



Not a String, not a Tangle, not an Aneurysm

Emerging Pattern of Large Parenchymal Bleeding in Younger Patients Associated with Abnormal Vessels on Imaging

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Abstract

Purpose Intracerebral hemorrhage (ICH) accounts for up to 20% of all strokes, and there is a high rate of associated morbidity and mortality. Computed tomography (CT) findings, such as a spot sign have been shown to be an independent predictor of poor outcome. We have recently encountered a succession of ICH patients who presented with a peculiar imaging finding, which we term the spot on a string sign. This is a rare imaging finding, and interestingly, all these patients presented to our institution over the last few weeks.

Methods This was a single high-volume center series of patients who presented to our institution between 1 April and 21 May 2020. All patients underwent initial non-contrast CT brain and subsequent CT angiography (CTA). We also present laboratory and clinical data. Our primary measure was the presence of the spot on a string sign on the CTA. We also report the clinical course of these patients.

Results In this study seven large-volume ICH patients with this imaging sign were identified, with a median age of 48 years (range 30–68 years). All had tested negative for coronavirus disease 19 (COVID-19).

Conclusion We have described an unusual imaging finding in a cohort of younger patients with large-volume ICH, all of whom presented in a 2-month period to a high-volume neurovascular unit. The cause of these ICH presentations and associated imaging findings are unclear, but we encourage other clinicians to be aware of and vigilant for this rare phenomenon, especially in younger patients with such a bleeding pattern.

Keywords Intracranial hemorrhage · ICH · Stroke · Hemorrhage · Vascular

Introduction

Nontraumatic intracerebral hemorrhage (ICH) accounts for up to 20% of all strokes [1]. A computed tomography angiogram (CTA) is often performed to exclude an underlying vascular pathology (e.g. aneurysm, arteriovenous malformation [AVM]). The CTA spot sign is defined as a uni-focal/multifocal area of contrast enhancement within the hematoma and is associated with poor clinical outcomes [2]. By definition, a spot sign should not be connected to a blood vessel as it is supposed to represent rupture of parenchymal microaneurysms. These were initially described in 1868 by Charcot and Bouchard and are reported to measure up to 2 mm in size [3]. One group has described a spot and tail sign in 15 patients with putaminal hemorrhage [4]. We have recently noticed a similar imaging pattern emerge in a series

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Table 1 Patient clinical and treatment characteristics

Patient	Age (years)	Sex	Comorbidities	Hemorrhage volume (cm ³)	Ventricular extension	Radiological investigations	Other investigations	Treatment and hospital course	Outcome
1	30	Female	None	60.8	Yes	CT: Large right frontal hemorrhage with intraventricular extension and hydrocephalus. "spot on a string" sign, no other abnormal vascular findings. DSA (x 2): no AVM/other vascular malformation found	<i>Echo</i> : no vegetation <i>Blood culture</i> : negative <i>Toxicology screen</i> : + methamphetamine and barbiturates <i>Coagulation profile</i> : normal <i>COVID status</i> : negative (sputum)	Decompressive craniectomy, Second evacuation of hematoma, prolonged EVD insertion, Developed takotsubo cardiomyopathy Subsequent tracheostomy, G-tube	Discharged to rehabilitation
2	42	Male	Hypertension (admission BP: 167/101 mm Hg) Cocaine use	66.1	Yes	CT: Large right frontal hemorrhage with intraventricular extension and hydrocephalus. "spot on a string" sign, no other abnormal vascular findings. DSA: no AVM/other vascular malformation found. MRI: no underlying brain lesion	<i>Echo</i> : no vegetation <i>Blood culture</i> : negative <i>Toxicology screen</i> : + cocaine <i>Coagulation profile</i> : normal <i>COVID status</i> : negative (nasopharyngeal swab)	Medical management	Discharged to rehabilitation
3	53	Female	None	56	No	CT/CTA: Large right frontal hemorrhage with intraventricular extension and hydrocephalus. "spot on a string" sign, no other abnormal vascular findings. DSA: Distal M3 branch aneurysm corresponding to the "spot on a string" sign seen on CTA. Pathology: Large artery with focal outpouching of intima/disruption of vessel wall. No neutrophilic invasion of vessel wall. PAS/Gram stains negative for fungal and bacterial microorganisms.	<i>Echo</i> : no vegetation <i>Blood culture</i> : negative <i>Coagulation profile</i> : normal. <i>Pathology</i> : Large artery with focal outpouching of intima/disruption of vessel wall. No neutrophilic invasion of vessel wall. PAS/Gram stains negative for fungal and bacterial microorganisms. <i>COVID status</i> : negative (nasopharyngeal swab)	Decompressive craniectomy, vessel sacrifice and excision of aneurysmal part of vessel wall	Discharged to rehabilitation
4	48	Female	None	6.6	No	Blood cultures: (peripheral): negative x3 CT/CTA: Left thalamic hemorrhage with a "spot on a string" sign	<i>Echo</i> : no vegetation <i>Blood culture</i> : negative <i>Coagulation profile</i> : normal <i>COVID status</i> : negative (nasopharyngeal swab X2)	Medical management, hematoma remained stable on serial imaging	Transferred back to referring institution

Table 1 (Continued)

Patient	Age (years)	Sex	Comorbidities	H em-orrhage volume (cm ³)	Ven-tricular exten-sion	Radiological investigations	Other investigations	Treatment and hospital course	Outcome
5	54	Female	None Hypertensive on arrival (admission BP: 200/99 mm Hg)	23	Yes	CT/CTA: Left thalamic hemorrhage with a “spot on a string” sign	<i>Blood culture</i> : negative <i>Toxicology screen</i> : negative <i>Coagulation profile</i> : normal <i>COVID status</i> : negative (nasopharyngeal swab X2)	Medical management. Developed non-convulsive status epilepticus	Currently inpatient (intensive care unit)
6	32	Male	Non-ischemic cardiomyopathy (LVAD) Non-ischemic cardiomyopathy with LVAD, anti-thrombotic use (warfarin and aspirin)	20.4	Yes	CT: Moderate left frontal parenchymal hematoma with intraventricular extension, hydrocephalus. CTA, DSA: aneurysmal segment of distal left anterior cerebral artery branch	<i>Echo</i> : no vegetation <i>Blood culture</i> : negative <i>Coagulation profile</i> : Abnormal (INR = 2.6) <i>COVID status</i> : negative (nasopharyngeal swab X2, sputum X1)	Right frontal EVD, no decompression. Endovascular treatment (glue embolization) of the aneurysmal segment of the left callosomarginal artery	Deceased
7	68	Female	Hypertension (admission BP: 136/76 mm Hg), type II diabetes, schizoaffective disorder	101.3	Yes	CT/CTA: Large right frontal parenchymal hemorrhage with midline shift and mass effect, “spot on a string” sign	<i>Echo</i> : no vegetation <i>Blood culture</i> : negative <i>Toxicology screen</i> : + methamphetamine <i>Coagulation profile</i> : Abnormal (hemoglobin = 95 g/dL) <i>COVID status</i> : negative (nasopharyngeal swabX1, throat swabX1 and sputum X1)	Decompressive craniectomy	Currently in-patient (intensive care unit)

CTA computed tomography angiogram, DSA digital subtraction angiogram, PAS periodic acid-Schiff, LAVD left ventricular assistance device, BP blood pressure, COVID coronavirus disease, EVD external ventricular drain

of younger patients with no underlying comorbidities, who presented to our institution with a new ICH. These patients all presented with a peculiar spot-sign which was connected to a vessel (lenticulostriate/choroidal/leptomeningeal perforators). We call this imaging finding a spot on a string sign. In this article, we describe the imaging and clinical features of these patients and discuss possible causes.

Methods

A prospectively collected database was maintained of patients who presented to our center with new primary ICH, and no history of trauma/active infective endocarditis or other potential causes. Patient clinical demographics were recorded. All images were re-read by a fellowship-trained neuroradiologist. The hematoma volume was measured using the well-established ABC/2 [5] method.

Results

A total of seven patients were identified (Table 1) with a spot on a string sign on CTA. Median age was 48 years (range 30–68 years), of which 2 had a history of hypertension while another (patient 5) was hypertensive on arrival and 3 had positive toxicology screens for either cocaine or methamphetamines. All were COVID-negative. Of the patients one underwent a multiphase study, and the “spot” did not expand on the delayed phases, six had negative echocardiograms, and all had serial negative blood cultures. Of the patients three underwent medical management, two underwent decompressive craniotomy and hematoma removal, while one underwent emergency embolization of the aneurysmal segment of the vessel. There was no extravasation of contrast medium present in the two patients who underwent digital subtraction angiograms. One underwent craniotomy, hematoma removal and resection of the abnormal vessel. Pathology in this case showed an aneurysmal

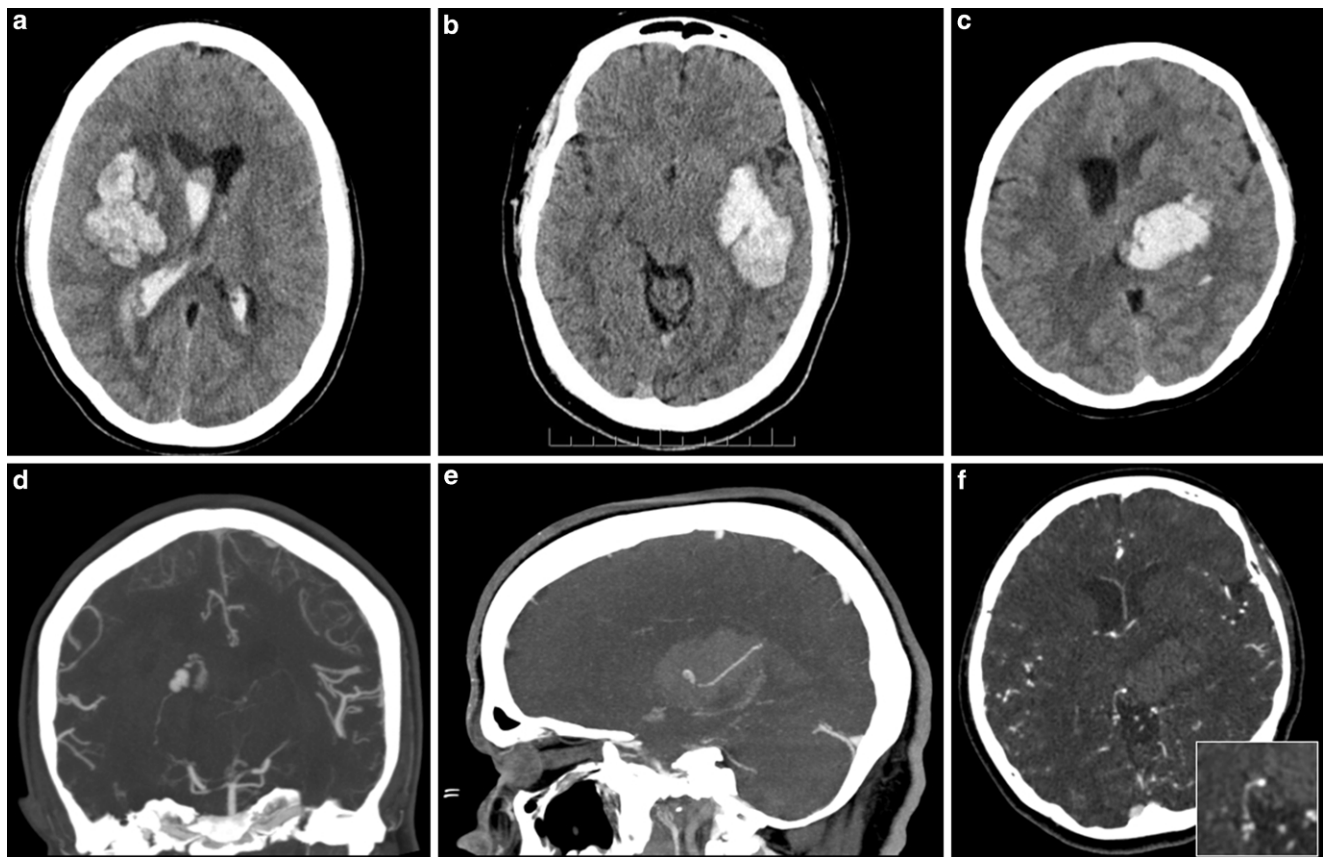
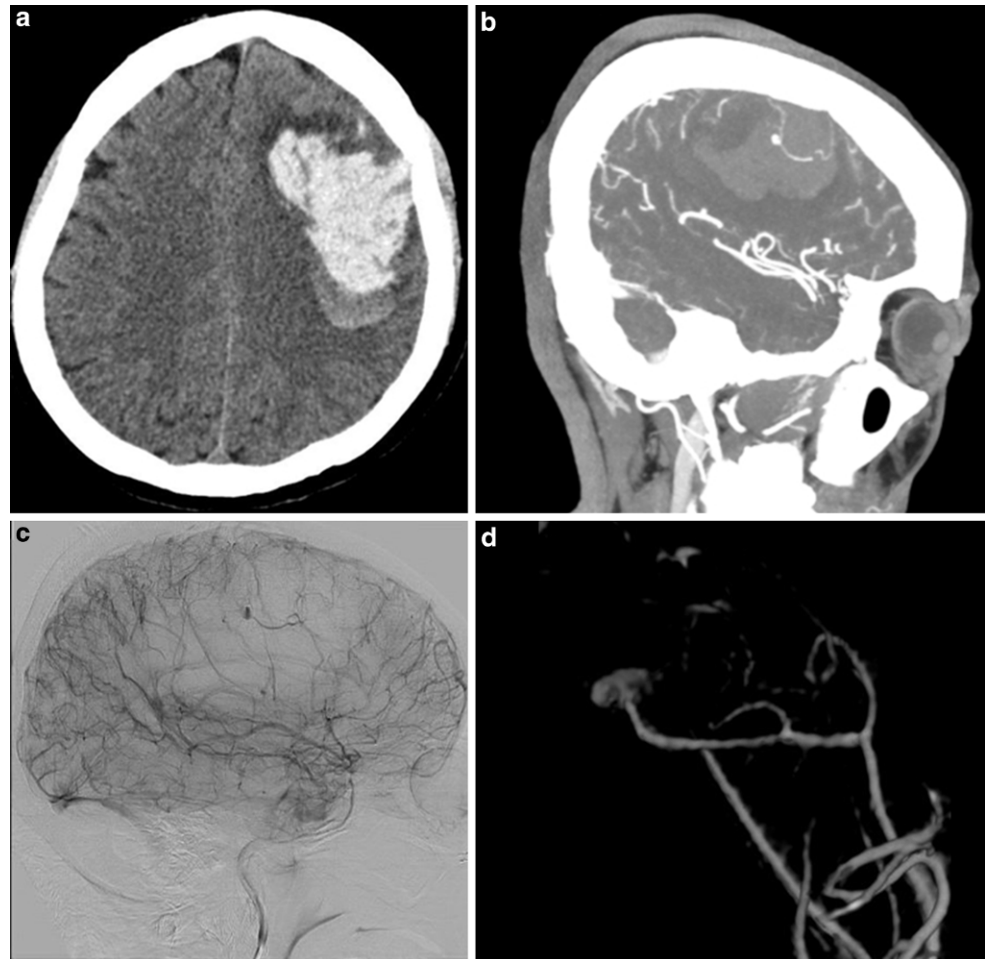


Fig. 1 Representative images from three patients: (**a, d**): patient 1: 30-year-old female, axial non-contrast CT (top row) showing a right frontal parenchymal hematoma with intraventricular extension. Coronal CTA (bottom row) showing a tortuous, dilated lenticulostriatal vessel coursing to the hematoma with a focal aneurysmal portion of the vessel distally, giving a spot on a string (SOAS) sign. (**b, e**): Patient 2: 42-year-old male, axial non-contrast CT (top row) showing a left temporal parenchymal hematoma, ventricular extension is not shown. Sagittal CTA (bottom row) showing a dilated distal MCA branch coursing into the hematoma with a SOAS sign. (**c, f**): Patient 5: 54-year-old female, axial non-contrast CT (top row) showing a large parenchymal hematoma centered on the left thalamus. Axial CTA (bottom row) showing a SOAS sign arising from a perforator artery arising from the right posterior cerebral artery

Fig. 2 Images from patient 3, clockwise from top left: **a** non-contrast CT showing a large left frontal hematoma with some layering of blood products within the hematoma. **b** CTA showing a left MCA branch with a SOAS sign coursing toward the hematoma. **c** Digital subtraction angiogram showing an aneurysmal dilatation of superior division branch of the left MCA, corresponding to the abnormal vessel seen on the CTA. **d** Volume-rendered 3-D reconstruction of the abnormal vessel, showing more clearly the aneurysmal “blown out” appearance of the vessel. This corresponded to the vessel wall disruption seen on the pathological specimen following surgical resection (not shown)



section of vessel wall with no microscopic or microbiological evidence of infection/microbial invasion. Overall, three patients were discharged to rehabilitation, three remained as inpatients and one patient died. Selected CT and DSA images are shown in Figs. 1, 2 and 3.

Discussion

Why are these Findings Interesting and Distinct from the Usual Pattern seen in ICH, e.g. Hypertensive Microangiopathy Related Bleeding?

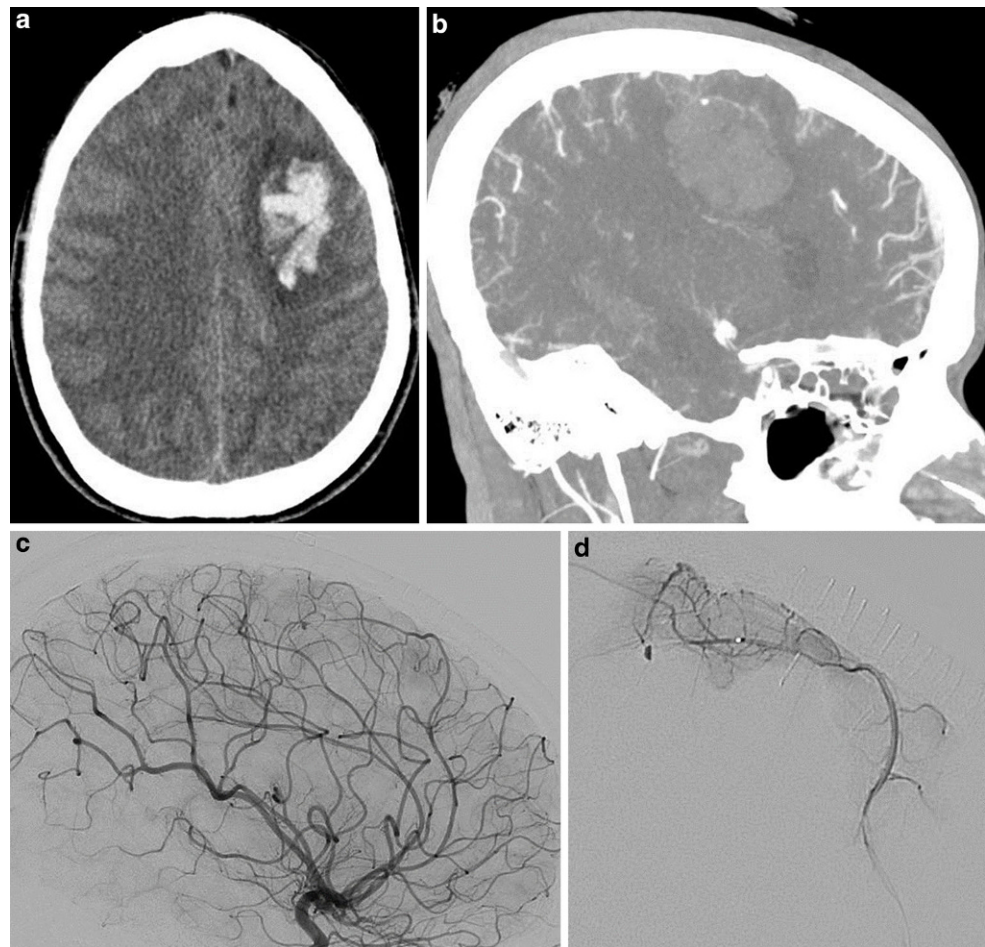
Patients with ICH tend to be older and are more frequently on anticoagulants. Our patients were younger than the typical ICH cohort (median age 48 years), and only 1 was taking warfarin prior to admission. Furthermore, while we often see a regular spot sign in ICH patients, we have never seen a series of patients with this rare appearance of a spot on a string sign. Patients with hypertensive hemorrhages can often have normal CTA studies and they can be related to ruptured microaneurysms (Charcot-Bouchard aneurysms

[6]), which are usually not seen on a CTA. In contrast, with our patients we were able to confidently identify the source of bleeding in all cases. Furthermore, while three of our patients had a positive toxicology screening for cocaine or methamphetamine, this has not been reported to result in such an abnormal vessel. In addition, urine-based toxicology screening has a significant false positive rate [7]. These findings also raise the importance of performing a CTA on patients with a large-volume parenchymal hematoma, especially in younger patients (e.g. <60 years of age).

Why are these Findings not just ICH Secondary to Mycotic Aneurysms?

Given the clinical presentations, we do not think that these represent a series of mycotic or infectious aneurysms. Apart from one patient, none had any infectious endocarditis or other risk factors, and none had clinical features suggestive of active infection. Indeed, the remaining patients all had negative echocardiograms and had no evidence of systemic infection on other scans or blood tests. In addition, the spot on a string sign is not the typical imaging appear-

Fig. 3 Images from patient 6, clockwise from top left: **a** non-contrast CT showing a left frontal parenchymal hematoma. There was also intraventricular extension (not shown). **b** Sagittal maximal intensity projection (MIP) from CTA showing a spot on a string (SOAS) sign coursing along the edge of the hematoma. **c, d** Left ICA injection, lateral view (**c**), and magnified microcatheter injection (**d**) of the left callosomarginal artery in the same projection, showing the aneurysmal segment of the vessel more distally, with some contrast medium stagnation within it



ance of mycotic aneurysms, which are often multiple and more commonly fusiform [8]. In our patients the abnormal vessels were unifocal and rather than being fusiform were comprised of an abnormal segment of vessel wall at the end of a tortuous feeding vessel that disappeared on follow-up imaging. Furthermore, in our unit (a tertiary referral neurovascular center) we see on average 1–2 mycotic aneurysms per year. It is therefore quite remarkable that all patients presented over the course of 2 months. Finally, in patient 3 who underwent surgical resection, in whom the imaging appearances were remarkably similar to the other patients in our series, the pathology showed no evidence of bacterial or neutrophilic invasion of the disrupted arterial wall.

How are these Findings Different from Common Vascular Malformations?

We certainly need to consider the atypical imaging and clinical appearances of the group overall. These patients had no evidence of a fistulous lesion (such as an AVM/dAVF) on either CTA or DSA. In addition, the clinical features

were unusual. Our patients had much larger bleeds than we commonly see in ICH patients (median hematoma volume 58.4 cm³), especially for a cohort of patients so young, the majority of whom had no significant comorbidities. For comparison, the median hematoma volume in a summary of recent ICH trials was approximately 10 cm³ [9], while another study of 277 patients on warfarin found an average hematoma volume of 22.1 cm³. The mean patient age in these studies was 65 years and 68.5 years, respectively, another reason why our patients would be expected to have smaller hematoma volumes. One would also expect patients on anticoagulants to have much larger bleeds. For example, in one study evaluating hematoma volume according to anticoagulation type, the median ICH volume was 8.9 cm³ in patients on warfarin, far smaller than the massive bleeds in most of our cohort.

Could there be an Environmental Factor in Play?

We are reluctant to label any unusual pathology that has been admitted to our institution in the recent past as possibly related to COVID-19, but the possibility should be

considered. One could point out that all our patients had negative COVID tests; however, the nasopharyngeal swab test has a poor sensitivity for the detection of SARS-CoV-2 [10]. Furthermore, there is emerging evidence for a systemic endotheliitis-type picture in patients with COVID-19 [11]. We also know that the ACE2 protein (which SARS-CoV-2 uses to enter cells) is expressed in vascular endothelium [12]. In addition, we have not seen this vascular pattern before now. There is therefore a remote possibility that our patients are suffering from a direct effect of this virus on the cerebral vasculature, with resultant arterial disruption and massive hemorrhage. This is merely speculative, however, and merely wish to draw the attention of clinical teams to this interesting and recent phenomenon of unusual intracerebral hemorrhages in younger patients all of whom have a spot on a string sign. Note should be made that this is a single center small series of patients, and while interesting, no firm conclusions can be made at this stage.

Conclusion

We have described an unusual and rare imaging finding in a cohort of younger patients with large-volume ICH, all of whom presented in a 2-month period. The cause is unclear, but we encourage other clinicians to be aware of and vigilant for this phenomenon, especially in younger patients with such a bleeding pattern.

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Author Contribution All authors contributed to the manuscript.

Compliance with ethical guidelines

Conflict of interest P. Nicholson, M. Gao, I. Radovanovic, V. Mendes-Pereira, M. Hodaie, A. Pikula and T. Krings declare that they have no competing interests.

Ethical standards This study was covered by institutional Research Ethics Board approval.

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