Stroke as The First Manifestation of Concealed Cancer

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ABSTRACT

Background and Purpose: Stroke is commonly occurring in a patient with known cancer. Stroke is seldom occur as the first manifestation of a cancer. The majority of these strokes were a consequence of hypercoagulability. We investigated the clinical, laboratory and radiological features of patients whose cancer was firstly diagnosed after time of stroke presentation. Methods: We reviewed the clinical, laboratory and radiological records of consecutive stroke patients, whose cancers were diagnosed at stroke presentation. Cancer-related stroke was defined if no definite cause for stroke was confirmed and malignancy was detected within 6 months of first stroke onset without cancer-related treatment. All patients underwent clinical, laboratory and radiological investigations including brain diffusion-weighted MRI (DWI), MR angiography, and echocardiography. The sizes, numbers, and locations of all hyperintense lesions in the DWI were noted. Results: 10 patients were finally analyzed. Lung cancer (40%) and prostate cancer (20%) were the commonest underlying malignancy, they were often of advanced stage. All patients has elevated D-dimer 100%, 5 of them (50%) has highly elevated D-dimer (50%). 9 of 10 cases (90%) showed bihemispheric numerous and variable size lesions in multiple territories in DWI. Conclusion: Consider a concealed cancer in multiple bihemispheric infarctions in DWI and an unknown etiology. (Egypt J. Neurol. Psychiat. Neurosurg., 2008, 45(2): 545-549)

INTRODUCTION

Cerebrovascular complications including hemorrhage and infarction are second only to metastases in frequency of CNS lesions in patients with cancer⁵. Stroke occurs commonly in patients with known cancer, yet undiagnosed malignancy rarely presents as stroke⁴. The majority of these strokes were a consequence of hypercoagulability². Malignancy is not a common underlying etiology of cerebral infarction; however, it may be the root cause of an unexplained stroke, particularly if infarction occurs in multiple vascular distributions, or recurs despite appropriate anticoagulation³. Cancer patients are hypercoagulable through a variety of mechanisms and are at significant risk for ischemic stroke. Though usually occurring in the later stages of neoplastic disease, stroke can rarely be the first manifestation of an occult malignancy⁴. Stroke is seldom encountered as a first manifestation of cancer knowing the clinical cancer is helpful to the management of stroke patients⁵. In this study, we investigated the clinical, laboratory and DWI features of ischemic stroke patients whose cancers were firstly diagnosed at the time of stroke presentation.

PATIENTS AND METHODS
Methods:
All clinical, laboratory and radiological records of 419 stroke patients were revised between December 2003 and December 2007. Nineteen (19) patients had cancers diagnosed at admission time following stroke onset. Nine (9) patients were excluded because the etiologies of their strokes were severe large-artery atherosclerosis and cardioembolism such as atrial fibrillation. Ten (10) patients were finally analyzed. They all had no cancer history. They had no specific systemic clues to underlying cancer. Cancer related stroke was defined if no definite cause was determined for stroke, and malignancy was detected immediately or within 6 months of stroke onset without cancer-related treatment. Definite cardioembolism and infective endocarditis were excluded. All patients were examined medically, neurologically including NIH stroke scale (NIHSS), all of them had no fever at admission and underwent brain DWI MR angiography, carotid duplex and transthoracic (TTE) and transoesophageal echocardiography (TEE). Blood test including CBC, ESR, liver profile, renal profile, glucose profile, lipid profile and coagulation profile including D-dimer were conducted within one month after stroke onset.

To study the radiological characteristics of presenting strokes, we analyzed initial DWI scans in all patients and subsequent DWI scans in patients who showed recurrence or stroke evolution. The sizes and locations of all hyperintense lesions were noted. Lesions were considered small when the largest axial diameter was <10 mm, medium if 10-30 mm, and large if >30 mm. Lesions are considered multiple if they are >1 lesion.

RESULTS

Clinical Results: Shown in Table (1)

Age and sex:
- Mean age of the 10 patients was 66 years (mean±SD, 66.2±8.5).
- 60% of the patients were men.

Symptoms and signs:
- Include: hemispaemic in 8 patients (80%), aphasia/dysarthria in 4 patients (40%), visual field defect in 2 patients (20%), ataxia in 3 patients (30%), headache in 3 patients (30%), and seizure in 1 patient (10%).

Type and spread of cancer:
- Lung (40%) and prostate (20%) cancer were the most common cancer origins.
- Systemic metastasis was frequently found at the time of cancer diagnosis in 70%.

Survival and outcome:
- Neurologic outcome could be ascertained for 9 cases, 1 patient had missing information. At discharge, most patients had neurological improvement (60%) from their stroke; however 50% had recurrence of stroke within 1 month.
- 30% had a fixed deficit that did not improved.
- The median overall survival was 5 months for all 10 patients from diagnosis of stroke.
- The main cause of death was not only related to stroke itself, but it was also related to cancer itself, poor systemic health, and other system complications.

Laboratory results: Showed:
- Mild anemia (Hb 10.5±0.8 gm%), and ↑ESR 38±11 mm/hour.
- Coagulopathy played a role in stroke pathogenesis, as D-dimer was high in all cases (≥2 ugm/ml, normally it is <0.21 ug/ml), and significantly high (>10 ugm/ml) in 50% of cases.
Radiological results:
- DWI showed numerous small (<10 mm), medium (10-30 mm) or large (>30 mm) lesions in bihemispheric territories in 9 cases (90%), while multiple lesions in a single territory in 1 case (10%).
- Lesions were all ischemic, except in one patient who had recurrent stroke and follow-up MRI revealed hemorrhagic transformation.
- MRA brain was normal in all cases.

- Carotid duplex showed insignificant findings in all cases.
- TT and TE echocardiography did not show intracardiac thrombi.

Treatment:
Treatment of these cases was not based on primary cancer, it was mainly related to stroke etiology. Patients were treated with anti-platelets, anticoagulants, or more frequently with both agents, especially after stroke recurrence.

Table (1): Shows stroke patients characteristics.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/age</th>
<th>Cancer diagnosis</th>
<th>Stage</th>
<th>Days from stroke to cancer diagnosis</th>
<th>Stroke recur</th>
<th>D-dimer ug/ml</th>
<th>Survival after stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/56</td>
<td>Breast cancer</td>
<td>Metastasis</td>
<td>2 months</td>
<td>+</td>
<td>13</td>
<td>14 months</td>
</tr>
<tr>
<td>2</td>
<td>M/68</td>
<td>Lung cancer</td>
<td>Metastasis</td>
<td>3 months</td>
<td>+</td>
<td>47</td>
<td>5 months</td>
</tr>
<tr>
<td>3</td>
<td>M/65</td>
<td>Lung cancer</td>
<td>Metastasis</td>
<td>3 days</td>
<td>-</td>
<td>2</td>
<td>2 months</td>
</tr>
<tr>
<td>4</td>
<td>M/71</td>
<td>Prostate cancer</td>
<td>UN</td>
<td>2 days</td>
<td>+</td>
<td>43</td>
<td>6 weeks</td>
</tr>
<tr>
<td>5</td>
<td>F/59</td>
<td>Pancreatic cancer</td>
<td>Metastasis</td>
<td>4 days</td>
<td>-</td>
<td>3</td>
<td>3 weeks</td>
</tr>
<tr>
<td>6</td>
<td>F/54</td>
<td>Colon cancer</td>
<td>UN</td>
<td>21 days</td>
<td>-</td>
<td>2</td>
<td>4 months</td>
</tr>
<tr>
<td>7</td>
<td>M/71</td>
<td>Lung cancer</td>
<td>UN</td>
<td>10 days</td>
<td>+</td>
<td>35</td>
<td>3 weeks</td>
</tr>
<tr>
<td>8</td>
<td>M/79</td>
<td>Lung cancer</td>
<td>Metastasis</td>
<td>3 months</td>
<td>-</td>
<td>2</td>
<td>6 months</td>
</tr>
<tr>
<td>9</td>
<td>F/70</td>
<td>Ovarian cancer</td>
<td>Metastasis</td>
<td>26 days</td>
<td>-</td>
<td>47</td>
<td>3 months</td>
</tr>
<tr>
<td>10</td>
<td>M/69</td>
<td>Prostate cancer</td>
<td>Metastasis</td>
<td>3 days</td>
<td>+</td>
<td>2</td>
<td>13 months</td>
</tr>
</tbody>
</table>


DISCUSSION

We found that patients with concealed cancer can present with multiple cerebral infarctions as an initial manifestation and that they showed multiple, and disseminated strokes of varying sizes.

In a cancer patient, thromboembolism was identified as a complication of cancer, malignant cells can release tumor necrosis factor and interleukins and thus cause endothelial damage, and convert the surfaces of heart valves to thrombogenic surfaces, which in combination with activated platelets and some coagulation factors may lead to thrombin generation.

Non-bacterial thrombotic endocarditis (NBTE) is characterized by the presence of relatively a cellular aggregates of fibrin and platelets attached to normal heart valves, NBTE made in this manner can migrate to various organs, including the brain. Non-bacterial thrombotic endocarditis (NBTE) is the most common etiology for stroke in cancer patients, and is the best explanation for multiple cerebral and systemic infarcts. Embolic strokes are the commonest cause of stroke in patients with cancer, due partially to hypercoagulability, whereas atherosclerosis accounts for only 22% of strokes in this population.
All our patients revealed multiple lesions in MRI brain in a single territory in one patient (10%) and in bihemispheric territories in 9 cases (90%). In one patient among those who developed recurrent stroke, follow up MRI brain revealed hemorrhagic transformation as a part of DIC.

TT and TE echocardiography is negative in all cases, as NTBE is usually diagnosed pathologically.

Adenocarcinoma was previously reported to have a 5-fold higher risk for NBTE than other histological types of malignant tumors. Our population often had adenocarcinoma which is consistent with the findings of previous study.

In our study, lung cancer was the commonest hidden malignancy causing strokes. Cestari et al. attributed this finding to the higher prevalence of diabetes and smoking in the lung cancer population.

Patients with strokes of embolic origin have bad outcome and once stroke occurred in patient with cancer the overall prognosis is poor and the median survival was 4.5 months.

In our study, the average survival following stroke diagnosis was 5 months, which is close to the previous study.

An elevated D-dimer level is seen in a wide variety of conditions with intravascular clotting, including stroke itself, particularly embolic stroke with levels of ≥2.0 µg/ml. Our 10 patients with an elevated D-dimer all had values of ≥2.0 µg/ml. In 5 cases D-dimer level was very highly increased, suggesting cancer-induced hypercoagulability. Therefore, a highly elevated D-dimer level alone may be used to assign stroke etiology in cases of negative echocardiography. More patients with cancer and stroke need to be studied to understand the utility of this test in the cancer population.

Inspite of the fact that most of our cases were treated with both anti-platelets and anticoagulants, 50% of them had recurrence, and maximizing dose of anticoagulants failed to prevent further recurrence.

Regardless of stroke etiology, treatment appeared to have little impact on outcome as stroke treatment has no effect on underlying cancer.

The optimal treatment for hypercoagulability associated with malignancy is treatment of the underlying tumor.

Several studies suggest that tumor treatment is the main step in controlling or at least stabilizing the neurological involvement.

Sometimes, treatment of cancer including chemotherapy, surgery, radiotherapy and hormone therapy increase risk of stroke.

When extensive stroke evaluation failed to identify a primary cerebrovascular explanation, a search for an underlying malignancy may be indicated in the evaluation of stroke, particularly when the patient has recurrent events in different vascular distributions especially with failure of anticoagulation.

**REFERENCES**


الملخص العربي

السكتة الدماغية كعرض أول للسرطان المستمر

تحدث السكتة الدماغية عادة في مريض يعاني من السرطان، ولكن نادراً ما تكون أول عرض له، حيث أن معظم هذه الحالات تأتي بسبب زيادة تجلط الدم في ظروف الفراغ. في هذه الدراسة، تبحث الخصائص الإكلينيكية والعملية والأشعة الخاصة بفحص الدم في السرطان. السرطان في بعض الحالات يسبب تجلط السكتة الدماغية، وتتوقف الحالات في الدراسة بوفاة المريض. إن النتائج كانت كالتالي: السكتة الدماغية وفاة المريض، وفقدان بعض الأعضاء والأنسجة المحيطة. ولذا، تتميز السكتة الدماغية كعرض أول للسرطان المستمر مع وجود علامات وعلامات مختلفة للحصين والجهاز البصري والوظائف الأخرى. ولذلك، فإن السكتة الدماغية قد تكون علامة أولية على وجود السرطان المستمر في مرض يعاني من السرطان المستمر. في حالة عدم وجود سبب واضح، فإن السكتة الدماغية قد تكون علامة أولية على السرطان المستمر.