

A patient with non-small cell lung cancer presenting with headaches and change in mental status

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A 79-year-old woman with a history of non-small cell carcinoma of the right lung, stage IIB (T3, N0, M0) was treated with definitive chemoradiation, with 6,480 cGy given to the right upper lobe and mediastinum with concomitant chemotherapy. On a follow-up visit 3 months later, PET-CT imaging showed remarkable improvement in her tumor response, with evidence of tumor regression on CT. The patient was in her normal state of health until 4 months later, when she began complaining of headaches and her son noted that she was disoriented, confused, mildly aphasic, and unstable.

On examination, we found that the patient was disoriented to place and time and that she had an unsteady gait. There was no evidence of motor or sensory deficits, but she had a right, lower-quadrant visual field deficit. She was started on steroid treatment in the emergency department, and her condition improved slightly. The patient had a magnetic resonance imaging (MRI) scan of the brain with and without contrast, which revealed multiple foci of subacute hemorrhage and a dominant center of acute hemorrhage within the left occipital region, which was likely hypertensive in origin (Figure 1). We consulted with our radiation oncology colleagues about possible radiotherapy, and after a thorough review of the imaging, there was no evidence of abnormal postcontrast enhancement considering the precontrast T1-weighted images of hyperintensity of several of the lesions. These overall findings—notably,

subacute left occipital hemorrhage—were consistent with generalized cerebral amyloid angiopathy, rather than metastatic disease.

Discussion

Cerebral amyloid angiopathy (CAA) is a vascular disorder that is characterized by amyloid protein deposition in the walls of small- and medium-sized cortical and leptomeningeal arteries, leading to lobar hemorrhage.¹ It was once considered to be a rare neurological entity, but is now known to be a major cause of intracerebral hemorrhage (ICH) and cognitive impairment in elderly patients. CAA typically occurs in the sporadic form in elderly patients, whereas rarer familial forms are known to occur in younger patients and tend to be associated with more severe clinical manifestations. Although sporadic CAA occurs mostly in elderly patients because of amyloid- β ($A\beta$) plaque deposition, there are other types as well. In the $A\beta$ form, β - and γ -secretases are believed to act on amyloid precursor protein, forming $A\beta$ in these lobar regions.² This $A\beta$ deposition is also closely linked to the development of Alzheimer's disease, and study data have demonstrated a CAA incidence of between 82% and 98% in patients with Alzheimer's disease, indicating a strong overlap between the two.³

CAA may eventually result in lobar hemorrhages, recurrent microhemorrhages, and microinfarcts. The $A\beta$ deposition in cerebral blood vessels leads to the effacement of smooth muscle cells, which weakens the tunica media and tunica adventitia, causing vessel rupture and hemorrhage.⁴ Clinically significant hemorrhage and infarction are most commonly seen in elderly men,

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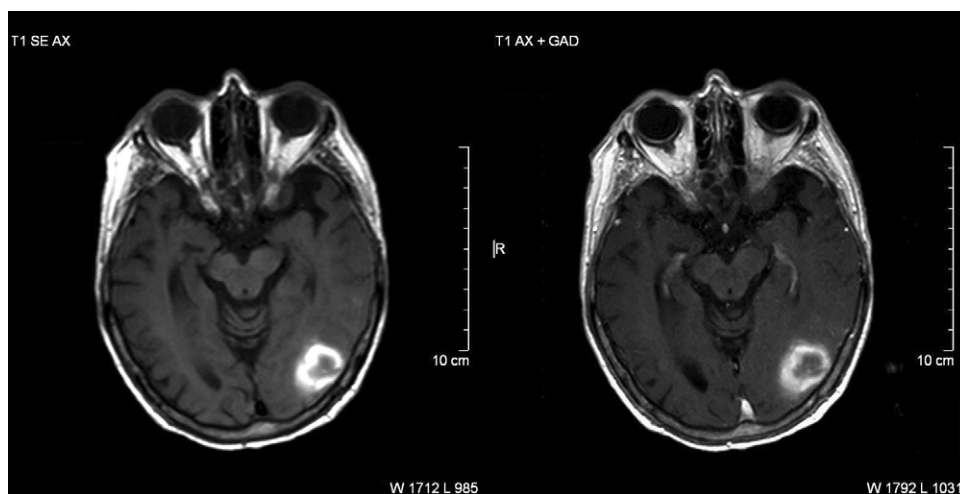


FIGURE 1 There is triangular shaped area of subacute hemorrhage (diameter, about 3 cm) with moderate surrounding edema within the left occipital lobe causing mild effacement of the adjacent cortical sulci and left occipital horn, but overall without any significant mass effect. There is no abnormal postcontrast enhancement considering the precontrast T1-weighted hyperintensity of several of the lesions. The overall findings are consistent with the generalized cerebral amyloid angiopathy associated with amyloid angiopathy related-inflammation with subacute hemorrhage in the left occipital lobe.

typically around the age of 70 years. The most common clinical manifestation is spontaneous lobar hemorrhage in the cortex and subcortical white matter. The hemorrhaging in CAA is characteristically confined to a single lobe, in contrast to the ICH seen secondary to hypertension. The lobar location reflects the distribution of amyloid deposits, which favor cortical vessels. Clinical presentation is dependent on the size of the lesion and its location, so that large lobar hemorrhages may cause depressed consciousness, hemiplegia, progressive dementia, and death, and small lobar hemorrhages may cause headaches, seizures, and more focal deficits, including spreading weakness, paresthesias, and numbness.⁵ Very small, asymptomatic hemorrhages seem to be more common and are most likely to cause transient neurological manifestations.⁶ The clinical presentation of the patient in the current report strongly suggested ICH and likely underlying metastatic disease, but further work-up was required to confirm that diagnosis and to determine the etiology of the ICH.

Although ICH is the most feared complication of CAA, there are no pathognomonic features. Headaches, focal neurological deficits, and disturbed consciousness are all common symptoms in patients with ICH, and reflect the location and size of the hematoma rather than pathophysiology of the disease. In the setting of previous malignancy, CAA can easily be mistaken for metastatic brain lesions. It is essential for oncologists to be aware of this to ensure proper diagnosis and treatment.

Use of the Boston Criteria is a noninvasive method of diagnosing CAA-related hemorrhage in a living patient

(Table 1). Based on the criteria, CAA is considered “probable” if there are appropriate clinical findings, in addition to imaging findings of multiple cortical-subcortical hematomas in a patient aged 55 years or older, without any other cause of hemorrhage. A similar patient with the imaging findings of a single cortical-subcortical hematoma would suggest “possible CAA.”⁷ The criteria require other causes of lobar hemorrhage to be ruled out, including hemorrhagic metastasis, lobar extension of a hypertensive hemorrhage, trauma, hemorrhagic transformation of an ischemic infarct, and an arteriovenous malformation.⁸

Hemorrhagic tumors may present in cortical-subcortical locations similar to those of CAA-related hemorrhages. MRI may identify further enhancing lesions, increasing suspicion of metastatic disease; this was not seen with the patient in the current report.⁹ The patient’s initial MRI scan did not demonstrate any abnormal postcontrast enhancement (Figure 1). Based on the patient’s age and the presence of multiple hemorrhages, the diagnosis of “probable CAA” was made.

The presence of ICH in a cortical-subcortical location on nonenhancing CT is suspicious for CAA and should always be further evaluated with MRI, preferably the gradient echo sequence. The gradient echo sequence can help make the diagnosis of “probable CAA” by demonstrating the presence two or more hemorrhages in lobar regions typically affected by CAA, such as cortex or grey-white junction. This method is presently the most sensitive for detecting chronic hemorrhage, by enhancing the signal dropout caused by hemosiderin deposits.¹⁰ For a definitive diagnosis of CAA, evacuated hematoma specimens and parenchymal tissue can be examined. Tissues are stained with Congo red and show classic yellow-green birefringence when viewed under polarized light. Evidence of advanced disease includes complete amyloid replacement of the smooth muscle layer. A novel technique that uses positron emission tomography imaging along with the beta-amyloid-binding compound, Pittsburgh Compound B, has recently been proposed as a noninvasive technique for detecting CAA in a living patient.¹¹

CAA-related ICH, as with other causes of ICH, may be treated surgically. Surgical hematoma resection in CAA related hemorrhage carries no additional risk when compared with other types of ICH, and should be performed when indicated.¹²

It is possible to prevent CAA-related hemorrhage recurrence by managing blood pressure and avoiding certain medications. Although the vascular pathology in CAA is not related to hypertension, results from the PROGRESS trial (Perindopril Protection Against Recurrent Stroke Study) suggest that CAA-ICH recurrence may be reduced by controlling blood pressure control.¹³

Since CAA-ICH has a high recurrence rate, it is generally advisable for physicians to avoid prescribing anticoagulant and antiplatelet medications to patients with CAA, because studies have demonstrated that warfarin and aspirin increase the frequency of cerebral hemorrhage.^{14,15} The SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial showed a higher risk of ICH in patients who were treated with atorvastatin; however, another study showed a reduced mortality and increased probability of a favorable outcome with statin use before ICH. Although the data are conflicting, the general recommendation is to weigh the benefits of statin therapy against the possible risks in patients with CAA. Additional research is necessary to fur-

TABLE 1 Boston criteria for diagnosis of CAA-related hemorrhage⁷

Definite CAA
Full postmortem examination demonstrating:
• Lobar, cortical, or subcortical hemorrhage
• Severe CAA with vasculopathy
• Absence of other diagnostic lesion
Probable CAA with supporting pathology
Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating:
• Lobar, cortical, or subcortical hemorrhage
• Some degree of CAA in specimen
• Absence of other diagnostic lesion
Probable CAA
Clinical data and MRI or CT demonstrating:
• Multiple hemorrhages restricted to lobar, cortical, or subcortical regions (cerebellar hemorrhage allowed)
• Age ≥ 55 y
• Absence of other cause of hemorrhage
Possible CAA
Clinical data and MRI or CT demonstrating:
• Single lobar, cortical, or subcortical hemorrhage
• Age ≥ 55 y
• Absence of other cause of hemorrhage

Abbreviation: CAA, cerebral amyloid angiopathy.

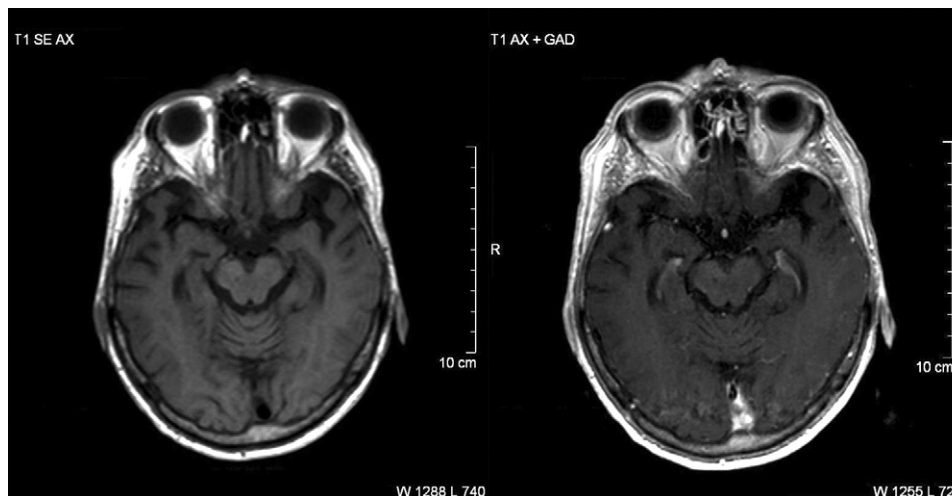


FIGURE 2 The follow-up MRI done 3 months after the diagnosis of amyloid angiopathy. The dominant focus of hemorrhage in the inferior left occipital lobe in Figure 1 is significantly decreased in size with decreased surrounding edema, minimal residual signal abnormality and with development of mild perfusion.

ther clarify the safety profile of statin therapy in CAA patients.¹⁶⁻¹⁸

Definitive treatment for CAA at the present time remains elusive. Several case reports have postulated that corticosteroid treatment may improve symptoms related

to CAA-related inflammation by reducing vasogenic edema. Indeed, in vitro research has shown that dexamethasone reduces the pro-inflammatory and cytotoxic effects of A β deposition on cerebral smooth muscle cells.¹⁹ Immunosuppressive treatments, including azathioprine, methotrexate, and mycophenolate mofetil, have been shown to influence the course of inflammation and may be appropriate alternatives to maintenance steroid treatment of inflammatory CAA, but evidence for their efficacy is limited.²⁰ Future medications seeking to cure CAA will assuredly involve specialized drugs targeting the development of amyloid- β formation, deposition, and toxicity. The patient in this report was taken off all anticoagulant/antiplatelet medication and followed with a repeat MRI scan 3 months after the diagnosis of CAA; that scan showed significant resolution of the dominant focus of hemorrhage (Figure 2).

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