CT Angiography "Spot Sign" Predicts Hematoma Expansion in Acute Intracerebral Hemorrhage

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Background and Purpose—Morbidity and mortality in spontaneous intracerebral hemorrhage (ICH) are correlated with hematoma progression. We hypothesized that the presence of tiny, enhancing foci ("spot sign") within acute hematomas is associated with hematoma expansion.

Methods—We prospectively studied 39 consecutive patients with spontaneous ICH by computed tomography angiography within 3 hours of symptom onset. Scans were reviewed by 3 readers. Patients were dichotomized according to the presence or absence of the spot sign. Clinical and radiological outcomes were compared between groups. The predictive value of this sign was assessed in a multivariate analysis.

Results—Thirteen patients (33%) demonstrated 31 enhancing foci. Baseline clinical variables were similar in both groups. Hematoma expansion occurred in 11 patients (28%) on follow-up. Seventy-seven percent of patients with and 4% without hematoma expansion demonstrated the spot sign ($P<0.0001$). Sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio for expansion were 91%, 89%, 77%, 96%, and 8.5, respectively. Interobserver agreement was high ($\kappa=0.92$ to 0.94). In patients with the spot sign, mean volume change was greater ($P=0.008$), extravasation more common ($P=0.0005$), and median hospital stay longer ($P=0.04$), and fewer patients achieved a good outcome (modified Rankin Scale score <2), although the latter was not significant ($P=0.16$). No differences in hydrocephalus ($P=1.00$), surgical intervention ($P=1.00$), or death ($P=0.60$) were noted between groups. In multiple regression, the spot sign independently predicted hematoma expansion ($P=0.0003$).

Conclusions—The computed tomography angiography spot sign is associated with the presence and extent of hematoma progression. Fewer patients achieve a good clinical outcome and hospital stay was longer. Further studies are warranted to validate the ability of this sign to predict clinical outcomes. **(*Stroke*. 2007;38:1257-1262.)**

Key Words: computed tomography angiography ■ intracerebral hemorrhage ■ prognosis ■ stroke

Intracerebral hemorrhage (ICH) accounts for between 10% and 30% of all strokes, affecting more than 60 000 people in the United States annually.[1] Outcomes are significantly worse than with ischemic stroke, with up to 50% mortality at 30 days.[2] Important etiologic factors in the elderly population in whom ICH is more common are hypertension, amyloid angiopathy, and anticoagulation.[3–6]

Hematoma size has been shown to be one of the most important predictors of 30-day mortality.[7] Hematoma expansion is highly predictive of neurological deterioration[8–10] and is an independent predictor of mortality and functional outcomes.[11] Accurate and reliable clinical and radiographic predictors of ICH growth are needed. With recombinant factor VIIa emerging as an investigational treatment for acute ICH, it will be particularly important to better predict which patients are most likely or least likely to benefit from such treatment.[12,13] Although the incidence of serious adverse events has been shown to be low at <1%, factor VII–related thrombotic complications can occur,[14] and it would be desirable to avoid treating patients in whom hematoma expansion is unlikely.

Computed tomography angiography (CTA) is a rapid, noninvasive investigation for patients with ICH and has proven useful for identifying potentially treatable entities such as aneurysms[15–20] and other vascular lesions.[21–23] In this report, we describe the CTA finding of tiny, enhancing foci, or the "spot sign," within hematomas, with or without clear contrast extravasation. We hypothesized that this sign is associated with hematoma expansion and poor clinical outcomes.

Patients and Methods

Study Group

At our regional stroke center in Toronto, Canada, patients presenting within 3 hours of stroke symptom onset undergo a standard CT protocol including CTA. Between January 2004 and May 2006, there were 48 patients with spontaneous ICH. Patients with underlying aneurysm, vascular malformation, dissection, hemorrhagic transfor-

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mation of ischemic stroke, or traumatic ICH or those who underwent interval surgery between baseline and follow-up study were excluded. Two patients were excluded because of poor CTA quality or lack of early CT follow-up at day 1 to 2 (n=3) or because they were enrolled in clinical trials (n=4). The baseline characteristics of these 9 patients were similar to the remaining study cohort of 39. The study had research ethics board approval. Clinical data were collected by 2 stroke neurologists during admission and at the 3-month follow-up.

Materials/Image Acquisition

The stroke protocol was performed on a 4-slice (2004 through 2005) or a 64-slice (2005 through 2006) CT (GE Lightspeed plus and VCT; GE, Milwaukee, Wis). Precontrast head imaging is followed by a CTA/CT perfusion study and immediately thereafter a postcontrast study 1 to 2 minutes after contrast injection. Precontrast and postcontrast head imaging is performed from the skull base to the vertex with the following imaging parameters: 120 kVp; 340 mA; 4×5 mm-collimation; 1 second/rotation; and a table speed of 15 mm/rotation. CTA studies are obtained from the C6 level to the vertex in the helical HS mode. CTA parameters are 0.7 mL/kg contrast (maximum of 90 mL through an antecubital vein via an 18- or 20-gauge angiocatheter); 5- to 10-second delay; 120 kVp; 270 mA; 1 second/rotation; 0.0625- to 1.25-mm slice thickness; and a table speed 3.75 mm/rotation.

CT technologists perform all postprocessing, including multiplanar reformats at the CT operator's console. Coronal and sagittal multiplanar reformat images are created as 10.0-mm-thick images, spaced by 3 mm. Bilateral rotational multiplanar reformat are created at each carotid terminus with a thickness of 7 mm and a spacing of 3 mm. All images were viewed on AGFA Impax 4.5 PACS workstations.

Imaging Analysis/Interpretation

All studies were prospectively evaluated by 3 neuroradiologists for the presence or absence of the CTA spot sign. This sign was defined as 1 or more 1- to 2-mm foci of enhancement within the hematoma on CTA source images (Figure 1B). Assessment is made by simple visual inspection and can easily be detected by nonradiologists. Spot location within the hematoma and the number of spots were noted. Extravasation was defined as enlargement of the contrast density on the immediately proceeding enhanced CT (Figure 1C). Hematoma location was classified as supratentorial or infratentorial. Supratentorial location was further subclassified as lobar or deep. Hematoma volumes were calculated on the initial and follow-up CTs at 1 to 2 days with the previously validated ABC/2 method.[24] An increase of hematoma size >30% or >6 mL was considered significant enlargement.[13,25]

Statistical Methods

The prevalence, number, and location of spots were recorded for each reviewer. The interobserver agreement for detection, number, and presence of extravasation was calculated with the multirater κ statistic.[26] Values of κ of 0.21 to 0.4, 0.41 to 0.6, 0.61 to 0.8, and 0.81 to 1 were considered fair, moderate, substantial, and nearly perfect, respectively.[27]

Patients were classified according to the presence or absence of the spot sign. Baseline variables, including age, sex, antiplatelet/anticoagulant use, glucose levels, clotting profile, blood pressure, and hematoma size, were compared with Student's *t* test and Fisher's test for continuous and categorical data, respectively. Thresholds of glucose >8.3 mmol/L and mean arterial pressure (MAP) >120 mm Hg were selected on the basis of previous data.[28]

Diagnostic performance characteristics of the spot sign for clinically significant hematoma expansion were calculated. Absolute and percent ICH volume changes, presence of extravasation, hydrocephalus, surgical intervention, and 3-month modified Rankin Scale score were compared for the 2 groups. Univariate analyses and multivariable linear regression were used to assess the dependence of hematoma volume change on clinical and radiological factors. In addition to the spot sign, 3 important factors were identified a priori for the multiple-regression model: extravasation or use of anticoagulants; a history of hypertension or a measured MAP >120 mm Hg; and an elevated glucose value (>8.3 mmol/L). Three patients with outlying values for change in ICH volume were identified and were excluded from the multiple-regression results presented here. A multiple regression for all subjects according to robust methods[29] gave essentially the same results. All data were analyzed with SPSS for Windows (version 14; SPSS, Inc, Chicago, Ill) and R, version 2.3.1.[30] Confidence intervals for differences in proportions were computed with Newcombe's method, and confidence intervals for differences in medians and for differences in percent changes in volume were computed with the bootstrap method. A value of $P<0.05$ was considered significant.

Results

Thirty-nine patients demonstrated spontaneous ICH (26 male, 13 female). The median age was 64 years (range, 31 to 85 years). ICH was deep, lobar, or within the posterior fossa in 14 (36%), 23 (59%), and 2 (5%) patients, respectively. Median hematoma size at presentation was 24.9 cm^3 (range, 1.4 to 154 cm^3). Thirteen patients demonstrated intrahematoma foci of enhancement (33%), exhibiting 31 discrete foci, of which 24 were peripherally positioned. The interobserver

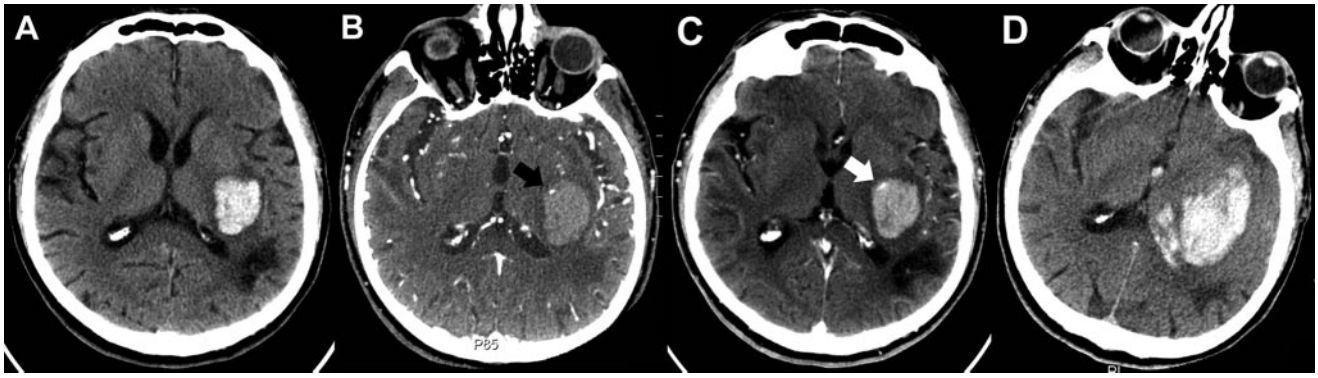

Figure 1. Patient with spot sign, demonstrating extravasation and hematoma expansion. CT slice selection has been optimized for hematoma configuration, not for head position. A, Unenhanced CT demonstrates left posterior putaminal and internal capsule hematoma with mild surrounding edema. An old parieto-occipital infarct is seen posterior to this. B, A small focus of enhancement is seen peripherally on CTA source images, consistent with the spot sign (black arrow). C, Postcontrast CT demonstrates enlargement of the spot sign, consistent with extravasation (white arrow). D, Unenhanced CT image 1 day after presentation reveals hematoma enlargement and intraventricular hemorrhage.

TABLE 1. Radiological and Clinical Outcomes in ICH Patients With and Without the CTA Spot Sign

	CTA Spot Sign			
	Positive (n=13)	Negative (n=26)	95% CI for Difference	*P* Value
Absolute volume change, cm^3	14.3 (17.6)	−1.7 (8.0)	5.0, 26.9	0.008
Percentage volume change	76.8 (132.7)	−3.0 (23.7)	33, 202	0.004
Extravasation on CTA, n (%)	6 (46)	0	18%, 72%	<0.001*
Patients with significant hematoma expansion, n (%)	10 (77)	1 (4)	49%, 97%	<0.001†
Median, days hospital stay (range)	19 (4–76)	9 (2–76)	−4, 20	0.042
Hydrocephalus, n (%)	2 (15)	3 (12)	−19%, 27%	1.000
3-month mRS score, n (%)	3 (31)	13 (50)	−57%, 3%	0.169
Hospital death, n (%)	3 (23)	4 (15)	−19%, 35%	0.666
Any surgical intervention, n (%)	2 (15)	4 (15)	−24%, 24%	1.000

mRS indicates modified Rankin scale. All values are expressed as mean (SD) except where specified.
*P=0.0005.
†P=0.0001.

agreement for the presence and multiplicity of the spot sign was nearly perfect (κ=0.85 to 0.94).

Overall, the baseline characteristics (sex, initial hematoma size, systolic blood pressure, MAP >120 mm Hg, glucose level >8.3 mmol/L, international normalized ratio [INR], activated partial thromboplastin time [APTT], and history of anticoagulants) of the groups with and without the spot sign were similar. Follow-up study results (Table 1) demonstrated 11 patients (28%) with clinically important hematoma growth; 10 of these demonstrated foci of enhancement (91%) on the initial CTA. The diagnostic performance measures of spot sign for hematoma expansion are given in Table 2. We dichotomized the group with the spot sign according to the presence of extravasation. Six of these patients demonstrated contrast extravasation (46%), 4 were on warfarin, accounting for a higher INR (mean±SD, 2.0±1.1 vs 1±0.1; P=0.04) than those without extravasation. There was no significant difference in final volume or change of volume in the patients with extravasation (P=0.18). When patients with extravasation were excluded, the patients demonstrating the spot sign were still more likely to have a larger final hematoma size (P=0.001). Patients on anticoagulation were more likely to have multiple foci of enhancement (P=0.03), but there was no association between the INR/APTT level and number of spots. Patients with multiple spots had a similar initial hematoma volume (P=0.15) but a greater final absolute volume (P=0.01) than those with a single spot. Univariate analyses demonstrated the spot sign (P=0.0004), extravasation (P=0.00007), and anticoagulants (P=0.04) to be associated with hematoma growth, whereas a history of hypertension, MAP >120, and glucose >8.3 mmol/L had no significant association. In multiple regression, the spot sign (P=0.0003), extravasation (P=0.001), and anticoagulant history (P=0.02) were independently associated with an increase in volume, but again, a history of hypertension, high MAP, and high glucose were not (Table 2).

Hematoma enlargement occurred significantly more frequently in patients with the spot sign than those without (P=0.0001). Mean absolute (P=0.008) and percentage (P=0.005) hematoma volume change, presence of extravasation (P=0.0005), and length of hospital stay (P=0.04) were greater when the spot sign was present. There was no statistically significant difference in the proportion of patients with surgical intervention or hydrocephalus between the 2 groups. Patients with the spot sign were less likely to achieve a good clinical outcome (Figure 2), although this did not reach statistical significance (P=0.15).

Discussion

A focus of enhancement within acute ICHs, termed the spot sign, is not a previously described entity. We speculate on its etiology and report the independent association with acute hematoma expansion. Initial hematoma size has been shown to be 1 of the most important predictors of 30-day mortality.[7]

TABLE 2. Univariate and Multivariate Analysis, Sensitivity, Specificity, PPV, NPV, and Positive and Negative Likelihood Ratio

	Univariate Analysis *P*	Multivariate Analysis *P*	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	+LR (95% CI)	−LR (95% CI)
Spot sign	0.0004	0.0003	91 (62–100)	89 (72–96)	77 (50–92)	96 (81–99)	8.5 (2.9–25)	0.1 (0.02–0.7)
Extravasation	0.00007	0.001	45 (21–72)	96 (82–100)	83 (43–99)	81 (66–91)	12.7 (1.7–97)	0.6 (0.3–0.9)
Anticoagulation	0.04	0.02	45 (21–72)	79 (63–94)	79 (61–90)	45 (21–72)	2 (0.8–5.5)	0.7 (0.4–1.2)
MAP >120 mm Hg	0.83	0.83	36 (15–65)	61 (42–76)	27 (11–52)	71 (51–85)	0.9 (0.4–2.3)	1.0 (0.6–1.8)
History of hypertension	0.24	0.6	54 (28–79)	57 (39–73)	33 (16–56)	76 (54–89)	1.3 (0.6–2.5)	0.8 (0.4–1.6)
Glucose >8.3	0.35	0.12	18 (5–48)	71 (53–85)	20 (5–51)	69 (51–83)	0.6 (0.2–2.5)	1.1 (0.8–1.6)

PPV indicates positive predictive value; NPV, negative predictive value; and LR, likelihood ratio, the preferred way to represent a single summary result of a diagnostic test. It estimates the posttest odds of an outcome (significant increase in ICH volume) changed relative to the pretest odds.

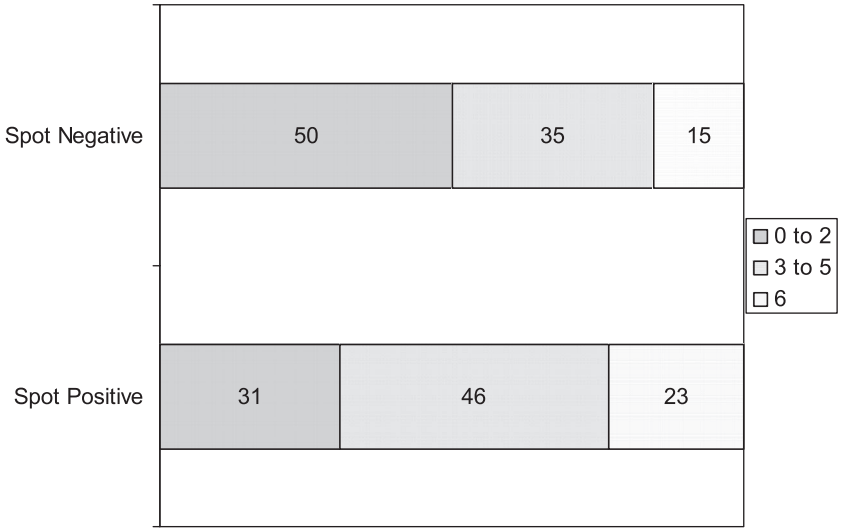

Figure 2. Modified Rankin Scale score at 3 months in patients with and without the spot sign.

However, it has been well established that initial hemorrhage volume is not static but frequently progresses, usually within the early hours after the ictus. Growth has been shown to occur in up to 38% of patients, most commonly within the first 6 hours of symptom onset.[9,10,31–33] A number of risk factors have been associated with hematoma progression, including hyperglycemia,[10,28] hypertension,[34] and anticoagulation.[35–37] An association between progression and poorer outcomes has been suggested for several years,[9,10] but more recently, expansion has been shown to be an independent predictor of mortality and diminished functional outcomes.[11]

Hematoma progression has been previously defined as an increase of between 33% and 50% or an absolute change in volume of between 12.5 and 20 mL.[9,31–33] However, studies evaluating hematoma growth in posttraumatic ICH have shown that an expansion of 5 mL predicted the need for late surgical evacuation.[25] In addition, Mayer et al[13] showed significantly worse outcomes in patients who did not receive factor VII, despite a difference in mean absolute increase of only 5.8 mL in the group treated with the highest dose. Accordingly, for the purposes of this study, a >30% or a >6-mL increase in volume was defined as hematoma expansion. Although the mechanisms of hematoma growth are not well understood, both primary and secondary vessel injury is proposed. A brief review is necessary to understand the possible etiology of these foci of enhancement, or spot sign.

Parenchymal microaneurysms and their rupture, initially described in 1868 by Charcot and Bouchard,[38] have been implicated in the development of hypertensive ICH. The aneurysms are reported to measure up to 2 mm in size,[39] well within the range of spatial resolution for CTA studies (0.5 mm). They occur in deep brain structures, including the basal ganglia and thalami, and are most commonly seen in elderly, hypertensive individuals.[40,41] Early work described these lesions as being true aneurysms[42]; however, controversy has persisted regarding the true nature of these lesions.[43] Possibilities suggested range from adherent clots or pseudoaneurysms,[44] "bleeding globes,"[45,46] and more recently, vascular tortuosity and coiling, artifactually producing the appearance of an aneurysm.[47,48] Microaneurysm formation has also been implicated in the mechanism of hemorrhage in amyloid angiopathy[49] and may be part of a common end pathway to hemorrhage in both hypertension and amyloid angiopathy.[50] Secondary hemorrhage into perihematoma tissue is a further mechanism of hematoma expansion.[51,52] Mechanical disruption and ischemia[53] have been proposed, but increasingly, inflammatory mediators are implicated.[54–64] Bleeding from surrounding vessels may explain the tendency for irregular hematomas to expand.[10] Whether expansion occurs more frequently from primary or secondarily damaged vasculature, both continued hypertension and coagulopathy are thought to contribute.[34–37]

Despite numerous pathologic descriptions, including recent reports of actual ruptured microaneurysms within parenchymal hematomas,[65,66] microaneurysms or evidence of vascular injury on conventional angiography or CTA are not well described. We demonstrated foci of contrast enhancement in 91% of expanded hematomas. Nearly half of the foci detected showed evidence of increased contrast puddling on the postcontrast CT performed immediately after CTA. The growth of contrast enhancement is presumed active extravasation. Anticoagulant administration and a higher mean INR in the extravasation group contributed to a larger hematoma size, but the spot sign remained an independent predictor of growth. Previous series showed that extravasation on CTA was predictive of hemorrhage enlargement from aneurysms and other vascular lesions.[67] More recently, diffuse contrast extravasation has been reported as an independent predictor of in-hospital mortality[28]; however, CT examination was performed outside the window recommended for factor VII (median, 4.6 to 6 hours). Extravasation on magnetic resonance imaging has also been shown to indicate persistent hemorrhage and is correlated with hematoma enlargement.[68] Active contrast extravasation on cerebral angiography associated with hematoma formation has been recognized since the 1970s.[69–72]

It is unclear whether the foci of enhancement represent primary or secondary vessel injury. The peripheral location of enhancement supports the assertion that these foci represent active hemorrhage from secondarily damaged or torn perfo-

rators in the absence of an underlying aneurysm or aneurysm-like lesions. However, given the putative underlying mechanisms of ICH in both hypertension and amyloid angiopathy, it is reasonable to speculate that these spots may represent pseudoaneurysms, Charcot-Bouchard aneurysms, or amyloid-related microaneurysms.

Despite the demonstration that the spot sign is highly associated with hematoma expansion and the well-known association between expansion and increased morbidity and mortality, we were unable to detect a difference between the 2 groups. This may be attributable to the relatively small sample size. Similarly, only a small number of patients underwent surgical intervention or developed hydrocephalus. Finally, the indications for CTA in ICH are not well established, and as a result, not all patients with ICH underwent CTA. However, we believe the presented cohort to be representative of the population of patients presenting with spontaneous ICH.

In conclusion, we report the CTA spot sign, the presence of tiny, focal areas of contrast enhancement in association with ICH, which are independent and highly predictive of hematoma expansion. The sign is easily and reliably detected. The presence of this sign may be a useful radiological marker that should be validated in a larger prospective cohort.

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Disclosures

None.

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