

Seizure syndrome as a first manifestation of solitary tumor-like mass lesion of PACNS

Two case reports

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Abstract

Rationale: Primary angiitis of the central nervous system (PACNS) is an inflammatory disease involving cerebrovascular and parenchymal, and solitary tumor-like mass lesion of PACNS (TLML-PACNS) is frequently misdiagnosed as neoplastic or other inflammatory diseases. However, seizure syndrome as a first manifestation of TLML-PACNS has rarely reported before.

Patient concerns: Here, we report 2 cases of seizure syndrome, which was the first sign that presented prior to the diagnosis of TLML-PACNS by brain biopsy.

Diagnoses: A mass lesion in the white and gray matters was detected by magnetic resonance imaging. The pathology for leptomeningeal lesion biopsy observed a transmural inflammation of the artery, with T lymphocyte infiltration. Patients were diagnosed with PACNS and epileptic seizure by biopsy and electroencephalogram.

Interventions: Patients were treated with glucocorticoid pulse therapy for 3 days, and subsequently oral prednisone was continued, in combination with immunosuppressant.

Outcomes: Luckily, both two patients were improved after treatment, and only mild cognitive impairment remained without adverse event.

Lessons: Patient with mass lesion in CNS, which is similar to tumor, presented with seizure, headache, or cerebrovascular events without any other risk factors for stroke or tumor, should be considered the feasible with the disease of TLML-PACNS.

Abbreviations: ANA = antinuclear antibody, ANCA = antineutrophil cytoplasmic antibody, Cho = choline, CRP = C-reactive protein, CSF = cerebrospinal fluid, CT = computed tomography, CyP = cyclophosphamide, DWI = diffusion-weighted imaging, EEG = electroencephalogram, ESR = erythrocyte sedimentation rate, FLAIR = fluid-attenuated inversion recovery, HIV = human immunodeficiency virus, IgG = immunoglobulin G, MCA = middle cerebral artery, MRA = magnetic resonance angiography, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy, OB = oligoclonal bands, PACNS = primary angiitis of the central nervous system, QALB = albumin quotient, RF = rheumatoid factor, TLML-PACNS = tumor-like mass lesion of PACNS, WBC = white blood cell.

Keywords: case report, central nervous system, primary angiitis, seizure, tumor-like lesion

1. Introduction

Primary angiitis of the central nervous system (PACNS) is a rare granulomatous vasculitis confined to the CNS that affects all age groups, with all the vessels of CNS invaded exclusively, and it

seems most common in medium- to small-sized vessels. The disease was first described by Cravioto and Feign in 1959, and its incidence is 2.4: 1000,000, with the ages range from 37 to 59 years.^[1,2] Solitary tumor-like mass lesion of primary angiitis of the CNS (TLML-PACNS) is a rare subtype of PACNS, and only

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This study was approved by the Institutional Review Board of Renji Hospital, School of Medicine, Shanghai Jiao Tong University. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

D-SZ and X-LY have contributed equally to the manuscript.

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4% of PACNS patients with the characteristic of tumor-like mass lesion.^[3] Accordingly, quite a few patients with TLML-PACNS were misdiagnosed as neoplastic or other inflammatory diseases in clinical practice.

The manifestations of TLML-PACNS are diverse. It can present with nonspecific symptoms such as headache, vomiting, cognitive decline, and behavioral disorders in the early course of the disease. As the disease progresses, multifocal neurologic deficits appear apparently in patients with TLML-PACNS. Previous studies showed that persistent neurological deficit or stroke can occur in 40% of the patients, transient ischemic attacks have been reported in 28% of patients, and aphasia and visual field deficits are commonly seen as well.^[2]

Seizure syndrome as a first manifestation of TLML-PACNS has been rarely reported before, although seizures have been reported in 16% of the patients during the disease course. Here, we report 2 cases of seizure syndrome, which was the first sign presented prior to the diagnosis of TLML-PACNS by brain biopsy. The paper describes clinical characteristics of 2 cases and discusses differential diagnosis by reviewing relevant literatures.

2. Case report

2.1. Case 1

A previously healthy 31-year-old man was admitted to our hospital presenting with recurrent unconsciousness accompany with right limbs convulsions for 12 days duration. Clinical manifestation showed recurrent unconsciousness, right limbs convulsions, aconuresis, or encopresis, which sustained 3 to 8 min. Subsequently the patient felt severe headache, and nausea after remission, and these symptoms could disappear after a rest within 24h. He reported no blurred vision, slurred speech, physically disability, or limb's numbness. He has no history of infection and vaccination within 6 weeks, and he has no other medical history. His family has no hereditary diseases. The patient was a primary school teacher. He was not married and reported no recent sexual contacts or recreational drug use. He drank alcohol and smoked occasionally.

The physical and neurological examinations were unremarkable. Serum C-reactive protein (CRP) was 11.78mg/L (normal range, 0–10), and erythrocyte sedimentation rate (ESR) was 18 mm/h (normal range, 0–15, Westergren method). Serum anti-neutrophil cytoplasmic antibody (ANCA), antinuclear antibodies (ANAs), rheumatoid factor (RF), antidouble-stranded DNA, cryoglobulins, and human immunodeficiency virus (HIV) testing were negative. Lumbar puncture showed the patient's intracranial pressure was 190mm Hg (normal range, 80–180), and cerebrospinal fluid (CSF) protein was 0.48g/L (normal range, 0–0.45). Additional testing of the CSF, including white blood cell (WBC), glucose, immunoglobulin G (IgG) index, oligoclonal bands (OB), and virus were negative. Other laboratory findings including complements 3 and 4 were within normal range, and no other clinically significant findings were noted.

A 24h electroencephalogram (EEG) test showed that complex, low-moderate amplitude δ waves occurred frequently in the left temporal lobe, and θ waves were sporadic in other lobes. Brain computed tomography (CT) plain showed a hypodensity space-occupying lesion with surrounding edema in cortex and subcortical of the left temporal lobe, and white matter hemorrhages also could be seen (Fig. 1A). Brain magnetic resonance imaging (MRI) showed that the lesion was hyperintensity on fluid-attenuated inversion recovery (FLAIR) sequences

(Fig. 1B). Brain magnetic resonance spectroscopy (MRS) showed that the metabolic peak of choline (Cho) within the lesion increased (Fig. 1C). Magnetic resonance angiography (MRA) suggested a complete occlusion in the third segment of the left middle cerebral artery (MCA) (Fig. 1D). An intensity change of the lesion on MRI T1, T2, diffusion-weighted imaging (DWI), and Gd-enhanced were showed in Fig. 1E–H, respectively. Mixed hyperintensity was presented on MRI T1 and T2 images, and hyperintensity was observed on DWI and Gd-enhanced images. Four weeks later, compared with previous images, the hyperintensity of the mass lesion was decreased on T1, T2, DWI, and Gd-enhanced images, respectively (Fig. 1I–L). A biopsy of leptomeningeal lesion before treatment was performed. Hematoxylin and eosin staining revealed a lymphocytic infiltrate targeting the vascular wall of a small muscular artery, with the intima hyperplasia and luminal stenosis (Fig. 2A). Immunohistochemical staining revealed a lot of T lymphocyte infiltrate within the lesion (Fig. 2B and C).

The patient was diagnosed with PACNS and epileptic seizure by biopsy and EEG. Intravenous pulse methylprednisolone 1g daily was given for 3 days, and epileptic seizure symptoms quickly disappeared, subsequently oral prednisone was continued at high dose (1 mg/kg per d) for 4 weeks in combination with cyclophosphamide (CyP) 2mg/kg per d for a total 6 months. Fortunately, the patient's condition was stable, and only mild memory impairment remained without adverse event 7 months later.

2.2. Case 2

A 22-year-old man was admitted to our hospital with partial seizures and progressive declined cognitive for 5 months duration. Clinical manifestation showed Jacksonian epilepsy, first weakness in the right thumb, occasionally the corner of the mouth, and then marched over a few seconds to the entire right hand, feet or facial muscles, usually followed by right limbs' paralysis for several hours. Meanwhile, the patient complained poor memory and mental disorders. He reported no loss of awareness. He has no brain injury or viral infections history such as HIV, hepatitis B and C, and his family has no hereditary diseases. His medications included the oxcarbazepine tablets (300mg orally twice per day) and levetiracetam tablets (500mg orally twice per day). The patient was a senior at university. He reported no history of recreational drug use, and he never drank alcohol and smoked.

The physical and neurological examinations were normal. Serum CRP was 10.52mg/L (normal range, 0–10), and ESR was 22mm/h (normal range, 0–15, Westergren method). Serum ANCA, ANA, RF, and HIV testing were negative. Lumbar puncture showed the patient's intracranial pressure was 210mm Hg (normal range, 80–180), CSF protein was 0.85g/L (normal range, 0–0.45), IgG index was 0.8 (normal range, 0–0.7), and albumin quotient was 11.5×10^{-3} (normal range, 0 to 7×10^{-3}). Additional testing of the CSF including WBC, glucose, OB, and virus were negative. Other laboratory findings were within normal range, and no other clinically significant findings were noted.

A 24h EEG test showed that low-moderate amplitude δ waves and θ waves arisen from the precentral gyrus area of the brain, which was an abnormal brain wave pattern that signified seizure activity. Brain CT plain showed a space-occupying mass lesion with surrounding edema in cortex and subcortical of the left temporal lobe (Fig. 3A). The mass lesion involving both

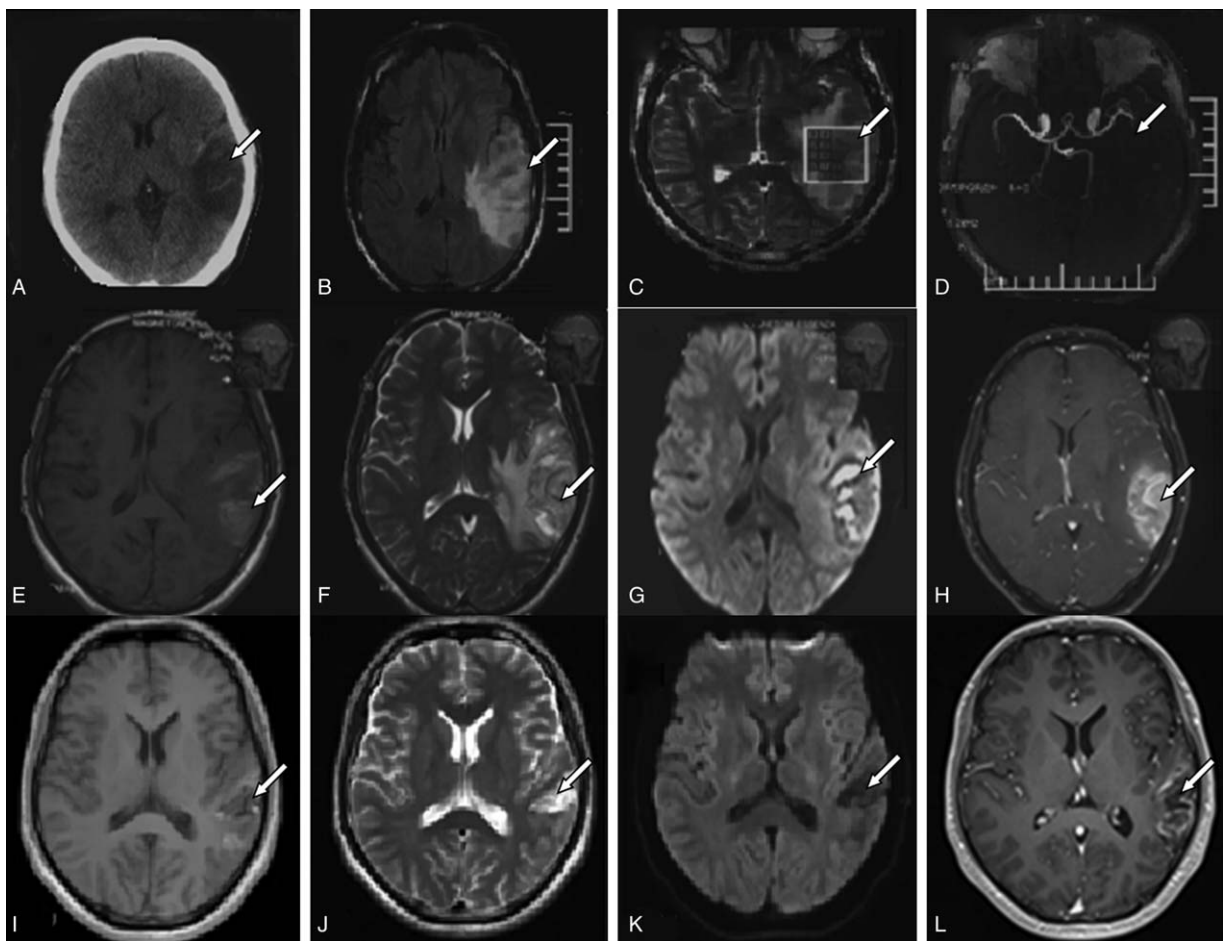


Figure 1. Case 1. Image features of the mass lesion. A mass lesion was in cortex and subcortical of the left temporal lobe. Hypodensity space-occupying lesion with surrounding edema and white matter hemorrhages on computed tomography plain (A), hyperintensity on fluid-attenuated inversion recovery sequences (B), decreased metabolism of choline on magnetic resonance spectroscopy (C), and an occlusion in the third segment of the left middle cerebral artery on magnetic resonance angiography (D). Mixed hyperintensity was presented on magnetic resonance imaging T1 and T2 images, and hyperintensity on DWI and Gd-enhanced images (E–H). Two weeks later, the hyperintensity of the mass lesion was decreased on T1, T2, DWI, and Gd-enhanced images (I–L). DWI = diffusion-weighted imaging.

white and gray matters was hypodensity on brain MRI T1 image, hyperintensity on MRI T2 image, and mild hyperintensity on MRI Gd-enhanced image (Fig. 3B–D). MRA detected a severe stenosis in the distal bifurcation of the left

MCA (Fig. 3E). Fifty days later, CT and MRI showed that the volume and mass effect of the lesion decreased. The lesion were equidensity on brain CT plain, hypodensity on brain MRI T1 image, mild hyperintensity on MRI T2 image, no enhanced

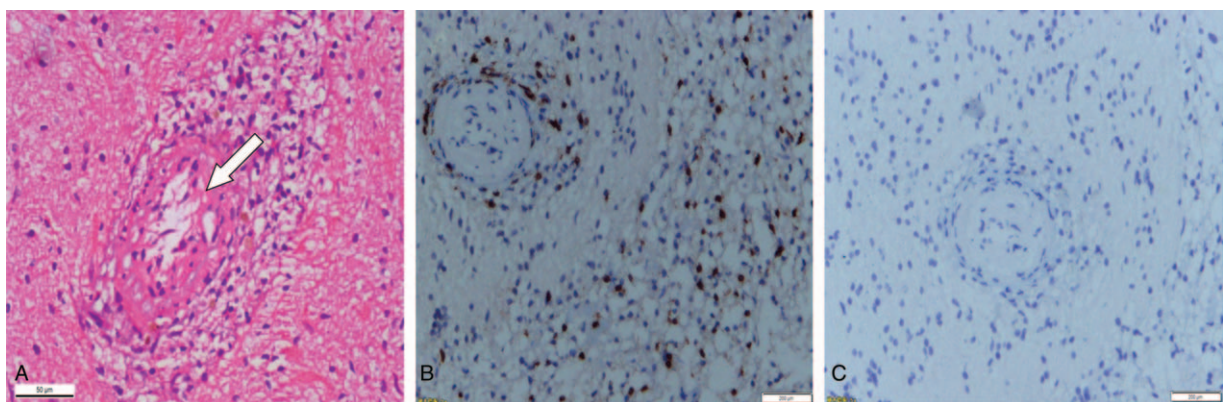


Figure 2. Case 1. Pathological characteristics of a leptomeningeal lesion. A biopsy of leptomeningeal lesion revealed a lymphocytic infiltrate targeting the vascular wall of a small muscular artery, with the intima hyperplasia and luminal stenosis by hematoxylin and eosin staining (A). Immunohistochemical staining revealed that a lot of T lymphocyte infiltrated within the lesion (B and C).

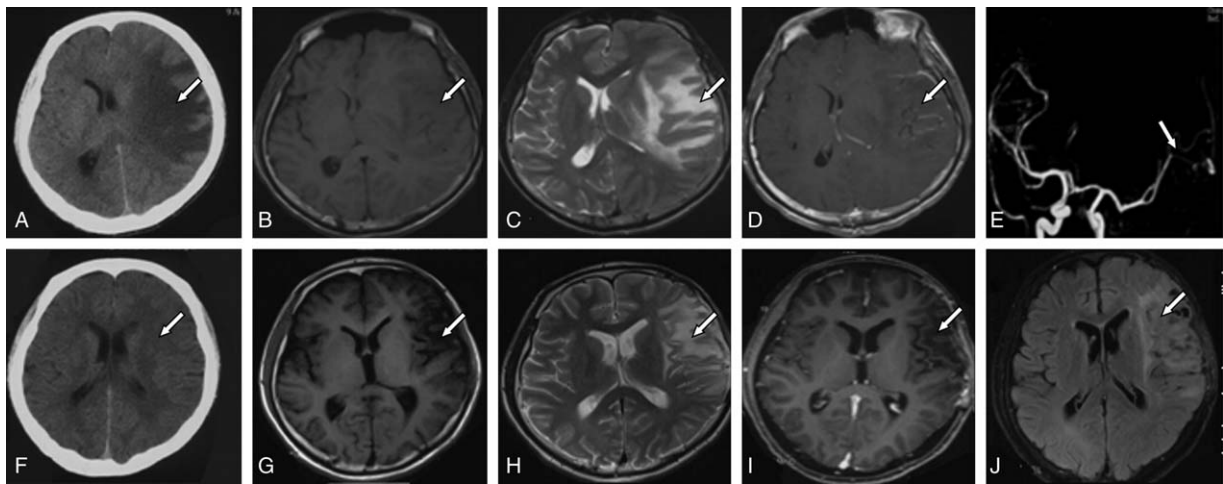


Figure 3. Case 2. Image features of the mass lesion. A space-occupying mass lesion involved with white and gray matter was detected in cortex and subcortical of the left temporal lobe. Hypodensity on brain CT plain (A), isointensity on brain MRI T1 image (B), hyperintensity on MRI T2 image (C), mild enhancement on MRI Gd-enhanced image (D), and a severe stenosis in the distal bifurcation of the left middle cerebral artery on magnetic resonance angiography (E). Fifty days later, a followed up CT and MRI showed that the intracranial mass effect of the lesion was significantly decreased on CT, MRI T1, T2, Gd-enhanced, and fluid-attenuated inversion recovery images (F–J). CT = computed tomography, MRI = magnetic resonance imaging.

signal on MRI Gd-enhanced image, and mild hyperintensity on MRI FLAIR image (Fig. 3F–J). A biopsy of leptomeningeal lesion before treatment detected a transmural inflammation of the artery, with lymphocyte infiltration by hematoxylin and eosin staining (Fig. 4A). Immunohistochemical staining demonstrated T lymphocyte activation and no evidence of B lymphocyte within the lesion (Fig. 4B and C).

The patient was diagnosed with PACNS and epileptic seizure by biopsy and EEG. He was administered with methylprednisolone 1g daily intravenously for 3 days, then tapered over 25 days to prednisone 30mg daily by oral administration, and the treatment was maintained for 6 months duration. The patient was followed up, and most of symptoms were relieved in 50 days after corticosteroid therapy, including the intractable seizures, no adverse event was observed, and the patient was able to return to work again in spite of mild cognitive impairment.

3. Discussion

TLML-PACNS is frequently misdiagnosed as neoplastic or other inflammatory diseases. However, seizure syndrome as a first manifestation of TLML-PACNS has rarely reported before. Here, we report 2 cases of seizure syndrome, which was the first sign that presented prior to the diagnosis of TLML-PACNS by brain biopsy.

Clinical manifestations of TLML-PACNS are diverse, and the onset varies from acute insidious to slowly progressive. Focal and diffuse neurological deficits' symptoms such as infarction, headache, and seizure are the predominant clinical features of TLML-PACNS. Epileptic seizure is mostly happened in TLML-PACNS patients with lesions lied in cortex and subcortical of the temporal lobe. It may be caused by the active inflammatory stimulation and the significant intracranial mass effect of a mass lesion. The exact etiology of TLML-PACNS is unknown, and it has been reported with amyloid angiopathy.^[4]

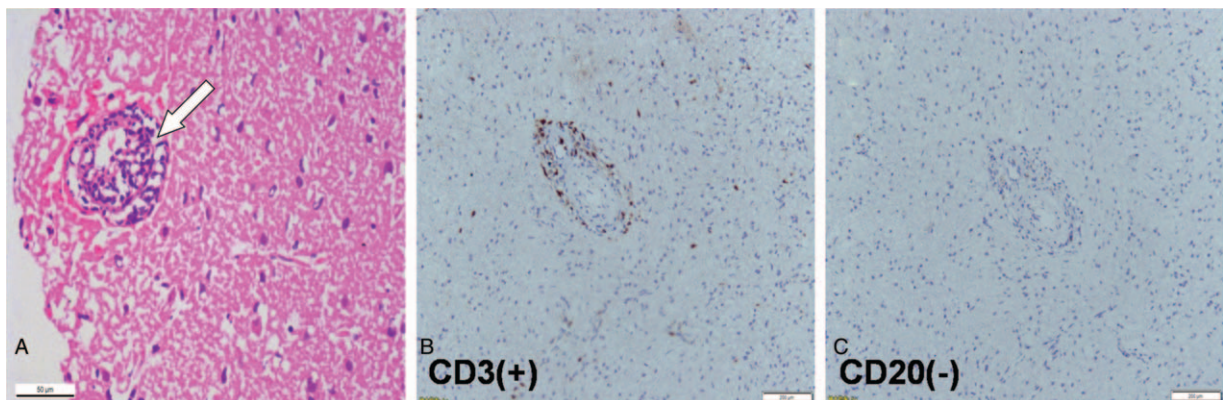


Figure 4. Case 2. Pathological characteristics of a leptomeningeal lesion. A biopsy of leptomeningeal lesion detected a transmural inflammation of the artery, with lymphocyte infiltration by hematoxylin and eosin staining (A). Immunohistochemical staining demonstrated T lymphocyte activation and no evidence of B lymphocyte within the lesion (B and C).

Brain biopsy (nondominant temporal lobe tip along with overlying leptomeninges) is the gold standard for the diagnosis of TLML-PACNS. Granulomatous, lymphocytic, and necrosis were the histopathological presentations for TLML-PACNS, and granulomatous was the most frequent (58%) change, and close to 50% was of β 4 amyloid deposition.^[3,4] In our study, both of the 2 patients' lesions showed CD3+ and CD20- by immunohistochemical staining, which suggested T lymphocyte infiltration but not B lymphocyte infiltration.

Cerebral angiography can support the diagnosis of TLML-PACNS but has low sensitivity and specificity, and MRI is the neuroimaging of choice in most hospitals. The typical feature of TLML-PACNS is that single stenotic areas in multiple vessels are more common than multiple stenotic areas in a single vessel.^[5] Abnormal imaging findings were seen in 90% to 100% of the patients, and cerebral cortex, deep white and gray matters' changes were commonly reported on CT and MRI.^[6] Supratentorial lesions with hyperintensity on FLAIR and T2-weighted MRI were the most frequent manifestation. Therefore, a tumor-like mass lesion in CNS with imaging features of signal alteration, contrast enhancement, infiltrating adjacent structures, and vasogenic edema surrounded should be considered the possibility of TLML-PACNS.

Differentiation between tumor-like lesions and tumors of the CNS was essential for medical intervention strategy. First, intracranial tumors, the following types of tumors may display as mass lesions on MRI: high-grade gliomas, glioblastoma multiforme, and primary central nervous system lymphomas. The Ki-67 index for most tumors was high, but low for inflammation lesions. Furthermore, the atypical cells may be detected by CSF cytology in patients with intracranial tumors. The relative regional blood volume of high-grade gliomas in the periphery was increased, and most of lymphomas were isodense or hyperdense on CT, and slightly restricted on diffusion.^[7] Second, intracranial abscess, which has the following features: abscess revealed predominantly as round, closed-ring-like enhancement, and thicker part of the wall toward the direction of the cortex; restricted diffusion of the center part could be presented, with apparent diffusion coefficient diminished markedly; low relative regional blood volume of necrotic wall was a characteristic on perfusion imaging; in addition, increased lactate, amino acids, and a dual rim sign were displayed on MRS and susceptibility weighted imaging, respectively.^[8] Furthermore, constitutional features, such as fever, were the common concomitant symptom, and the lesion was reduced after several weeks of antibiotic treatment. Third, inflammatory pseudotumor, the most common neuroimaging manifestation, involved the brain infrequently. On MRI, iso- to hyperintense lesions were on T1, interdigitation with the adjacent cortex was on T2, and Cho peak was increased on

MRS.^[9] Furthermore, PACNS should be distinguished from secondary vasculitis of the CNS related to rheumatological disorders such as Wegener granulomatosis, sarcoidosis, and Behçet disease. Our 2 patients did not have any skin lesions or orogenital ulcers, and the results were negative for serological tests of connective tissue disease and autoimmune diseases.

No prospective studies suggested a specific guideline for the treatment of PACNS, and most of the treatment is similar to the therapies used for other cerebral vasculitis. A combination of glucocorticoid and immunosuppressant were the recommended treatment of TLML-PACNS, and aggressive immunosuppressive therapy was associated with improved outcomes compared with glucocorticoids immunotherapy.^[10,11] In our study, patients with severe lesion were improved with methylprednisolone and CyP therapy.

4. Conclusion

In conclusion, seizure could be a first manifestation prior to a diagnosis of TLML-PACNS. Therefore, patients, especially those individuals with mass lesion similar to tumor, presented with seizure, headache, or cerebrovascular events without any other risk factors for stroke or tumor should be considered the feasible with the disease of TLML-PACNS.

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