J Neurol (1997) 244 : 94–100

ORIGINAL COMMUNICATION

Kunihiko Yamauchi
Yoshikatsu Umeda

Symptomatic intracranial haemorrhage in acute nonlymphoblastic leukaemia: analysis of CT and autopsy findings

Received: 7 May 1996
Received in revised form: 30 July 1996
Accepted: 26 August 1996

K. Yamauchi (✉) · Y. Umeda
Department of Internal Medicine,
Tokai University School of Medicine,
Bohseidai, Isehara-shi,
Kanagawa-ken, 259-11, Japan
Tel.: 81-463-93-1121,
Fax: 81-463-94-9058

Abstract We studied the CT and autopsy findings in patients with symptomatic intracranial haemorrhage (ICH) in acute nonlymphoblastic leukaemia (ANLL). From 1982 to 1994, 38 (20%) of 194 patients with ANLL were diagnosed as having ICH, by CT in 17 patients, by autopsy in 11 and by both examinations in 10. Intracerebral haemorrhage occurred in 30 patients. Twenty-four patients with subcortical haemorrhage were classified into three types: a single haematoma (7), clustered multifocal haematomas (11), and separated multifocal haematomas (6). Subarachnoid haemorrhage (SAH) occurred in 22 patients; 15 with subcortical haemorrhage, 1 with subdural haemorrhage (SDH) and 6 without any other ICH. SDH was also found in 4 patients with parenchymal haemorrhage or SAH or both. Concurrent, multiple haemorrhages consisting of various combinations of intracerebral haemorrhage, SAH and SDH are characteristic of ICH in ANLL. Multiple or confluent haematomas occur preferentially in subcortical brain.

Key words Subcortical brain haemorrhage · Subarachnoid haemorrhage · Computed tomography · Acute nonlymphoblastic leukaemia

Introduction

Although advances in platelet transfusion procedures and management of disseminated intravascular coagulopathy (DIC) have reduced the incidence of severe haemorrhagic complications in patients treated with intensive chemotherapy for acute leukaemia, spontaneous intracranial haemorrhage (ICH) is still frequently the immediate cause of death in this disorder [4, 17, 22]. Analysis of some small autopsy series [6, 9] has revealed that subcortical brain haemorrhages occurring multifocally are characteristic of ICH in acute leukaemia. ICH appears to arise from several factors, such as vessel wall lesions, low platelet count, platelet dysfunction, liver damage with the delayed synthesis of coagulation factors, increased plasmin- or elastase-induced fibrinolysis, DIC and the anticoagulant therapy, hyperleukocytosis, hypoxia and sepsis [3–5, 19, 21].

In recent years, computed tomography (CT) has come to be used broadly for diagnosis in the early stage of ICH, and a classification by criteria of the French-American-British (FAB) cooperative group was introduced for acute nonlymphoblastic leukaemia (ANLL) [2].

In this study, we analysed ICHs that were diagnosed by CT and/or autopsy in 38 patients with ANLL who were classified by FAB criteria, and compared the CT findings with those at autopsy in 10 patients.

Subjects and methods

Patient data

From January 1982 to December 1994, 243 patients with acute leukaemia were admitted to Tokai University Hospital and died at presentation or during a relapse despite treatment by the haematologists dealing with adult acute leukaemia. There were 194 patients with ANLL and 49 with acute lymphoblastic leukaemia (ALL).

Table 1 Distribution of FAB types in 243 patients with acute leukaemia (*ICH* intracranial haemorrhage, *M* myeloid, *L* lymphoid)

Type	Patient no	No. with ICH (%)
M 1	67	8 (12)
2	33	5 (13)
3	33	16 (48)
4	26	4 (15)
5	14	3 (20)
6	13	2 (15)
	194	38 (20)
L	49	3 (6)

Table 2 Diagnostic criteria of disseminated intravascular coagulopathy (*FDP* fibrinogen-fibrin degradation products)

	Points scored			
	0	1	2	3
Leukaemia	No	Yes	–	–
Organ dysfunction due to DIC	No	Yes	–	–
Prothrombin test (patient/normal value)	< 1.25	1.25 <, < 1.67	1.67 <	–
Plasma fibrinogen (mg/dl)	150 <	100 <, < 150	< 100	–
Serum FDP (μg/ml)	< 10	10 <, < 20	20 <, < 40	40 <

Only the former are considered in this article. As shown in Table 1, 194 patients with ANLL were classified according to the FAB criteria [2]: 67 had myeloblastic leukaemia without maturation (M1), 33 myeloblastic leukaemia with some maturation to promyelocytes (M2), 33 promyelocytic leukaemia (M3), 26 myelomonocytic leukaemia (M4), 14 monocytic leukaemia (M5), and 13 had erythroleukaemia (M5). Remission induction chemotherapy was given which consisted of either daunorubicin, 1-β-D-arabinofuranosyl cytosine (Ara-C) or N^4-behenoyl Ara-C, 6-mercaptopurine and prednisolone or a regimen using aclarubicin instead of daunorubicin [11]. Patients with meningeal infiltration received intrathecal chemotherapy consisting of methotrexate, Ara-C and prednisolone. Reinduction chemotherapy with a single agent or combinations of mitoxantorone, etoposide, vincristine/vinblastine and high- or low-dose Ara-C was given for relapsed patients. Patients with M3 who received differentiation therapy with *all-trans* retinoic acid in 1994 are not included in this series because they survived.

A supportive treatment consisted of single- or multiple-donor platelet transfusion to maintain platelet counts (performed every other day) above 20×10^9/l and greater than this if there was evidence of haemorrhage [7]. Packed red blood cell transfusions were administered to maintain haemoglobin above 8.5 g/dl. Routine laboratory examinations were as follows: white blood cell count (WBC), count of leukaemic blasts or promyelocytes, platelet count, haemoglobin, and coagulation analyses (prothrombin time, activated partial thromboplastin time, fibrinogen, fibrinogen-fibrin degradation product and antithrombin III).

Disseminated intravascular coagulopathy

DIC was diagnosed by the diagnostic criteria based on the scoring system proposed by the Japanese Ministry of Health and Welfare [1]. The definite diagnosis of DIC requires a total score of 4 points or more (Table 2). DIC was treated with low-dose heparin infusion or gabexate mesilate or a combination of the two without an increase of bleeding manifestations in any of the patients.

Evaluation of ICH

Forty of 194 patients with ANLL were clinically suspected to suffer from ICH. The presence and location of the haematoma were confirmed by CT and/or autopsy in 38 patients (20%): CT in 17 patients, autopsy in 11, and both in 10. ICH could not be evaluated in 2 patients because CT records preceding death and autopsy reports were missing.

CT was performed by either a HSA/RP or a W1000 scanner (General Electric Medical Systems Group, Milwaukee, USA or Hitachi, Japan, respectively) with 10-mm intersection spacing. In most patients CT was performed within 4 h after the stroke.

The incidence of ICH was compared between ANLL subtypes, patients with WBC of higher or lower than 10×10^9/l, and between patients with and without DIC. Whether CT findings differed from those at autopsy was evaluated in 10 patients who underwent both examinations. The shape or type of subcortical haematomas was specified.

The level of consciousness was evaluated within 30 min of the stroke, using the neuropsychological grades described by Markwalder et al. [14]. The grading system is as follows: grade 0, patient neurologically normal; grade 1, patient alert and oriented, mild symptoms such as headache, absent or mild neurological deficit such as reflex asymmetry; grade 2, patient drowsy or disoriented with variable neurological deficit such as hemiparesis; grade 3, patient stuporous but responding appropriately to noxious stimuli, severe focal signs such as hemiplegia; grade 4, patient comatose with absent motor responses to painful stimuli, decerebrate or decorticate posturing. The time interval from initial grades at diagnosis to development of coma (grade IV) was also recorded.

Extracranial haemorrhages

Massive gastrointestinal haemorrhage was diagnosed from heamatemesis or melena accompanied by a fall in blood pressure or massive blood clot in the tract at autopsy. Serious pulmonary haemorrhage was diagnosed from haemoptysis accompanied by acute respiratory failure or massive blood clot in the lungs at autopsy.

Statistical methods

Either χ^2 analysis or Fisher's exact test was used for statistical evaluation. A P-value of < 0.05 was considered significant.

Results

Incidence and location of ICHs

Terminal ICH occurred significantly more often in 194 patients with ANLL (38; 20%) compared with 3 (6%) of 49 patients with ALL ($\chi^2 = 5.06$, $P = 0.025$) (Table 1). The incidence in each subtype of ANLL varied from 12% in M1 to 48% in M3, average 20%. The patients with ICH

Table 3 Location of intracranial haemorrhage (n = 38)

Location	No. (%)
Brain	30 (79)
Subcortical	24
Putaminal	4
Thalamic	3
Mixed	1
Cerebellar	4
Pontine	3
Subarachnoid	23 (61)
Subdural	5 (13)
Ventricular	14 (37)

Table 4 Combination of haemorrhagic locations (n = 38)

Location	No. (%)
Brain	14 (37)
Brain + subarachnoid	13 (34)
Brain + subdural	1 (3)
Brain + subarachnoid + subdural	2 (5)
Subarachnoid	6 (16)
Subdural	1 (3)
Subarachnoid + subdural	1 (3)

in ANLL consisted of 23 males and 15 females, ranging in age from 16 to 82 years (mean 50). ICH occurred in 18 patients before treatment began and 17 relapsed patients who were resistant to intensive chemotherapy for remission induction. The remaining 3 patients suffered ICH during the first induction therapy. One patient had borderline hypertension before ICH. The incidence of subcortical haemorrhage, subarachnoid haemorrhage (SAH), subdural haemorrhage (SDH) and ventricular haemorrhage (VH) was found to be high (Table 3). As shown in Table

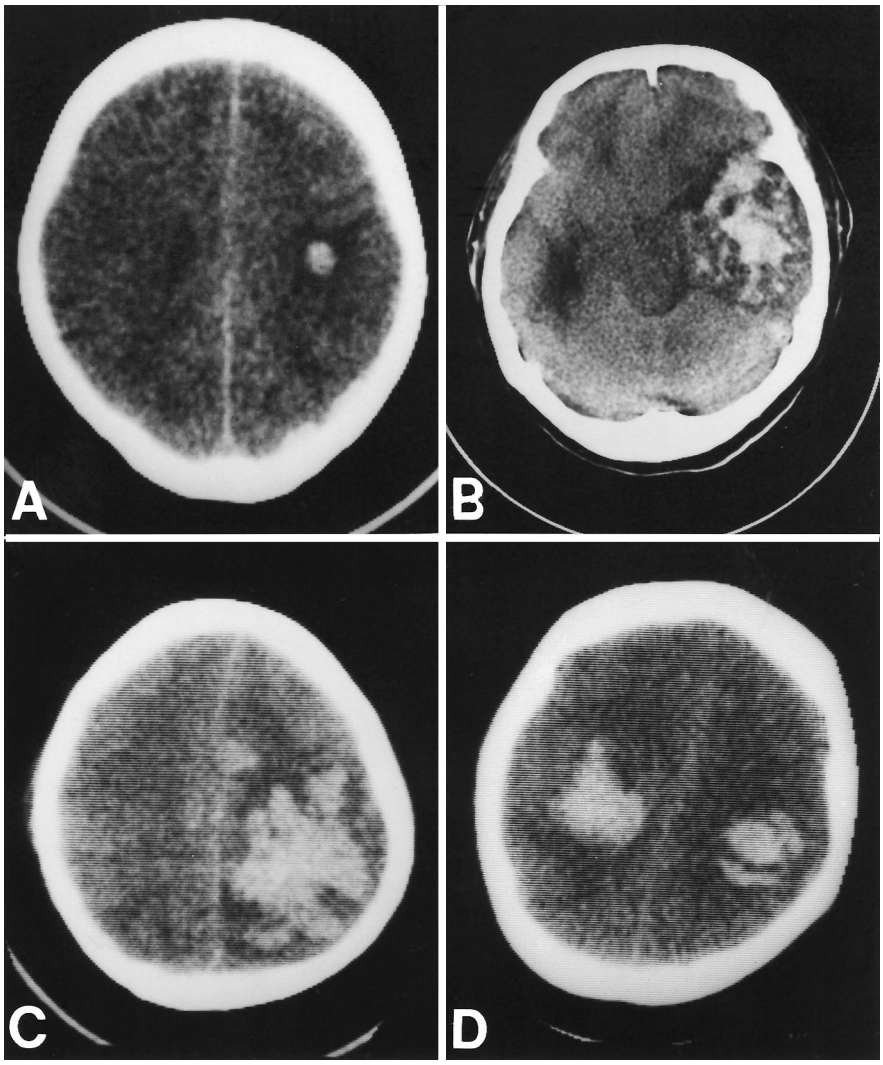

Fig. 1 A–D Nonenhancing CT scans of subcortical brain haemorrhages. **A** Type I is a single haematoma with smooth contour that occurs frequently in patients without haemorrhagic diathesis or leukaemia, **B** Type IIa, clustered multifocal haematomas consisting of a large blood clot and surrounding small clots. **C** Type IIb, single haematoma with lobulated contour that was formed by confluence of some multifocal clots. **D** Type III, separate multifocal haematomas

Table 5 Classification of subcortical brain haemorrhages on nonenhancing CT scans (n = 24)

Type		No.
I	Single haematoma	7
II	Clustered multifocal haematomas	11
a	with satellites	3
b	with lobulated form	4
a + b	with mixed form of a and b	4
III	Isolated multifocal haematomas	6

4, SAH occurred in 15 (50%) of 30 patients with brain haemorrhage. A single event of SAH occurred in 6 patients. SDH occurred in 1 patient with brain haemorrhage, 2 with brain haemorrhage and SAH, and 1 without any other event. Plain CT in 30 patients with brain haemorrhage showed one or more high-density consolidated nonenhancing lesions that varied in size from small haematomas to large confluent haematomas. Among 24 patients with subcortical brain haemorrhage, the condition was accompanied by SAH, VH and SDH in 13 patients (54%), 12 (50%) and 3 (13%), respectively. Subcortical brain haemorrhages were classified morphologically into three types: type I (Fig. 1 A), a single haematoma with smooth contour like that which occurs frequently in patients without haemorrhagic diathesis or leukaemia; type II (Fig. 1 B, C), clustered multifocal haematomas; and type III (Fig. 1D), isolated multifocal haematomas (Table 5). The shape of haematomas in type II was specified as follows: (1) a larger haematoma and the surrounding smaller ones, and (2) a haematoma with a lobulated contour that was formed probably because small haematomas around a large one in group 1 became confluent. Seventeen (71%) of the 24 patients had multifocal haematomas. There was no difference between the patients with and without leukocytosis in the incidence of each type. Subcortical haematomas were located in approximately the same incidence in all lobes except for the occipital lobe.

Relationship between stroke times of brain haemorrhage and SAH

Among 10 patients with brain haemorrhage who had both CT and autopsy, only 1 (case 8) was shown to have SAH by CT that was performed 71.5 h after haemorrhage. Six patients were not found to have SAH by CT performed after a mean of 3.4 h while the condition was shown by autopsy performed after a mean of 107 h (Table 6). These results suggest that SAH is secondary to brain haemorrhage in most patients with both.

Table 6 Comparison between CT and autopsy findings in 10 patients with both examinations [*BH* brain haemorrhage, *SAH* subarachnoid haemorrhage, *VH* ventricular haemorrhage, *SDH* subdural haemorrhage, *F* frontal lobe, *P* parietal lobe, *T* temporal lobe, *Crb* cerebellar, *R* right, *L* left, (*h*) hours from the time of BH to either CT or autopsy]

Case	Age (years) /sex	FAB type	CT				Autopsy				
			BH	SAH	VH	(h)	BH	SAH	VH	Other	(h)
1	50/M	M1	F-P (L)	–	–	(1.5)	F-P-T (L)	–	–	–	(53)
2	59/F	M1	F (L)	–	+	(1)	F (L)	+	+	–	(33.8)
3	67/M	M2	Th (L)	–	+	(2)	Th (L)	+	+	–	(574)
4	64/F	M2	P (R)	–	–	(1.3)	P (R)	+	–	SDH	(50.5)
5	74/F	M3	F (L)	–	–	(1.75)	F (L)	–	–	–	(12)
6	45/M	M3	P (R)	–	+	(1.5)	P (R)	+	+	–	(13.5)
7	37/F	M3	F (L)	–	+	(12.5)	F (R)	+	+	–	(37.5)
8	30/F	M3	Crb (R)	+	–	(71.5)	Crb (R)	+	–	–	(168)
9	38/F	M3	F (R)	–	–	(5)	F (R), Crb	–	+	–	(86.5)
10	48/F	M6	P, T (L)	–	–	(4)	P, T (L)	+	–	–	(103)

Table 7 Incidence of intracranial haemorrhage (*ICH*) in patients with and without leukocytosis and patients who developed coma (neuropsychological grade IV) within 4 h in FAB types. M6 was excluded because there were only 2 patients. [( ) number of patients who became comatose within 4 h, [ ] percentage of patients with ICH to total patients]

WBC ($\times 10^9$/l)	M1 + M2		M3		M4 + M5		Total	
	No.	With ICH	No.	With ICH	No.	With ICH	No.	With ICH
0–10	85	8 (5) [9]	24	10 (7) [42]	26	4 (1) [15]	135	22 (11) [16]
10–	22	5 (4) [23]	10	6 (4) [60]	14	3 (3) [21]	46	14 (11) [30]
Total	107	13 (9) [12]	34	16 (11) [47]	40	7 (4) [18]	181	36 (22) [20]

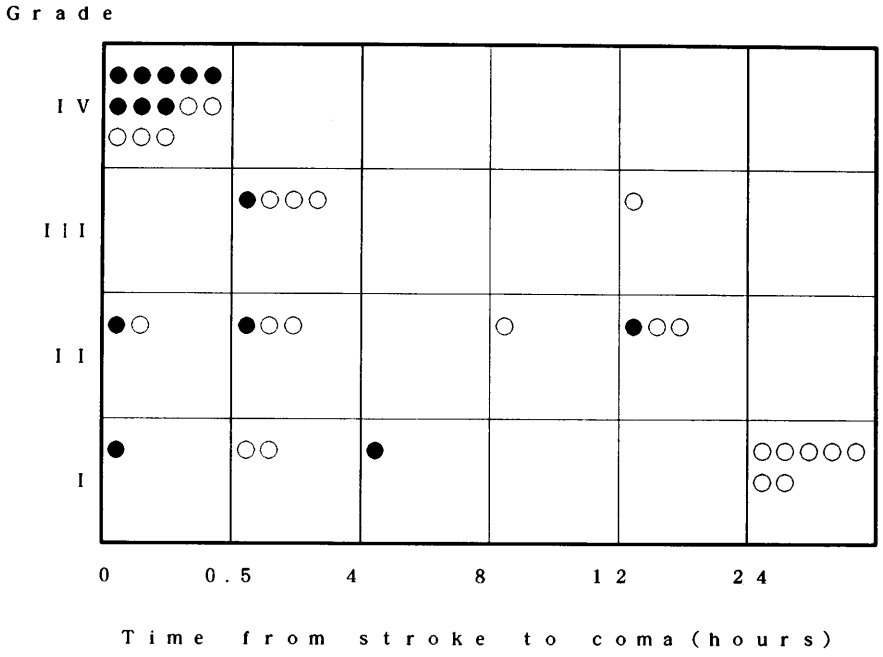

Fig. 2 Relationship between neuropsychological grades of consciousness at the time of stroke and time (hours) to development of coma (grade IV) in patients with white blood cell count higher than 10×10^9/l (●) and lower counts (○)

Clinical features

Platelet counts measured within 2 days before the time of haemorrhage ranged from 1 to 380×10^9/l, with a mean of 44×10^9/l. Platelet counts of patients with and without DIC did not differ significantly. DIC was found at the time of the stroke in 26 (68%) of 38 patients with ICH. Distribution among the FAB types was: M1 = 5/8, M2 = 2/5, M3 = 14/16, M4 = 3/4, M5 = 2/3, M6 = 0/2. The incidence of ICH was significantly greater among patients with DIC than those without DIC (30/126 vs 8/68, $\chi^2 = 4.07$, $P = 0.044$). The high incidence of ICH and DIC in M3 patients suggests an association between the two.

When ICH occurred, 14 patients had leukocytosis with an increase of blast cells or promyelocytes. These consisted of 8 patients with WBC of greater than 50×10^9/l and 6 with WBC of between 50 and 10×10^9/l. Twenty-four patients had normocytosis or leukopenia due to intensive chemotherpay. The incidence of ICH was significantly higher in patients with leukocytosis than normocytosis or leukopenia (14/47 vs 24/147, $\chi^2 = 4.10$, $P = 0.043$) (Table 7). Twelve (86%) of 14 patients with leukocytosis developed coma within 4 h, while 13 (54%) of 24 patients with normocytosis or leukopenia (Fisher, $P = 0.014$; $\chi^2 = 6.13$, $P = 0.013$) did so (Fig. 2). Seven of the latter patients became comatose after 24 h. Neuropsychological grade IV [14] was observed within 30 min after the stroke in 13 (34%) of 38 patients with ICH, suggesting an abrupt, massive haemorrhage (Fig. 2). Twelve (48%) of 25 patients with less than grade III developed coma (grade IV) within 4 h, suggesting that the rapid shift to coma occurred despite mild disturbance in consciousness at the time of the stroke. The other patients worsened in a stepwise manner.

The strokes occurred during sleep in 6 patients and while awake in 32 patients. Strokes tended to increase within 2 h after rising and before sleeping despite stable normal blood pressure as measured every 30 min.

Extracranial haemorrhages

Gastrointestinal haemorrhage occurred at approximately the same time as ICH in 12 (33%) of 38 patients with ICH and pulmonary haemorrhage in 2 patients (5%). Both haemorrhages occurred in 4 patients.

Discussion

As found by previous authors, this study indicates that the risk factors of ICH in ANLL are leukocytosis (more than 10×10^9/l) and DIC. This study also showed that (1) concurrent, multiple ICH consisting of various combinations of brain haemorrhage, SAH, SDH and VH; (2) multifocal haematomas occurring preferentially in the subcortical portion; and (3) SAH secondary to brain haemorrhage are characteristic of ICH in ANLL. ICH in acute leukaemia can be broadly divided into two types: leukocytosis and leukopenic. In the former, ICH occurs at presentation or during a relapse when leukaemic cells are unresponsive to chemotherapy. Although ICH may occur in both ANLL and ALL with hyperleukocytosis of more than 50×10^9/l

[4, 5], our results indicated a much higher incidence in ANLL, even when the leukocytosis was lower, and there was a rapid shift to coma after the stroke. The larger size of leukaemic myeloblasts as compared with lymphoblasts makes circulation through small vessels more difficult and leads to a greater blood viscosity, leukostasis, vascular dilatation, tissue hypoxia and vascular damage, and eventually induces haemorrhage [12, 13]. Hyperleukocytosis also induces increased fibrinolysis in the blood because of the high concentration of the active proteolytic enzyme elastase in leukaemic cells, particularly promyelocytes [21]. Although Creutzig et al. [5] reported that M5 with leukocytosis has an increased risk for ICH in association wiht vascular damage due to leukaemic cell infiltration into the central nervous system, the significant increase in M5 was not confirmed in this series, probably because of the small number of the patients.

Thrombocytopenia is an almost constant concomitant of ICH. In many cases, it is the result of platelet consumption due to DIC, reduced platelet production secondary to leukaemic cell infiltration in the bone marrow and/or the myelotoxic effect of intensive chemotherapy. In the absence of any other abnormality such as coagulation or an accompanying platelet dysfunction, ICH is unusual if the platelet count is greater than 20×10^9/l [7]. DIC was clearly associated with the higher incidence of ICH in this study. DIC is a prominent feature of M3 and is particularly marked in patients with hyperleukocytosis. It appears soon after the beginning of chemotherapy, presumably occurring because a tissue factor with procoagulant activity is released from the granules of destroyed leukocytes, particularly promyelocytes [1]. DIC itself and the treatment are likely to induce multiple ICHs involving simultaneously subcortical brain haemorrhage, SAH, SDH and VH. The haematomas also continue to enlarge rapidly after the diagnosis is made by CT immediately after the stroke, resulting in a rapid progress to deep coma and finally death [20]. Our analysis of brain haemorrhages indicates that the subcortical portion of the cerebral hemispheres is most frequently implicated in ANLL. McCormick and Rosenfield [15] reported that subcortical bain haemorrhage occurred in 10 (47%) of 21 leukaemic patients with intracerebral haemorrhage. The vasculature of subcortical white matter is characterized by multiple small, tortuous vessels with a thin media, no external elastic lamina and little adventitia [17]. Stagnant blood circulation or congestion occurs easily in the white matter because of the coarse capillary network and poor collateral circulation. Such an anatomically fragile structure is a probable explanation for the preferential location. Subcortical brain haemorrhages tend to occur multifocally. The incidences were 71% (17/24) in this series and 17% (8/46) in a previous report [8].

In this series, SAH was common and frequently accompanied brain haemorrhage. Price and Johnson [18] reported that SAH results from the destruction of the pia mater by leukaemic infiltrate or interference with local perfusion through constriction of the blood vessels by perivascular arachnoid infiltration. Molinari et al. [16] suggested another mechanism for SAH as follows: an infected embolus formed by sepsis or bacterial endocarditis is lodged in a cerebral vessel, and the aneurysmal enlargement is produced by pulsations against the necrotic wall of an occluded vessel or a weakened wall of a recanalized vessel and finally induces SAH. SAH from a ruptured aneurysm without haemorrhagic diathesis sometimes induces brain haemorrhage because the forceful bleeding disrupts brain tissue adhering to the aneurysm. In many patients with ANLL presented here the SAH followed brain haemorrhage. In these patients with ANLL, the rapid rise of cerebral tension due to massive brain haemorrhage may lead to a rupture of the pia mater and cause intracerebral blood to flow into subarachnoid spaces. VH secondary to brain haemorrhage also could result in the appearance of blood in the subarachnoid space.

In this series, 3 of 5 patients had SDH accompanied by SAH. When the dome of the aneurysm adheres to the arachnoid, the arachnoid may be torn by the dome, causing an egress of blood into the subdural space. SDH associated with brain haemorrhage may occur because the arachnoid covering the cortex is disrupted by rapid enlargement of the intracerebral haematoma. Jourdan et al. [10] reported that in hyperleukocytic M4 and M5 lumbar punctures frequently triggered SDH because of a downward displacement of the brain caused by the removal of cerebrospinal fluid. In 5 patients with SDH reported here, however, lumbar puncture was not performed before ICH.

Despite more intensive chemotherapy given for patients with relapsed ANLL, the incidence of fatal ICH did not increase during this 13-year period. The higher toxicity of the newly administered agents may have been offset by more effective supportive care.

References

1. Andoh K, Kubota T, Takada M, Tanaka H, Kobayashi N, Maekawa T (1987) Tissue factor activity in leukemic cells. Special reference to disseminated intravascular coagulation. Cancer 59: 748–754
2. Bennett JM, Catovsky D, Daniel M-T, Flandrin G, Galton DAG, Gralnick HR, Sultan C (1985) Proposed revised criteria for the classification of acute myeloid leukemia. A report of the French-American-British cooperative group. Ann Inter Med 103: 620–625
3. Bratt G, Blombäck M, Paul C, Schulman S, Törnebohm E, Lockner D (1985) Factors and inhibitors of blood coagulation and fibrinolysis in acute nonlymphoblastic leukaemia. Scand J Haematol 34: 332–339

4. Bunin NJ, Pui C-H (1985) Differing complications of hyperleukocytosis in children with acute lymphoblastic or acute nonlymphoblastic leukemia. J Clin Oncol 3:1590–1595
5. Creutzig U, Ritter J, Budde M, Sutor A, Schellong G and The German BFM Study Group (1987) Early deaths due to hemorrhage and leukostasis in childhood acute myelogenous leukemia. Cancer 60:3071–3079
6. Freireich EJ, Thomas LB, Frei E III, Fritz RD, Forkner CE (1960) A distinctive type of intracerebral hemorrhage associated with "blastic crisis" in patients with leukemia. Cancer 13:146–154
7. Gmür J, Burger J, Schanz U, Fehr J, Schaffner A (1991) Safety of stringent prophylactic platelet transfusion policy for patients with acute leukaemia. Lancet 338:1223–1226
8. Graus F, Rogers LR, Posner JB (1985) Cerebrovascular complications in patients with cancer. Medicine 64:16–35
9. Groch SN, Sayre GP, Heck FJ (1960) Cerebral hemorrhage in leukemia. Arch Neurol 2:439–451
10. Jourdan E, Dombret H, Glaisner S, Micléa JM, Castaigne S, Degos L (1995) Unexpected high incidence of intracranial subdural haematoma during intensive chemotherapy for acute myeloid leukaemia with a monoblastic component. Br J Haematol 89:527–530
11. Kimura K, Ohno R, Amaki I, Hattori K, Hirota Y, Hoshino A, Ichimaru M, Ito M, Kimura I, Maekawa T, Masaoka T, Nakamura T, Ogawa M, Oguro M, Ohta K, Osamura S, Shimoyama M, Takaku F, Uzuka Y, Yamada K (1985) Treatment of acute myelogenous leukemia in adults with N^4behenoyl-1-β-D-arabinofuranosylcytosine. Cancer 56:1913–1917
12. Lichtman MA, Rowe JM (1982) Hyperleukocytic leukemias: rheological, clinical, and therapeutic considerations. Blood 60:279–283
13. Lichtman MA, Gregory A, Kearney E (1973) Rheology of leukocytes, leukocyte suspensions, and blood in leukemia. Possible relationship to clinical manifestations. J Clin Invest 52:350–358
14. Markwalder T-M, Steinsiepe KF, Rohner M, Reichenbach W, Markwalder H (1981) The course of chronic subdural hematomas after burr-hole craniostomy and closed-system drainage. J Neurosurg 55:390–396
15. McCormick WF, Rosenfield DB (1973) Massive brain hemorrhage: a review of 144 cases and an examination of their causes. Stroke 4:946–954
16. Molinari GF, Smith L, Goldstein MN, Satran R (1973) Pathogenesis of cerebral mycotic aneurysms. Neurology 23:325–332
17. Phair JP, Anderson RE, Namiki H (1964) The central nervous system in leukemia. Ann Intern Med 61:863–875
18. Price RA, Johnson WW (1973) The central nervous system in childhood leukemia. I. The arachnoid. Cancer 31:520–533
19. Rodeghiero F, Mannucci PM, Viganò S, Barbui T, Gugliotta L, Cortellaro M, Dini E (1984) Liver dysfunction rather than intravascular coagulation as the main cause of low protein C and antithrombin III in acute leukemia. Blood 63:965–969
20. Schwartzman RJ, Hill JB (1982) Neurologic complications of disseminated intravascular coagulation. Neurology 32:791–797
21. Törnebohm E, Egberg N, Sablica H, Wallin R, Lockner D, Paul C (1992) Elastase activity in leukaemic cells and plasma in patients with acute leukaemia. Eur J Haematol 49:98–104
22. Törnebohm E, Lockner D, Paul C (1993) A retrospective analysis of bleeding complications in 438 patients with acute leukaemia during the years 1972–1991. Eur J Haematol 50:160–167