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The Clinical Features and Treatment Outcomes of Intracranial Hemorrhage With Acute Leukemia and Disseminated Intravascular Coagulation

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Although intracranial hemorrhage（ICH）-complicating leukemia is life-threatening, its clinical features remain unclear due to the limited number of previous reports. In a retrospective study of 16 patients with hematological malignancy complicated by disseminated intravascular coagulation（DIC）, including three patients with ICH, from 2018 to 2021 in Miyazaki Prefectural Miyazaki Hospital, we analyzed clinical features, laboratory markers, and treatment outcomes. The cumulative incidence of ICH was 18.7% and all patients presented with leukocytosis and DIC. Surprisingly, two patients died within a day due to ICH with brain herniation. One patient with ICH achieved complete remission. Notably, clinical markers showing higher leukocyte counts, higher LDH, higher FDP/d-dimer, higher HMGB-1, and poorer overall survival were identified in patients with leukemia with ICH. In conclusion, ICH should be considered a severe complication of hematological malignancies. Furthermore, the leukocyte count, and LDH and HMGB-1 levels may be related to leukemia with ICH.

Keywords: coma, intracranial hemorrhage, hematological malignancy with DIC, leukocytosis, circulating intranuclear proteins, HMGB-1

INTRODUCTION

Patients with intracranial hemorrhage（ICH）are transferred to the emergency room（ER）because of the high potential for poor outcomes［1］. Generally, older age, hypertension, cerebral amyloid angiopathy, and oral anticoagulant treatment are the most important risk factors for ICH［1］. Furthermore, ICH should be considered as a complication of hematological malignancy because of the aggressive clinical course of hematological diseases and the necessity of treatment intervention. Although ICH-complicating leukemia is seriously life-threatening, the clinical features of this condition remain unclear because of the limited number of previous reports［2-5］.

One of the important mechanisms of ICH in he-

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matological malignancies is disseminated intravascular coagulation (DIC), a life-threatening clinical condition with high mortality [2-5].

Although the mechanism of DIC differs depending on the underlying disease, there is a common process for all patients and it is characterized by excessive thrombi that cause fibrin generation and deposition. Furthermore, fibrinolytic activation and excessive administration of anticoagulation factors can lead to systemic hemorrhage [6].

In the pathogenesis of DIC, with sepsis and hematological disease, damage-associated molecular patterns (DAMPs) [e.g., high mobility group box 1 (HMGB-1), histones)] and pathogen-associated molecular patterns (PAMPs) (e.g., lipopolysaccharides) have become a focus of worldwide attention [6]. Notably, Ikezoe *et al.* showed that circulating intranuclear proteins, including HMGB-1 and Histone H3, might play a role in the development of DIC, in patients with acute leukemia [7].

To date, previous reports on patients with ICH with acute leukemia complicated by DIC, are limited in Japan [2-5]. Thus, the relationships between ICH, hematological malignancy, and DIC remain unresolved. Furthermore, DAMPs, including HMGB-1 and Histone H3, are crucial proteins common to DIC and central nervous system (CNS) diseases [7, 8].

Therefore, we retrospectively analyzed the clinical features and outcomes of patients with ICH with acute leukemia complicated by DIC.

MATERIALS AND METHODS

We searched for hematological malignancy cases of DIC treated at Miyazaki Prefectural Miyazaki Hospital between 2018 and 2021. DIC was diagnosed using the diagnostic criteria of the Japanese Ministry of Health and Welfare (JMHW) for hematological diseases (> 3 points) [9]. ICH was diagnosed with a CT scan. Subsequently, hematologists and neurosurgeons evaluated the treatment strategy for ICH cases. Treatment of the diseases underlying DIC and supportive modalities, such as platelet concentrates and fresh frozen plasma, play an important role in controlling DIC [9, 10]. Furthermore, ICH was diagnosed and managed in our study according to the protocol for diagnosis and management of acute ICH reported by Morotti *et al*. [1] and Ochiai *et al*. [11].

In addition to the general laboratory data, DAMPs related data were extracted. Serum levels of HMGB-1 were measured as previously described (Shino-Test Corporation, Sagamihara, Japan) [12]. Serum levels of Histone H3 were measured using a newly developed enzyme-linked immunosorbent assay (ELISA) (Shino-Test Corporation) [12].

Groups with or without ICH were compared and analyzed based on clinical features, molecular analysis, and treatment outcomes.

The measured parameters from patients with ICH with acute leukemia complicated by DIC and from patients without ICH with acute leukemia complicated by DIC were compared using the Mann–Whitney U test. Significance was determined using a 2-sided P-value as $P < 0.05$. The Kaplan-Meier method was used to estimate the probabilities of overall survival (OS), and log-rank tests were used to compare the OS between the two groups of patients. The statistical analysis was performed by using 'EZR' software for medical statistics [13].

RESULTS

Summary of three patients with ICH with acute leukemia complicated by DIC among 16 patients with a hematological malignancy complicated by DIC

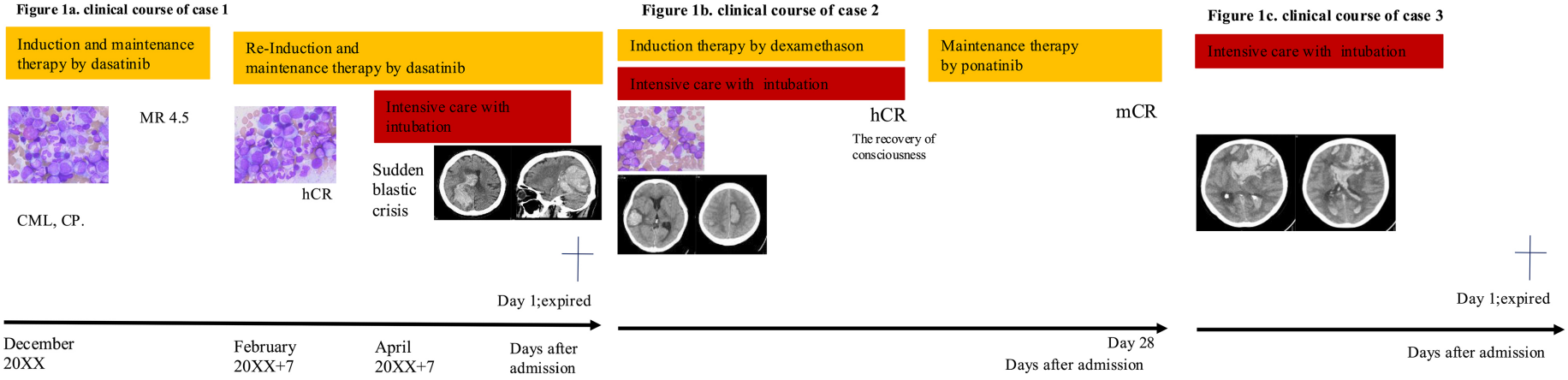
First, of the 16 acute leukemia cases with DIC, three were accompanied by ICH. The clinical features, laboratory findings, and outcomes according to the presence or absence of ICH are summarized in Table 1 and Fig. 1. The cumulative incidence of ICH in patients with acute leukemia complicated by DIC was 18.7% (3/16).

Second, the three ICH cases are described in detail in Fig. 1/Table 1 (including DAMPs values). The median age of the patients was 61 and there was one male and two females. The initial manifestation of ICH was coma in all three patients (GCS score 3). All three patients with ICH were transferred to the ER due to an unknown etiology. One patient developed ICH after chemotherapy (dasatinib). The underlying diseases included acute

Table 1. The comparison of laboratory findings of Syndecan 1, HMGB1, and Histone H3 between patients with acute leukemia with ICH and patients with acute leukemia without ICH.

Factor	Group	ICH		p.value
		Presence (+)	None (-)	
n		3	13	
age		61.00 [44.00, 76.00]	59.00 [24.00, 81.00]	0.736
sex (%)	F	2 (66.7)	5 (38.5)	0.55
	M	1 (33.3)	8 (61.5)	
WBC		**594280.00 [127840.00, 882350.00]**	**12280.00 [850.00, 82370.00]**	**0.009***
Hb		8.00 [6.30, 11.20]	8.60 [2.80, 13.50]	0.737
Plt		2.90 [2.20, 5.30]	2.30 [0.40, 6.30]	0.382
T.Bil		0.76 [0.64, 0.90]	0.69 [0.33, 2.20]	0.59
LDH		**3190.00 [1672.00, 6711.00]**	**711.00 [199.00, 3029.00]**	**0.013***
Alb		3.30 [2.90, 3.30]	3.40 [1.70, 4.40]	0.379
Cr		0.78 [0.72, 2.83]	0.92 [0.48, 7.77]	0.946
CRP		7.86 [4.91, 19.20]	15.00 [0.38, 42.60]	0.84
CRP_Alb_ratio		2.38 [1.49, 6.62]	3.66 [0.10, 16.59]	0.84
PT_INR		1.29 [1.25, 1.88]	1.42 [1.15, 2.10]	0.637
Fib		169.00 [139.40, 310.00]	102.00 [92.00, 706.00]	0.201
FDP		46.00 [28.30, 85.20]	29.12 [3.12, 189.60]	0.459
D.dimer		21.90 [16.80, 46.80]	23.26 [2.53, 124.60]	1
FDP/DD		**1.82 [1.68, 2.10]**	**1.31 [1.00, 1.86]**	**0.021***
AT		82.00 [62.50, 84.00]	95.40 [65.40, 124.80]	0.122
Histone.H3		15.50 [1.70, 145.70]	3.70 [0.00, 25.00]	0.382
HMGB1		**34.70 [13.10, 217.70]**	**7.40 [1.30, 18.80]**	**0.013***
syndecan.1		9.30 [0.00, 19.30]	4.70 [1.70, 42.10]	0.815
DIC.score (JMWH) (%)	5	0 (0.0)	5 (38.5)	0.554
	6	2 (66.7)	3 (23.1)	
	7	1 (33.3)	3 (23.1)	
	8	0 (0.0)	2 (15.4)	
DIC.score (JSCT) (%)	3	0 (0.0)	1 (7.7)	0.75
	4	1 (33.3)	6 (46.2)	
	5	2 (66.7)	2 (15.4)	
	6	0 (0.0)	1 (7.7)	
	7	0 (0.0)	2 (15.4)	
	8	0 (0.0)	1 (7.7)	
Dx (%)	ALL	0 (0.0)	2 (15.4)	0.157
	ALL, L2	0 (0.0)	1 (7.7)	
	ALL, Ph+	1 (33.3)	0 (0.0)	
	AML	1 (33.3)	2 (15.4)	
	AML, M1	0 (0.0)	1 (7.7)	
	AML, M2	0 (0.0)	3 (23.1)	
	APL	0 (0.0)	4 (30.8)	
	CML, sudden BC	1 (33.3)	0 (0.0)	

The parameters between acute leukemia complicating DIC with ICH cases and acute leukemia complicating DIC without ICH cases were compared using the Mann–Whitney U test. Significance was determined using a 2-sided P-value (should be <0.05). The Kaplan-Meier method was used to estimate probabilities of OS, and log-rank tests were used to compare OS between acute leukemia complicating DIC with ICH cases and acute leukemia complicating DIC without ICH cases. Written informed consent was obtained from all patients.



Case	Underlying diseases	age	sex	onset	GCS	Location of ICH	Volume of hematoma	Middle Shift	Venticular Penetration	OS (days)
1	CML, sudden BC	61	M	2021	3	the right parieto-occipital subcortical hematoma perforating to the right lateral ventricle	116ml	+	+	1
2	ALL, Ph+	44	F	2021	3	the multiple intracerebral hematoma (right temporal subcortical, right thalamus, left putamen left frontoparietal subcortical)	43ml	-	+	28
3	AML	76	F	2021	3	the bilateral frontal subcortical hematoma perforating to the lateral ventricle	128ml	+	+	1

Figure 1. The clinical course of Patients 1-3.

Figure 1（a）the clinical course of Patient 1, Figure 1（b）the clinical course of Patient 2, Figure 1（c）the clinical course of Patient 3. Here, we presented three patients with ICH（Patients 1-3）with acute leukemia complicated with DIC in Figure 1（1a-1c）.

myelogenous leukemia (AML) (n = 1), chronic myelogenous leukemia (CML) (blastic phase) (n = 1), and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) (n = 1). All three patients presented with extreme leukocytosis (> $10x10^9$/L) at admission. Furthermore, all the patients presented with DIC upon admission.

Based on Ikezoe's report regarding the importance of circulating intranuclear proteins, including HMGB-1 and Histone H3 in the pathogenesis of acute leukemia [10], we assayed molecular markers, including HMGB-1, Histone H3, and Syndecan 1, for 16 patients with a hematological malignancy complicated by DIC, including 3 with ICH and 13 without ICH (Table 1). For Patient 1, the serum levels of Syndecan 1, HMGB-1, and Histone H3 were 19.3, 13.1, and 145.7 ng/ml, respectively, for Patient 2, they were 9.3, 34.7, and 15.5 ng/ml, respectively, and for Patient 3, they were 0.0, 217.7, and 1.7 ng/ml, respectively. Thus, for the three patients the median serum levels of Histone H3, HMGB-1, and Syndecan 1 were 15.50 [1.70, 145.70], 34.70 [13.10, 217.70], and 9.30 [0.00, 19.30], respectively.

The radiological findings of ICH in Patients 1-3 are shown in Fig. 1. Patient 1 had a right parieto-occipital subcortical hematoma perforating the right lateral ventricle. Patient 2 had multiple intracerebral hematomas (right temporal subcortical, right thalamus, left putamen, and left frontoparietal subcortical regions). Patient 3 had a bilateral frontal subcortical hematoma perforating the lateral ventricle. Notably, Patients 1, 2, and 3 were estimated to have 116 ml, 43 ml, and 127 ml of hemorrhage, respectively.

Treatment for DIC mainly consists of supportive care including blood transfusion due to ICH complications. The three patients were supported by blood transfusion therapy only. For Patient 2, to reduce the risk of tumor lysis syndrome, leukapheresis was performed to control the activity of the hematological malignancy. Notably, for Patient 2, additional treatments, including molecular targeted therapy for Ph+ALL (dexamethasone and ponatinib), were also useful. Thus, based on ICH and DIC status, we performed a patient-by-patient approach to manage DIC and ICH.

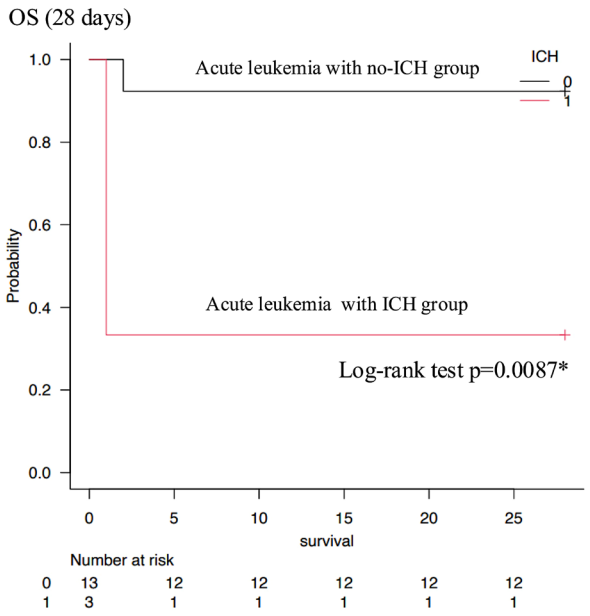


Figure 2. The Overall survival of acute leukemia patients with ICH group and without ICH group.

Regarding the outcomes, Patient 2 was alive with CR. However, both patients 1 and 3 died on Day 1 because of massive ICH and brain herniation.

Finally, the differences between the presence and absence of ICH are shown in Table 1 and Fig. 2. To elucidate the laboratory characteristics of patients with ICH, we compared laboratory findings between patients with hematological malignancies with ICH (n = 3) and those with hematological malignancies without ICH (n = 13) (Table 1).

Thus, we identified clinically significant markers of higher leukocyte counts (p = 0.009*), higher LDH values (p = 0.013*), higher FDP/d-dimer (p = 0.021*), and higher HMGB-1 values (p = 0.013*) in the acute leukemia with ICH group than in the group without ICH (Table 1). In addition, although the number of patients was small, there was a significant difference in OS (28 days) (Log-rank test p = 0.0087*) (Fig. 2).

DISCUSSION

In the present study, we showed the detailed clinical course of patients with ICH with acute leukemia complicated by leukocytosis and DIC. All three patients with ICH were immediately transferred to the ER. Thus, ICH should be considered as a complication of hematological malignancies because of the

aggressive clinical course of hematological diseases and the necessity of treatment intervention. Furthermore, our study suggests that extreme leukocytosis and high LDH and HMGB-1 levels may be risk factors for ICH with acute leukemia complicated by DIC.

Thus, our research is the first to show that HMGB-1 levels were significantly higher in ICH patients than in non-ICH patients with acute leukemia and DIC. Notably, in patients with leukemia, HMGB-1 levels differ significantly with or without DIC and even more significantly with or without ICH. We speculated that the clinical peripheral immunological response to ICH may be related to the increase in HMGB-1 in leukemia patients with DIC and ICH, although the precise mechanism remains unknown [14].

We discuss and focus on the importance of elucidating the underlying disease of ICH and the impact of the molecular pathogenesis of DAMPs, including HMGB-1 and Histone H3, on the development of DIC and ICH in patients with leukemia.

First, we showed the detailed clinical course of patients with ICH with acute leukemia complicated by extreme leukocytosis and DIC, suggesting the importance of elucidating the underlying disease of ICH.

Confronting ICH, in addition to the patient's condition, including vital signs, the elucidation of the underlying disease, including hematological disease, is essential to initiate subsequent treatment. Navi *et al*. reported that intratumoral hemorrhage (61%) and coagulopathy (46%) accounted for the majority of hemorrhages in patients with cancer [15]. Furthermore, the median OS was 3 months, and 30-day mortality was 31% [15]. Raghavan *et al*. reported that the median OS for all 634 patients with ICH ranged from 20 days to 1.5 months, whereas the median OS of patients with ICH with hematological malignancy was five days [16]. Intraparenchymal hemorrhage, multiple foci of hemorrhage, a transfusion-resistant low platelet count, leukocytosis, coma at presentation, and ICH early in the treatment course are associated with worse outcomes [16]. In Japan, according to a literature search, 20 of the 22 cases (90.9%), including 19 cases, and the present reported 3 cases were deceased [2-5] (Table 2).

In our study, consistent with previous reports [2-5], Patient 1 and Patient 3 died on Day 1, due to massive cerebral hemorrhage and brain herniation. Furthermore, consistent with Ochiai *et al*., a hematoma volume greater than 60 mL may be an important risk factor affecting the outcome of ICH [11], Patients 1, 2, and 3 had intracerebral hemorrhage with intraventricular hemorrhage with an estimated 116 ml, 43 ml, and 127 ml of hemorrhage, respectively. Consequently, although there was a small number of patients, there was a significant difference in OS (28 days), showing a poor outcome for the acute leukemia with ICH group (Table 2). In our study, the three patients with DIC were only supported with blood transfusion therapy because of ICH complications.

Second, we confirmed that HMGB-1 may be associated with the development of DIC in patients with acute leukemia and extreme leukocytosis. Notably, we are the first to show that high levels of HMGB-1 may be associated with the development of ICH in patients with acute leukemia, leukocytosis, and DIC.

Recently, Harada-Shirado *et al.* showed that circulating intranuclear proteins, including HMGB-1 may play a role in the development of DIC in patients with acute leukemia [7]. They also revealed that serum levels of both HMGB-1 in patients with DIC were significantly higher than in patients without DIC (HMGB-1, median 14.45 (1.7–213.1) ng/mL vs median 6.65 (0.4–110.5) ng/ mL, $P = 0.036$) ng/mL [7]. Mori *et al*. reported the prognostic value of serum HMGB-1 levels in patients with DIC with hematological diseases, in a multicenter prospective cohort study [12].

Furthermore, Zhu XD reviewed novel biomarkers and the therapeutic potential of HMGB-1 in the pathogenesis of subarachnoid hemorrhage (SAH) [17]. Zhu *et al.* also reported that after SAH, the plasma HMGB-1 level, on admission, in patients, was statistically significantly higher than that in healthy controls (8.5 ± 3.6 ng/mL vs. 1.3 ± 0.4 ng/mL; $P < 0.001$) [17].

Importantly, higher circulating HMGB-1 levels are associated with poorer outcomes after ICH [14]. This study highlights the clinical importance of the inflammatory response in ICH [14]. Thus, to date,

Table 2. The previous reports of intracranial hemorrhage with hematological malignancy and DIC in Japan.

	No.	Age/ sex	Disease	Clinical Presentation	Location of lesions	WBC ($x10^9$/L)	Plt ($x10^9$/L)	FIB (mg/dL)	FDP (μg/dL)	DIC (JMHW)	Intracranial hemorrhage	Treatment for leukemia and DIC	Outcome
Kawanami T, et al. Intern Med, 2002	1	46/M	AML (M1)	Right hemiparesis	Bil. Cerebral hemispheres	22.4	n.d.	n.d.	n.d.	-	n.d.	n.d.	Dead
	2	52/M	ALL (L2)	Coma	Bil. Cerebral hemispheres Basal ganglia, Pons	12.4	n.d.	n.d.	n.d.	-	n.d.	n.d.	Dead
	3	17/F	AML (n.d.)	Coma	Frontal lobe	0.15	n.d.	n.d.	n.d.	-	n.d.	n.d.	Dead
	4	17/F	APL (M3)	Lt. N. VII palsy Rt. Hemiparesis	Pontine	7.8	n.d.	n.d.	n.d.	DIC	n.d.	n.d.	Dead
	5	41/F	APL (M3)	Coma	Lt. subdural hematoma Cerebral hemorrhage	0.07	n.d.	n.d.	n.d.	DIC	n.d.	n.d.	Dead
	6	54/F	APL (M3)	Coma	Lt. thalamus Intraventicular hemorrhage	0.09	n.d.	n.d.	n.d.	DIC	n.d.	n.d.	Dead
Matsushita T et al. Thromb Res, 2014.	1	63	APL (M3)	n.d.	Brain	n.d.	0.4	n.d.	n.d.	DIC	Day 10	TM-α (6 days)	Dead
	2	77	APL (M3)	n.d.	Brain	n.d.	4.9	90	n.d.	DIC	Day 10	TM-α (5 days)	Dead
	3	73	APL (M3)	n.d.	Brain	n.d.	7	117	n.d.	DIC	Day 1	TM-α (2 days)	Dead
	4	47	APL (M3)	n.d.	Putamen	n.d.	5.9	392	n.d.	DIC	Day 1	TM-α (2 days)	Dead
	5	81	APL (M3)	n.d.	Brain	n.d.	3.9	156	n.d.	DIC	Day 4	TM-α (7 days)	Dead
	6	47	APL (M3)	n.d.	Brain	n.d.	5.4	521	n.d.	DIC	Day 1	TM-α (1 day)	Dead
	7	59	APL (M3)	n.d.	Brain	n.d.	10.6	115	n.d.	DIC	Day 3	TM-α (2 days)	Dead
	8	31	APL (M3)	n.d.	Brain	n.d.	1.2	180	n.d.	DIC	Day 2	TM-α (2 days)	Alive
Koyama C, et al. Rinsho Ketsueki, 2021	1	14/M	CML	Altered consciousness Gait disturbance	Intracranial hemorrhage	72.8	18.6	166	0.6	-	Day 1	HU rasburicase	Dead
Kusuda M et al. IJH, 2023	1	49	AML with MRC	Coma	Intracranial hemorrhage	221	49	n.d.	n.d.	Unlikely	Day 0	No treatment	Dead
	2	70	AML with MRC	dyspnea	Intracranial hemorrhage	24	9	n.d.	n.d.	DIC	Day 5	No treatment	Dead
	3	55	AML (M5a)	Coma	Intracranial hemorrhage	377.9	77	n.d.	n.d.	DIC	Day 0	No treatment	Dead
	4	51	AML (M3)	Coma	Intracranial hemorrhage	55.3	16	n.d.	n.d.	DIC	Day 0	No treatment	Dead
Present study	**1**	**61/M**	**CML, sudden BC**	**Coma**	**The right parieto-occipital subcortical hematoma perforating to the right lateral ventricle**	**126**	**29**	**310**	**46**	**DIC (7 scores)**	**At admission**	**Dasatinib none**	**Dead (1day)**
	2	**44/F**	**ALL, Ph+**	**Coma**	**The multiple intracerebral hematoma (right temporal subcortical, right thalamus, left putamen left frontoparietal subcortical)**	**882**	**22**	**169**	**85.2**	**DIC (6 scores)**	**At admission**	**Dexa and ponatinib Leukopheresis rasburicase**	**Alive (2 years)**
	3	**76/F**	**AML**	**Coma**	**The bilateral frontal subcortical hematoma perforating to the lateral ventricle**	**594**	**53**	**139**	**28.3**	**DIC (6 scores)**	**At admission**	**No treatment none**	**Dead (1day)**

DAMPs including HMGB-1 play a crucial role in the pathogenesis of DIC and CNS disease, including ICH.

In our study, we first identified clinically significantly high HMGB-1 levels in the acute leukemia with ICH group (Table 2). Notably, in patients with leukemia, HMGB-1 differs significantly with or without DIC, and even more significantly with or without ICH.

Finally, Kusuda *et al.* reported important aspects of the care for patients with ICH with AML, where it might not be possible to perform advanced care planning and palliative care delivery to improve end-of-life care [5]. Physicians and staff should consider these aspects of care for patients with IHC with AML [5].

A limitation is that the sample size of three patients is too small to fully determine the roles of HMGB-1, DAMPS, and Histone H3 in ICH associated with acute leukemia. Thus, future prospective studies are required to validate the importance these markers in ICH associated with acute leukemia.

CONCLUSION

In the present study ICH should be considered a complication of hematological malignancy because of the aggressive clinical course of hematological malignancies and the necessity of treatment intervention.

Ethical approval

Written informed consent was obtained from all the patients. This study was approved by the Institutional Ethics Review Board of the Miyazaki hospital (23-14).

Author's contribution

NK designed the study and wrote the manuscript. HS statistically analyzed the clinical data. TI, HW, HO, and IK reviewed the study and MS. KT, TT, TN, KK, and KM provided the patient care.

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Conflict of interest disclosure

All authors declare no conflicts of interest.

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