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Acute Promyelocytic Leukemia is a Distinct Subset of Acute Myelocytic Leukemia with Unique Clinicopathologic Characteristics Including Longer Duration of Relapse Free Survival : Experience in 13 Cases

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Acute promyelocytic leukemia(APL) is a subtype of acute myelocytic leukemia(AML) associated with unique features such as the presence of atypical promyelocytes and bleeding tendency due to disseminated intravascular coagulation(DIC). In a retrospective study, we analyzed 96 cases of AML seen at our hospital between June, 1989 and December 1993. Thirteen cases of APL(14%) were identified and their clinicopathologic characterisitics were analyzed. The 86 cases of other types of AML served as controls. The distinct clinicopathologic features of APL as contrasted to other types of AML included younger age of patients, shorter duration of symptom before diagnosis, higher level of albumin at presentation, and a higher proportion of patients having coagulation abnormalities (75 vs. 25%). Bone marrow cellularity was higher in APL when compared to other types of AML (100 vs. 90%, P=0.013). Of 13 patients with APL, 4 died of bleeding/sepsis between days 2 to 4 after admission. Seven of 9 patients who received induction therapy achieved complete remission(CR). CR rate in APL was similar to other types of AML (78 vs. 64%, P=0.743). Five of seven patients who achieved CR remain in continuous CR at 9^+ to 42^+ months. CR duration is significantly longer in APL when compared to other types of AML (P=0.029).

In conclusion, this study showed that APL is a distinct entity among subtypes of AML with clinically significant bleeding tendency and rapidly fatal course if untreated. With appropriate antileukemic therapy, CR can be achieved in the majority of patients and the patients show a longer duration of CR when compared to other types of AML.

Key Word : *Acute promyelocytic leukemia.*

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INTRODUCTION

Acute promyelocytic leukemia(APL) is a subset of acute myelocytic leukemia(AML) characterized by the presence of atypical promyelocytes in the peripheral blood and bone marrow and typically associated clinical features of disseminated intravascular coagulation(DIC) (Stone and Mayer, 1990). In a series of Korean patients with acute leukemia reported by Ko et al. (1983) APL comprised 18% of AML. For the last 4 to 5 years, there have been important advances in the treatment and understanding of the pathogenesis of this unique disease : (1) administration of retinoic acid to patients with APL can induce complete remission in a high proportion of patients through the mechanism of terminal differentiation of APL blasts (Warrell Jr et al., 1991) ; (2) description of a specific cytogenetic abnormality, t (15 ; 17) (McKenna et al., 1982) ; and (3) description of the presence of an anomalous protein, the PML/RARα protein, a mutant of one of the retinoic acid receptors in APL blasts (de The et al., 1990 ; Borrow et al., 1990). These findings not only provided insight into the pathogenesis of APL but also altered the way in which we approach and treat patients with APL.

The purpose of our study was to describe the clinicopathologic characteristics of APL seen at our hospital over the last 5 years by retrospective analyses. The therapeutic implications of the findings are also discussed.

MATERIALS AND METHODS

Adult patients who were admitted to the Department of Medicine, University of Ulsan, Asan Medical Center, Seoul, Korea from June, 1989 to December 1993 and subsequently diagnosed to have AML were included in the study. Various clinical data of the patients at the time of diagnosis, such as age, sex, initial symptoms, duration of symptoms, complete blood count, and blood chemistry were collected retrospectively. Bone marrow smears and core biopsy sections were examined by a pathologist (H.S.C) and the cases were further classified according to the standard FAB criteria(Bennet et al., 1985 ; Bennet et al., 1976). Leukemic cell immunophenotype studies were done using a panel of monoclonal antibodies including HLA-DR, CD13, CD33, CD14, and CD61. Prothrombin time expressed as international normalized ratio(INR) and fibrinogen level at the time of diagnosis were recorded. The data regarding treatments and subsequent clinical courses of the patients such as presence of complete remission(CR), duration of CRs, or cause of death were recorded.

The clinicopathologic characteristics of APL were compared to those of AML other than APL(other AML). The categorical variables were compared using Fisher's exact test. The continuous variables were compared using Wilcoxon's rank sum test. Survival curves were obtained by Kaplan-Meier method and compared using Wilcoxon test.

RESULTS

Patients

A total of 96 patients with AML were seen between June, 1989 and December, 1993. The median age of these 96 patients was 41.5 years (range 15-81) and there were 48 male patients (50%). Of those, 13 patients (14%) had APL. The median age of the 13 patients with APL was 28 years (range 18-55) and there were 7 male patients (54%) (Table 1 and 2). Of the 13 cases of APL, 8 were hypergranular type and 5 were microgranular type (Table 3).

Clinical characteristics of APL

When compared to patients with other AML, patients with APL were significantly younger (Table 2, P=0.011). There was no significant difference in sex ratio between the two groups. A higher proportion of patients with APL presented with various types of bleeding (31%) when compared to patients with other AML (13%) but the difference was not statistically significant. Of 4 the patients with APL who presented with symptoms of bleeding, 3 had gum bleeding and 1 had skin ecchymoses. The duration of symptoms before diagnosis was significantly shorter in patients with APL when compared to that in patients with other AML (0.2 vs. 1.0 month, P<0.001).

Peripheral blood findings

Median white blood cell(WBC) count at presentation was lower in patients with APL (5.1×10^3 vs. $14\times10^3/\mu l$) but the difference was not statistically significant(Table 4). Eight of 13(62%) patients with APL and 7 of 83(8%) with other AML had promyelo-

Table 1. Summary of the 13 patients with APL

Case No	Age/ Sex	Dx Date (mo/yr)	Hb (gm/dl)	WBC (/μl)	Platelet (/μl)	PBPro (%)	PBBla (%)	INR	Fibrinogen (mg/dl)	BMCell (%)	BMBla (%)	BMPro (%)	Ind chemo	CR	Dur CR (mo)	Result
1	18/F	09/89	6.7	4.6	31	73	12	6.61	110	100	70.8	22.4	No	No	—	died of bleeding on 2nd day of diagnosis
2	19/M	11/90	12.8	5.1	27	10	37	1.58	188	95	6.6	83.6	Ara-C+DNR	Yes	42^+	alive in CR
3	24/F	02/91	8.5	25.1	86	6	84	—	183	100	45.4	47.0	No	No	—	died of bleeding on 4th day of diagnosis
4	22/F*	05/91	8.2	51.4	34	79	10	1.81	192	80	12.2	73.6	No	No	—	died of sepsis on 3rd day of diagnosis
5	28/M*	07/91	13.9	1.1	65	16	17	1.40	154	100	20.0	36.2	Ara-C+ mitoxantrone	Yes	32^+	alive in CR
6	48/M	10/91	12.3	1.2	98	0	0	1.01	240	95	11.8	43.8	Ara-C+DNR	Yes	28^+	alive in CR
7	30/M	12/91	5.8	2.5	13	22	7	1.16	302	100	7.0	70.2	Ara-C+DNR	No	—	died of bleeding during ind chemo
8	38/F*	02/92	9.0	94.8	19	92	0	—	—	90	71.8	24.4	Ara-C+DNR	No	—	died of bleeding after ind chemo failure
9	53/M	03/92	12.1	0.8	98	0	0	1.32	132	95	1.4	39.2	Ara-C+DNR	Yes	23^+	alive in CR
10	18/M*	10/92	15.1	68.4	47	56	0	—	—	100	70.4	18.0	No	No	—	died of sepsis on 2nd day of diagnosis
11	55/F	11/92	7.1	14.0	41	2	0	1.10	357	100	9.8	85.6	oral isotretinoin	Yes	14	alive in relapse
12	26/F*	01/93	6.6	19.7	13	88	2	1.32	263	100	57.2	26.0	Ara-C+DNR	Yes	13	died in relapse
13	41/M	06/93	6.6	3.7	25	82	5	1.24	314	100	31.4	61.0	Ara-C+DNR	Yes	9^+	alive in CR

*patients with APL, microgranular type

**abbreviations : Dx=diagnosis, Hb=hemoglobin, WBC=white blood cells, PBPro=peripheral blood promyelocytes, PBBla=peripheral blood blasts, BMCell=bone marrow cellularity, BMBla=bone marrow blasts, BMPro=bone marrow promyelocytes, Ind chemo=induction chemotherapy, Dur CR=duration of CR, Ara-C=cytarabine, DNR=daunorubicin

Table 2. Clinical characteristics of patients, APL vs. other AML

	APL(%) (N=13)	other AML(%) (N=83)	*P* value
Age(yr)			0.011
20 or less	3(23)	8(10)	
21—30	5(38)	13(16)	
31—40	1(8)	17(20)	
41—50	2(15)	8(10)	
51—60	2(15)	14(17)	
61—70	0	15(18)	
>70	0	8(10)	
Sex			1.000
Male	7(54)	41(49)	
Female	6(46)	42(51)	
Initial symptom			0.135
Infection	3(23)	28(34)	
Bleeding	4(31)	11(13)	
General weakness	4(31)	42(51)	
Pain	0	2(2)	
Duration of symptom(mo)			<0.001
Median(range)	0.2(0—1.0)	1.0(0.2—36)	

Table 3. Initial hematologic findings, hypergranular vs. microgranular type

	Hypergranular type(n=8) median(range)	Microgranular type(n=5) median(range)	*P* value
WBC count(x10³/μl)	3.1(0.8-25.1)	51.4(1.1-94.8)	0.092
Hemoglobin(g/dl)	7.8(5.8-12.8)	9.0(6.6-15.1)	0.379
Platelet(x10³/μl)	36(13-98)	34(13-65)	0.735
Prothrombin time(INR)	1.28(1.01-6.61)	1.55(1.32-1.81)	0.307
Fibrinogen(mg/dl)	214(110-357)	192(154-263)	0.919

Table 4. Initial laboratory findings, APL vs. other AML

	APL (N=13) median(range)	other AML (N=83) median(range)	*P* value
WBC count(x10³/μl)	5.1(0.8-94.8)	14.0(0.2-340)	0.387
Myeloblasts(%)	22(0-92)	37(0-99)	0.383
Promyelocytes(%)	5(0-84)	0(0-2)	<0.001
Hemoglobin(gm/dl)	8.5(5.8-15.1)	8.0(2.7-14.6)	0.126
Platelets(x10³/μl)	34(13-98)	36(2-555)	0.860
Albumin(gm/dl)	4.0(3.1-5.3)	3.6(2-5)	0.018
Globulin(gm/dl)	2.7(2.2-3.5)	2.9(1.9-4.9)	0.147
LDH(IU/l)	1013(368-11524)	987(266-5591)	0.709
Prothrombin time(INR)	1.36(1.01-6.61)	1.15(0.73-2.58)	0.012
Fibrinogen(mg/dl)	192(110-357)	461(88-1158)	<0.001
Bone marrow			
Cellularity	100(80-100)	90(5-100)	0.013
Blasts(%)	20.0(1.4-71.8)	67.2(22.4-98.4)	<0.001
Promyelocytes(%)	43.8(18.0-85.6)	0.2(0-18.6)	<0.001

cyte in their peripheral blood smear. Also the proportion of promyelocytes in total WBC was significantly higher in APL($P<0.001$). There was no significant difference in serum hemoglobin level and platelet count between patients with APL and other AML. Microgranular types of APL had higher median WBC counts when compared to hypergranular types of APL but this was not statistically significant (Table 3). There was no significant difference in serum hemoglobin level and platelet count between hypergranular and microgranular types of APL (Table 3).

Blood chemistries

Serum albumin level at presentation was significantly higher in patients with APL when compared to that in patients with other AML (Table 4, $P=0.018$). There was no significant difference in serum globulin, lactate dehydrogenase (LDH), aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, or uric acid levels.

Blood coagulation profiles

Either prothrombin time(INR) or fibinogen level or both at presentation were available in 12 of 13 patients (92%) with APL and 71 of 83 patients (86%) with other AML. INR was significantly higher in patients with APL when compared to patients with other AML(median 1.36 vs. 1.15, $P=0.012$, Table 4). Plasma fibrinogen level was significantly lower in patients with APL (median 192 vs. 461 mg/dl, $P<0.001$). When a normal INR value of 1.0 to 1.3 and a normal plasma fibrinogen level of 200 to 400mg/dl were applied, 8/12 (75%) patients with APL and 18/71 (25%) patients with other AML had abnormal values of either INR or fibrinogen level or both ($P<0.001$). There was no significant difference in INR and serum fibrinogen level at presentation between hypergranular and microgranular types of APL (Table 3).

Bone marrow findings

Median bone marrow cellularity was significantly

higher in APL(Table 4, 100 vs. 90%, P=0.013). In APL, predominant malignant cells were atypical promyelocytes (median 43.8%, range 18.0-85.6%). In other AML, promyelocytes comprised a smaller portion of nucleated cells (median 0.2%, range 0-18.6%, P<0.001).

Immunophenotype studies

A majority of cases of APL showed positivity for the CD 13 and CD 33 antigens (8/10 and 9/10 respectively, Table 5). Characteristically, leukemic cells from APL showed negativity for the HLA-DR antigen (0/10) which was in contrast to leukemic cells from other AML where the majority of cases were HLA-DR antigen positive (53/68).

Treatment results and relapse free survival

Of 13 patients, 4 patients died before the initiation of induction chemotherapy (Table 1, case 1, 3, 4, 10 ; two patients died of central nervous system hemorrhage ; two patients died of sepsis). Nine patients received induction chemotherapy (7 patients received cytarabine 100-200 mg/m^2/day for 7 days plus daunorubicin 40 mg/m^2/day for 3 days ; one patient received cytarabine 200 mg/m^2/day for 7 days plus mitoxantrone 12 mg/m^2/day for 3 days ; one patient received oral isotretinoin 100 mg/m^2 daily) (Kim et al., 1993 ; Lee et al., 1993). Two patients (cases 7 and 8) died of pulmonary hemorrhage during induction chemotherapy and after a failure of induction chemotherapy respectively. Seven patients achieved CR (CR rate 78%, Table 6). Postremission therapy included high dose cytarabine (1 gm/m^2 every 12 hours daily for 5 days) plus anthracycline in 5 patients (cases 2, 5, 6, 12, and 13) and regular dose cytarabine (100-200 mg/m^2 daily for 5 days) plus anthracycline in 2 patients (cases 9 and 11). Two patients (cases 11 and 12) relapsed after CR duration of 13 and 14 months respectively. The remaining 5 patients are alive in CR for 9$^+$ to 42$^+$ months (cases 2, 5, 6, 9, and 13).

Table 6. CR rate and relapse after CR, APL vs. other AML

	APL(%) (N=9)	other AML(%) (N=67)	P value
CR	7(78)	43(64)	0.743*
Relapse after CR	2(29)	27(63)	0.029**

*by Fisher's exact test
**by Wilcoxon test

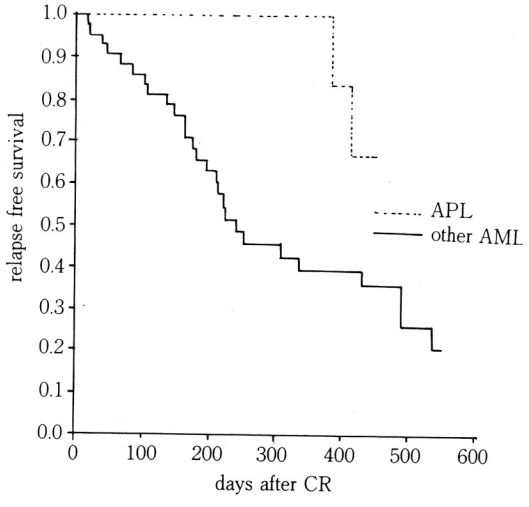

Fig. 1. Kaplan-Meier estimate of relapse free survival in patients with APL vs. other AML.

Table 5. Pattern of immunophenotypes according to FAB subtypes

	HLA-DR	CD13	CD33	CD14	CD61
	(No of positive cases*/No of tested cases)				
FAB subtypes					
M1(N=36)	24/34	27/34	28/34	0/12	0/27
M2(N=19)	12/14	13/15	12/15	0/5	0/11
M3(N=13)	0/10	8/10	9/10	1/6	0/7
M4(N=13)	9/11	10/11	8/11	7/9	0/9
M5(N=6)	2/3	3/3	2/3	2/3	0/3
M6(N=3)	2/2	1/2	1/2	0/2	0/2
M7(N=4)	4/4	2/4	2/4	1/2	4/4

*The cases were considered positive if 20% or more of cells were reactive to particular monoclonal antibody.

Of 83 patients with other AML in our study, 16 patients did not receive induction chemotherapy due to old age and/or poor performance status and were excluded from the analysis of treatment results. Of the remaining 67 patients, 43 (64%) achieved CR (Table 6). The CR rate was not significantly different between APL and other AML (Table 6). Postremission therapy given to patients with other AML included regular dose cytarabine (100-200 mg/m^2 daily for 5 days) plus anthracycline in 23 patients, high dose cytarabine (1-3 gm/m^2 every 12 hours daily for 5-6 days) plus anthracycline in 19 patients, and none in 1 patient. Twenty seven of 43 patients (63%) with other AML who achieved CR relapsed. The CR duration was significantly longer for APL when compared to other AML (P=0.029, Table 6, Fig. 1).

DISCUSSION

APL comprised 14% of AML in our study. Patients with APL were younger, more likely to present with bleeding and had shorter duration of symptoms before diagnosis. The shorter duration of symptoms may be explained by the fact that the majority of patients with APL have coagulation abnormalities(75%) and symtoms of bleeding tend to make patients seek medical attention sooner. It is not certain whether the lower WBC count and higher level of serum albumin level at presentation in patients with APL is due to earlier diagnosis of APL in the course of the disease or to inherent differences between APL and other types of AML. Bone marrow examination showed that patients with APL had higher median marrow cellularity (100 vs. 90%, P=0.013). Atypical promyelocytes comprised a significant proportion of marrow cells (18.0-85.6%) in APL, which was in contrast to other types of AML (0-18.6%). Cell surface marker studies showed that both hypergranular and microgranular types of APL showed negative reactivity to HLA-DR antigen, which is a very useful finding when one differentiates the microgranular variant of APL from acute monocytic leukemia (M5). In our study 2 of 3 cases of acute monocytic leukemia were positive for HLA-DR antigen (Table 5). Although the number of cases is small, our study showed that patients with the microgranular variant of APL had a higher median WBC count at presentation (51.4×10^3 vs. $3.1\times10^3/\mu l$, P=0.092) and the finding is consistent with other published data (McKenna et al., 1982 ; Stone and Mayer, 1990).

Although 4 of 13 patients died 2 to 4 days after diagnosis, 7 of 9 patients who received induction therapy achieved CR and the CR rate was not significantly different from that of other AML. Once the patients achieved CR and when the appropriate post remission therapy were given, they had better disease free survival when compared to other AML. Three patients (case 2, 5, and 6) have been leukemia free for over 2 years and they are likely to be long term survivors.

Since the original description by Hillestad (1957), APL has been considered to be a distinct entity among AML with a rapid downhill course for patients which is usually due to a severe bleeding tendency. The bleeding syndrome is attributed to a DIC which has been shown to result from release of a procoagulant factor by blast granules (Gralnick and Abrell, 1973). Traditionally, therapeutic strategy in these patients included combination chemotherapy plus aggressive management of the coagulopathy including heparin infusion and transfusion of platelets and fresh frozen plasma, which resulted in CR in approximately 70% of patients (Kantarjian et al., 1985 ; Cunningham et al., 1989). Ten to 30% of patients experienced fatal hemorrhage during induction therapy.

Recent introduction of all transretinoic acid in the treatment of APL has improved the outlook of patients with APL significantly (Fenaux et al., 1993 ; Frankel et al., 1994). CR can be induced in approximately 90% of the newly diagnosed patients with APL with a lesser degree of coagulopathy and a shorter duration of neutropenia. Also leukemia free survival improved significantly (Fenaux et al., 1993).

Our study showed that patients with APL present with short duration of symptoms (median 0.2 months, range 0-1.0) and follow rapidly fatal courses due to bleeding and/or sepsis if the patients are left untreated. However, CR can be acheived in the majority of patients if aggressive antileukemic therapy and supportive care are instituted. Once the patients achieve CR, the patients require further post remission therapy. The patients with APL enjoy longer leukemia free survivals when compared to other types of AML. Thus, it is of the utmost importance to diagnose the patients with APL early and initiate appropriate therapy without any delay.

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