Should Cerebral Ischemic Events in Cancer Patients Be Considered a Manifestation of Hypercoagulability?

Seemant Chaturvedi, MD; Jack Ansell, MD; Lawrence Recht, MD

Background and Purpose Previous studies, mainly autopsy-based, suggest that the spectrum of stroke in cancer patients differs from that of the general population. These studies also suggest that cerebrovascular events frequently are a manifestation of hypercoagulability. However, no studies that address this question in the adult oncological population from a clinical perspective are available. We therefore assessed the clinical impact of cerebral ischemic events in cancer patients and attempted to determine whether their occurrence represents a manifestation of Trousseau's syndrome.

Methods A computerized database that records all neurological admissions and consultations at a tertiary medical center was used to retrospectively identify all patients with cerebral ischemic events and cancer.

Results Thirty-three patients representing 3.5% of all stroke consultations and admissions seen at the University of Massachusetts Medical Center were identified during the period 1988 through 1992. Large-vessel atherosclerosis was the most frequent cause of stroke. Furthermore, although 30% were determined to have hypercoagulability as a cause using clinical criteria, in only one of nine patients in whom tests were done was sufficient evidence present to make a presumptive diagnosis of disseminated intravascular coagulation. Irrespective of therapy, recurrent cerebral ischemic events were noted in only 6% of patients during a follow-up period averaging greater than 9 months, a figure that is similar to that for the risk of repeated events in the noncancer population.

Conclusions Recognizing the limitations of this retrospective study, it appears nonetheless that conventional stroke origins account for the majority of cerebral ischemic events in the adult cancer population. Although hypercoagulability is present to a greater extent than in the nononcological population, recurrent strokes seem to occur no more frequently than in the nononcological population, and antplatelet agents seem sufficient therapy for most patients.

Key Words • cerebral ischemia • coagulation • neoplasm

The relation between cancer and hypercoagulability has been recognized since 1865, when Trousseau first identified an association between venous thrombosis and malignancy. Subsequently, the syndrome that bears his name has been extended to also include arterial events and even accelerated atherosclerosis. These thromboses are frequently migratory and the cancer often occult and difficult to diagnose.

Because stroke is such a common occurrence in the general population, it is unclear whether a cerebral ischemic event that occurs in a cancer patient represents a manifestation of this syndrome or a coincidence. This distinction has therapeutic implications because the hypercoagulability syndrome associated with cancer (known as Trousseau's syndrome) may require immediate heparin therapy and long-term anticoagulation.

Cerebrovascular disease is second only to metastases as a cause of central nervous system pathology in the cancer patient. Most of the previous studies that have examined the issue of stroke in the cancer patient have been autopsy-based and have suggested that the pathophysiology of stroke is unique in this population. In the largest series, Graus and coworkers found evidence of cerebral infarction in 7% of 3426 autopsied cancer patients. Among symptomatic patients, the three leading causes of ischemic stroke were nonbacterial thrombotic endocarditis (NBTE), disseminated intravascular coagulation (DIC), and septic emboli. Atherosclerosis accounted for only 14.5% of symptomatic infarctions.

One of the few studies to address this issue from a clinical perspective assessed a pediatric population. During a 4-year period, Packer et al identified 26 patients with either brain hemorrhage or infarction. Of the 17 patients with stroke, unique predisposing conditions such as DIC and L-asparaginase administration were again identified.

It has been our observation, however, that cerebral ischemic events in adult patients with cancer often are indistinguishable in terms of their clinical behavior from similar events occurring in the general population. To investigate this issue, therefore, we retrospectively analyzed our institution's experience. We hypothesized that if ischemic events in these cancer patients represent part of Trousseau's syndrome, then infarctions would occur early in the course of the cancer, would be correlated with tumor types previously linked with the syndrome, would be associated with arterial and venous thromboses at other sites, and would coexist with hematologic evidence of hypercoagulability.
Subjects and Methods

A computerized database that records all admissions and consultations seen at our medical center was used to retrospectively identify all inpatients with nonhemorrhagic stroke or transient ischemic attack and cancer seen by the Neurology Service between 1988 and 1992. The medical records were then reviewed to obtain detailed case histories, including results of radiographic and coagulation studies. When possible, a cause was assigned for each event using criteria modified from those used in the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study. Briefly, strokes were attributed to atherosclerosis if there were risk factors present and greater than 50% stenosis in the appropriate vessel. Patients with infarcts consistent with small-vessel disease were included in the atherosclerotic category if there was greater than 50% stenosis in the appropriate proximal vessel. Cardiogenesis was judged to be the cause if there was a plausible mechanism (e.g., atrial fibrillation). Hypercoagulability was considered the cause if there were clinical (e.g., thromboses at other sites) or laboratory findings (e.g., thrombocytosis) to support this mechanism, as well as an absence of other more likely causes. Subsequent outcomes were obtained from chart review, the hospital tumor registry, or a telephone interview.

Results

Thirty-three patients were identified with cerebral ischemic events in which the event occurred either within 2 months of or after the diagnosis of systemic cancer. This group represented 3.5% of stroke consultations and admissions and 5.5% of all neurological consultations for oncological patients during this period. The median age of the patient cohort was 70 years (range, 32 to 82 years); 61% of patients were men. Twenty-four patients (73%) presented with a fixed deficit (completed stroke); in the other nine, the event either completely or almost completely resolved within 24 hours. Twenty-one patients had infarcts documented on computed tomographic or magnetic resonance scanning; 86% of these events involved the anterior circulation.

Eighteen percent of strokes occurred at the time of the original cancer diagnosis (Table 1); 73% of events occurred within 6 months of diagnosis. Lung and gynecologic tumors were the most frequently associated tumor types (Table 2).

Definitively establishing the cause of individual strokes was not always possible because the extent to which patients were investigated varied according to physician practices. Twenty (61%) of 33 patients had noninvasive vascular studies performed, 55% underwent echocardiography, and 27% had complete hematologic investigations for DIC. No cerebral angiograms were performed, usually because serious systemic illness precluded the consideration of endarterectomy. In only one patient was an autopsy performed, which demonstrated systemic metastases only. Using the aforementioned modified TOAST criteria, the mechanism of ischemic events in those patients in whom it could be ascertained with reasonable certainty is tabulated in Table 3. From a radiographic perspective, there was no particular predilection for one vascular territory to be preferentially affected by a particular cause (i.e., not all subcortical infarcts were secondary to atherosclerosis), although the numbers were small.

Although unequivocal laboratory evidence of DIC was only present in one patient (prothrombin time, 16.5 seconds; partial thromboplastin time, 34 seconds; platelet count, 136 x 10^3/mm³; fibrinogen level, < 85 mg%; and fibrin degradation products, > 40 mg% at the time of the event), we also considered a stroke to be associated with (and possibly secondary to) hypercoagulability if there were no risk factors for atherosclerosis or cardioembolism and there was evidence of other sites of thrombosis. Despite only two patients having developed deep venous thromboses some months after their cancer diagnosis but before their strokes and there being no patient who received a chemotherapeutic agent linked with thrombosis in temporal proximity to the ischemic event, hypercoagulability was believed to be an important determinant of the cerebral ischemic event on clinical grounds in 10 patients (30%). Interestingly, not one case of stroke secondary to presumptive NBTE was observed in this series.

In terms of administered antistroke therapies, 42% of patients received aspirin, 21% warfarin, and another 12% were treated with intravenous heparin only during their inpatient stay. Eight patients (24%) received no antithrombotic therapy for a variety of reasons, mainly because of either the presence of potentially life-threatening medical problems that precluded the use of

### Table 1. Interval From Time of Cancer Diagnosis to Occurrence of Cerebral Ischemic Event or Transient Ischemic Attack

<table>
<thead>
<tr>
<th>Time of Ischemic Event, mo After Cancer Diagnosis</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>At time of cancer diagnosis</td>
<td>6</td>
<td>18.2</td>
</tr>
<tr>
<td>&lt;3</td>
<td>11</td>
<td>33.3</td>
</tr>
<tr>
<td>3-6</td>
<td>7</td>
<td>21.2</td>
</tr>
<tr>
<td>&gt;6</td>
<td>9</td>
<td>27.3</td>
</tr>
</tbody>
</table>

### Table 2. Incidence of Cerebral Ischemic Event or Transient Ischemic Attack According to Tumor Type

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. of Patients</th>
<th>No. of Neurol Consults</th>
<th>% Neurol Consults for Cl or TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gynecologic</td>
<td>7</td>
<td>34</td>
<td>20.6</td>
</tr>
<tr>
<td>Renal/genitourinary</td>
<td>4</td>
<td>38</td>
<td>10.5</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>4</td>
<td>38</td>
<td>10.5</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>4</td>
<td>50</td>
<td>8.0</td>
</tr>
<tr>
<td>Prostate</td>
<td>3</td>
<td>40</td>
<td>7.5</td>
</tr>
<tr>
<td>Lung</td>
<td>9</td>
<td>176</td>
<td>5.1</td>
</tr>
<tr>
<td>Breast</td>
<td>2</td>
<td>107</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Neurol indicates neurological; Cl, cerebral ischemic event; TIA, transient ischemic attack.

### Table 3. Pathogenesis of Ischemic Events

<table>
<thead>
<tr>
<th>Pathogenesis of Ischemic Events</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis</td>
<td>11</td>
<td>33.3</td>
</tr>
<tr>
<td>Hypercoagulability</td>
<td>10</td>
<td>30.3</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>7</td>
<td>21.2</td>
</tr>
<tr>
<td>Uncertain</td>
<td>5</td>
<td>15.1</td>
</tr>
</tbody>
</table>
anticoagulants or because it was decided to treat the underlying neoplasm instead. Interestingly, however, whatever the treatment, the incidence of recurrent stroke was apparently no greater than would be expected in the general population after an ischemic event. Thus, although 48% of patients in this series died during the follow-up period, only one death was secondary to neurological disease, and only two patients developed recurrent strokes during a combined follow-up period of 295 patient-months (an average of >9 months per patient). Of these latter patients, one had a subtherapeutic prothrombin time while on warfarin and the other had a recurrent stroke while receiving a therapeutic dose of intravenous heparin. None of the patients treated with aspirin had a recurrent stroke.

Discussion

The optimal treatment of hypercoagulability in the cancer patient is best directed against the underlying neoplasm; complete tumor remissions may be associated with remission of the coagulation abnormalities. In severe cases, administration of heparin to activate residual antithrombin III can be used; in contrast, warfarin may not be effective. A similar approach might also be considered when a stroke occurs secondary to NBTE. Thus, the approach to the patient with cancer who develops a stroke would be different than that for the nononcological patient if it is deemed secondary to chronic DIC/hypercoagulability.

Because it is a retrospective study, our results are subject to several potential criticisms. First, patients were accrued from a computerized database that recorded all neurological inpatient consultations and admissions; as such, patients for whom consultation was not requested would not be included. From our center's practice patterns, however, it would be unusual for the neurology service to not be consulted in the event of new neurological signs developing in a cancer patient, and therefore we believe that accrual was close to complete or complete. Another potential confounding feature is that a complete evaluation of coagulation parameters that included fibrinogen and fibrin degradation products was only obtained in 27% of patients. Furthermore, it would have been optimal if coagulation parameters were measured not only during the acute ischemic episode but also at a time 2 to 3 weeks after the event, since such tests can often be transiently abnormal in the acute phase of stroke.

Despite these drawbacks, however, this cohort is unique in that unlike past reports, which addressed this relation in adults mainly through examination of autopsy material, it represents a clinical experience with this condition. Somewhat unexpectedly, differences in the spectrum of stroke origins were noted between our study and previous studies; thus, while these previous studies have emphasized such unusual stroke origins as NBTE and DIC, such origins were uncommon in this series. Recognizing that NBTE is difficult to diagnose antemortem and that hypercoagulability in cancer patients is not always accompanied by abnormal laboratory findings, several additional observations may be made.

First, ischemic events tend to occur proximate to the diagnosis of cancer, frequently at a time when the patient is not otherwise ill. Furthermore, there seemed to be a trend for ischemic events to occur more frequently in certain tumor types, such as gynecologic cancers. Since it is known that other neurological paraneoplastic syndromes occur early, often preceding a cancer diagnosis, and that specific tumors such as pancreatic, ovarian, lung, mucin-producing gastrointestinal carcinomas, and acute progranulocytic leukemias are associated with thrombotic episodes, both of these observations could be used as evidence to support the hypothesis that ischemic cerebral events represent a paraneoplastic syndrome of hypercoagulability.

In contrast, however, several observations tend to refute this hypothesis. First, coagulation parameters consistent with DIC were noted in only one of nine patients tested, and thromboses at other sites occurred in only two. Thus, it is probable that we overestimated the incidence of hypercoagulability as a cause of stroke. Even with our broad clinical definition of hypercoagulability, however, this condition still accounted for less than one third of stroke origins (Table 3). By the criteria used, atherosclerosis was still the most prevalent condition (33%); together with cardioembolism (secondary to atrial fibrillation in six of seven patients), it accounted for over half the pinpointed causes of stroke. That factors other than hypercoagulability were responsible for the majority of strokes is also supported by the rate of stroke recurrence in this cohort, which was only 6% during an average follow-up period greater than 9 months. This figure is not appreciably different from recurrent stroke incidence in the general stroke population. Thus, when compared with other stroke risk factors such as atrial fibrillation, which is associated with a stroke risk of 7% per year if untreated, the recurrence rates reported here appear no more frequent. This generally good outcome was noted irrespective of administered therapy; together with the lack of other associated thrombotic events, it supports the contention that a prothrombotic state was not frequently present in this cohort of patients.

This is not to imply, however, that ischemic events in cancer patients cannot be a manifestation of a generalized hypercoagulable state; certainly this occurs more frequently than in the general population. Rather, the explanation for why the origin of stroke in these subjects differs from those reported from a pediatric age group probably reflects the high incidence of atherosclerosis and cardiac disease in this elderly cohort.

Based on this retrospectively accumulated cohort of patients, it therefore seems that ischemic cerebral events in adult cancer patients should not be considered prima facie evidence of Trousseau's syndrome. The question of exactly how frequent and important a role hypercoagulability plays in cancer-related strokes awaits a prospective study. Until then, we would recommend that if an adult patient with cancer presents with such an event, in addition to those tests performed routinely in all stroke patients, a systematic assessment for the presence of hypercoagulability should be performed including prothrombin time, partial thromboplastin time, platelet count, fibrinogen, and fibrin degradation products/d-dimer). Additional hematologic studies such as fibrinopeptide A assay, antithrombin III, and protein C/protein S may also provide useful information. An evaluation for concomitant deep venous thrombosis is also indicated.
If evidence of hypercoagulability exists and a nononcological origin of ischemia is not apparent, consideration should be given to directing therapy at the underlying neoplasm or, if this is not possible, to long-term administration of heparin. Our data suggest, however, that most adult cancer patients will not fall into this category and can be managed, for the most part, in a manner similar to that of their nononcological counterparts.

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References

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