Amyloid β -Related Central Nervous System Angiitis Presenting With an Isolated Seizure

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Abstract

Amyloid beta-related angiitis (ABRA) of the central nervous system (CNS) is a very rare inflammatory disorder that causes destruction of CNS arteries and subsequent neuronal injury. Most patients with ABRA are old and present with cognitive dysfunction and stroke; however, some patients may present atypically. In this article, we report a 44-year-old man who presented with a first-time seizure but was otherwise neurologically intact and denied any headache. Brain MRI showed right hemispheric and bilateral medial frontal lobe hyperintensities and microhemorrhages that were most suspicious for a mass lesion. An extensive diagnostic evaluation including CSF analysis and catheter angiography was unremarkable. A brain biopsy with specific stains for amyloid surprisingly demonstrated ABRA and led to immunosuppressive treatment. The patient has remained neurologically intact and seizure-free 1 year after presentation. This case demonstrates that ABRA can occur in young patients without headache or neurologic deficits, and should be considered in patients with new-onset seizures and mass lesions. It also reinforces the need to consider a brain biopsy in patients with idiopathic brain lesions and negative non-invasive testing, as it is virtually impossible to confirm the diagnosis of ABRA otherwise.

Keywords

central nervous system vasculitis, seizures, neuropathology, imaging

Introduction

Amyloid β -related angiitis (ABRA) of the central nervous system (CNS) is a very rare inflammatory disorder that was first described as a distinct clinicopathologic entity from primary CNS angiitis (PCNSA) in 2005.¹ It is pathologically characterized by amyloid- β deposition in the cerebral vasculature with surrounding granulomatous inflammation.^{1,2} Only ~50 cases have been reported in the literature, and most have been in elderly patients who presented with cognitive dysfunction and stroke.¹⁻⁴ We report an atypical case of pathologically confirmed ABRA presenting in a young patient with just a single seizure.

Case Description

A 44-year-old man with a history of gout and aseptic meningitis (1 year prior) presented with a generalized seizure preceded by a visual aura. He denied any headache or other neurologic symptoms, and his initial examination was normal. Brain magnetic resonance imaging (MRI) demonstrated right parietal, right temporal, and bilateral medial

frontal lobe nonenhancing hyperintense lesions on T2-weighted, fluid-attenuated inversion recovery (FLAIR) sequences and small scattered foci of hypointensity on gradient echo sequence suggestive of hemosiderin deposition from microhemorrhages (Figure 1). Laboratory analysis including a full rheumatologic panel was unremarkable. Cerebrospinal fluid (CSF) analysis demonstrated 0 white blood cell/mm³, 0 red blood cell/mm³, protein 53 mg/dL, glucose 63 mg/mL, and immunoglobulin G index 0.59 (normal). The CSF infectious markers were negative.

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Figure 1. Magnetic resonance imaging (MRI) of brain at initial presentation. A and B, Axial T2-weighted, fluid-attenuated inversion recovery (FLAIR) sequences show hyperintensities in the right parietal, right temporal, and bilateral medial frontal lobes that suggested cerebral edema. C and D, Corresponding axial gradient echo images show small circular hypointensities suggestive of microhemorrhages, mainly in the areas of T2-FLAIR signal abnormality.

Digital subtraction catheter cerebral angiography was normal. Whole-body positron emission tomography-computed tomography scans showed no hypermetabolic lesions to suggest primary malignancy. Surveillance brain MRI 2 months later was unchanged, so a brain biopsy was performed. Pathology revealed small vessel inflammation and deposits of waxy, eosinophilic, acellular material that displayed apple-green birefringence under polarized light and stained positive for Congo red and β -amyloid (by

immunohistochemistry). These pathological findings confirmed a diagnosis of primary CNS angiitis with amyloid angiopathy (Figure 2). The patient was started on prednisone and cyclophosphamide. Brain MRI performed 3 months after initiation of immunosuppressive therapy demonstrated near complete resolution of the patient's T2-FLAIR hyperintense lesions (Figure 3). He remains asymptomatic, seizure free, and neurologically normal 1 year after presentation.

Figure 2. Right temporal lobe brain biopsy specimen. A, Hematoxylin and eosin stain showing a small penetrating vessel from the pial surface with lymphocyte and macrophage infiltration and microscopic extravasation of red blood cells. B, Brain parenchyma vessel wall with macrophage infiltration including a multinucleated giant cell stained by immunohistochemistry with CD68 antibody, a macrophage marker, and hematoxylin counterstain. C, Brain parenchyma vessel with lymphocytic infiltration stained with CD3 antibody, a T cell marker, and hematoxylin counterstain. D, A brain parenchyma vessel with amyloid deposition stained with amyloid- β antibody and hematoxylin counterstain. Scale bar equals 50 μ m (A–D).

Discussion

Amyloid β -related angiitis is a rare and unusual CNS inflammatory disorder characterized by amyloid- β deposition in cerebral blood vessels with surrounding inflammation.^{1,2} The etiology of ABRA is unclear, although it has been hypothesized that amyloid- β deposition in the vessels of susceptible individuals may trigger an inflammatory response.^{1,2} To date, there have only been about 50 published reports of ABRA, with most being isolated case reports or small case series.^{1–4} However, brain biopsies are not always obtained in patients with suspected PCNSA, and some biopsies are not evaluated for amyloid- β , so ABRA may be underdiagnosed. Additionally, one series reported that 26% of patients with histologically confirmed PCNSA have amyloid deposition, again suggesting underdiagnosis of ABRA.²

Based on the data from 2 small case series, ABRA appears clinically similar to PCNSA (recurrent infarcts or hemorrhages, chronic headache, and cognitive decline).^{1,2} However, there are some notable differences. Patients with ABRA are usually older than those with PCNSA (median age at diagnosis, 67 years [range 43–82] vs 45 years), often have a more acute onset, and may present with hallucinations (12% in 1 series).¹ Our patient

is remarkable because of his presentation at age 44 with only an isolated seizure and no neurological disability or headaches, suggesting that ABRA also occurs in young persons and can present atypically. Furthermore, although 8 (24%) of 34 cases reported by Scolding et al had seizures at presentation, nearly all of these patients had concomitant cognitive dysfunction, while our patient was cognitively normal.¹

Previous studies have not found major differences in imaging findings between PCNSA and ABRA, although the presence of focal microhemorrhages on MRI as seen in our patient may be more suggestive of ABRA. Similarly, CSF findings are equally nonspecific, typically consisting of pleocytosis and elevated protein, but the CSF may also be normal.^{1,2} Therefore, it is virtually impossible to discern ABRA from PCNSA or from other inflammatory or neoplastic lesions without pathological analysis for β -amyloid deposition in or around cerebral vessels. Making a definitive diagnosis between ABRA and PCNSA is clinically important, because patients with ABRA should avoid antithrombotics due to an increased risk of hemorrhage, while patients with PCNSA may be prescribed antithrombotics as part of their medical management.

Figure 3. Magnetic resonance imaging (MRI) of brain after 3 months of treatment with steroids and cyclophosphamide. A and B, Axial T2-weighted, fluid-attenuated inversion recovery (FLAIR) sequences shows near complete resolution of previously seen right hemisphere and bilateral medial frontal lobe T2-FLAIR signal hypertintensities.

The ABRA also shares some pathophysiological features with cerebral amyloid angiopathy, which is characterized by the deposition of amyloid- β in small to medium-sized cerebral blood vessels although typically without a robust vascular inflammatory response. In a study of 42 patients with pathologically diagnosed cerebral amyloid angiopathy, 7 had perivascular inflammation including giant cells; however, these patients did not have inflammation within the vessel wall with vessel destruction and necrosis, which is the pathological hallmark of ABRA.⁵ Interestingly, these patients with cerebral amyloid angiopathy and perivascular inflammation clinically resembled typical patients with ABRA more than those with cerebral amyloid angiopathy without perivascular inflammation, as most were diagnosed at a young age with subacute dementia and seizures rather than at old age with intracerebral hemorrhage.⁵ Therefore, cerebral amyloid angiopathy with perivascular inflammation and ABRA may represent a single disease entity with some pathological distinctions due to a variable inflammatory response to amyloid- β deposition in cerebral vessels. Conversely, as discussed previously, ABRA and PCNSA have many overlapping clinical, laboratory, and radiographic features; however, the abundant and consistent presence of amyloid- β deposition in affected blood vessels distinguishes ABRA from PCNSA.

The optimal treatment and prognosis for ABRA are unclear due to its rarity. However, patients may benefit from corticosteroids and/or other immunosuppressants, and 1 small series reported that 75% of the patients with ABRA had no neurological disability at last follow-up (median duration 24 months).² Continued vigilance in identifying cases of ABRA

is warranted to further elucidate the clinical features of ABRA and to develop better therapeutic options.

Declaration of Conflicting Interests

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