
Case Report

Cortical Petechial Hemorrhage, Leukoencephalopathy, and Subacute Dementia Associated With Seizures Due to Cerebral Amyloid Angiopathy

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Although cerebral amyloid angiopathy is a well-known cause of cerebral lobar hemorrhage, subacute dementia, seizures, and acute encephalopathy without lobar hemorrhage are infrequently recognized as manifestations of this disease. In this report, we describe a case of cerebral amyloid angiopathy in a 74-year-old woman who had subacute progressive dementia and a superimposed rapid acute neurologic deterioration associated with seizures and the presence of cerebral edema on computed tomographic scans and leukoencephalopathy and cortical petechial hemorrhages on magnetic resonance imaging. A diag-

nosis of cerebral amyloid angiopathy in conjunction with small cortical infarcts and petechial hemorrhages was confirmed by antemortem biopsy. This clinical and radiologic picture is being increasingly recognized as characteristic of cerebral amyloid angiopathy.

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CAA = cerebral amyloid angiopathy; CSF = cerebrospinal fluid; CT = computed tomographic; MRI = magnetic resonance imaging

Cerebral amyloid angiopathy (CAA) is a common finding in autopsy studies of hospitalized geriatric patients; it is found in 27 to 32% of elderly patients without dementia, cerebral hemorrhage, or infarction.^{1,2} The prevalence increases to 82 to 88% in patients with dementia of the Alzheimer type,^{1,3} in comparison with 35 to 42% of patients with dementia of the non-Alzheimer type.^{1,3} Pathologic studies of CAA frequently identify small cortical infarcts, punctate cortical hemorrhages, and lobar hemorrhages. Clinical correlation shows that patients with CAA most commonly have dementia or vascular events (or both) at the time of initial examination.⁴ Lobar hemorrhages are highly suggestive of CAA and are easily identified with cranial computed tomographic (CT) scanning.⁵

In recent reports, the initial manifestations of CAA have been subacute dementia or focal seizures in conjunction with magnetic resonance imaging (MRI) evidence of small cortical hemorrhages, with or without the larger more typical

lobar hemorrhages usually associated with CAA.^{6,9} Although commonly noted at pathologic examination, these small cortical hemorrhages are beyond the resolution of CT scans, and only with the development of MRI has this finding been recognized.

Herein we describe a patient with CAA in whom an acute encephalopathy developed, superimposed on a subacute progressive dementia. The MRI findings were characteristic, and the diagnosis was confirmed by antemortem biopsy.

REPORT OF CASE

In a 74-year-old woman with a subacute dementia and superimposed acute encephalopathy, further medical assessment was requested. She had a history of type II diabetes mellitus treated with insulin and borderline hypertension. She was a nonsmoker and before the current illness had no history suggestive of cerebrovascular disease. Ten months before admission, a mild change in personality, including increased irritability and depression, was noted. Eight months before admission, she began to have difficulty walking and to drag her left leg. Mild cognitive changes were first detected as a deterioration in memory for conversations, birthdays, and new names. Cognitive problems gradually progressed; poor appetite developed, her interest in current events and reading diminished, and her writing deteriorated. The rate of worsening increased in the weeks before admission.

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On the day of admission, the patient awoke from sleep at 2:30 AM and complained of a severe generalized headache. Her husband noted twitching of her shoulders during the next few hours and was unable to awaken her. After admission, she had two generalized tonic-clonic seizures and was treated with midazolam and phenytoin. A cranial CT scan demonstrated mass effect and edema of the right hemisphere (Fig. 1). MRI revealed mass effect in association with widespread changes in the white matter, maximal in the right hemisphere, and a small subacute hemorrhage in the posterior right frontal lobe. Throughout both hemispheres, multiple tiny foci of low signal were noted in the cortical areas (Fig. 2), most likely representative of hemosiderin because the CT scan at these levels showed no evidence of calcium and the foci became darker and more prominent with progressive T2 weighting. This finding was most obvious on gradient-recalled echo sequences ("blooming effect"). Dexamethasone treatment (16 mg/day) was commenced.

On examination, the patient's blood pressure was 160/90 mm Hg, and she demonstrated Cheyne-Stokes respiration. The other findings on the general examination were normal. The patient opened her eyes when her name was called, but no reliable verbal response was elicited. She had bilateral grasp, snout, and palmomental reflexes. The pupils were symmetric and reacted to light. The ocular fundi were normal, and the corneal reflexes were symmetric. No facial weakness was noted; the gag reflex was reduced. Tone was increased in all limbs, and she had semipurposeful limb movements to painful stimuli. The reflexes were brisk and symmetric, with bilaterally upturning plantar reflexes.

The following investigations yielded normal results: hemoglobin, leukocyte count, platelets, urea, electrolytes, and liver function tests. The serum creatinine was mildly increased at 1.3 mg/dL (normal, 0.6 to 0.9). The activated partial thromboplastin time and prothrombin time were initially normal. Six days after admission, the activated partial thromboplastin time remained normal, whereas the prothrombin time was 14.0 seconds (normal, 10.9 to 12.8), which was readily corrected by administration of vitamin K. The patient was taking no medications that could have explained the slightly prolonged prothrombin time. No evidence of disseminated intravascular coagulation was found on a coagulation screen, which showed normal fibrinogen, fibrinogen split products, and D-dimers. Normal or negative results were noted for antinuclear antibody, anticardiolipin antibody, liver enzymes, and cryoglobulins. The cerebrospinal fluid (CSF) opening pressure was 13 cm, in conjunction with protein 522 mg/dL (normal, 14 to 45), glucose 225 mg/dL, and a nonreactive Venereal Disease Research Laboratory test. Studies showed 13 nucleated cells/ μ L (2% neutrophils, 85% lymphocytes, and 13% monocytes) and 140 erythrocytes/ μ L. An electroencephalogram revealed bilat-

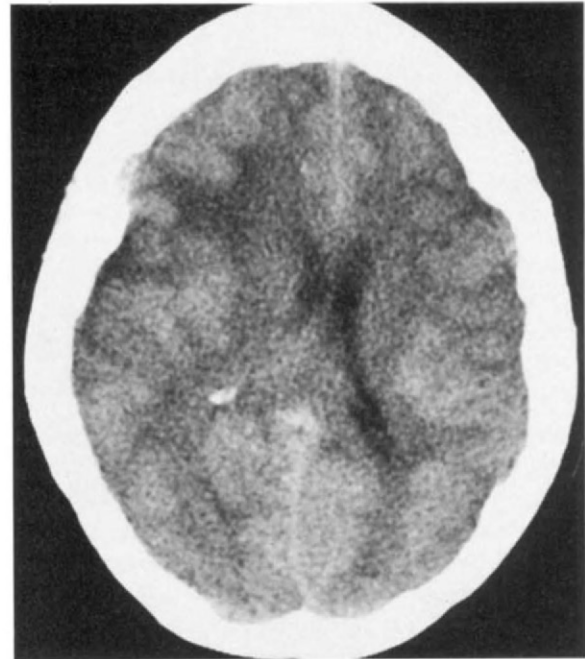


Fig. 1. Computed tomographic scan of head with use of contrast agent, showing edema within right cerebral hemisphere, mass effect, and shift of midline structures to left in 74-year-old woman with subacute dementia and acute encephalopathy.

eral independent periodic lateralized epileptiform discharges and generalized slowing of the background activity, which was maximal over the right hemisphere. Angiography showed some irregularity and slow filling of distal branches of the anterior division of the right middle cerebral artery and distal branches of the left posterior cerebral artery, thought to be attributable to mass effect and edema. No evidence of vasculitis was noted, and venous sinus thrombosis was not detected on the venous phase of the angiogram.

A biopsy was performed through a right frontal trephine craniotomy; the dura, meninges, and a section of the right middle frontal gyrus (2 by 2 cm), including the underlying white matter, were removed. Histopathologic examination revealed extensive amyloid angiopathy that involved leptomeningeal and cortical vessels, associated with predominantly acute and subacute cortical ischemic infarcts (Fig. 3), but no evidence of angioendotheliomatosis or vasculitis. Bielschowsky-stained sections demonstrated sparse neuritic plaques and no neurofibrillary tangles. The result of a repeated CSF protein determination 17 days after the first test was 75 mg/dL. The patient died 6 weeks after admission. Autopsy examination was not performed.

DISCUSSION

Our patient had a subacute dementia and then rapid deterioration in association with seizures, cerebral edema, changes

in the white matter, and cortical petechial hemorrhages on neuroimaging. Biopsy of the brain revealed multiple small cortical infarcts, extensive amyloid angiopathy, and infrequent neuritic plaques. Although this patient had a progressive dementia and nonspecific neurodegenerative changes (insufficient for the diagnosis of Alzheimer's disease), the most prominent histologic findings and the clinical and radiologic picture were indicative of CAA. The histologic overlap between Alzheimer's disease and CAA has previously been noted.^{8,10} Okazaki and associates⁴ reported 23 pathologic cases of CAA in patients who had progressive dementia, single or multiple cerebrovascular events, or a combination of both. Lobar hemorrhages, now well recognized to be associated with CAA, were described in 9 of the 23 patients, multiple small cortical infarcts in 21, and petechial hemorrhages in 19. Although that series selected patients on the basis of "significant cerebral amyloid angiopathy," it described petechial hemorrhages that were not detectable by brain imaging until the advent of MRI.

Our case demonstrated MRI findings that are now being increasingly recognized as highly suggestive of CAA. Multiple petechial cortical hemorrhages, deposition of hemosiderin from previous hemorrhage, changes in the white matter, and mass effect are consistent with CAA pathologically, but until recently, the diagnosis of CAA would not have been considered in most clinical differential diagnoses.⁷ In a recent review of the clinical spectrum of CAA, Greenberg and colleagues⁸ described seven patients who had recurrent transient neurologic symptoms suggestive of focal seizures or a rapidly progressive dementia. Multiple small cortical hemorrhages were identified in three of the five patients who underwent MRI, and changes in the white matter were present in an additional three. In a report by Hendricks and coworkers,⁶ a 66-year-old man with histologically confirmed CAA had a several-month history of cognitive decline and a focal-onset seizure with secondary generalization. CT demonstrated extensive edema of the right cerebral hemisphere, and MRI showed changes in the white matter of the right hemisphere and multiple petechial hemorrhages in both hemispheres.

Leukoencephalopathy is a common pathologic finding in brains affected by CAA. On examination of 12 affected brains, Gray and associates¹¹ found severe leukoencephalopathy in 8; only minimal cerebral changes were noted in the 4 patients with a brief history of this disorder. Because the leukoencephalopathy seemed most severe in the regions underlying the involved cortical areas, the issue of hypoperfusion of the white matter was raised, possibly related to amyloid involvement of the long perforating meningo-cortical arterioles. These findings of leukoencephalopathy are prominent on MRI, but the pathologic findings are non-specific.¹²

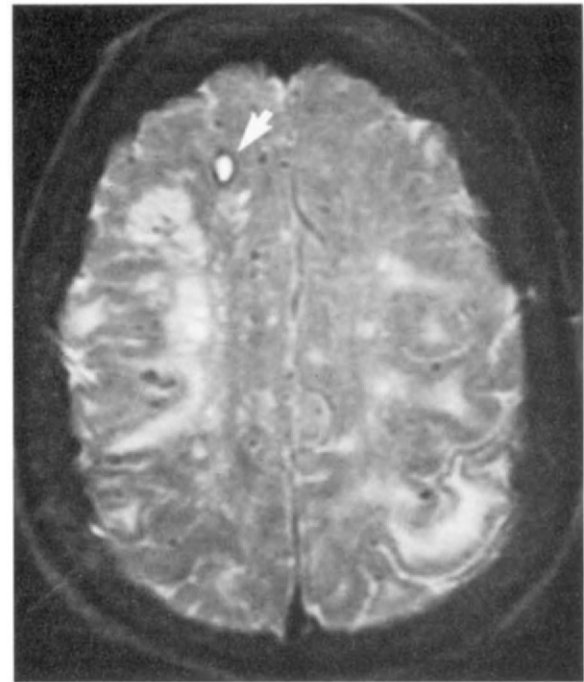


Fig. 2. Axial T2-weighted magnetic resonance imaging section, demonstrating 8-mm subacute hemorrhage within right frontal lobe (arrow). Note early hemosiderin ring surrounding the hemorrhage, patchy increased T2 signal within deep white matter of both hemispheres (right greater than left), and multiple tiny foci of hemosiderin deposition. (Repetition time, 2,500 ms; echo time, 80 ms.)

The neuroimaging in our patient demonstrated an appreciable mass effect. We believe that this finding relates to the areas of recent infarction and associated edema. Mass effect associated with cortical amyloid angiopathy, as noted in our case, has also been reported previously.⁶⁻⁸ Similar cases have been described with CT and neuropathologic confirmation but without performance of MRI.¹³ Although amyloidomas have manifested with mass effect, the cortical petechial hemorrhages that are so prominent pathologically and on MRI have been absent in the reported cases.¹⁴

Transient vascular events suggestive of transient ischemic attacks are well recognized in CAA and may even precede lobar hemorrhage. Such transient vascular events may be due to cortical petechial hemorrhage or small cortical infarcts.^{5,15,16} In addition, affected patients often have other major vascular risk factors such as hypertension and diabetes mellitus (as did our patient) that increase the possibility of cerebrovascular events related to atherosclerosis, including lacunar infarction. In our patient, an early feature was an apparent stroke that caused weakness of the left leg. The patient had no symptoms referable to the upper limbs or the face, and the exact site and cause of the lesion can only be speculated in the absence of neuroimaging at the time, although the findings were consistent with a cortical stroke.

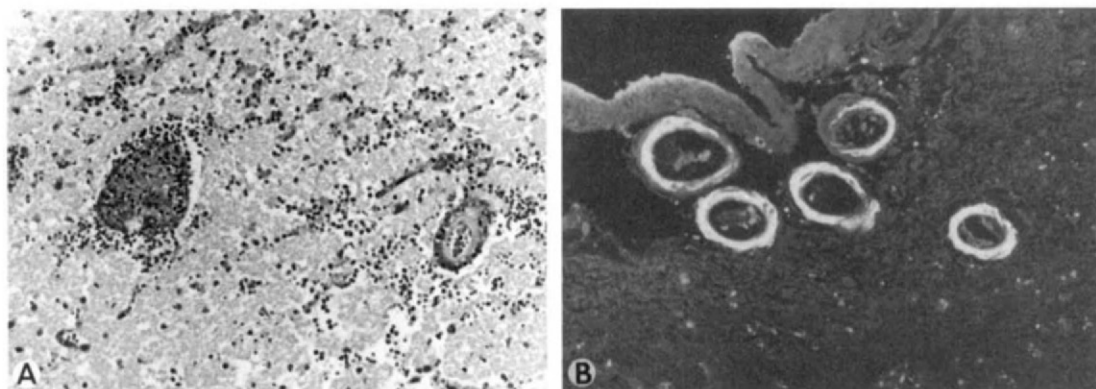


Fig. 3. Histopathologic appearance of brain biopsy specimens. A, Area of subacute infarction characterized by infiltration of necrotic parenchyma by lipid-laden macrophages and chronic inflammatory cells. (Hematoxylin-eosin; original magnification, $\times 240$.) B, Strong fluorescence of leptomeningeal and cortical vessel walls, indicating presence of amyloid. (Thioflavine S; original magnification, $\times 76$.)

The rapid deterioration in our patient after the initial headache and seizures has also been reported by other investigators.^{7,8} Cerebral edema may have been due to increased petechial hemorrhages after the seizure activity, with resultant increased CSF protein. Previously reported cases have shown only mildly increased CSF protein.^{6,7} Possible explanations in our case include the extensive cortical petechial hemorrhages, which may have developed subacutely after the initial prolonged generalized tonic-clonic seizure activity or, alternatively, may have preceded and caused the seizures. The result of a repeated CSF protein determination was nearly normal, consistent with resolution of an acute event.

Subacute manifestations of dementia prompt a lengthy differential diagnosis that must be narrowed by clinical examination, neuroimaging, and laboratory tests. The spectrum of neuroradiologic features of CAA is broad, and a high index of clinical suspicion is needed to consider the diagnosis before biopsy. The clinical and MRI findings associated with CAA will continue to be determined, and further reporting is encouraged to help clarify this entity. Confirmation of a characteristic MRI appearance would facilitate a definitive diagnosis and eliminate the need for additional investigation, including invasive testing such as brain biopsy. Therapy for this condition remains problematic.

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