Immunocytochemical evidence of lymphocytic derivation of neoplastic cells in malignant angioendotheliomatosis

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Malignant angioendotheliomatosis is a rare entity characterized by the presence of neoplastic cells within the lumina of small and intermediate-sized blood vessels. Blood vessels in the skin and central nervous system (CNS) are primarily affected, although vessels in a variety of organs may be involved. Even though it has been noted repeatedly that malignant angioendotheliomatosis lacks the architectural and cytological features of a vascular neoplasm, the concept that this is an endothelial malignancy was an early theory that continues to persist. The nature of these neoplastic cells has been a point of controversy, with various authors suggesting that malignant angioendotheliomatosis might also represent disseminated carcinoma from undiscovered primary sites or, more recently, neoplasia of a lymphoid origin. A review of the literature shows fewer than 40 such cases with signs and symptoms confined to the CNS; a majority of these reports in the neurological or neurosurgical literature consist of single case reports and perpetuate the concept of an endothelial origin for the neoplasm.

The purpose of this study was the immunohistochemical examination and confirmation of the cell of origin of this neoplasm based on five previously unreported cases of malignant angioendotheliomatosis with primarily CNS symptoms, and the first report of a T cell-derived intravascular lymphoma.

Clinical Material and Methods

Five previously unreported cases of autopsy-confirmed malignant angioendotheliomatosis were seen over a period of 25 years. In each of these cases, appropriate histopathological specimens were cut from paraffin sections and immunostaining was performed.

Histological Studies

The morphological studies were performed using for-
malin-fixed, paraffin-embedded material. Slides stained with hematoxylin and eosin (H & E) were reviewed, and the diagnosis of malignant angioendotheliomatosis was confirmed. In one of the five cases, blocks and unstained slides were not available, so selected H & E slides were destained then reprocessed for immunohistochemical study. In the other four cases, unstained slides or post-paraffin-embedded blocks were available and prepared for immunohistochemical studies. Slides were treated with murine monoclonal anti-human B lymphocyte (LN-1 and LN-2), anti-leukocyte common antigen, or anti-human T-cell antibodies according to the manufacturer's instructions.* For lectin immunohistochemical examination, slides were treated with Ulex europaeus.† Bound primary antibody or lectin was then detected by standard methods using the appropriate biotinylated antibody and the avidin-biotin-horse-radish peroxidase method with diaminobenzidine as the substrate. A counterstain with hematoxylin was then applied. Sections of lymph node processed in the same manner served as positive controls. Omission of the primary antibody resulted in no specific staining and served as a negative control.

Case Reports

Case 1

This 36-year-old man initially presented for diagnosis of vertebrobasilar transient ischemic attacks (TIA's). Four-vessel cerebral angiography was within normal limits. He returned 1 month later with supratentorial TIA's lateralized to the left side. A repeat arteriogram was again within normal limits. The only abnormal finding was that of a hypercoagulability syndrome associated with the presence of the lupus anticoagulant. All deficits cleared rapidly on each occasion.

The patient then presented 4 months later with right-sided weakness and aphasia which gradually improved over several days. After this episode, he remained confused and completely disoriented to time, person, and place. After 4 days, the paresis on the right side worsened and progressed to the left side. He became quadriparetic and quite demented, although he remained awake and alert. He subsequently developed pneumonia and died 4 months after his initial TIA. Computerized tomography (CT) and magnetic resonance imaging were performed during the patient's terminal course and demonstrated bilateral areas of abnormally low density in the basal ganglia (Fig. 1).

Case 2

This 54-year-old woman was admitted because of a change in her mental status. She had previously been receiving high-dose steroids for a presumed lumbosacral meningoradiculitis, and had been doing well until 2 days prior to the present admission, when she suddenly became confused and poorly responsive. A four-vessel arteriogram was within normal limits. Electroencephalograms (EEG) showed slowing in the 5 to 7 CPS range. A CT scan revealed a low-density area in the right posterior thalamic region, and a stereotactic biopsy specimen was obtained from this area. Brisk bleeding was encountered at the time of biopsy, and the patient subsequently developed an intracerebral hematoma as well as a subdural hematoma. She was taken to surgery, where the hematomas were evacuated. Despite removal of the intracranial masses, she continued to fare poorly and in the postoperative period she suffered cardiopulmonary arrest and died.

Case 3

This 68-year-old woman was in apparent good health until 6 months prior to her admission in 1965, when she noticed "acute spells of weakness" which lasted 30 to 45 minutes then slowly subsided. Approximately 4 months prior to presentation, she became so weak that she could neither walk nor stand without aid. She also felt "drowsy" but did not experience pain until 1 week prior to presentation, when she noted pain in the sacral area.

Examination on this admission showed spastic paralysis of the legs. Sensory examination revealed loss of position and vibration sense. Deep-tendon reflexes were equal or slightly hyperactive on the left. The toes were upgoing on both sides, with a Hoffman's sign on the left. Myelography revealed no obstruction. Cerebrospinal fluid (CSF) contained eight lymphocytes, one red blood cell, and a total protein of 128 mg%. The patient then became aphasic, but could still move both upper extremities. Her condition progressively worsened. Although the initiation of steroid therapy briefly halted her downhill course, she did not improve significantly. Over the next few days, she became less alert, had a grand mal seizure and cardiopulmonary arrest, and died on the 15th day of hospitalization.

Case 4

This 63-year-old man was admitted in 1964 because of numbness and weakness in both legs. On the day following admission, he noted weakness of both legs, worse on the left. The leg weakness progressed to a staggering gait, and he subsequently developed difficulty in voiding. He was noted to have weakness of both quadriceps and of the extensors of the left foot; there was decreased sensation in both legs, greater on the right than the left, with a sensory level at T-12 on the right and L-1 on the left. There was a decreased response to pinprick around the anus on the right but not on the left. Rectal sphincter tone was decreased. Position sense was normal. Babinski responses were not present.

A myelogram was suggestive of a lesion on the right side at about the T-8 level, and the patient subsequently

* Murine monoclonal antibodies LN-1 and LN-2 obtained from ICN Immunobiologics, Lisle, Illinois; anti-leukocyte common antigen and anti-human T-cell antibodies obtained from DAKO Corp., Santa Barbara, California.
† Ulex europaeus obtained from Sigma Chemical Co., St. Louis, Missouri.
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underwent exploratory surgery and biopsy of what was thought to represent a spinal angioma. Following surgery, he was completely paraplegic and became quite confused. His paraplegia then progressed to quadriplegia, and steroid therapy was begun. Diagnostic studies showed no evidence of a postoperative hematoma or direct pressure on the spinal cord. The patient improved with steroid therapy to the extent that he was paraplegic rather than quadriplegic. He continued to be confused, and this confusion progressed. He became disoriented with intermittent episodes of hypertension. He subsequently suffered a generalized seizure and cardiopulmonary arrest and died.

Case 5

This 64-year-old man was admitted with a history of acute confusion. Two days prior to presentation he lost his ability to recognize people and became very quiet and nonaggressive. He responded only to simple commands but would eat or drink if asked to do so. His symptoms progressed, and by the 5th day of hospitalization he was very drowsy, noncooperative, and unable to speak. On examination he had bilateral upgoing toes. A CT scan showed subtle low-density changes in the left frontal lobe and the left parietal area. On the 12th day of hospitalization, he had a cardiac arrest from which he was successfully resuscitated. Following this, he was flaccid and areflexic but with intact doll's eyes. Five days later a repeat CT scan showed marked low-density changes throughout the white matter of both hemispheres. Subsequently, the patient suffered cardiopulmonary arrest and died on the 25th day of hospitalization.

Pathological Studies

Gross Pathology

In all cases, the gross findings were most consistent with multiple areas of recent and resolving infarction.

Close examination of the vessels themselves revealed no evidence of arteriopathy.

Histological Studies

Microscopic examination of sections from all brain regions showed atypical cells filling the lumina and involving blood vessel walls in the subarachnoid space, cortex, deep gray matter structures, and white matter. Although involvement of any type of vessel could be demonstrated, in most cases the cells showed a predilection for venules and capillaries. The tumor cells were relatively large and moderately pleomorphic. Nuclei were occasionally folded, demonstrating hyperchromasia or irregular clearing of chromatin. Amorphophilic cytoplasm was evident and generally scanty, but occasionally present in moderate amounts. Mitotic figures were abundant in both intraluminal and subendothelial collections of cells (Fig. 2).

Immunoperoxidase staining methods revealed all cases to be positive for the leukocyte common antigen. Staining patterns with the LN-1 and LN-2 antibodies revealed that the intraluminal infiltrates in four cases were of B-cell origin (Fig. 3). In Case 1, scattered tumor cells stained strongly for the T-cell antigen, while the rest of the tumor cells did not stain for either B- or T-cell antigens (Fig. 4). In the three cases where immunostaining was performed for the Factor VIII antigen, all cases were negative (Fig. 5).

Discussion

Literature Review

Malignant angioendotheliomatosis is a rare, generally fatal disease characterized by massive proliferation of mononuclear neoplastic cells within the blood vessels.

Fig. 1. Case 1. Coronal section of the cerebral hemispheres demonstrating bilateral necrotizing lesions in the basal ganglia.

Fig. 2. Case 1. Photomicrograph of a section from the frontal lobe treated to detect the immunohistochemical presence of the leukocyte common antigen. Note that every vascular space, including the large venule near the center, contains leukocyte common antigen-positive cells. Mitotic figures are present. Original magnification × 200.
embedded materials allows investigation and typing of tissues in archival material such as would not have been possible earlier.31

Clinical Presentation

We have examined five cases of malignant angioendotheliomatosis similar to those reported in the literature. Although the clinical symptoms varied, all patients showed signs of a subacute progressive dementia, often accompanied by clinical symptoms suggestive of TIA’s with multiple low-density abnormalities on cerebral CT scans indicating areas of infarction. This pattern, implying a cerebrovascular disorder, has been noticed by other investigators.2,3,15,20,22,27 Also consistent with earlier reports are our two cases in which the patient developed a major spinal cord paralysis.4,9,17,26,27 In all of the cases reported here, angiography was unrevealing and cytological examination of the CSF demonstrated no malignant cells. None of the cases presented were positive for human immunodeficiency virus (HIV), and none manifested signs of immunocompromise.

The clinical presentation is perplexing, but the fact that most other subacute dementing processes exhibit characteristic features assists in the differential diagnosis.3 The absence of myoclonus, seizures, and periodic discharges in the EEG helps to exclude Creutzfeldt-Jakob disease.3,24 Progressive multifocal leukoencephalopathy usually occurs in an immunocompromised patient.3,23 Multiple cerebral emboli may result in multi-infarct dementia, but the patient’s history usually discloses abrupt episodes of neurological deterioration.3 By contrast, in malignant angioendotheliomatosis, the onset of neurological impairment is insidious, with sudden stroke-like deficits distinctly uncommon.

Pathological Findings

The pathological findings remain the key to the diagnosis of this condition. The histogenesis of the neo-
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TABLE 1
Cases of neoplastic angioendotheliomatosis with CNS manifestations

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs.)</th>
<th>Sex</th>
<th>Origin of Disease</th>
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<tr>
<td>Braverman &amp; Lerner, 1961</td>
<td>66</td>
<td>F</td>
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<td>31</td>
<td>F</td>
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<tr>
<td>Shtern &amp; Likhachev, 1963</td>
<td>59</td>
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<tr>
<td>42</td>
<td>M</td>
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<tr>
<td>Strouth, et al., 1965</td>
<td>63</td>
<td>M</td>
<td>lymphoma</td>
</tr>
<tr>
<td>60</td>
<td>F</td>
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<td></td>
</tr>
<tr>
<td>Fievez, et al., 1971</td>
<td>52</td>
<td>M</td>
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<td>73</td>
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<td></td>
</tr>
<tr>
<td>Bots, 1974</td>
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<td>NA</td>
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<tr>
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<td>NA</td>
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<td>Sunohara, et al., 1984</td>
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<td>Ferry, et al., 1988</td>
<td>54</td>
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<tr>
<td>60</td>
<td>M</td>
<td>lymphoma</td>
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plastic cells confined to the vascular lumina in the CNS has been suggested to be derived from endothelium,11,12,26,27 carcinoma, or malignant histiocytosis. More recent studies have raised the possibility of a lymphoid origin of these cells, with various authors suggesting that the disorder would be more properly identified as angiotropic lymphoma or intravascular malignant lymphomatosis. Immunophenotyping of the cases in this report supports the concept of a lymphoid derivation of this neoplasm and discounts an endothelial origin. All five cases were positive for leukocyte common antigen, a lymphoid marker, and four of the five were immunophenotyped as B-cell neoplasms. Interestingly, our Case 1 was uniformly negative for the two B-cell markers which we evaluated, while a significant proportion of the tumor cells stained strongly for the T-cell antigen. We believe this is the first reported example of an intravascular T-cell lymphoma, and this also provides a ratio of B-cell to T-cell neoplasms in our series which is similar to that reported for CNS lymphoma in general.10

Treatment

Several attempts at treatment have been reported in the literature. In some cases, steroid administration was successful in temporarily arresting the otherwise relentless progression of the disease.2,3,9,12 Steroids were used in three of our cases and did result in improvement in the clinical status, although this improvement was not sustained. While some success has been reported with various chemotherapeutic agents, this has usually been on a single case basis, with little in the way of a documented, reproducible therapeutic regimen. The therapeutic implication of the designation of this disorder as angiotropic lymphoma or intravascular lymphomatosis is that administration of steroids, irradiation, and chemotherapy might be expected to induce remissions or extend survival times if the condition is recognized premortem. Although it may be difficult to diagnose this condition premortem (one of five in the present series was diagnosed during life), the diagnosis should be considered in persons with subacute dementia or multi-infarct dementia without documented cerebrovascular disease or immunosuppression. The overall threefold increase in incidence of CNS lymphoma in the nonimmunosuppressed population over recent years may also mean that this condition is becoming much more common than has been previously recognized.

Conclusions

This series includes the first reported case of an intravascular T-cell lymphoma and provides support for the concept of a lymphoid origin of the intraluminal neoplastic cells encountered in the disease known as "malignant angioendotheliomatosis." As a result, the condition should more properly be designated angiotropic lymphoma or intravascular lymphomatosis, and treatment should be rendered accordingly when the disease is recognized premortem.

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