

# UCSF

## UC San Francisco Previously Published Works

### Title

Intracranial atherosclerotic disease associated with moyamoya collateral formation: histopathological findings.

### Permalink

<https://escholarship.org/uc/item/1w52h6xp>

### Journal

Journal of Neurosurgery, 118(5)

### ISSN

0022-3085

### Authors

Jiang, Thomas  
Perry, Arie  
Dacey, Ralph G  
[et al.](#)

### Publication Date

2013-05-01

### DOI

10.3171/2013.1.jns12565

Peer reviewed



Published in final edited form as:

*J Neurosurg.* 2013 May ; 118(5): 1030–1034. doi:10.3171/2013.1.JNS12565.

## Intracranial atherosclerotic disease associated with moyamoya collateral formation: histopathological findings

Thomas Jiang, M.D.<sup>1</sup>, Arie Perry, M.D.<sup>2</sup>, Ralph G. Dacey Jr., M.D.<sup>3</sup>, Gregory J. Zipfel, M.D.<sup>3,4</sup>, and Colin P. Derdeyn, M.D.<sup>1,3,4</sup>

<sup>1</sup>Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri

<sup>2</sup>Department of Pathology, Washington University School of Medicine, St. Louis, Missouri

<sup>3</sup>Department of Neurosurgery, Washington University School of Medicine, St. Louis, Missouri

<sup>4</sup>Department of Neurology, Washington University School of Medicine, St. Louis, Missouri

### Abstract

Atherosclerotic disease has been suspected as a cause of moyamoya disease in some patients but has not, to the authors' knowledge, been confirmed by pathological studies. The authors present the histopathological findings in a patient with moyamoya collateral formation associated with atherosclerotic occlusive disease of the distal internal carotid artery (ICA). Typical atheromatous changes were evident in the distal ICA and proximal middle cerebral artery. In addition, intimal thickening, fibrosis, and abnormal internal elastic lamina were present in these vessels. These findings are common in moyamoya but not in atherosclerotic disease. Proliferation and enlargement of the lenticulostriate arteries in the basal ganglia was also identified. Moyamoya phenomenon secondary to atherosclerotic disease has similar histopathological features to idiopathic moyamoya phenomenon, both in the affected large basal arteries and lenticulostriate collaterals. These findings support the hypothesis advanced by Peerless that moyamoya is a 2-step process involving an obliterative vasculopathy of the terminal ICA and a secondary proliferative response.

### Keywords

moyamoya disease; vasculopathy; stroke; histopathological study; atherosclerosis; lenticulostriate artery; vascular disorders

---

Address correspondence to: Colin P. Derdeyn, M.D., 510 South Kingshighway Boulevard, St. Louis, Missouri 63110. Derdeync@wustl.edu.

#### Disclosure

Dr. Derdeyn was supported by NIH NINDS Grant No. RO1 51631. The authors have no industry affiliations or financial support from industry related to this topic.

Author contributions to the study and manuscript preparation include the following. Conception and design: Derdeyn, Dacey. Acquisition of data: Derdeyn, Jiang, Dacey, Zipfel. Analysis and interpretation of data: Derdeyn, Perry, Dacey, Zipfel. Drafting the article: Derdeyn, Jiang, Perry, Zipfel. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Derdeyn. Administrative/technical/material support: Derdeyn.

Moyamoya collaterals develop in response to diverse occlusive vasculopathies affecting the basal arteries, most frequently the distal ICA and proximal segments of the ACA and MCA.<sup>19</sup> Although atherosclerotic disease is a presumed cause of moyamoya collateral formation in some patients,<sup>2,19</sup> pathological descriptions of the secondary proliferative vasculopathy (the moyamoya collateral vessels) are scarce.<sup>8,10,13,17,25,26</sup> In this report we present the histopathological findings in a 44-year-old man with moyamoya phenomenon secondary to atherosclerosis.

## Case Report

### Patient History

This 44-year-old Caucasian man with significant atherosclerotic risk factors presented with an ischemic stroke involving his left MCA territory. His angiogram (Fig. 1) demonstrated occlusion of the left supraclinoid ICA, with associated moyamoya collaterals. There was extensive intracranial occlusive disease: both A<sub>1</sub> segments of the ACA were absent. Collateral flow to the left MCA was via moyamoya and pial collaterals from the distal branches of the ACA.

The patient underwent a PET study as part of a research protocol. This demonstrated significant increased oxygen extraction in the affected hemisphere (not shown). Plans were made for surgical revascularization; however, he suffered a fatal symptomatic hemorrhagic transformation of his basal ganglionic ischemic infarct.

### Pathological Findings

On gross inspection the brain appeared edematous and congested, with associated herniation syndromes, most notably involving the left uncus and subfalcine regions. Coronal sections demonstrated the large intracerebral hemorrhage, with much of the surrounding tissue appearing soft and necrotic. Additionally, there was focal Duret (secondary brainstem) hemorrhage in the pons as further evidence of cerebral herniation. The brain was generally soft and friable, but the circle of Willis was carefully dissected prior to sectioning and showed widespread abnormalities (Fig. 2). This included yellow-white atheromatous plaques involving proximal portions of both MCAs, increased branching of the left MCA, 2 large branches of the left ACA, only a short attenuated right ACA, patchy atherosclerosis of other major vessels, and clusters of small arterial branches seen at multiple sites.

Sections of the arteries of the circle of Willis (Fig. 3) showed patchy atherosclerosis with narrowed to completely occluded lumens, fibrocellular intimal thickening, marked tortuosity of the IEL, and attenuation of the media; there were also numerous small collateral branches, especially in sections from the left MCA, probably correlating with the “puff of smoke” appearance described on angiography. Sections cut through the left MCA and right PCA (Fig. 4) show atherosclerotic changes with intimal thickening at bifurcations (Fig. 4A) and multiple small-caliber collateral branches (Fig. 4B, smooth-muscle actin immunostain) adjacent to the main artery. Sections through the basal ganglia (Fig. 5) demonstrated enlarged (Fig. 5C; hypertrophy) lenticulostriate arteries, with multiple parallel adjacent channels.

## Discussion

Peerless<sup>19</sup> suggested in 1997 that the moyamoya phenomenon is probably a secondary and variable response to a variety of occlusive vasculopathies, including atherosclerotic disease, that involve the terminal ICA and its branches. This report provides histopathological evidence that atherosclerotic occlusive disease can indeed lead to secondary moyamoya collateral formation. In addition, this report adds to the literature regarding the histopathological nature of moyamoya collaterals themselves.

Patients with bilateral idiopathic arterial occlusive disease and moyamoya collateral formation are considered to have moyamoya disease, although it is not clear that their diseases share a common source.<sup>7</sup> In those with known occlusive vasculopathies, such as the patient presented in this report, the disorder has been defined as secondary moyamoya disease. The phenotype of moyamoya disease differs considerably between Asian and North American patients. In Asia, the disorder is most common in children and has a bimodal distribution.<sup>11,12,24</sup> Asian adults present more frequently with hemorrhage than with ischemic events. There is a slight predilection for males in the adult population.<sup>11</sup> In North America and Europe, the most common presentation is in young adult women with ischemic events.<sup>4-6,9,14,19</sup> Some recent registry data from Japan suggest that the Asian phenotype may be shifting to resemble the North American form.<sup>3</sup>

Histopathological studies of the basal arteries in Asian patients with moyamoya disease performed at autopsy have demonstrated intimal thickening with smooth-muscle proliferation and abnormal IEL, without features of atherosclerotic disease.<sup>16,21,23,25</sup> Similar findings of intimal thickening, fibrosis, and abnormal IEL have been shown in North American patients with moyamoya.<sup>1,4,6,15</sup> In the present case, atherosclerotic stenosis and occlusion were identified on gross inspection and histological examination (Figs. 2–4). Interestingly, duplication and abnormal thickening of the IEL was also present (Fig. 3E), similar to that reported in the idiopathic occlusive process associated with moyamoya collateral formation. This is not common in atherosclerotic disease and may reflect some response related to the vasoproliferative signals that trigger the development of the moyamoya collaterals.

The pathological descriptions of the lenticulostriate vessels (the moyamoya collaterals) have been variable. Yamashita and colleagues<sup>25</sup> reported on 22 Asian patients with moyamoya disease, 19 of whom presented with hemorrhage. These investigators described 2 types of moyamoya-associated perforating vessels. The first are moyamoya collateral vessels, which are predominantly perforating dilated arteries with thin walls, attenuated media, and segmentation of the IEL.<sup>22,25</sup> Microaneurysms are common in this group of vessels and are thought to be the cause of hemorrhage.<sup>18</sup> The second type of perforating vessels are thick-walled stenotic arteries with concentric fibrocellular intimal thickening, duplication of the IEL, and fibrosis of the tunica media.<sup>25</sup> These are often collapsed and thrombosed, and may account for ischemic symptoms. In our patient we found multiple thin-walled vessels in the subarachnoid space (Fig. 4B) and evidence of proliferation, with multiple small new vessels adjacent to perforating arteries in the basal ganglia (Fig. 5C). No microaneurysms were identified.

In one other North American autopsy case of moyamoya phenomenon, the patient was found to have occlusion secondary to arterial dissection, without the typical intimal thickening and discontinuity of IEL reported in Asian patients meeting the definition of moyamoya disease.<sup>20</sup>

In this patient with moyamoya phenomenon secondary to atherosclerotic occlusive disease, the large-artery occlusive process shared many similarities with patients with moyamoya disease: intimal thickening, fibrosis, IEL irregularity, and duplication were found in the stenotic and occluded basal arteries. These findings are unusual in atherosclerotic disease and may reflect responses to vasoproliferative signals. In addition, we found that the moyamoya collateral vessels were characterized by both hypertrophy and proliferation. These findings support the hypothesis that moyamoya disease is a 2-step process involving a potentially multifactorial underlying occlusive vasculopathy and then a secondary vasoproliferative response that results in moyamoya collateral vessels in some patients.

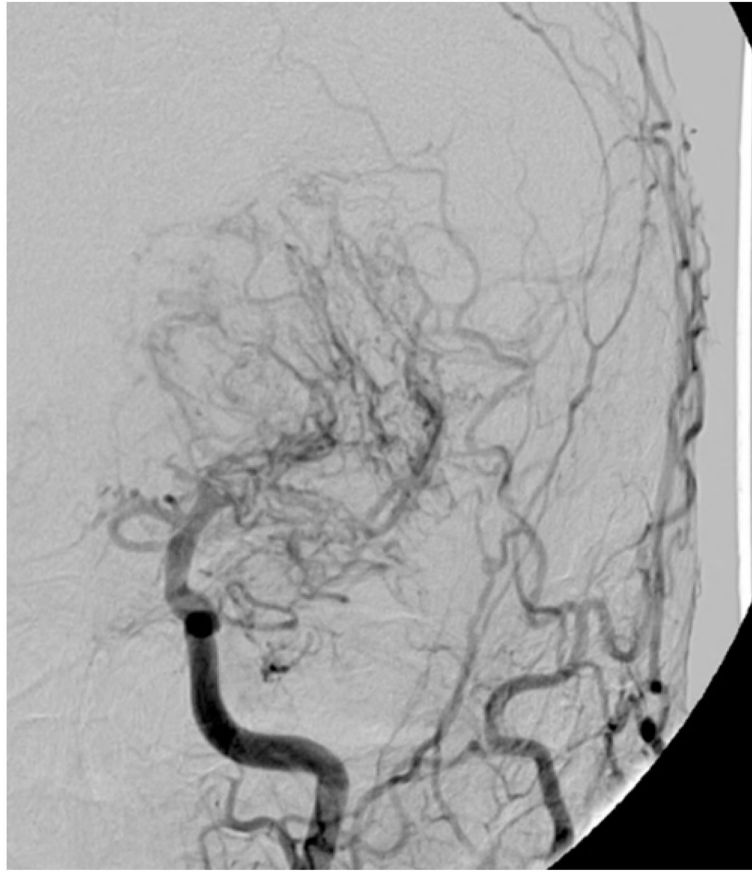
### Abbreviations used in this paper

<b>ACA</b>	anterior cerebral artery
<b>ICA</b>	internal carotid artery
<b>IEL</b>	internal elastic lamina
<b>MCA</b>	middle cerebral artery
<b>PCA</b>	posterior cerebral artery

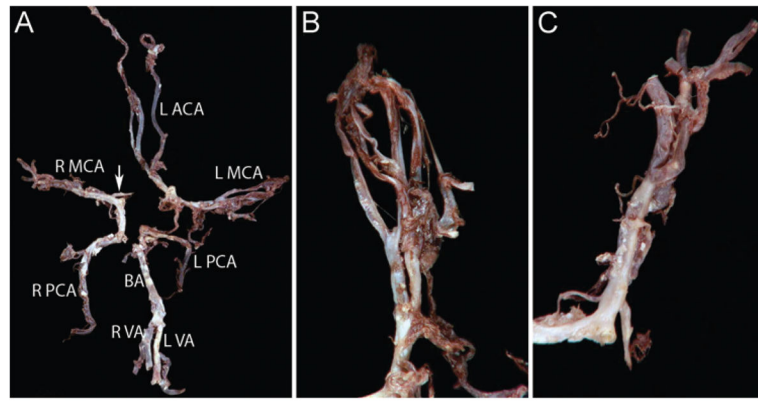
### References

1. Ahmadi J, Keane JR, McCormick GS, Fallis RJ, Miller CA. Ischemic chiasmal syndrome and hypopituitarism associated with progressive cerebrovascular occlusive disease. *AJNR Am J Neuroradiol.* 1984; 5:367–372. [PubMed: 6431771]
2. Ashley WW Jr, Zipfel GJ, Moran CJ, Zheng J, Derdeyn CP. Moyamoya phenomenon secondary to intracranial atherosclerotic disease: diagnosis by 3T magnetic resonance imaging. *J Neuroimaging.* 2009; 19:381–384. [PubMed: 19021845]
3. Baba T, Houkin K, Kuroda S. Novel epidemiological features of moyamoya disease. *J Neurol Neurosurg Psychiatry.* 2008; 79:900–904. [PubMed: 18077479]
4. Bruno A, Adams HP Jr, Biller J, Rezai K, Cornell S, Aschenbrener CA. Cerebral infarction due to moyamoya disease in young adults. *Stroke.* 1988; 19:826–833. [PubMed: 3260417]
5. Chiu D, Shedden P, Bratina P, Grotta JC. Clinical features of moyamoya disease in the United States. *Stroke.* 1998; 29:1347–1351. [PubMed: 9660385]
6. Cloft HJ, Kallmes DF, Snider R, Jensen ME. Idiopathic supraclinoid and internal carotid bifurcation steno-occlusive disease in young American adults. *Neuroradiology.* 1999; 41:772–776. [PubMed: 10552029]
7. Fukui M. Guidelines for the diagnosis and treatment of spontaneous occlusion of the circle of Willis ('moyamoya' disease). *Clin Neurol Neurosurg.* 1997; 99:S238–S240. [PubMed: 9409446]
8. Fukui M, Kono S, Sueishi K, Ikezaki K. Moyamoya disease. *Neuropathology.* 2000; 20 (Suppl):S61–S64. [PubMed: 11037190]
9. Hallemeier CL, Rich KM, Grubb RL Jr, Chicoine MR, Moran CJ, Cross DT III, et al. Clinical features and outcome in North American adults with moyamoya phenomenon. *Stroke.* 2006; 37:1490–1496. [PubMed: 16645133]

10. Hoshimaru M, Takahashi JA, Kikuchi H, Nagata I, Hatanaka M. Possible roles of basic fibroblast growth factor in the pathogenesis of moyamoya disease: an immunohistochemical study. *J Neurosurg.* 1991; 75:267–270. [PubMed: 2072165]
11. Ikezaki K, Han DH, Kawano T, Kinukawa N, Fukui M. A clinical comparison of definite moyamoya disease between South Korea and Japan. *Stroke.* 1997; 28:2513–2517. [PubMed: 9412642]
12. Ikezaki K, Inamura T, Kawano T, Fukui M. Clinical features of probable moyamoya disease in Japan. *Clin Neurol Neurosurg.* 1997; 99 (Suppl 2):S173–S177. [PubMed: 9409431]
13. Kono S, Oka K, Sueishi K. Histopathologic and morphometric studies of leptomeningeal vessels in moyamoya disease. *Stroke.* 1990; 21:1044–1050. [PubMed: 2368105]
14. Kraemer M, Heienbrok W, Berlit P. Moyamoya disease in Europeans. *Stroke.* 2008; 39:3193–3200. [PubMed: 18787200]
15. Matri AR, Silverstein PM, Gold L, Eselius EP. Multiple progressive intracranial arterial occlusions. *Stroke.* 1973; 4:380–386. [PubMed: 4713025]
16. Masuda J, Ogata J, Yutani C. Smooth muscle cell proliferation and localization of macrophages and T cells in the occlusive intracranial major arteries in moyamoya disease. *Stroke.* 1993; 24:1960–1967. [PubMed: 7902623]
17. Nanba R, Kuroda S, Ishikawa T, Houkin K, Iwasaki Y. Increased expression of hepatocyte growth factor in cerebrospinal fluid and intracranial artery in moyamoya disease. *Stroke.* 2004; 35:2837–2842. [PubMed: 15528455]
18. Oka K, Yamashita M, Sadoshima S, Tanaka K. Cerebral haemorrhage in Moyamoya disease at autopsy. *Virchows Arch A Pathol Anat Histol.* 1981; 392:247–261. [PubMed: 7269227]
19. Peerless SJ. Risk factors of moyamoya disease in Canada and the USA. *Clin Neurol Neurosurg.* 1997; 99 (Suppl 2):S45–S48. [PubMed: 9409404]
20. Pilgreen KL, Lum GB, Hamilton WJ, Nelson GA. Medical pathology conference. Altered level of consciousness and right hemiparesis in a 24-year-old woman. *Ala J Med Sci.* 1986; 23:296–302. [PubMed: 3752406]
21. Rao M, Zhang H, Liu Q, Zhang S, Hu L, Deng F. Clinical and experimental pathology of Moyamoya disease. *Chin Med J (Engl).* 2003; 116:1845–1849. [PubMed: 14687471]
22. Scott RM, Smith ER. Moyamoya disease and moyamoya syndrome. *N Engl J Med.* 2009; 360:1226–1237. [PubMed: 19297575]
23. Takagi Y, Kikuta K, Nozaki K, Hashimoto N. Histological features of middle cerebral arteries from patients treated for Moyamoya disease. *Neurol Med Chir (Tokyo).* 2007; 47:1–4. [PubMed: 17245006]
24. Wakai K, Tamakoshi A, Ikezaki K, Fukui M, Kawamura T, Aoki R, et al. Epidemiological features of moyamoya disease in Japan: findings from a nationwide survey. *Clin Neurol Neurosurg.* 1997; 99 (Suppl 2):S1–S5. [PubMed: 9409395]
25. Yamashita M, Oka K, Tanaka K. Histopathology of the brain vascular network in moyamoya disease. *Stroke.* 1983; 14:50–58. [PubMed: 6823686]
26. Yoshimoto T, Houkin K, Takahashi A, Abe H. Angiogenic factors in moyamoya disease. *Stroke.* 1996; 27:2160–2165. [PubMed: 8969773]



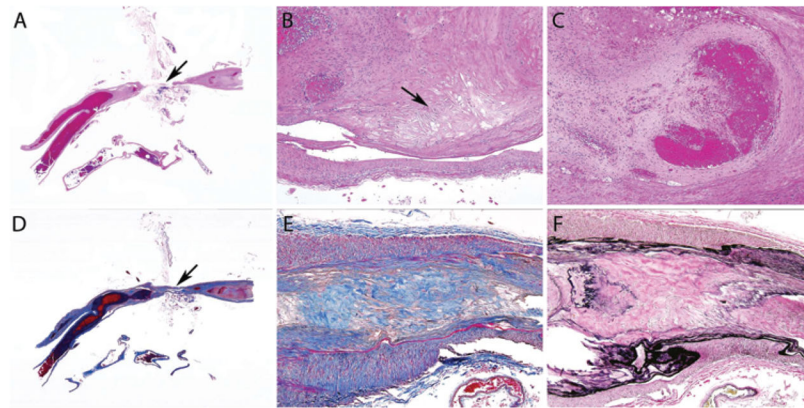
**Fig. 1.** Anterior projection cerebral angiogram obtained after left common carotid injection showing occlusion of distal ICA and extensive moyamoya collateral formation.



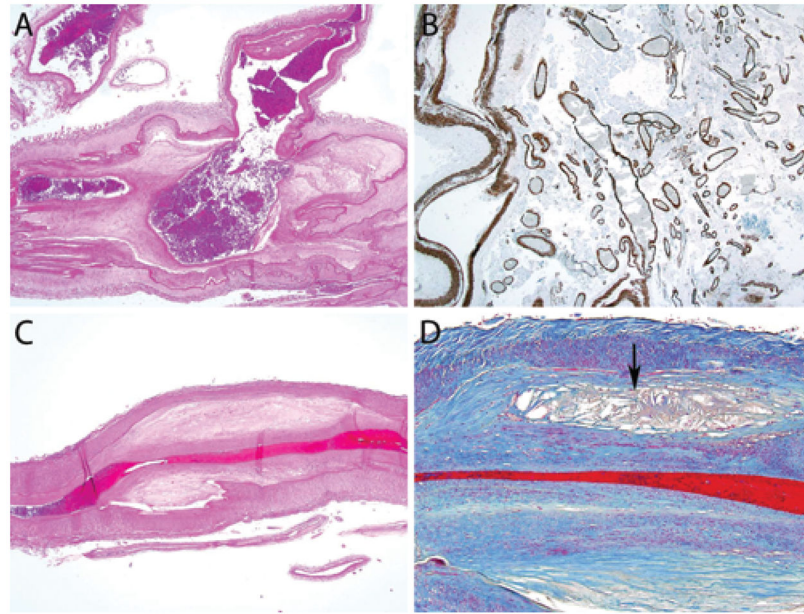
**Fig. 2.**

Photographs of the circle of Willis at autopsy. Only a short, markedly attenuated A<sub>1</sub> ACA segment was seen on the right (*arrow*), whereas the left A<sub>1</sub> segment had 2 major branches (**A**). At closer inspection, the left MCA (**B**) shows increased branching beyond that of the usual trifurcation, whereas both the left and right MCAs (**C**) demonstrate extensive yellow-white atheromatous deposits proximally. Small vascular branches are seen coming off the main trunks in both MCAs as well as other large arteries. BA = basilar artery; VA = vertebral artery.

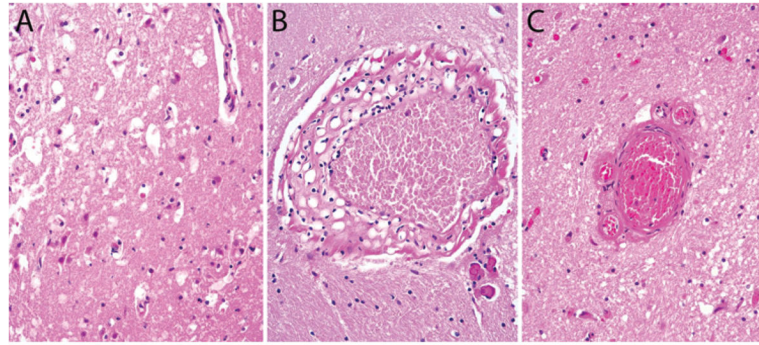




**Fig. 3.** Photomicrographs of sections from the left ACA revealing foci of luminal narrowing with complete occlusion focally (*arrows*, **A** and **D**). At higher magnification, cholesterol-rich atheromatous plaques (*arrow*, **B**) and partially recanalized thrombi (**C**) were seen. Foci of intimal fibrosis and distortion/reduplication of the IEL were highlighted on trichrome- (**E**) and Verhoeff-van Gieson- (**F**) stained sections, respectively. H & E (A–C), trichrome (D and E), and Verhoeff-van Gieson (F). Original magnification  $\times 1$  (A and D),  $\times 100$  (B and C), and  $\times 200$  (E and F).



**Fig. 4.** Photomicrographs of sections obtained at autopsy. Changes in the left MCA (**A and B**) and right PCA (**C and D**) showed similar features. These included marked atherosclerotic changes and intimal thickening at vascular branch points (**A**) and innumerable small-caliber collateral branches (**B**) adjacent to the main artery (left side of image in panel **B**), probably representing the histological correlate of the “puff of smoke” sign often encountered on angiography. Patchy foci of marked intimal thickening and luminal narrowing were also noted (**C**), along with cholesterol-rich atheromatous material (*arrow*, **D**). H & E (**A** and **C**), smooth-muscle actin immunostain (**B**), and trichrome (**D**). Original magnification  $\times 100$  (**A** and **B**),  $\times 40$  (**C**), and  $\times 400$  (**D**).



**Fig. 5.** Photomicrographs of sections from the basal ganglia and thalamus revealing acute eosinophilic neuronal necrosis (A), scattered arterioles with lipid-rich deposition (B), and arterioles giving rise to multiple small-caliber collateral vessels (C). H & E; original magnification  $\times 200$  (A) and  $\times 400$  (B and C).