The Value of Histopathological Examination of Surgically Removed Blood Clot in Determining the Etiology of Spontaneous Intracerebral Hemorrhage†

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SUMMARY The surgical specimens from all evacuated spontaneous intracerebral and intracerebellar hemorrhages at the Toronto General Hospital from 1976 to 1981 were reviewed. Cases resulting from trauma or from pre-operatively diagnosed aneurysms or arteriovenous malformations were excluded, leaving 84 cases in which the etiology was unknown. Seventy-five of the cases were intracerebral hemorrhages, while 6 were intracerebellar and 3 were intraventricular. Brain tissue was received with the blood clot in 54 cases (64%). From this tissue, an anatomic diagnosis was made in 37 cases; and in 14, the specific etiology of the hemorrhage could be determined. The specific etiologic diagnoses were tumor (7), amyloid angiopathy (6) and abscess (1). In 4 other cases, vasculopathy associated with hypertension was suggested as a possible etiologic diagnosis.

The high incidence of a specific etiologic diagnosis made from specimens in which tissue was included (25%) suggests that biopsy of adjacent brain tissue or preservation of tissue fragments identified at the time of surgery is of diagnostic value.

HISTOLOGIC EXAMINATION of surgically removed blood clot from patients with intracerebral hemorrhage of uncertain etiology is not always performed and has been the subject of only a few reports. In a series of 112 operated cases, reported by Jellinger,1 61 angiomas, 12 tumors and 5 angitides were found on histologic examination. The number of these cases in which the diagnosis was not known before surgery is not commented upon. In contrast, in a series published by Luyendijk,2 examination of the clot revealed an etiologic diagnosis in eight cases in which the diagnosis was not suspected clinically or at the time of surgery. Five of these cases were tumors while three were vascular malformations. With this information, we decided to review the anatomical features of all surgical specimens from cases of spontaneous intracerebral or intracerebellar hemorrhage of unknown etiology at the Toronto General Hospital from 1976–1981 in order to determine the value of this examination.

Materials and Methods

All cases diagnosed clinically as spontaneous intracerebral or intracerebellar hemorrhage who came to surgery from 1976–1981 were reviewed. Cases resulting from trauma, aneurysm or known arteriovenous malformation or tumor were excluded. This produced 84 cases for further analysis.

In all of these cases, the blood clot was received fixed in formalin. The amount of clot received varied from 1 cc to 100 cc (mean 9.4 cc). In many cases, only a portion of the ICH was submitted. The clot was filtered through gauze or filter paper and in all cases any tissue fragments found were submitted for histologic preparation. In seven cases clinically suspicious of tumor, biopsies of adjacent brain were taken, or tissue fragments found at surgery were preserved and submitted separately. In 55 of the 84 cases, the entire clot was processed for microscopic examination while in 29, representative areas were selected. Hematoxylin and eosin (H&E) stained tissue sections from these formalin fixed paraffin embedded clots and tissue fragments were examined retrospectively. Where blood vessels were identified, a Congo Red stain was performed and the section was examined under polarized light. Other special stains were completed in individual cases. The sites of the hematomas were identified according to the surgeon’s operative report.

Results

Eighty-four cases satisfied the review selection criteria and were included in the study. The vast majority of the hemorrhages (75/84) were intracerebral; 6 were intracerebellar and 3 were intraventricular. The lesions showed no side predilection, however, 13/20 parietal lobe lesions were situated in the right hemisphere. Of
TABLE 1  Cases In Which All Etiologic Diagnoses Could Be Made

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age</th>
<th>Sex</th>
<th>Site</th>
<th>Past history</th>
<th>Diagnosis</th>
<th>Associated diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73</td>
<td>F</td>
<td>temporal</td>
<td>hypertension</td>
<td>malignant astrocytoma</td>
<td>old infarction</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>F</td>
<td>temporal</td>
<td>abnormal behaviour x dys coma x 6 hours</td>
<td>malignant astrocytoma</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>M</td>
<td>frontal</td>
<td>coma x 6 hours</td>
<td>astrocytoma, low grade</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>M</td>
<td>frontal</td>
<td>dysphasia x 2 mo focal seizures x 1 dy</td>
<td>glioblastoma multiforme</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>M</td>
<td>frontal</td>
<td>headache and hemiparesis x 24 hr</td>
<td>oligodendroglioma</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>M</td>
<td>occipital</td>
<td>malignant melanoma x 1 yr severe headache x 6 hr</td>
<td>metastatic melanoma</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>M</td>
<td>parietal</td>
<td>lymphoma x 8 years hemiparesis x 8 days</td>
<td>metastatic lymphoma</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>79</td>
<td>F</td>
<td>occipital</td>
<td>hypertension coma x 12 hr</td>
<td>congophilic angiopathy</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>9</td>
<td>68</td>
<td>F</td>
<td>parietal</td>
<td>3 cerebral infarctions dysphasia x 4 dys</td>
<td>congophilic angiopathy</td>
<td>hemorrhagic infarction</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
<td>F</td>
<td>frontal</td>
<td>dysphasia and confusion x 10 dys</td>
<td>congophilic angiopathy</td>
<td>old hemorrhage and infarction</td>
</tr>
<tr>
<td>11</td>
<td>76</td>
<td>F</td>
<td>parietal-occipital</td>
<td>dysphasia and hemiparesis x 12 hr</td>
<td>congophilic angiopathy</td>
<td>senile changes</td>
</tr>
<tr>
<td>12</td>
<td>71</td>
<td>F</td>
<td>parietal-occipital</td>
<td>temporal arteritis headache x 24 hr</td>
<td>congophilic angiopathy</td>
<td>old infarction</td>
</tr>
<tr>
<td>13</td>
<td>67</td>
<td>F</td>
<td>parietal</td>
<td>Parkinson’s disease coma x 12 hr</td>
<td>congophilic angiopathy</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>58</td>
<td>M</td>
<td>parietal</td>
<td>recent craniotomy</td>
<td>abscess</td>
<td>—</td>
</tr>
</tbody>
</table>

those in the cerebellum, 5/6 were located in the left hemisphere.

Twelve patients had a bleeding diathesis (10 on anti-coagulant, one idiopathic thrombocytopenic purpura, one thrombotic thrombocytopenic purpura). In none of these cases could a diagnosis be made on examination of the clot. Of the remaining 72 cases, 18 had no parenchymal tissue submitted with the clot. In these 18 cases, no diagnosis could be made except in one case from a patient with known chronic lymphocytic leukemia (CLL) where the clot’s appearance was consistent with CLL. Of the 54 remaining cases in which tissue was received, a diagnosis could be made from the tissue in 37. In 14 of these, the diagnosis was of etiologic significance. Table 1 lists the clinical data, etiologic diagnoses and associated diagnoses for these cases. No specific etiology for the hemorrhage could be determined in the other 23 cases.

A. Etiologic Diagnoses (table 1)

1. Tumors

Tumors were identified in seven cases. Five were gliomas including 1 low grade astrocytoma, 2 malignant astrocytomas, 1 glioblastoma multiforme and 1 oligodendroglioma. Two of these 5 cases were grossly suspect of tumor at the time of surgery, while the remaining three cases were unexpected. Three of the gliomas showed vascular proliferation while two demonstrated areas of necrosis and one showed evidence of previous hemorrhage. The two patients with metastatic tumors had known primaries before surgery but there had been no other evidence of brain metastases.

2. Amyloid Angiopathy

In six cases amyloid angiopathy was found on H&E section and confirmed by Congo Red staining (fig. 1). This was the only diagnosis to show a site predilection with 5/6 cases in the parieto-occipital lobes. Two of the cases were associated with areas of old infarction, one with evidence of old hemorrhage, and three with senile plaques. In one case the diagnosis of Alzheimer’s disease could be made based on the presence of neurofibrillary tangles.

3. Infection

One patient had developed an ICH for unknown reasons after surgical evacuation of a traumatic ICH. At reexploration, a fragment of gel foam was found associated with an acute bacterial abscess.

B. Possible Etiologic Diagnoses

1. Hypertensive Change

In four cases, small vessels showed severe hyalinosis and fibrous degeneration of vessel walls suggestive of hypertensive vascular disease. One of these cases was associated with hemosiderin deposition suggesting previous hemorrhage. All four of these patients had a clinical history of hypertension.

In four other cases, mild hyalinosis and muscular hypertrophy were found, however, the degree of change was thought to be insufficient to implicate hypertension as an etiology. In no cases were Charcot-Bouchard micro-aneurysms identified.
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C. Associated Diagnoses

1. Recent Infarction
   In eight cases there was evidence of recent infarction. In 6 of these, the area of infarction was small and was interpreted as being secondary to the hematoma. In two of the cases, the specimen consisted almost entirely of large fragments of hemorrhagic and necrotic brain tissue. In view of the time interval from ictus to surgery of 4 days in one case and 2 weeks in the other, no definite comment could be made as to whether the infarct was a primary or secondary event.

2. Old Infarction
   Seven cases showed evidence of infarcted brain tissue which was at least several weeks old. Two were associated with congophilic angiopathy while one was associated with a malignant astrocytoma. The other four cases were not associated with any etiologic diagnoses, however, all four had a history of symptoms for one to two weeks prior to surgery.

3. Hemorrhage
   In six cases, there was evidence of old hemorrhage as shown by hemosiderin deposition. This was found in association with one case each of congophilic angiopathy, hypertension, chronic gliotic reaction and a malignant astrocytoma. In two cases, no other diagnoses could be made.

4. Gliosis
   Gliosis was found in 15 cases. Seven of these were associated with infarction, three with old hemorrhage, two with congophilic angiopathy and two with malignant astrocytoma. In one case gliosis was found in association with chronic edema.

5. Organization of Blood Clot
   Organization of the blood clot was found in five cases. It was associated in one case each with recent focal infarction, old infarction, congophilic angiopathy and mild gliosis.

6. Alzheimer's Disease
   In one case with congophilic angiopathy, Alzheimer's disease was diagnosed based on the presence of senile plaques and neurofibrillary tangles in a cortical fragment.

   In seven cases, portions of hematoma wall or tissue fragments preserved at surgery were submitted separately for histologic preparations. Two of these cases showed astrocytoma while one showed congophilic angiopathy. In two other cases gliosis was present.

FIGURE 1. Case 9. A. Tissue fragment showing thickened vessel wall stained with Congo Red. B. The same vessel under polarized light showing birefringence of the vessel wall confirming the presence of amyloid. The bar measures 50 μ.
Discussion

Spontaneous intracerebral hemorrhage is a common cause of morbidity and mortality. The etiology of these hemorrhages is often determined before surgery, however, in a significant proportion of operated cases the diagnosis is not made prior to surgical intervention, and is usually thought to be hypertensive in origin. Examination of the surgically removed blood clot is an important aspect of the assessment of these patients.

In this retrospective study of 84 patients, 12 had bleeding diathesis. Although the hemorrhage was likely secondary to the bleeding diathesis, this could not be substantiated histologically. In another 18 cases, no tissue fragments were submitted and no significant anatomical diagnosis could be made except in one case in which the clot's appearance was consistent with CLL. The varying degrees of organization seen in the clots did not aid in assessing the etiology of the hemorrhage.

In those patients from whom tissue was submitted, however, (54 cases), a diagnosis was made in 37 cases. In 18 of these the etiology for the hemorrhage was found or could be implied. Many of the other abnormalities noted such previous hemorrhage and gliosis were significant but could not on their own imply an etiologic diagnosis.

Tumors were identified in seven cases. Recent studies have reported that between 1 and 10.2 per cent of ICH are associated with intracranial tumor. They have also emphasized that the hemorrhage may be the presenting feature of the tumor. As in this series, the most common tumors to present as hemorrhages are malignant gliomas. Several of the tumors were identified on only small fragments of tissue found within the clot. Predisposition to hemorrhage was suggested by the presence of vascular proliferation or necrosis. In one case, there was evidence of previous hemorrhage.

Congophilic angiopathy has recently been recognized as an important cause of intracerebral hemorrhage particularly in normotensive elderly patients. Biopsy of the hematoma wall has resulted in diagnosis of this lesion in several cases. Several authors have cautioned however, that disturbing the wall of the hematoma cavity in these cases could precipitate further bleeding. In the present study, six cases of congophilic angiopathy were found. Congophilic angiopathy increases with age and is found predominantly in the parieto-occipital lobes. It is difficult to prove that the angiopathy is the etiology of these hemorrhages, however, the consistent parieto-occipital location of the hemorrhages, and evidence of previous hemorrhage in one of the cases would favour this. In one patient shown to have congophilic angiopathy, an incidental finding was the presence of cortical senile plaques and neurofibrillary tangles sufficient to make a diagnosis of Alzheimer's disease. The knowledge of such a diagno-

References

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