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Recurrent Subarachnoid Bleeding and Superficial Siderosis in a Patient with Histopathologically Proven Cerebral Amyloid Angiopathy

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Key Words

Amyloid angiopathy · Subarachnoid bleeding · Superficial siderosis

Abstract

A 68-year-old man with a history of hypertension presented with recurrent subarachnoid bleeding. Brain MRI showed superficial siderosis, and diagnostic cerebral angiograms did not show any intracranial vascular malformation or arterial aneurism. Post mortem neuropathological examination of the brain was consistent with a diagnosis of cerebral amyloid angiopathy. Clinicians should be aware that cerebral amyloid angiopathy should be considered in patients with unexplained recurrent subarachnoid bleeding, even in cases without familial clustering or transthyretin variant.

Introduction

Most cases of spontaneous subarachnoid hemorrhage (SAH) are due to a ruptured cerebral aneurysm; however, the source of bleeding cannot be determined in 8–23% of total spontaneous SAH [1]. When the bleeding is chronic, hemosiderin is deposited in the subpial layer of the CNS leading to a pathological/radiological condition named superficial siderosis. A possible cause of superficial siderosis is cerebral amyloid angiopathy (CAA): it has been reported that this condition is responsible for about 3% of cases of superficial siderosis [2]. In most cases of CAA, superficial siderosis is associated

with subcortical intracerebral bleeding, whilst CAA rarely causes primary SAH [3]. Moreover, superficial siderosis has been considered a potential marker of CAA in demented patients [4]. Here, we report a patient with relapsing SAH of undetermined origin with a neuroradiological picture of hemosiderosis and post mortem evidence of leptomeningeal amyloidosis.

Case Report

The patient was a 68-year-old man with a history of hypertension, who had experienced an episode of confusion followed by seizures 3 years earlier. On that occasion, subarachnoid bleeding was demonstrated, but the source of bleeding could not be detected by either brain CT angiography or MR angiography. Following an acute onset of aphasia and confusion associated with vomiting, the patient was admitted to our Stroke Unit. The patient's relatives reported a transitory speech impairment of 1 h on the day before admission.

Axial non-enhanced CT brain scan (fig. 1a) performed in the Emergency Department revealed a focal small hyperdensity in the right subarachnoid space of the sylvian scissure, compatible with acute subarachnoid microhemorrhage. The patient was obtunded (GCS = 12). His vital signs were the following: blood pressure 160/80 mm Hg, heart rate 90 beats/min, respiratory rate 18 breaths/min, and body temperature 36.8°C. Neurologic examination showed severe global aphasia without limb weakness, deep tendon reflexes were normal, and there was no sensory impairment or ataxia, and no evidence of meningeal signs, neck stiffness, or Kernig's sign. Shortly after admission, an EEG was performed showing an epileptiform continuous activity over the left temporal region that was abolished after intravenous administration of 4 mg of lorazepam in 10 min. White-cell count was 10,800/mm³, with an increased percentage of neutrophils (88%); erythrocyte sedimentation rate was 16 mm/h; C-reactive protein was 4.3 mg/dl (normal value <3 mg/dl), and fibrinogen level was 777 mg/mm³ (normal value 200–400 mg/mm³). blood biochemistry and lipid levels, urine chemical analysis, prothrombin time, partial thromboplastin time, homocysteine, lipoprotein A, complement C3 and C4, γ globulin, and protein C and S levels were within normal ranges. Antinuclear antibody, anti-double-stranded DNA, antineutrophil cytoplasmic anticardiolipin, anti- β 2-glycoprotein, extractable nuclear antigens anticardiolipin and antiphospholipid antibodies, rheumatoid factor, and Coombs test were all negative. Transthyretin gene mutation was also investigated with negative results. Oral antiepileptic drug treatment was started with carbamazepine (which was gradually increased up to 800 mg/day).

Brain MRI showed diffuse hyperintensity of the subarachnoid spaces (fig. 1b), hemosiderin deposit on CNS surfaces (fig. 1c), and isolated microbleeds in the left frontal lobe and in the occipital lobes. T₁-weighted images revealed linear and thin leptomeningeal contrast enhancement.

Cerebrospinal fluid examination was performed 3 days after the onset of symptoms. Cerebrospinal fluid was xanthochromic, cell count was 11/mm³, protein concentration was 263 mg/dl, and bacterial culture was sterile.

Diagnostic cerebral angiography, performed 1 week after MRI scan, did not show any intracranial vascular malformation or arterial aneurism.

The level of consciousness gradually improved during the following days. About 2 weeks after the onset of symptoms, neurological status worsened again: the patient became obtunded, aphasic, and showed a mild right hemiparesis and focal motor seizures in the right side of the body. A brain unenhanced CT scan was performed which suggested re-bleeding (fig. 1d).

During the subsequent days, the neurological condition gradually improved. About 1 month later, the patient died of pneumonia, and a neuropathological examination of the brain was performed. Macroscopically, the brain was diffusely edematous and congested with leptomeningeal small blood clots. No mass lesion was found. Willis's circle vessels were grossly normal; serial coronal sections of the cerebral and cerebellar hemispheres revealed multiple petechial streaks of hemorrhage involving both grey and white matter. Histological examination revealed focal collection of hemosiderin-laden macrophages around the congophilic vessels in the subpial region, most extensively on the lower surface of the temporal lobe (fig. 1e–h). Amyloid angiopathy was also seen in intraparenchymal vessels.

Examination of the parenchymatous organs revealed terminal congestion. There was no bacterial vegetation or thrombus of the heart valves.

The findings were consistent with a diagnosis of leptomeningeal siderosis in amyloid angiopathy according to the CAA Boston Criteria.

Discussion

The most common causes of chronic subarachnoid hemorrhage that lead to superficial siderosis include CNS tumors, head and neck trauma, and arteriovenous malformations. Although the source remains unidentified in over one third of all cases [2], a possible diagnosis in these cases can be leptomeningeal amyloid angiopathy. Familial superficial siderosis of the CNS due to subarachnoid bleeding was reported in association with a transthyretin variant [5, 6]; however, in our patient, the family history was unremarkable and no transthyretin variant was demonstrated. In a recent study, 38 histopathologically proven CAA cases were retrospectively analyzed. In 2 of them, SS and acute SAH were the only MR-detectable hemorrhagic lesions, and no microbleeds were found [7]. On the basis of their findings, the authors suggested that inclusion of superficial siderosis in the Boston Criteria for CAA-related hemorrhage might enhance the sensitivity for CAA-related hemorrhage without loss of specificity [7]. However, it should be considered that, according to the Boston Criteria for CAA, before neuropathological examination, our patient could not be characterized as probable or possible CAA because of the absence of lobar, cortical or cortico-subcortical hemorrhage. The present case confirms that superficial siderosis associated with recurrent intracranial bleeding can be the main manifestation of CAA and that, in cases without familial clustering or transthyretin variant, meningeal amyloidosis should be considered as a possible cause in unexplained recurrent subarachnoid bleeding.

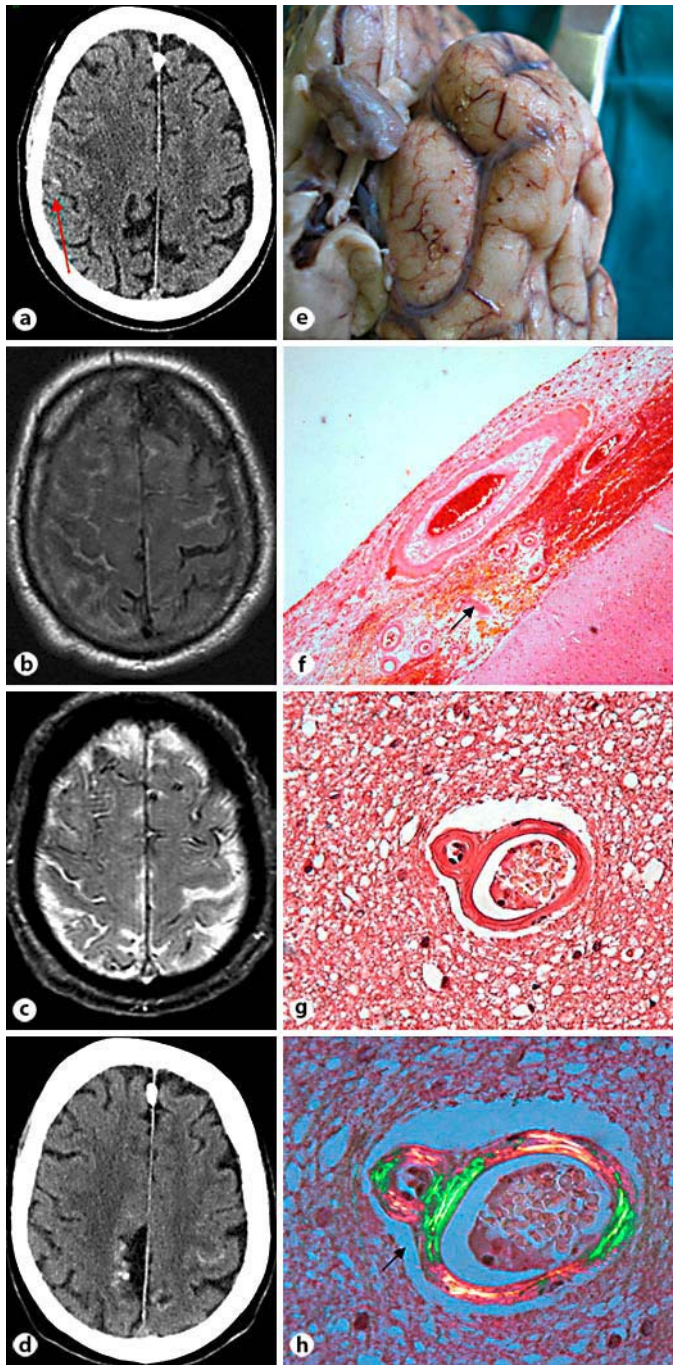


Fig. 1. Axial non-enhanced brain CT scan revealed a focal small hyperdensity in the right subarachnoid space of the sylvian scissure (arrow; **a**) compatible with acute subarachnoid microhemorrhage. MRI axial fluid attenuation inversion recovery (FLAIR) images showed diffuse hyperintensity of the subarachnoid spaces (on the right more than on the left; **b**), while T_2^* -weighted images (**c**) demonstrated less diffuse hemosiderin deposit on CNS surfaces. A brain unenhanced CT scan showed multiple and bilateral foci of hyperdensity in the subarachnoid spaces, mainly in the left rolandic scissure (**d**), suggesting re-bleeding. Macroscopic neuropathological examination revealed multiple leptomeningeal blood clots (**e**). **f** Specimen of CNS including the leptomeningeal space. A perivascular hemorrhage and hematoidin deposits (arrow) are visible. **g** Intraparenchymal vessel (Congo red stain). **h** Spots of patchy amyloid deposits in the vascular wall.

References

- 1 Jung JY, Kim YB, Lee JW, Huh SK, Lee KC: Spontaneous subarachnoid haemorrhage with negative initial angiography: a review of 143 cases. *J Clin Neurosci* 2006;13:1011–1017.
- 2 Levy M, Turtzo C, Llinas RH: Superficial siderosis: a case report and review of the literature. *Nat Clin Pract Neurol* 2007;3:54–58, quiz 59.
- 3 Yamada M, Itoh Y, Otomo E, Hayakawa M, Miyatake T: Subarachnoid haemorrhage in the elderly: a necropsy study of the association with cerebral amyloid angiopathy. *J Neurol Neurosurg Psychiatry* 1993;56:543–547.
- 4 Feldman HH, Maia LF, Mackenzie IR, Forster BB, Martzke J, Woolfenden A: Superficial siderosis: a potential diagnostic marker of cerebral amyloid angiopathy in Alzheimer disease. *Stroke* 2008;39:2894–2897.
- 5 Mascalchi M, Salvi F, Pirini MG, D'Errico A, Ferlini A, Lolli F, Plasmati R, Tessa C, Villari N, Tassinari CA: Transthyretin amyloidosis and superficial siderosis of the CNS. *Neurology* 1999;53:1498–1503.
- 6 Jin K, Sato S, Takahashi T, Nakazaki H, Date Y, Nakazato M, Tominaga T, Itoyama Y, Ikeda S: Familial leptomeningeal amyloidosis with a transthyretin variant Asp18Gly representing repeated subarachnoid haemorrhages with superficial siderosis. *J Neurol Neurosurg Psychiatry* 2004;75:1463–1466.
- 7 Linn J, Halpin A, Demaerel P, Ruhland J, Giese AD, Dichgans M, van Buchem MA, Bruckmann H, Greenberg SM: Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology* 2010;74:1346–1350.