Central Nervous System Siderosis Associated with Multiple Cerebral Aneurysms: Literature Review and Description of an Additional Case

Victoria Dembour[1], Charles Henry Mallereau[1], Salvatore Chibbaro[1], Felix K.K. Segbedji[1], Raoul Pop[2], Hélène Cebula[1], Benoit Lhermitte[3], Julien Todeschi[1]

Key words
- Aneurysm wall enhancement
- Cortical superficial siderosis
- Hemorrhagic suffusion
- Hemosiderin deposition
- Unruptured aneurysm

Abbreviations and Acronyms
CNS: Central nervous system
IA: Intracranial aneurysm
MCA: Middle cerebral artery
MRI: Magnetic resonance imaging
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
SAH: Subarachnoid hemorrhage
SS: Superficial siderosis

From the Departments of [1]Neurosurgery, [2]Interventional Neuroradiology, and [3]Histopathology, Strasbourg University Hospitals, Strasbourg, France

To whom correspondence should be addressed: Victoria Dembour, M.D. [E-mail: victoriadembour@gmail.com]

Citation: World Neurosurg. (2024) 188:128-135. https://doi.org/10.1016/j.wneu.2024.05.085

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

BACKGROUND: **Superficial siderosis (SS) of the central nervous system is a rare disease characterized by deposition of hemosiderin along the leptomeninges due to chronic or recurrent bleeding into the subarachnoid space. The association of unruptured intracranial aneurysm (IA) and cortical SS is quite rare.**

METHODS: **A systematic literature review to assess possible commonalities and/or differences of previous reported cases was undertaken. We report an additional case from our institution.**

RESULTS: **A 40-year-old woman presented with a history of generalized seizures over the past year. There was no clinical history suggestive of aneurysm rupture. Magnetic resonance imaging revealed 2 aneurysms of the right middle cerebral artery (MCA) bifurcation associated with hemosiderin deposition along the right sylvian fissure and a third aneurysm of the left MCA bifurcation. Magnetic resonance imaging showed wall enhancing thickening of the larger right MCA aneurysm. The patient underwent surgical clipping of all 3 MCA aneurysms in a staged procedure. Histological examination revealed hemosiderin deposits within the aneurysm wall and surrounding gliosis.**

CONCLUSIONS: **Our literature review found 24 reported cases of unruptured IA associated with cortical SS. The possible source for leakages could be neovessels visible in IA walls. The case reported illustrates an uncommon presentation of recurrent bleeding from an IA as a source of SS. The presence of an apparently unruptured IA surrounded by cortical SS on imaging studies is of high relevance as this should be considered a sign of aneurysm wall instability and should indicate prompt treatment.**

INTRODUCTION

Superficial siderosis (SS) of the central nervous system (CNS) is a rare disease characterized by hemosiderin deposition along the leptomeninges in regions of the brain or spinal cord due to chronic or recurrent bleeding into the subarachnoid space.[1,2] The most common form of SS is characterized by hemosiderin deposition on the cerebellar and brainstem surface, resulting in a clinical syndrome of sensorineural deafness, cerebellar ataxia, and pyramidal signs. A more localized form has also been described, called cortical SS by a few authors, and is characterized by asymmetric and focal areas of hemosiderin deposition in supratentorial cortical sulci.[1] Hemosiderin has a paramagnetic compound that is best appreciated on T2-weighted and susceptibility-weighted imaging, which reveals a black rim beneath the CNS surface.[3,4] Current identified sources of bleeding in patients with SS include amyloid angiopathy, vascular malformations, CNS tumor, craniospinal surgery, brachial plexus lesion, dural tears, CNS trauma, or other causes of subarachnoid hemorrhage (SAH).[1,2] In SS, the source of bleeding is not always detected. The association of apparently unruptured intracranial aneurysm (IA) with SS is a rare occurrence reported in a few published case reports in the literature.[4-6] Here, we present a systematic literature review along with an additional case of a patient harboring an SS associated with multiple IAs.

MATERIALS AND METHODS

Database Selection and Search Strategy

A literature review was performed searching PubMed, Embase, and Cochrane databases for CNS SS and cerebral aneurysm cases from 1969 to 2023 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[7] using the following key terms: "hemosiderin deposition" OR "hemosiderin depositions"

OR "siderosis" AND "cerebral aneurysm" OR "intracranial aneurysm" AND "unruptured."

Inclusion and Exclusion Criteria

The search yielded 33 results. Full-length publications as well as posters and oral presentations were considered for inclusion if they reported on the association between SS and cerebral aneurysms. Abstracts were excluded if they 1) did not have an accompanying full-length manuscript or presentation in English, 2) discussed nonaneurysmal etiologies of SS, or 3) failed to differentiate aneurysms from other intracranial vascular abnormalities (i.e., arteriovenous malformations). Full-text articles were excluded if 1) they did not establish a clear relationship between SS and aneurysms or 2) SS was observed after SAH from aneurysm rupture so as to focus specifically on cases where aneurysms had not ruptured. Studies that did not focus exclusively on IA but provided relevant information on the IA subgroup were also included.

Data Extraction and Review

Included articles underwent thorough review, focusing on study design, sample size, demographic characteristics, and outcomes related to cerebral aneurysm, including formation, growth, rupture, treatment, and management. A flowchart of the review process according to PRISMA guidelines is presented in Figure 1.

Case Description

A 40-year-old woman was referred to our department with a history of 3 inaugural generalized seizures over the past year. These seizures prompted the initiation of antiepileptic treatment. Further assessment of the patient's medical history revealed that she was a current smoker and had no documented history of high blood pressure or familial cerebral aneurysms. Additionally, she reported no history of previous headaches. On admission to the department, the patient presented fully alert, responsive, and without any functional symptoms or abnormalities in cognitive or motor function. A comprehensive clinical examination revealed no remarkable findings; there were no signs of focal neurological deficits, such as weakness, numbness, or abnormalities in coordination. The patient's sensory perception appeared normal.

Magnetic resonance imaging (MRI) revealed hemosiderin deposition along the right sylvian fissure and insular cortical sulci on T2-weighted sequences (Figure 2A). Time-of-flight magnetic resonance angiography revealed bilateral middle cerebral artery (MCA) aneurysms (Figure 2B). Digital subtraction angiography confirmed the presence of 2 right MCA aneurysms—one arising from the sylvian bifurcation and a smaller one located more distally at the

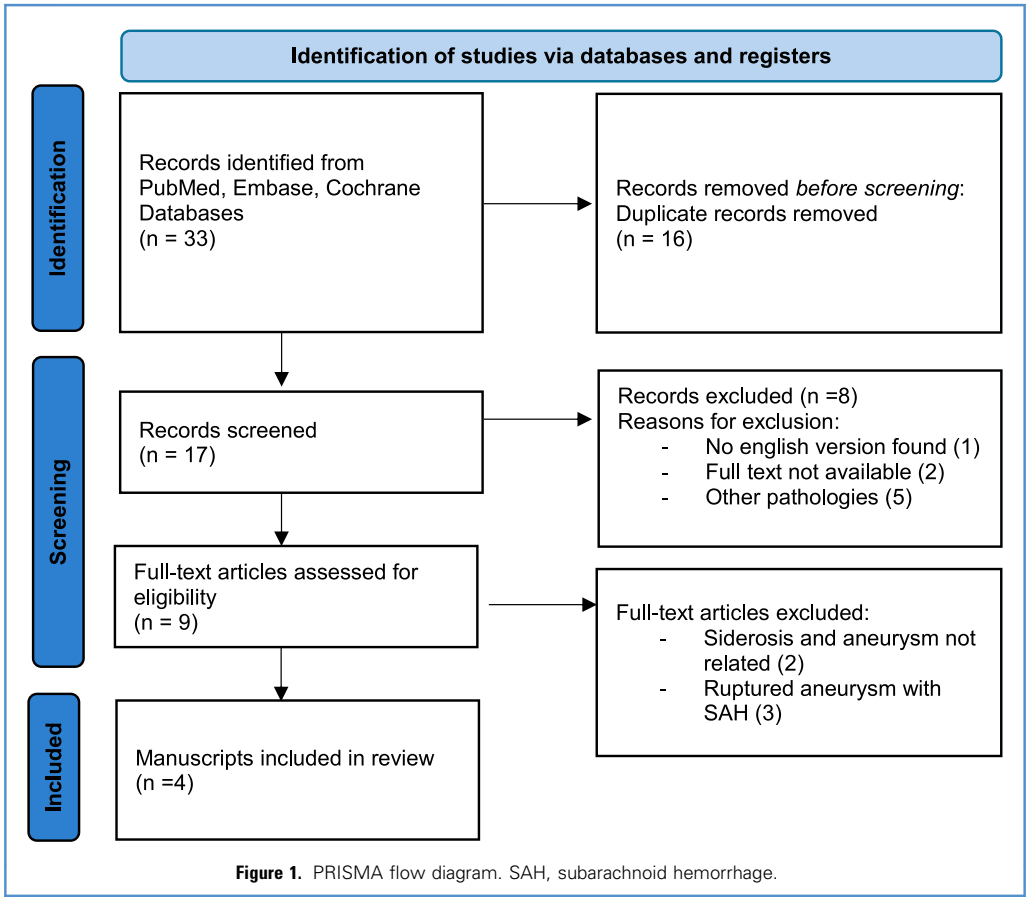

Figure 1. PRISMA flow diagram. SAH, subarachnoid hemorrhage.

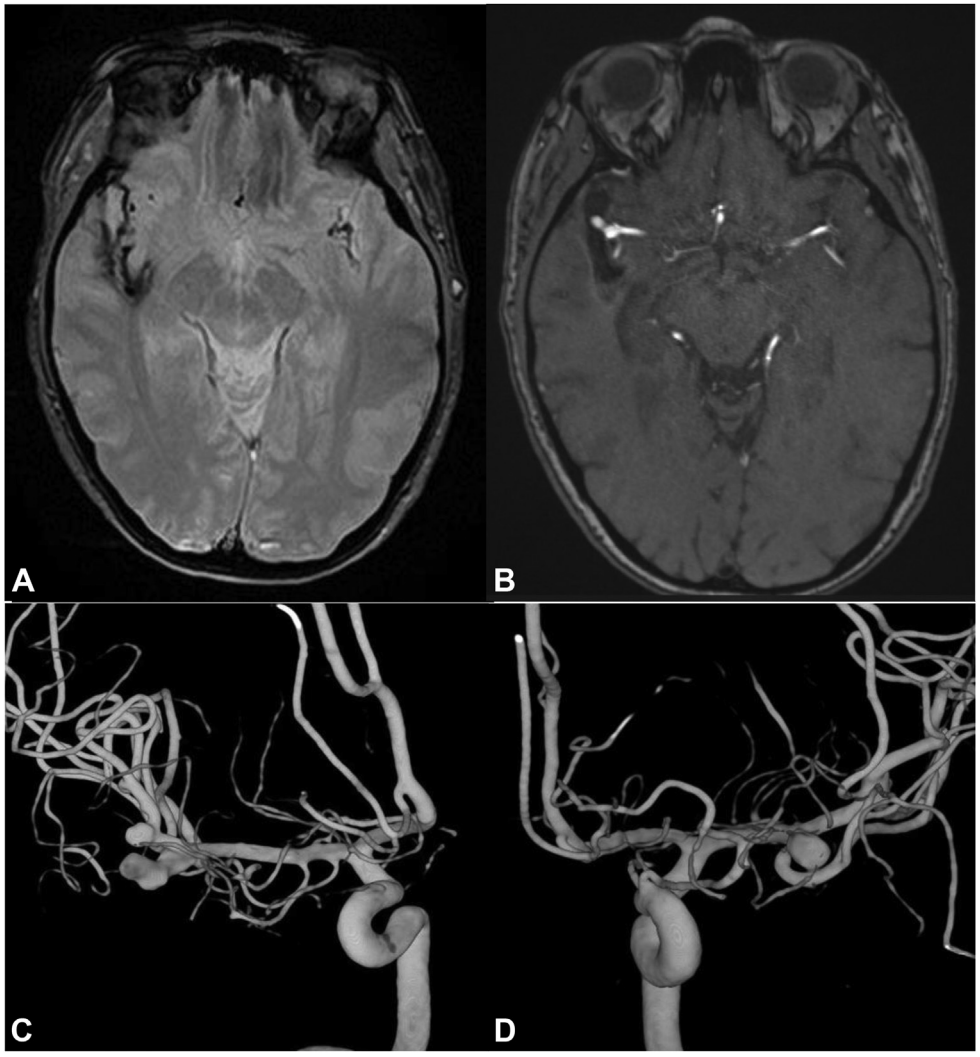

Figure 2. Magnetic resonance imaging susceptibility-weighted imaging (**A** and **B**) and three-dimensional digital subtraction angiography (**C** and **D**). (**A**) Susceptibility-weighted imaging demonstrating superficial siderosis in the right sylvian fissure and insula. No superficial siderosis is observed on the left side. (**B**) Time-of-flight magnetic resonance angiography sequences revealing a right middle cerebral artery aneurysm surrounded by a porencephalic cavity. (**C** and **D**) Volume-rendering reconstructions of rotational digital subtraction angiography of the right and left internal carotid arteries, respectively, showing 2 aneurysms of the right middle cerebral artery bifurcation (inferior 6.4 mm and superior 2.3 mm) (**C**) and showing a left middle cerebral artery aneurysm of 3.8 mm (**D**).

origin of a temporal branch. Another aneurysm was detected at the left MCA bifurcation (Figure 2C and D). The 2 right MCA aneurysms were surrounded by hemosiderosis. Aneurysmal wall imaging using a T1 turbo spin echo with selective fat suppression sequence, or black blood sequence, was acquired before and after gadolinium enhancement showing a circumferential wall enhancing thickening of the larger right MCA aneurysm. No parietal enhancement was seen either in the more distal right MCA aneurysm or in the left MCA aneurysm (Figure 3). The patient underwent surgical clipping of the right MCA aneurysms. Intraoperatively, there was no evidence of acute SAH. A porencephalic cavity was found embedded in the right superior temporal gyrus, lined with yellowish gliotic tissue, and the inferior aneurysmal sac was found surrounded by the same yellowish deposits. The aneurysm wall was heterogeneous, with thin and vascularized parts and other parts much thicker and atherosclerotic. Macroscopically, the wall appeared unruptured (Figure 4A). After dissection of the gliotic tissue, the smaller aneurysm, which did not show enhancement on MRI, appeared with a more homogeneous wall (Figure 4B). Histological examination of the inferior aneurysm dome showed a continuous

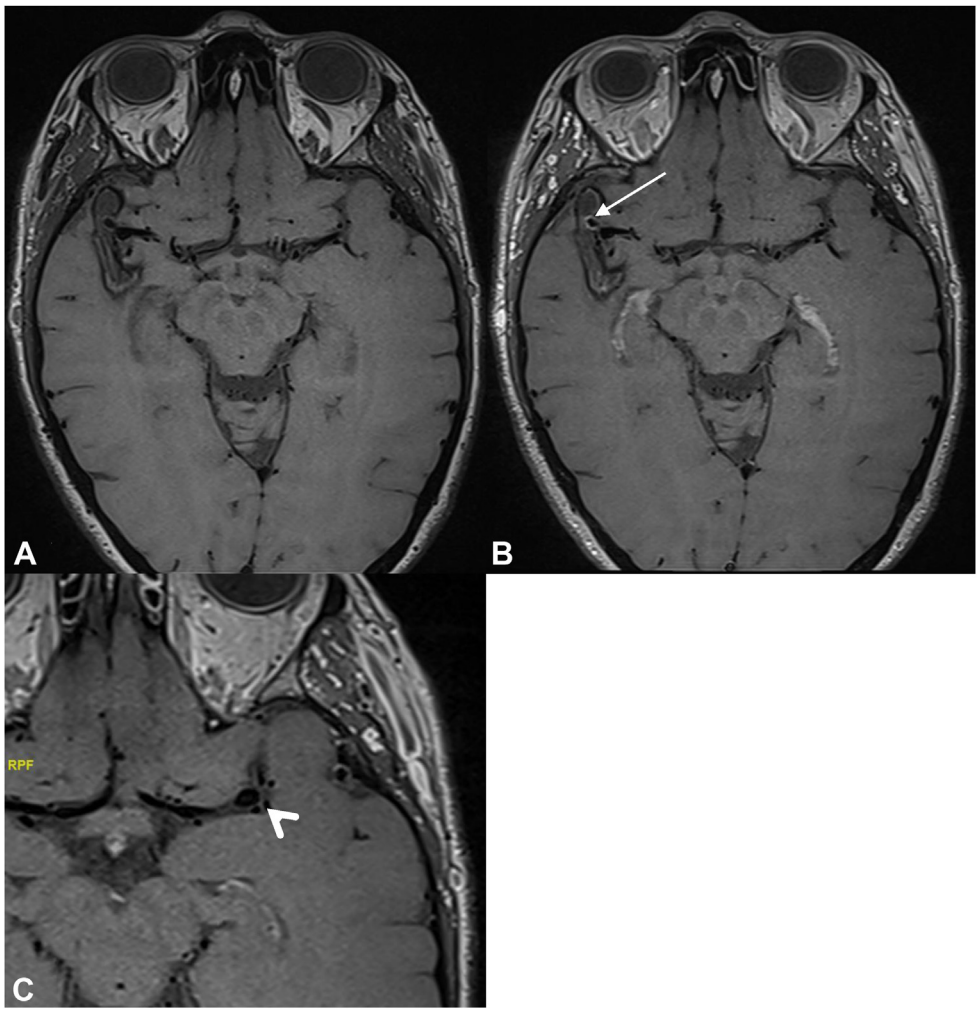

Figure 3. Dark blood T1 turbo spin echo sequences with selective fat suppression before (**A**) and after (**B** and **C**) gadolinium enhancement. Circumferential aneurysm wall enhancement is observed in the inferior right middle cerebral artery bifurcation aneurysm (*arrow*); there is no wall enhancement in the superior right and left middle cerebral artery aneurysms (*arrowhead*).

arterial wall; however, intense inflammatory changes were found (Figure 4C). Deposits of hemosiderin and vasa vasorum were found within the adventitia (Figure 4D). Examination of the gliotic tissue showed a process characterized by the proliferation of glial cells in response to injury or pathology, sampled from the white matter surrounding the aneurysms, revealing hemorrhagic suffusions, indicating previous episodes of bleeding, and punctuated by hemosiderin deposits, as demonstrated by Perls staining (Figure 4E and F). Additionally, the absence of amyloid deposits was confirmed using antibody directed against βA4 amyloid protein. The patient underwent a second clipping procedure 3 months later to manage the left MCA aneurysm. The postoperative course after both procedures was uneventful. Postoperative computed tomography angiography showed complete exclusion of all 3 aneurysms. At 1-year follow-up, neurological examination was unremarkable, and the patient reported general well-being.

DISCUSSION

Following recurrent bleeding into the subarachnoid space, hemosiderin production by the nervous system microglial cells represents a protective mechanism against the neurotoxic effect of heme and free iron.[2] Hemorrhagic products that exceed the limited CNS red blood cell clearance capacity can therefore result in iron-induced glioneuronal damage.

Cortical SS is a localized form of SS characterized by focal hemosiderin deposits, affecting ≥1 supratentorial cortical sulci, related to repeated, isolated bleeding episodes in the subarachnoid space. It has been differentiated from the classical form of SS, which involves predominantly the infratentorial compartment.[1] Etiologies of SS include amyloid angiopathy, vascular malformation,

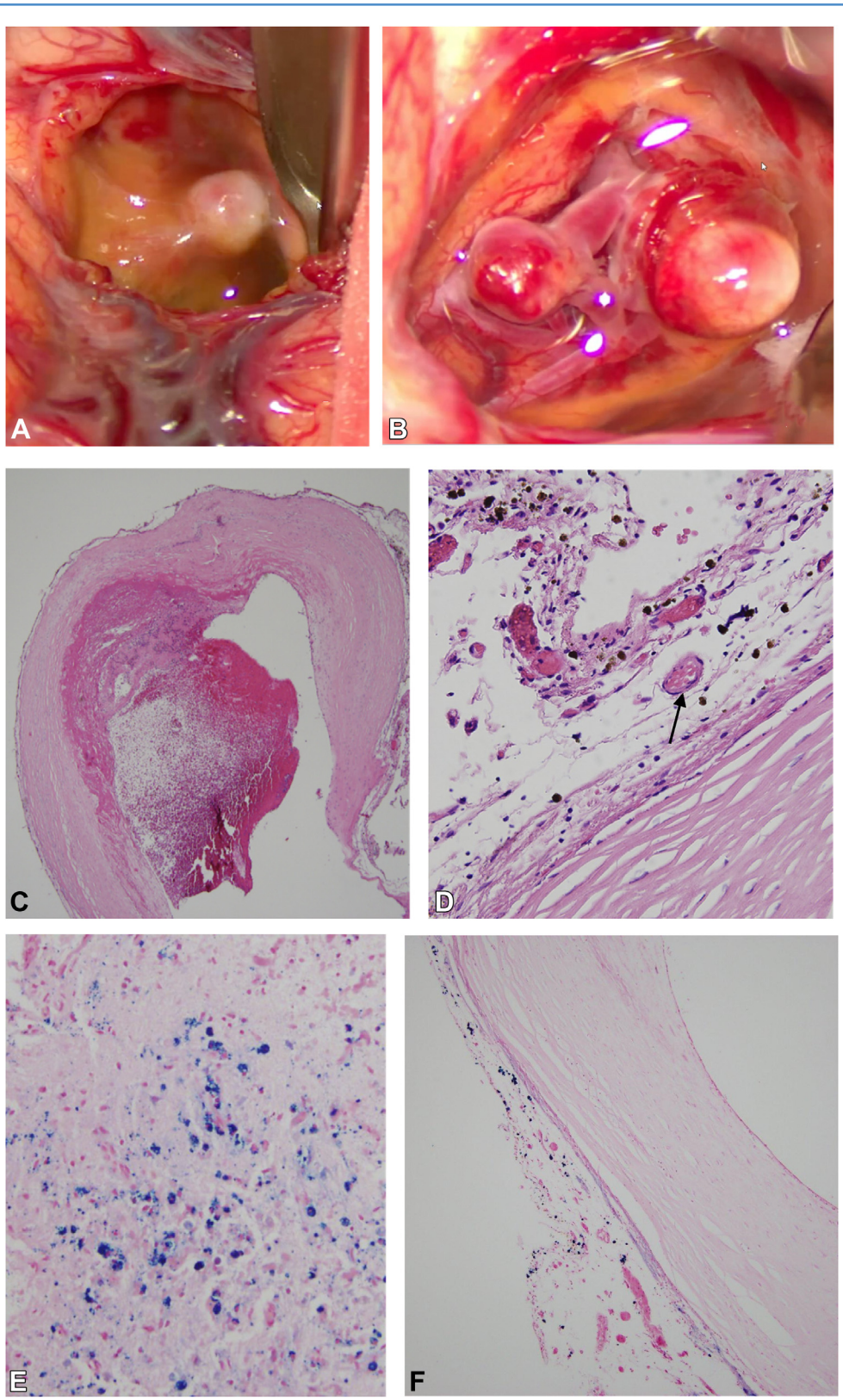

Figure 4. Perioperative microscopic pictures (**A** and **B**) and histopathological studies (**C**–**F**) of unruptured saccular aneurysms. (**A**) Intraoperative view of a middle cerebral artery aneurysm. (**B**) The aneurysm

(continued)

Table 1. Summary of Studies Reporting Cases of Unruptured IA Associated with Cortical SS

Case	Authors, Year	Study Design	Number of Patients	Clinical Findings	Aneurysm Location	MRI SWI	Histopathological Findings	Treatment	Intraoperative Hemosiderosis
1	Yalo et al., 2016[6]	Case report	1	Sensorineural hearing loss, cognitive impairment, left lower limb weakness	AComA	+	–	Endovascular	NA
2	Choh et al., 2009[10]	Case report	1	Sensorineural hearing loss, left hemiparesis	BA	+	NR	NR	NR
3	Nussbaum et al., 2014[5]	Case series	13	Remote headache	ICA: 54% MCA: 23% AComA: 15% ACA: 8%	–	NR	Surgical clipping	+
4	Takada et al., 2011[4]	Case series	9	NR	ICA: 1 AComA: 1	+	NR	Surgical clipping	4 of 9

MRI, magnetic resonance imaging; SWI, susceptibility-weighted imaging; AComA, anterior communicating artery; NA, not applicable; BA, basilar artery; NR, not reported; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery.

trauma, CNS tumor, craniospinal surgery, or dural tears. The bleeding source is unknown in 25%–65% of cases.[6,8] More specific causes have been described in the pathogenesis of cortical SS, including reversible cerebral vasoconstriction syndrome, vasculitis, arterial proximal high-grade stenosis, cerebral vein and/or sinus thrombosis, and aneurysm-related SAH.[9]

Although cortical SS is frequently observed after SAH due to aneurysm rupture,[3] it has been reported in only a few cases of unruptured aneurysms in the literature.[4-6,10] The current literature review yielded 33 articles. After removal of duplicates, 17 articles remained for examination. We excluded all studies that did not meet the inclusion criteria and retained 4 relevant studies discussing unruptured aneurysms associated with SS (**Table 1**). Yalo et al.[6] reported a case of interhemispheric and bifrontal cortical SS in association with an anterior communicating aneurysm showing partial wall enhancement on appropriate MRI sequences, whereas a left posterior communicating aneurysm showed no wall enhancement. The authors considered the wall enhancement to be a marker of inflammation and remodeling of the aneurysm wall, resulting in chronic hemorrhagic suffusion in the subarachnoid spaces. The patient underwent embolization of the anterior communicating artery aneurysm; thus no additional details (i.e., surgical observation or histopathological findings) were available.

A case of SS associated with an aneurysm arising from the top of the basilar artery was reported by Choh et al.[10]; this finding was thought to be related to the infratentorial siderosis distribution on the surface of both cerebral hemispheres, the pons, the cerebellar folia, and the medulla. The authors hypothesized that SS was the consequence of bleeding or leaking of multiple tiny basilar artery aneurysms. A study of 421 patients with unruptured aneurysms who underwent surgical clipping revealed the presence of hemosiderin deposits on cerebral parenchyma surrounding the aneurysm in 13 patients, accounting for approximately 3.1% of the cohort. This highlights that, while infrequent, such deposits are not an exceptional occurrence.[5] In this series, susceptibility-weighted MRI that could show radiological evidence of minor hemorrhage was not performed, and the diagnosis of SS was based solely on intraoperative findings.

Takada et al.[4] investigated the correlation between SS and the observation of hemosiderin deposition during surgery in patients who underwent surgical clipping of incidentally detected unruptured aneurysms. In 9 of 49 patients (18%), hemosiderin deposits were seen in the subarachnoid space during surgery. Notably, SS was detected on T2-weighted MRI close to the aneurysm wall in 4 of the 9 patients. As in our case, no obvious site of rupture was identified around the aneurysm wall during surgery in these 9 patients, assuming that hemosiderin deposits are likely to be related to prior minor bleeding/leakage or wall healing after minor previous aneurysm rupture. To our knowledge, this is the first report to provide evidence of a highly probable relationship between apparently unruptured aneurysms and SS based on clinical, imaging, intraoperative, and histopathological findings. Despite the lack of clinical or anamnestic features

wall appears heterogeneous with thin vascularized and thick areas. (**C** and **D**) Hematoxylin-eosin staining of a sagittal cross section through a portion of the larger middle cerebral artery aneurysm wall, low-power (**C**) and high-power (**D**) magnification. (**C**) The middle cerebral artery aneurysm wall shows significant atherosclerotic lesions along with intense inflammatory changes illustrated by the presence of an atheromatous plaque, necrosis, and neutrophilic infiltration. There is no external elastic lamina. (**D**) The outermost layer is the adventitia. Hemosiderin deposits (*black*) and vasa vasorum are seen in the adventitia (*arrow*). (**E** and **F**) Perls Prussian blue iron staining demonstrating hemorrhagic suffusions and hemosiderin deposits within reactive gliosis (**E**) and aneurysm wall (**F**).

suggestive of SAH due to aneurysm rupture in the present case, the extensive hemosiderin deposition observed on imaging studies along the right insular sulci prompted consideration of its likely association with the right MCA aneurysms. This observation strongly implies the possibility of recurrent bleeding originating from an unstable aneurysm wall.

Perioperative inspection supported our hypothesis of local microbleeding from the aneurysm vasa vasorum, as a substantial number of microvessels were clearly visible on the arterial wall under the operating microscope. Moreover, hemorrhagic suffusions were confirmed by histological studies of the arterial wall and surrounding reactive gliosis. Despite the presence of a structurally intact arterial aneurysm wall, the pronounced inflammatory changes suggest ongoing pathological processes within the vessel wall. These inflammatory alterations may contribute to the weakening of the arterial wall and predispose it to hemorrhagic events. While vasa vasorum are normally absent in intracranial arteries, it has been proposed that pathological wall remodeling due to chronic inflammation and microvascular injury, leading to parietal hypoxia, may stimulate the production of angiogenic factors. These factors promote the development of vasa vasorum, resulting in repetitive minor bleeds that could lead to further aneurysm wall weakening and enlargement.[11,12]

Structural differences that involve adventitial vaso vasorum were found between ruptured and unruptured aneurysms, suggesting that such inflammation markers are more frequent in unstable aneurysms.[13,14] As a consequence, indirect detection of vasa vasorum using specific dedicated imaging can provide important prognostic information to help/assist therapeutic decision making. High-resolution vessel wall MRI, or dark blood T1 fat saturation sequences and gadolinium enhancement, is an emergent technique that is very useful in the detection of vessel wall inflammatory changes. This magnetic resonance angiography sequence technique is based on blood and cerebrospinal fluid signal suppression and allows vessel wall study. Aneurysm wall enhancement can be observed in cases of atherosclerotic wall thickening with inflammatory cell infiltration and presence of neovascularization, associated with compromised endothelial barrier integrity, and increased endothelial permeability or intramural hematoma.[11,15] As previous studies have demonstrated that ruptured IA may exhibit a thick vessel wall enhancement in comparison to unruptured IA, dark blood imaging is now proposed to be used to identify unstable IA, based on the presence of aneurysm wall enhancement.[15-17] This enhancement pattern may indicate active inflammation or neovascularization within the aneurysmal wall, further supporting its potential role in epileptogenesis. Therefore, precontrast and postcontrast T1 dark blood sequences are very useful in the detection of aneurysm wall inflammatory changes and provide an additional argument suggestive of aneurysm instability. After radiological investigations and intraoperative inspection, we consider the following: 1) In apparently unruptured cerebral aneurysm, preoperative susceptibility T2-weighted MRI sequences are useful for the detection of surrounding SS as a sign of aneurysm wall instability, particularly in patients presenting with neurological signs. 2) The presence of multiple vasa vasorum identified on histological specimens corresponds to the aneurysm wall enhancement usually detected on contrast-enhanced dark blood T1-weighted MRI. 3) Finally, as in our case, chronic and recurrent bleeding from the unstable aneurysm wall with its vasa vasorum is likely to be the source of SS.

CONCLUSIONS

The present case illustrates an extremely uncommon presentation of chronic/recurrent minor bleeding from the aneurysm wall vasa vasorum as a presumptive source of cortical SS. The literature review aimed to comprehensively identify, evaluate, and synthesize evidence regarding the association between cortical SS and IA, providing valuable insights into their clinical relevance and implications for patient management. Neovascularization within the aneurysmal wall in response to tissue injury or inflammation may contribute to microhemorrhages or microbleeds within the aneurysm wall, disruption of the blood-brain barrier, and accumulation of blood products such as hemosiderin that can further exacerbate neuronal hyperexcitability and promote epileptogenesis. Detection of focal SS surrounding an apparently unruptured aneurysm, along with wall enhancement on appropriate MRI sequences, has substantial implications for clinical decision making. Consequently, clinicians may prioritize these cases for more aggressive intervention strategies, such as surgical clipping or endovascular coiling, to secure the aneurysm and achieve seizure management.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Victoria Dembour: Writing — original draft, Writing — review & editing, Formal analysis. **Charles Henry Mallereau:** Supervision, Writing — review & editing. **Salvatore Chibbaro:** Methodology, Validation, Writing — review & editing. **Felix K.K. Segbedji:** Resources. **Raoul Pop:** Resources. **Hélène Cebula:** Conceptualization. **Benoit Lhermitte:** Resources. **Julien Todeschi:** Supervision, Conceptualization, Data curation.

REFERENCES

1. Kumar N. Superficial siderosis: a clinical review. *Ann Neurol*. 2021;89:1068-1079.
2. Koeppen AH, Michael SC, Li D, et al. The pathology of superficial siderosis of the central nervous system. *Acta Neuropathol*. 2008;116:371-382.
3. Imaizumi T, Chiba M, Honma T, Niwa J. Detection of hemosiderin deposition by T2*-weighted MRI after subarachnoid hemorrhage. *Stroke*. 2003;34:1693-1698.
4. Takada S, Inoue T, Niizuma K, Shimizu H, Tominaga T. Hemosiderin detected by T2*-weighted magnetic resonance imaging in patients with unruptured cerebral aneurysms: indication of previous bleeding? *Neurol Med Chir (Tokyo)*. 2011;51:275-281.
5. Nussbaum E, Defillo A, Zelensky A, Pulivarthi S, Nussbaum L. "Microbleeding" from intracranial aneurysms: local hemosiderin deposition identified during microsurgical treatment of unruptured intracranial aneurysms. *Surg Neurol Int*. 2014;5:28.
6. Yalo B, Pop R, Zinchenko I, et al. Aneurysmal wall imaging in a case of cortical superficial siderosis and multiple unruptured aneurysms. *BMJ Case Rep*. 2016;2016:bcr2016012680.
7. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Int J Surg*. 2021;88:105906.
8. Lai M-T, Ohmichi T, Yuen K, Egusa K, Yorizane S, Masuda Y. Superficial siderosis of the central

nervous system: a case with an unruptured intracranial aneurysm. *J Laryngol Otol*. 1995;109:549-552.

9. Weidauer S, Neuhaus E, Hattingen E. Cerebral superficial siderosis: etiology, neuroradiological features and clinical findings. *Clin Neuroradiol*. 2023;33:293-306.

10. Choh NA, Kirmani OS, Choh SA, Jehangir M. Superficial siderosis. *Neurol India*. 2009;57:687-688.

11. Portanova A, Hakakian N, Mikulis DJ, Virmani R, Abdalla WMA, Wasserman BA. Intracranial vasa vasorum: insights and implications for imaging. *Radiology*. 2013;267:667-679.

12. Krings T, Piske RL, Lasjaunias PL. Intracranial arterial aneurysm vasculopathies: Targeting the outer vessel wall. *Neuroradiology*. 2005;47:931-937.

13. Scanarini M, Mingrino S, Giordano R, Baroni A. Histological and ultrastructural study of intracranial saccular aneurysmal wall. *Acta Neurochir(Wien)*. 1978;43:171-182.

14. Frösen J, Piippo A, Paetau A, et al. Remodeling of saccular cerebral artery aneurysm wall is associated with rupture: histological analysis of 24 unruptured and 42 ruptured cases. *Stroke*. 2004;35:2287-2293.

15. Hu P, Yang Q, Wang D-D, Guan S-C, Zhang H-Q. Wall enhancement on high-resolution magnetic resonance imaging may predict an unsteady state of an intracranial saccular aneurysm. *Neuroradiology*. 2016;58:979-985.

16. Texakalidis P, Hilditch CA, Lehman V, Lanzino G, Pereira VM, Brinjikji W. Vessel wall imaging of intracranial aneurysms: systematic review and meta-analysis. *World Neurosurg*. 2018;117:453-458.e1.

17. Wu X, Zhong J, Wang S, et al. Circumferential wall enhancement with contrast ratio measurement in unruptured intracranial aneurysm for aneurysm instability. *Brain and Behavior*. 2022;12:e2568.

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 13 November 2023; accepted 14 May 2024

Citation: World Neurosurg. (2024) 188:128-135.
https://doi.org/10.1016/j.wneu.2024.05.085

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

Available online: ***www.sciencedirect.com***