The association between carotid artery disease and stroke has been recognized for more than a century, but the pathophysiology of ischemic events ipsilateral to carotid plaques remains uncertain. Artery-to-artery embolism is one of several mechanisms causing either transient ischemic attacks (TIAs) or stroke ipsilateral to atherosclerotic plaques. Thrombus at the site of arterial occlusion,1 atherosclerotic debris,2 and vertebral artery stenosis or occlusion3 are well-documented sources of emboli. Ulceration is a frequent finding in carotid plaques,4 but the role of ulceration as a source of artery-to-artery embolism is unclear. Controversy exists because of the difficulty in establishing a uniform definition of ulceration and because of the limited diagnostic accuracy of radiological techniques.

Little is known about the nature of embolic material released from ulcerated plaques. Grumous material is occasionally observed in carotid plaques, leading to speculation that it may enter the carotid circulation and occlude cerebral vessels. Cholesterol emboli appear in retinal vessels and usually signify ipsilateral carotid artery atherosclerosis.5 These emboli characteristically do not obstruct flow and are frequently observed without visual symptoms. Cholesterol emboli may also enter the cerebral circulation and cause TIAs.6 Fibrin-platelet thrombus forms in carotid plaques with severe stenosis. Thrombus also occurs in cavities within plaques and overlying intimal disruptions. Thrombi can be large enough to occlude intracerebral vessels and cause ischemic symptoms.

In 1968 Moore and Hall7 reported complete relief of TIAs in nine patients with ulcerated “nonstenotic” carotid artery plaques following endarterectomy. Since then, many operations have been performed because of the possible embolic potential of ulcerated plaques independent of the severity of stenosis. To justify this approach one must establish a relationship between ulcerated plaques and ischemic symptoms and demonstrate that the natural history of these lesions is sufficiently adverse to warrant the risk of endarterectomy.

**Diagnosis of Ulceration**

Many studies of ulcerated plaques appeared after the report by Moore and Hall.7 These reports are difficult to compare because definitions and methodology differed considerably. Ulceration was frequently determined by examination of plaques in the operating room or by review of photographs. After gross inspection some plaques were further examined by light microscopy. Two studies examined plaques by electron microscopy.8,9 Pathological definitions of ulcers ranged from gross pits or depressions to any microscopic break in the intima. Angiographic definitions were similarly vague and in some studies combined irregularity of the lumen with ulceration. Many authors failed to define ulceration pathologically or radiologically.

The accuracy of angiography in diagnosing ulceration has been estimated at 50–86%.10-12 This discrepancy results from differences in radiological and pathological criteria. Because ulceration is difficult to distinguish from irregularity by angiography,13 angiography tends to overestimate ulceration.14 Penetrating niches may be the most reliable radiological sign of ulceration,15 but depressions between adjacent areas of plaque or intraplaque hemorrhage have a similar appearance. Pockets of retained contrast and niches with narrow necks or overhanging edges possibly correlate better with pathological ulceration, but no studies have specifically examined these criteria. Intimal ulceration is not always seen radiologically since small ulcers and microscopic breaks do not appear on angiography. Finally, when ulceration is identified both radiologically and pathologically, the abnormal findings may not correspond to the same area of the plaque. Some authors contend that B-mode ultrasound imaging is superior to angiography for identification of plaque ulceration.15 Others find poor interobserver reliability and only 30–40% agreement between ultrasound diagnosis and pathological or radiological evidence of ulceration.16-18

The extent of ulceration necessary to produce emboli and ischemic symptoms is unknown. Intimal disruption exposes platelets to components of atheroma, causing clumping and formation of potentially embolic fragments. Intimal breaks may be detected only by light microscopy or even by electron microscopy.10 If microscopic intimal disruption produces emboli, angiography would be of no value in the detection of potentially embolic carotid lesions. In contrast, if turbulent flow in irregular areas of plaque causes thrombus formation and predisposes to emboli, pathological examination for intimal disruption would not predict occurrence of cerebral symptoms. The likelihood of thrombus formation may depend on the size or shape of a pit or depression within a plaque. These issues must be resolved before the relationship between ulceration and cerebral ischemia can be understood.
Ulcervation and Ischemic Symptoms

An association between ulcervated plaques and TIAs or stroke was first suggested by case reports of small groups of patients. Moore and Hall described four patients with TIAs and ulcervated plaques with minor stenosis in whom TIAs stopped after endarterectomy. They later expanded their series to 49 operations in 35 patients. Endarterectomy relieved symptoms in all patients with lateralsizing symptoms and in seven to ten with nonlateralsizing symptoms. Case descriptions were given only in the original report. In at least three patients, TIAs were not typical of carotid territory symptoms and may have been unrelated to the ulcervated plaque. Julian et al described four patients with ulcervated plaques and ischemic symptoms; in one the TIAs were in the vertebral-basilar territory, and in two others there was severe carotid artery stenosis or occlusion. The remaining patient had sudden onset of coma and right hemiplegia and a deeply ulcervated plaque with minor stenosis at the carotid bifurcation ipsilateral to the stroke. The ulcer contained thrombus that could have been the source of embolic material, but no information was provided concerning other potential sources such as arrhythmias or cardiac disease.

Bartynski et al reported two patients with light-headedness and dizziness who had endarterectomy and findings of microscopic ulcervation. The symptoms were possibly not related to the pathological findings. Ulcervation with minor stenosis was found in only four of 44 plaques ipsilateral to ischemic symptoms studied pathologically by Imparato et al. Three patients had a single TIA, and one had a stroke. Reports by Ehrenfeld et al and Gunning et al included several patients with stroke or TIA ipsilateral to ulcervated carotid lesions, but all had severe stenosis or occlusion. Thus, in most case reports either the symptoms were not appropriate to the ulcervated lesion, or significant stenosis was present in addition to ulcervation. A few reports suggest that ulcervated plaques can sometimes be a source of symptomatic embolism, but whether this is a frequent cause of TIAs and stroke remains uncertain.

Examination of plaque morphology in large groups of patients with symptomatic or asymptomatic carotid disease provides additional information about the relationship of ulceration to cerebral ischemia. Since case descriptions are not provided, the accuracy of diagnosis must be assumed. Ulcervation is found in 40–50% of symptomatic carotid plaques. In a pathological study in which plaques were examined in situ for ulceration by the surgeon, photographed, and subjected to microscopic examination, Imparato et al found no difference in the frequency of ulceration in symptomatic and asymptomatic patients. However, ulcervation was somewhat more common in plaques ipsilateral to “focal” symptoms than in asymptomatic plaques (51% vs. 41%). Houser et al identified ulcervation on angiography and later confirmed the findings by examination of surgical specimens. Ulcerations occurred in 49% of plaques ipsilateral to TIAs, 45% ipsilateral to strokes, and 33% of asymptomatic plaques. The importance of ulcervation versus stenosis cannot be differentiated on the basis of these figures since plaques with all degrees of stenosis were considered.

When only plaques with <70% stenosis were included, Imparato et al found ulceration in 55% of symptomatic plaques and 41% of asymptomatic plaques. In lesions with <40% stenosis, the corresponding figures were 50% and 11%, but the number of plaques studied in the last group was quite small. In this study plaques with minor degrees of stenosis were somewhat more likely to be ulcervated when symptomatic than asymptomatic, but half of the plaques ipsilateral to ischemic symptoms were not ulcervated. Houser et al found ulceration more common in asymptomatic than symptomatic patients when only plaques with <85% stenosis were included. Many asymptomatic plaques are ulcervated, and many symptomatic plaques are not. No compelling evidence supports a strong association between ulceration in carotid plaques and ischemic symptoms.

Thiele et al reviewed arteriograms of 104 symptomatic patients with carotid territory ischemia. Irregularity was included in the definition of ulceration. More than half the ulcervated or irregular lesions also had stenosis of >50%. Eighty-four percent of all patients with TIAs had ulcervated or irregular lesions, but only 41% of symptomatic lesions with <50% stenosis were ulcervated or irregular. In patients with stroke, 62% of plaques were ulcervated or irregular, but when only stenosis of <50% was included, these findings occurred in only 17%. Thus, the majority of TIAs and strokes in patients with <50% stenosis occurred without ulceration shown by angiography. Ulcervation was more common with greater degrees of stenosis, but the coexistence of stenosis obscures the relationship between ulceration and symptoms.

Ulcervated Plaques and Prognosis

Ulcervated plaques may be discovered during investigation for ischemic symptoms in the artery ipsilateral or contralateral to symptoms. Only one study examined the risk of recurrent stroke or TIA in symptomatic patients with ipsilateral ulcervated plaques. This retrospective study included 33 ulcervated lesions with <50% stenosis and 12 with >50% stenosis. Mean follow-up was 15.5 months, and only events ipsilateral to the carotid lesion were recorded. One stroke occurred in a patient with ulceration and <50% stenosis. Fourteen others had only TIAs: two with >50% stenosis and 12 with <50% stenosis. In patients with ischemic symptoms and ulcerated plaques, the risk of ipsilateral stroke in 15 months’ follow-up was small. TIAs in the study occurred more frequently but were not followed by strokes.

Studies of prognosis of asymptomatic “nonstenotic” ulcervated plaques provide conflicting results. Moore et al reviewed the clinical course of 72 ulcervated lesions with <50% stenosis in 67 patients. Ulcerations were divided into three groups on the basis of their radiological appearance: type A ulcers were small minimal excavations, type B large obvious excavations, and
type C ulcers with multiple cavities or cavernous appearance. Although these definitions attempted to standardize nomenclature, terms such as "large" and "cavernous" are not specific enough to avoid variations in interpretation. Forty ulcers were type A and 32 type B or C. In follow-up of up to 7 years (mean 2.5 years), 10 strokes occurred ipsilateral to type B or C ulcers, and one occurred ipsilateral to a type A ulcer. The stroke rate for type B and C ulcers combined was 12.5% per year. A few strokes occurred in the first year of follow-up, but then no further events were recorded until 54 months. Between 60 and 78 months the cumulative incidence of stroke increased from 25% to 87% of the patients at risk. A small number of patients remained at risk late in the follow-up period so that a few events produced a dramatic increase in stroke incidence. Significant progression of stenosis could occur in 5–7 years although the authors later indicated that repeat angiography at the time of events during follow-up in two thirds of patients with type B and C ulcers showed that they remained ulcerated with minor degrees of stenosis. The difference between the stroke-free survival curve for type A ulcers and type B and C ulcers did not become statistically significant until 66 months of follow-up. No TIA occurred in the entire series.

Dixon et al later expanded these data by including 74 ulcerated lesions followed at another hospital. In this larger series the annual stroke rate for type A ulcers was 0.9%, type B 4.5%, and type C 7.5%. The same precipitous increase in ischemic events occurred between 5 and 7 years as in the previous study. The difference in stroke-free survival curves for type A and B ulcers again was not statistically significant until 72 months, and for type A and C ulcers 78 months. Forty percent of the strokes occurred in the first 24 months, indicating some early potential for embolization. Ten patients in this series had TIA, but none preceded a stroke.

Kroener et al found a more benign prognosis for asymptomatic ulcerated plaques with minor stenosis. In a retrospective review of 91 ulcerated plaques, only one stroke occurred in 79 patients in a mean follow-up of 36 months (range 1–7 years). Four other patients had TIA. This study differs from the previous series in that only 24 type B ulcers were included and no type C ulcers. Thus, the majority of the lesions were type A, a group that had a relatively benign prognosis in the other studies. Nevertheless, a dramatic increase in stroke rate at 5–7 years was not seen in the small group of type B ulcers. Harward et al later extended the mean length of follow-up in this group of patients to 54 months. Only one additional patient had a stroke, and this occurred after 84 months of follow-up.

Grotta et al reviewed the clinical course of 20 asymptomatic ulcerated lesions with <50% stenosis followed for a mean of 15.5 months. Only one TIA occurred and no strokes were seen during an average follow-up of 6 years.

Most ulcerated plaques with minor degrees of stenosis have a benign prognosis. The stroke risk for type C ulcers may be higher, but this is delayed several years and may reflect a change in the morphology of the lesion. In addition, the distinction between "large" ulcers (type B) and those with a "cavernous appearance" (type C) may not always be clear. Evidence that surgery improves on the natural history is lacking. At least one study suggests perioperative stroke rates may be higher for ulcerated lesions because of the potential for intraoperative emboli.

Conclusions

The importance of ulceration in carotid plaques as a cause of cerebral ischemic symptoms remains controversial. Ulceration is frequently found in plaques ipsilateral to ischemic symptoms but usually in association with significant stenosis. When stenosis is minor, ulceration is found with nearly equal frequency in symptomatic and asymptomatic plaques. In addition, nonulcerated and ulcerated plaques occur with equal frequency ipsilateral to ischemic symptoms. The subsequent stroke risk for small ulcerations in plaques with minor stenosis is low and probably does not warrant surgical intervention. Diagnosis of ulceration by angiography or B-mode ultrasound imaging is not very accurate. Thus, it is difficult to base therapeutic decisions aimed at reducing the potential for artery-to-artery emboli on these tests. Further information is needed about the nature of the embolic material responsible for ischemic symptoms and local factors predisposing to thrombus formation at the site of atherosclerotic plaques.

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