Natural History of Nonstenotic, Asymptomatic Ulcerative Lesions of the Carotid Artery

A Further Analysis

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Indications for operation in symptomatic disease of the carotid bifurcation have been well identified, but surgery for asymptomatic carotid lesions remains controversial. As carotid endarterectomy becomes safer, the indications for operation broaden. Understanding the natural history of asymptomatic lesions is important in establishing the role of operation and subsequent management. This report, an expansion of a previous study, attempts to further define the natural history of asymptomatic, nonstenotic ulcerative lesions of the carotid bifurcation.

Two previous reports have dealt with this subject. The first, a retrospective review of the clinical course of 72 untreated, asymptomatic, nonstenotic ulcerations of the carotid bifurcation, showed a worse prognosis for stroke risk in patients with large and cavernous (B) or compound (C) ulcers than in a similar group who underwent operation for symptomatic, nonstenotic, ulcerative lesions. Small (A) ulcers were shown to have a relatively benign prognosis. A subsequent report by Kroener and colleagues retrospectively reviewed the natural history of 91 A and B ulcers followed at the University of California Hospitals, San Diego, demonstrating a benign course for both sizes.

To help resolve these conflicting data, we have expanded our series by retrospectively reviewing a ten-year experience at UCLA Hospital (Los Angeles) with patients shown to have nonstenotic, asymptomatic ulcers who were not operated on. These results were combined with our previous data to provide a representative series.

PATIENTS AND METHODS

Carotid arteriograms obtained at UCLA Hospital during the past ten years were reviewed, and those showing nonstenotic ulcerative lesions were selected. The ulcerative plaques were then classified by the radiologist into three categories as previously described. An A ulcer was defined as a minimal discrete excavation within an atherosclerotic plaque, B ulcer as a large, obvious excavation, and a C ulcer as one having multiple cavities or possessing a cavernous appearance on roentgenogram.

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The appropriate medical records were then reviewed, and cases with a history of cerebrovascular symptoms related to the side of the lesion were eliminated, thus retaining cases with asymptomatic, nonstenotic ulcerative lesions of the carotid bifurcation demonstrated by angiography. Angiography had initially been performed to evaluate the contralateral carotid artery or to study an asymptomatic carotid bruit.

All surviving patients were contacted, and follow-up data were obtained. Follow-up on those who had died was obtained from the medical records department, the patients' former physicians, and their relatives. End points of analysis were neurologic events, including territorial transient ischemic attacks (TIAs) or strokes appropriate to the lesion being followed, whichever occurred first. Those in whom TIA was the first symptom were excluded from further follow-up because they were no longer in the asymptomatic category. Data on mortality were also documented and analyzed.

The UCLA Hospital data were then combined with previously reported data from the series accumulated at the San Francisco Veterans Administration Hospital, to increase our sample size and improve statistical validity of results.

The combined data were analyzed by life-table methods that included determination and t test analysis of SEMs and comparison of groups by age using the t test. The annual stroke rate and death rate were determined by averaging their respective six-month interval occurrence.

The review at UCLA Hospital yielded 74 cases of asymptomatic, nonstenotic ulcerative lesions of the carotid bifurcation, of which 34 were in women and 40 in men. Data from this review were combined with the data from 67 patients reviewed at the San Francisco VA Hospital, of whom four were women. The combined groups comprised 141 patients who had appropriate ulcerative lesions in 153 carotid arteries. When subdivided according to ulcer type, there were 72 carotid arteries with type A ulcerations, (mean patient age, 64 years), 54 carotid arteries with type B ulcerations, (mean age, 68 years), and 27 carotid arteries with type C ulcerations (mean age, 66 years).

**RESULTS**

The two end points, death and stroke, were analyzed separately for the three ulcer categories. There was no significant difference in age among the three groups ($P < .05$). Patients were followed up for as long as ten years, and the follow-up information was separated into six-month intervals for purposes of life-table analysis.

**Mortality**

Interval survival rates were calculated for patients in each of the three ulcer groups and then displayed in graph format (Fig 1). Survival rates among patients with type A and type B ulceration were similar. These curves were also similar to survival rates in an age-adjusted normal population. However, those with type C ulceration had a distinctly worse survival curve than patients in the other two groups.

To determine the statistical significance of these differing survival rates, SEMs were calculated for each follow-up interval for each ulcer type, and then analyzed. When groups A and C were compared, there was a significant difference in survival ($P < .001$), starting at 12 months and lasting throughout the entire follow-up interval. When comparing groups B and C, the survival rate was significantly worse ($P < .05$) for group C between 12 and 24 months and between 36 and 48 months. There was no significant difference in survival rates among groups A and B and an age-adjusted normal population. The annual mortality rates were calculated for each ulcer group. For patients with type A ulceration it was 3.4%; with type B, 5.2%; and with type C, 8.6% (Table 1). During the overall period of study, 15% of patients with type A ulcers, 25% with type B, and 48% with type C died (Table 1).

Myocardial infarction was the predominant cause of late mortality, as shown in Table 2. Seven deaths were due to stroke, of which three occurred in patients with type A ulceration, all involving the cerebral hemisphere opposite the asymptomatic lesion. These patients had a history of
Fig 2.—Stroke-free survival rates. Ulcers were categorized as follows: A indicates minimal discrete excavation within atherosclerotic plaque; B, large, obvious excavation; and C, multiple cavities or cavernous appearance on roentgenogram.

Table 3.—Neurologic Complications as a Function of Ulcer Size

<table>
<thead>
<tr>
<th>Ulcer Size*</th>
<th>No. of Ulcers</th>
<th>No. of Strokes</th>
<th>No. of TIAs†</th>
<th>Total No. of Initial Neurologic Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>72</td>
<td>2</td>
<td>3</td>
<td>5 (7)</td>
</tr>
<tr>
<td>B</td>
<td>54</td>
<td>10</td>
<td>3</td>
<td>13 (24)</td>
</tr>
<tr>
<td>C</td>
<td>27</td>
<td>5</td>
<td>4</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Total</td>
<td>153</td>
<td>17</td>
<td>10</td>
<td>27</td>
</tr>
</tbody>
</table>

*A indicates a minimal discrete excavation within an atherosclerotic plaque; B, a large, obvious excavation; and C, multiple cavities or a cavernous appearance on roentgenogram.

†TIA indicates transient ischemic attack.

Table 4.—Mean Ages of Patients According to Ulcer Size

<table>
<thead>
<tr>
<th>Ulcer Size*</th>
<th>No. of Patients</th>
<th>Mean Age, yr</th>
<th>Mean Age of Stroke Patients, yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>66</td>
<td>64</td>
<td>69</td>
</tr>
<tr>
<td>B</td>
<td>48</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>C</td>
<td>27</td>
<td>66</td>
<td>62</td>
</tr>
</tbody>
</table>

*A indicates a minimal discrete excavation within an atherosclerotic plaque; B, a large, obvious excavation; and C, multiple cavities or a cavernous appearance on roentgenogram.

prior stroke ipsilateral to the side of the eventual fatal stroke. Four patients with type B ulceration suffered fatal strokes, all on the side appropriate to the ulcer under observation. One of these, however, occurred postoperatively in a patient who had been operated on for TIAs and died as a result of the stroke. No fatal strokes occurred in patients with type C ulcerations.

Cerebral Infarction

The stroke-free survival rates were calculated separately for each six-month interval of follow-up for patients in each of the three ulcer groups and are plotted in Fig 2. There was a higher incidence of stroke for patients with type B and C ulcers than for patients with type A ulcers. This difference was small at first but became progressively larger over time, especially after 60 months of follow-up. However, seven of 17 strokes (41%) occurred within the first 24 months after ulcer discovery.

The stroke rate for patients with type A ulceration changed minimally over time. In contrast, the stroke rates for types B and C showed a significant increase until the 84th month of follow-up, when they leveled off, probably owing to the small number of patients followed for this period of time.

The SEM was calculated for each six-month interval on the stroke-free survival curve and then compared by using the t test. When the values for A and B ulcers were compared, there was a highly significant difference (P<.05) in stroke rates starting at 72 months. When comparing groups A and C, the stroke rates achieved a significant (P<.05) difference at 78 months of follow-up.

The annual stroke rate for each group, determined by averaging the interval stroke rates was 0.9% for group A, 4.5% for group B, and 7.5% for group C. For the period of study, 3% of patients with A ulcers, 21% with B ulcers, and 19% with C ulcers suffered hemispheric strokes on the side appropriate to the lesion (Table 1).

Overall, there were 17 strokes appropriate to the lesions being followed (Table 3), and when we examined the contralateral carotid circulation in these 17 patients, we found that there were three patients who had carotid arteries with marked stenosis by angiography. Two of them had TIAs appropriate to the lesion and underwent carotid endarterectomy. Three others had TIAs without marked stenosis and underwent uneventful carotid endarterectomy. None of the five patients operated on had subsequent symptoms appropriate to the operated side. Of the remaining 11 patients, two had type A ulceration, one had type C, and the rest evidenced contralateral carotid bifurcations that appeared relatively normal by angiography.

The mean and median age for those patients in whom stroke developed was 66 years; the range, 45 to 82 years. Patients with larger ulcers tended to be younger at the time of stroke than those with smaller ones (Table 4).

Ulcer Size

If ulcer size is to be useful in assessing patient risk, we must employ a reproducible method for grading ulcers. Initially our radiologist used a qualitative assessment to grade ulcer size, but subsequently considered methods to quantitate size. It was determined that the actual ulcer measurement was a suitable means to quantitate ulcer size and to categorize ulcers into A, B, and C groups. This was done by measuring the maximum depth and length of each ulcer (Fig 3) in millimeters and determining the product of the two dimensions. The ranges of these ulcer size products turned out to be distinctly different for each ulcer group (Fig 4). Type A ulcer products were less than 10; type B ulcer products, from 10 to 40; and type C products, at least 40. These measurements were made in nonmagnified views. There were few exceptions and, in retrospect, with the radiologist’s greater experience in grading ulcers, they might justify reclassification.
In addition to size, it was noted that almost all A and B ulcers had a smooth base, whereas C ulcers tended to have an irregular or shaggy base in about half of the cases. Some C ulcers had multiple cavities (compound ulcers).

**COMMENT**

The presence of a nonstenotic, asymptomatic carotid ulcer, as an individual angiographic finding, was considered inconsequential until the report of Moore et al in 1978. The observation that large B and C ulcers were associated with an alarmingly high incidence of stroke on late follow-up was cause for concern. This observation became controversial with a report by Kroener et al two years later, which confirmed the original observation by Moore et al that A ulcers were associated with a benign prognosis, but found no increased stroke incidence with B ulcers. It is important to recognize some differences between these two reports. First, Kroener et al had no C ulcers in their series because of their earlier decision to operate prophylactically on these lesions, thus removing the most serious lesion, according to our data, from contention. Second, as the majority of ulcers in Kroener's series (63) were in the A group, they reported on only 24 B ulcers. Finally, the qualitative grading of ulcer size allows for possible differences of opinion concerning what constitutes an A, B, or C ulcer.

Our current report, in contrast to the two earlier reports, represents a large series with specific breakdown of each ulcer category, yielding 72 A, 54 B, and 27 C ulcers. Perhaps a more important development has been the establishment of quantitative criteria to establish ulcer size so that these observations can be clearly communicated among various observers.

The life-table analysis curves show a distinct separation in stroke-free survival among the three groups. The curves are somewhat smoother than in our original report, reflecting the larger number of patients available for analysis. Of special interest is the annual stroke rate among the three groups. Patients with type A ulcers had a stroke rate comparable to that of a normal population. Those with type B ulcers had an annual stroke rate of 4.5%, whereas those with type C ulcers had an annual stroke rate of 7.5%, similar to the approximate annual stroke rate of 6% for patients with a history of TIA.

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**Fig 3.** Quantitative method of grading ulcers. Depth and length were measured in millimeters.

**Fig 4.** Relationship of ulcer type to ulcer product. Ulcer product was defined as product of ulcer's maximum length and depth in millimeters. Ulcers were categorized as follows: A indicates minimal, discrete excavation within atherosclerotic plaque; B, large, obvious excavation; and C, multiple cavities or cavernous appearance on roentgenogram.
The stroke rate for asymptomatic ulcers appears to increase gradually with length of follow-up, differing distinctly from the stroke rate in patients with initial TIA; the stroke rate in TIA patients appears to be especially high during the first year of follow-up, but begins to level off after five years. It is unclear whether the delayed stroke rate is related to an increased probability of embolization from these ulcerative lesions over a period of time or whether it represents progression to stenosis or occlusion. In either case, the larger ulcers represent a significant marker for subsequent stroke and carry an annual stroke risk comparable to that of patients who have monocular or hemispheric TIA.

It has been suggested that patients with asymptomatic lesions be observed and treated surgically only after symptoms appear. As in our previous report, we found that patients who had strokes had had no antecedent TIA's, and thus there was no warning of impending stroke. It is tempting to suggest that ulcerative lesions be followed by noninvasive studies, as the major risk appeared in the life table after five years. However, as more than 40% of all strokes occurred within the first two years, this late occurrence may be more apparent than real.

We also examined patient survival according to degree of carotid ulceration. Our data reveal significantly worse survival rates for patients with larger ulcers. This undoubtedly reflects the degree of generalized atherosclerosis, born out by the fact that most patients who died died of myocardial infarction, whereas only three suffered fatal strokes appropriate to the lesion being followed, all of whom had type B ulcers.

The question arises whether the high mortality rate, which exceeds the risk of stroke in patients with large ulcers, obviates the need for stroke-preventive surgery. The life-table method used for this analysis takes mortality into account, thus allowing stroke rates to be calculated in the live population, and shows a stroke rate high enough to produce significant morbidity and justify our concern.

On the basis of our expanded series, we conclude that large and compound or cavernous ulcers of the carotid bifurcation represent significant markers for subsequent stroke. In considering operation for these lesions, the surgeon must take into account the patient's general medical condition and his or her own operative experience. We recommend prophylactic operation for large ulcers (B and C) when the patient is a good anesthetic risk and the surgeon's combined morbidity and mortality rate for operation on asymptomatic lesions is less than 2%.

References

Discussion
EUGENE F. BERNSTEIN, MD, San Diego: I would like to thank Dr Dixon and his associates for persisting in their efforts to resolve and attempt to clarify what I think is a very important problem, but I am not certain that they really have resolved the problem for all of us.

As Dr Dixon indicated, there is clear agreement among all the data available that type A ulcers are benign. We have had no data on C ulcers since that type of lesion has been operated on in our hospital. The debate is about B ulcers. As you recall, however, in the initial report by Moore et al, the B ulcers were grouped with the C ulcers, as there were relatively few of each type.

Two years ago, my colleagues and I reported 94 asymptomatic lesions in 70 patients, and we showed that the patients who were stroke-free after 84 months included 99% of those who had survived, but the number that had survived decreased to about 60% after five years.

There are no miracles among friends, only explanations. Therefore, we have to think about how to resolve this major discrepancy in the available information. Are there differences in our selection of patients, for example, in age, sex, or number of VA patients? I think not. Were there differences in the indications for the original angiogram, ie, did Moore et al have more patients who had had prior stroke as the indication for angiogram? Were the patients sicker? Might the angiographic data contain the answer? Did their patients have more transient disease or more intracerebral disease?

We don't know the answers, but there are certainly areas in which the two series may differ. Are there differences between our data in the radiologic definition of ulcer or the classification? The landmark paper we just heard this morning by Lusby and associates suggests that perhaps the distinction between A and B ulcers is artificial. Our data show no difference in prognosis between the two groups.

Are the statistics valid? In the San Francisco series, most of the strokes occurred after five years of observation. Had the ulcers changed in terms of grade during that time? We have no interval information about how the lesions progressed, or what they were like at the time of the strokes.

We are also not told the mean duration of follow-up. In the original study it was approximately 2½ years. Our patients have now been studied for a mean of close to five years.

Finally, what do the UCLA findings look like when they are analyzed separately? Are they really identical to the original San Francisco data, or are they somewhere between those findings and ours?

I hope that the continuing debate will stimulate others to look at their data regarding asymptomatic carotid ulcers and will motivate those who can to follow such cases carefully, because I believe the situation is still unresolved.

EDWIN J. WYLIE, MD, San Francisco: We have been shown arteriograms of atheromatous lesions with an irregular surface. The hollow, or niche, between adjacent mounds or crags has been considered to represent an ulcer. This is a term commonly applied by radiologists when this type of irregularity is seen. There is an implied assumption that subsequent cerebral complications are the
result of pathologic events in the so-called ulcer and that the deeper and more irregular the "ulcer," the greater the probability of future trouble.

In a study that has now been extended to more than 150 consecutive endarterectomy specimens, my colleagues and I examined a substantial number of lesions that carried the preoperative radiologic diagnosis of ulcer because of similar surface irregularities. In describing the pathologic features of the operative specimens, we confined the term ulcer to any microscopically identified break in endothelium.

As a result of this study, we have been led to abandon the concept of ulceration in the bottom of the surface crypts and all that this concept implies. Ulcers, when present, were uniformly on the side or near the crest of adjacent mounds and almost never in the bottom of the crypt. They overlay sites of recent or old intramural hemorrhage. They tended to heal rapidly and were usually small and often invisible on multiplane arteriograms. The preoperative arteriographic irregularities in surface contour in patients in whom an ulcer was found could not be distinguished from irregularities of an intact atheroma.

To reconcile these observations with the data just presented, we have concluded that the luminal protrusion of large mounds or crags adjacent to hollows of lesser involvement may represent the friable, vascular residue from former hemorrhage and that their location in the moving blood stream in a vibrating arterial wall makes them vulnerable to disruption.

Jesse E. Thompson, MD, Dallas: I would like to ask Drs Dixon and Moore a question that has puzzled me all along. If these ulcers were asymptomatic and nonstenotic, what were the indications for arteriograms? If the patients were asymptomatic, one would not necessarily have obtained arteriograms. If the ulcers were nonstenotic, I would presume that the patients did not have a bruise. What then has been the indication for the arteriograms that have brought these ulcers to light? If they were contralateral unoperated lesions in patients who had had previous endarterectomy for symptomatic lesions—-with TIA's or stroke—then they cannot properly be called asymptomatic. It is the patient who is symptomatic or asymptomatic, not the lesion.

Dr Dixon: I will answer Dr Thompson's comments first. The indications for the arteriograms, as I mentioned, were contralateral carotid symptoms or asymptomatic bruits. Granted, these patients were selected patients; otherwise, they would not have undergone arteriography. They were all patients that had vascular disease; otherwise, we wouldn't have been seeing them. I don't think that negates our point. The point is that these large ulcers are sometimes discovered when evaluating vascular patients, and when they are seen, they should be recognized as markers for future stroke.

Next, I would like to respond to Dr Wylie's comments. We agree that many of the defects seen on arteriogram that we call ulcers may have reendothelialized by the time they are discovered. We are not saying that these "angiographic ulcers" are undergoing active embolization, nor are we saying that the ulcer itself will reharvest. What we are saying is that these defects represent the cavities left after embolization from soft plaques at some time in the past and are therefore markers for plaques that have the potential for causing future stroke. As we have said, we don't know if the mechanism is mainly embolization from the plaque substance or whether these larger plaques that are associated with larger ulcers have the tendency to progress to occlusion. What we do know is that the size of the ulcer is predictive of the plaque in causing a stroke-producing event.

I appreciate Dr Bernstein's comments and his extending the follow-up on their series. It would have been interesting if they had examined their ulcers with our quantitative method of classification, to see if the B ulcers in Dr Bernstein's series were truly B ulcers. I might also comment again that there were only 24 B ulcers in their series, which is not a very representative number, and there were no C ulcers, which are the most threatening of the ulcerative lesions.

There were not many differences between the UCLA and San Francisco series. The main difference was that there were more men in the San Francisco series. Overall, the distribution of stroke and TIA in the various categories of patients was almost identical, and the period of follow-up was also nearly identical. So although this was not an ideal way to produce a sizable series, it was the best available. We feel that the two series are comparable enough that the data derived from their combination is meaningful.