Rupture of Atheromatous Plaque as a Cause of Thrombotic Occlusion of Stenotic Internal Carotid Artery

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We analyzed the clinical profiles and autopsy findings of five patients who died shortly after developing cerebral infarction following thrombotic occlusion of the internal carotid artery. In all five cases, thrombotic occlusion was caused by rupture of the fibrous lining over the gruel of atheroma at the origin of the internal carotid artery showing tight stenosis of the lumen. The mean±SD shorter diameter of the lumen at the site of occlusion was 1.5±0.4 mm. Our results show that an internal carotid artery with tight stenosis of the lumen by atheroma containing gruel harbors a risk of thrombotic occlusion, which may give rise to cerebral infarction by artery-to-artery embolism or by reduced cerebral perfusion. (Stroke 1990;21:1740-1745)

Although plaque morphology of patients with atherosclerotic disease of the internal carotid artery (ICA) has been evaluated by clinical means such as angiography, B-mode scanning, and Doppler ultrasonography and by histologic examination of carotid endarterectomy specimens,1 there are only a few reports analyzing mechanisms of thrombotic occlusion of the ICA in patients who died shortly after the occlusion.2,3 Postmortem study, which enables us to examine the entire length of the extracranial and intracranial cervicocephalic arteries and the brain, is a golden opportunity to analyze plaque complication leading to thrombotic occlusion of the ICA and the mechanism for occurrence of stroke. We had previously reported a patient with recent thrombotic occlusion of a stenotic ICA due to rupture of the plaque.2 We extensively reviewed all the autopsy cases in our hospital and found four more patients with recent thrombotic occlusion of the ICA, which urged us to report the clinical features and postmortem pathologic findings of the five patients to add to the body of knowledge that would influence the formulation of a treatment plan.

Subjects and Methods

Among 1,550 patients autopsied in the National Cardiovascular Center from 1977 to 1988, ICA occlusion was found in 48. Of the 48 patients, five died ≤60 days after developing thrombotic occlusion of an atherosclerotic ICA, 16 (including one with a recent thrombus on the other side [case 2 in this report]) had an atherosclerotic ICA occluded by organized thrombi, 26 had an ICA occluded by fresh or organized thromboemboli of cardiac origin, and two (one suffering from Behçet's syndrome and the other from aortitis syndrome) had an ICA occluded by organized thrombi. We analyzed the clinical profiles and autopsy findings of the five patients with recent thrombotic occlusion of the ICA. These patients comprised three men and two women aged 61-78 (mean 69) years (Table 1).

At autopsy, the brain and extracranial arteries were removed and fixed in 10% formalin. After fixation, the arteries at the base of the brain and the extracranial arteries were decalcified in 45% formic acid in 10% sodium citrate solution for 2 days, then histologically examined at approximately 3-mm intervals with hematoxylin and eosin staining and other methods as needed.

The clinical and pathologic features of case 5 have been reported previously.2

Results

Table 1 summarizes the profiles of the five patients. All were hypertensive, and case 1 had diabetes mellitus. Case 2 experienced right hemiparesis 7 years before the last stroke and dysarthria lasting for several days 10 months before the last stroke, case 4 experienced a single transient ischemic attack consisting of left hemiparesis 9 days before the last stroke, and case 5 developed cerebral infarction due to occlusion of a cortical branch of the left middle
TABLE 1. Profiles of Five Patients With Thrombotic Occlusion of Internal Carotid Artery

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Survival after last stroke (days)</th>
<th>Cerebral infarct</th>
<th>Vascular territory</th>
<th>Nature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>M</td>
<td>57</td>
<td></td>
<td>R MCA prefrontal branches</td>
<td>Hemorrhagic</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>M</td>
<td>7</td>
<td></td>
<td>B ICAs</td>
<td>Pale</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>F</td>
<td>13</td>
<td></td>
<td>R MCA</td>
<td>Pale</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>M</td>
<td>56</td>
<td></td>
<td>R MCA</td>
<td>Pale</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>F</td>
<td>8</td>
<td></td>
<td>L MCA</td>
<td>Pale</td>
</tr>
</tbody>
</table>

M, male; F, female; R, right; L, left; B, bilateral; MCA, middle cerebral artery; ICA, internal carotid artery.

cerebral artery (MCA) 22 months before the last stroke.

No anticoagulation or antiplatelet therapy was given to the patients before or after the stroke, except for case 4, to whom 0.75 g aspirin/day was begun 47 days after the last stroke. This patient died of bleeding from a gastric ulcer 9 days after the initiation of aspirin treatment. Case 1 died of congestive heart failure and cases 2, 3, and 5 of tentorial herniation due to cerebral infarction.

The onset of the last stroke was abrupt with maximal deficit at onset in cases 1, 2, and 5, whereas onset showed a progressive course over hours in cases 3 and 4.

In case 1, angiography performed shortly after the onset of stroke demonstrated occlusion of the right ICA. Although the right MCA trunk was filled by collateral blood flow crossing the anterior communicating artery and from the right posterior communicating artery, the right MCA prefrontal branches were occluded. At autopsy, however, such occlusion was not demonstrable by histologic study of the corresponding branches supplying the area of hemorrhagic infarction. Thus, reopening of an artery-to-artery embolism to the prefrontal branches of the right MCA from the occluding thrombus formed at the origin of the right ICA (Figure 1) was considered to be a mechanism of the stroke.

In case 2, angiography performed 3 days after the onset of stroke demonstrated occlusion of both ICAs at their origins. Although there was some retrograde collateral filling to the leptomeningeal branches of the right MCA and anterior cerebral artery, no collateral blood flow was observed in the left ICA territory. At autopsy 7 days after the stroke there was a large pale infarct of both ICA areas and thrombotic occlusion of the ICA on both sides. The left ICA showed fresh thrombotic occlusion (Figure 2), whereas the right ICA was occluded with an organized thrombus. The posterior communicating arteries were bilaterally small. The infarct was considered to have been caused by diffuse ischemia of the bilateral ICA areas due to failure of collateral blood flow.

In case 3, occlusion of the right common carotid artery was shown by angiography performed 9 days after the onset of stroke. Cross-filling of the right MCA from the left ICA was observed but delayed. Histologic study at autopsy showed that thrombotic occlusion due to rupture of the plaque extended longitudinally 6 mm from the distal end of the right common carotid artery to the origin of the ICA (Figure 3). However, the distal ICA and the right

FIGURE 1. Case 1. A: Serial cross-sectional slices as observed from proximal surface of right internal carotid artery (ICA). Lumen of ICA is occluded at levels c, d, and e. Bar=0.5 cm. B: Rupture (between arrows) of fibrous lining (asterisks) over gruel is seen at origin of ICA immediately distal to flow divider between levels c and d. T, thrombus; G, gruel of atheroma; E, external carotid artery. Elastic van Gieson's stain. Bar=2 mm.
MCA were patent. In addition, the left ICA showed 90% stenosis at the origin due to atherosclerosis. Thus, infarction of the area supplied by the right MCA was suggested to have been caused by failure of collateral blood flow, though the possibility of reopening of an artery-to-artery embolism from the thrombus occluding the right ICA is not entirely excluded.

Autopsy of case 4 showed a pale infarct of the right MCA area. The proximal portion of the right ICA was occluded with a thrombus (Figure 4), while the distal ICA and right MCA were patent. There were stenotic atherosclerotic lesions throughout the cerebral arteries, and the posterior communicating arteries were bilaterally small. Reduced cerebral perfusion due to acute thrombotic occlusion of the ICA was suggested to have been responsible for the stroke.

In case 5, angiography performed 22 months before the last stroke demonstrated occlusion of a cortical branch of the right MCA and severe stenosis of the origin of the left ICA. The patient developed a neurologic deficit 8 days before death. Autopsy revealed fresh thrombotic occlusion of the left ICA that was similar in histology to the thrombi occluding the left MCA trunk. Since histologic study of serial sections of the ICA and MCA showed discontinuity of these thrombi, the mechanism of the last stroke was considered to have been artery-to-artery embolism from the thrombus occluding the ICA to the MCA trunk.

Figure 5 is a schematic drawing of the postulated mechanisms for the strokes in the five autopsied patients. In all five cases, histologic specimens of the
occluded sites of the ICAs demonstrated tight stenosis due to atheromatous plaques and rupture of the fibrous lining over the gruel of atheroma as a cause of thrombotic occlusion. The rupture of plaque occurred at and/or immediately proximal to the most stenotic portion of the ICA. In cases 1, 2, 3, and 5 the gruel was discharged into the arterial lumen and the lumen was occluded with a fibrin thrombus with some red blood corpuscles. Rupture is likely to occur at the site with a thin fibrous lining over the gruel of atheroma. Except for the areas demonstrating plaque rupture, the luminal surface of the entire ICA was devoid of ulcer crater. In cases 3, 4, and 5 fresh hemorrhage within the fibrous lining was associated with rupture of the plaque. In case 3 the hemorrhage appears to have been responsible for the plaque rupture. Calcification was seen in the plaque and vessel wall in cases 2 and 3.

The shorter luminal diameter of the ICA at the site of plaque rupture as measured in the histologic sections in cases 1–5 was 1.6, 1.9, 1.0, 1.3, and 1.8 (mean±SD 1.5±0.4) mm, respectively, and the plaque occupied 91%, 92%, 91%, 97%, and 94% (mean±SD 93±3%) respectively, of the original luminal area.

**Discussion**

In all five patients the ICA occluded with thrombi showed advanced atherosclerotic changes, with tight stenosis of the lumen. Thrombi had formed at or immediately proximal to the most stenotic site of the
artery due to rupture of the fibrous lining over the
gruel of atheroma. Cerebral infarction is considered
to have developed by artery-to-artery embolism from
the tail of the thrombi in the ICA to the ipsilateral
MCA in cases 1 and 5 and by reduced perfusion to
the area supplied by the occluded ICA with failure of
collateral blood flow in cases 2, 3, and 4.

Two major mechanisms have been proposed to
explain cerebral ischemic events in patients with
acute ICA occlusion: artery-to-artery embolism and
hemodynamic insufficiency due to failure of collat-
eral blood flow. Pessin et al4 demonstrated angiog-
ographic evidence of these two mechanisms in patients
with acute carotid stroke. Approximately two thirds
of their patients had evidence of embolism distal to
the extracranial carotid lesion, and many of the other
patients had evidence of a low-perfusion state, which
was inferred to be the mechanism of their strokes.
Our results in five autopsied patients principally
agree with that observation and provide convincing
evidence of the mechanism of stroke by virtue of
analysis of the clinical history, angiography, and
postmortem pathologic study of the entire length of
the cervicocephalic arteries and the brain.

Our study emphasizes that a carotid plaque con-
taining gruel covered by a thin fibrous lining harbors
a risk of rupture to cause thrombotic occlusion of a
stenotic ICA. Torvik et al3 histologically examined
specimens from 11 patients with recent occluding
thrombi at the carotid bifurcation to study local
factors in the vessel wall. Specimens from almost half
of the patients showed only moderate stenosis. Spec-
imens from three patients showed ulcerations, spec-
imens from one patient showed intraplaque hemor-
rhage without a fibrous lining separating the plaque
from the thrombus, and specimens from one patient
showed massive plaque rupture. Therefore, complica-
tions seen in five patients involved breakage of the
intima, but specimens from more than half of the
patients showed no complications. On the contrary,
all five patients in our series showed stenosis due to
atherosclerotic plaque and plaque rupture. The rea-
son for the difference between our results and those
of Torvik et al3 is not entirely clear. We examined
details of the clinical profiles and postmortem patho-
logic findings of the whole body of five patients who
died ≤60 days after developing cerebral infarction
following thrombotic occlusion of the ICA. We ex-
cluded patients whose ICAs were occluded with
thrombi in the absence of localized atherosclerotic
narrowing since such occlusions were categorized as
cardiembolic stroke as judged by the evidence of an
abrupt onset of focal neurologic symptoms with a
probable source of emboli in the heart and/or single
or multiple emboli to other organs.

Several authors5-8 who examined carotid endarter-
ectomy specimens have shown that intraplaque hemor-
rhage is the most important factor predicting focal
neurologic symptoms. The proposed mechanisms for
focal neurologic symptoms produced by intraplaque
hemorrhage are acute luminal narrowing due to ex-
panding intraplaque hematoma or a break in the
intima to produce local thrombus. Other authors,2,3,9-11
however, have been unable to verify these findings. In
only one of our five patients does intraplaque hemor-
rhage appear to have been responsible for plaque
rupture. Among 11 patients examined by Torvik et al,3
intraplaque hemorrhage, which narrowed the lumen
markedly and may have been important for formation
of the occluding thrombus, was seen only in one. There-
fore, these observations indicate that intraplaque
hemorrhage is not responsible for the formation of an
occluding thrombus of the ICA in most patients.

Thrombotic occlusion is recognized to occur fol-
lowing rupture of the fibrous lining of atheroma in the
coronary12,13 and cerebral14 arteries. This denotes
that thrombotic occlusion by such a mechanism may
occur in arteries with small diameters. Our results
show that even the carotid artery, ordinarily much

greater in diameter than the coronary or cerebral
arteries, would be occluded by a thrombus formed by
rupture of the fibrous lining of atheroma when
stenosis of the lumen is tight.

Antiplalet or anticoagulation therapy would have
preventive effects for thrombotic occlusion of a
stenotic ICA and stroke caused by artery-to-artery
embolism or reduced cerebral perfusion. Therefore,
randomized prospective trials of carotid endarterec-
tomy for the treatment of carotid stenosis15-17
are expected to show the extent to which antiplalet
agents plus risk factor modification affect the incidence
of thrombotic occlusion of the ICA with tight stenosis.

Acknowledgments

The authors wish to thank Drs. Masami Imakita
and Hatsue Ishibashi-Ueda for permission to study
their autopsy cases and Dr. Teruo Omae for his
suggestions in the preparation of the manuscript.

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**KEY WORDS** • arterial occlusive diseases • carotid arteries • thrombosis
Rupture of atheromatous plaque as a cause of thrombotic occlusion of stenotic internal carotid artery.
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Stroke. 1990;21:1740-1745
doi: 10.1161/01.STR.21.12.1740

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