


# A 5-year-old child presenting with tumor-like primary angiitis of the central nervous system

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## ABSTRACT

**Introduction:** Primary angiitis of the central nervous system (PACNS) is a vasculitis confined to the CNS. A small proportion of the lesions may present as a tumor-like mass, which is rarely seen in children.

**Case presentation:** A 5-year-old girl was admitted to our hospital because of an intermittent headache. Brain imaging suggested a space-occupying lesion in the right cerebral hemisphere. The final diagnosis was PACNS with a lymphocytic pattern by stereotactic brain biopsy. Her condition improved after immunotherapy.

**Conclusion:** Pediatricians should consider the possibility of PACNS when encountering intracranial tumor-like lesions. Early diagnosis of tumor-like PACNS and prompt immunotherapy could improve the long-term prognosis and avoid surgery.

## KEYWORDS

Primary angiitis, Central nervous system, Tumor, Children

## INTRODUCTION

Approximately 5% of cases of primary angiitis of the central nervous system (PACNS) are characterized by solitary tumor-like mass lesions, known as tumor-like PACNS.<sup>1</sup> PACNS mainly involves small vessels and often leads to hemorrhage and infarction owing to inflammatory cell infiltration into the vascular walls. Distinguishing tumor-like PACNS from malignant tumors is challenging. Digital subtraction angiography and brain biopsy are often necessary because the clinical presentation and cranial imaging findings are non-specific. To date, only a few cases of tumor-like PACNS in children have been reported.<sup>2-4</sup> We describe in detail a case of tumor-like PACNS confirmed by brain biopsy to remind pediatricians of the possibility of this

disease when dealing with intracranial tumor-like lesions. Early diagnosis and prompt immunotherapy can improve the prognosis and avoid surgery.

## CASE REPORT

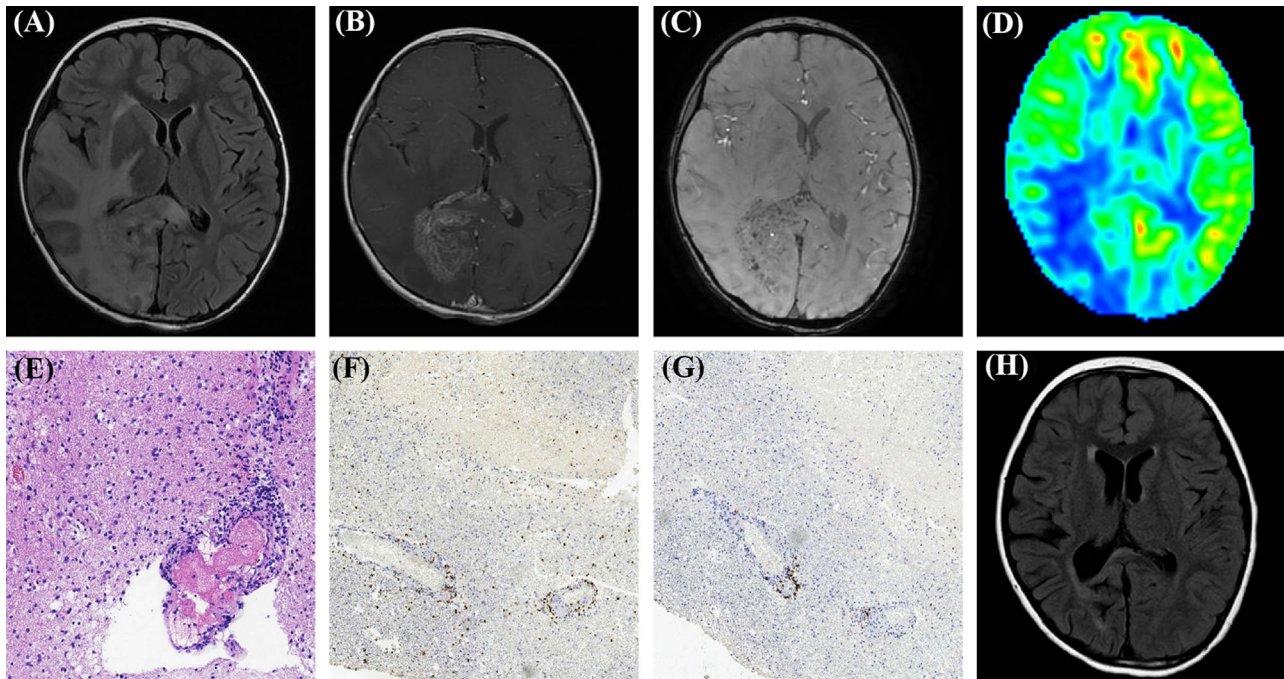
A previously healthy 5-year-old girl was hospitalized with intermittent headache, dizziness, and vomiting for 41 days. She had no history of prodromal infections, and no signs of systemic inflammatory manifestations were reported. Neurological examination revealed left homonymous hemianopsia.

Brain magnetic resonance imaging (MRI) revealed a space-occupying lesion in the right cerebral hemisphere involving

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**FIGURE 1** Images of the brain and the pathologic findings in a patient with tumor-like primary angiitis of the central nervous system. (A) Fluid attenuation inversion recovery (FLAIR) sequence suggested hyperintensity in the right cerebral hemisphere, involving the frontal, temporal, parietal, and occipital lobes, as well as the basal ganglia and ipsilateral brainstem. (B) Post-contrast gadolinium revealed irregular band-like enhancement of the focus region. (C) Susceptibility weighted imaging (SWI) showed multiple low-intensity spots. (D) The arterial spin labeling (ASL) perfusion imaging revealed hypoperfusion of the region. (E) Lymphocytes infiltrated the vascular wall, resulting in hemorrhagic infarction (HE staining,  $\times 20$ ). Immunohistochemical staining was positive for (F) cluster of differentiation-3 T cells and (G) a few clusters of differentiation-20 B cells. (H) After 24 months, the lesion shrunk significantly, with brain atrophy in the right cerebral hemisphere on the FLAIR sequence.

the frontal, temporal, parietal, and occipital lobes, as well as the ipsilateral brainstem, and the basal ganglia. Part of the lesion showed significant irregular band-like enhancement on T1 contrast-enhanced MRI. Multiple microbleeds in the lesion were detected by susceptibility-weighted imaging (SWI). Findings with brain magnetic resonance angiography and magnetic resonance venography were normal. Arterial spin labeling (ASL) suggested hypoperfusion in the lesion (Figure 1A–D).

Further examination was performed considering that the intracranial space-occupying lesion might be inflammation mimicking a malignant tumor. Cerebral spinal fluid (CSF) examination revealed an increase in CSF opening pressure of 380 mmH<sub>2</sub>O. The protein content of the CSF was 1079 mg/L (250–450 mg/L), and the white blood cell count was  $16 \times 10^6/L$  ( $0\text{--}10 \times 10^6/L$ ). The results of an immunological examination of the CSF, including the immunoglobulin G index, oligoclonal bands, anti-aquaporin-4 antibody, and myelin oligodendrocyte glycoprotein antibody, were negative. CSF cytological analysis revealed several lymphocytes and monocytes, but no malignant neoplastic cells. Metagenomic next-generation sequencing of the CSF showed no evidence of bacterial, fungal, or parasitic infections.

Routine laboratory test results for complete blood count, C-reactive protein, erythrocyte sedimentation rate, serum ferritin, and D-dimer all were unremarkable. Autoimmune antibodies were tested to identify the systemic rheumatic disease but no positive results. Pathogens indicating infectious diseases, such as *Treponema pallidum*, *Mycobacterium tuberculosis*, human immunodeficiency virus, fungi, and parasites were screened, but none were identified.

The patient had a subacute onset, elevated leukocytes in the CSF, multiple microbleeds in the tumor-like area, hypoperfusion of the lesion on ASL, all of these alerted us the intracranial lesion might be inflammatory. However, it was still necessary to rule out intracranial malignancies. Therefore, a stereotactic biopsy was performed by a neurosurgeon, and the target area was the right occipital lobe lesion where enhancement was present. Histopathology of the biopsy specimen showed lymphocyte infiltration in the vascular wall and perivascular area. Immunohistochemical staining showed inflammatory infiltration, mainly a cluster of differentiation-3-positive T cells and a few clusters of differentiation-20-positive B cells, which indicated a lymphocytic pattern. The pathological findings were consistent with PACNS (Figure 1E–G).

Finally, the patient received methylprednisolone and six cycles of intravenous cyclophosphamide followed by 18 months of maintenance treatment with mycophenolate mofetil. There were no new-onset neurological symptoms; however, homonymous hemianopsia remained after a 24-month follow-up. Imaging suggested atrophic change in the right cerebral hemisphere (Figure 1H).

## DISCUSSION

PACNS is a rare inflammatory disease, with an estimated annual incidence of approximately 2.4 per million.<sup>5</sup> Approximately 5% of primary CNS vasculitis cases manifest as a tumor-like mass lesion.<sup>1</sup> It is speculated that some individuals with a genetic predisposition have an increased risk of vasculitis when they are exposed to a specific antigen that “triggers” the immune system.<sup>6</sup> Tumor-like PACNS should be considered an important differential diagnosis for intracranial mass lesions, and since 2008, this has been considered a subtype of PACNS.<sup>1</sup>

Similar to PACNS in adults, PACNS in children usually has a subacute onset. Headache and stroke are the most common manifestations.<sup>7</sup> In adults, tumor-like PACNS is more likely to be characterized by seizures, while headache and transient ischemic attacks are relatively rare.<sup>8,9</sup> However, it is unknown whether this exists in children.

MRI findings of tumor-like PACNS are sensitive but not specific. The lesions in patients with PACNS usually show uneven enhancement on T1 contrast-enhanced MRI. It was reported that enhancement of intracranial lesions in tumor-like PACNS was more common than that in non-tumor-like PACNS.<sup>8,9</sup> One possible mechanism for the formation of the tumor-like lesion is the infiltration of inflammatory cells in the perivascular and parenchymal areas, leading to the breakdown of the blood-brain barrier formed by small vessels, resulting in enhanced tumor-like lesions.<sup>10</sup> To date, the majority of the reported lesion have been located in the supratentorial subcortical or deep white matter.<sup>11</sup> Intracranial tumor-like lesions could be single or multiple. A retrospective study of 10 cases of tumor-like PACNS showed that the proportion of patients with single and multiple lesions was similar.<sup>8</sup> A study from the Mayo Clinic suggested that approximately 83% of multiple lesions were located in both hemispheres.<sup>9</sup>

Typical angiographic changes in PACNS are segmental narrowing, occlusion, or dilation of multiple small arteries with a “beaded” appearance.<sup>12</sup> Traditional magnetic resonance angiography and digital subtraction angiography findings might be normal because PACNS mainly involves small vessels. Alrawi et al.<sup>13</sup> retrospectively evaluated 14 cases of adults with PACNS, nine (64%) cases showed normal angiographic findings. In tumor-like PACNS, it appears that multiple bilateral infarctions and positive angiographic

changes are less frequent.<sup>9</sup> Our patient underwent a brain biopsy without undergoing angiography, considering the latter might be negative. Because small vessels in PACNS are prone to rupture with hemorrhage, SWI is important for the diagnosis of PACNS. The multiple low-intensity areas on SWI were consistent with the characteristics of small-vessel vasculitis in this patient. Muccio et al.<sup>14</sup> found that perfusion-weighted imaging was of great value in distinguishing tumor-like PACNS from tumors, as the former often shows decreased blood perfusion in the lesion, in contrast to the latter. The focal area of our patient had a significant decrease in blood flow on ASL suggesting inflammation rather than the tumor.

The diagnostic criteria for adult PACNS include acquired neurological or psychiatric symptoms, angiographic or histopathological features of vasculitis, and the absence of secondary vasculitis from systemic disease.<sup>15</sup> Brain biopsy is the gold standard for diagnosis for the lack of specificity of angiography. However, owing to the multifocal and segmental distribution of the involved vessels, the sensitivity of brain biopsy is only 75%.<sup>16</sup> Therefore, the diagnosis still requires a comprehensive evaluation of the clinical manifestations and auxiliary examinations. Among the cryptogenic neurological diseases, the most frequently diagnosed by brain biopsy is PACNS.<sup>17</sup> To improve the diagnostic rate, biopsy specimens must contain leptomeninges and gray and white matter tissues. Histopathological types comprise granulomatous, lymphocytic, and necrotizing patterns. The granulomatous pattern is the most frequently reported, accounting for approximately 53%–61.5% of cases.<sup>1,5</sup> The histopathology of this patient suggested lymphocytic vasculitis, which was consistent with previously reported cases in children.<sup>2,7</sup> More research are needed to identify the histopathological features of tumor-like PACNS in children.

PACNS is a treatable disease; however, because of the rarity, treatments are based on prior clinical experience owing to the lack of randomized controlled trials. It is unclear whether immunosuppressive therapies other than corticosteroids are required within the first episode of the disease. Most researchers use steroids and cyclophosphamide in combination for the first 6 months of the induction period, and use methotrexate, azathioprine, or mycophenolate for prolonged maintenance therapy.<sup>18,19</sup> For our patient, we selected mycophenolate as an immunosuppressive agent for maintenance therapy. No obvious adverse effects were observed.

In conclusion, we remind pediatricians to consider the possibility of PACNS when encountering intracranial tumor-like lesions. Brain biopsy is the gold standard for diagnosis. SWI and ASL examinations appear to be of value in differentiating tumor-like PACNS from tumors.

## CONSENT FOR PUBLICATION

Written informed consent was obtained from the parent of the patient.

## CONFLICT OF INTEREST

The authors declared no conflicts of interest.

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