors may be overestimated, because it has been mentioned that the more common B-
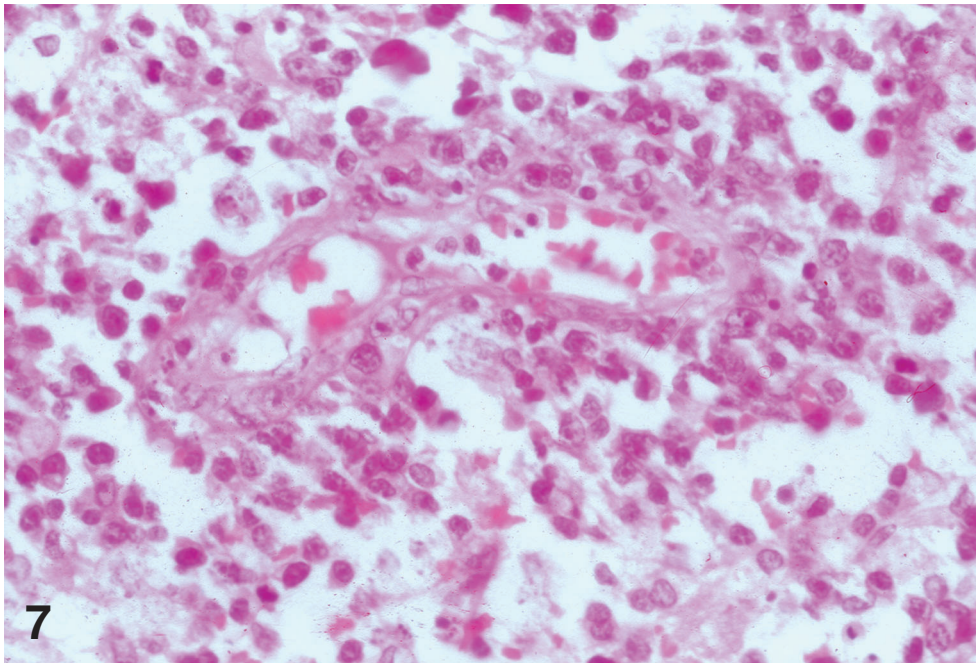
Fig. 7. Primary anaplastic malignant lymphoma with marked pleomorphic changes. x 320
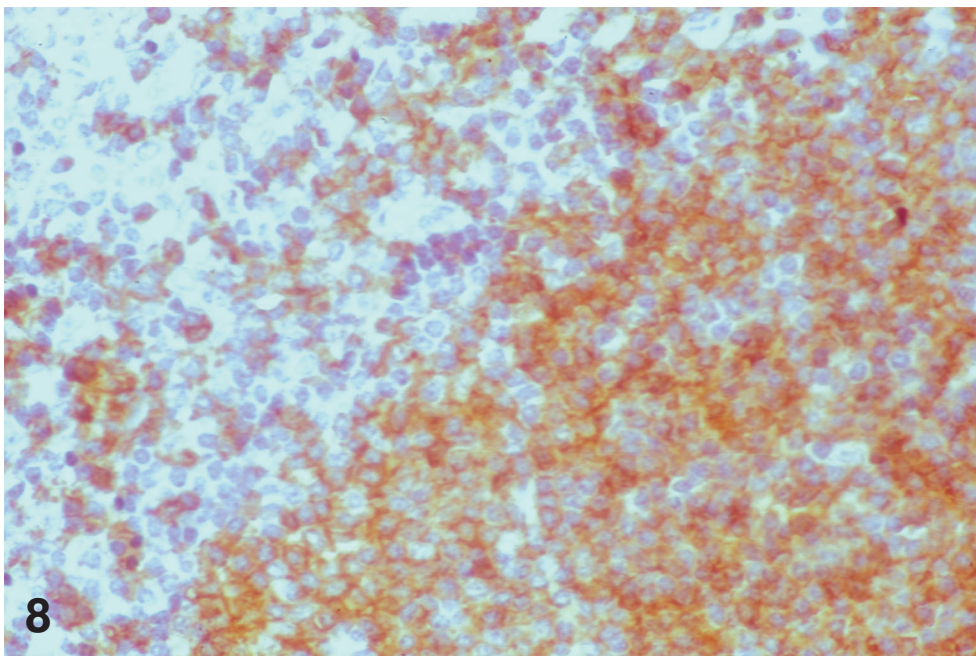
Fig. 8. Most of the tumor cells express the B-cells marker (Immunohisto-chemistry PAN-B. x 250

cell neoplasms are frequently infiltrated by reactive T-cells, complicating the interpretation of Immunohistochemical results (Bashir et al., 1996). This becomes particularly true if corticosteroids have been administrated before biopsy, causing lysis of malignant B-cells and tumor regression on MRI. When biopsy is performed, only the reactive T-cells are sampled, and they may be misinterpreted as a T-cell tumor (Gijtenbeek et al., 2001).

There are some clinical differences reported between T or B-cell tumors in PCNSL, but the information is controversial. A younger age at diagnosis for T-cells compared with B-cells lymphomas has been reported but not always confirmed, also higher male to female ratio in favor to T-cells tumors has been mentioned (McCue et al., 1993) and finally, a more frequent location in the infratentorial region has been found in these tumors. Spite of this, no statistical difference in prognosis and therapeutic response has been established between these two groups of tumors.

Even though there is no a histological classification that specifically includes PCNSL, there are four most frequently referred. The International Working Formulation (IWF) is based on clinical correlations and is relatively easy to understand and apply. According to this, PCNSL can be classified in ten categories that reflect three prognostic levels: low, intermediate, and high grade. The main problem with this classification is that it is a method of translating between previously existing classifications (Paulus et al., 2000). Thus, IWF was proposed as an inclusive scheme, in which all categories of pre-existent classifications could be included. Another problem is that IWF is based only on hematoxylin and eosin-stained sections, without special stains or Immunohistochemical data. The second classification is the revised Kiel (K) (Stansfeld et al., 1988), which is based on morphological differentiation of lymphocytes with less regard to clinical outcome; it considers B- and T-cells separately, placing them in two cytologically defined categories: low and high grade. This classification uses both detailed morphologic analyses and immunologic studies to define specific disease entities. However, it excludes primary extranodal lymphomas other than mycosis fungoides, does not admit the morphologic and clinical heterogeneity of follicular lymphomas, and it requires morphologic subclassification of entities such as large B-cell lymphoma and peripheral T-cell lymphomas, which may be difficult and poorly reproducible. Finally, the Revised European-American lymphoma (REAL) classification (Harris et al., 1994), which is very similar to the World Health Organization classification (WHO), defines entities on the basis of morphological, immunological, genetic and clinical information. It is very simple in referring to PCNSL and so, it is one of the most used systems nowadays.

The majority of PCNSLs in ICP are histologically high grade. According to the IWF, it has been reported that more than 90% of cases can be included within groups G (diffuse large cells) and H (immunoblastic), only 5% are group J (Burkitt), while the remaining are low-grade (small lymphocytic) (Blay et al., 1998). With the K, tumors have been classified as low grade malignancy in 22.4% of cases, and high grade of malignancy in 77.6%. However, there are a considerable number of cases, some time referred as high as 50% of them that can not be categorized using these two classifications. Finally, according to REAL,
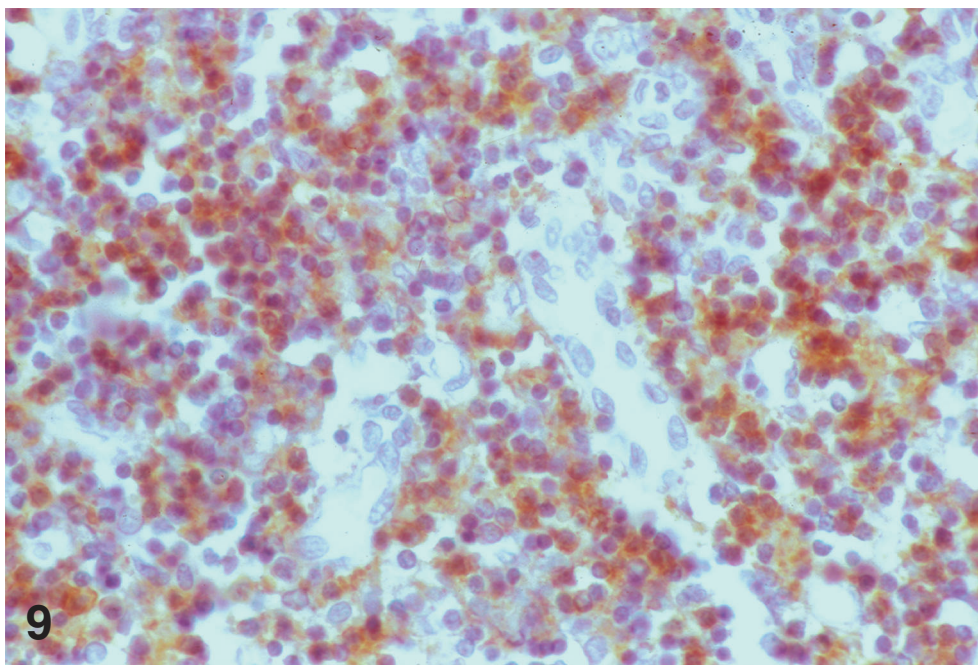
Fig. 9. B-cells lymphoma with the typical angiocentric arrangement. Immunohistochemistry, x 28

approximately 62% of cases belong to the group of diffuse large cells tumors. High grade Burkitt-like, large cell anaplastic lymphomas, T cell-rich B-lymphomas, true T-phenotype lymphomas and primary Hodgkin's disease of the brain are very rare (Villegas et al., 1997; Haeglen et al., 2001). It is clear that REAL and WHO classifications have greatly simplified PLCNS subtyping, since the great majority of tumors can be included in only one group, but is debatable whether that simplification represents a real help, because to date, this fact is considered of a little or no clinical importance. As conclusion, using the different classifications is only of morphological value, but there are no clinical differences between the groups on each one.

Electron microscopic appearance is not different from the findings described for the subtypes of systemic non-Hodgkin lymphoma, and does not give useful information for the diagnosis. The most notable features are tumor cells containing few organelles, abundant free ribosomes, large nucleoli and scant cytoplasm (Hirano, 1975; Ishida, 1975; Houthoff et al., 1978).

Diagnosis

Even though the imaging studies and the CSF analyses can be very suggestive of this disease, the pathological confirmation is necessary. Because of the fact that most of the lesions are deeply located in the brain parenchyma, the best procedure to obtain tissue is Stereotactic biopsy (Remick et al., 1990; Jellinger and Paulus, 1992). However, the pathological study based on Stereotactic biopsy represents some problems. Firstly, because of the small size of lesions and their location, it becomes difficult for surgeon to obtain enough tissue for its correct study. Secondly, most of the patients that are submitted to a biopsy procedure have already been treated with corticosteroids. As it was mentioned earlier, steroids can be cytotoxic for neoplastic cells in lymphomas, resulting in marked shrinkage or even disappearance of tumor, becoming difficult not only the pathological analysis, but the biopsy procedure itself.

Considering that HIV-negative PCNSL is more frequent in the elderly patients, it is possible that the clinical status do not allow even a biopsy procedure. Or also, sometimes the pathological diagnosis may be inconclusive. In these cases, the diagnosis may be acceptable based only on radiological imaging and/or CSF analyses. SPECT and PET are recommended, but not indispensable. Corticosteroids should not be used as diagnostic test, because other pathological entities such as sarcoidosis or multiple sclerosis can occasionally mimic PCNSL and respond to this therapy.

As most of the imaging studies of patients with PCNSL show a growing cerebral mass (unique or multiple) with perilesional edema, along with a clear neurological deficit, in some cases it becomes unavoidable an immediate institution of a steroid regimen. As it was already mentioned, this "treatment" may cause a marked reduction or even disappearance of the tumor; that is why PCNSL is also known as

"disappearing" or "ghost" tumor. However, it has been demonstrated that disease invariable recurs within a few months and becomes poorly responsive to a second treatment with steroids (Pirotte et al., 1997). The reason for this resistance to steroid-induced apoptosis is not clear. Mutations of steroid nuclear receptors and/or hyperexpression of the anti-apoptotic protein bcl-2 have been proposed, but it seems to be other unknown factors related. On the other hand, steroids can also alter the CSF analyses (cytology and protein determination). For these reasons, patients suspected as having PCNSL should not be given steroids before histological diagnosis, unless the brain edema being a threatening problem.

Treatment

It has been clearly demonstrated that surgical resection does not contribute to survival (Murray et al., 1986; O'Neill and Illig, 1989), as a matter of fact, it has been reported that partial resection not only does not offer any advantage, but it represents an unfavorable prognostic factor.

Although PCNSL is remarkable sensitive to irradiation (response rate >90%), historical trials with patients treated with radiotherapy alone reported that more than 80% of patients relapsed within 10-14 months with a rapid fatal outcome (Filla et al., 1989; Blay et al., 2000), and this therapeutic modality offers only 12-18 months, with a 5-year survival of 3-4% (Nelson et al., 1992). However, the addition of chemotherapy increases the medial survival to about 40 months with a 22% 5-year survival rate (DeAngelis et al., 1992). Standard radiation treatment at present consists of 40 Gy to the whole brain (because the relatively high frequency of multifocal presentation in these tumors), with or without an additional boost of 10 Gy on the tumor bed. It is very important to mention that radiation must not be greater than 50 Gy, because of the high risk of postirradiation leukoencephalopathies in long-term survivors.

It is now generally accepted that all patients with PCNSL must receive chemotherapy, and this must be given before radiotherapy (Nasir and DeAngelis, 2000). No other single chemotherapeutic agent has demonstrated its effectiveness than methotrexate (MTX), which is administrated intravenously at high doses (3-8 g/m^2) to penetrate areas with an intact blood-brain barrier. This is because several studies have revealed that the majority PCNSL extensively infiltrate the brain (Lai et al., 2002), even though imaging studies do not confirm this. It is now known that MRI frequently underestimates the tumor burden in this disease, because this study only shows areas of disruption of blood-brain barrier, particularly on contrast-enhancing images, but microscopic tumor infiltration may not be apparent. The main problem with the administration of high doses of MTX is the risk of acute and late neruotoxicity (NT), which is considerable potentiated by radiotherapy. This syndrome is characterized by progressive dementia, ataxia and urinary incontinence. MRI shows cortical

atrophy and white matter density abnormalities (leukoencephalopathy) (Schlegel et al., 1999). The possibility of NT is not negligible, because it has been reported in 13-26% of the patients, but its frequency can reach 50% in patients older than 60-years (Abrey et al., 1998). In an effort to reduce this complication, there are several clinical trials exploring the use of chemotherapy as the sole modality of treatment (Freilich et al., 1996; Sandor et al., 1998), but the results are not conclusive yet.

Current therapy of PCNSL in ICP offers response rates of 85%, with a median survival of 17-44 months and overall survival of 40-70% at 2 years and 25-45% at 5 years (Paulus et al., 2000).

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