Cerebellar PACNS in an Elderly Patient Present as a Tumor-Like Mass Lesion: A case Report

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Abtract

Purpose: PACNS has a broad spectrum of clinical manifestations without typical features, and its clinical diagnosis is challenging. We report an elderly patient of cerebellar PACNS (Primary angiitis of central nervous system) presented as a brain tumor by MRI, and primary angiitis was proven by pathology.

Case report: We report an 81-year-old female who complained about vertigo for 3 weeks with right arm dysmetria. There were no other neurologic symptoms/signs, and the patient was free from headache. Brain CT showed a space-occupying lesion over the right cerebellum, and a high-grade glioma was suspected by brain MRI and MRS. The pathologic result of brain biopsy showed granulomatous variant of PACNS. The patient received immunosuppressant therapy as long-term therapy, and had favorable response during a 2-year follow up.

Conclusion: Due to variations in clinical presentation and nonspecific findings on imaging studies, PACNS is not easily diagnosed, especially in the aged population. PACNS should be considered as one of the differential diagnoses of any CNS dysfunction. PACNS is also an exclusionary diagnosis. Although brain biopsy is limited for its low sensitivity, its application is still important to exclude the possibility of other diseases. Although there have been reports of fulminant cases, PACNS can be treated successfully with immunosuppressant as maintaining therapy.

Key words: Primary angiitis of central nervous system, tumor-like lesion, glioma

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INTRODUCTION

The primary angiitis of the central nervous system (PACNS) is a rare disease of unknown cause , with annual incidence rate of 2.4 cases per million person-years in the USA[(1)]. The median age of onset is 50 years, and 50% of patients are diagnosed between 37 and 59 years of age[(2)]. Clinical presentation of PCANS can manifest with a

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variable spectrum from headache, focal neurologic deficit, cognitive impairment, seizure, to recurrent ischemic stroke[1-3]. Only about 4-12% of patient with PACNS present with a tumor-like mass lesion[4,5]. Mostly, the mass lesions had a supratentorial area[6,7], and seizure is usually a complication during the disease course[8]. We present a case of a mass lesion of PACNS in the cerebellum, and the patient was treated with immunosuppressant therapy without recurrence for two years.

CASE REPORT

The 81 year-old female with history of myocardial infarction, dyslipidemia, and hypertension had suffered from subacute onset of vertigo for three weeks. Right arm dysmetria and unsteady gait were detected. The cranial nerve function, motor system, and sensory system were intact.

The brain MRI showed hypointensity on T1-weighted imaging and hyperintensity on T2-weighted FLAIR over right cerebellar hemisphere and right middle cerebellar peduncle with mild linear enhancement (Figure 1). MR spectroscopy (MRS) showed increased ratio of choline (Cho)-to-creatine (Cr) and reduced ratio of N-acetylaspartate (NAA)-to-Cho, so that high-grade glioma was first considered. The following brain MRI one month later showed mild progression of the infiltrative mass lesion. Surgical tumor removal via suboccipital craniectomy was performed. The pathology revealed that the blood vessels in cerebellar parenchyma and leptomeninges exhibited changes ranging from necrotizing vasculitis (angiitis) featuring fibrinoid necrosis and neutrophils infiltration, intimal injury with transmural inflammatory infiltrate associated with fibroblastic intimal proliferation resulting in severe luminal stenosis, obliteration and recent organizing thrombus to fibroblastic obliteration of the lumen (Figure. 2). The results of Periodic Acid–Schiff and Acid-Fast stains for microorganisms were negative. The results of immunohistochemistry stains for treponema, Herpes virus, toxoplasmosis, and cytomegalovirus were all negative. Occasional small blood vessels in the leptomeninges also showed a picture of amyloid angiopathy highlighted by Congo red and thioflavin-T stains. Focal remote infarction was also identified. Combining information of clinical and imaging studies, the most appropriate pathological

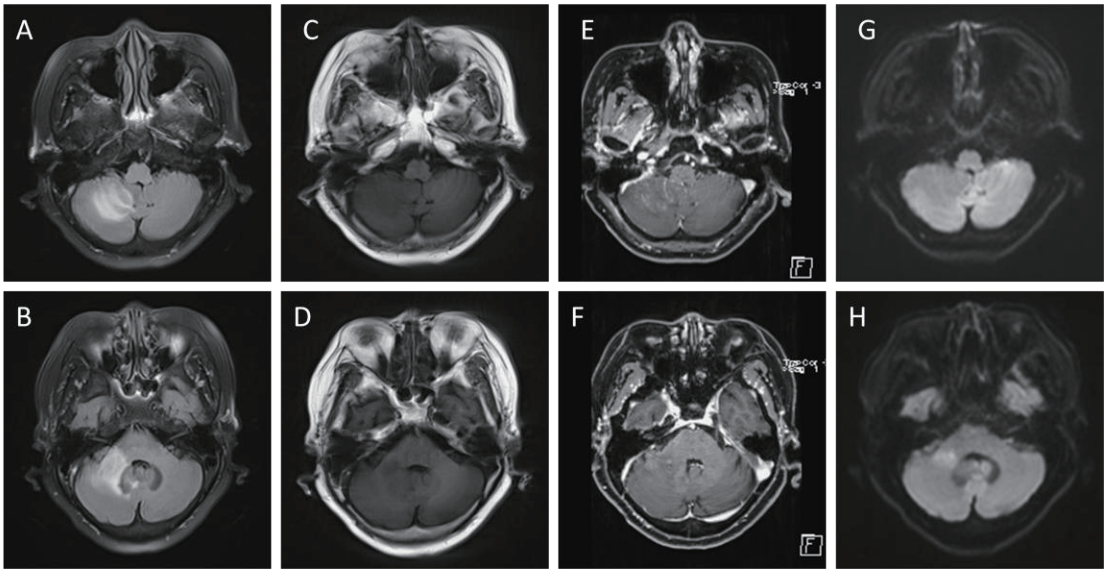

Figure 1. Initial finding of brain MRI. An infiltrative mass lesion was noted over right cerebellar hemisphere and right middle cerebellar peduncle. Hyperintensity on T2-weighted FLAIR (A and B) and hypointensity on T1-weighted images (C and D). The T1-weighted contrast-enhancing study revealed mild heterogenous and linear enhancement (E and F). No evidence of acute infarction on DWI (G and H).
FLAIR: Fluid Attenuated Inversion Recovery; DWI: Diffusion Weighted Imaging;

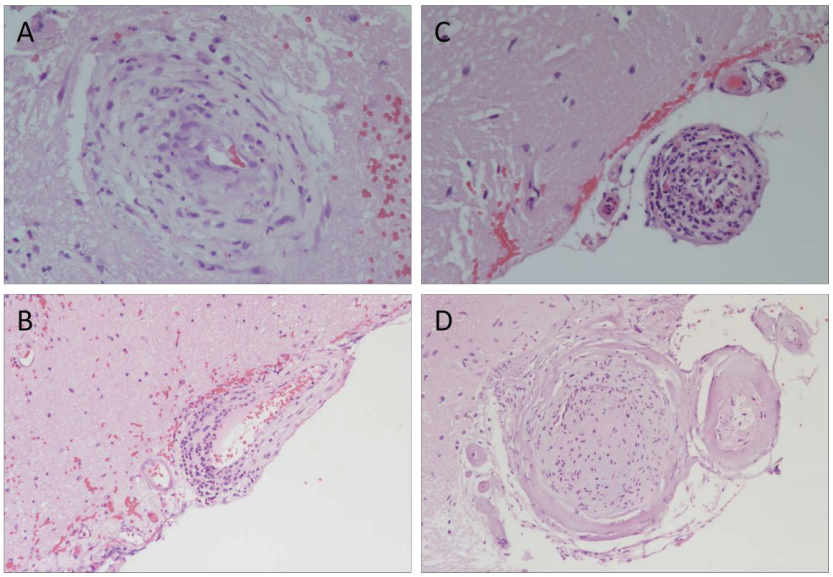

Figure 2. A. Vasculitis of a small cerebellar parenchymal artery featuring intimal injury with endothelial cell swelling, fibroblastic intimal proliferation, and transmural small lymphocyte and occasional neutrophils infiltration with luminal stenosis (HE, x400).
B. Transmural small lymphocyte infiltration in a small leptomeningeal artery (HE, x200).
C. Trasmural neutrophils and small lymphocytes infiltration in another small leptomeningeal artery with severe luminal stenosis (HE, x400).
D. Marked fibroblastic intimal proliferation causing obliteration of a leptomeningeal blood vessel (HE, x200)

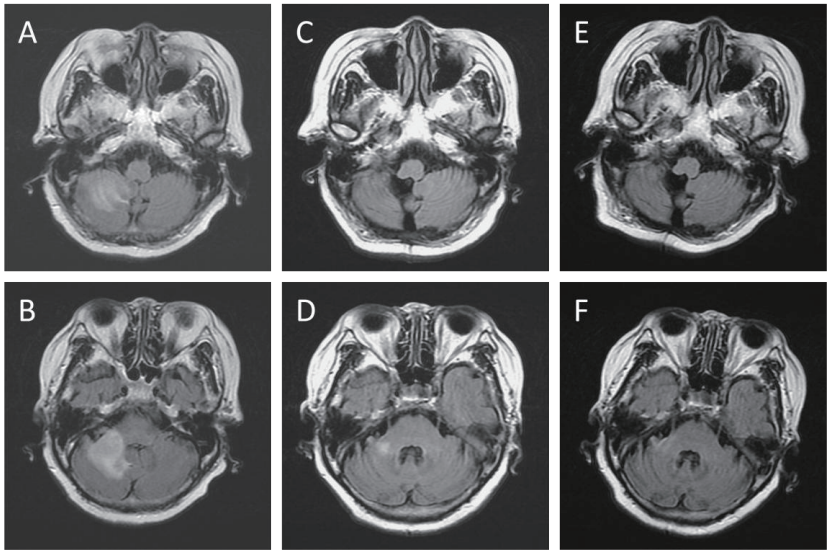

Figure 3. Serial brain MRI changes on T2-weighted FLAIR imaging. The brain MRI just before craniectomy (A and B), 6 months after immunosuppressant therapy (C and D), and one year after therapy showed regression of lesions (E and F).
FLAIR: Fluid Attenuated Inversion Recovery

diagnosis was primary angiitis of the central nervous system[9].

Serum C-reative protein(CRP) was 0.47 mg/dL and erythrocyte sedimentation rate (ESR) was 17mm/hr. Autoantibodies in systemic autoimmune diseases, including antinuclear antibodies (ANAs), antidouble-stranded DNA, antineutrophil cytoplasmic antibody (ANCA), rheumatoid factor (RF) and anti- extractable nuclear antigens (ENA) screen findings were all negative. Human immunodeficiency virus (HIV) and venereal disease research laboratory (VDRL) testing were also negative. The diagnosis criteria set by Calabrese and Mallek was achieved, and primary angiitis of central nervous system was diagnosed[10].

Afterward, the patient received azathioprine (50mg daily) at the first 6 months and hydroxychloroquine (200mg daily) was prescribed as add-on therapy later.

The following brain MRI at six months and one year later revealed regression of the original lesion (Figure 3). During 2-year follow-up, the patient did not have newly developed symptoms.

DISCUSSION

Posterior fossa tumors are uncommon in adults where the most common "mass" is a subacute stroke and the most common tumor is a cerebellar metastasis[11]. In our report, the brain MRI of this patient indicated a highly suspect a high-grade glioma in the cerebellar hemisphere initially. The diagnosis of primary angiitis of the central nervous system was achieved by brain pathological study.

The PACNS is a vasculitis affecting major in small- and medium-sized arteries of brain, spinal cord, and leptomeninges where occasionally larger vessels are affected[1,2,12]. The symptoms of PACNS are variable and non-specific, depending on the affected region. The most common manifestation of PACNS is subacute onset of headache (63%) and encephalopathy (50%)[2]. Mass-lesion-like PACNS is uncommon and the most common features are headache (74%), focal neurological deficits (64%), and diffuse neurological deficit (50%)[4]. The median age at diagnosis is about 40-50 years ranging from 17 to 84 years of age with slightly more frequency in males[1,2,4,5]. In our report, this elderly female had non-specific vertigo, and was free from both headache and seizure. For no typical manifestation in particular population for the PACNS, PACNS should be one of the differential diagnoses of any CNS dysfunction.

Magnetic resonance imaging (MRI) often shows abnormal but nonspecific findings, including multiple FLAIR lesions, cortical and subcortical infraction, intracranial hemorrhage, and parenchymal and leptomeningeal enhancement where the most common lesions are infarction[1,5,8,13-16]. As in our report, PACNS can present as tumor-like mass lesions and the pattern of mass is still variable by previous reports[4,6-8, 17,18]. Elevated choline peak and reduced NAA peak are associated with high grade glioma, but both of them are also described in mass-lesion-like PACNS[18]. The brain MRI of our case showed a mass lesion over right cerebellum, which had hypointensity on T1-weighed images and hyperintensity on T2-weighed FLAIR with mild linear enhancement that suggested a high-grade glioma. Even with a combination of clinical history and neuroimaging, the diagnosis of PACNS was still difficult.

Brain biopsy with histologic confirmation remains the gold standard for diagnosis of PACNS, but may miss patients with medium-sized arteries involved or with too many focal changes[1,9,12,15]. There are three histopathological patterns of PACNS: granulomatous, lymphocytic and necrotizing vasculitis and granulomatous pattern is the most common[2,9]. In our patient, necrotizing vasculitis was diagnosed by fibrinoid necrosis and neutrophilic infiltration with transmural inflammation. Even with no strong evidence of infraction by brain MRI, focal remote infarction was still identified by pathology. Although exhibiting necrotizing change in brain tissue, our patient still had good response to therapy without rapid progression, consistent with previous reports of necrotizing vasculitis[9]. Cerebral amyloid angiopathy has been mentioned concerning association with PACNS, especially in older patients[2,4,9]. Patients associated with amyloid angiopathy have a monophasic disease course and respond to immunosuppressant therapy well according to a previous report[19]. Amyloid deposition was also found in our patient. However, the role of amyloid in PACNS is still uncertain as amyloid deposition is also found in normal aging brains[20].

It is still controversial if PACNS should be diagnosed by imaging-based or biopsy-proven means[1,15,21].

Diagnostic sensitivity of brain biopsy is about 60% in previous reports[5,9], and even down to 22-25% in patients with angiographic findings suggesting vasculitis[15].The pseudo-negativity of brain biopsy may be attributed to limitations of the biopsy field[9]. On the other hand, pseudo-positivity of angiography may be caused by other cerebral vasculopathies that mimic vasculitis, such as atherosclerosis, infections, and vasospasm[9]. The major difference between PACNS diagnosed by imaging-based and biopsy-proven means is the affected vessel size[15]. Biopsy-proven patients have good outcome due to only small arteries being affected as has been hinted in one study[22], but did not have the same result in another study[5].

There is still no standard treatment protocol for these patients with PACNS as no clinical randomized control trial is available[4].The initial therapy for PACNS is glucocorticoids (1mg/kg/day) with/without cyclophosphamide a [1,2,5,16]. Other immunosuppressants, including mycophenolate mofetil[16,23], rituximab[5,16,24], and azathioprine[25] have also been reported as part of induction therapy with prednisone. Maintenance therapy can bring better functional outcomes and lower relapse rates, and azathioprine(2mg/kg/day) is most commonly used[5,16]. In consideration of the indolent nature of the disease course and advanced age of our patient, glucocorticoids and cytotoxic drugs are spared. Our patient only received azathioprine with low dose (50mg daily) and add-on hydroxychloroquine (200mg daily) 6 months later with a satisfactory response.

CONCLUSION

As there is a broad-spectrum of manifestation and nonspecific findings on imaging studies, PACNS is still a challenge for diagnosis. Even brain biopsy for histological study could only provide partial information for PACNS, but it is still important for the exclusion of other diseases. The difficulty in diagnosis creates limitations in analysis for treatment. We report an elderly patient of cerebellar PACNS presenting as a tumor-like lesion by MRI as biopsy-proven. Low potential immunosuppressant therapy could have good disease control for two years. As the disease is rare, we wish to provide this experience from this patient for further study in classification and therapy for PACNS.

REFERENCES

1. Salvarani C, Brown RD, Calamia KT, Christianson TJH, Weigand SD, Miller DV, et al. Primary central nervous system vasculitis: analysis of 101 patients. Annals of Neurology. 2007;62(5):442-51.
2. Salvarani C, Brown RD, Jr., Hunder GG. Adult primary central nervous system vasculitis. Lancet. 2012;380(9843):767-77.
3. Nogueras C, Sala M, Sasal M, et al. Recurrent stroke as a manifestation of primary angiitis of the central nervous system in a patient infected with human immunodeficiency virus. Archives of Neurology. 2002;59(3):468-73.
4. Molloy ES, Singhal AB, Calabrese LH. Tumour-like mass lesion: an under-recognised presentation of primary angiitis of the central nervous system. Annals of the Rheumatic Diseases. 2008;67(12):1732-5.
5. de Boysson H, Zuber M, Naggara O, Neau JP, Gray F, Bousser MG, et al. Primary angiitis of the central nervous system: description of the first fifty-two adults enrolled in the French cohort of patients with primary vasculitis of the central nervous system. Arthritis Rheumatol. 2014;66(5):1315-26.
6. Zhu DS, Yang XL, Lv HH, Bai CG, Yang PP, Li ZZ, et al. Seizure syndrome as a first manifestation of solitary tumor-like mass lesion of PACNS: Two case reports. Medicine (Baltimore). 2017;96(9):e6018.
7. Gan C, Maingard J, Giles L, Phal PM, Tan KM. Primary angiitis of the central nervous system presenting as a mass lesion. Journal of Clinical Neuroscience. 2015;22(9):1528-31.
8. de Boysson H, Boulouis G, Dequatre N, Godard S, Neel A, Arquizan C, et al. Tumor-Like Presentation of Primary Angiitis of the Central Nervous System. Stroke. 2016;47(9):2401-4.
9. Miller DV, Salvarani C, Hunder GG, Brown RD, Parisi JE, Christianson TJ, et al. Biopsy findings in primary angiitis of the central nervous system. Am J Surg Pathol. 2009;33(1):35-43.
10. CALABRESE LH, MALLEK JA. Primary Angiitis of the Central Nervous System: REPORT OF 8 NEW CASES, REVIEW OF THE LITERATURE,

AND PROPOSAL FOR DIAGNOSTIC CRITERIA. Medicine. 1988;67(1):20-39.
11. Shih RY, Smirniotopoulos JG. Posterior Fossa Tumors in Adult Patients. Neuroimaging Clin N Am. 2016;26(4):493-510.
12. Powers WJ. Primary Angiitis of the Central Nervous System: Diagnostic Criteria. Neurologic Clinics. 2015;33(2):515-26.
13. Birnbaum J, Hellmann DB. Primary angiitis of the central nervous system. Archives of Neurology. 2009;66(6):704-9.
14. Niu, Wang, Yin, Li, Wang. Role of magnetic resonance imaging in the diagnosis of primary central nervous system angiitis. Experimental and Therapeutic Medicine. 2017;14(1):555-60.
15. Schuster S, Bachmann H, Thom V, Kaufmann-Buehler A-K, Matschke J, Siemonsen S, et al. Subtypes of primary angiitis of the CNS identified by MRI patterns reflect the size of affected vessels. Journal of Neurology, Neurosurgery & Psychiatry. 2017;88(9):749-55.
16. de Boysson H, Parienti JJ, Arquizan C, Boulouis G, Gaillard N, Regent A, et al. Maintenance therapy is associated with better long-term outcomes in adult patients with primary angiitis of the central nervous system. Rheumatology (Oxford). 2017;56(10):1684-93.
17. Sun LI, Zhu L, Zhao T, Wang D, Ma D, Zhang R, et al. A rare case of tumor-mimicking primary angiitis of the central nervous system. Mol Clin Oncol. 2016; 4(5):827-9.
18. Kumar PP, Rajesh A, Kandadai RM, Purohit AK, Sundaram C. Primary CNS vasculitis masquerading as glioblastoma: A case report and review. Asian J Neurosurg. 2017;12(1):69-71.
19. Salvarani C, Brown RD, Jr., Calamia KT, Christianson TJ, Huston J, 3rd, Meschia JF, et al. Primary central nervous system vasculitis: comparison of patients with and without cerebral amyloid angiopathy. Rheumatology (Oxford). 2008;47(11):1671-7.
20. Kovari E, Herrmann FR, Bouras C, Gold G. Amyloid deposition is decreasing in aging brains: an autopsy study of 1,599 older people. Neurology. 2014;82(4): 326-31.
21. Alrawi A, Trobe JD, Blaivas M, Musch DC. Brain biopsy in primary angiitis of the central nervous system. Neurology. 1999;53(4):858-60.
22. Salvarani C, Brown RD, Jr., Hunder GG. Adult primary central nervous system vasculitis: an update. Curr Opin Rheumatol. 2012;24(1):46-52.
23. Rosati A, Cosi A, Basile M, Brambilla A, Guerrini R, Cimaz R, et al. Mycophenolate mofetil as induction and long-term maintaining treatment in childhood: Primary angiitis of the central nervous system. Joint Bone Spine. 2017;84(3):353-6.
24. Salvarani C, Brown RD, Huston J, Morris JM, Hunder GG. Treatment of primary CNS vasculitis with rituximab: Case report. Neurology. 2014;82 (14):1287-8.
25. Salvarani C, Brown RD, Christianson TJH, Huston J, Giannini C, Miller DV, et al. Adult Primary Central Nervous System Vasculitis Treatment and Course: Analysis of One Hundred Sixty-Three Patients. Arthritis & Rheumatology. 2015;67(6):1637-45.