Cerebral arterial dissection

A case report with histopathologic and ultrastructural findings[1]

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Cerebral artery dissection is an uncommon cause of cerebral infarction, but should be considered in young stroke patients who lack stroke risk factors. A case and autopsy results are reported of a 23-year-old female with dissection of the middle cerebral and anterior cerebral arteries. Multiple factors potentially related to the pathogenesis in this case include migraine headaches, trauma, and alcohol intake. The clinical, histopathologic, and ultrastructural findings are discussed and the literature is reviewed.

Index terms: Aneurysm, dissecting • Cerebral arteries • Cerebral infarction

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Three percent of strokes occur in young adults under 40 years of age, according to a recent population-based study of cerebral infarction.[1] Of these strokes, arterial dissections or dissecting aneurysms of cervical and cerebral arteries accounted for 4%.[1,2] Although uncommon, arterial dissection or dissecting aneurysm should be considered as a cause of cerebral ischemia, especially in adolescents or young adults who lack predisposing stroke risk factors. We report a case of intracranial arterial dissection involving the middle cerebral and anterior cerebral arteries, including histopathologic and electron microscopic findings, and review the literature relating to this disorder.

Case report

A 23-year-old, right-handed, white, female student was transferred to the Cleveland Clinic Hospital (CCH). The evening prior to admission the patient had consumed an unknown quantity of alcohol. Approximately 12 hours later, she became nauseated, and vomited several times. She was found lying in the bathroom limp and unresponsive. Apparently while vomiting she may have fallen and struck her head (right fronto-temporal region) on the toilet. She was taken to a local hospital where she was unconscious and had decreased responsiveness to painful stimuli on her right side. A lumbar puncture revealed normal pressure and clear fluid. Her medical history was remarkable for infrequent "migraine-type" headaches. Her mother had a history of similar headaches. The patient's birth, growth, and development had been normal. She had no history of hypertension, diabetes mellitus, seizures, heart disease, alcohol abuse, or smoking. The patient had never been pregnant and was not taking any medications, including oral contraceptives.

On admission to CCH vital signs were: temperature 35.8° C, pulse 75, and blood pressure 130/82 mmHg. The patient was lethargic, mute, but arousable to pain. Pertinent physical findings included: contusions over the right side of the face with no palpable fracture or hematoma, a supple neck with no bruits, and no cardiac dysrhythmias or murmurs.

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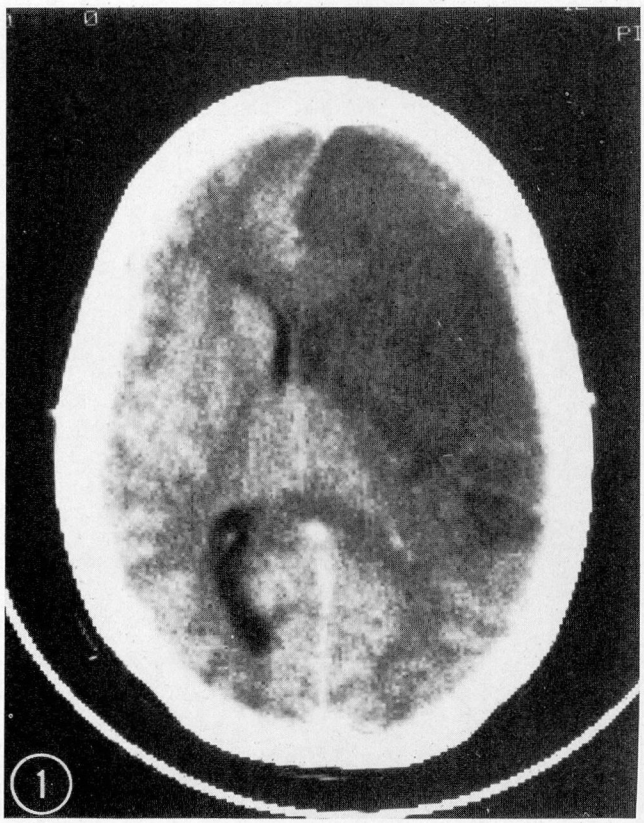

Fig. 1. CT scan 2 days after onset of unconsciousness, showing marked low density and swelling in the distribution of the left anterior and middle cerebral arteries and a shift of the midline structures to the right.

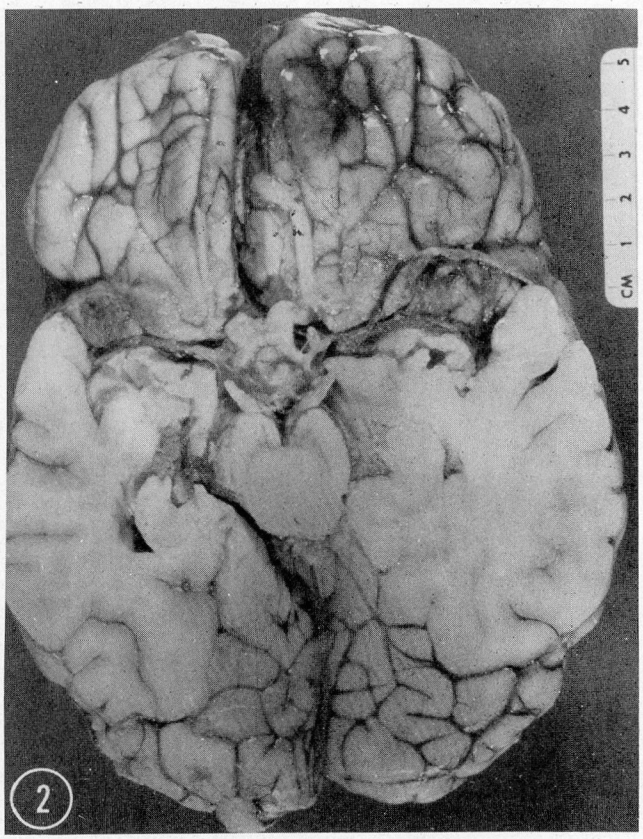

Fig. 2. Basal view of the brain showing occluded but not dilated left middle cerebral artery (LMCA) and its branches. Note the right middle cerebral artery (RMCA) is free of occlusion.

Neurologic examination revealed right hemiparesis, left gaze preference, and global aphasia. Laboratory studies included hemoglobin 14.5 g/dL, hematocrit 42.5%, white blood cell count 21,300/mL, platelet count 323,000/mL, prothrombin time 13 seconds (normal, 12 sec), partial thromboplastin time 24 seconds (normal, 21–31 sec), and normal SMA-17 values. Electrocardiography showed normal sinus rhythm. An echocardiogram showed normal cardiac valves and heart chambers, and no evidence of thrombus. Sedimentation rate was 1 mm/hr and ANA (antinuclear factor) testing was negative. Head computed tomography (CT) showed an infarct in the left frontal lobe with mild mass effect.

Her hospital course was complicated by bradycardia and hypotension, secondary to increased intracranial pressure (ICP). Initial ICP was 40 mmHg and was treated with mannitol, Decadron (dexamethasone), and Lasix (furosemide). Thirty-six hours after hospitalization, repeat CT (*Fig. 1*) showed a large infarct in the left anterior and middle cerebral artery distribution with marked edema compressing the left lateral ventricle and a shift of midline structures from left to right. Hypothermia and barbiturate coma were induced in an attempt to lower ICP. Eight days after hospitalization, the patient's ICP was greater than 20 mmHg and her pupils were dilated and fixed. Pentobarbital was tapered and she was pronounced dead 2 days later.

General autopsy findings included: normal heart (weight 250 g), no vegetations on the cardiac valves, minimal atherosclerosis, no vascular anomalies or aneurysms, bilateral acute bronchopneumonia, and mild lymphocytic thyroiditis.

The brain (weight 1430 g) showed gyral flattening and sulcal narrowing consistent with severe cerebral edema. The left cerebral hemisphere was soft, swollen, and discolored. Infrafalcial herniation from left to right and parahippocampal herniation were present. The left head of the caudate was hemorrhagic and necrotized. Examination of the cerebral arteries showed small-caliber vessels. The left middle cerebral artery (LMCA) near its origin was firm and dark blue but not bulging (*Fig. 2*). The left anterior cerebral artery (LACA) was similar in appearance. Both the LMCA and LACA were occluded 3 to 4 cm from their origins. No significant atherosclerosis was present, there was no subarachnoid hemorrhage, and no saccular aneurysms or vascular malformations were found. The other cerebral vessels were normal. The intracranial and extracranial carotid arteries had no significant atherosclerosis and were grossly patent.

Microscopic examination of the LMCA and the LACA showed disruption and irregularities of the internal elastic lamina with loss of the endothelial cell layer. There was subintimal intramural hemorrhage with dissection of the vessel wall in a plane between the intimal and medial layers.

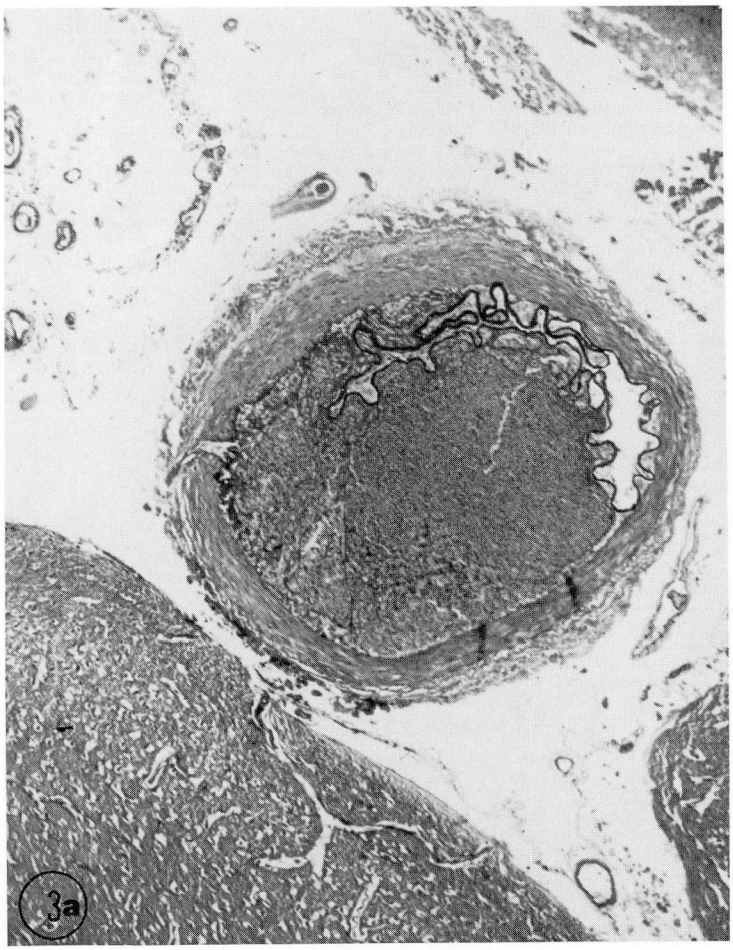

Fig. 3A. Elastica-stained histologic section of the left middle cerebral artery (LMCA) showing subintimal hematoma between the intimal and medial layers, causing collapse of the lumen and creating a false lumen (×260).

The intramural hematoma caused collapse of the arterial lumen and created a false lumen (*Fig. 3*). The internal elastic lamina was focally disrupted and displaced. No tear in the intima could be identified. No inflammation, medial necrosis, or cystic degeneration were present in the arterial walls. Sections of the left cerebral hemisphere showed changes consistent with a recent ischemic infarction in the distribution of the LMCA and LACA.

For ultrastructural studies, formalin-fixed segments of anterior and middle cerebral arteries were obtained. Corresponding arterial segments from a 27-year-old male adult were used as a control. The specimens were osmicated, embedded in Spurr resin, sectioned, and stained as routine electron microscopy specimens. Toluidine-blue-stained 1-μm thick sections (*Fig. 4*) demonstrate differences between patient and control. In the patient, there is loss of the endothelial cell layer, as well as abnormalities within the medial layer. Separation of the elastica from the media, decreased cellularity, and defective, acellular spaces are present. Electron microscopy (*Figs. 5* and *6*) shows that absence of the endothelial cell lining is a constant finding, with the internal elastica *internally* covered by collagen fibrils. These changes are not present in the control. The most striking findings are degenerative changes and calcium deposits in smooth muscle cells immediately under the elastic lamina. Many defective spaces are sparsely filled by collagen fibrils, probably corresponding to the site of pre-existing smooth muscle cells (*Fig. 7*). Many scattered smooth muscle cells are present within the control internal elastica (*Fig. 5*, arrows).

Discussion

Although this patient's lesion would best be described as a dissecting intramural hematoma,[3] the term "cerebral dissecting aneurysm" (CDA) is entrenched in the literature and is a misleading descriptive term for the changes the lesions typically manifest.[4,5] CDA is relatively uncommon. Since 1915,[6] approximately 40 cases have been

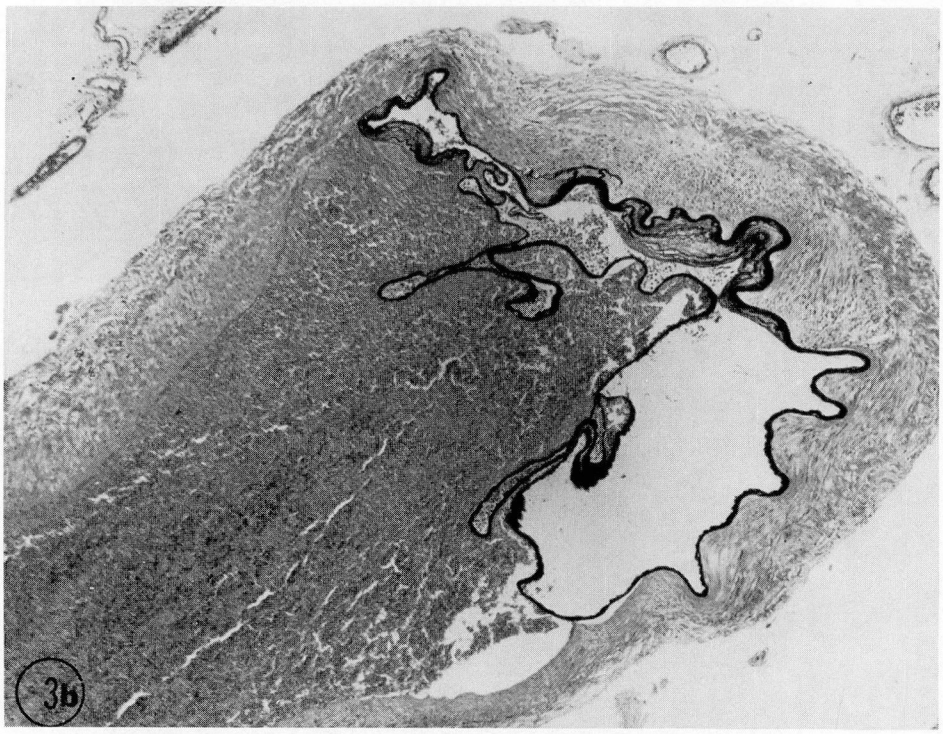

Fig. 3B. Section of the LMCA showing displacement and irregularities of the internal elastic lamina (IEL) (×1040).

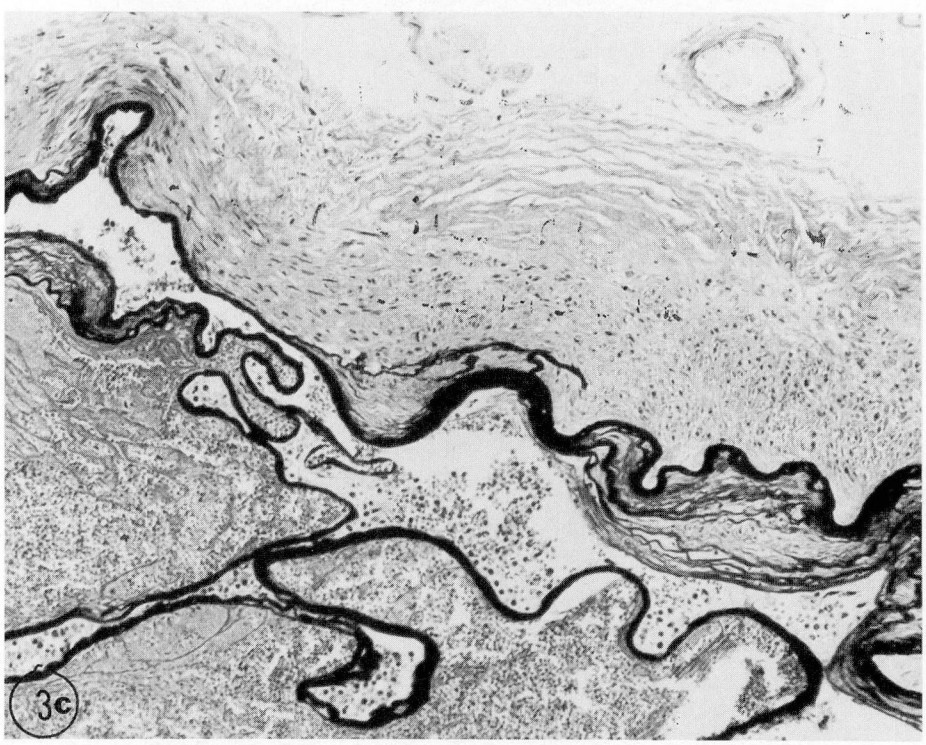

Fig. 3C. Higher magnification of **B** showing irregularities, focal fraying, and reduplication of the IEL (×2600).

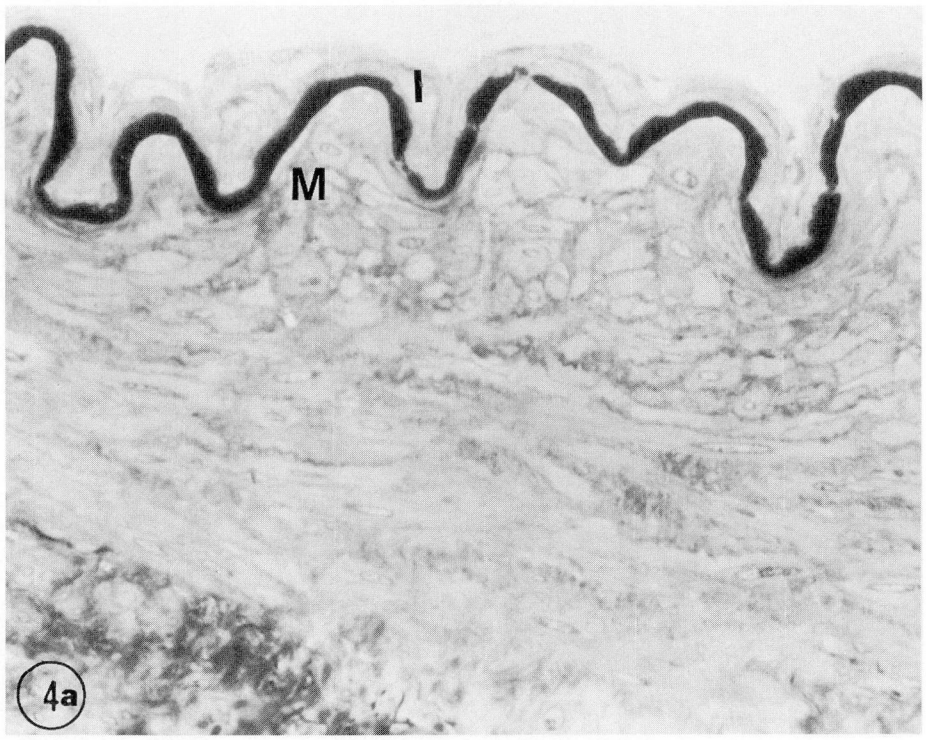

Fig. 4A. Toluidine-blue-stained semithin section of control artery demonstrating intima (*I*) with endothelial cell lining and media (*M*) with tightly packed smooth muscle cells.

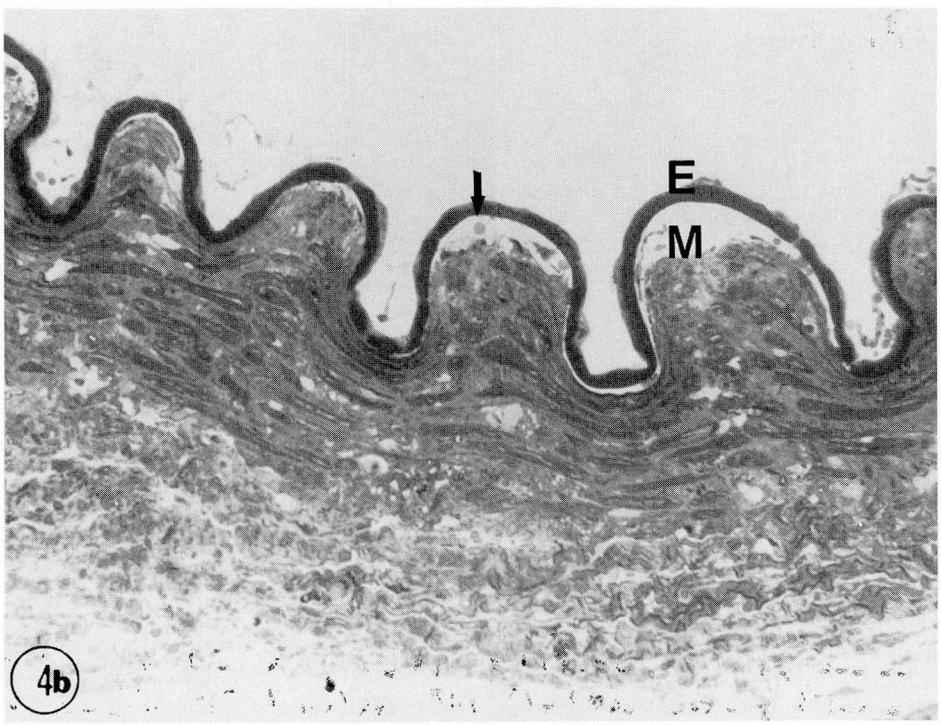

Fig. 4B. Toluidine-blue-stained semithin section of patient's left middle cerebral artery showing loss of the endothelial cell layer, separation of the elastica (*E*) from the media (*M*), with a red blood cell (arrow) in the space (×5200).

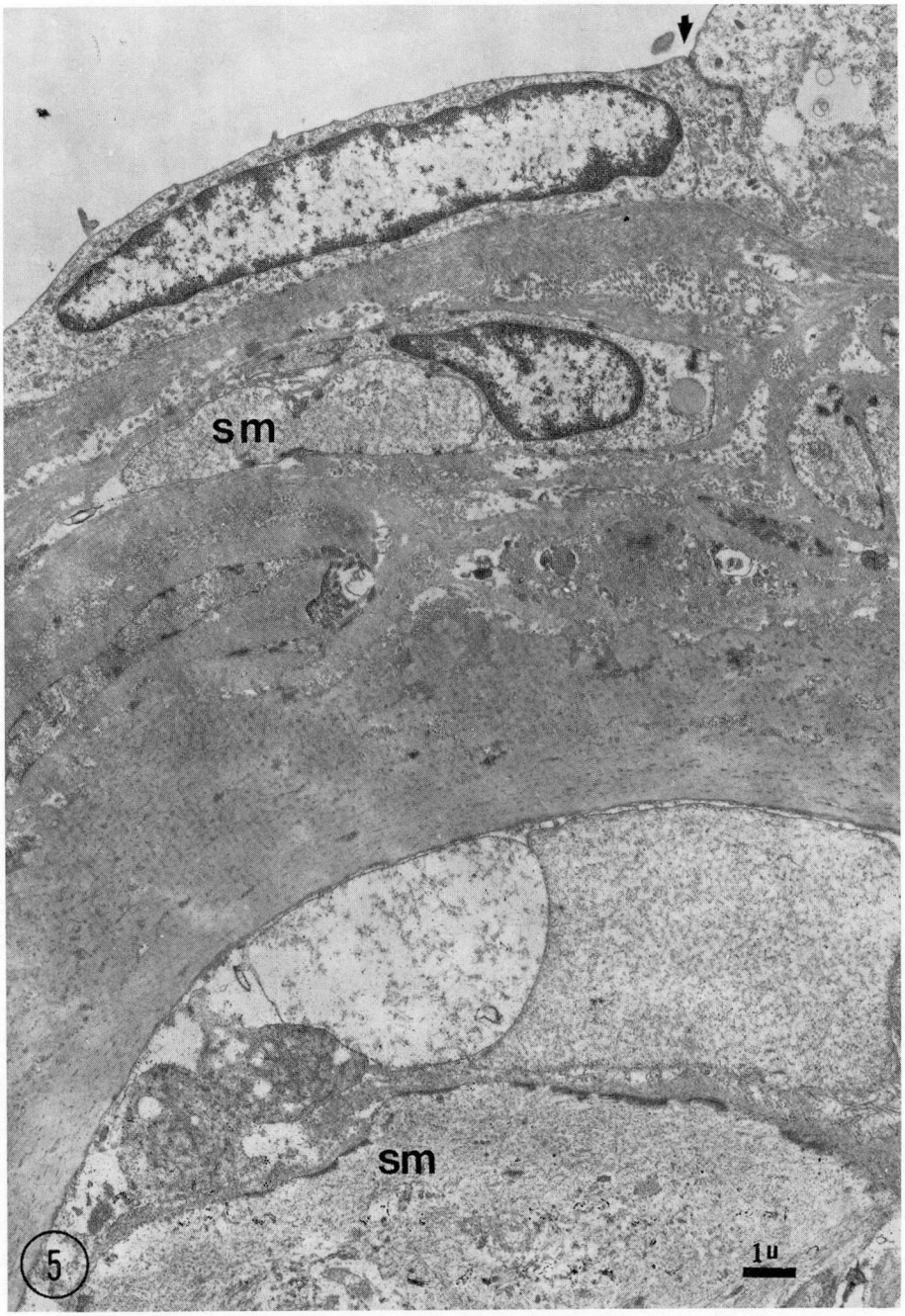

Fig. 5. Electron micrograph of control middle cerebral artery showing a tight junction between endothelial cells (arrow) and smooth muscle cells (*SM*) on both sides of the elastica (×6400).

reported in the literature.[7] Characteristic clinicopathologic features include: occurrence in young patients with an age peak between 20 and 30 years; acute onset in previously healthy persons without any predisposing risk factors for stroke; a subintimal dissection plane, instead of medial or submedial plane as seen in extracranial dissection; primary intimal damage with subsequent subintimal dissection by blood; and clinical presentation as an acute cerebral infarction, the middle cerebral arteries being most commonly involved.[8–11] Multiple etiologic factors and patho-

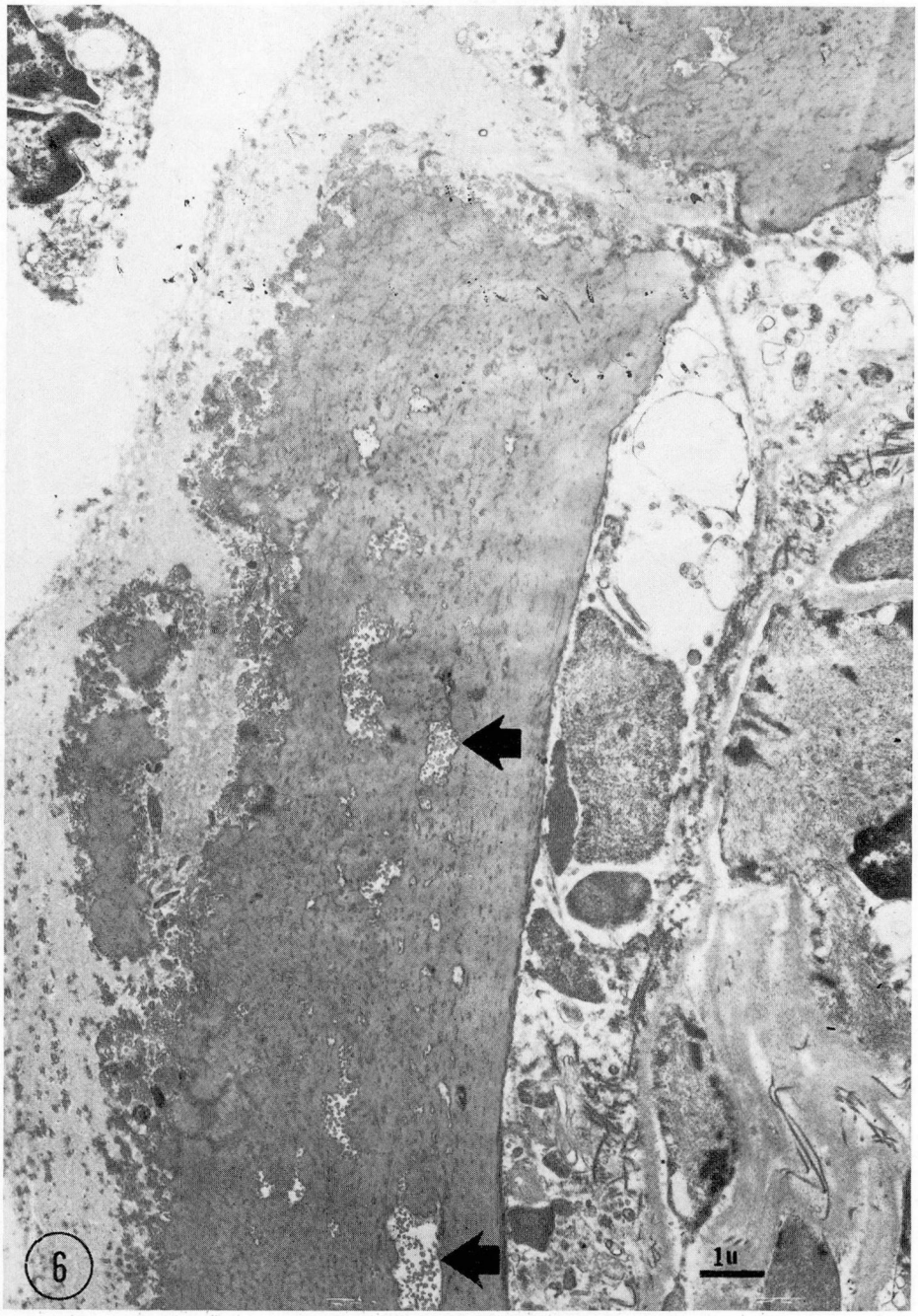

Fig. 6. Electron micrograph of patient's left middle cerebral artery showing loss of endothelial cell lining and replacement by collagen fibrils, and defective spaces within the internal elastic lamina containing collagen fibrils (arrows) without smooth muscle cells (×6400).

genic mechanisms have been proposed, including syphilitic arteritis, mucoid or cystic medial arterial degeneration, and congenital defects.[12–14] A few cases of dissection have been associated with atherosclerosis, allergic arteritis, and migraine headaches.[4,5,15] Reports of CDA secondary to trauma have emphasized shearing forces and blood pressure fluctuations following trauma.[16,17] These act upon pre-existing congenital weaknesses in the internal elastic lamina to produce the dissection. In most cases, however, no specific cause for pathologic change has been discussed.[9]

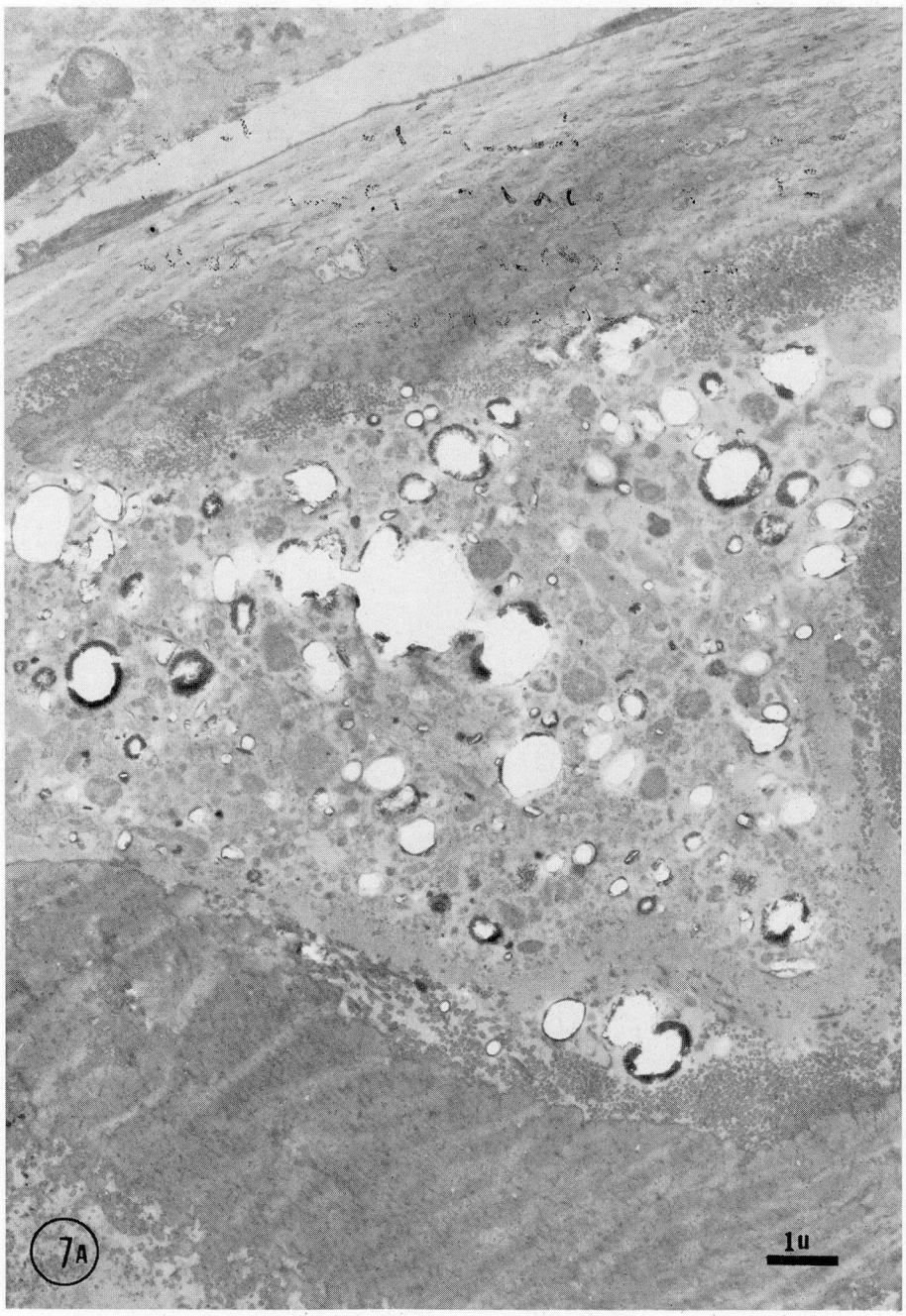

Fig. 7A. Patient's left middle cerebral artery (LMCA) showing defective spaces within the internal elastic lamina (IEL), sparsely filled by collagen fibrils, cell debris, and calcium deposits (×9200).

Reported cases have a greater than 75% mortality rate; most patients die within one week of onset of symptoms secondary to massive cerebral edema with herniation.[2,18]

In the present case, no specific etiology for the intracranial arterial dissection could be established. Multiple factors possibly related to the pathogenesis in the present case include: the patient's migraine history and family history of migraine; history of trauma, although uncertain; and preceding alcohol intake. We are left with these three factors, which may have acted together or independently to produce or aggravate an intimal injury or to weaken the arterial wall,

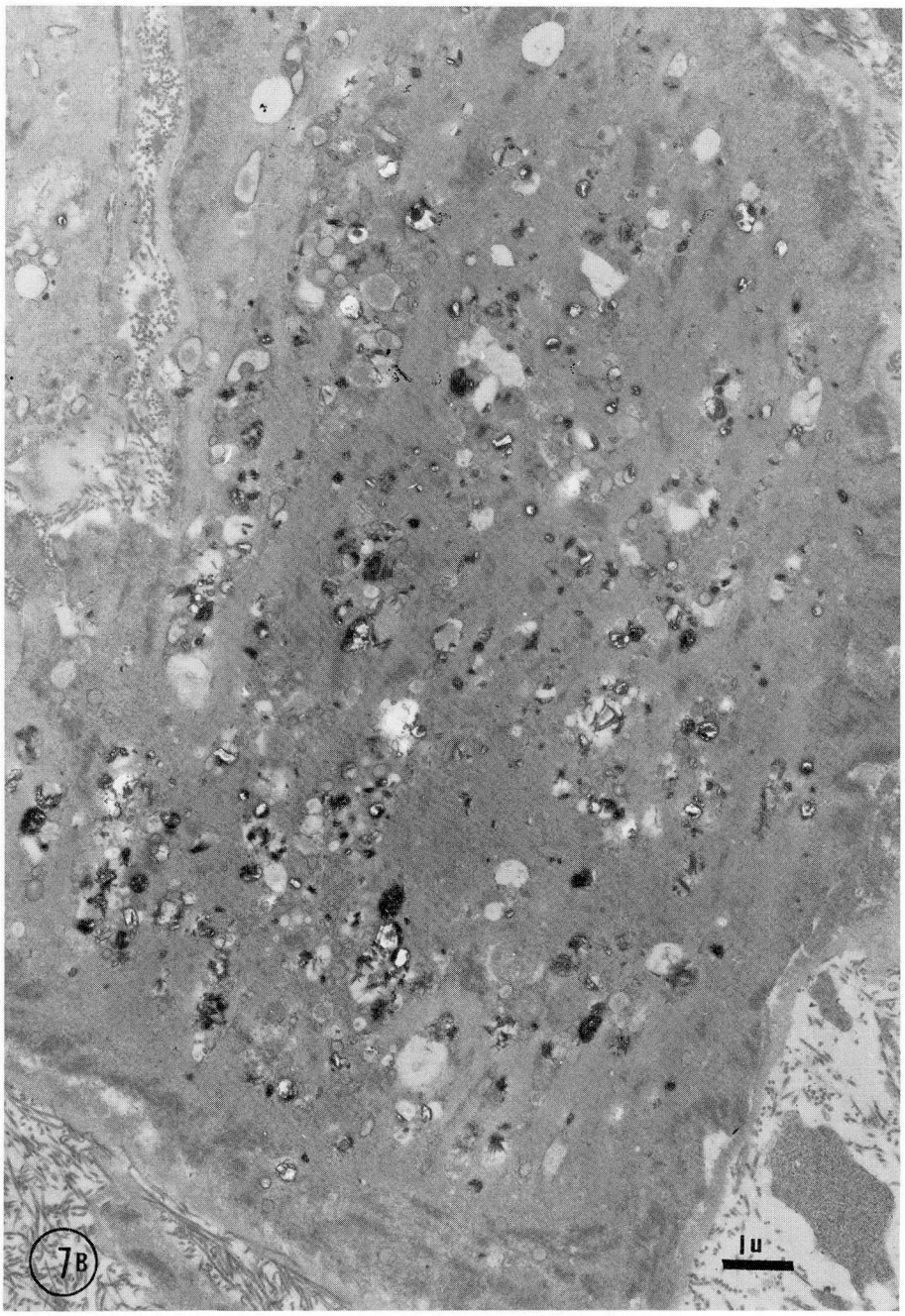

Fig. 7B. Patient's LMCA showing degenerative changes and calcium deposits within a smooth muscle cell underlying the IEL (×9200).

thus predisposing a previously healthy 23-year-old white female to a spontaneous arterial dissection.

Recent studies have found occasional alcohol intoxication and heavy drinking to be risk factors for ischemic brain infarction in young adults.[19,20] In one study, acute alcohol intoxication preceded 40% of cerebral infarctions in young adults.[20] Both occasional ethanol intoxication and chronic heavy drinking were found to increase the risk of ischemic brain infarction. The presumed mechanism is alcohol-induced alterations in coagulation, cerebral dysautoregulation, or cardiac dysrhythmias with embolism.[19] Endothelial cell injury should be considered, in view of the de-endothelialized arteries in the present case.

Farrell et al[21] studied seven patients with fatal intracranial arterial dissections. In three cases the dissection plane was between the internal elastic lamina and media. In all cases an intimal/elastic lamina tear was identified. The elastic lamina was forced into the vessel lumen by a dissecting hematoma. This resulted in vessel occlusion, usually with superimposed vessel thrombosis. These authors believe that all intracranial dissecting hematomas originate within the vessel lumen and extend for a variable distance through the intima and elastic lamina into the media. Factors that determine the subsequent course of the dissection include systolic blood pressure, vessel location, and the presence of underlying vasculopathy. In their patients lacking primary vasculopathy other etiologies considered included vessel wall weakening due to congenital gap defects in the internal elastic lamina, physical exercise, and trauma.

In our case, there may have been an inherent defect in the elastic layer that was obscured by the progression and extension of the dissecting subintimal hematoma involving the middle and anterior cerebral arteries and their major branches. In order to develop a subintimal hematoma, the internal elastica must be disrupted. The vulnerable spot(s) may result from degenerated smooth muscle cells within the elastica layer, visualized as empty spaces with collagen fibrils. Degenerative changes and calcium deposits in subintimal smooth muscle cells tend to suggest an acquired injury to smooth muscle cells rather than a developmental defect. To our surprise many scattered smooth muscle cells were present in the subendothelial and elastica layer of the control vessel (*Fig. 5*, arrows); they were lost and replaced by defective spaces in our patient's artery, suggesting also the smooth muscle cell as the primary site of injury.

Histopathologic findings previously reported in CDA include reduplication, absence, fraying, and splitting of the internal elastica as shown in *Figure 3C*. Such an alteration is frequently accompanied by focal thickening of the smooth muscle coat, as show in *Figure 3B*, which may mimic the "intimal cushion" previously described in cases of CDA.[9] Whether these changes, previously described in saccular aneurysms, reflect congenital abnormalities or are within normal range is questionable. In this context the case reported by Wolman[5] in 1959 is remarkable; a small saccular aneurysm was found at the origin of the CDA.

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