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Cerebral amyloid angiopathy-related inflammation presenting with a cystic lesion in young-onset Alzheimer's disease

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Abstract

We describe a patient with cerebral amyloid angiopathy-related inflammation (CAA-ri) presenting as Alzheimer's disease (AD) with a mass lesion with symptom onset at age 59. He was found to have a non-enhancing lesion in the right temporal lobe on MRI without evidence of hemorrhage. He underwent a biopsy which showed amyloid beta in blood vessel walls and a perivascular inflammatory infiltrate consistent with CAA-ri. Neurofibrillary tangles were present and a flortaucipir PET showed bilateral signal highest in the lateral temporal and parietal cortices. A lumbar puncture showed tau, p-tau, and amyloid beta levels consistent with AD without evidence of inflammation. He was homozygous for the *APOE* ε4 allele. He died at age 67. A focus of CAA-ri can be present in the context of AD with a mass lesion and without evidence of hemorrhage, significant ischemic changes, or overt inflammation on cerebrospinal fluid examination.

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Background

Deposition of amyloid-beta protein, or Aβ, in the brain parenchyma is a hallmark feature of Alzheimer's disease (AD). A moderate to severe degree of concurrent deposition of Aβ in the walls of small cerebral blood vessels, or cerebral amyloid angiopathy (CAA), is found in 36 - 39% of patients with AD and is associated with the ε4 allele of the Apolipoprotein E (*APOE*) gene[1,2]. Rarely CAA can have an inflammatory component, presenting as a vasculitis termed CAA-related inflammation or CAA-ri. CAA-ri typically presents subacutely with cognitive or behavioral changes, focal findings, headaches, or seizures[3,4]. MRI typically demonstrates focal or multifocal edema, often with mass effect, though 15-25% of the time CAA-ri can present as a mass lesion suggesting a neoplasm[4]. We describe a patient presenting with an AD-like syndrome with a focus of CAA-ri without evidence of more widespread CAA or inflammation.

Methods

We present a case report with clinical, imaging, biochemical, genetic, and brain biopsy results. The patient and his legal representative provided written informed consent and participated in an IRB-approved research protocol at the University of Southern California.

Results

With a medical history significant only for hyperlipidemia treated with simvastatin, a Mexican-American mestizo man was noted to have the onset of forgetfulness at age 59, followed by word-finding difficulties. At age 61 he was treated for AD with donepezil. At age 64 he scored 13/30 on the MMSE, had difficulty saying the days of the week in reverse, could produce only 4, 4-legged animals in 30 seconds, and was concrete when describing similarities between objects. Overall, he had difficulties with executive function, memory, language, and visuospatial abilities on the bedside neurobehavior exam. Formal neuropsychological testing was not obtained. His symptoms progressed and by age 65 he was having difficulties with self-care activities such as feeding and dressing. There was no history of headaches, seizures, and he had no focal neurological findings such as hemiparesis. Though increasingly paranoid, he had no history of hallucinations. At age 65 his MoCA and MMSE scores were 3/30 and Clinical Dementia Rating (CDR) score was 2, representing moderate dementia. The patient's mother had died at age 73 after a 10 year history of dementia and at least 3 of her siblings developed AD beginning in their early 60's. The patient's sister had been residing in a nursing home with dementia, her symptoms having started at age 64. She died at age 68. Brain MRI of the current patient at age 64 showed an isolated 2.4 by 3.5 cm non-contrast enhancing lesion with mild mass effect in the anterior aspect of the right temporal lobe (Figure 1a–c). Also present were mild cortical atrophy and mild microangiopathic white matter disease on FLAIR imaging (Figure 1b) without evidence of macro- or microhemorrhage or superficial siderosis on gradient-recalled echo (GRE, Figure 1e) sequences or susceptibility-weighted (SWI, Figure 1f).

Based on suspicion of a low-grade glioma, a subtotal brain biopsy was performed which did not show a neoplasm and was negative for IDH1 R132H immunoreactivity. Blood

vessel walls showed Congo red positive refractile eosinophilic material with apple-green birefringence and transmural histiocytes, vessel wall injury and fibrinoid necrosis, consistent with CAA-ri (Figure 2). There was a leptomeningeal perivascular infiltrate (Figure 2a) consisting of CD3-immunopositive T-cells and CD68 positive macrophages (Figure 2c, d). Immunostains for $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ showed staining in the walls of meningeal and cortical arterioles with CAA (Figure 2b), and occasional diffuse plaques. Tau immunostaining highlighted frequent neuropil threads and neurofibrillary tangles, consistent with a Braak stage of VI. After the biopsy and possibly as a result of it, the patient's personality changed such that he became more irritable and disinhibited.

A lumbar puncture was unremarkable, including a normal total protein level, one white blood cell, and the absence of elevated intrathecal IgG synthesis. Cerebrospinal fluid was examined at a commercial laboratory which identified diminished levels of $A\beta_{1\text{-}42}$ (233.05 pg/ml) and elevated levels of total tau protein (530.1 pg/ml) for a normalized ratio of Aβ42/t-tau of 0.27 (ratio less than 0.8 consistent with AD). Phosphorylated tau was elevated at 78.25 pg/ml (normal less than 54 pg/ml), also consistent with the diagnosis of AD. Positron emission tomography (PET) with flortaucipir showed a widespread elevated signal, particularly (SUVR's greater than 5.0) in the inferior and middle temporal gyri, the lateral and medial parietal lobes (including the precuneus), and the frontal pole and middle frontal gyri bilaterally (Figure 1g–i). Amyloid PET imaging was not obtained. Genetic testing revealed homozygosity for the ε4 variant of *APOE*.

At age 67 he was placed on hospice but then worsened subacutely such that his speech was incomprehensible and he was not eating, drinking, or ambulating independently. In light of a possible contribution from inflammation, treatment with dexamethasone at 4 mg/day was initiated. After two days, he was described as being more alert, having more understandable speech, and eating, drinking and walking with less assistance. However, due to poor sleep at night and increasing combativeness, the dexamethasone was discontinued after 3 weeks with a return to his baseline state. The patient died 4 months later. An autopsy was not performed due to the COVID-19 pandemic.

Discussion

CAA-ri is an inflammatory condition in which autoantibodies are directed towards the β-amyloid protein[5]. It is associated with the *APOE* ε4/4 genotype in up to 70% of cases[4]. Though frequently causing diffuse inflammation, it can present with severe hemorrhage and edema[6] and 15-25% of the time CAA-ri can present as a mass lesion[4]. In a review of 28 cases of CAA-ri initially suspected of having tumors[7], 64% presented with cognitive impairment with 36% having focal deficits, 25% having seizures, and 21% having headaches. Microhemorrhages were present in all cases.

Our patient presented with progressive changes in memory and executive function, later involving other aspects of cognition evolving over an 8 year period. The older age of onset, presence of changes in cognition, and lack of focal findings such as hemiparesis or vision changes is consistent with CAA-ri and differentiates it from primary CNS vasculitis[8]. However, without headaches, seizures, or evidence of hemorrhage on imaging or

inflammation in the cerebrospinal fluid, the focal inflammatory lesion in the temporal lobe almost represented an incidental finding. Immunosuppressive treatment was therefore not initiated until a subacute deterioration later in the patient's disease course.

Diagnostic criteria for CAA-ri have been proposed which include the presence of patchy or confluent T2 or hyperintensities and evidence of lobar microhemorrhages or superfical siderosis suggesting pre-existing CAA on GRE or SWI[9]. Our case of biopsy-proven CAA-ri had no evidence of hemorrhage and only minimal FLAIR hyperintensities and therefore would not meet these criteria. It is exceptional for the isolated, cystic-appearing nature of the lesion and typical, if relatively rapid, non-focal, AD-like presentation.

Conclusions

Our patient had the presence of inflammatory CAA presenting with a cystic lesion in the absence of evidence of prior hemorrhage or significant FLAIR hyperintensities. It demonstrates that CAA-ri can occur on a spectrum from being a diffuse, multifocal inflammatory disease of subacute onset to a focal process concurrent with young onset but otherwise typical AD. We are unaware of any prior description of CAA-ri occurring as an almost incidental MRI finding in AD.

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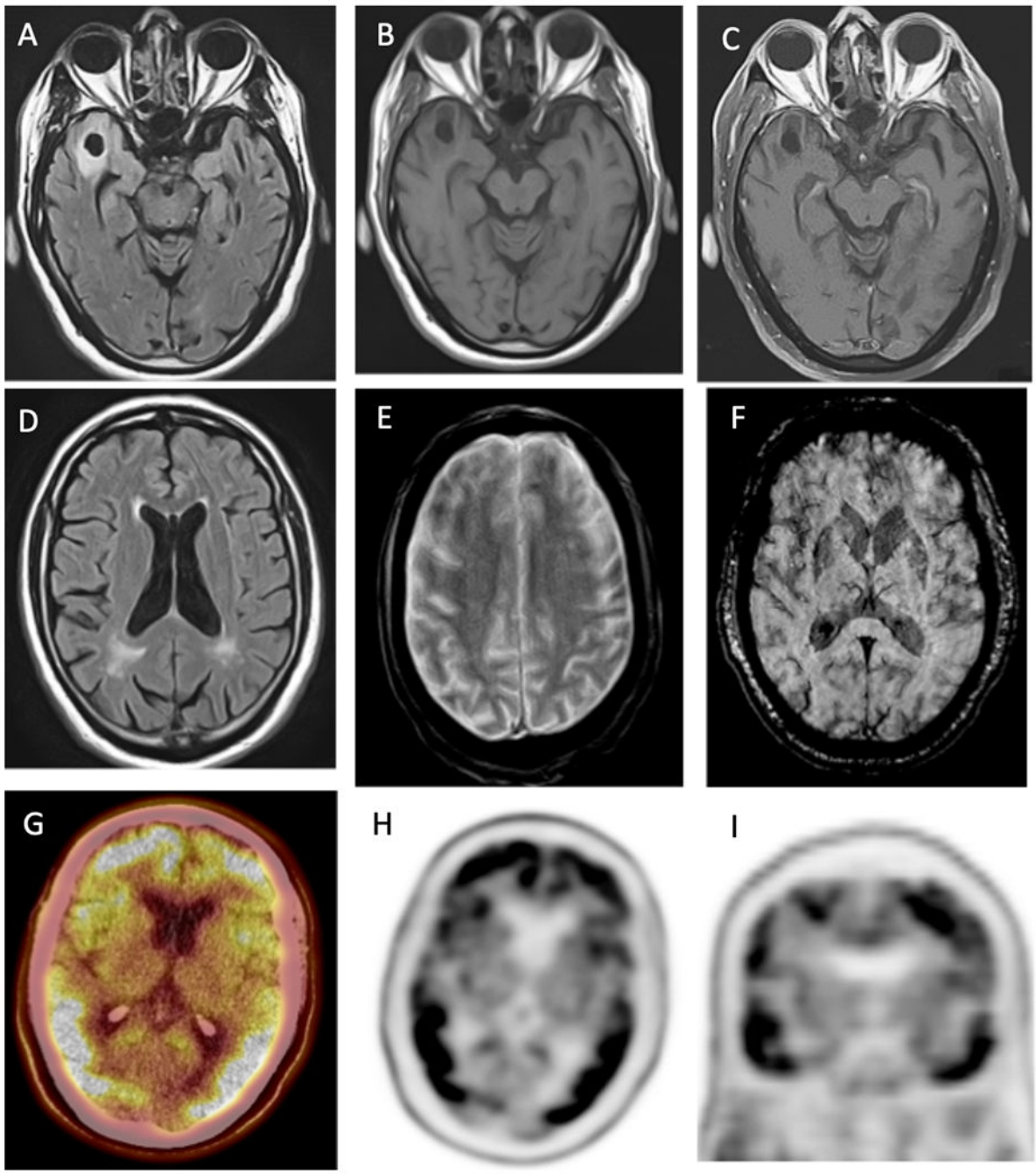

Figure 1.

a) Axial FLAIR image showing the low intensity cystic mass in the right anterior temporal lobe with rim of hyperintensity, b) Axial T1 pre- and post- contrast (c) images at the level of the right temporal lesion showing no evidence of enhancement, d) white matter hyperintensity changes around the ventricles and centrum semiovale, e) axial gradient recalled echo and f) susceptibility weighted images show no evidence of cerebral microbleeds or superficial siderosis, g) axial PET-CT co-registered image and h) axial and

i) coronal flortaucipir PET images demonstrate the significant cortical uptake of tau in the lateral temporal, parietal and frontal cortices.

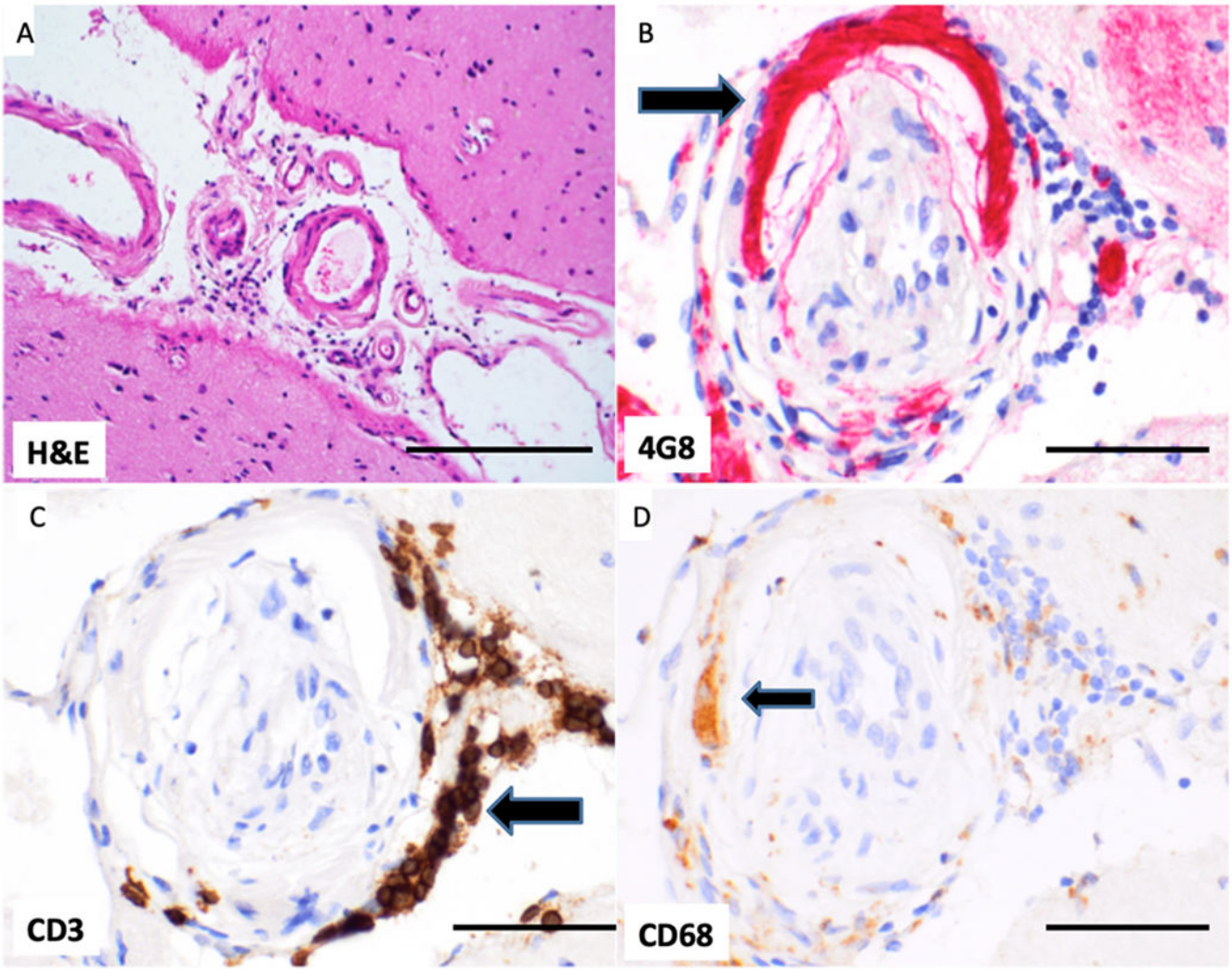

Figure 2.

a) Leptomeningeal vessels with amyloid deposition surrounded by chronic perivascular infiltrate (scale bar=500 [mu]m), b) High power 4G8 immunostain is highlighting beta-amyloid in the walls (black arrow) of a disrupted vessel located in the leptomeninges that is surrounded by an inflammatory infiltrate (scale bar=160 [mu]m), c)(Most of the perivascular and leptomeningeal lymphocytes are CD3-immunopositive T cells (black arrow) (scale bar=160 [mu]m), d)) CD68 is highlighting the macrophages around the vessel (black arrow) in the same areas as the amyloid deposition (scale bar=160 [mu]m).