

# Defining the CT Angiography 'Spot Sign' in Primary Intracerebral Hemorrhage

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**ABSTRACT: Purpose:** The computed tomogram angiography (CTA) 'spot sign' describes foci of intralésional enhancement associated with hematoma expansion in primary intracerebral hemorrhage patients. A consistent radiological definition is required for two proposed recombinant Factor VIIa trials planning patient dichotomization according to 'spot sign' presence or absence. We propose radiological criteria for diagnosis of the CTA 'spot sign' and describe different morphological patterns. **Material and Methods:** A prospective cohort of 36 consecutive patients presenting with primary intracerebral hemorrhage (ICH) were enrolled in a multicenter collaborative study, and have been included for the present analysis. Three reviewers analyzed the CTA studies in a blinded protocol. Analysis of specific ICH and 'spot sign' features was performed including prevalence, number, size, location, morphology and Hounsfield unit density. **Results:** Twelve of thirty-six patients (33%) demonstrated a total of 19 enhancing foci consistent with the CTA 'spot sign'. Mean maximal axial 'spot sign' dimension was  $3.7 \pm 2.2$  mm and mean density was  $216 \pm 57.7$  HU. No significant differences in age or blood pressure ( $p=0.7$ ), glucose ( $p=0.9$ ), INR/PTT ( $p=0.3$  and  $0.4$ ) or hematoma location ( $p=0.3$ ) were demonstrated between patients with or without the 'spot sign'. Consensus definition and classification criteria for the CTA 'spot sign' are proposed. **Conclusion:** The 'spot sign' is defined as spot-like and/or serpiginous foci of enhancement, within the margin of a parenchymal hematoma without connection to outside vessels. The 'spot sign' is greater than 1.5 mm in maximal dimension and has a Hounsfield unit density at least double that of background hematoma density.

**RÉSUMÉ: Définition du « spot sign » à l'angiographie CT dans l'hémorragie intracérébrale primitive. Objectif :** Le spot sign à l'angiographie par tomographie assistée par ordinateur (angio CT) désigne des foyers intralésionnels de rehaussement associés à une expansion de l'hématome chez les patients qui présentent une hémorragie intracérébrale primaire. Il faudra utiliser une définition radiologique fiable dans le cadre de deux essais cliniques portant sur le facteur VIIa recombinant, dans lesquels les patients seront classifiés selon la présence ou l'absence du spot sign. Nous proposons des critères radiologiques pour le diagnostic du spot sign à l'angio CT et nous décrivons différents aspects morphologiques. **Matériel et méthodes :** Une cohorte prospective composée de 36 patients consécutifs qui ont consulté pour une hémorragie intracérébrale primaire (HIP) ont été inclus dans une étude multicentre effectuée en collaboration dont nous présentons les données. Trois réviseurs ont analysé les études angio CT en double insu. L'analyse de manifestations spécifiques d'HIP et de spot sign a été effectuée, dont la prévalence, le nombre, la taille, la localisation, la morphologie et la densité en unités Hounsfield (UH). **Résultats :** Au total, 19 foyers rehaussants compatibles avec un spot sign à l'angio CT ont été observés chez douze des trente-six patients (33%). La moyenne de la dimension axiale maximale du spot sign était de  $3,7 \pm 2,2$  mm et la densité moyenne de  $216 \pm 57,7$  UH. Aucune différence significative quant à l'âge ou à la pression sanguine ( $p = 0,7$ ), la glycémie ( $p = 0,9$ ), l'INR/PTT ( $p = 0,3$  et  $0,4$ ) ou la localisation de l'hématome ( $p = 0,3$ ) n'a été observée entre les patients présentant ou non le spot sign. Nous proposons une définition de consensus et des critères de classification du spot sign à l'angio CT. **Conclusion :** Le spot sign est défini comme étant des foyers de rehaussement punctiformes et/ou serpiginoux à l'intérieur des marges d'un hématome parenchymateux, sans connexion aux vaisseaux extérieurs. Le spot sign a une dimension maximale de plus de 1,5 mm et une densité UH qui est au moins deux fois celle de l'hématome dans lequel il est situé.

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Intracerebral hemorrhage (ICH) is responsible for 10 to 30 % of stroke presentations<sup>1</sup> and is responsible for greater morbidity and mortality compared to ischemic stroke<sup>2</sup>. Hematoma expansion within the first few hours following ictus is recognized as a poor prognostic marker<sup>3,4</sup>. The recently reported computed tomogram angiography (CTA) 'spot sign' describes foci of enhancement within the acute hematoma on CTA that are associated with hematoma expansion<sup>5,6</sup>. The identification of potential imaging markers that predict hematoma expansion and thus increased morbidity and mortality may have important implications for patient selection for investigational treatment

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with recombinant Factor VIIa. Studies that intend to dichotomize patient groups according to 'spot sign' presence or absence require a robust and inclusive definition that provides clinicians with the confidence needed to identify the target population.

The PREDICT study (Predicting hEmatoma growth and outcome in Intracerebral hemorrhage using contrast bolus CT) is a prospective multicenter cohort study evaluating the use of CTA in predicting hematoma growth and functional outcome in spontaneous intracerebral hemorrhage patients presenting within six hours of symptom onset. The primary objectives of PREDICT are to validate the 'spot sign' as an independent predictor of hematoma expansion and clinical outcome.

The purpose of the current study is to review prospective ICH cases from the PREDICT study database to formally define the CTA 'spot sign' and to propose a classification scheme based on morphological appearances.

## MATERIALS AND METHODS

### Study group

The PREDICT group has prospectively enrolled consecutive patients presenting with spontaneous ICH undergoing CTA within six hours of ictus. For the purpose of this study, the initial 36 patients enrolled in the PREDICT database have been included for analysis, irrespective of 'spot sign' status. Institutional research ethics board approval was obtained.

PREDICT inclusion criteria are: Spontaneous ICH including anticoagulation related ICH less than 100 cc in volume, age greater than 18, presentation less than six hours from last seen well, premorbid modified Rankin Scale of 3 or less and ability to have a 24 hour follow-up CT scan with informed consent. Exclusion criteria include ICH greater than 100 cc volume, secondary causes of ICH ( tumor, arteriovenous malformation etc.), surgical evacuation of hematoma planned within 24 hours of symptom onset, deep coma (GCS 3-5) at admission, major comorbid or terminal illness, known renal impairment or patient arriving outside the six hour window.

### Imaging protocol

The imaging protocol was performed on multidetector CT scanners. The most widely used scanners were multidetector CT (Somatom sensation 40, Siemens Medical Solutions, Forchheim,

Germany) or 64-slice CT (VCT; GE, Milwaukee, Wis.). Imaging parameters vary according to local scanners. Typical parameters are indicated. Five millimeter contiguous, non-contrast CT (NCCT) axial sections from skull base to vertex parallel to the inferior orbitomeatal line were obtained. Typical parameters include: helical scan, 120 kVp, 340 mA, 4 x 5 mm collimation, 1s per rotation, and a table speed of 15 mm per rotation. The CTA utilizes a bolus-tracking method with injection of 90-100 ml of nonionic iodinated contrast injected through an 18 or 20 gauge angiocatheter at 5cc/s followed by a 40 ml saline bolus. Parameters: 120 kVp; 270 mA; 1.25 mm thick slices reconstructed to 0.625 mm. Scans are automatically triggered between 10-15 seconds.

All post processing, including multiplanar reformats were performed by the CT technologist at the CT operator's console. Coronal and sagittal multiplanar reformat images were created as 10.0 mm thick images, spaced by 3 mm. Bilateral, rotational multiplanar reformat images were created at each carotid terminus with a thickness of 7 mm and a spacing of 3 mm.

### Image analysis

All imaging studies in the PREDICT database were anonymized and loaded into an open source DICOM viewer (Osirix medical imaging software). The cases were then prospectively and randomly reviewed by a neuroradiologist and two neurologists experienced in ICH and 'spot sign' recognition. Reviewers were blinded to clinical history. Studies were evaluated for the presence or absence of the 'spot sign'. 'Spot sign' mimics have previously been described and were not considered. These include calcific densities present on non-contrast CT, presence of a communication with a vessel beyond the hematoma margin and extra-axial contrast densities<sup>7</sup>. Morphological characteristics of 'spot sign' positive patients were recorded including hematoma location (basal ganglia/lobar), density (Hounsfield units) and volume. Custom software utilizing the Insight Segmentation and Registration Toolkit (ITK; National Library of Medicine, Bethesda, MD) enabled threshold-based volumetric intraparenchymal hematoma and intraventricular hematoma analysis. The sum of intraparenchymal and intraventricular hematoma volumes represented the total intracranial hematoma volume. The automatically calculated volumes were reviewed by consensus and modified where

**Table 1: Demographic presentation data dichotomized for presence or absence of CTA 'spot sign'**

	Spot Positive (n=12)	Spot Negative(n=24)	95% CI for difference	P value
Age (years)	69.2 (13.8)	67.7 (14.9)	-8.857 to 12.02	0.7597
Initial hematoma volume (ml)	34.1 (27.1)	18.3 (22.7)	-33.19 to 1.655	0.0279
Baseline systolic BP (mmHg)	175.1 (41.9)	170.3 (38.3)	-22.70 to 32.20	0.7270
Baseline NIHSS *	16.5 (5.0-24.0)	9.0 (4.8-15.6)	-0.7815 to 8.698	0.0986
Glucose (mmol/L)	7.1 (3.1)	7.0 (1.4)	-1.776 to 1.960	0.9207
INR	1.4 (1.0)	1.1 (0.3)	-0.2324 to 0.7277	0.3010
Prothrombin Time(s)	33.6 (13.9)	30.3 (9.6)	-4.900 to 11.41	0.4224

mRS - modified Rankin Scale, NIHSS – National Institutes of Health Stroke Scale; All values expressed as mean (SD) except \*median (range)

**Table 2: Summary of 'spot sign' patterns**

Pattern	Morphology
I	Line only
II	Line and spot
III	Single spot
IV	Confluent branching spots and lines

necessary to ensure accurate representation of hematoma volumes. Analysis of the 'spot sign' included morphology, size (maximal dimension in axial plane), number, location (central/peripheral), density (Hounsfield units, HU) and presence of, and relationship to surrounding vascular structures. A classification of patterns of morphological appearance was devised based upon the imaging characteristics.

#### Statistical methods

Baseline clinical data for each patient included: age, gender, ethnicity, cerebrovascular risk factors, time last seen normal, side of symptoms, handedness, initial triage blood pressure recording, serum glucose, International Normalised Ratio (INR) and admission platelet count. Baseline National Institutes of Health Stroke Score (NIHSS) and Glasgow outcome scale (GOS) were obtained. Premorbid mRS and Barthel Index were obtained from the patient or next of kin. A 24 hour follow up NIHSS was obtained. The Fisher's exact test, unpaired t test and Mann-Whitney test were utilized for group comparisons for categorical and continuous data. Data was analyzed using SPSS for Windows. A p value < 0.05 was considered significant.

#### RESULTS

There were 36 patients (19 male, 17 female) with a median age of 70 years (range 37-92). ICH location was deep in 19 (53%); basal ganglia 8 (22%), thalamus 7 (19%), caudate 4 (11%) and superficial in 17 (47%); lobar 14 (39%) and posterior fossa in 3 (8%) patients. Overall mean intraparenchymal hematoma volume was 23.6 ml (SD 25.0) with a total mean intracranial hematoma volume of 27.3 ml±26.2. Mean intraparenchymal hematoma density was 76±3.8 HU.

Baseline demographic data of patients with and without the 'spot sign' are presented in Table 1. No significant difference in age (p=0.760) or presenting intraventricular hematoma volume (p=0.364, Mann-Whitney test) was present. Baseline mean intraparenchymal hematoma volume, was significantly different between 'spot sign' positive and negative patients (34.1 ml ± 27.1 and 18.3 ml ± 22.7 respectively; p=0.028, Mann-Whitney test). There was no significant difference in hematoma location for patients with or without the 'spot sign' (p=0.302).

Twelve patients (33%) demonstrated a total of 19 enhancing

**Table 3: Numbers demonstrating pattern/morphology**

Pattern	Number of spots
I	0
II	5
III	10
IV	4

foci consistent with the 'spot sign'. Four patients each harbored a lobar, basal ganglia or caudate nucleus hemorrhage respectively. Single and multiple lesions were present in seven and five patients respectively. The mean lesion longest axial dimension was 3.7 mm±2.2 mm. Mean 'spot sign' density was 216.0±57.7 HU. By consensus, only 'spots' with Hounsfield values twice that of hematoma density were considered because densities less than this were not reliably distinguishable from hematoma background. This resulted in the exclusion of four additional discrete 'spots' in two patients with densities of 110, 115, 125 and 143 HU respectively. It should be noted that the cases demonstrating these excluded lesions were retained by virtue of one and two other 'spots' in each case respectively which did fulfill definition criteria. Four morphological patterns have been identified by the authors retrospectively in previous patients with ICH (Table 2). These patterns were prospectively applied to the current study group, the number of patients assigned to each pattern is listed in Table 3.

#### DISCUSSION

The CT angiography 'spot sign' is a prognostic sign in acute ICH that has been previously described as tiny foci of enhancement seen on CTA within 3 hours of spontaneous ICH onset<sup>5</sup>. There is intense interest in the sign in view of promising

**Table 4: Defining criteria of the 'spot sign'**

- Appearance:** serpiginous and/or spot-like appearance
- Location:** within the margin of the parenchymal hematoma without connection to an outside vessel
- Size:** >1.5 mm diameter in maximal axial dimension
- Density:** at least double the density (HU) compared to background hematoma
- Lesion number:** multiple or single

Phase IIa but disappointing Phase III studies of recombinant Factor VIIa therapy<sup>8</sup>. Better targeting of patients at high risk of hematoma expansion is needed and it is thought that the CTA 'spot sign' may facilitate better patient selection. Several 'spot' mimics have been recently described having important implications for studies planning to dichotomize patient groups based on 'spot sign' presence or absence<sup>7</sup>. Following consensus review of a prospective cohort of primary ICH patients, we propose a refined definition of the 'spot sign' that should aid reproducibility and reliability of 'spot sign' identification for future research studies and clinical use.

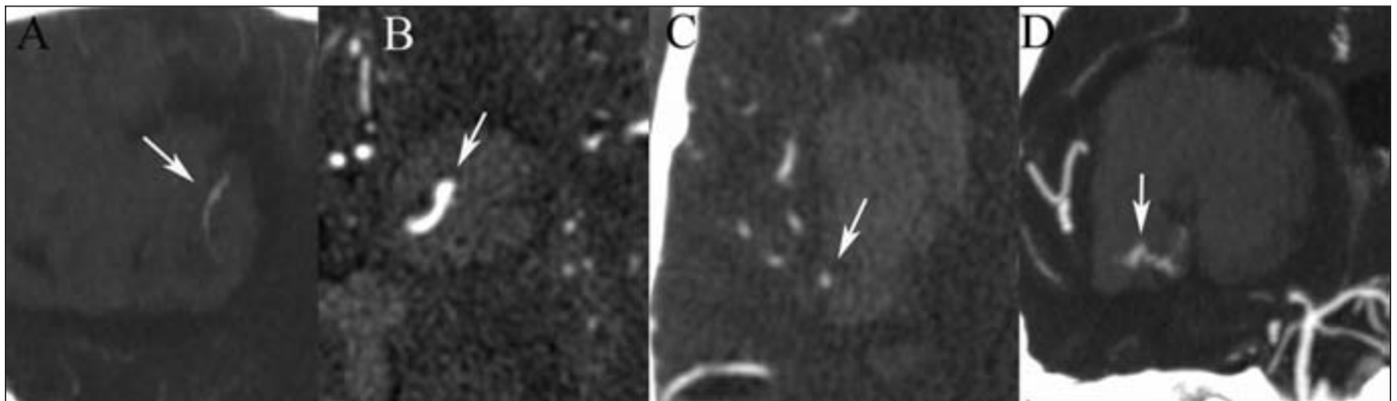
The 'spot sign' definition is provided in Table 4. The 'spot sign' has a serpiginous and/or spot-like appearance, may be multiple or single, is greater than 1.5 mm, occurs within the hematoma margin without connection to outside vessels and has a density twice that of the background hematoma density. Using our definition, the 'spot sign' can be identified on simple visual inspection (without post-processing) and can be easily recognized by non-radiologists. The prevalence of the 'spot sign' in this prospective series (33%) is consistent with two other reports (5, 6). Several pathologic correlates have been described that may explain the 'spot sign' appearance<sup>9-18</sup> including:

1) Saccular aneurysms resembling true berry aneurysms, as described by Charcot and Bouchard<sup>16,19</sup>. 2) Asymmetric fusiform aneurysms involving penetrating arteries of 150  $\mu$  comprising dilated vessel lumens without recognizable elastic or muscular components<sup>18</sup>. 3) Lipohyalinotic aneurysms on vessels of 80 to 300  $\mu$ m. Fisher suggested these were the sequelae of fibrinoid necrosis demonstrating elastica and media integrity loss with secondary arteriolar dilation and microaneurysm formation. The process may involve only part of, or the entire vessel, producing either fusiform or globular shaped lesions. Segmental enlargement extending along the length of the vessel wall may result in up to a ten times diameter increase compared to the adjacent uninvolved segment. The lesions described ranged in size from 0.5 to 1.5 mm. Red blood cell extravasation is demonstrated in chronic lesions<sup>18,19</sup>. 4) Fibrin globes or pseudoaneurysms affect vessels 100 to 200  $\mu$ m in size<sup>13</sup>. These

are lesions comprising masses of red cells enclosed in concentric rings of fibrin adjacent to an arteriolar defect. These lesions are thought to be due to traumatic vessel disruption secondary to hematoma expansion. Lesional size varies between 0.3-1 cm<sup>17,18</sup>. 5) More recently Fisher reported a case of hypertensive thalamic hemorrhage where the pathologic substrate was shown to be focal rupture of an elongated aneurysmal dilatation, 5 mm in length and 600  $\mu$ m in diameter arising from a parent vessel of 150  $\mu$ m in diameter<sup>20</sup>. Focal lipohyalinotic change was seen at the junction between the aneurysmal vessel and the parent vessel.

The size, location and multiplicity of the 'spot sign' most closely resembles the pathological description of fibrin globes. The recently described elongated aneurysmal dilatation as a pathologically confirmed cause of hypertensive hemorrhage also demonstrates a strong resemblance to the CTA 'spot sign'<sup>20</sup>. The absence pathologically, of a bleeding source in ICH patients has led to contention as to whether fibrin globes obscure or in fact represent the primary bleeding source or are a secondary pathological entity. Fisher did not preclude a primary role and proposed a 'domino' effect whereby a single vascular lesion may rupture, contributing to most of the hematoma growth<sup>13</sup>. This may explain why extravasation is variably demonstrated in apparently similar lesions on post contrast CT studies. Whether delayed bleeding from these lesions is associated with secondary hematoma expansion is unknown but plausible.

The 'spot sign' is found exclusively within the hematoma margin with no external vascular communications. Segmental vessel involvement and an origin of lesions from parent vessels of 100  $\mu$ m magnitude would explain the inability to demonstrate vessel continuity beyond the hematoma margin. This characteristic is an important distinguishing feature from a variety of vascular mimics<sup>7</sup>. Micro-arteriovenous malformations and Moya Moya are associated with small pseudoaneurysms that are seen to project into parenchymal hematoma. A contiguous vessel can be identified extending into the hematoma from the surrounding parenchyma and communicating with the focal pool of contrast<sup>7</sup>. Aneurysms and arteriovenous malformations do not



**Figure:** CT Angiographic sagittal (a), axial (b, c) and coronal (d) images demonstrating (a) Pattern I, line (b) Pattern II, line and spot (c) Pattern III, spot and (d) Pattern IV, confluent spots and lines.

usually cause diagnostic confusion because of a clear connection with a subarachnoid vessel and nidus respectively. In cases of ICH, vessels are often deviated around the hematoma bulk, especially in the basal ganglia and high convexity regions, but no extension into the hematoma is seen.

The 'spot sign' was consistently found to have a density greater than 150 HU. This is twice the average hematoma density (60-70 HU) facilitating easy recognition. Occasionally slight hematoma heterogeneity is seen with individual pixel values approaching 100 HU, however these densities are typically less than 1 mm in size. Current spatial resolution of CT does not permit confident diagnosis of enhancing foci less than 1-1.5 mm in maximal axial dimension, because of partial volume averaging of adjacent hematoma density. Accurate caliper placement for 'spot sign' density measurement is also more difficult, with assessment of smaller lesions yielding values of 100-140 HU. For this reason we agreed by consensus that the 'spot sign' should be at least 1.5 mm in size. This measurement does not preclude visualization of the most likely pathological entities implicated in hematoma formation and growth discussed above.

The unenhanced CT should be evaluated in the region of the suspected 'spot sign' as calcification may mimic enhancement<sup>7</sup>. These non-vascular mimics include tumoral, choroidal, infectious, inflammatory and physiological calcification. They are easily excluded with non-contrast enhanced CT evaluation. These mimics are usually peripherally displaced by hematoma mass and external to hematoma margins. Difficulties may arise where tumoral calcification is present within the hematoma margin, and where parenchymal hematoma extends into and compresses the lateral ventricles. In the latter case, the junction between parenchymal and intraventricular blood may be unclear and the compressed and partially calcified choroid plexus may appear within the hematoma.

All 'spot sign' positive cases share similar imaging characteristics that can be further categorized into four morphological patterns (Table 2, Figure). The segmental nature of vessel involvement accounts for the pathological variations described. Many 'spot signs' on axial imaging have serpiginous appearances when viewed with multiplanar reformats. It may be that histological cross sections produced similar misconceptions of the fibrin globes and focal lipohyalinotic vessel dilatations. In support of this, a coronal figure from Fisher, depicting fibrin globes within a putaminal hematoma bears a striking similarity to 'spot sign' appearances seen on CTA (Figure 7 in<sup>13</sup>). One marginal fibrin globe was enlarged measuring 800  $\mu$  and was associated with a leash of abnormal vessels affected by lipohyalinosis similar to our Pattern IV lesion. The proposed Pattern I lesion, although not present in this prospective cohort, has been previously demonstrated in a retrospective cohort<sup>5</sup>. Whether the different 'spot sign' patterns, or the number of 'spot signs' within a hematoma will provide additional prognostic value for prediction of the extent of hematoma expansion remains to be evaluated from the final PREDICT/Sunnybrook study patient cohort. The lack of success of a recent phase III study with recombinant Factor VIIa in primary ICH has widely been attributed to significant patient baseline variances. Differences in baseline CTA 'spot sign' prevalence may also have been responsible given that CTA was not part of the ICH imaging protocol. Two studies are currently seeking grant

approval for a multicenter study that will investigate the impact of the CTA 'spot sign' on radiological and clinical outcome. The success of these studies will depend on the correct identification of the 'spot sign' before patient dichotomization to recombinant Factor VIIa treatment or placebo.

In conclusion, the CTA 'spot sign' is defined as single or multiple, serpiginous and/or spot-like foci of enhancement, within the margin of a parenchymal hematoma without connection to outside vessels. It is greater than 1.5 mm in maximal axial dimension and has a Hounsfield unit density at least double that of background hematoma. We identify four different patterns of 'spot sign' appearance and speculate upon potential vascular pathologic substrates. Histopathological review provides new insight into the presumed pathophysiology of the CTA 'spot sign'. Whether the different patterns indicate different lesion grades with varying risk of further extravasation or hematoma enlargement will be determined in a larger prospective CTA ICH dataset and future 'spot sign' based clinical trials. Prospective imaging or animal studies in ICH with modern postmortem pathologic analysis may enable accurate imaging correlation of the underlying vascular pathologies.

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