Neurological Sciences (2019) 40:417–419
https://doi.org/10.1007/s10072-018-3595-8

LETTER TO THE EDITOR

A case of primary angiitis of the central nervous system presenting with diffuse cerebral microbleeds and recurrent intracranial hemorrhage

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Received: 12 July 2018 / Accepted: 28 September 2018 / Published online: 4 October 2018

Dear Editor,

Primary angiitis of the central nervous system (PACNS) refers to a rare single-organ vasculitis that results in inflammation and destruction of the small and medium vessels restricted to brain, spinal cord, and the meninges [1]. It is one of the foremost diagnostic challenges since it produces vague and unspecific signs and symptoms, presents variable laboratory and imaging manifestations, and requires extensive investigation to rule out various differential diagnoses. Biopsy of the brain remains the gold standard diagnostic test. Here, we present a case of PACNS presenting with cerebral microbleeds (CMBs) and recurrent intracranial hemorrhage (ICH).

A 36-year-old man was admitted to our hospital because of sustained confusion after a generalized tonic-clonic seizure 1 week ago. The seizure occurred during sleep, lasted for 30 min and reoccurred 1 day before admission. Over the previous week, the patient was drowsy and dull. He did not experience headache, nausea, or vomiting. Six years ago, the patient was diagnosed with multiple sclerosis because of dizziness and extensive periventricular white-matter damages in brain MRI (Fig. 1a, b). He had taken low-dose glucocorticoid for weeks and withdrew gradually. Then, he suffered recurrent ICH in cerebellum and basal ganglia 15 and 12 months ago respectively (Supplemental Fig. 1). His mother died of thyroid cancer, and he denied any family history.

There were no other deficits on physical examination except for neck stiffness and positive Kernig's sign. His cognition was impaired mildly and the mini-mental state examination (MMSE) score was 23/30. Brain MRI demonstrated intracranial hemorrhage (ICH) in the right temporal lobe and diffused white-matter lesions and cerebral microbleeds (CMBs) in bilateral hemispheres (Fig. 1c, d), and brain MRA showed no obvious vascular stenosis (Fig. 1e). Electroencephalography showed extensive θ and δ waves. The erythrocyte sedimentation rate was 23 mm/h (0–20). Other laboratory evaluations were normal, such as complete blood count, biochemical tests, coagulation function, thyroid function, serologic testing for viruses (HIV, syphilis and hepatitis virus), a series of serum antibodies (antinuclear antibodies, anti-double-stranded DNA antibodies, anti-neutrophil cytoplasmic antibodies, anti-ribonucleoprotein antibodies, and anti-Smith antibodies), immunoglobulins (IgG, IgE, IgA, and IgM), and complement system. Besides, *Leptospira*, *Brucella*, and lyme were also negative. A lumbar puncture was performed with normal pressure (165 mmH_2O). CSF analysis showed elevated proteins (0.72 g/L) with normal cell counts and chloride and glucose levels. Herpes simplex virus, cytomegalovirus, EB virus, *Cryptococcus*, or tuberculosis have not been detected. There was no abnormity in the extracranial vasculature by ultrasound testing. A heterozygous mutation in *COL4a1 gene (c.4666A>G chr13:110807719 p.M1556V)* was identified by next-generation sequencing. Type IV collagen α1 (COL4a1) is a major component of basement membranes and dominant mutations in *COL4a1 gene* may be predisposed to ICH [2]. The diagnosis depends on skin biopsy and gene sequencing. However, skin biopsy of this patient showed regular basement membranes (Supplemental Fig. 1f) and his father carried the same gene mutation without any clinical manifestations or abnormity in brain MRI (Supplemental Fig. 1d, e), which both confirmed the mutation was nonsense. Finally, brain biopsy was carried out and small-vessel granulomatous angiitis was

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10072-018-3595-8) contains supplementary material, which is available to authorized users.

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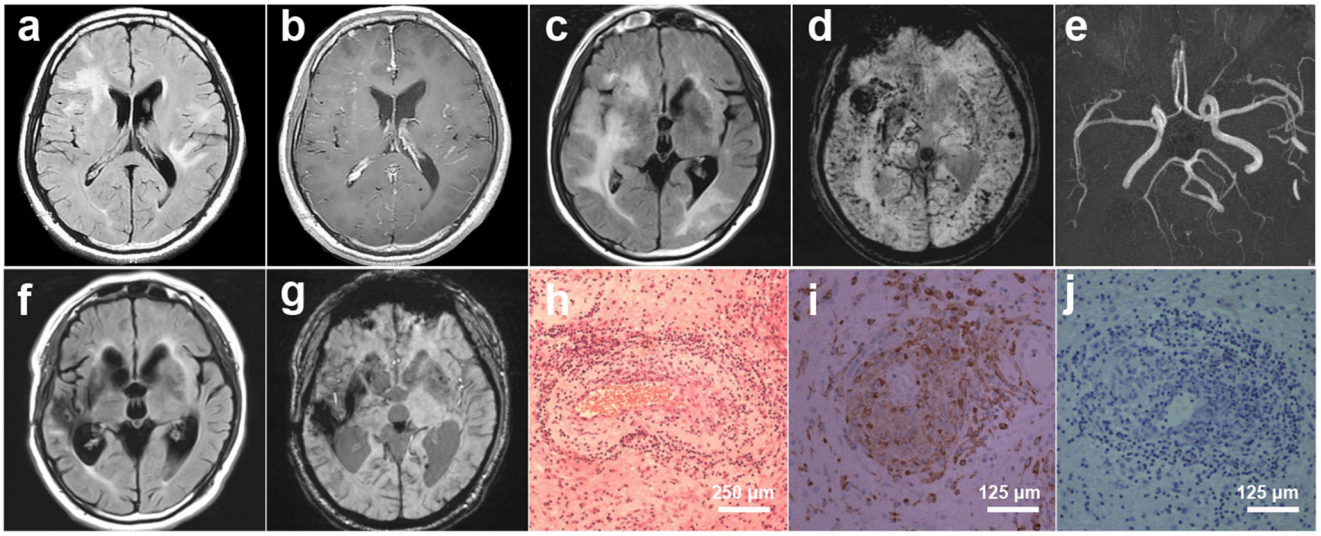

Fig. 1 Brian MRI (**a-g**) and brain biopsy results (**h-j**) of the patient. Fluid-attenuated inversion recovery (FLAIR)-weighted image showed multiple white-matter hyperintensities in bilateral hemispheres (**a**). Gadolinium-enhanced T1-weighted image showed enhancement in leptomeninges and parenchyma (**b**). Diffused white-matter hyperintensities of T2 FLAIR (**c**) were accompanied by microbleeds in SWI (**d**). No obvious vascular stenosis was observed in brain MRA (**e**). With treatment, the lesions were dramatically diminished 8 months later (**f**, **g**). Hematoxylin-eosin stain revealed vessel wall damages with marked inflammatory infiltration and granulomas (**h**, × 100). Immunostaining of brain tissue revealed extensive CD68 labeling (**i**, × 200) and no β-amyloid 1–40 deposits (**j**, × 200).

observed in the tissues (Fig. 1h). Immunostaining showed extensive CD68 labeling without β-amyloid deposits (Fig. 1i, j). Furthermore, there was no indication of secondary vasculitis or systemic disease. Taken together, PACNS was diagnosed. The patient was treated with methylprednisolone 1000 mg/day for 5 days and reduced gradually. Then, it was replaced by oral prednisone with a maintenance dose of 10 mg/day. Cyclophosphamide (CTX) was administered with an accumulated dose of 4.8 g and mycophenolate mofetil was maintained at 1.0 g/day. The total course was 1.5 years. His cognitive function was improved with MMSE score was 27/30 and he was seizure-free during the treatment. The lesions in brain MRI were lessened remarkably as well (Fig.1f, g). Unfortunately, he suffered limb numbness and confusion when he suspended prednisone and mycophenolate mofetil 2 weeks later. PACNS relapse was considered after auxiliary examinations have been completed (Supplemental Fig. 2a–c) and other disease has been excluded. Then, the above treatment regimen was repeated and the clinical manifestations as well as brain imaging were improved dramatically once again (Supplemental Fig. 2d–f).

Discussion

CMBs, as a manifestation of cerebral small-vessel disease (CSVD), are associated with hypertensive arteriopathy (arteriolosclerosis) and cerebral amyloid angiopathy (CAA) detected by using susceptibility-weighted magnetic resonance imaging (SWI). Severe CMBs with symptomatic ICH in a younger patient is most frequently related to vascular malformation and hereditary vascular diseases. However, it also can be observed in other less frequent CSVD, such as PACNS. It might be difficult to figure out the underlying etiology of CBMs by means of non-invasive findings. Brain biopsy should be performed to recognize the treatable etiology earlier.

PACNS could manifest with headache, cognitive impairment, and focal neurological deficits. Stroke or transient ischemic attacks are common. Though recurrent ICH was not a typical presentation, the finding of small-vessel granulomatous angiitis on brain biopsy, as well as no evidence of PACNS mimics and the dramatic improvement with glucocorticoids and cyclophosphamide, supported the diagnosis. There were 12.2% patients had ICH in a PACNS cohort study [3], whereas 63.6% was reported in a recent research [4]. These results indicated that ICH might be underestimated, and SWI scan should be performed when PACNS is suspected. Histopathologically, fibrinoid necrosis is supposed to be more frequent in PACNS with ICH [3]. It is deduced that inflammatory process could cause severe vessel wall injury which resulted in CMBs and ICH. As well, there might be angiostegnosis in the inflammatory artery which caused ischemia. It is notable that this patient presented with ischemic symptoms in the early stage and ICH during the later period. Thus, we speculate that diffuse CMBs and recurrent ICH may be the outcome of long-lasting inflammatory damage to vessels and a diagnosis of PACNS should be considered for recurrent ICH patient with a prolonged course and without definite nosogenesis.

The early brain MRI of this patient mimicked multiple sclerosis; however, multiple cortical and subcortical lesions together with the linear and punctate enhancement in both leptomeningeal and parenchyma indicated small-sized vessel abnormity but not demyelination had been involved in the

pathogenesis. Any isolated clinical feature might be lack of specificity, whereas extensive CMBs accompanied with the characteristic of enhancement is one typical symptom of cerebral vasculitis, which is helpful to discriminate PACNS from other mimics. In addition, recurrent ICH and CMBs are hallmarks of cerebral amyloid angiopathy (CAA) or CAA-related inflammation (CAA-RI) [5] of which are two foremost differential diagnoses for this patient. The onset age of CAA is over 45 years generally and immunohistochemical staining revealed no amyloid deposits in this case, which indicated CAA was excluded. Besides, β-amyloid related angiitis (ABRA), a subtype of PACNS, is one kind of transmural vasculitis characterized by amyloid deposits [1, 6], which was excluded also because of no amyloid deposits.

Glucocorticoids with or without combination of immunosuppressants, such as cyclophosphamide (CTX), mycophenolate mofetil, methotrexate, and azathioprine, may be the effective treatment based on retrospective observational data and experts' opinion [1]. However, there is no consensus regarding the optimal drug, duration or dosage. According to one recent study, immunosuppressive treatment was promising in PACNS with ICH [4]. For this patient, immunosuppressive therapy should be kept for longer even throughout his life to reduce recurrence.

In conclusion, we propose that CMBs may be underestimated in PACNS, and it is likely to develop into symptomatic ICH if the treatment is delayed. The diffuse cortical-subcortical damages, CMBs/ICH, linear or punctate enhancement in parenchyma or leptomeningeal, and space-occupying lesion with ring enhancement are imaging manifestations in PACNS, even in the same patient. Immunosuppressive treatment is effective and promising, and the duration should be longer if there are no obvious adverse reactions. Recognition of atypical manifestation and early diagnosis could be crucial to reduce the neurological damage and improve the prognosis.

Acknowledgments This research was supported by grants from the Shandong provincial key research and development plan (2018GSF121009).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from the patient.

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