

Primary central nervous system vasculitis: Description based on Chapel Hill Conference Consensus 2012 and a case report

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INTRODUCTION

Primary central nervous system vasculitis (PCNSV) is an uncommon form of vasculitis that predominantly affects small and medium-sized blood vessels of the brain parenchyma, spinal cord, and leptomeninges. It is difficult to estimate the true incidence rates due to the diagnostic difficulties. The diagnostic criteria recommended for the diagnosis of PCNSV have yet to be validated due to the rarity of the disease. PCNSV is among the single-organ vasculitis (SOV), and systemic diseases with cerebral vascular involvement should be excluded before the diagnosis. Initial symptoms may be acute or subacute and nonspecific. Most affected cases may present with recurrent vascular events, cognitive dysfunction, headache, and seizures. Nonspecific presentations lead to delays in diagnosis, complications, and poor prognosis. This article aims to highlight the specific clinical, laboratory, and imaging features of PCNSV and presents a case report.

Definition

Single-organ vasculitis refers to vasculitis in arteries or veins of any size in a single organ. There should be no feature of systemic vasculitis, infection, or systemic disease [1]. When vasculitis findings are observed in a single organ, if there is an impression that it is a limited form of systemic vasculitis, it is not categorized as SOV. Clinical, laboratory, and pathological features help distinguish SOV from

systemic vasculitis with isolated organ involvement [2].

The involved organ and vessel type should be included in the name [3]. Some SOV cases may show clinical manifestations of systemic vasculitis in the later stages of the disease. In this case, the categorization of the disease also changes.

Epidemiology

PCNSV is a rare disease, and the cause is unknown. Its incidence is reported as 2.4 cases per million per year [4]. It is difficult to estimate the true incidence rates due to the low awareness and diagnostic difficulties. In a study conducted in the USA, it was determined that annual hospitalization of the disease is 5.1 cases per 1.000.000 person-years [5]. It is observed twice as often in men [6,7]. Although it can be seen at any age, the median age at diagnosis is 50 years [4,7].

Clinical Features

PCNSV can affect any part of the central nervous system, so the symptoms are varied and nonspecific. Symptoms can be acute or insidious. But in most cases, there is a long prodromal period [7]. PCNSV does not have a pathognomonic clinical picture and may present with non-specific symptoms. Headache is often the first symptom but can also occur with stroke-related focal deficits [8]. There

is no typical type of headache in PCNSV, but “thunderclap headache” is rarely seen. Reversible cerebral vasoconstriction syndrome (RCVS) should be considered when this type of headache is present [8].

Other clinical conditions include; recurrent vascular events, cognitive dysfunction, and seizures. PCNSV should be considered when recurrent stroke and transient ischemic attack occur in young patients without risk factors for atherosclerosis and hypercoagulability [9].

Diagnosis (Radiology & Pathology)

The diagnostic criteria recommended for the diagnosis of PCNSV have yet to be validated due to the rarity of the disease [10]. These criteria;

- Presence of unexplained neurological deficit after detailed clinical and laboratory evaluation,
- Evidence of either vasculitic process in the central nerve system (CNS) by cerebral angiography and/or histopathology,
- Absence of evidence of another systemic vasculitis or other condition with which angiographic or pathological abnormalities may be associated.

There is no specific laboratory or imaging method for the diagnosis of PCNSV. Therefore, a comprehensive diagnostic examination is recommended. This diagnostic examination includes neuropsychiatric evaluation, blood and cerebrospinal fluid analysis, brain magnetic resonance imaging, and angiographic modalities [11].

Various neuroimaging modalities can be used to assess for both parenchymal and vascular abnormalities in the evaluation of possible PCNSV [7]. The first step in diagnosis is brain MR imaging to monitor the lesions. High-resolution magnetic resonance vessel wall imaging (HRVWI) is a promising new imaging modality for diagnosis [12,13], but its use is currently limited.

Angiographic and/or histological evidence of vasculitis is required as the next step. Although angiographic methods are not pathognomonic for PCNSV, they can detect segmental narrowing of vascular structures. It is useful in excluding alternative diagnoses such as atherosclerosis, moyamoya disease, and dissection [7].

Histopathological evaluation is still the gold standard diagnostic method for PCNSV [7]. In addition, it is very useful in terms of excluding possible causes. In a meta-analysis, biopsy demonstrated a diagnostic yield of 74.7% (95% confidence interval [CI] 64.0-84.1%) for a suspected diagnosis of PCNSV [14]. However, it should be kept in mind that segmental inflammation may reduce the sensitivity of the biopsy [9].

Differential Diagnosis

The differential diagnosis of PCNSV includes viral and bacterial infections, demyelinating and neoplastic diseases, and other inflammatory lesions of the CNS [13]. In such cases, primarily infectious and malignant processes should be excluded.

The absence of signs and symptoms suggestive of systemic vasculitis, such as fever, weight loss, rash, or peripheral neuropathy, and negative immunological marker results indicate that vasculitis is primary. Differentiation from systemic vasculitis or other autoimmune diseases is important in terms of investigating other organ involvements and choosing treatment.

Management

There are no controlled, randomized, prospective studies to guide PCNSV management. Treatment of PCNSV should be individualized according to the severity and the extent of the neurologic deficit. Usually, the recommended treatment scheme is similar to polyarteritis nodosa [7]. In addition to systemic corticosteroids, cyclophosphamide or rituximab are preferred in induction treatment. Prednisone is initiated at high doses, usually around 1 mg/kg or 60 mg daily, and tapered over months. Cyclophosphamide can be used orally or intravenously and usually lasts 3-6 months [8]. Some clinicians recommend continuing treatment with azathioprine and mycophenolate mofetil as maintenance therapy [8]. The use of oral immunosuppressive agents for maintenance after induction therapy has resulted in prolonged remission [13,15]. Symptoms, neurological findings, and radiological imaging are important in the follow-up of treatment. If treatment failure is experienced after appropriate treatment, a re-evaluation should be performed, and alternative diagnoses should be reviewed.

Prognosis

This rare form of vasculitis, which is difficult to recognize, results in severe morbidity and mortality if not treated aggressively with immunosuppressive agents. Because it is a highly heterogeneous disease, its prognosis is variable. The relapse rate is around 25-30%, but there are also publications reporting it as 55%. [16-18]. The presence of small vessel vasculitis and lesions with high gadolinium involvement is associated with a high relapse rate, whereas the use of oral maintenance therapy and the presence of headache at disease onset is associated with a low relapse rate risk. [13]. In one study, approximately 35% of cases were discharged to a rehabilitation center, while 5% died before discharge [5]. Mortality has been reported as 6-16% [16-17].

CASE PRESENTATION

Abstract

Herein, we would like to present a case of PCNSV with a focal mass lesion as a preliminary diagnosis in cross-sectional imaging and diagnosed with vasculitis by biopsy.

Keywords: Central nervous system, vasculitis, focal mass lesion.

A 41-years-old male patient presented with dysphasia, facial asymmetry, peripheral sensory deficit, and weakness in the left upper and lower extremities. The symptoms started a few months ago. There was no history of oral aphthae and genital ulcer active/scarring and uveitis. Physical examination revealed left hemihypoesthesia/hemiparesis with findings consistent with left facial paralysis. Laboratory findings were normal except for mild acute phase elevation (Crp: 10.5 mg/L, reference range 0-5 mg/L). Immunological marker results were negative (Table 1).

Brain Magnetic Resonance Imaging (MRI) revealed a focal mass lesion starting from the thalamus level to the mesencephalon in the deep white matter of the right hemisphere at the supratentorial level. The focal lesion is T2 FLAIR hyperintense and indistinguishable in T1 with patchy contrast enhancement (Figure 1). A stereotaxic biopsy was performed by neurosurgery.

After fixation of the biopsy specimen with 10% formaldehyde, it was embedded in paraffin. Afterward, sections with a thickness of 5µm were taken and examined by staining with Hematoxylin-Eosin. Inflammatory infiltration consisting of lymphocytes, histiocytes, and rare eosinophils was observed in the perivascular areas and vessel walls (Figure 2). It was determined that lymphocytes concentrated around the vascular structures were extensively stained with immunohistochemical CD3 and not with CD20. Findings were interpreted as vasculitis and secondary brain parenchyma involvement.

Pulse steroid therapy was administered at a dose of 1 g/day methylprednisolone for three days. Afterward, oral methylprednisolone at a dose of 1 mg/kg was started. As remission induction therapy, cyclophosphamide 1000 mg intravenously was given for 6 cycles every 21 days. After the completion of the induction therapy, maintenance immunosuppressive therapy was initiated with azathioprine at a dose of 2 mg/kg. Corticosteroid treatment was discontinued due to clinical and radiological complete response after one year of treatment. The maintenance immunosuppressive treatment of the patient, who was followed up in complete remission, was also discontinued at the end of the third year.

Table 1. Laboratory findings at admission

	Laboratory results	Reference range
Hemoglobin (g/dl)	15.5	12-16
Leukocyte count (10 ³ /mm ³)	8.14	4-1
Platelet count (10 ³ /mm ³)	387	150-450
C-reactive protein (mg/L)	10.5	0-5
Erythrocyte sedimentation rate (mm/h)	11	0-20
Creatinine (mg/dl)	0.96	0.7-1.3
GFR (CKD-EPI) (ml/min)	97	60-150
Proteinuria (UPCR)(mg/mg)	0.07	<0.2
Albumin (gr/dl)	4.7	3.5-5.2
ANA	Negative	-
ANCA	Negative	-
HLA-B51	Negative	-
C3 mg/dl	139	90-180
C4 mg/dl	27	10-40

GFR, Glomerular filtration rate; UPCR, urine protein/creatinine ratio; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; HLA-B51, Human leucocyte antigen-B51; C3, complement 3; C4, complement 4.

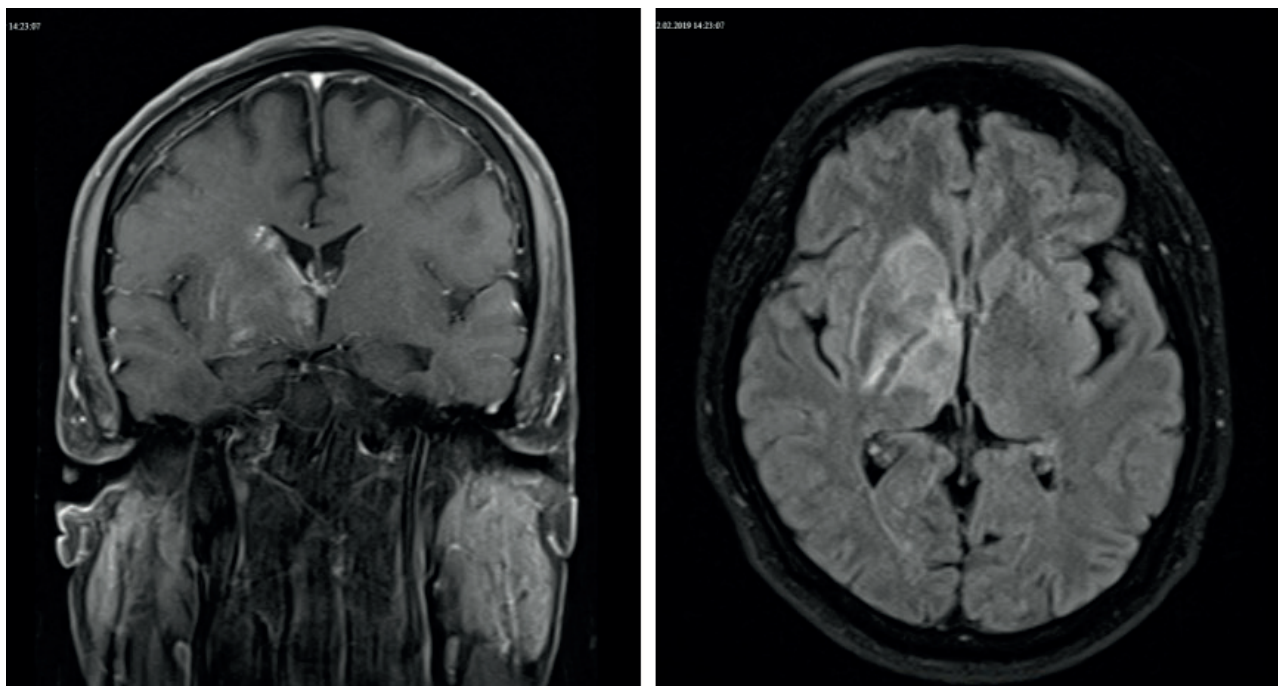


Figure 1. T2W hyperintense focal mass lesion observed in the right hemisphere on frontal and sagittal sections.

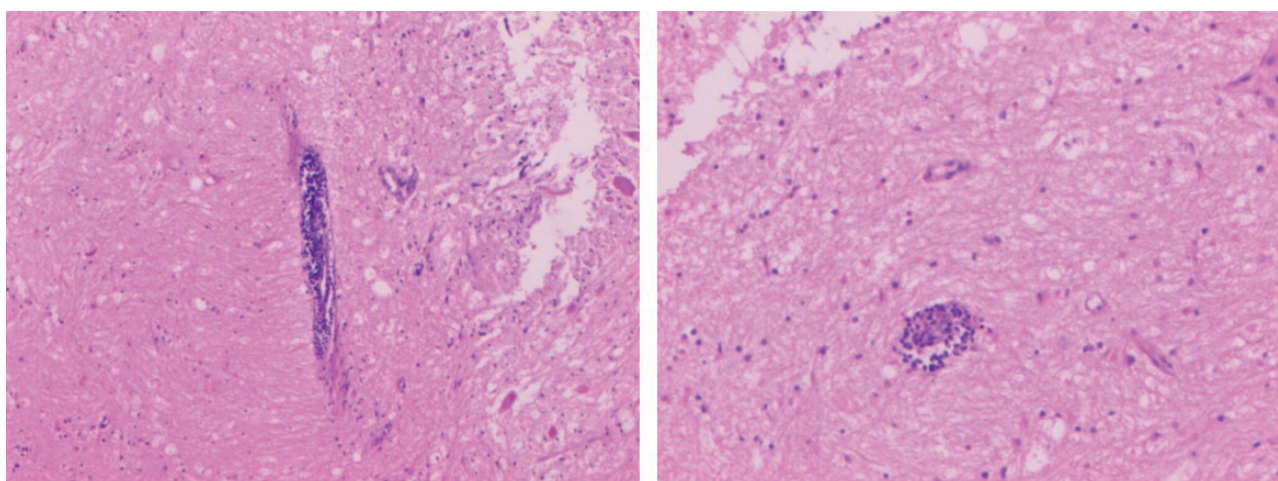


Figure 2. Inflammatory infiltration consisting of lymphocytes, histiocytes, and rare eosinophils was observed in the perivascular areas and vessel walls.

Key messages

- PCNSV is a rare form of vasculitis that causes heterogeneous clinical presentations.
- Due to the rarity of the disease, the diagnostic criteria could not be validated. They are diseases that can result in serious morbidity and mortality if not treated with immunosuppressives.
- Establishing consensus in diagnostic processes and treatment management, making algorithms, and determining their differences from secondary vasculitides are important goals.

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