Illustrative Teaching Cases

Section Editors: Scott Silverman, MD, and Sophia Sundararajan, MD, PhD

Carotid Stenosis
Role of Plaque Morphology in Recurrent Stroke Risk

Thananan Thammongkolchai, MD; Anum Riaz, MD; Sophia Sundararajan, MD, PhD

A 74-year-old woman with past medical history of hypertension and hyperlipidemia developed transient left arm weakness and slurred speech. Computed tomography (CT) of the head was unremarkable, and the patient was referred for outpatient workup. Magnetic resonance imaging (MRI) a few days later showed numerous small diffusion positive lesions in the right middle cerebral artery distribution. Magnetic resonance angiography revealed bilateral carotid bulb stenosis (35% to 40% stenosis on the left and 50% stenosis on the right). CT angiogram (CTA) was ordered to clarify the percentage stenosis and need for intervention. In the meantime, her aspirin dose was increased from 81 to 325 mg. She was not on a statin. Five days after the MRI, the patient awoke complaining of pixilated vision. In the emergency room, a CT of the head showed a small subacute right parietal infarct. Immediately after CT, she developed a flaccid left hemiparesis (National Institutes of Health Stroke Scale score of 7). She was not given tPA (tissue-type plasminogen activator) because of her recent stroke and was transferred to a Comprehensive Stroke Center for possible endovascular intervention. On arrival at the Stroke Center, she had a National Institutes of Health Stroke Scale score of 15 with forced gaze deviation, left homonymous hemianopsia, left hemiparesis, dysarthria, left sensory loss, and neglect. Emergent MRI/magnetic resonance angiography of the brain showed a large right middle cerebral artery infarct and an occluded right internal carotid artery. There was no significant penumbra, and therefore, revascularization angiogram (CTA) was ordered to clarify the percentage stenosis and need for intervention. In the meantime, her aspirin dose was increased from 81 to 325 mg. She was not on a statin. Five days after the MRI, the patient awoke complaining of pixilated vision. In the emergency room, a CT of the head showed a small subacute right parietal infarct. Immediately after CT, she developed a flaccid left hemiparesis (National Institutes of Health Stroke Scale score of 7). She was not given tPA (tissue-type plasminogen activator) because of her recent stroke and was transferred to a Comprehensive Stroke Center for possible endovascular intervention. On arrival at the Stroke Center, she had a National Institutes of Health Stroke Scale score of 15 with forced gaze deviation, left homonymous hemianopsia, left hemiparesis, dysarthria, left sensory loss, and neglect. Emergent MRI/magnetic resonance angiography of the brain showed a large right middle cerebral artery infarct and an occluded right internal carotid artery. There was no significant penumbra, and therefore, revascularization was not attempted. Her hospital course was complicated by cerebral edema, which was treated with hypertonic saline and aspiration pneumonia requiring prolonged intubation. She required a gastrostomy tube for feeding and was discharged to a skilled nursing facility with a National Institutes of Health Stroke Scale score of 12. At 3 months, she had a modified Rankin Scale score of 5. Stroke pathogenesis was thought to be secondary to probable plaque rupture in the right internal carotid artery with distal embolization to the right middle cerebral artery.

Discussion

Current guidelines for the management of carotid stenosis are based on the degree of vessel stenosis. The most recent guidelines issued from the American Stroke Association recommend revascularization of carotid stenosis for patients with average to low surgical risk for symptomatic patients with stenosis of >70% as identified by noninvasive imaging and symptomatic patients with 69% to 50% stenosis as identified by catheter angiogram or noninvasive imaging with corroboratory (magnetic resonance angiography or CTA) depending on patient-specific factors, such as age, sex, and comorbidities. These guidelines are based in large part on the 3 largest randomized trials, all of which were conducted in the 1990s (NASCET [North American Symptomatic Carotid Endarterectomy Trial], ECST [European Carotid Surgery Trial], and VACS [Veterans Affairs Cooperative Study program]). It should be noted that medical therapy in these studies generally consisted of aspirin alone. Given advances in medical therapy, including the use of statins and newer antiplatelet agents along with more aggressive control of risk factors, such as diabetes mellitus, hypertension, and smoking, many have called for new clinical trials that incorporate modern medical therapy to better guide treatment recommendations. CREST-2 is one such trial (The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study) aimed at testing aggressive modern medical therapy versus revascularization in asymptomatic carotid stenosis.

Although clinical trials, and thus, clinical guidelines, have focused on degree stenosis, this does not necessarily correlate with stable and unstable plaques and may not adequately determine stroke risk as illustrated by our patient. Use of plaque morphology in medical decision making regarding carotid endarterectomy/carotid artery stenting is controversial. Improved plaque imaging allows better characterization of the plaque than was possible at the time of the original carotid endarterectomy trials and may provide additional insight to aid in clinical decision making.

What Is An Unstable Plaque?

An unstable plaque has a tendency to rupture, leading to thrombus formation and subsequent embolization leading to infarction. The gold standard for classifying atherosclerotic plaque is histological. Six types of plaques are defined by their stage of development (Table and Figure). The first stage of atherosclerotic plaque formation is the deposition of macrophages and foam cells (type I). Lipids then accumulate within the plaque to the point where a fatty dot or streak can be visualized (type
II). Extracellular lipids are also deposited (type III). As plaque morphology advances, extracellular lipids become dense and more extensive forming a lipid core (type IV). At this point, the plaque is also known as atheroma. Fibrous connective tissue forms in part of the plaque (with or without a lipid core; type V). Around the lipid core, there is increased capillary proliferation and an inflammatory response, including lymphocytes and macrophages. Microhemorrhages are also seen in type V plaque. Both types IV and V are unstable and prone to fissure and rupture, forming ulcerations that expose the necrotic lipid core. A ruptured plaque (type VI) is a complicated lesion characterized by hemorrhage within the plaque and in situ thrombosis, which can lead to embolization or vessel occlusion.3

Assessing Plaque Vulnerability
A variety of noninvasive methods have been used to study plaques, including ultrasonography, MRI, CTA, transcranial Doppler, positron emission tomography/CT. Each method has unique strengths and weakness.

Ultrasonography is a powerful technique that assesses the degree of plaque stenosis and plaque morphology. Its advantages include easy accessibility, low cost, and minimal radiation exposure. Two modes of ultrasonography are used in plaque assessment, brightness (B)-mode and contrast-enhanced ultrasonography. In B-mode, carotid intima-media thickness is determined and then graded by echogenicity. In B-mode ultrasound, the gray scale median score differentiates blood (gray scale median score 0) from adventitia (gray scale median score 190), and these criteria can be used to determine plaque heterogeneity. Low GSM scores correlate with high lipid content and hemorrhage within a necrotic core.4 Heterogeneity of content is assessed using the criteria of Gray-Weale et al,5 which describes 4 plaque types ranging from a predominantly echolucent thin cap to a predominantly echogenic plaque. Contrast-enhanced ultrasonography assesses carotid lumen, plaque ulceration, and neovascularization. A microbubble contrast agent is injected intravenously and stays within the vessel not diffusing into surrounding tissues, Thus, all signals from contrast-enhanced ultrasonography are intravascular.6 Unfortunately, ultrasonography is highly operator-dependent and time-consuming, and results can be inconsistent.

High-resolution contrast MRI characterizes carotid plaque morphology and measures components, such as intraplaque hemorrhage, lipid deposition, presence of a necrotic core, and calcification. Intraplaque hemorrhage is the most important marker of plaque instability and increased risk of ischemic stroke. There is a modified American Heart Association classification of atherosclerotic plaque by MRI7 that incorporates measurements of plaque thickness, the presence of calcification, surface defects, hemorrhage, and thrombus. Multiple sequences are used to characterize plaque, including proton density–weighted fast spin echo, proton density–weighted echo planar imaging, and T2-weighted echo planar imaging, which can define lipid or necrotic core, as well

Table. Plaque Types and Components in Each Type Based on Histology3

<table>
<thead>
<tr>
<th>Components</th>
<th>Stable Plaque</th>
<th>Unstable Plaque</th>
<th>VI Complicated Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Intimal thickening</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>II Macrophage foam cells or fatty steak</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>III Preatheroma</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>IV Atheroma</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>V Fibroatheroma</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>VI Complicated Lesion</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Components</th>
<th>Stable Plaque</th>
<th>Unstable Plaque</th>
<th>VI Complicated Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Intimal thickening</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>2 Macrophage foam cells or fatty steak</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>3 Extracellular lipid accumulation or lipid core</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>4 Calcification</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5 Neovascularity</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6 Fibrous cap</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>7 Intraplaque hemorrhage</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8 Surface defect or fissure</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>9 Thrombus</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

Figure. Plaque progression from type I to VI. Numbers 1 to 9 indicate plaque components mentioned in Table.
as detect calcification. T1-weighted images and T1 gradient echo images are good for identifying intraplaque and recent hemorrhage. The fibrous cap can be seen in the time of flight sequences. A disadvantage of MRI is that it is difficult to characterize small plaques in which individual components of the plaque may be missed. High-resolution MRI is time-consuming and may be contraindicated because of claustrophobia, implanted devices, or renal insufficiency, limiting the use of gadolinium contrast.

CTA is less time-consuming and more widely available than high-resolution MRI. CTA can detect a calcified fibrous cap; however, it has limited ability to differentiate a lipid core from intraplaque hemorrhage unless the plaque is large. Newer multidetector CT and dual source CT use 2 x ray generators and detectors, significantly increasing the quality of CTA. Multidetector CT has a high resolution; however, beam hardening artifact caused by calcification limits the ability of dual source CT to differentiate between intraplaque hemorrhage and calcification. A disadvantage of CTA is increased radiation exposure relative to ultrasound and MRI.

Less commonly used methods of evaluating carotid plaque include transcranial Doppler, which can detect microemboli or high-intensity transient signals originating from an unstable plaque with overlying thrombus. Although it has a high specificity, it has low sensitivity and can be affected by multiple factors, including patient’s body habitus, operator skill, and the duration of the study. 19F-fluorodeoxyglucose positron emission tomography/CT assesses metabolism within atheroma detecting microcalcification and inflammation, which have been found to correlate with microembolic signals on transcranial Doppler.

In summary, examination of plaque morphology may provide a more nuanced assessment of stroke risk and aid in determining if patients should undergo revascularization. However, the incorporation of this information into medical decision making has not been tested in clinical trials, and guidelines are lacking.

**TAKE-HOME POINTS**

- The risk of ischemic stroke is determined not only by the degree of vessel stenosis but also by plaque morphology.
- An unstable plaque has a tendency to rupture, leading to thrombus formation and subsequent embolization causing transient ischemic attack and stroke.
- Several imaging modalities can be used to characterize plaque morphology.
- Patients with unstable plaque may need more aggressive management, regardless of the degree of stenosis.

---

**Acknowledgment**

We thank Pichet Termsarasab, MD, for helpful comments and review of the article.

**Disclosures**

None.

**References**


**Key Words:** brain edema ▪ carotid endarterectomy ▪ carotid stenting ▪ plaque morphology ▪ stroke
Carotid Stenosis: Role of Plaque Morphology in Recurrent Stroke Risk
Thananan Thammongkolchai, Anum Riaz and Sophia Sundararajan

Stroke. 2017;48:e197-e199; originally published online July 13, 2017;
doi: 10.1161/STROKEAHA.117.017779
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/48/8/e197

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/