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# Carotid artery dissection in a young adult: cystic medial necrosis associated with an increased elastase content

D.R. THAL[1,2], R. SCHOBER[2] and W. SCHLOTE[1]

[1]*Department of Neuropathology, University of Frankfurt, Frankfurt/Main, and*
[2]*Department of Neuropathology, Institute of Pathology, University of Leipzig, Leipzig, Germany*

**Abstract.** A dissecting aneurysm of the right internal carotid artery was found in a 22-year-old man, who rapidly became unconscious and hemiparetic after an accident occuring during sport. The dissection was limited to the intima and internal elastic lamina. Patterns of cystic medial necrosis with mucoid degeneration were present in the right internal carotid artery proximal to the site of dissection, in the thoracic aorta, and in several visceral arteries. In the region of the right internal carotid artery affected with cystic medial necrosis, calcification and also splitting of the internal elastic lamina was found. Such calcification was also present at the site of the dissection, at the tip of the ruptured and recoiled elastic lamina. These changes, dissection as well as cystic medial necrosis, were associated with an elevated elastase content, a decrease of desmin and an increase of vimentin expression. Ultrastructurally, in areas affected by cystic medial necrosis a corresponding transformation of medial smooth muscle cell phenotype from the contractile to the metabolic state was found. The topographical relation of dissecting aneurysm, cystic medial necrosis, and an increased elastase content is suggestive of a causal relation, and the possibility of common etiological factors is discussed.

**Key words:** carotid artery – cystic medial necrosis – dissecting aneurysm – elastase – smooth muscle cells

## Introduction

Dissecting aneurysms and cystic medial necrosis are often associated [Chang et al. 1991, De Caro et al. 1991, De Virgilio et al. 1990, Hartman and Eftychiadis 1990, Kita et al. 1990, Klima et al. 1983, Nakashima et al. 1990, Sariola et al. 1986]. This association has been challenged by several authors who found cystic medial necrosis in thoracic aortas in cases of dissection as well as in cases of age-related normal patients, and it was thought that cystic medial necrosis is a physiological process and not responsible for thoracic aorta dissection [Kita et al. 1990, Schlatmann and Becker 1977a,b, Wilson and Hutchins 1982]. However, at the site of aortic dissection the elastase activity was higher than in age-related controls [Derouette et al. 1981].

Dissection of intracranial arteries is rare. Conditions most commonly associated are traumatic injury, atherosclerosis, fibromuscular dysplasia, cystic medial necrosis, intimal fibroelastic aberrations, and moja-moja disease [Adams et al. 1982, Adelman et al. 1974, Farrell et al. 1985, Friedman and Drake 1984, Grosman et al. 1980, Hegedüs 1982, Pilz 1982, Smith et al. 1993, Wassmann and Gullotta 1993, Wolman 1959, Yonas et al. 1977]. Alteration of the internal elastic lamina was discussed as a cause of dissection [Hegedüs 1982, Sasaki et al. 1991, Wolman 1959].

Here we report a case of internal carotid artery dissection associated with cystic medial necrosis and alteration of the internal elastic lamina with special reference to elastase immunohistochemistry.

## Case history

A 22-year-old man in good health developed anesthesia in his left foot, approximately 1 hour after being hit on the head with a football and while doing jiu jitsu. He finished training and a few minutes later his entire left leg and arm were aching. Ensuing this, he experienced loss of vocal articulation and consciousness. Examination in the hospital revealed loss of consciousness and left-sided hemiparesis. An occlusion of the right internal carotid artery was found by angiography. Heart dilatation was seen and it was known that 4 years ago the patient was under medical attendence because of rheumatism of the knee. He was submitted to an intensive care unit but died 2 days later

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Correspondence to Dr. D.R. Thal, Anatomisches Institut I, Universität Frankfurt am Main, Theodor Stern Kai 7, 60596 Frankfurt am Main, Germany.

with arrhythmia and central stretching convulsions as signs of increased intracranial pressure.

Necropsy revealed a degenerative disease of the aorta and larger arteries, especially the cranial arteries with degeneration of the internal elastic lamina. A dissecting aneurysm of the right internal carotid artery in continuity with the medial cerebral artery was associated with thrombosis, infarction of the territory of the right anterior, and medial cerebral arteries with spotted subarachnoidal hemorrhages, signs of increased intracranial pressure, and secondary pontine hemorrhages. Other findings included a small colloidal cyst in the anterior lobe of the hypophysis; congestion of spleen, liver, and kidneys; calcification and ossification of the right adrenal gland with compensatory hypertrophy of the left one; doubled renal pelvis and ureter duplex on the left side; mucosal hemorrhages of the urinary bladder, and subepicardial hemorrhages of the left cardiac ventricle attributed to reanimation.

## Material and methods

Samples of right and left internal carotid arteries, common carotid arteries, right middle cerebral artery, vertebral arteries, basilar artery, visceral arteries, femoral arteries, coronary arteries, thoracic and abdominal aorta were prepared, fixed in 4% formaldehyde, embedded in paraffin, and sectioned. All sections were stained with hematoxylin and eosin and Verhoeff's elastica van Gieson. The sections of the right internal carotid artery and thoracic aorta additionally were stained with alcian blue.

Samples of the right internal carotid artery were submitted to immunohistochemistry with antibodies against vimentin (VIM3B4; Progen; 1/200) and desmin (D33; DAKO; 1/100) intermediate filaments, detected with diaminobenzidine (avidin-biotin complex method/hemalum counterstaining), and against human leukocyte elastase (MAB1478; Chemicon; 1/1,000) detected with the APAAP method (hematoxylin counterstaining). For the slices submitted to elastase immunohistochemistry, enzyme blocking by $H_2O_2$ was avoided. Immunohistochemical reactions against human immunoglobulins, detected by direct fluorescence, were examined as well.

A sample of the right internal carotid artery affected by cystic medial necrosis was prepared for electron microscopy. 100 µm paraffin sections were cut, stained with osmiumtetroxide and uranyl acetate, and flat-embedded in araldite. The area affected by cystic medial necrosis was marked in an adjacent elastica van Gieson-stained section. The flat-embedded section was led over the marked slice in an identical position, and the marker was copied to the flat-embedded section. This marked area was prepared for semi- and ultrathin sections. They were cut with an ultramicrotome Om U3 and an IVIC diamond knife. Ultrathin sections were stained with lead citrate and uranylacetate. Electron microscopy was performed with a Philips EM 301.

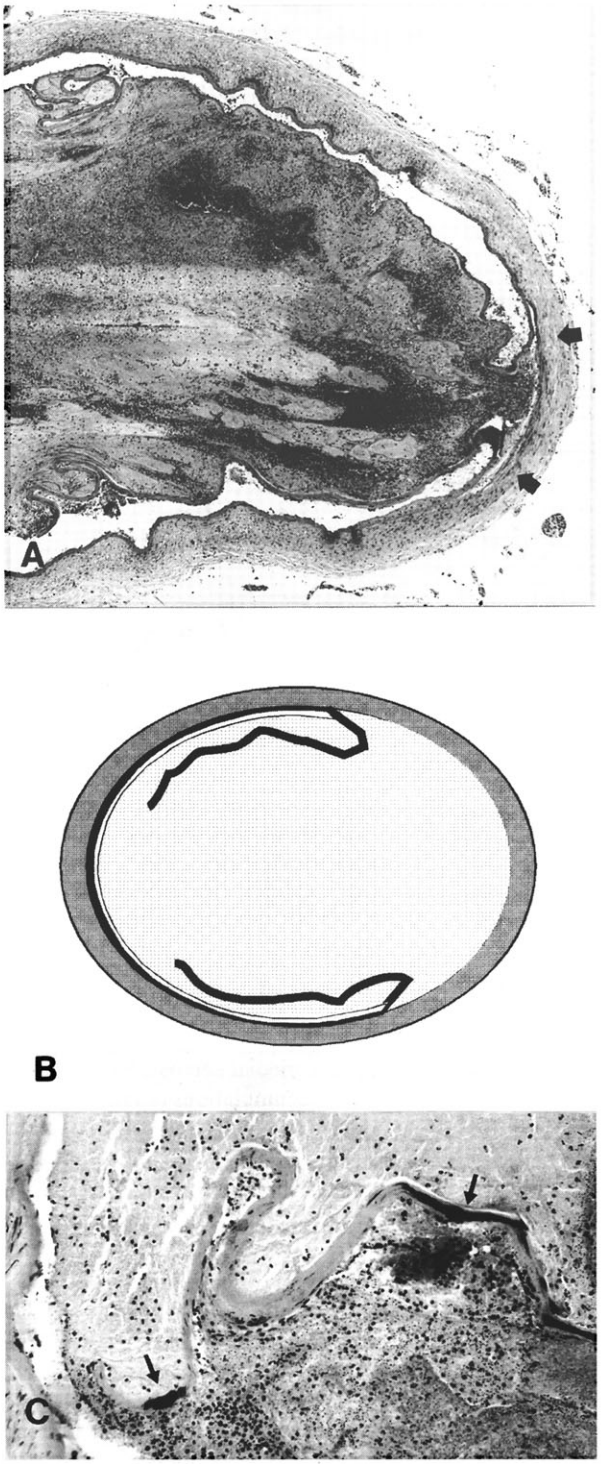


*Fig. 1* Dissecting aneurysm of the right internal carotid artery, showing dissection of internal elastic lamina and thrombotic occlusion. Cystic medial necrosis is not present at this level. A: HE staining (magnification: × 16), B: schematic representation, C: focal calcification of the dissected lamina elastica interna; HE staining (magnification: × 64).

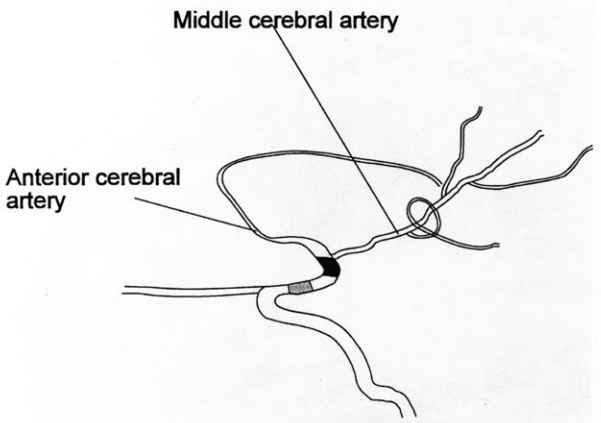


*Fig. 2* Schematic representation of right internal carotid, anterior, and middle cerebral artery. The site of dissection (■) is distant from the area affected by cystic medial necrosis (▩).

## Results

Sections of the right internal carotid artery revealed an intracranial dissecting aneurysm near the bifurcation. The lumen was occluded by fresh vascular thrombosis extending into the middle cerebral artery. The intima and internal elastic lamina were dissected. There were focal calcifications, including a calcific spur at the end of the ruptured internal elastic lamina, that was wrapped back into the lumen of the medial cerebral artery (Figure 1a,b,c). The media showed no pathological alterations. In sections ~ 1 – 2 cm proximal to this site in the internal carotid artery, i.e. distant of bifurcation and not affected by dissection (Figure 2), patterns of cystic medial necrosis were present. These included large focal accumulations of mucoid material with loss of smooth muscle cells and splitting of the internal elastic lamina (Figure 3).

Patterns of cystic medial necrosis were also seen in the thoracic aorta, the splenic and the superior mesenteric artery. Other arteries were not affected.

Immunohistochemistry revealed a focally decreased desmin and an increased vimentin expression in the arterial media restricted to the site of dissection, the mucoid medial degeneration, and the cystic medial necrosis in the right internal carotid artery. Here a focally increased elastase content was found, especially at the site of dissection (Figure 4a,b). Immunoglobulins were not detected.

Ultrastructural investigation of the media affected by cystic medial necrosis revealed images of smooth muscle cells consistent with a metabolic state. Such cells displayed a diminished number of myofilaments, vacuolated cytoplasm, and dilated endoplasmatic reticulum (Figure 5). The intercellular space was enlarged containing some irregularly orientated collagen fibers.

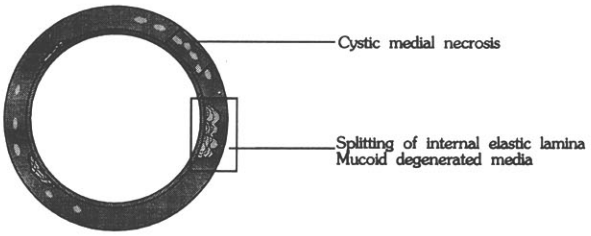


*Fig. 3a*

*Fig. 3b*

*Fig. 3* A: Schematic representation of degenerative changes in the right internal carotid artery distant from that shown in Figure 1, B: pattern of cystic medial necrosis (c), splitting and degeneration (s) of the internal elastic lamina and mucoid degeneration (m) of the media in a section of the right internal carotid artery distant from the dissection; HE staining (magnification: × 132).

## Discussion

The question of a causal relation between cystic medial necrosis and dissecting aneurysm has been discussed by many authors. With reference to the aorta, most authors have found no significant difference in the pattern of cystic medial necrosis between not dissected and dissected aortas [Becker 1977a,b, Hasleton and Leonard 1979, Kita et al. 1990, Larson and Edwards 1984, Schlatman and Wilson et al. 1982]. However, some authors have observed cystic medial necrosis more frequently in dissected aortas [Klima

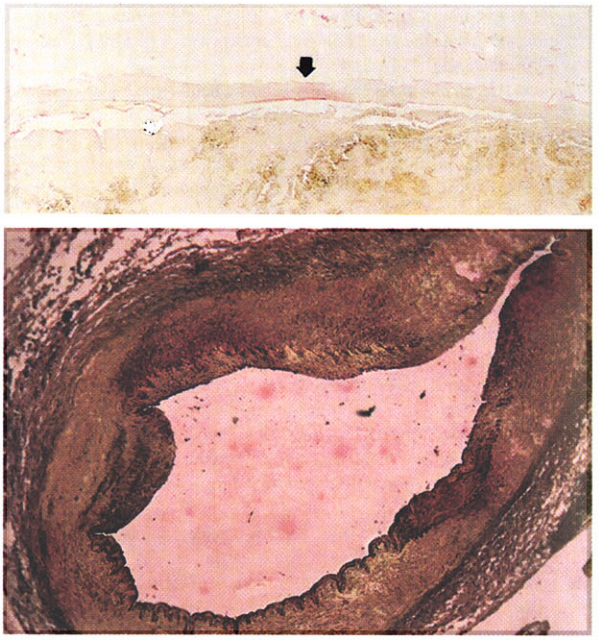

*Fig. 4* Immunohistochemical staining for human elastase visualized by APAAP-technique, counterstaining with hematoxylin. A: Increased elastase content at the site of dissection (magnification: × 28), B: section of right internal carotid artery not affected by dissecting aneurysm. Increased elastase content is demonstrated in areas with splitting of internal elastic lamina, mucoid degeneration of the media, and cystic medial necrosis (magnification: × 28).

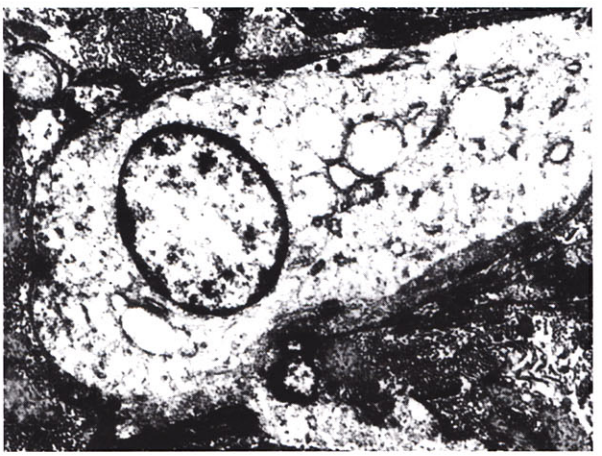

*Fig. 5* Electron microscopy of smooth muscle cell of the right internal carotid artery, showing loss of myofilaments and increase of granular endoplasmatic reticulum consistent with a metabolic state (magnification: × 9,000).

et al. 1983, Nakashima et al. 1990, Wyler 1989]. Contrary to the original concept, current opinion favors cystic medial necrosis as a physiological change of aortic wall structure in aging [Hasleton and Leonard 1979, Schlatman and Becker 1977a].

With reference to cerebral arteries, a causal relation of cystic medial necrosis to dissecting aneurysms with affection of intima, internal elastic lamina, and media was discussed [Adams et al. 1982, Farrell et al. 1985, Yonas et al. 1977]. In the present case, cystic medial necrosis was associated with changes of the internal elastic lamina and mucoid medial degeneration in a region distant from the dissecting aneurysm (Figure 3). In these areas, splitting of the internal elastic lamina was found near large areas of mucoid degeneration of the media with loss of collagen fibers. In these areas smooth muscle cells switched from the contractile to the metabolic state, and an increased elastase immunoreactivity was observed. An increased elastase activity has been observed in aortic dissecting aneurysms and was discussed as a causal factor for dissection [Derouette et al. 1981]. Therefore, an increased elastase activity occurring during mucoid medial degeneration may explain changes in the structure of collagen and elastic fibers as described by Derouette et al. [1981], Sariola et al. [1986], Whittle et al. [1987, 1990] and Kita et al. [1990]. This may correlate with the splitting of the internal elastic lamina and the enlarged intercellular space with irregularly orientated collagen fibers between the smooth muscle cells. The presence of increased human leukocyte elastase immunoreactivity in our case in areas of cystic medial necrosis and near the site of dissection may be responsible for elastic and collagen fiber damage [Thomas 1993, Werb and Gordon 1975]. Thus, a causal relation between an increased elastase immunoreactivity at the site of dissection and these changes leading to dissection can be postulated. The calcification at the tip of the recoiled elastic lamina might be the expression of degenerative changes in this context.

Increased elastase activity means an increased level of a proteolytic enzyme with potential destruction of cellular proteins, fiber proteins, and functional proteins [Thomas 1993, Werb and Gordon 1975]. Probably, the increased elastase activity may be triggered by the local loss of proteinase inhibitors, such as $\alpha_1$-antitrypsin [Thomas 1993]. The loss of proteinase inhibitors might possibly be caused by abnormalities of smooth muscle cell function.

Functional change of smooth muscle cells from the contractile to the metabolic state leading to production of proteoglycans and elastases may lead to loss of stability and manifestation of the dissection [Hartman and Eftychiadis 1990]. A decrease of desmin and a slight increase of vimentin immunoreactivity as observed in our case indicates the metabolic state of smooth muscle cells [Campbell et al. 1988]. The ultrastructure in regions of cystic medial necrosis in our case correlates to that found by Becker [1975]. Such changes of smooth muscle cell function are thought to cause changes in collagen and elastic fibers by a decrease of pyridinoline, a collagen-specific covalent crosslink [Whittle et al. 1987].

For medico-legal considerations it is important to know that the type of aneurysm seen in our study may be

correlated to an acute head trauma, not necessarily associated with brain injury [Farrell et al. 1985, Friedman and Drake 1984, Yonas et al. 1977]. On the other hand, a correlation between dissecting aneurysm and cystic medial necrosis has been described repeatedly [Adams et al. 1982, Chang et al. 1991, Friedman and Drake 1984, Nedwich et al. 1963, Pilz 1982, Wolman 1959, Yonas et al. 1977]. It was stated by Yonas et al. [1977] as well as by other authors [Hegedüs 1982, Nedwich 1963, Sasaki et al. 1991, Wolman 1959] that dissecting aneurysms of group 1, with dissection between the internal elastic lamina and the media according to Yonas et al. [1977], may be caused by a defect of the internal elastic lamina and cannot be correlated to traumatic injury only. The dissection in our case might have been triggered by head trauma, but we believe a dissection would not have happened without the presence of cystic medial necrosis and without involvement of the internal elastic lamina by the regional increase of elastase. A genetic defect predisposing for these changes was proposed by Wolman [1959] and may be possibly discovered by molecular biological techniques in the future.

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**Note added in proof**

After submission of this manuscript, experimental models for elastase induced aneurysms have been developed (Halpern et al. 1994, J Vasc Surg 20: 51-60). Therefore, our finding of an increased elastase content at the site of the dissection supports this concept even in the case of dissecting aneurysms.

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