Cerebrovascular Disease in Acute Leukemia: A Clinicopathological Study of 14 Patients

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Abstract

Objective Cerebrovascular disease (CVD) is a serious complication of acute leukemia, and the underlying conditions are different from the common risk factors for CVD. The aim of this study was to characterize the clinical and pathological features of CVD in patients with acute leukemia.

Patients or Materials In our series of 116 autopsied cases of acute leukemia during the period between January 1978 and December 1998, we had 14 patients who had CVD during the course of acute leukemia. The neuropathological and clinical features of those patients were examined.

Results Neuropathological examination showed hemorrhagic infarction due to disseminated aspergillosis or mucormycosis (5 cases), multiple hemorrhages due to leukemic cell infiltration (2 cases) and a single massive hemorrhage with petechial hemorrhages in various regions of the brain (4 cases). Three patients had CVD due to miscellaneous causes. Clinicopathological correlation revealed that fungal disseminations occurred under agranulocytosis, while leukemic cell infiltration occurred under a marked leukocytosis (peripheral white blood cell count >100,000/μl). Four patients with coagulopathy, including three with disseminated intravascular coagulation (DIC) had a single massive hemorrhage.

Conclusion Our study demonstrated that there were at least three types of CVD with specific clinicopathological features. Hemorrhagic infarction due to disseminated aspergillosis or mucormycosis (5 cases), multiple hemorrhages due to leukemic cell infiltration (2 cases) and a single massive hemorrhage with petechial hemorrhages in various regions of the brain (4 cases). Three patients had CVD due to miscellaneous causes. Clinicopathological correlation revealed that fungal disseminations occurred under agranulocytosis, while leukemic cell infiltration occurred under a marked leukocytosis (peripheral white blood cell count >100,000/μl). Four patients with coagulopathy, including three with disseminated intravascular coagulation (DIC) had a single massive hemorrhage.

Key words: aspergillosis, mucormycosis, hemorrhagic infarction, multiple hemorrhage, DIC

Introduction

Cerebrovascular disease (CVD) is a serious complication of leukemia (1, 2) as well as bleeding or thrombosis in other organs of the body (3). A representative cause of CVD in those patients is abnormal coagulation or coagulopathy such as disseminated intravascular coagulation (DIC) (1, 2, 4, 5). Therefore, hematologists have developed supportive therapies for coagulopathy associated with leukemia. However, in spite of these therapies, we had 14 CVD patients in a series of 116 autopsied cases of adult acute leukemia. This indicates that CVD is still frequent in leukemia patients who undergo advanced therapies for coagulopathy.

Previous studies of leukemia patients have shown that CVD is due to unusual causes (2, 4, 5). One example is cerebral infarction due to fungal embolism (2, 4). Accordingly, several pathological conditions other than coagulopathy could also play significant roles in the pathogenesis of CVD in leukemia patients. To clarify the causes of CVD in acute leukemia, we examined 14 CVD patients with acute leukemia both neuropathologically and clinically. Our results showed that at least three groups of CVD could be defined by their pathogenesis and by their underlying hematological conditions.

For editorial comment, see p 1081.

Subjects and Methods

During the period between January 1978 and December 1998, there were 116 autopsied cases of adult acute leukemia in the autopsy registry at Yamagata University School of Medicine. Using the clinical record registry system, we identified 14 autopsied patients who had CVD during the course of acute leukemia. The diagnosis of acute leukemia was based on cytochemical examinations of the bone marrow blood smears according to the proposal of The French-American-British (FAB) Study Group (6). The diagnosis of CVD was made by neurological and neuroradiological studies.
Neuropathological examination of the 14 brains was done both macroscopically and microscopically. Representative sections of the brains were processed for 6-μm thick paraffin sections and stained with hematoxylin-eosin and luxol fast blue stains. When appropriate, stains for microorganisms including Gram’s, periodic acid-Schiff (PAS) and Grocott were applied. Blood vessels were examined with elastica Masson-Goldner stain.

Clinicopathological correlation of the 14 patients was made by review of clinical records including neuroradiological studies with CT scan or MR imaging. Common risk factors for CVD such as hypertension and hyperlipidemia were checked in all of the patients. General autopsy records were also reviewed to obtain information on any underlying pathological conditions possibly related to the pathogenesis of CVD.

Table 1. Fourteen Cases of Acute Leukemia with Cerebrovascular Disease

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/ Sex</th>
<th>Type of Leukemia*</th>
<th>Clinical presentation</th>
<th>Location of Lesion (fungus)</th>
<th>At the onset of CVD</th>
<th>WBC (μL) Bleeding Tendency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic infarction due to fungal embolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>62/F</td>
<td>AML (M1)</td>
<td>lt. hemiparesis</td>
<td>rt. fronto-parietal lobe (mucormyces)</td>
<td>500</td>
<td>no</td>
</tr>
<tr>
<td>2</td>
<td>71/F</td>
<td>AMMoL (M4)</td>
<td>coma</td>
<td>lt. temporo-occipital lobe, lt. cerebellar hemisphere (aspergillus)</td>
<td>500</td>
<td>no</td>
</tr>
<tr>
<td>3</td>
<td>71/F</td>
<td>AMoL (M5)</td>
<td>lt. hemiparesis</td>
<td>rt. fronto-temporal lobe, rt. cerebellar hemisphere (aspergillus)</td>
<td>500</td>
<td>no</td>
</tr>
<tr>
<td>4</td>
<td>50/F</td>
<td>EL (M6)</td>
<td>lt. hemiparesis</td>
<td>lt. parieto-occipital lobe (mucormyces)</td>
<td>400</td>
<td>no</td>
</tr>
<tr>
<td>5</td>
<td>57/F</td>
<td>ALL (L2)</td>
<td>rt. hemianopsia</td>
<td>rt. temporal lobe, rt. basal ganglia (aspergillus)</td>
<td>400</td>
<td>no</td>
</tr>
<tr>
<td>Multiple cerebral hemorrhages around leukemic cell nodules</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>46/M</td>
<td>AML (M1)</td>
<td>rt. hemiparesis</td>
<td>bil. cerebral hemispheres**</td>
<td>224,000</td>
<td>no</td>
</tr>
<tr>
<td>7</td>
<td>52/M</td>
<td>ALL (L2)</td>
<td>coma</td>
<td>bil. cerebral hemispheres**, basal ganglia, pons</td>
<td>124,600</td>
<td>no</td>
</tr>
<tr>
<td>Cerebral hemorrhage due to coagulopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>17/F</td>
<td>AML (n.d.)***</td>
<td>coma</td>
<td>frontal lobe hemorrhage</td>
<td>1,500</td>
<td>thrombocytopenia</td>
</tr>
<tr>
<td>9</td>
<td>17/F</td>
<td>APL (M3)</td>
<td>lt. N. VII palsy rt. hemiparesis</td>
<td>pontine hemorrhage</td>
<td>78,100</td>
<td>DIC</td>
</tr>
<tr>
<td>10</td>
<td>41/M</td>
<td>APL (M3)</td>
<td>coma</td>
<td>lt. subdural hematoma cerebellar hemorrhage</td>
<td>700</td>
<td>DIC</td>
</tr>
<tr>
<td>11</td>
<td>54/M</td>
<td>APL (M3)</td>
<td>coma</td>
<td>lt. thalamic hemorrhage intraventricular bleeding</td>
<td>900</td>
<td>DIC</td>
</tr>
<tr>
<td>CVDs due to miscellaneous causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>63/M</td>
<td>EL (M6)</td>
<td>aphasia rt. hemiparesis drowsiness</td>
<td>lt. subdural hematoma</td>
<td>700</td>
<td>no</td>
</tr>
<tr>
<td>13</td>
<td>69/F</td>
<td>AML (M1)</td>
<td></td>
<td>cerebral cortical hemorrhage (multiple)</td>
<td>600</td>
<td>no</td>
</tr>
<tr>
<td>14</td>
<td>83/M</td>
<td>AML (M1)</td>
<td>rt. hemiparesis</td>
<td>lt. subdural hematoma</td>
<td>1,200</td>
<td>no</td>
</tr>
</tbody>
</table>

**usually in the subcortical white matter. ***n.d.: not determined in FAB classification.

Results

The 14 cases included in this study are summarized in Table 1. We have divided those cases into four groups as defined by neuropathological findings.

General features

The patients consisted of 6 men and 8 women and the age of onset of CVD ranged from 17 to 83 (mean 55) years. Twelve patients had CVD during the course of standard antileukemic chemotherapy, but in two patients (cases 7 and 8), CVD had occurred before the chemotherapy was started. There was no patient who underwent bone marrow transplantation. No neurological presentations correlated with the different types of
CVD. Results of hematological examinations at the onset of CVD were varied among the patients. Repeated transfusions of red blood cells and platelets relieved severe anemia and thrombocytopenia in all patients except for one (case 8) who had refused any medical treatment. Three cases with acute promyelocytic leukemia (cases 9 to 11) had DIC. The other patients were not found to have any symptoms caused by bleeding tendency. Some cases had risk factors for CVD, but there was no relationship between the neuropathological changes in the patients and the risk factors, including hypertension, hyperlipidemia and diabetes.

1) Hemorrhagic infarction due to fungal embolism (cases 1 to 5)

Neuropathology

Five brains showed a single or two separate hemorrhagic necrotic lesions macroscopically. Microscopic examination of those brains revealed numerous fungal hyphae within blood vessels in and around the necrotic lesions. Those hyphae were clearly demonstrated with PAS or Grocott stains, and the morphological features were consistent with aspergillus in three cases (cases 2, 3 and 5) and with mucormyces in two (cases 1 and 4). Because several medium-sized vessels were occluded by clusters of fungal hyphae, decorated with fibrin meshwork, those 5 brains were diagnosed as having hemorrhagic infarction caused by fungal embolism.

General autopsy findings

All the patients in this group had hypoplastic bone marrow, consistent with bone marrow suppression due to chemotherapy. The lungs were infected with aspergillus or mucormyces. In all patients, the fungi were the same as those noted in the brain lesions. The thyroid gland, spleen and liver also showed dissemination of those fungi. There was no evidence of endocarditis.

Clinical analysis

Review of clinical records revealed that the patients in this group suffering a single massive hemorrhage (WBC count <500/μl) or agranulocytosis (WBC count <100/μl). Pneumonia, which was not improved by anti-bacterial and anti-fungal therapies, was another common feature of those patients. All the patients were in a bone marrow suppressive state due to antileukemic chemotherapy at the onset of CVD. Because four cases (cases 1, 3, 4 and 5) were remission induction failure and one (case 2) was a relapsed case, salvage chemotherapies had been administrated, which resulted in severe and prolonged agranulocytosis. Two patients were examined with CT scan and diagnosed as having hemorrhagic infarction. Clinical findings other than the presence of agranulocytosis and pneumonia did not help in distinguishing those patients from the other groups. Along with the wide use of antifungal therapies and the rapid diagnosis of fungal infection by the examination of serum β-D-glucan, there was no patient in this neuropathological group subsequent to case 2 in 1995.

2) Multiple cerebral hemorrhages around leukemic cell nodules (cases 6 and 7)

Neuropathology

Two cases showed macroscopic multiple cerebral hemorrhages. Each hemorrhagic lesion was generally round in shape and up to 2 cm in diameter. The lesions were located in the subcortical white matter and basal ganglia of the cerebrum. Microscopically, the hemorrhagic lesions consisted of leukemic cell nodules surrounded by numerous red blood cells, forming hemorrhagic lesions. There was no leptomeningeal leukemic cell infiltration.

General autopsy findings

The bone marrow showed proliferation of leukemic cells. Leukemic cells also invaded the spleen, lungs, lymph nodes and myocardium. Unlike the brain, leukemic cell infiltration into the organs of the body was not surrounded by the red blood cell layer.

Clinical analysis

Review of clinical records revealed a marked increase in leukemic cells in the peripheral blood (WBC count >100, 000/μl) at the onset of cerebral hemorrhage. This abnormal hematological condition occurred a few days after (case 6) or before (case 7) the antileukemic chemotherapy was started. Brain CT scan of the patients showed multiple cerebral hemorrhages. Among the various clinical findings, marked leukocytosis was characteristic in this group of patients.

3) Cerebral hemorrhage due to coagulopathy (cases 8 to 11)

Neuropathology

Patients of this group suffered a single massive hemorrhage (cases 8, 10 and 11) as well as numerous tiny hemorrhagic foci in various regions of the brain. One case (case 9) had subdural hematoma in addition to the pontine hemorrhage. Microscopic examination of the brain did not show any microorganisms, leukemic cell infiltration nor vascular alterations. Because of multiple hemorrhagic lesions and exclusion of other causes, those four autopsy cases were diagnosed as having cerebral hemorrhage due to coagulopathy.

General autopsy findings

Macro- and micro-scopic hemorrhagic foci were noted in various organs of the body. Intestinal bleeding from mucosal hemorrhagic lesions was a representative finding. One case (case 9) had a hematoma in the mediastinum.

Clinical analysis

Bleeding tendency was a common clinical feature in those patients; skin purpura and oral or nasal bleeding were observed. Bleeding tendency was due to thrombocytopenia (case 8) or DIC (cases 9, 10 and 11). The patients with DIC had acute promyelocytic leukemia as an underlying disease. One patient (case 9) was treated with all-retinoic acid (ATRA), but had the pontine hemorrhage and subdural hematoma before the reduction of leukemic cells and resolution of DIC. Two cases (case
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<td>agranulocytosis</td>
</tr>
<tr>
<td>multiple hemorrhages</td>
<td>leukemic cell infiltration</td>
<td>extreme leukocytosis</td>
</tr>
<tr>
<td>massive hemorrhage</td>
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10 and 11) had relapsed acute promyelocytic leukemia, and had been treated with salvage chemotherapy. One case (case 9) was examined with MR imaging, which showed a concurrence of pontine hemorrhage and subdural hematoma.

4) Cerebrovascular disease due to miscellaneous causes (cases 12 to 14)

There were three patients in this group who had no pathological condition related to acute leukemia. A 63-year-old man (case 12) did not have any specific neuropathological changes that could explain the cause of his subdural hematoma. A 69-year-old woman (case 13) had several episodes of cerebral hemorrhage before and during the course of acute leukemia. Neuropathological examination revealed cerebral amyloid angiopathy, which was likely to be the cause of her recurrent brain hemorrhages. An 83-year-old man (case 14) suffered an acute subdural hematoma after he fell and hit his head on the floor.

Discussion

Our study demonstrated that at least three types of CVD could be identified, and they were associated with specific clinical and neuropathological features in leukemia patients (Table 2).

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<td>coagulopathy</td>
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Table 2. Clinicopathological Subtypes of CVD in Acute Leukemia

Hemorrhagic cerebral infarction was caused by fungal embolism resulting from agranulocytosis induced by antileukemic chemotherapy. Multiple cerebral hemorrhages occurred due to leukemic cell infiltration under an extremely increased number of leukemic cells. A single massive cerebral hemorrhage was associated with coagulopathy, especially DIC.

Five cases of hemorrhagic infarction constitute a distinct group among the leukemia patients with CVD in that its etiology is fungal embolism (2, 7). Regardless of the subtypes of acute leukemia, the underlying condition in those patients was bone marrow suppression and subsequent agranulocytosis during or after antileukemic therapy. Agranulocytosis can induce fungal hyphae dissemination from the lung (pneumonia) to the brain, resulting in fungal emboli, instead of abscess (8) or granuloma (9) formation. Disseminated fungal infection often causes hemorrhagic infarction in neutropenic leukemia patients (2, 7, 8), although hemorrhagic infarction in leukemia patients could be diagnosed clinically as a result of abnormal coagulation (10).

Fungal infection frequently complicates acute leukemia (11). The causative microorganisms are generally candida, and sometimes aspergillus or mucormyces (11). The question then arises as to why aspergillus and mucormyces and not candida cause hemorrhagic infarction. According to Scaravelli and Cook (12), there is a relationship between the size of fungal hyphae and the types of brain lesions. The large hyphae of aspergillus or mucormyces would be trapped within the blood vessels of large to medium size, resulting in cerebral embolism. On the other hand, the smaller-sized pseudohyphae of candida would be trapped in the preterminal blood vessels, causing multiple microscopic lesions, commonly called abscess. The above hypothesis supports our observation that patients with hemorrhagic infarction had occlusions of the medium-sized branches of the cerebral arteries.

Patients with multiple cerebral hemorrhages had marked leukocytosis as a common clinical finding. The first case with such a clinicopathological entity was described by Freireich et al in 1960 (13). To date, leukemic cell infiltration has been reported in patients with chronic leukemia in blastic crisis or acute monocytic leukemia (14). In the present study, one case of acute myelogenous leukemia (case 6) and one case of acute lymphocytic leukemia (case 7) had the same pathology. Marked leukocytosis could be a more significant risk factor for multiple cerebral hemorrhages than the different types of leukemia.

At this moment, there was no definite explanation for the pathogenesis of cerebral hemorrhages around leukemic cell nodules. One explanation is based on the observation by Freireich et al (13) who noted the blood vessels filled with leukemic cells in and around the hemorrhagic foci. Aggregated leukemic cells would injure the vascular endothelial cells as well as the local circulation, resulting in hemorrhage. Another explanation is vascular wall damage by the direct invasion of leukemic cells (14).

Coagulopathy caused a single massive hemorrhage in four out of 14 patients. A noteworthy finding is that three out of four patients (cases 9 to 11) in this group had acute promyelocytic leukemia (APL) with DIC. APL is frequently associated with DIC in the early stage of the disease (3). Therefore, in spite of the advanced supportive therapies against coagulopathy, APL is still an important risk factor for cerebral hemorrhage among the FAB subtypes of acute leukemia.

The new therapy with ATRA has decreased the complications of coagulopathy as well as increased the rate of complete remission among APL patients (15). Accordingly, the use of ATRA could decrease the risk of cerebral hemorrhage in pa-
patients with APL. In the present study, we could not conclude whether there is a decrease in frequency of cerebral hemorrhage associated with APL because the number of our autopsy cases was too few (cases 9 to 11).

In conclusion, this study can provide clues to identify the causes of CVD in leukemia patients (Table 2). In the case of a leukemia patient diagnosed as having CVD by either CT scan or MR imaging of the brain, hemorrhagic infarction associated with agranulocytosis and pneumonia would be due to aspergillosis or mucormycosis. Multiple hemorrhages associated with marked leukocytosis would be a sign of leukemic cell infiltration. A single massive hemorrhage could be associated with coagulopathy, usually resulting from DIC complicated with APL.

Another implication of the present study is that the causes and types of CVD in leukemia patients (Table 2) depend largely on the therapeutic modalities. A review of literature and the results of our study show changes in the predominant causes and types of CVD along with improved therapeutic innovation. Preceding the introduction of effective chemotherapeutic agents, multiple cerebral hemorrhage due to leukemic cell infiltration was reported (13). At present, such patients seem to be exceptional cases who were not responsive to remission induction therapy. Around the 1990s, the introduction of effective chemotherapeutic regimens improved the remission rate of acute leukemia patients, but it also increased the rate of severe agranulocytosis. Cases of hemorrhagic infarction due to fungal infection occurred at a time when there were no effective antifungal agents (7–9, 12). In our autopsy series, there were no patients with hemorrhagic infarction after the wide use of the antifungal agents commenced. CVD due to DIC in APL patients (2, 3) could decrease in number with the use of ATRA instead of conventional chemotherapy (15). In the future, CVD with unexpected pathomechanisms could occur in patients with acute leukemia due to the newly introduced therapies. Cerebral hemorrhage associated with the use of cyclosporin-A/FK506 after bone marrow transplantation seems to be such an example (16).

References