Comparison of laboratory characteristics between acute promyelocytic leukemia and other subtypes of acute myeloid leukemia with disseminated intravascular coagulation

Hee-Jeong Lee, Hyung-Jin Park, Hyun-Wook Kim, Sang-Gon Park

Department of Internal Medicine, Hematology–Oncology, Chosun University Hospital, Gwangju, Korea

Background
Acute promyelocytic leukemia (APL) is an acute myeloid leukemia (AML) subtype with distinctive cell morphology, molecular presentation, clinical course, and treatment. About 90% of APL patients present with hemorrhagic complications due to disseminated intravascular coagulation (DIC). When APL is suspected, all-trans retinoic acid (ATRA) treatment is recommended even before confirmation by molecular tests. Specific criteria for differentiating unconfirmed APL from other AML subtypes with DIC are currently lacking. We aimed to achieve the early diagnosis of APL from other AML types with DIC by restricting the DIC criteria.

Methods
We retrospectively analyzed 29 patients newly diagnosed with AML accompanied by DIC from January 2005 to January 2013.

Results
Fibrin degradation products (FDP) (77.7 μg/mL vs. 23.7 μg/mL, \(P=0.026\)), D-dimer (7,376.2 ng/mL vs. 1,315.2 ng/mL, \(P=0.018\)), and TIBC (264.4 μg/dL vs. 206.8 μg/dL, \(P=0.046\)) were higher, while fibrinogen (133.8 mg/dL vs. 373.2 mg/dL, \(P<0.001\)), WBC (14.988×10⁹/L vs. 70.755×10⁹/L, \(P=0.015\)), and ESR (7.1 mm/h vs. 50.0 mm/h, \(P<0.001\)) were lower in APL patients than in the patients with other AML subtypes. FDP ≥ 27 μg/mL, D-dimer ≥ 2,071 ng/mL, and fibrinogen ≤ 279 mg/dL were our threshold values. These markers may be characteristic to APL and helpful in presumptive diagnosis.

Conclusion
APL may be differentiated from other AML subtypes by core markers of DIC (FDP, D-dimer, and fibrinogen). We suggest that clinicians set new diagnostic thresholds by restricting the DIC criteria. These findings support the early initiation of ATRA, prior to confirmation by PML-RARA molecular testing.

Key Words
Acute myeloid leukemia, Acute promyelocytic leukemia, Disseminated intravascular coagulation

INTRODUCTION

Acute promyelocytic leukemia (APL) accounts for 10% of the total number of acute myeloid leukemia (AML) cases. APL patients have cellular structures that are distinct from those observed in patients with other AML subtypes; further APL is accompanied by translocations in chromosomes 15 and 17 that result in a fused protein [1, 2]. Clinically, APL has a high frequency of hemorrhage due to disseminated intravascular coagulation (DIC), which contributes to the high mortality rate of this disease [2, 3]. In contrast to the treatment for other subtypes of leukemia, all-trans retinoic acid (ATRA) has been used in the early-stage treatment of APL since the 1980s. After the introduction of the ATRA treatment, complete remission and patient survival rates have increased, with many reports demonstrating complete remission in over 90% of patients. ATRA can induce the differentiation of APL cells, which decreases the frequency of coagulopathy [4]. Because of this, when APL is suspected...
based on cell morphology, immunophenotype, and/or coagulopathy with a positive DIC screen, physicians recommended prompt ATRA treatment before confirmation by chromosomal diagnosis [1, 5]. However, most patients with other types of AML exhibit cytopenia with DIC due to severe infection. Further, data on the differences in the patterns of laboratory characteristics including the DIC profile of patients with suspected APL and other types of AML with DIC are lacking.

MATERIAL AND METHODS

Patients

We retrospectively analyzed 29 patients newly diagnosed with AML accompanied by DIC at Chosun University hospital from January 2005 to January 2013. Blood tests were performed for all patients at admission to establish the diagnostic criteria for DIC. Fourteen patients were diagnosed with APL and the other 15 patients were diagnosed with other subtypes of AML. The APL patients were diagnosed based on the translocations in chromosomes 15 and 17.

Diagnosis

Diagnostic criteria for DIC

DIC was diagnosed using the overt DIC criteria of the International Society on Thrombosis and Hemostasis. The DIC score for all patients in this study was calculated based on the assumption that they had risk factors for DIC (Table 1) [6, 7].

Statistical analyses

SPSS software 21.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Independent sample T test was used to compare the 2 groups and a P value less than 0.05 was considered statistically significant. Receiver operating characteristics (ROC) curve was used to set the diagnostic cut-off value for the blood test.

RESULTS

Characteristics of patients

The 14 patients (5 men and 9 women) diagnosed with APL were aged 28–79 years (mean age, 49.3 years). The 15 patients (9 men and 6 women) who were diagnosed with other subtypes of AML with DIC were aged 20–79 years (mean age, 57.5 years). There was no significant difference between the ages or genders of the 2 groups (Table 2).

Results of blood tests, including those for DIC

There was a significant difference in the mean number of leukocytes (WBC) between the APL group and the other AML group (APL: 14.988×10^9/L vs. AML: 70.755×10^9/L, P=0.015). However, there was no significant difference in the number of platelets (APL: 26.78×10^9/L vs. AML: 33.80×10^9/L, P=0.324) or the hemoglobin levels (APL: 8.03 g/dL vs. AML: 7.36 g/dL, P=0.412). There were significant differences in fibrin degradation product (FDP) (APL: 77.7 μg/mL vs. AML:

| Variable | APL | Other AML subtype | P |
|----------|-----|-------------------|---|
| Male/Female | 5/9 | 9/6 | 0.272 |
| Age (years) | 49.3 | 57.5 | 0.23 |
| WBC (×10^9/L) | 14.988 | 70.755 | 0.015 |
| Hb (g/dL) | 8.03 | 7.36 | 0.412 |
| Platelet (x10^9/L) | 26.78 | 33.80 | 0.324 |
| PT (s) | 16.0 | 14.6 | 0.107 |
| INR | 1.43 | 1.26 | 0.071 |
| aPTT (s) | 28.7 | 29.6 | 0.691 |
| FDP (μg/mL) | 77.7 | 23.7 | 0.026 |
| D-dimer (ng/mL) | 7,376.2 | 3,152.5 | 0.018 |
| Fibrinogen (mg/dL) | 133.8 | 373.2 | <0.001 |
| LDH (U/L) | 830.9 | 1,022.3 | 0.565 |
| AST (U/L) | 27.9 | 38.1 | 0.393 |
| ALT (U/L) | 21.0 | 36.3 | 0.305 |
| Total bilirubin (mg/dL) | 0.77 | 0.96 | 0.294 |
| BUN (mg/dL) | 16.6 | 21.1 | 0.518 |
| Cr (mg/dL) | 0.98 | 1.48 | 0.123 |
| Triglyceride (mg/dL) | 206.2 | 109.9 | 0.006 |
| Cholesterol (mg/dL) | 159 | 112 | 0.001 |
| Fe (μg/dL) | 135.4 | 120.0 | 0.469 |
| TIBC (μg/dL) | 264.4 | 206.8 | 0.046 |
| Ferritin (ng/mL) | 776.6 | 7,282.1 | 0.70 |
| Transferrin (g/L) | 1.79 | 1.29 | 0.005 |
| CRP (mg/dL) | 4.79 | 7.43 | 0.323 |
| ESR (mm/h) | 7.1 | 50.0 | <0.001 |

Abbreviations: APL, acute promyelocytic leukemia; AML, acute myeloid leukemia; DIC, disseminated intravascular coagulation; WBC, white blood cell; Hb, hemoglobin; PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time; FDP, fibrin degradation product; LDH, lactate dehydrogenase; AST, aspartate transference; ALT, alanine transference; BUN, blood urea nitrogen; Cr, creatinine; Fe, ferrous iron; TIBC, total iron binding capacity; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
DIC and hemorrhage are highly probable in APL patients and those with other subtypes of AML because of the accompanying thrombocytopenia and infection [6, 7]. To our knowledge, no study has compared the differences in the patterns of laboratory characteristics, including the DIC profile. Therefore, we conducted this study to establish a molecular profile for DIC between patients with suspected APL and those with other types of AML with DIC.

In this study, among the components of the DIC criteria (platelet count, prolonged PT, fibrinogen, and elevated fibrin-related markers such as FDP and D-dimer), FDP, D-dimer, and fibrinogen levels significantly differed between APL patients and the patients with other subtypes of AML with DIC. FDP and D-dimer levels were higher and the fibrinogen level was lower in APL patients. With respect to the acute phase markers, APL patients showed a significantly higher TIBC and transferrin level and lower WBC count and ESR. Moreover, the APL patients had higher TG and cholesterol levels than those with other types of AML with DIC.

Acute phase proteins are a group of blood proteins that help in restoring homeostasis and limiting microbial growth in an antibody-independent manner in animals subjected to infection, inflammation, surgical trauma, or stress [16]. The severity of the inflammatory response in sepsis is determined by measuring changes in the levels of acute phase proteins. During sepsis, ESR and CRP are increased and the transferrin level is decreased. In addition, hypcholesterolemia may be observed owing to metabolic decompensation.

### TABLE 3. Cut-off values for significant markers based on the ROC curve.

| Variable          | Cut-off value | Sensitivity (%) | Specificity (%) |
|-------------------|---------------|-----------------|-----------------|
| WBC (10^9/L)      | 15.090        | 78.6            | 66.7            |
| D-dimer (mg/mL)   | 2.071         | 90.9            | 86.7            |
| FDP (µg/mL)       | 27            | 92.9            | 86.7            |
| Fibrinogen (mg/dL)| 279           | 92.9            | 86.7            |
| ESR (mm/hr)       | 22.5          | 100             | 80              |
| Transferrin (g/L) | 1.52          | 78.6            | 78.6            |
| TIBC (µg/dL)      | 244           | 61.5            | 64.3            |
| TG (mg/dL)        | 116           | 92.9            | 86.7            |
| Cholesterol (mg/dL)| 128          | 85.7            | 73.3            |

Abbreviations: WBC, white blood cell; FDP, fibrin degradation product; ESR, erythrocyte sedimentation rate; TIBC, total iron binding capacity; TG, triglyceride.
DIC in APL vs. that in other AML subtypes

The level of hypocholesterolemia can be quantified based on the level of acute phase response as well [17, 18]. In conclusion, the DIC profile (increased FDP and D-dimer and decreased fibrinogen levels) and the acute phase response (increased ESR and decreased transferrin levels) as well as hypocholesterolemia observed in patients with other subtypes of AML are similar to those observed during infection. In the APL group, ESR and the levels of transferrin and cholesterol were within the reference range.

Based on our results, we established the cut-off value of significant markers. The present findings can provide an early diagnostic tool for APL. However, the study has some limitations. The numbers of patients with APL is quite small (N=14), because of which we are unsure if the proposed laboratory score to identify APL cases from other AML patients with DIC would be valid. Therefore, further investigation using comparative study with another cohort of patients is necessary. Nevertheless, thus far, there has been no study about the presumptive diagnosis of APL using a simple blood test. In addition, typical morphological traits were not found in all the APL cases studied. In such cases, physicians often require PML/RARA identification for APL diagnosis. In this case, our findings support the early initiation of ATRA treatment, prior to confirmation of PML-RARA rearrangement.

In summary, APL is a distinct subtype of AML, which is characterized by DIC. Among the components of the DIC criteria (platelet count, prolonged PT, fibrinogen, and elevated fibrin-related markers such as FDP and D-dimer), there were significant differences in the FDP, D-dimer, and fibrinogen levels. Among the acute phase reactants, the other significant markers were ESR, transferrin, and TIBC.

Authors’ Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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