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Amyloid Beta-Related Angiitis—A Case Report and Comprehensive Review of Literature of 94 Cases

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ABSTRACT

Background: Amyloid Beta-Related Angiitis (ABRA) is a rare cause of central nervous system vasculitis complicating cerebral amyloid angiopathy. Data regarding its prevalence, clinical features, management, and outcomes are scant.
Objectives: To describe a patient with ABRA and discuss clinical features and management of ABRA.
Methods: A case report and review of literature were conducted of all reported cases of ABRA in the English literature.
Results: The exact etiology of ABRA is not clear, though it is thought to be secondary to an inflammatory response to beta amyloid (Aβ) in the walls of blood vessels. Role of ApoE e4/e4 genotype and its association with autoimmune diseases have been reported. ABRA shares many clinical features with primary CNS vasculitis. Patients with ABRA are relatively younger than those with non-inflammatory cerebral amyloid angiopathy (CAA), but older than patients with primary central nervous system vasculitis (PCNSV). Acute-onset cognitive behavioral abnormalities, focal neurological deficits, seizures, or unusual headaches are the most common presentations of ABRA. Majority have elevated CSF proteins. Up to 70% of patients have ApoE e4/e4 genotype. MRI is the most important diagnostic tool and is almost always abnormal. Characteristically, MRI shows hyperintensities on T2-weighted (T2W) or fluid-attenuation inversion recovery (FLAIR) images with minimal gadolinium enhancement. On susceptibility-weighted images (SWI), a majority of the patients have the presence of microbleeds at cortico-subcortical junction. It may be possible to diagnose typical patients based on clinical features and MRI findings alone, obviating the need for brain biopsy. Brain biopsy is the gold standard and shows transmural granulomatous vasculitis superimposed on CAA. ABRA responds well to steroids in majority. Patients usually need additional immunosuppressants, especially to prevent relapse. MRI abnormalities resolve with treatment and recur with the relapse.
Conclusions: ABRA is a rare but treatable cause of progressive dementia and should be considered in the differential diagnosis of rapid-onset CNS dysfunction in patients older than 60 years. It has characteristic MRI findings and responds well to steroids and other immunosuppressant therapy.

Introduction

Amyloidosis is a disorder of protein folding in which normally soluble proteins are deposited in the extracellular space as insoluble fibrils that progressively disrupt the tissue structure and function [1]. Cerebral amyloid angiopathy (CAA) is localized amyloidosis affecting cerebral blood vessels, commonly resulting from imbalance between production and clearance of normally produced beta amyloid (Aβ) from the brain [2]. CAA is responsible for 12–15% of cases of lobar intracranial hemorrhages in elderly and can also cause cognitive decline [3], transient ischemic attacks, and focal seizures [4]. Very rarely, patients with CAA develop secondary central nervous system (CNS) vasculitis triggered by immune response to Aβ, which is called "inflammatory CAA" or Amyloid Beta-Related Angiitis (ABRA).

We present our experience with this condition and the largest comprehensive case review about ABRA. We discuss several new insights into the etiopathogenesis, diagnosis as well as management of ABRA.

Case report

A 63-year-old right-handed Caucasian woman was admitted for evaluation of an episode of seizure. She was in her usual state of health until the day of admission when she had witnessed an

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episode of generalized tonic–clonic seizure preceded by aura consisting of seeing wavy dancing lines in front of her eyes. She was admitted to a local hospital where computed tomography (CT) scan of the brain was performed. The CT showed two subcortical hypodense lesions in the right and the left fronto-parietal lobes surrounded by edema. The lesions were suspected to be metastases given her history of breast cancer. She was referred to our hospital for neurosurgical evaluation. On arrival at our hospital, the patient was asymptomatic. There was no history of fever, night sweats, loss of appetite or weight, headaches, visual disturbances, loss of memory, abnormal behavior, and focal weakness. She did not have any symptoms suggestive of well-defined rheumatic disease including systemic vasculitides. Her medical history was significant for breast cancer diagnosed 1 year prior to the presentation, treated with lumpectomy followed by radiation therapy. The patient also had a history of pernicious anemia and Grave's disease treated with radioiodine therapy. Her home medications included anastrozole, levothyroxine, aspirin, calcium, monthly cyanocobalamin injections, ferrous sulfate, and subcutaneous injections of denosumab every 6 months for osteoporosis prophylaxis. Her sister and brother had rheumatoid arthritis. She lived with her husband and ran a candy business. She denied current or past smoking, alcohol, or illicit drug use.

On physical examination, pulse was 84 beats per min, blood pressure was 137/64 mmHg, and respiratory rate was 14 breaths per min. General examination included skin which was normal. Neurological examination was completely normal including higher cognitive functions, cranial nerves, motor, sensory as well as cerebellar examination results. Results of her routine laboratory tests were unremarkable and those of serological tests as well as CSF are shown in Table 1.

She underwent contrast-enhanced magnetic resonance imaging (MRI) of the brain (Fig. 1), which showed abnormal cortical and subcortical hyperintensities in both temporal and frontal lobes on T2W and FLAIR images with vague contrast enhancement of bi-temporal lesions and left frontal perisylvian lesion. Gradient-echo imaging (GEI) demonstrated innumerable punctate hypointense foci, probably due to micro-hemorrhages within or around each lesion. Cerebrospinal fluid studies were unremarkable except for elevated proteins.

As per the neurosurgery team, MRI features were atypical for metastases and biopsy was recommended to guide further management. Stereotactic right temporal lobe brain biopsy was done. It did not show any evidence of malignancy or infection.

Table 1

Lab test	Patient's result	Normal value
Cerebrospinal fluid	Clear colorless	
Proteins	57	15–45
Glucose	59	40–70
Cells		
WBC	4	0–5 per hpf
RBC	263	< 1 per hpf
Culture	Negative	
Flow cytometry	No malignant cells Small lymphocytes CD4:CD8 ratio 2.8:1.0	
ANA	Negative	
Rheumatoid factor	< 10	< 15
ANCA	Negative	
HBsAg	Negative	
HCV Ab	Negative	
Quantiferon	Negative	
SPEP	Normal	
Cryoglobulins	Negative	

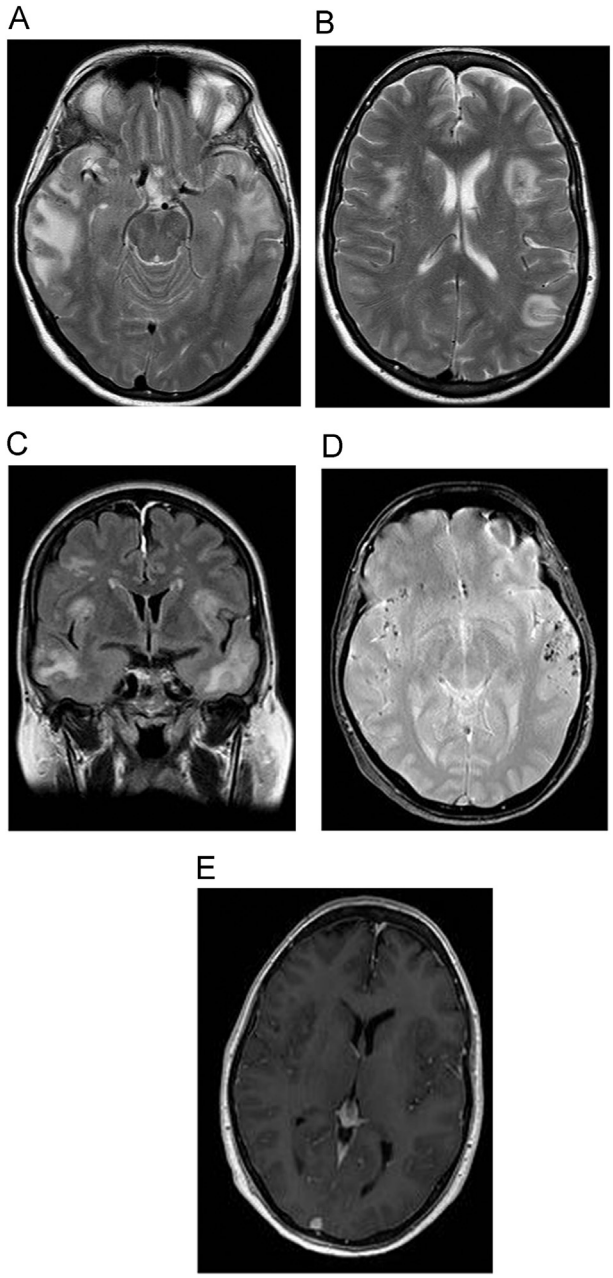

Fig. 1. (A–C) T2W sequences showing abnormal cortically and subcortically based hyperintensities throughout both temporal lobes, and in the frontal lobes. (D) Gradient-echo imaging study showing punctate hypointense foci due to microbleeds corresponding areas. (E) No significant enhancement with gadolinium contrast.

However, the brain biopsy showed typical findings of ABRA (Fig. 2), mainly transmural infiltration of vessel walls by lymphocytes and macrophages with the formation of granulomas and multinucleated giant cells in the background of cerebral amyloid angiopathy. Focal hemorrhage, fibrinoid necrosis, thrombosis, and recanalization were also present. No organism was identified on GMS, PAS, Gram, AFB, and Steiner stains. Immunohistochemical stains revealed Aβ in blood vessels walls and abundant $CD68^+$ macrophages, some of which contained Aβ. $CD3^+$ T cells with few $CD20^+$ B cells were also seen.

The patient was treated with high-dose prednisone (1 mg/kg/day) and six monthly infusions of cyclophosphamide. She was also given Levetiracetam for seizure prophylaxis. Repeat MRI 3 months after the admission showed almost complete resolution