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Pathology-Proven Cerebral Amyloid Angiopathy in a Patient with Spontaneous Intracerebral Hemorrhage

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ABSTRACT

Cerebral amyloid angiopathy (CAA) related intracerebral hemorrhage (ICH) accounts for 20% of all types of spontaneous ICH. Results of brain magnetic resonance imaging (MRI) supports the clinical diagnosis of suspected CAA and can help predict the future risk of ICH. A definitive diagnosis of CAA requires brain biopsy and histopathological analysis.

Here we report a case of a patient with biopsy proven CAA without any evidence of typical MRI brain markers of the condition as described in Boston criteria version 2.0.

A 63-year-old man with a history of hypertension, type 2 diabetes mellitus, coronary artery disease on aspirin, and melanoma presented to the emergency department with acute headache and confusion. He was not anticoagulated. He had no history of dementia or head trauma. CT head showed an acute left temporal-parietal ICH with 2 mm midline shift. CTA head and neck were unremarkable. MRI of the head with and without contrast demonstrated a left temporal ICH with no underlying mass and no evidence suggestive of amyloid angiopathy on susceptibility weighted imaging (SWI) sequence. The mechanism of ICH was thought to be due to hypertension or an underlying neoplasm given his history of melanoma. Surgical evacuation of the hemorrhage was performed and histology was suggestive for CAA.

Our case is noteworthy because the diagnosis of CAA was unsuspected based on MRI findings described in Boston criteria version 2.0.

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Abbreviations

CAA: Cerebral Amyloid Angiopathy
MRI: Magnetic Resonance Imaging
ICHP: Intracerebral Hemorrhage
TFNE: Transient Focal Neurologic Episodes
CI: Cognitive Impairment
CMB: Cerebral Microbleed
cSS: Cortical Superficial Siderosis
cSAH: Convexity Subarachnoid Hemorrhage
CSO-PVS: Visible Perivascular Spaces in the Centrum Semiovale
WMH-MS: White Matter Hyperintensities in a Multispot Pattern

Introduction

Cerebral amyloid angiopathy (CAA) is characterized by the accumulation of amyloid beta-peptide within the leptomeninges and small to medium-sized cerebral blood vessels [1]. The occipital lobes are most affected [2]. The pathophysiology of intracerebral hemorrhage (ICH) in CAA is not completely understood, but is thought to be due to weakening of small and medium-sized blood vessels from amyloid protein deposition [1]. CAA-related ICH accounts for 20% of all types of spontaneous ICH [3]. Results of brain magnetic resonance imaging (MRI) supports the clinical diagnosis of suspected CAA and can help predict the future risk of ICH. A definitive diagnosis of CAA requires brain biopsy and histopathological analysis [4,5].

Here we report a case of a patient with biopsy proven CAA without any evidence of typical MRI brain markers of the condition, such as cortical superficial siderosis, microbleeds, convexity subarachnoid hemorrhage, or white matter changes, as described in Boston criteria version 2.0 [6]. Our case is noteworthy because the diagnosis of CAA was unsuspected based on these MRI findings.

Case Description

A 63-year-old man with a history of hypertension, type 2 diabetes mellitus, coronary artery disease, percutaneous coronary intervention 1 week prior to presentation, melanoma resected from the left cheek in 2001, and prostate cancer resected in 2006 presented to the emergency department with acute headache and confusion. He was receiving aspirin for coronary artery disease but was not anticoagulated. He had no history of dementia and no recent head trauma. His father had an ischemic stroke at age 40-years, but there was no family history of dementia or brain hemorrhage. He did not use combustible tobacco, consume alcohol, or use illicit drugs.

His neurological examination was notable for mild expressive aphasia, mild to moderate decreased sensation to light touch on the right upper extremity, and pronator drift in the right upper extremity. His National Institutes of Health Stroke Scale (NIHSS) score was 3-points. His ICH score was 1. Laboratory studies

showed no significant abnormalities, including a normal platelet count, an undetectable anti-factor Xa level, and INR 1.2. His SARS-CoV2/Covid-19 PCR was negative. Initial head CT showed an acute left temporal-parietal ICH with 2 mm midline shift (Figure 1). CT angiogram of the head and neck showed no thrombus, large vessel occlusion, or aneurysm. The mechanism of ICH was thought to be due to hypertension or an underlying neoplasm given his history of melanoma. MRI of the head with and without contrast demonstrated a left temporal ICH with no underlying mass (Figures 2A and 2B) and no evidence suggestive of amyloid angiopathy on susceptibility weighted imaging (SWI) sequence (Figure 2C).

Surgical evacuation of the hemorrhage was performed. Histological evaluation with hematoxylin-eosin staining showed medium to small arteries with severely thickened and smudgy eosinophilic rigid walls, suspicious for amyloid angiopathy (Figures 3A and 3B). This was confirmed by a positive Congo-red staining (Figures 3C and 3D).

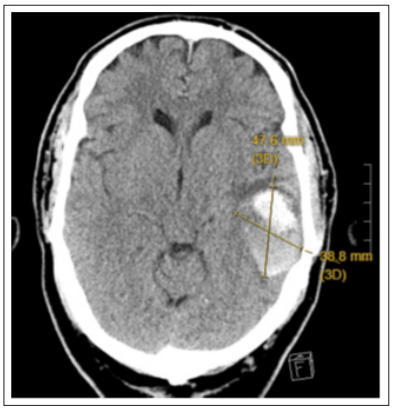

Figure 1: CT Head without Contrast Demonstrating Acute ICH in the left Temporal-Parietal Region

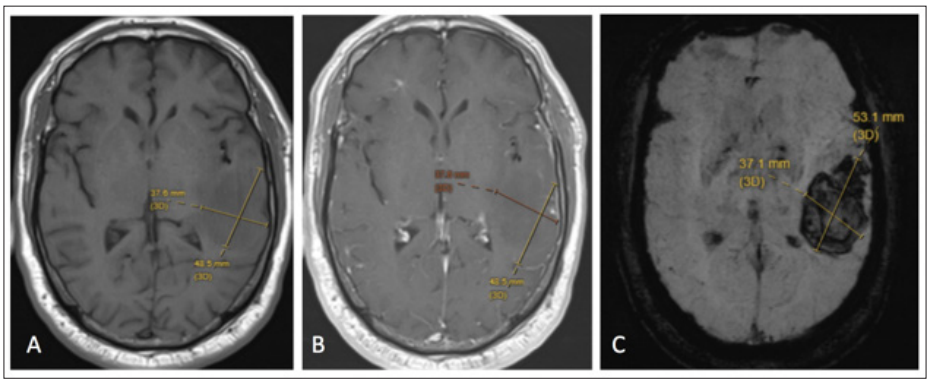

Figure 2: MRI Head, from Left to Right, (A) T1 without Contrast, (B) T1 with Contrast, (C) SWI sequence

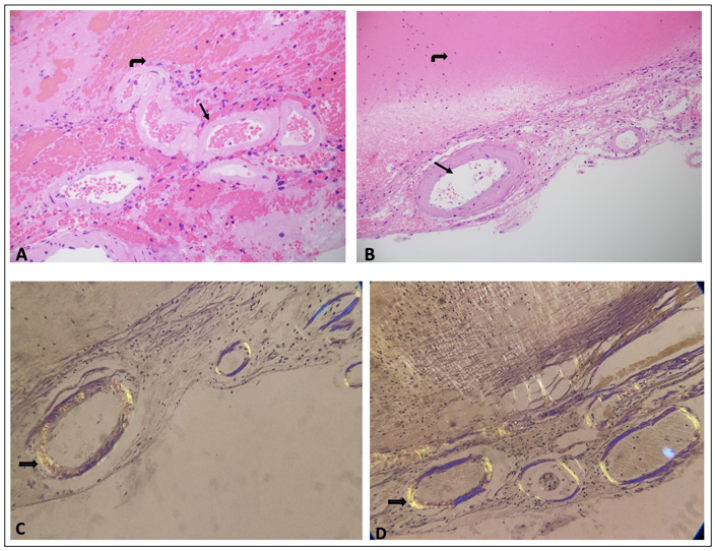

Figure 3: (A, B) H&E Stain Demonstrating Medium to small Arteries with Severely Thickened and Smudgy Eosinophilic Rigid wall in a Background of Bleeding. BLEED is Superficially Located in the Cerebral Cortex (lobar) or Subarachnoid Space. (C, D) Congo Red Special Stain viewed with Polarized Light Shows the Apple Green Refractile Color that is Associated with Cerebral Amyloid Angiopathy.

Immediately post-operatively the patient had generalized seizure-like activity and was treated with levetiracetam 1000 mg twice daily. He was discharged to an acute rehabilitation facility and then home with outpatient physical, occupational, and speech therapy. Four months later, he denied any further stroke or seizure symptoms. He complained of a post-ICH headache that was treated with gabapentin. A year later his NIHSS score had improved to 1-point.

Discussion

CAA and hypertensive angiopathy are two common causes for cerebral microbleeds. In CAA, amyloid-B deposition is typically found in the cortical and leptomeningeal blood vessels. In hypertensive angiopathy, the deep perforator arteries are affected, causing leakage from damaged vessels. It is important to understand the mechanism as the recurrent hemorrhage rate differs based on the underlying pathology [7]. A meta-analysis found that the annual risk of recurrent ICH was higher in patients with CAA compared to other types of ICH (7.4% vs 1.1 %) [8].

The Boston criteria was developed to standardize the clinical diagnosis of CAA and to help differentiate underlying etiologies. CAA is categorized into 4 types: definite, probable with supporting pathology, probable, and possible [9]. Lobar hemorrhages or cortical superficial siderosis on MRI are associated with a pathological diagnosis of CAA. Topographical patterns of microbleeds can be used clinically to understand the vascular pathology which can help in management [7].

The latest Boston criteria version 2.0 has updated the definition of probable CAA to incorporate emerging MRI markers [6]. Notably, the revised criteria support the diagnosis of probable CAA based on the presence of multifocal convexity subarachnoid hemorrhages, cortical superficial siderosis, or both, without the requirement for accompanying parenchymal intracerebral hemorrhage or cerebral microbleeds. The incorporation of multifocality of cortical superficial siderosis and multifocal convexity subarachnoid hemorrhage or cortical superficial siderosis as at least two hemorrhagic lesions that can alone meet the definition of probable CAA are important changes to the revised criteria. Another important update in the Boston criteria version 2.0 is the inclusion of CAA-related white matter lesions, which are defined as several perivascular spaces (more than 20) in the centrum semi-ovale or 10 white matter hyperintensities in a multispot pattern. Our patient did not have any evidence of superficial siderosis, convexity subarachnoid hemorrhage, white matter disease, or increased perivascular spaces. It is possible that the microbleeds were too small to be visualized on MRI. According to the recent article by Susanne J. van Veluvw @ al, the sensitivity Boston Criteria Version 2.0 for the diagnosis of CAA in a community-based sample was only 38.8 % but the specificity was 83.5 %. Even though the sensitivity of Boston criteria version 2 was better than the Boston criteria versions 1.0 and 1.5 (sensitivity 26.5 % in both), still there could be higher chances of MRI negative but biopsy proven CAA. [10].

Amyloid deposition in the vascular wall increases the risk for cerebral hemorrhage and platelet antiaggregants and anticoagulants should be used with caution [11]. In our patient, aspirin was stopped after the diagnosis of CAA [12,13].

Boston Criteria Version 2.0 for Sporadic Cerebral Amyloid Angiopathy [6].

	Boston Criteria (Version 2)	
1. Definite CAA	Full post-mortem examination demonstrating: • Presentation with spontaneous ICH, TFNEs, cSAH, or CI/dementia • Severe CAA with vasculopathy • Absence of other diagnostic lesion	
2. Probable CAA with Supporting Pathology	Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating: • Presentation with spontaneous ICH, TFNEs, cSAH, or CI/dementia • Some degree of CAA in specimen • Absence of other diagnostic lesion	
3. Probable CAA	Clinical data and MRI demonstrating: • Age ≥50 years • Presentation with spontaneous ICH, TFNEs, or CI/dementia • ≥2 of the following strictly lobar haemorrhagic lesions on T2*-weighted MRI, in any combination: ICH, CMB, cSS/cSAH foci	
	OR	
	• One lobar hemorrhagic lesion + one white matter feature (severe CSO-PVS or WMH-MS) • Absence of any deep hemorrhagic lesions (ICH, CMB) on T2*weighted-MRI • Absence of other cause of hemorrhagic lesions • Hemorrhagic lesion in cerebellum not counted as either lobar or deep hemorrhagic lesion	

	4. Possible CAA	Clinical data and MRI demonstrating: • Age ≥50 years • Presentation with spontaneous ICH, TFNEs, or CI/dementia • Absence of other cause of hemorrhage • One strictly lobar hemorrhagic lesion on T2*-weighted MRI: ICH, CMB, cSS/cSAH focus OR • One white matter feature (severe CSO-PVS or WMH-MS) • Absence of any deep hemorrhagic lesions (ICH, CMB) on T2*-weighted MRI • Absence of other cause of hemorrhagic lesions • Hemorrhagic lesion in cerebellum not counted as either lobar or deep hemorrhagic lesion

Notable changes from currently used criteria indicated in bold font.

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Conflict of Interest Statement
The authors declare that there is no conflict of interest. The findings and conclusions in this manuscript are those of the authors alone and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Statement of Ethics
This research does not include pertinent patient information.

Author Contributions
M. K. and H.A.A. collected the data and interpreted the diagnosis. M.K. and M.T. analyzed the literature and wrote the manuscript. H.A.A. helped in collecting the data. K.J.S., M.K., and M.T. provided framework for the study and reviewed and edited the manuscript. All authors read and agreed to the final version of the manuscript.

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