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Leukemia – Lymphoma and Myeloma

Application of the International Society on Thrombosis and Haemostasis Scoring System in Evaluation of Disseminated Intravascular Coagulation in Patients with Acute Leukemias

Aditi Aggarwal[1] Deepti Mahajan[1] Poonam Sharma[1]

[1]Department of Pathology, Government Medical College, Jammu, Jammu and Kashmir, India

Address for correspondence Poonam Sharma, MD, House no 109, Sector-7, Channi Himmat 180015, Jammu Jammu and Kashmir, India (e-mail: sharmapoonam59@gmail.com).

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Abstract

Poonam Sharma

Background Coagulation abnormalities are common in acute leukemia (AL) and disseminated intravascular coagulation (DIC) frequently complicates the onset of AL.

Aim To determine the prevalence of overt DIC in AL using the International Society on Thrombosis and Haemostasis (ISTH) scoring system.

Materials and Methods This prospective observational study was performed on 57 newly diagnosed or relapsed cases of AL. Detailed clinical history and coagulation profile of the patients were evaluated. Diagnosis of overt and nonovert DIC was established using the ISTH scoring system and results tabulated.

Observations A total of 57 patients with AL participated in the study, including 31 (54.39%) patients with acute lymphoblastic leukemia (ALL) and 26 (45.61%) with acute myeloid leukemia (AML). In total, 18 of 57 patients (31.58%) with AL fulfilled the criteria of overt DIC according to the ISTH scoring system, including 10 (32.25%) patients with ALL and 8 (30.76%) patients with AML. The highest prevalence of DIC was seen in the M3 subtype among AML and the L1 subtype among ALL, respectively. The mean ISTH score in patients of overt DIC in ALL and AML patients was 5.1 and 5, respectively. Abnormalities in platelet count and D-dimer levels were the most useful parameters in diagnosing overt DIC and the difference between overt DIC and nonovert DIC groups was highly significant.

Conclusions Overt DIC was observed in approximately one-third of patients with AL. Prevalence of overt DIC was found to be comparable in patients with ALL and AML. Mean platelet count and D-dimer levels were the most useful parameters in detecting overt DIC.

Keywords

- coagulation
- acute leukemia
- platelet count
- D-dimer
- fibrinogen

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Introduction

Acute leukemia (AL) is a hematopoietic stem cell disorder characterized by neoplastic proliferation of lymphoid or myeloid cells in the bone marrow. AL can be classified according to the type and degree of differentiation of the predominant leukemic cell population into acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). ALL is a malignant neoplasm of hematopoietic stem cells of lymphoid lineage, while AML is a malignant neoplasm of hematopoietic stem cells of myeloid lineage.

The coagulation system in the human body comprises clotting and fibrinolytic mechanisms; the former prevents excessive blood loss whereas the latter ensures circulation within the vasculature.[1] Occurrence of coagulation abnormalities in AL is well established in the literature.[2,3] Malignancy is associated with a hypercoagulable state and has a high risk for thrombo-hemorrhagic complications. Patients with solid tumors and leukemias commonly present with abnormalities in laboratory tests of blood coagulation and the clinical manifestations can vary from localized deep venous thrombosis to life-threatening bleeding.

Disseminated intravascular coagulation (DIC) is defined as an acquired syndrome characterized by the intravascular activation of coagulation with a loss of localization arising from different causes.[4] Hemorrhage alone or as a result of DIC is the commonest coagulation disorder in patients with AL and up to 60% of leukemias may have some form of bleeding manifestations at presentation.[5] AML is more commonly associated with DIC, but the association with ALL has also been recognized.[5] The diagnosis of DIC due to leukemia carries important therapeutic implications and in such patients the phenomenon may become exaggerated with the initiation of specific chemotherapy and may lead to death due to hemorrhage or organ failure.

The Scientific Subcommittee on DIC of the International Society on Thrombosis and Haemostasis (ISTH) put forward a concept of DIC and a scoring system with the ultimate aim of improving outcome in this area.[6] The ISTH scoring system provides a framework for diagnosing DIC and the score has been validated in different settings using prothrombin time (PT), platelet counts, fibrinogen (FBG), and D-dimer levels. Limited studies have assessed the importance of DIC and its clinical relevance in patients with AL at presentation using these criteria. So the present study was conducted to determine the prevalence of DIC in patients with AL at presentation with the help of ISTH criteria.

Materials and Methods

This prospective observational study was conducted in the hematology section of department of pathology in a tertiary care institute from November 1, 2018 to October 31, 2019. The study was approved by the institutional ethics committee and informed written consent was obtained from all patients. A total of 57 newly diagnosed or relapsed cases of AL formed the material of the study. The patients of AL already on treatment or who were partially treated before presentation were excluded from the study.

After obtaining detailed clinical history and recording the general and systemic examination findings, blood samples from the patients were collected at presentation before the start of chemotherapy and the following investigations were performed: (1) complete blood count, (2) platelet count, (3) PT, (4) activated partial thromboplastin time (aPTT), (5) D-dimer levels, and (6) plasma FBG levels. For coagulation testing, 9 volumes of blood were added to 1 volume of anticoagulant (3.2% trisodium citrate) and platelet-poor plasma was obtained by centrifugation at 1,500 to 2,000 g for 15 minutes at 4°C (~4,000 rev/min in a standard bench cooling centrifuge). Plasma was collected in a clean test tube and testing was performed immediately. Certain assays were performed in batches at a later date on deep frozen plasma (stored at −40°C to −80°C).

Diagnosis of overt DIC was made according to the scoring system proposed by the ISTH (►Table 1). A cumulative score of 5 or more was considered positive for overt DIC, while a score below 5 was suggestive but not affirmative for DIC.[6] The results were tabulated and the data were evaluated using a statistical package for the social sciences. All statistical analyses were performed using two-tailed tests and *p*-values recorded. *p*-Value <0.05 was considered statistically significant.

Results

Fifty seven patients of newly diagnosed or relapsed AL formed the material of the study with the age range of 4 months to 85 years and median age of 26 years. Majority of the patients were seen in the 0 to 12-year age group followed by more than 60-year age group. Out of 57 patients, 38 (66.67%) were males and 19 (33.33%) were females with the male:female (M:F) ratio of 2:1. A total of 31 (54.39%) patients had ALL while 26 (45.61%) patients had AML. ALL was predominant in children in the age group of 0 to 12 years while AML was more common in the elderly population (>60 years).

Among the ALL group, 21 cases had ALL-L1 morphology while 10 cases had ALL-L2 morphology (►Table 2). None of the ALL cases depicted L3 morphology. In the AML group, AML-M1, M2, M3, M4, and M5 subtypes were seen in 6, 5, 5, 6, and 4 cases, respectively. None of the patients belonged to AML-M0, M6 and M7 subtypes (►Table 2).

The coagulation parameters of the patients were scored as per the ISTH scoring system and the cases were categorized as having overt DIC if the cumulative score was ≥5. Overt DIC was observed in 18 (31.57%) cases of AL (►Table 3). In total, 10 out of 31 patients (32.25%) of ALL had overt DIC and 8 out of 26 patients (30.76%) of AML had overt DIC at the time of presentation (►Table 3). Among ALL subtypes, ALL-L1 patients (33.33%) had a higher prevalence of DIC than ALL-L2 patients (30%). Among AML cases, the highest prevalence of DIC was seen in the AML-M3 subtype (3 out of 5 cases) followed by AML-M5 (2 out of 4 cases) and AML-M4 (2 out of 6 cases).

Table 1 ISTH scoring system for overt disseminated intravascular coagulation

Sl. No.	Parameter	Value	Score
1.	Platelet count	>100 × 10^9 /L	0
		<100 × 10^9 /L	1
		<50 × 10^9 /L	2
2.	Prolongation of prothrombin time	<3 s	0
		≥3 but <6 s	1
		≥6 s	2
3.	Plasma fibrinogen level	>1 g/L	0
		<1 g/L	1
4.	D-dimer level	No increase	0
		Moderate increase	2
		Marked increase	3

Abbreviation: ISTH, International Society on Thrombosis and Haemostasis.

Table 2 Categorization of patients with acute leukemia as per FAB nomenclature (n = 57)

Type of acute leukemia	Subtype	Number	Percentage
Acute lymphoblastic leukemia (ALL)	ALL-L1	21	67.74
	ALL-L2	10	32.26
	ALL-L3	0	0
	Total	31	54.39
Acute myeloid leukemia (AML)	AML-M0	0	0
	AML-M1	6	23.08
	AML-M2	5	19.23
	AML-M3	5	19.23
	AML-M4	6	23.08
	AML-M5	4	15.38
	AML-M6	0	0
	AML-M7	0	0
	Total	26	45.61

Abbreviation: FAB, French–American-British.

Table 3 Mean ISTH score in ALL and AML patients with overt DIC

Type of acute leukemia	No. of patients with overt DIC	Mean score	p-Value
ALL (n = 31)	10	5.1 ± 0.01	*0.99*
AML (n = 26)	8	5 ± 0	
Total (n = 57)	18	5.05	

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; DIC, disseminated intravascular coagulation; ISTH, International Society on Thrombosis and Haemostasis.

The mean ISTH score in 18 patients of AL with overt DIC was 5.05 (►Table 3). The mean ISTH score in the ALL and AML patients with overt DIC was 5.1 and 5 respectively (►Table 3) and the difference between the two groups was statistically insignificant (p = 0.99). All the parameters of ISTH score (mean platelet count, mean PT, mean FBG levels, and mean D-dimer levels) were compared between the overt DIC positive and overt DIC negative groups (►Table 4). The observed mean platelet count was significantly lower and the mean D-dimer level was significantly higher in the overt DIC positive group as compared with the overt DIC negative group (p = 0.0001). The mean PT in the overt DIC positive as well as overt DIC negative group was within the normal range and the difference between the two groups was statistically insignificant (p = 0.067). The mean value of plasma FBG of the positive group was slightly lower (3.72 g/L) than that of the negative group (4.24 g/L) and the difference was statistically insignificant (p = 0.16).

Table 4 Comparison of parameters of the ISTH scoring system in overt DIC positive and overt DIC negative groups

DIC group	DIC positive group	DIC negative group	p-Value
Mean platelet count (10^9/L)	18.4 ± 12.97	88.38 ± 68.41	*0.0001*
Mean prothrombin time (s)	16.8 ± 2.48	15.83 ± 1.43	*0.067*
Mean plasma fibrinogen level (g/L)	3.72 ± 1.41	4.24 ± 1.22	*0.16*
D-dimer level (μg/mL)	3.74 ± 1.91	1.65 ± 1.74	*0.0001*

Abbreviations: DIC, disseminated intravascular coagulation; ISTH, International Society on Thrombosis and Haemostasis.

Discussion

DIC may be defined classically as an excessive and uncontrolled activation of the coagulation, fibrinolytic, and platelet systems as diagnosed by an increase in PT, aPTT, and bleeding time with a simultaneous decrease in platelet count and FBG. No single laboratory test can establish or rule out the diagnosis of DIC and in a relevant clinical scenario, several laboratory parameters are analyzed together as part of a diagnostic algorithm.[4] The ISTH scoring system provides an appropriate framework for diagnosing overt DIC and also standardizes criteria for clinical studies.[7] The score has been validated in different settings using PT, platelet counts, and FBG levels along with elevated fibrin degradation products and a cumulative score of 5 or more is considered positive for overt DIC.[8]

A total of 57 newly diagnosed or relapsed cases of AL formed the material of current study. Ages of the patients in our study ranged from 4 months to 85 years with the median age of 26 years. Dixit et al[5] in their study evaluated 67 newly diagnosed or relapsed patients (not on ongoing chemotherapy or partially treated) with AL with a median age of 25 years. Majority of patients in our study were males with the M:F ratio of 2:1, similar to observations of Dixit et al.[5] Out of the 57 patients, 31 patients (54.39%) had ALL and 26 patients (45.61%) had AML. Dixit et al[5] and Nur et al[9] also found a higher proportion of patients with ALL as compared with AML in their studies. Among 31 patients with ALL,

21 cases had L1 morphology and 10 cases had L2 morphology with no case of L3 morphology. Dixit et al[5] observed 21 cases with L1 morphology and 22 cases of L2 morphology in their study. Among the AML cases in our study, the distribution of patients was AML-M1 (6 cases), AML-M2 (5 cases), AML-M3 (5 cases), AML-M4 (6 cases), and AML-M5 (4 cases).

The diagnosis of overt DIC in patients of AL at the time of presentation was established with the help of the ISTH scoring system (►Table 1). The coagulation parameters of the patients were scored as per the ISTH scoring system and the cases were categorized as having overt DIC, if the cumulative score was ≥5. Overt DIC was observed in 18 (31.57%) cases of AL in our study. Out of 31 patients with ALL, 10 patients had overt DIC, while 8 out of 26 patients with AML had overt DIC. So the frequency of DIC was found to be comparable in ALL and AML patients (32.25 vs. 30.76%) in our study. The mean ISTH score of the patients positive for overt DIC in the ALL and AML groups was 5.1 and 5 respectively in our study (►Table 3). Hassab et al[4] and Yanada et al[10] observed DIC in 40 and 29% of patients with AL in their studies. However Dixit et al[5] observed a lower incidence of DIC in their study (14.9%). Ribeiro et al[11] reported 5.2% prevalence of DIC in a large series of children with AL and a significantly higher percentage of positive DIC at presentation for AML as compared with ALL (13.8 vs. 3.1%). This could be attributed to the fact that the diagnostic criteria for DIC were not unified and the ISTH scoring system was not available at that time. DIC was most frequent in AML-M3 subtype (60%), followed by AML-M5 (50%), AML-M4 (33.33%), and AML-M1 (16.66%) subtypes. Nur et al[9] in their study observed DIC in 75% of patients with AML-M3 subtype. Among the ALL subtypes, ALL-L1 (33.33%) had a higher percentage of development of DIC compared with ALL-L2 (30%). Our results were in contradiction to findings of Higuchi et al[12] and Dixit et al[5] who observed higher incidence of DIC in L2 subtype as compared with L1 subtype. This difference could be random in nature and needs evaluation with further studies.

In our study, the mean platelet count was lower in patients with overt DIC than those without overt DIC at presentation and the difference was statistically significant (►Table 4). Ribeiro et al[11] in their study found that children with ALL or AML and coagulopathy had a lower platelet count. Higuchi et al[12] also observed that DIC-positive children with ALL had significantly lower platelet counts at presentation in their study. In our study the mean PT was higher in patients with overt DIC than in those without overt DIC and the difference was statistically insignificant (►Table 4). Dixit et al[5] reported significantly prolonged PT in patients with ALL; however, the difference between DIC and non-DIC groups was statistically insignificant, similar to the results obtained in our study. Mean FBG levels were lower in patients with DIC than in those without DIC in our study and the difference between the two groups was statistically insignificant (►Table 4). However, Dixit et al[5] in their study observed that mean FBG levels were significantly lower in patients with ALL with DIC. FBG levels were not sensitive in identifying DIC in our study and this can be explained by the fact that FBG levels may be elevated as part of the inflammatory response associated with the disease. In the present study, the mean D-dimer levels were found to be raised in both the groups (with overt DIC and without overt DIC); however, the levels were significantly higher for the overt DIC group (►Table 4). Hassab et al[4] also found significantly higher levels of D-dimer in patients with DIC. Nur et al[9] found significant difference in the PT, aPTT, plasma FBG, and fibrin degradation product levels between the ALL patients with DIC and without DIC.

The present study had a few limitations. First limitation was the lack of our ability to exclude variables like liver disease, presence of other malignancies, concomitant infections, chemotherapy, etc., which by themselves are known to cause DIC. ISTH criteria have poor sensitivity, especially with regard to infectious diseases.[13] Sepsis-associated DIC ultimately causes microthrombi, microcirculation disorders, and organ dysfunction and the ideal DIC scoring system should include DIC-related molecular biomarkers (endothelial cells, neutrophils, platelets), traditional coagulation-related indicators, novel coagulation-related indicators, and organ function.[13] Further, the ISTH scoring system is designed to identify the progression of overt DIC and should not be applied in diagnosing early phases of nonovert DIC in children.[6] The second limitation of the study was the small sample size, as this was a single center study. So, more such studies incorporating larger patient populations are required in future to reveal the exact clinical significance of the results obtained in our study.

Conclusions

Coagulation disturbances are common at presentation in patients of AL. DIC was observed in approximately one-third patients of AL. The highest prevalence of DIC was seen in the M3 subtype among AML and the L1 subtype among ALL cases. Two of the four parameters of the ISTH score (platelet count and D-dimer levels) were most valuable in detecting DIC, whereas FBG levels were least useful in identifying DIC. So, all newly diagnosed patients with AL must be investigated for the presence of DIC and a common diagnostic system is essential for the standardization of clinical practice.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgment

Nil.

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