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When Brain Biopsy Solves the Dilemma of Diagnosing Atypical Cerebral Amyloid Angiopathy: A Case Report

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 67-year-old
Final Diagnosis: Cerebral amyloid angiopathy related inflammation
Symptoms: Headache, Behavioral Changes • Seizures
Medication: —
Clinical Procedure: —
Specialty: Neurology • Neurosurgery

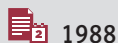
Objective: Rare disease
Background: Cerebral amyloid angiopathy-related inflammation (CAA-ri) is an acknowledged syndrome of reversible encephalopathy, also known as cerebral β -related angiitis. It is characterized by brisk progressive higher mental dysfunctions, headaches, seizures/epilepsy, and behavioral changes, and is highly responsive to immunosuppressive medications. To quickly and properly determine patients' management plans and prognoses, doctors are left with only CAA-ri-associated behavioral changes and seizures, in addition to a high index of suspicion of the correct diagnosis.

Case Report: A 67-year-old woman was presented to the emergency room (ER) with behavioral changes and seizures. Upon screening, the patient was found to have radiological evidence of asymmetrical cortical-subcortical white-matter lesions accompanied by multiple cerebral microbleeds in the background of the negative screening for infectious/neoplastic and paraneoplastic processes. After undergoing a brain biopsy, the diagnosis was confirmed to be amyloid deposition within the inflammatory vessel walls. The patient showed a dramatic improvement after methylprednisolone pulse therapy, plasma exchange, and rituximab maintenance.

Conclusions: We encourage and support brain biopsies to confirm highly suspicious CAA-ri atypical cases to initiate early treatment and achieve the best outcome without any further delays.

Keywords: Amyloid angiopathy • Biopsy • Dementia, Vascular

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/933869>



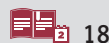
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Background

Cerebral amyloid angiopathy-related inflammation (CAA-ri) is a distinct subtype of cerebral amyloid angiopathy. It is characterized by an autoimmune reaction to cerebrovascular β -amyloid deposits in the blood vessel walls [1]. It was first described in 1995 at Massachusetts General Hospital [2] and is considered one of the causes of reversible encephalopathy [3,4]. CAA-ri presents with a wide variety of clinical symptoms and radiological features [1]. These collective features are under the umbrella of Chung et al's [5] diagnostic criteria, identified with clinical presentations of any form of focal neurological deficits, along with encephalopathy, in addition to MRI features suggestive of autoimmune/inflammatory processes in the absence of neoplastic infectious or other etiologies [2].

Here, we present a case of an elderly patient with atypical clinical and radiological features where a cerebral biopsy was required to confirm a CAA-ri diagnosis.

Case Report

A 67-year-old right-handed housewife was admitted to the Neurology Department reporting a left-sided unilateral headache. The headache was progressive for about 1 week prior to her admission to the ER, followed by behavioral changes of episodic delusional and illusionary ideations (reported by the family), with the development of generalized tonic clonic seizures. She had no history of suicidal thoughts or self-inflicted injury and reported no history of fever, neck stiffness, numbness, or weakness. Furthermore, she had no history of toxic exposure, herbal intake, nausea, vomiting, or visual changes.

The patient was presented to the ER in status epilepticus condition and was managed immediately by the neurology critical care unit. The seizures were aborted, but the patient again started experiencing symptoms of delusion, confusion, and agitation along with fluctuations in consciousness. The informant reported that the patient had a 3-year history of type 2 diabetes mellitus, hypertension, left lacunar subcortical anterior circulation ischemic stroke with a residual left-sided deficit, and 1 known attack of symptomatic seizure followed by post-ictal confusion for 2 weeks. The family history was unremarkable for epilepsy, cognitive disorders, or any inherited disease.

The patient's general physical examination was within normal limits and she was vitally stable. Upon her neurological examination, the patient was confused and exhibited noncoherent speech with disorientation to time and place. Neuropsychological tests were limited, given that the patient was illiterate. Furthermore, short-term memory and calculations were impaired. The cranial nerves were intact except



Figure 1. Brain computed tomography scan (CT). Yellow arrows indicate multiple bilateral subcortical hypodensities involving bilateral frontal, frontoparietal, and left temporal lobes with likely vasogenic edema that concerned underlying cortically-based lesions.

for the right upper motor neuron facial weakness. Regarding muscle power, her right-sided upper and lower limbs were 4/5 proximal and distal, but her tone was normal and symmetrical. Deep tendon reflexes were symmetrical, +1 all over, and she could still perform coordinated movements of bilateral upper and lower extremities in proportion to the weakness. Routine blood tests were initially unremarkable.

A brain computed tomography (CT) scan (**Figure 1**) showed multiple bilateral subcortical hypodensities involving bilateral frontal, frontoparietal, and left temporal lobes with likely vasogenic edema that were concerning for underlying cortically-based lesions.

These findings were elaborated extensively on brain magnetic resonance imaging (MRI)-contrasted images (**Figure 2**), which showed diffused white and gray matter edema involving the supratentorial structure with sparing of basal ganglia, brain stem, and cerebellum, associated with leptomeningeal enhancement, left frontal intraparenchymal subacute hemorrhage, and left frontoparietal and temporal old sequela of subarachnoid hemorrhage, given the impression of meningoencephalitis vs vasculitis.

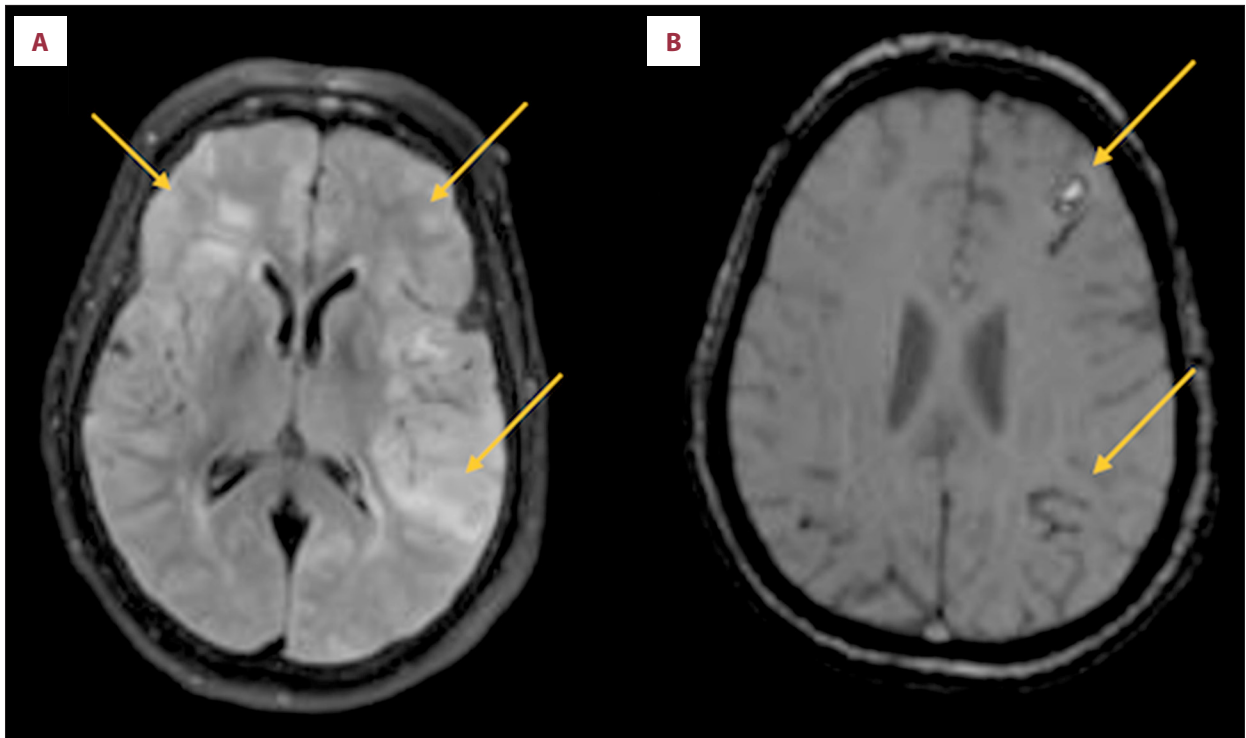


Figure 2. Magnetic resonance imaging (MRI)-contrasted images (A, B). Yellow arrows in (A) show diffused white and gray matter edema involving a supratentorial structure with sparing of basal ganglia, brain stem, and cerebellum associated with leptomeningeal enhancement. Yellow arrows in (B) show left frontal intraparenchymal subacute hemorrhage, and left frontoparietal and temporal old sequela of SAH, given the impression of meningoencephalitis vs vasculitis.

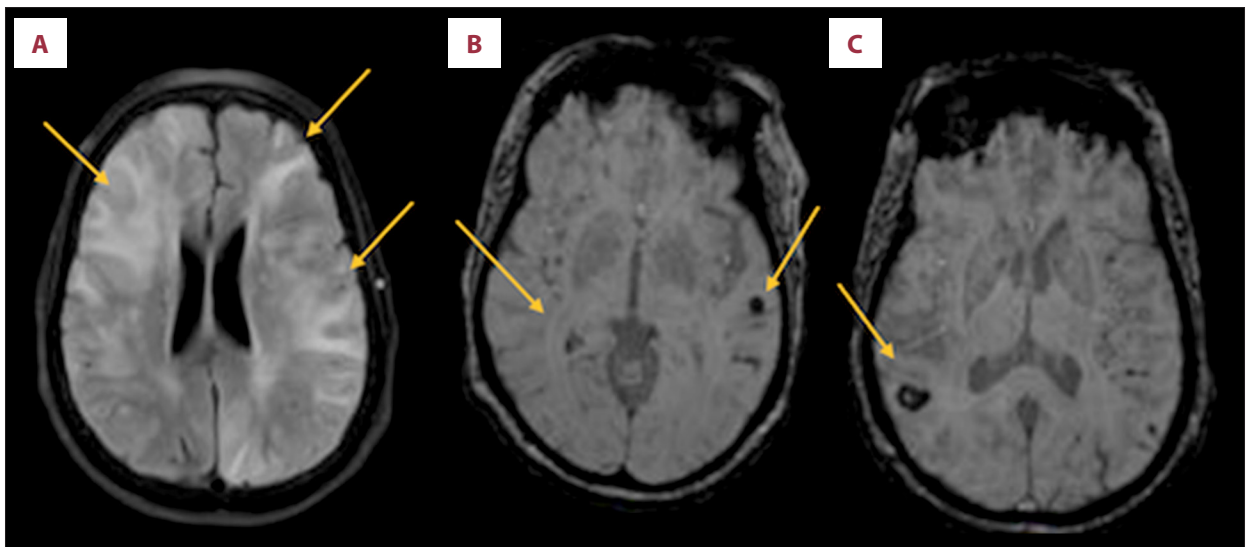


Figure 3. Follow-up head MRI (A-C). Yellow arrows in (A) show minimal progression compared to the prior exam. Yellow arrows in (B, C) show multiple-sided intraparenchymal microhemorrhage and evidence of leptomeningeal enhancement.

Further diagnostic workups, such as brain magnetic resonance angiography, could not be completed due to her complex behavioral agitations interfering with the workup process. During her hospitalization, infectious and autoimmune etiologies required investigation, such as viral encephalitis/meningitis,

central nervous system angiitis/vasculitis, acute disseminated encephalomyelitis (ADEM), and metastatic bleeding, which were all considered as differential diagnoses. Accordingly, certain laboratory workups had to be conducted, including a spinal fluid analysis, gram stain and culture, meningitis/



Figure 4. Post-biopsy CT images show no evidence of new hemorrhagic lesions or progression of the previous edema, with regression of prior lesions.

encephalitis panel, India ink stain, acid-fast stain, and cellular cytology and Oligoclonal bands, which were all within normal limits. Extensive laboratory workups, including an autoimmune profile and infectious panel, were negative except for the antinuclear antibody (ANA): 640 IU/mL, C-reactive protein (CRP): 2.23 mg/dL, and erythrocyte sedimentation rate (ESR): 48 mm/h. The thyroid function test and vitamin B12 levels were within the standard limit and the syphilis and HIV serological tests were negative.

Unfortunately, on the following days of admission, the patient deteriorated clinically and radiologically. A follow-up head MRI (Figure 3) showed minimal progression compared to the prior exam and a multiple-sided intraparenchymal microhemorrhage and evidence of leptomeningeal enhancement.

After excluding the infectious, autoimmune, neoplastic, and/or paraneoplastic process along with the collection of her clinical presentation and radiographic picture, a preliminary diagnosis of CAA-ri was considered and the patient began a methylprednisolone pulse therapy course for 5 days. Later, the patient underwent 5 sessions of plasma exchange, which fortunately stabilized her symptoms with no progression of her condition.

In the following weeks, the patient's condition improved partially day-by-day, but there was still no definitive diagnosis, and other differentials were still possibilities. However, an urgent decision was needed. As such, the neurological team advised and discussed the importance of a definitive diagnostic procedure such as a brain biopsy to confirm the CAA-ri diagnosis and provide a long-term medical plan. The risks and benefits were

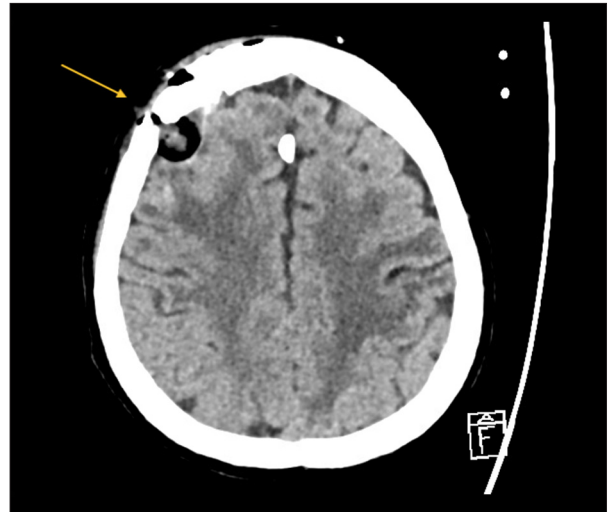


Figure 5. Post-operative changes at the right frontal area, with yellow arrow indicating localized pneumocephalus.

evaluated in collaboration with the Neurosurgery Department. Afterwards, an open biopsy was taken from the right frontal hemorrhagic lesion and preferred over the stereotactic biopsy since it is suitable for the cortical/subcortical lesions, it can provide better control for the hemorrhage, and it has high yield for positive tissue results due to the sample size. Although stereotactic biopsy has less invasive advantage, it is usually indicated for small and deep lesions, contraindicated in patients with bleeding disorders, and the rate of false-positive results is high due to the small tissue sample [17,18]. Upon analysis, the biopsy showed a variable degree of perivascular inflammatory cuffing, where the inflammatory infiltrates were composed predominantly of lymphocytes and gliosis, along with positivity for Congo red stain, which confirmed the CAA-ri diagnosis. Post-biopsy CT images (Figures 4, 5) showed no evidence of new hemorrhagic lesions or progression of the previous edema and confirmed the regression of the previous lesions. The patient started monoclonal antibody rituximab therapy, and her clinical condition returned entirely to normal baseline.

Discussion

In this report, we presented an elderly patient who had recurrent behavioral changes and seizure disorders in the presence of abnormal radiographic parenchymal changes. These symptoms represent a vast and heterogeneous group of diseases that are responsible for reversible encephalopathic pictures and are mostly treatable if discovered early. Their diagnosis is challenging and requires high clinical suspicion along with the aid of imaging modalities. Reversible encephalopathy disorders can be defined by the presence of recurrent clinical and radiographic evidence of heterogeneous etiologies that affect brain parenchyma and vasculature. Moreover, its

clinical features are usually variable, like headaches, seizures, psychiatric disorders, blurred vision, and motor/sensory focal neurological deficits. At the same time, the radiographic features are typically nonspecific like vasogenic edema, infarctions, or hemorrhages [14].

In the presence of similar clinical presentations, a list of crucial differential diagnoses should be ruled out by different imaging modalities versus laboratory workups. Most common are the rare variants of cerebral amyloid angiopathy-related inflammation, central nervous system (CNS) vasculitis/angiitis, infective encephalitis/meningitis, reversible posterior leukoencephalopathy syndrome (PRESS), and brain tumors [15].

CAA consists of cerebrovascular amyloid deposition and is categorized into multiple classes according to the pathological amyloid protein deposition [6]. The clinical subset of CAA is the spectrum of CAA-ri, which is mainly composed of rapidly progressive encephalopathy (76%), headaches (41%), seizures (31%), and stroke-like focal neurological deficits [7,15].

Most commonly, sporadic amyloid β -protein (A β)-type CAA is found in patients with Alzheimer disease [3]. To a lesser extent, CAA-associated vasculopathies complicated by hemorrhagic/ischemic lesions, encephalopathies, and superficial siderosis have also been reported, including, more rarely, CAA-associated inflammation/angiitis [8]. CAA-associated inflammation and angiitis share the same clinical features; however, they differ on the pathological standard of view: the former has perivascular infiltration around the vasculature and the latter has transmural and intramural inflammation with the development of a granuloma [3]. With this report, we focused on discussing one of the etiologies of reversible encephalopathy, the rare entity of CAA-ri [3,4], which was first reported in 1995 at Massachusetts General Hospital [2]. Its prevalence among the asymptomatic elderly population is 23-57% [9], and it affects men and women equally, mainly around 70 years of age [10].

Because CAA-ri has a wide variety of clinical syndrome mimickers, a straightforward diagnosis is quite challenging. Due to this fact, Chung and colleagues [5] proposed a list of diagnostic criteria that help distinguish CAA-ri from other potential diagnostics. As such, a CAA-ri diagnosis requires the following 4 findings: (1) presentation with a variable clinical feature like headache, fluctuation in consciousness, behavioral change, focal neurological deficits, and seizures; (2) MRI with asymmetrical, patchy, or confluent lesions at T2-weighted images or fluid-attenuated inversion recovery (FLAIR), with or without mass effect, and leptomeningeal or parenchymal enhancement; (3) new or old multiple lobar/intracerebral microhemorrhages, and (4) the absence of other etiology like neoplastic, paraneoplastic, or infectious causes [2,5]. Later, the diagnostic criteria were further improved and now rely on the following: (1)

clinical symptoms previously demonstrated, (2) the presence of white-matter hyperintensities patterns that extend to the immediately subcortical white matter, and (3) the presence of superficial siderosis used as a bleeding indicator with or without true bleeding [2,11].

Even with a relatively long list of diagnostic criteria, a definitive CAA-ri diagnosis can only be achieved with a brain biopsy and clear histological confirmation of Congo red. Sakaguchi et al [7] and Aghetti et al [12] have also previously reported this fact. Our case supports this fact as there are many cases like our own that do not satisfy the CAA-ri list of criteria. Furthermore, we suggest that the clinical spectrum of CAA-ri is more variable than previously thought. Therefore, a brain biopsy should be performed in neurological diseases of unknown etiology, and, more specifically, in atypical presentations.

Several risks and complications have been addressed with the biopsy, particularly in the background of patients with multiple comorbidities, like infectious processes and coagulopathies, and brain biopsies should be considered and discussed with multidisciplinary teams depending on the patient's overall condition. However, the procedure's benefit increases with the presence of a radiological lesioned target and 83.1% of biopsies yielded a final diagnosis, leading to a better patient treatment plan [15,16].

A brain biopsy carries a mortality risk in 0% to 1% of cases and morbidity in 3% to 5% of these cases [2]. However, as Du and colleagues previously suggested, the decision must be encouraged in case the patient fails to respond to the corticosteroid/immunosuppression therapy within the limited time of approximately 3 weeks or shows any atypical presentation, as in our case [3]. From this prospective, a brain biopsy revealed our patient's diagnosis after failure to respond to corticosteroid therapy.

Mathon and Le Joncor's article supported the early consideration of brain biopsy in patients with unknown etiology as it has high diagnostic yield and low frequency of severe complications [16].

Lastly, no standard treatment protocol has been established to date for the definitive treatment of CAA-ri, and the best therapy remains to be determined. However, corticosteroid/immunosuppression therapy seems to be a mainstay treatment [13]. Further studies should aim to compare the effectiveness of specific immunosuppressive medications. As in our case, the prolonged use of monoclonal antibody rituximab (monoclonal antibody against the protein CD20) after an initial methylprednisolone pulse therapy significantly improved the patient's condition.

Conclusions

We report the case of a patient with CAA-ri whose cortical dysfunctions, seizure risk, and radiological imaging status dramatically improved with immunosuppressive medication. Our case also supports the importance of brain biopsies in reference to previous literature and its value for earlier diagnosis of CAA-ri. A correct diagnosis and treatment are crucial for an efficacious recovery and good prognosis in these rare patients.

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