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Primary Central Nervous System Angiitis Mimicking a Space-Occupying Lesion

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Abstract

Background and Purpose Intracranial space-occupying lesions are a sine qua non for neoplastic lesions; however, occasionally non-neoplastic lesions mimic neoplastic lesions, leading to diagnostic dilemmas. We report our experience with three patients who presented with a progressive hemispheric syndrome and the diagnostic considerations involved in the cases.

Materials and Methods In this retrospective study, we included three patients with primary angiitis of central nervous system (PACNS) who underwent craniotomy and biopsy, suspecting it to be mass lesions. Demographic features, clinical features, radiological features, histopathology, treatment, and clinical outcomes were studied.

Results Majority were males. The male:female ratio was 2:1. Lobar involvement was common. MR brain with contrast showed features of high-grade glioma. Despite hemispheric involvement, there was no mass effect. Perilesional edema was seen in all cases. All underwent craniotomy and biopsy; histopathology was consistent with PACNS. All patients were treated with corticosteroids and cyclophosphamide. Rituximab was used in addition to cyclophosphamide in one patient. At 2 years follow-up, two patients were in disease remission and one patient died due to disease progression.

Conclusion PACNS has a protean clinical manifestation. A high index of suspicion is required in cases with atypical clinical presentations, radiological features, and normal angiograms. Early histological diagnosis and aggressive immunotherapy with high-dose corticosteroids combined with intravenous cyclophosphamide yields favorable outcomes.

Keywords
- primary CNS angiitis
- craniotomy
- corticosteroids
- cyclophosphamide

Introduction

Central nervous system (CNS) angiitis is a rare disease with variable neurological manifestations. It depends on the size and location of the involved vessels. CNS angiitis when associated with systemic disorders like autoimmune diseases or infectious diseases is labeled as secondary CNS angiitis. Primary angiitis of the central nervous system (PACNS) is a rare lesion causing inflammation and destruction of the blood vessels in CNS. PACNS is restricted only to CNS.[1–4] Accurate diagnosis is challenging due to the rarity, presentation, and absence of any specific serological tests. Differential diagnoses include secondary angiitis, reversible cerebral vasoconstriction syndrome, and

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noninflammatory vasculopathies.[1] It has various subsets of presentations, of which tumor-like presentation is seen in 9% of these patients.[1,2]

Materials and Methods

This was a retrospective study. Three patients with a diagnosis of PACNS were included in the study (January 2017–March 2019). Demographic features, clinical features, radiological features, histopathology, treatment, and clinical outcomes were studied. All patients were thoroughly evaluated by MRI brain with contrast and MR angiogram, digital subtraction angiography (DSA), and positron emission tomography-fluorodeoxyglucose (PET-FDG). Laboratory tests included erythrocyte sedimentation rate, C-reactive protein, antibody panel assessments for ds-DNA, rheumatoid factor, antineutrophil cytoplasmic antibody, and complement levels. They were all normal for all the three patients. Thrombotic workup and hypercoagulable state workup were normal for all the three patients. HIV status was negative for all the three patients. All patients underwent craniotomy and biopsy. The diagnosis of PACNS was established in all the three cases. All cases were treated with systemic steroids and underwent immunomodulation with cyclophosphamide, and one case received rituximab. Progression-free survival (PFS) and overall survival (OS) were studied. This study has been approved by the institutional review board.

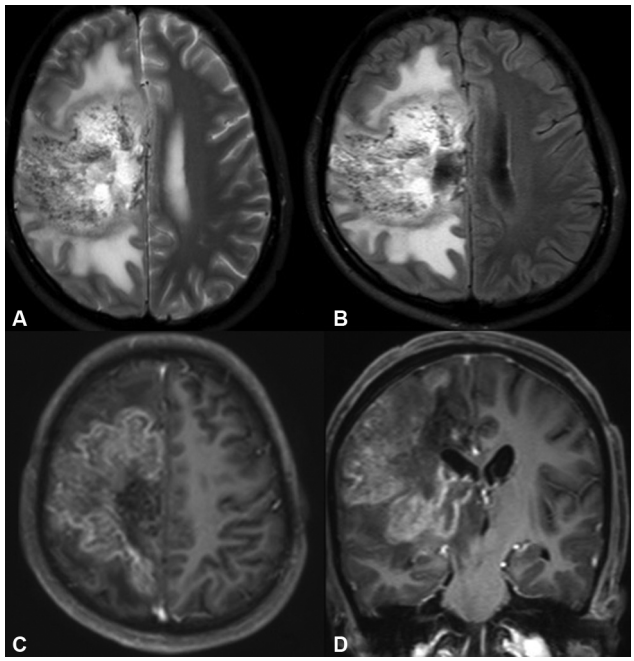

Fig. 1 (**A**, **B**) MR brain T2-weighted axial imaging showing hyperintense lesion involving the right frontal and parietal lobe with areas of microbleeds. There is extensive perilesional edema with mild mass effect. (**C**, **D**) T1-weighted axial and coronal images with contrast showing diffuse heterogeneous enhancement with the involvement of gray and white matter. There is evidence of subcortical extension into the insula and periventricular white matter. There are areas of necrosis within the lesion. Imaging features favor a mass lesion, high-grade glioma.

Results

All patients were admitted to our neurology unit. Male:female ratio was 2:1. They presented with headache and progressive hemiparesis at presentation. One patient had seizures at presentation. MR brain with gadolinium showed features of high-grade glioma in all the three patients (►**Table 1**). The lesions were hemispheric and lobar in location. There were areas of heterogeneous contrast enhancement with areas of necrosis (►**Fig. 1**). There was no significant mass effect. All patients had perilesional edema. MR spectroscopy showed lactate peak in all the cases. Susceptibility-weighted imaging (SWI) showed areas of hemorrhage within the involved hemisphere. Magnetic resonance angiography was normal. DSA was normal in all the patients. There was no evidence of vascular beading. The possibility of a high-grade lesion versus lymphoma versus gliosarcoma was considered in all the patients. The other possibilities of infectious (mycobacterial or fungal) or inflammatory disorders were considered less likely. Cerebrospinal fluid (CSF) analysis was deferred due to mass-like presentation in the setting of raised intracranial pressure. FDG-PET CT was normal in all the patients. Leptomeningeal enhancement was seen in two patients. Tissue diagnosis through a craniotomy was considered in all the patients. Histopathological examination showed areas of infarction in the cortical region, comprising foamy macrophages (with ingested myelin) and necrotic debris bordered by reactive astrocytes (►**Fig. 2A**). The adjoining region showed perivascular inflammation. The blood vessels involved were of small and medium size (►**Fig. 2B–D**). The inflammatory cell infiltrate comprised lymphocytes (CD3 + ve, CD20-ve) and histiocytes (CD68 + ve), including occasional multinucleated forms as well. There was evidence of transmural infiltration of inflammatory cells, with destruction of the blood vessel wall along with fibrinoid-like material deposition (►**Fig. 2B**). Perivascular and transmural inflammation were also noted in the leptomeninges, with extension in Virchow–Robin spaces (►**Fig. 2E, F**). Special stains for acid-fast bacilli (AFB) and fungi were negative. Immunohistochemistry was performed to rule out a lymphoid neoplasm.

Bacterial, mycobacterial, and fungal cultures were negative. Postoperative period was uneventful with no neurological worsening. All patients received intravenous (IV) methylprednisolone in the acute phase with pulsed therapy. Cyclophosphamide therapy was given for a duration of 6 months, and the drug response was assessed. This was followed by 6months of cyclophosphamide/rituximab. Patients were assessed by MR brain with contrast at follow-up. At 2 years follow-up, two patients had disease remission; one patient had progression of disease and succumbed to the disease despite aggressive immunotherapy (►**Table 2**).

Discussion

The most frequent diagnosis in patients with space-occupying lesions (SOL) is primary brain tumors like glioma, metastatic

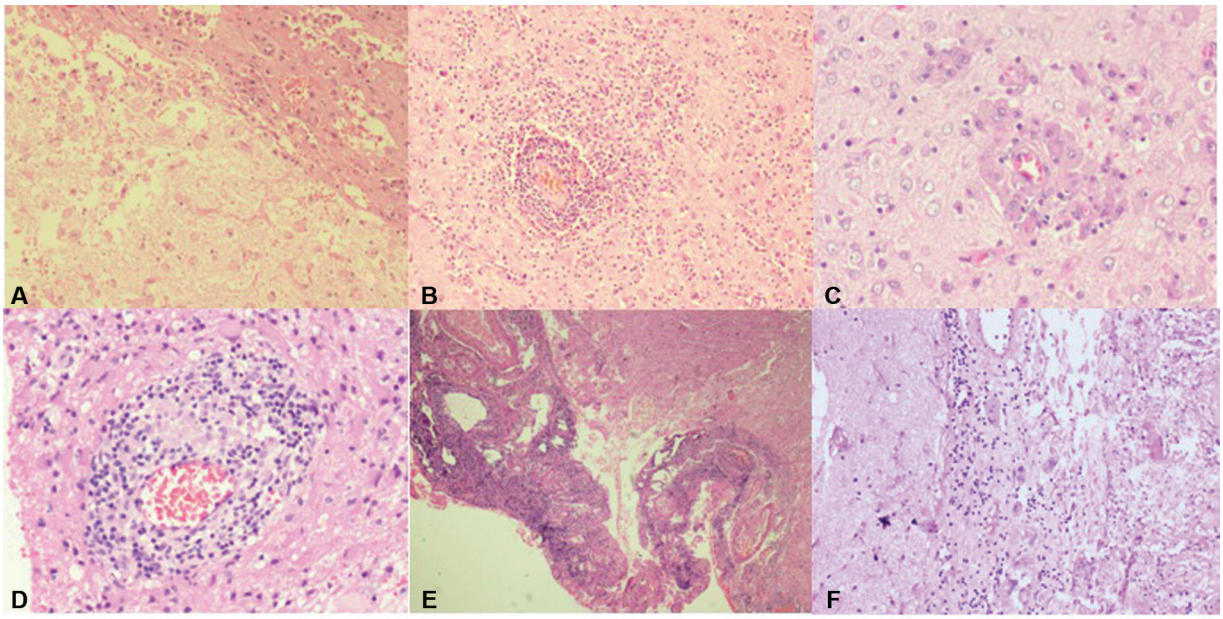

Fig. 2 Shows (**A**) nervous tissue with an infarction containing foamy macrophages bordered by reactive astrocytes, (**B–D**) different caliber blood vessels showing perivascular and transmural infiltrates of lymphocytes and histiocytes, including occasional multinucleated forms, (**E**) leptomeningeal chronic inflammation, (**F**) leptomeninges with perivascular chronic inflammation and occasional multinucleated giant cells.

Table 1 Clinical and radiological profile of our patient cohort[a]

Patient	Clinical features	MRI features	Differential diagnosis
1	Headache, right hemiparesis with right upper motor neuron facial paresis	Left hemispheric gyri swelling, with areas of heterogeneous enhancement, subtle leptomeningeal enhancement, areas of blooming on SWI images, perilesional edema, minimal mass effect	High-grade glioma, lymphoma
2	Headache associated with vomiting, blurring of vision, right hemiparesis	Left hemispheric swelling, gyral enhancement, areas of microbleed, blooming on SWI images. Areas of necrosis	High-grade glioma, lymphoma, gliomatosis cerebri
3	Progressive left hemiparesis, seizure	Diffuse enhancement of the right cerebral hemisphere, leptomeningeal enhancement was absent, areas of necrosis, prominent perilesional edema	High-grade glioma, gliosarcoma

Abbreviation: MRI, magnetic resonance imaging; SWI, susceptibility-weighted imaging.
[a]This corresponds to the clinical, radiological features and possible differential diagnosis that were considered in the current study.

lesions, lymphomas, and infections.[2] Many non-neoplastic lesions like demyelinating, noninfectious inflammatory lesions, and infective lesions can mimic brain neoplasms.[3] Establishing an early definitive diagnosis based on histopathology is paramount for optimal management of these patients.

Most cases of CNS angiitis develop secondary to systemic disease; however, if lesions are confined only to the CNS, it is referred to PACNS. PACNS accounts for 1% of systemic angiitis.[4] PACNS causes inflammation and destruction of the blood vessels of the CNS. PACNS manifests as a single large mass lesion in around 5 to 12% of cases.[5,6]

The most common manifestations are headache, episodic encephalopathy, progressive cognitive impairment, stroke, transient ischemic attacks, cranial neuropathy, myelopathy, and ataxia.[7] CT, MRI, and angiography are all useful diagnostic imaging modalities. The sensitivity of MRI is estimated at 90% or better,[8] although findings such as parenchymal or leptomeningeal enhancement, cerebral infarction, intracranial hemorrhage, and T2-weighted or fluid-attenuated inversion recovery (FLAIR) hyperintensities are not pathognomonic.[9–11] Differentiation from multiple sclerosis, gliomatosis cerebri, and primary intravascular CNS lymphoma

Table 2 Treatment outcomes[a]

Patient	Treatment	Outcome
1	Methyl prednisolone+ Cyclophosphamide	Disease in remission
2	Methyl prednisolone+ Cyclophosphamide	Disease in remission
3	Methyl prednisolone+ Cyclophosphamide + Rituximab	Disease progression at two years and succumbed to disease

[a]Long-term outcomes of the three patients after receiving immuno suppresive therapy.

may be difficult.[12] Calabrese et al[13] proposed diagnostic criteria for PACNS: an acquired, otherwise unexplained, neurological or psychiatric deficit; classic angiographic or histopathological features of angiitis within the CNS; and no evidence of systemic angiitis or any disorder that could cause or mimic the angiographic or pathological features of the disease. Brain biopsy remains the gold standard in diagnosis.[14]

Histopathological examination is essential not only for making the diagnosis of PACNS but also to rule out other mimickers, particularly of infectious or malignant nature. The histological patterns described in PACNS are granulomatous inflammation, lymphocytic inflammation, and acute necrotizing vasculitis. Granulomatous vasculitis is characterized by vasculocentric mononuclear inflammation associated with well-formed granulomas, multinucleated giant cells and, at least, focal vessel wall destruction. Lymphocytic vasculitis is characterized by marked perivascular lymphocytic inflammation with occasional plasma cells and vascular destruction. Acute necrotizing vasculitis is characterized by acute inflammation and transmural fibrinoid necrosis. A study by Sundaram et al[15] had lymphocytic dominant pattern (58%), while granulomatous inflammation was seen in 16% and necrotizing pattern in 26% cases. Suri et al[16] had granulomatous inflammation (65%) as the most common pattern, while lymphocytic vasculitis was seen in 25% and acute necrotizing vasculitis in 12.5% cases. In the series of 101 patients from the Mayo Clinic, granulomatous pattern was seen in 56%, pure lymphocytic in 20%, and acute necrotizing pattern in 22% of cases. Concurrent parenchymal ischemia/infarct was found in 51% of cases.[17] A rapidly progressive course has been reported previously to be associated with granulomatous inflammation. In the present series, although lymphocytic pattern was the most common finding, however this was associated with significant histiocytic aggregates and occasional giant cells.

Unihemispheric necrotic CNS angiitis is rarely reported in the literature. Although uncommon, PACNS should be considered in the differential diagnosis of intracerebral SOL, even though there are no specific clinical, neuroimaging, angiographic, or CSF findings that can reliably distinguish PACNS (with a presentation like a mass lesion) from other SOL. Boulouis et al[18] in their retrospective study of adult patients from the French COVAC (cohort of patients with primary vasculitis of the central nervous system) found that majority of patients (42%) had multiterritorial, bilateral distal acute stroke-like presentation involving the small and medium arteries in the carotid circulation. They had 55% of their study cohort with hemorrhagic infarctions on the MRI, 42% of their patients exhibited leptomeningeal enhancement, and 12% had tumor-like presentation.

Alrawi et al[14] in their study of 61 patients who underwent brain biopsy for PACNS found that approximately 25% of biopsies were nondiagnostic and 39% were false negative. Biopsy was conclusive in only 36/61 (59%) of the patient cohort. All these biopsy-proven patients had parenchymal lesions and 77% of them showed leptomeningeal involvement. Powers et al[19] in their review article on PACNS found very high false negative rate after biopsy for suspected PACNS. The reason for false negative biopsies could be segmental involvement of the disease within the same vessel, inadequate target selection, inadequate sample size, and subtle vascular changes not sufficient to diagnose a vasculitis. To overcome the high false negative biopsies, the current recommendations include target selection from the involved area, and large wedge biopsy (measuring 1 cm $\times$ 1 cm $\times$ 1 cm) that involves the leptomeninges, cortex and subcortical white matter.[20,21] Infections and malignancies can also cause secondary inflammatory changes and need exclusion.[19]

The most recent cohort studies on PACNS have described favorable outcomes with early recognition and aggressive therapy. In the Mayo series, out of 101 patients with PACNS, glucocorticoids alone or in combination with cyclophosphamide showed good outcomes in 81% of patients.[22] Those patients with lesser neurological deficits at presentation continued to have lesser deficits at follow-up and those with severe disability at presentation continued to have debilitating deficits at follow-up.[22]

Conclusion

A high index of suspicion is required in cases with atypical clinical presentations, radiological features, and normal angiogram. Early histological diagnosis and aggressive immunotherapy with particularly high-dose corticosteroids combined with IV cyclophosphamide improve the outcomes.

Ethical Approval Statement

This study has been approved by institutional review board, Christian Medical College, Vellore, India.

Authors' Contribution

K.P.R. contributed in the concept and design of study; E.J.G., B.P., and V.M. in data collection and analysis; E.J.

G. and V.M. in manuscript preparation; K.P.R. and V.M. in the critical revision of manuscript; and K.P.R. as guarantor.

Conflict of Interest
None declared.

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