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Review

Primary angiitis of the central nervous system

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Summary

Primary angiitis of the central nervous system (CNS) is an uncommon inflammatory disorder, with highly variable clinical presentation. It needs to be differentiated from several mimickers, such as CNS involvement in systemic vasculitides, connective tissue disorders, infectious disease, and leukodystrophy as well as neoplastic diseases. The diagnosis requires a combination of clinical and laboratory investigations, multimodal imaging, and histopathological examination, which should be available for confirmation. In the present paper, the histopathological features of primary angiitis of the CNS are described and highlighted to help pathologists avoid misdiagnosis of a treatable acquired disease.

Key words: cerebral vasculitis, primary angiitis of the central nervous system, cerebral ischemia, brain biopsy

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Introduction

Vasculitides of the central nervous system (CNS) are an uncommon inflammatory disease, affecting the brain and/or the spinal cord, with an estimated annual incidence rate of 2.4 cases per 1,000,000 person/year [1].

CNS vasculitis may be primary or secondary. In a recent study on the United States (US) population, an annual hospitalization of 5.1 cases per 1,000,000 person-years for Primary Angiitis of the Central Nervous System (PACNS) has been estimated [2]. PACNS needs to be differentiated from several mimickers, such as CNS involvement in systemic vasculitides, connective tissue disorders, infectious disease, and leukodystrophy [3,4].

A few patients may present with a mass lesion, mimicking a cerebral tumor, hence a neoplastic disease must be excluded [5]. PACNS is constantly characterized by inflammation and injury of the walls of the CNS blood vessels, but it displays a highly variable clinical presentation, including headache and nonspecific and often non-focal neurological signs [6-9].

From the early clinical descriptions of PACNS in 1959 through 1986, 46 cases were identified in the literature. The disease was considered rare and highly fatal, with most patients diagnosed at post-mortem examina-

tion [10,11]. In the 1970s and 1980s, with the increasing availability of cerebral angiography, PACNS was more frequently reported. Therefore, more recently cases have been frequently defined by angiography alone [12]. Since the proposal for diagnostic criteria by Calabrese and Mallek in 1988 [13], there have been significant advances in the understanding of PACNS.

The recent European Stroke Organisation guidelines on PACNS questioned the usefulness of current diagnostic criteria and recommended caution in the interpretation of non-invasive vascular imaging compared to digital subtraction angiography and histopathological analyses [14].

To date, the diagnosis demands a combination of clinical and laboratory investigations, multimodal imaging, and histopathological analysis, which should be required for confirmation according to the diagnostic criteria by Calabrese and Mallek in 1988 [13] and by Birnbaum and Hellmann in 2009 [15]. Neuropathological examination represents the gold standard, although neuroimaging is currently the most widely used diagnostic tool, considering that brain biopsy is an invasive procedure and may produce a confounding result, owing to non-representative tissue or post-treatment effects.

In this paper, we overview the histopathological features and the clinico-radiological correlations of PACNS to help pathologists reach a correct diagnosis.

Clinical and neuroradiological features

In the early stage of the disease, the clinical presentation of PACNS is not specific, as previously reported in the main retrospective studies [6-9].

Headache and cognitive dysfunction are observed in almost 50% of patients at the onset of the disease. Further symptoms such as motor deficits, speech disorders, seizures, visual impairment, and symptoms related to spinal cord involvement are also reported. Currently, no specific clinical pattern is associated with PACNS. The median peak incidence of PACNS is within the fifth decade without significant difference in terms of sex [6-9].

Serological markers of inflammation are usually normal. Cerebrospinal fluid abnormalities are present in approximately 80-90% of cases [16].

Neuroimaging is often abnormal, including cortical and sub-cortical infarctions, intracranial hemorrhages, leptomeningeal and parenchymal enhancement, tumor-like lesions, and very rarely, a diffuse leukoencephalopathy (Tab. I) (Figs. 1, 2) [4,16-23].

In a recent report indicating the outcomes among patients with PACNS in a Nationwide United States analysis, a poor outcome at discharge was correlated with older age, male sex, presence of comorbidities and complications (i.e. pneumonia, urinary tract infection, and fluid and electrolyte disorder), and a longer overall length of hospitalization. One-third of these patients were discharged to facilities and 5% died in hospital [2].

Table I. Clinico-radiological features and histological patterns of PACNS.

Neuroradiological features	Histopathological findings
Cortical and sub-cortical infarctions Intracranial hemorrhages Leptomeningeal and parenchymal enhancement Tumor-like lesions Diffuse leukoencephalopathy	Granulomatous Lymphocytic Necrotizing

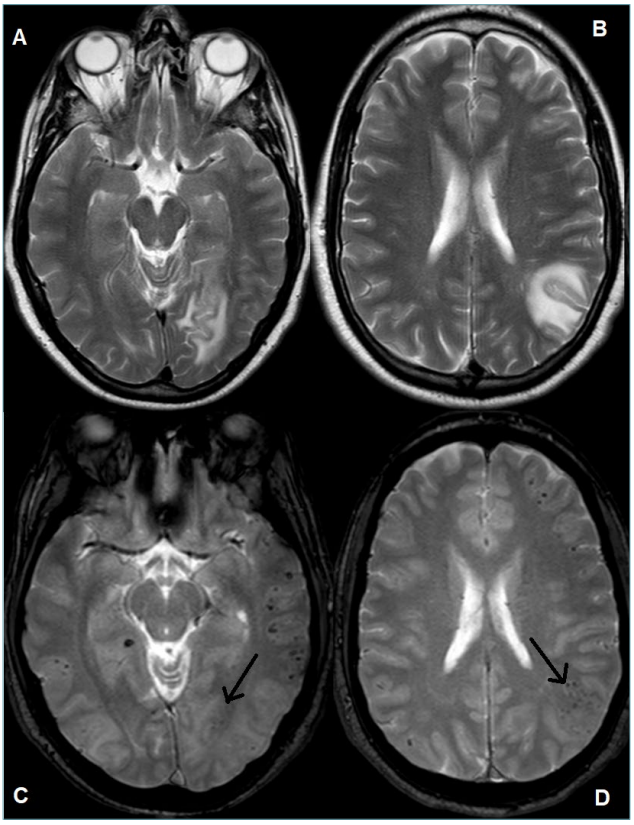

Figure 1. Axial T2 w.i. (A, B) and T2* w.i. (C, D). Note in A and B multiple asymmetric swollen white matter lesions; no areas of bleeding are seen. Microhemorrhages (arrows) are detected on T2*. Histological examination evidenced a granulomatous PACNS associated with beta-A4 amyloid deposition (the so-called Ab-related angiitis or ABRA)(not shown).

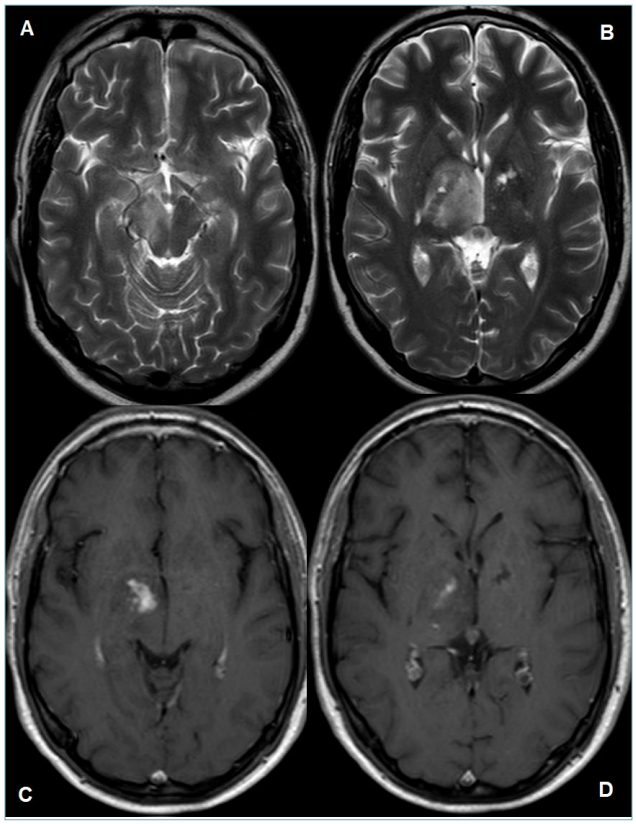

Figure 2. Axial T2 w-i (A, B), T1 w-i with contrast enhancement (C, D) show multiple infarcts in thalami and basal ganglia. Note recent infarction with edema and enhancement in the thalamic-capsular region on the right side. Histological examination evidenced a lymphocytic PACNS (see Fig. 4).

Histopathological findings

Histopathology is considered the gold standard for the diagnosis of PACNS. However, the distribution of pathological abnormalities may be focal and segmental, and thus the diagnostic yield ranges between 50% to 75% of cases [13,24,25]. Brain biopsy leads to a direct change of the therapeutic regimen in about 55% of patients [26]. PACNS involves medium-sized arteries and small vessels (leptomeningeal and parenchymal), including arterioles, capillaries, and to a lesser extent venules [27]. Though cortical samples are crucial in obtaining a neuropathological diagnosis of PACNS, it is useful to collect parenchymal and leptomeningeal specimens to enhance the possibility of achieving a diagnostic biopsy [26]. The diagnosis of vasculitis certainly requires the presence of vasculocentric transmural inflammation with damage to the vascular wall, even if histopathological findings of PACNS are quite variable. Three morphological patterns of PACNS have been recognized: granulomatous, lymphocytic, and necrotizing (Tab. I) [25].

At present it is not clear whether these patterns represent distinct diseases with overlapping clinical features or rather a broad histopathological spectrum of the same disease.

Granulomatous pattern

Granulomatous vasculitis represents the most frequent pattern of PACNS in US population: well-formed granulomas and multinucleated giant cells constitute the inflammatory population permeating and destroying the vascular walls. [25] The granulomas may be seen throughout the vascular wall from the intima to the adventitia (Fig. 3). Histochemical stains for fungi and mycobacteria should be performed to exclude an infectious etiology. In a subgroup of patients with granulomatous PACNS, the inflammatory infiltrate may be associated with beta-A4 amyloid deposition (the so-called Ab-related angiitis or ABRA) [28].

Lymphocytic pattern

Lymphocytic vasculitis is the second most common pattern characterized by predominantly lymphocytic infiltrates, with occasional plasma cells, extending through the vascular walls which appear distorted and disrupted (Fig. 4).

Lymphocytic infiltrates around/within vessel may be a poorly specific finding, observed in different CNS disorders: therefore, a histological pattern may be reliably considered suspicious for lymphocytic PACNS if the presence of vasculocentric lymphocytic infiltrate is not accompanied by significant parenchymal inflammation.

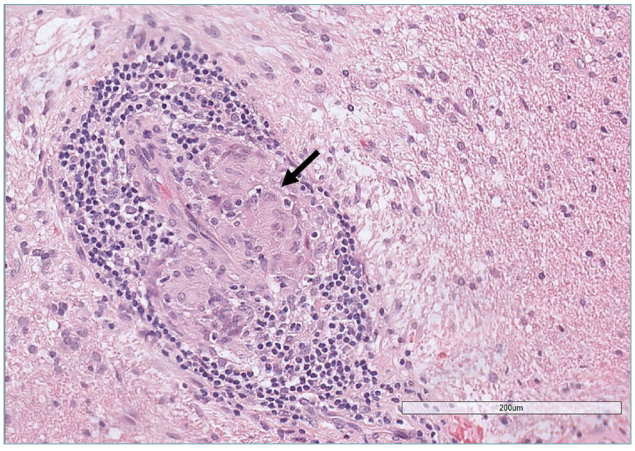

Figure 3. Granulomatous pattern showing transmural inflammation with prominent mononuclear and granulomatous adventitial inflammation (arrow) (H&E, 200X magnification).

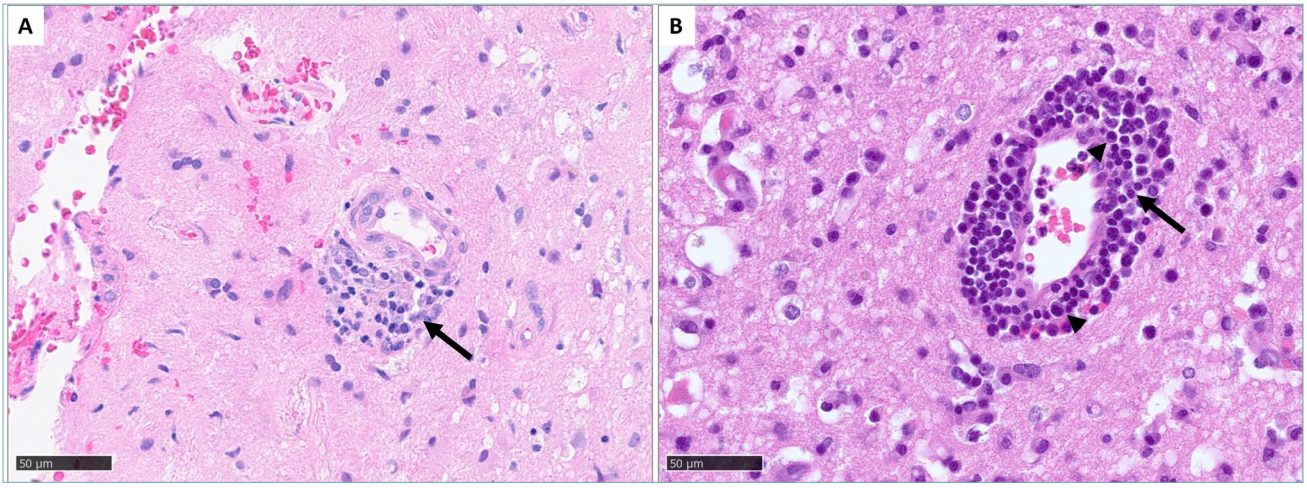

Figure 4. Lymphocytic pattern involving intraparenchymal vessels exhibiting perivascular cuffing (A) as well as transmural (B) lymphocytic infiltrates (arrow), with occasional plasma cells (arrowhead) (H&E, 400X magnification).

Necrotizing pattern

Necrotizing vasculitis is the least commonly observed pattern, featuring acute necrotizing vasculitis, with transmural fibrinoid necrosis and acute inflammation (Fig. 5). Necrotizing PACNS predominantly affects small muscular arteries with disarray of the internal elastic lamina. It should be kept in mind that in areas of acute tissue necrosis, abscess, or hemorrhage histological findings of vascular wall necrosis and neutrophilic infiltration may be encountered as a secondary phenomenon. Thus, in such cases, they should not be considered diagnostic of PACNS.

Discussion

PACNS is an uncommon disease whose rarity is partly due to the difficulty in recognizing it. The diagnosis of PACNS is usually challenging and requires a multidisciplinary approach in specialized centers. In clinical practice these patients may be more widely encountered with common working diagnoses, including high-grade glial tumors, primary CNS lymphomas, brain abscesses, infectious encephalitis, demyelination, and a variety of other tumor and non-tumor conditions [29].

For this reason, it is crucial for pathologists to be aware of the histopathological features of PACNS to make a

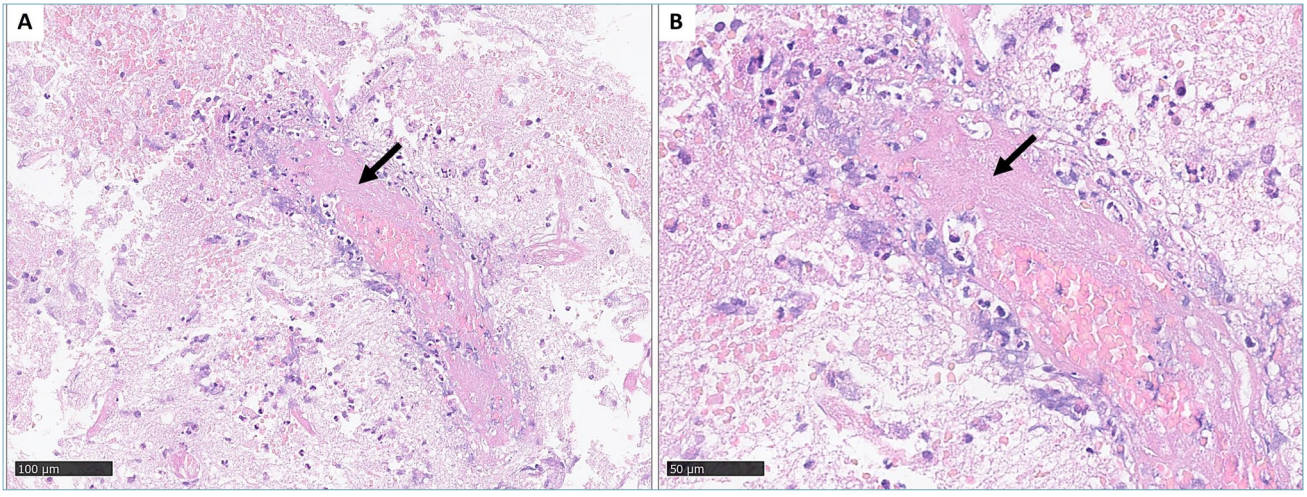

Figure 5. Necrotizing pattern showing transmural fibrinoid necrosis (arrow) with karyorrhectic debris and acute neutrophilic inflammation (H&E. A: 200X magnification, B: 400X magnification).

prompt and accurate diagnosis: in this way, clinical decision-making will be tailored to a correct understanding of the patient's health problem and may offer the best opportunity for more appropriate treatment.

There is a correlation between the size of the involved vessel and the clinical outcome: vasculitis of small cortical/leptomeningeal vessels has been associated with a more benign disease course, while the involvement of larger/proximal cerebral vessels has been observed in patients with a less favorable prognosis, who should therefore be treated more aggressively [30]. Accurate diagnosis is crucial to avoid delayed treatment and to define the population requiring longer term glucocorticoid and immunosuppressive treatment, taking into account the potential benefit and side effects of each agent [14]. To date, in most patients with PACNS the treatment protocol includes glucocorticoid therapy with the addition of an immunosuppressant, while the use of glucocorticoids alone might be considered in milder disease [14].

In addition, the histopathologic pattern seems to be correlated with the disease clinical course: there is some literature evidence that lymphocytic PACNS presents a more benign clinical course, with reduced disability and mortality compared to granulomatous or necrotizing PACNSs [31].

The pathogenesis and immunopathological mechanisms of PACNS still need to be elucidated; meanwhile, it has been reported that endosomal, mitochondrial, and ribosome dysfunction, along with alterations in protein synthesis and noncoding RNAs might be involved in PACNS [32].

Granulomatous PACNS show higher levels of genes associated with macrophage and T cells activation, high levels of long noncoding RNAs and miR-616 have been demonstrated in ABRA while lymphocytic PACNS display higher levels of genes encoding immunoglobulins [32].

In conclusion, early recognition and treatment may have a favorable impact on the clinical outcome of PACNS. When non-invasive diagnostic investigations do not drive to a definite diagnosis, brain biopsy in patients with suspected PACNS should not be delayed.

Characterization of the histopathologic phenotype of PACNS may be of great importance to improve understanding of the pathogenetic mechanisms of the disease and ultimately permit the development of novel targeted treatment strategies.

Conflict of interest statement

The authors declare no conflicts of interest.

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Authors' contributions

All authors contributed to the article and read and approved the final version of the manuscript.

Ethical consideration

As a review article, the present study is exempt from ethical approval.

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