The Spot Sign Is More Common in the Absence of Multiple Prior Microbleeds

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Background and Purpose—Mural thickening and permeability changes in patients with amyloid angiopathy (CAA) and chronic hypertension are implicated in the pathophysiology of multiple, chronic subclinical microbleeds. The Spot sign, contrast extravasation on CT angiography, predicts hematoma expansion and is presumed to represent acute vessel damage. We hypothesize that the Spot sign is more common in patients without multiple prior chronic microbleeds.

Methods—A retrospective study was conducted of 59 patients presenting within 6 hours of primary intracranial hemorrhage onset undergoing CT angiography and MRI. CT angiography spot sign presence was documented blinded to MRI. Hematoma expansion was defined as >6 mL or 30% enlargement. The Boston criteria were applied to microbleed interpretation dichotomizing subjects into probable and negative CAA. Basal ganglia, thalamic, and brain stem microbleed location were interpreted as chronic hypertensive pattern. Univariate logistic regression and ordinal logistic regression analysis identified significant predictive factors between spot-positive and -negative patients or microbleed pattern.

Results—The incidence of spot positivity was 42%, 22%, and 0% for CAA-negative, chronic hypertensive, and CAA-positive patients, respectively (P 0.01). CAA-negative patients had higher baseline National Institutes of Health Stroke Scale (P 0.039), larger follow-up hematoma volume (P 0.02), and poorer Rankin score (P 0.049) than chronic hypertensive or CAA-positive patients. After age adjustment, spot-positive (P 0.023), age-related white matter change (P 0.041), number of microbleeds (P <0.0001), and modified Rankin score (P 0.027) remained significantly different between groups.

Conclusion—Boston criteria-defined CAA-negative status demonstrates the highest risk of spot positivity compared with patients with probable CAA and chronic hypertension. (Stroke. 2010;41:2210–2217.)

Key Words: cerebral amyloid angiopathy ■ computed tomography angiography ■ contrast extravasation ■ CTA spot sign

Intracerebral hemorrhage (ICH) occurs in 10% to 15% of all strokes and accounts for a high rate of mortality. ICH is considered primary in 78% to 88% of cases often attributed to hypertensive vasculopathy and cerebral amyloid angiopathy (CAA). CAA accounts for the majority of primary lobar ICH in the elderly. Determination of ICH pathophysiology and etiology has been facilitated by the MRI detection of microbleeds on sequences susceptible to blood products. Fazekas first demonstrated the association between MRI-detected microbleeds and focal hemosiderin deposition. These findings, together with others, suggested that microbleeds may be considered as imaging indicators of prior chronic, hemorrhagic episodes from bleeding-prone vessels demonstrating moderate to severe lipohyalinosis and/or amyloid deposits. Several studies have reported a correlation between microbleed number as a predictor of future ICH occurrence and pattern. A set of validated criteria, the Boston criteria, allows for radiographic diagnosis of probable CAA based on microbleed location. This distribution is distinctive from chronic hypertensive (CH) pathologies in which microbleeds predominate in the deep gray matter structures.

Both amyloid deposition and hypertension histopathologically demonstrate vessel wall thickening increasing with disease duration and severity. The degree of wall thickening may have implications for the type and incidence of future hemorrhage. Based on MRI-detected microbleeds, supported by histopathology in a modest subset, Greenberg hypothesized that patients presenting with acute ICH can be divided into micro- or macrobleeders. Microbleeders present with multiple small microbleeds and histopathologically demonstrate wall thickening in association with amyloid...
deposition. The findings are consistent with prior studies demonstrating that extensive mural amyloid deposition is frequently associated with multiple subclinical microbleeds. In contrast, macrobleeders demonstrated few prior microbleeds and were characterized by vessel wall thinning histopathologically.

Recently, the CT angiographic (CTA) “spot sign” has been suggested to be an independent predictor of hematoma growth and clinical outcome. These enhancing foci of contrast during CTA are of uncertain etiology but are postulated to represent pseudoaneurysms, Charcot-Bouchard aneurysms, fibrin globules, or a focal vessel defect in an abnormal vessel segment. Whatever the true pathophysiology, the spot sign is regarded as a radiological marker of acute primary, or possibly secondary, vessel damage.

Considering that mural thickening increases with disease severity in CAA and CH, and the reported normal differences between micro- and macrobleeders, we hypothesize that the CTA spot sign is more common in patients without multiple prior chronic microbleeds.

Methods and Materials

Study Group
We retrospectively reviewed a prospectively acquired database of 250 consecutive patients with ICH presenting between January 2004 and July 2009 with acute nontraumatic ICH undergoing a standard protocol, including CTA and MRI with a T2*-weighted sequence. These 250 patients presented with primary or secondary ICH. Patients with secondary vascular etiologies diagnosed by CTA or conventional angiography were excluded (n = 73). Etiology of secondary hemorrhage was arteriovenous malformation (including microanteriorovenous malformation/dural arteriovenous fistula) 28 (38%), aneurysm 19 (27%), tumor 13 (18%), venous sinus thrombosis 6 (9%), vasculitis and moyamoya 3 each (4%). MRI studies were not performed in 55 patients due to death, dependence, or nursing home admission (modified Rankin Score [mRS]). Sixty-three patients who initially bypassed their local hospitals due to a regional acute stroke protocol were repatriated to those local hospitals without available follow-up. A total of 59 patients were identified for review. The study was approved by the hospital’s research ethics board. Clinical data were collected prospectively by a research assistant in conjunction with a stroke neurologist during admission and at follow-up.

Image Acquisition
The stroke imaging protocol was performed on a 4-slice (2004 to 2005) and 64-slice (2005 to 2009) CT scanner (GE Lightspeed plus and VCT; GE, Milwaukee, Wis). Precontrast head imaging was followed by a CTA. A postcontrast study was performed 1 to 2 minutes after contrast injection. Parameters for pre- and postcontrast CTA were 120 kVp; 340 mA; 4 × 5 mm collimation; 1 second/rotation; and table speed of 15 mm/rotation. CTA studies were obtained from the CTPA view on AGFA Impax 4.5 PACS workstation (Agfa Healthcare, Mortsel, Belgium).

Statistical Methods
Results were expressed as mean, SD, median, and interquartile range (IQR) for continuous variables and as number and percentage for categorical variables. A log-transform was applied to several variables to normalize distributions. Univariate logistic regression analysis identified significant predictive factors between spot-positive and -negative patients. Univariate ordinal logistic regression analysis was also applied for identifying significant predictive factors among CAA-negative, CH, and probable CAA-positive microbleed patterns. OR and its 95% CI were calculated, and a probability value < 0.05 was considered significant. Fisher exact test was used to search for the relationship between drug use (aspirin, clopidogrel, and warfarin), hematoma location and pattern type, and the effect of PTT elevation on spot sign frequency within the CAA-negative group. After adjusting for age as a confounder and also removing 7 patients with any PTT prolongation, the logistic regression analysis was reapplied to the previously mentioned analysis. Results were considered significant at the 5% critical level (P < 0.05). All calculations were performed using Statistical Analysis Software (SAS, Version 9.2 for Windows).
Results

Fifty-nine patients (59% male; mean age of 61 ± 14 years; range, 30 to 85 years) were included in the study cohort. The mean time from symptom onset to emergency department presentation was 268 ± 40 minutes. Baseline hematoma volume was 16 cm³ (IQR, 5.1 to 30.8). The “spot sign” was present in 17 patients (29%) none of whom fulfilled criteria for probable CAA (Group A). Two patients demonstrated a CH pattern of microbleed. In Group B, 14 (33%) fulfilled criteria for probable CAA, 21 (50%) did not meet CAA criteria, and 7 (16%) demonstrated a CH pattern. Median time to MRI was 30 days (IQR, 3 to 127 days).

Echoplanar–gradient recalled echo was performed in 25 patients, multiplanar gradient recalled echo in 23, and susceptibility-weighted in 11. There was no difference in MRI susceptibility imaging sequence type performed for CAA-positive, -negative, or hypertensive groups (P = 0.72). No significant association between aspirin (P = 0.91), clopidogrel (P = 0.34), or warfarin (P = 0.95) use between groups was present. No patients had abnormal liver function tests, history of liver disease, or received heparin.

Table 1 summarizes demographics and clinical characteristics of Group A and B patients. Baseline clinical characteristics were similar between Group A and B patients. Baseline hematoma volume in group A was not significantly different from group B (P = 0.12). Partial thromboplastin time (PTT) values were higher in Spot positive patients reaching borderline significance. Group A patients tended to be younger and were more likely of male gender although this was not statistically significant. Table 2 demonstrates a higher ARWMC score (P = 0.02) and number of microbleeds (P < 0.011) in Group B patients. Group A patients demonstrated a larger hematoma volume change by criteria than Group B (P < 0.003). Extravasation was seen in half of Group A patients (P < 0.0001). There was a trend to poorer clinical outcome in Group A (P = 0.08).

Table 3 demonstrates a significantly increased age, white matter score, and number of microbleeds between CAA-positive (Figure 1), -negative (Figure 2), and CH patients (Figure 3; P < 0.001). CAA-negative patients demonstrated a 42% incidence of spot positivity compared with 22% in

Table 1. Baseline Clinical Characteristics of All Patients

<table>
<thead>
<tr>
<th></th>
<th>Spot-Positive (n=17)</th>
<th>Spot-Negative (n=42)</th>
<th>Logistic Regression Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56 (14)</td>
<td>64 (14)</td>
<td>0.080 0.96 0.92 1.01</td>
</tr>
<tr>
<td>Male gender, no. (%)</td>
<td>12 (70%)</td>
<td>23 (55%)</td>
<td>0.267 1.98 0.59 6.63</td>
</tr>
<tr>
<td>Baseline hematoma volume, cm³ (IQR)*</td>
<td>20.76 (30)</td>
<td>9.04 (16)</td>
<td>0.121 1.53 0.89 2.61</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>182 (47)</td>
<td>179 (43)</td>
<td>0.841 1.00 0.98 1.02</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>98 (32)</td>
<td>100 (28)</td>
<td>0.857 0.99 0.97 1.02</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>142 (39)</td>
<td>138 (34)</td>
<td>0.707 1.00 0.98 1.02</td>
</tr>
<tr>
<td>NIHSS median (IQR)</td>
<td>6.0 (17)</td>
<td>6.5 (7)</td>
<td>0.866 1.08 0.43 2.71</td>
</tr>
<tr>
<td>PTT, seconds</td>
<td>36.8 (13.8)</td>
<td>29.9 (3.6)</td>
<td>0.049 1.16 1.00 1.34</td>
</tr>
<tr>
<td>INR*</td>
<td>1.38 (0.92)</td>
<td>1.33 (1.58)</td>
<td>0.587 1.44 0.39 5.36</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>7.31 (2.12)</td>
<td>7.29 (2.05)</td>
<td>0.982 1.00 0.76 1.32</td>
</tr>
<tr>
<td>Hyperglycemia, &gt;8.2 mmol/L</td>
<td>12% (2)</td>
<td>21% (9)</td>
<td>0.395 0.49 0.09 2.54</td>
</tr>
<tr>
<td>Positive history of hypertension</td>
<td>12 (71%)</td>
<td>25 (60%)</td>
<td>0.490 1.54 0.46 5.19</td>
</tr>
</tbody>
</table>

All values are the mean and SD in parentheses unless specified. *Log-transform was applied in the univariate logistic regression analysis.

Table 2. Radiological and Clinical Outcomes of All Patients

<table>
<thead>
<tr>
<th></th>
<th>Spot-Positive (n=17)</th>
<th>Spot-Negative (n=42)</th>
<th>Logistic Regression Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARWMC*</td>
<td>6.0 (4.3)</td>
<td>10.7 (6.9)</td>
<td>0.026 0.41 0.18 0.90</td>
</tr>
<tr>
<td>No. of microbleeds*</td>
<td>0.53 (0.80)</td>
<td>8.4 (14.0)</td>
<td>0.011 0.35 0.16 0.79</td>
</tr>
<tr>
<td>Follow-up hematoma volume, cm³ (IQR)*</td>
<td>28.86 (29)</td>
<td>9.24 (18)</td>
<td>0.130 1.51 0.89 2.58</td>
</tr>
<tr>
<td>Change in hematoma volume by criteria, (yes/no)</td>
<td>7 (41%)</td>
<td>1 (2.4%)</td>
<td>0.003 27.3 3.00 248.23</td>
</tr>
<tr>
<td>Extravasation present, no. (%)</td>
<td>8 (47%)</td>
<td>0 (0%)</td>
<td>&lt;0.0001 42.8 5.93 ...</td>
</tr>
<tr>
<td>Graeb score*</td>
<td>2.63 (3.35)</td>
<td>1.55 (2.61)</td>
<td>0.515 1.24 0.65 2.38</td>
</tr>
<tr>
<td>mRS, median (IQR)*</td>
<td>3.0 (2.5)</td>
<td>2.0 (3.0)</td>
<td>0.075 2.94 0.90 9.61</td>
</tr>
<tr>
<td>Hospital stay, days*</td>
<td>27.8 (30.5)</td>
<td>14.7 (15.9)</td>
<td>0.109 1.62 0.90 2.92</td>
</tr>
</tbody>
</table>

All values are the mean and SD in parentheses unless specified. Probability modeled is spot-positive in the logistic regression analysis. There is no estimate for upper level of CI for extravasation due to quasicomplete separation of data points (0 patients in spot-negative with extravasation present).

*Log-transform was applied in the univariate logistic regression analysis.
patients with CH, whereas no CAA-positive patients exhibited a spot sign (P<0.01; Figure 4). CAA-negative patients had a higher baseline NIHSS (P<0.039) and borderline significant poorer mRS (P<0.049) than CH or CAA-positive patients. Patients with a CH microbleed pattern demonstrated intermediate values for age, ARWMC, number of microbleeds, follow-up volume, baseline NIHSS, and mRS compared with CAA-positive and -negative patients. Mean arterial pressure and glucose levels were highest in patients with CH. PTT was highest among CAA-negative patients, but the mean value was within normal limits. There was no significant difference in liver function tests between patient groups. After adjusting for age, spot-positive (P<0.023), ARWMC (P=0.041), number of microbleeds (P<0.0001), PTT (P=0.026), positive history of hypertension (P=0.016), and mRS (P=0.027) remained significant.

Review of PTT in CAA-negative patients demonstrated 7 of 36 (20%) patients with values above the upper institutional range of 36 seconds. Five patients had values that were only modestly elevated at 36.6 seconds, 37.5 seconds (2 patients), 37.6 seconds, and 39.5 seconds. None of these patients were receiving any medication that may have attributed to these

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Figure 1. A 78-year-old male patient presenting at 120 minutes. Axial noncontrast CT (NCCT; A) and CTA (B) demonstrate a left occipital lobar hematoma but no spot sign. Extensive white matter changes consistent with ARWMC score 18 are seen on NCCT and fluid-attenuated inversion recovery (C) sequences. D, Several susceptibility foci are present on echoplanar–gradient echo MRI sequence (arrowheads) fulfilling Boston criteria for probable CAA pattern.
findings. Two patients demonstrated higher values of 59.5 seconds and 76.5 seconds. Both patients were on warfarin (INR, 2.3 and 4.3, respectively) and the patient with the highest PTT and INR was also taking clopidogrel and aspirin. No difference in frequency of the spot sign was present in the 7 patients with any PTT elevation and the remaining CAA-negative group ($P=0.10$). The results of repeat logistic regression analysis after removing the 7 patients with any PTT elevation from the CAA-negative study group was unchanged (Table 4).

A deep intracranial hemorrhage location was more frequent with a CH or CAA-negative than probable CAA-positive pattern ($P=0.36$ and $P=0.03$, respectively). Lobar hemorrhage was more commonly attributed to CAA-positive patients than CH ($P=0.02$), but no difference between CAA-positive and CAA-negative patients was seen (Table 5). For a baseline lobar ICH location, CAA-negative patients were younger than CAA-positive patients (59 ± 14 years versus 78 ± 6 years, respectively; $P<0.001$).

**Discussion**

Our results show that CTA contrast extravasation or spot sign positivity was highest among CAA-negative patients who also exhibited less advanced white matter changes and younger age than CAA-positive patients. The spot sign was not seen in probable CAA patients based on the Boston criteria.$^{15}$ Patients with CH microbleed patterns had intermediate values of age, ARWMC score, microbleed number, and spot positivity.

Cerebral microbleeds correspond pathologically with hemosiderin deposition. Microbleed prevalence is estimated at approximately 6% within the healthy population being more common with advanced age, male gender, and Asian ethnicity.$^6$ Microbleeds may be important imaging markers associated with recurrent stroke (ischemic and hemorrhagic), cognitive impairment, white matter disease severity, diabetes, low serum cholesterol, hypertension, amyloid angiopathy, and cerebral autosomal-dominant arteriopathy with stroke and ischemic leukoencephalopathy.

Mural changes in CAA and chronic hypertension occur in leptomeningeal vessels, cortical arteries, arterioles, and capillaries.$^{17}$ Both CAA and hypertension are characterized radiologically by the presence of microbleed deposition. Microbleeds represent chronic, rather than acute, leakage of blood products and are indicative of underlying mural dysfunction.$^{7,11}$ Cerebral amyloid initially deposits within the vessel wall without lumen narrowing.$^{15}$ Progressive concentric intimal proliferation causes wall thickening and lumen reduction.$^{21}$ Despite a well-established link between CAA and acute ICH, the cause of symptomatic ICH is rarely identified. Fibrinoid necrosis, focal vessel wall fragmenta-
tion, segmental dilatation of vascular segments, and microaneurysm formation are all implicated.32 Parallels can be drawn between vessel wall changes in CAA and CH. CH produces compensatory vessel hyperplasia in response to high arteriolar pressures. Inadequate smooth muscle proliferation or smooth muscle cell death results in wall thinning and predisposes to hemorrhage.16 CH-induced wall changes, however, appear less predictable than CAA. Segmental involvement with variable degrees of wall thickening or ectasia is described.17 Wall thickening and lumen narrowing is implicated in ischemic presentations, whereas ectasia is considered causative in hemorrhage.

Table 4. Radiological and Clinical Characteristics of 52 Patients by Microbleed Pattern (Excluding 7 Patients With Any PTT Elevation From CAA-Negative Study Group)

<table>
<thead>
<tr>
<th></th>
<th>CAA-Positive (n=14)</th>
<th>Hypertension Pattern (n=9)</th>
<th>CAA-Negative (n=29)</th>
<th>P</th>
<th>Logistic Regression Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>75 (9)</td>
<td>60 (10)</td>
<td>59 (14)</td>
<td>0.0008</td>
<td></td>
</tr>
<tr>
<td><strong>Spot-positive</strong></td>
<td>0 (0%)</td>
<td>2 (22%)</td>
<td>10 (35%)</td>
<td>0.023</td>
<td>0.030 0.16 0.029 0.84</td>
</tr>
<tr>
<td><strong>ARWMC, median (IQR)</strong></td>
<td>14.7 (7)</td>
<td>11.9 (14)</td>
<td>7.0 (8)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td><strong>No. of microbleeds</strong></td>
<td>16 (16.5)</td>
<td>11 (16)</td>
<td>1.2 (4.5)</td>
<td>0.0001</td>
<td>0.0001 5.35 2.64 10.9</td>
</tr>
<tr>
<td><strong>Follow-up volume, mL</strong></td>
<td>18.7 (16.0)</td>
<td>15.6 (28.0)</td>
<td>25.4 (30.3)</td>
<td>0.04</td>
<td>0.322 0.78 0.48 1.27</td>
</tr>
<tr>
<td><strong>Change in volume by criteria</strong></td>
<td>1 (8%)</td>
<td>2 (22%)</td>
<td>5 (18%)</td>
<td>0.666</td>
<td></td>
</tr>
<tr>
<td><strong>Active extravasation</strong></td>
<td>0%</td>
<td>1 (13%)</td>
<td>5 (18%)</td>
<td>0.216</td>
<td></td>
</tr>
<tr>
<td><strong>Graeb</strong></td>
<td>1.2 (1.8)</td>
<td>1.9 (2.7)</td>
<td>2.2 (3.5)</td>
<td>0.766</td>
<td></td>
</tr>
<tr>
<td><strong>Platelet, 10^3 cells/mm^3</strong></td>
<td>200 (53.3)</td>
<td>289 (74.8)</td>
<td>235 (59.1)</td>
<td>0.020</td>
<td>0.419 1.00 0.99 1.01</td>
</tr>
<tr>
<td><strong>PTT, seconds</strong></td>
<td>27.7 (2.9)</td>
<td>31.0 (3.2)</td>
<td>30.0 (3.1)</td>
<td>0.032</td>
<td>0.107 0.86 0.71 1.03</td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td>1.1 (0.09)</td>
<td>2.2 (3.4)</td>
<td>1.1 (0.37)</td>
<td>0.241</td>
<td></td>
</tr>
<tr>
<td><strong>Glucose</strong></td>
<td>7.1 (1.8)</td>
<td>9.0 (2.4)</td>
<td>7.1 (2.1)</td>
<td>0.027</td>
<td></td>
</tr>
<tr>
<td><strong>Positive history of hypertension</strong></td>
<td>11 (85%)</td>
<td>8 (89%)</td>
<td>14 (48%)</td>
<td>0.020</td>
<td>0.010 6.21 1.55 24.8</td>
</tr>
<tr>
<td><strong>mRS, median (IQR)</strong></td>
<td>1.0 (1.0)</td>
<td>1.0 (2.0)</td>
<td>3.0 (3.0)</td>
<td>0.112</td>
<td></td>
</tr>
<tr>
<td><strong>Hospital stay, days</strong></td>
<td>16 (19)</td>
<td>9 (6)</td>
<td>22 (25)</td>
<td>0.430</td>
<td></td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td>40.4 (4.5)</td>
<td>43.2 (3.6)</td>
<td>39.9 (3.2)</td>
<td>0.308</td>
<td></td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
<td>17.9 (6.8)</td>
<td>12.5 (2.5)</td>
<td>19.9 (36.2)</td>
<td>0.102</td>
<td>0.764 1.00 0.97 1.03</td>
</tr>
<tr>
<td><strong>AST</strong></td>
<td>24.4 (13.7)</td>
<td>25.5 (5.9)</td>
<td>30.1 (16.2)</td>
<td>0.504</td>
<td></td>
</tr>
<tr>
<td><strong>ALT</strong></td>
<td>20.7 (15.0)</td>
<td>28.3 (11.9)</td>
<td>24.8 (11.5)</td>
<td>0.310</td>
<td></td>
</tr>
<tr>
<td><strong>ALP</strong></td>
<td>83.9 (31.7)</td>
<td>81.3 (8.0)</td>
<td>69.2 (17.6)</td>
<td>0.319</td>
<td></td>
</tr>
</tbody>
</table>

All values are the mean and SD in parentheses unless specified. Probability modeled in logistic regression analysis is cumulated over the following order: 2 = CAA-positive, 1 = hypertension, 0 = CAA-negative.

*Log-transform was applied in the univariate logistic regression analysis.

AST indicates aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.
Assessment of the status of vessel wall thickening in our patient group is beyond the imaging resolution of conventional CT or MRI. However, the association between wall thickening and increased disease severity and disease severity, leukoaraiosis severity, and number of microbleeds is consistent with a prior study of 2060 brains in previously reported. It is plausible to suggest that the same mural characteristics producing chronic blood leakage described here may also impact on vessel contractility, bleeding rate, hematoma growth, and spot sign frequency. The segmental and heterogeneous nature of mural involvement and variability of severity of involvement may explain the intermediate position of CH for rates of spot sign presence and white matter changes compared with CAA-positive and -negative patients. However, ICH growth is multifactorial and many factors other than mural changes may influence hematoma expansion, including systemic blood pressure, intrinsic interstitial pressure, and clotting status.

Baseline hematoma location in this study reflects the expected distribution for each etiology. The majority of probable CAA and hypertensive patterns demonstrated lobar and deep hematoma locations, respectively. Our prevalence of a nonlobar hematoma location in CAA-positive patients is consistent with a consecutive autopsy study of 2060 brains in which 21.4% of ICH occurred in a nonlobar location. Similarly, consistent with a prior study of 367 patients with ICH, we did not see a significant regional predilection of spot sign and deep or lobar locations. Overall, a lobar hematoma location in this study was more common in CAA-negative than probable CAA-positive patients likely reflecting the lower mean age and larger number of CAA-negative compared with probable CAA-positive subjects. These findings are consistent with a prior study in which 38% of lobar hemorrhage was attributable to CAA but lower than 74% described by Knudson et al. An interesting observation was an increased mean PTT in spot-positive patients. After removing the 7 patients from the analysis with any PTT increase, logistic regression results remained unchanged, suggesting that the PTT elevation was not significantly contributing to the increased spot sign frequency. Additionally, the mean PTT for each group remained within our institutional normal range with only 2 patients demonstrating significant outlying values. No difference in incidence of aspirin, anticoagulation, or antiplatelet use between patient groups was demonstrated. No patients received heparin. No history of liver disease was elicited on chart review or evident from laboratory tests. The significance of this finding remains to be determined; however, minor coagulopathic changes are commonly described in traumatic brain injury. These coagulopathies are associated with modest elevations of PTT and INR and thought to be secondary to tissue factor or thromboplastin release triggering a consumptive coagulopathy and hyperfibrinolysis. The higher mean value in the presence of extravasation may reflect a larger amount of parenchymal damage and tissue factor release than those patients without contrast extravasation.

The limitations of the study are its retrospective design, a relatively small sample size, and high number of exclusions. Addressing the number of exclusions, our institution is bound to regionally mandated rules requiring patients, who initially bypass their local hospitals for acute stroke, to be repatriated after acute stroke diagnosis and management in our regional stroke center. There were 63 patients who met these criteria and were returned to their local hospitals without available follow-up. Although not known for certain, there is no reason to assume that the baseline characteristics of repatriated patients were different from those included in the study and that their exclusion introduced a selection bias. This is an assumption based on the fact that the only criteria mandating patient repatriation was a geographic location remote from a tertiary referral stroke center. Considering that these criteria are applied equally to all patients who live remote to a tertiary hospital, it is unlikely that the baseline characteristics of these repatriated patients would differ significantly from our included cohort. Furthermore, it would be ethically questionable to obtain MRI studies on patients with poor clinical outcome in which study results would not affect subsequent management. Finally, patients with secondary ICH were appropriately excluded because these patients represent a distinct population from primary patients with ICH, the main focus of this study. CAA-positive designation is probable based on established MRI criteria but was not histopathologically confirmed. The diagnosis of probable CAA according to criteria used in this study has been shown to be relatively specific for CAA-related hemorrhage compared with autopsy specimens, although the sample size was small (n=13). Further studies are required to determine whether our findings can be generalized to other patient cohorts. It is the intent of the Predicting hEmatoma growth anD outcome in Intracerebral hemorrhage using contrast bolus CT study (PREDICT) study group, a prospective multicenter study investigating the predictive value of the spot sign in ICH growth, to validate these findings.

In conclusion, we demonstrate that Boston criteria-defined CAA-negative status confirms the highest risk of spot positivity, extravasation, and final hematoma size compared with probable CAA-positive patients. The findings provide novel insight into potential differences of hematoma expansion in different primary ICH groups and may help better define a subgroup of patients that will benefit most from prothrombotic treatments in acute ICH. Patient selection is especially important in light of 2 grant-funded randomized controlled
studies, STOP-IT (The Spot sign for predicting and treating ICH growth study) and SPOTLIGHT (The Spot Sign Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy study), studying the effect of recombinant factor 7 on hematoma growth.

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Disclosures
None.

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The Spot Sign Is More Common in the Absence of Multiple Prior Microbleeds
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