Acute Myeloid Leukemia Accompanied by Multiple Thrombophlebitis

Yuki Tsumita, Takafumi Matsushima, Hideki Uchiumi, Nobuhiro Narahara, Jun’ichi Tamura, Masamitsu Karasawa, Hirokazu Murakami* and Takuji Naruse

A 66-year-old woman suffering from fever and thrombophlebitis was referred to our hospital. A peripheral blood examination revealed hyperleukocytosis with 96% blast cells and thrombocytopenia. The patient was diagnosed as having acute myeloid leukemia (AML) accompanied by disseminated intravascular coagulation (DIC). A marked decrease in protein C (PC) antigen and activity were observed. In this case, PC levels were lower than those observed in AML with DIC. Induction therapy for leukemia and treatment of DIC were started on the first day of hospitalization. The patient achieved complete remission, with PC antigen and activity levels normalized. (Internal Medicine 36: 595-597, 1997)

Key words: acute myeloid leukemia (AML), thrombosis, protein C (PC)

Introduction

Clinical evidence of the role of protein C (PC) as a major antithrombotic factor arose from the observation that homozygous PC deficiency led to fatal neonatal purpura fulminans. We report an AML patient suffering from thrombophlebitis, and discuss the relationship between PC levels and leukemic cells.

Case Report

A 66-year-old woman was referred to hospital for a common cold at the beginning of November 1995. Laboratory data was as follows: hemoglobin (Hb) 12.7 g/dl, white blood cell count (WBC) 8.6×10^9/l (fraction unclear), and platelet count (Plt) 195×10^9/l. Liver function was normal. Redness along the blood vessels appeared, together with fever, swelling, and pain throughout the right superior limb. At this time, the patient became aware of malaise in the left knee and swelling in the right lower jaw, accompanied by pain. She was referred to the department of cardiovascular surgery on November 13 and diagnosed with thrombophlebitis. She was treated with a continuous intravenous drip of antibiotics and heparin. Laboratory data then became as follows: WBC 144.6×10^9/l with 96% blast cells, Plt 45×10^9/l, aspartate aminotransferase (AST) 31 IU/l, aramine aminotransferase (ALT) 30 IU/l, lactate dehydrogenase (LDH) 899 IU/l, C-reactive examination for leukocytosis. Findings were leg edema with redness (Fig. 1), pain, and Homans and Lowenberg signs. No bleeding tendency, hepatosplenomegaly, or lymphadenopathy were observed. Laboratory data then became: Hb 11.2 g/dl, WBC 144.6×10^9/l with 96% blast cells, Plt 45×10^9/l, aspartate aminotransferase (AST) 31 IU/l, aramine aminotransferase (ALT) 30 IU/l, lactate dehydrogenase (LDH) 899 IU/l, C-reactive

Figure 1. Thrombophlebitis of the left lower limb on admission to our hospital. The finding was leg edema with redness along the blood vessel.
protein (CRP) 9.8 mg/dl, and endotoxin 73.2 pg/ml. Bone
marrow was hypercellular with 95.4% blast cells, and almost all
blast cells were positive for myeloperoxidase. The patient was
diagnosed as having acute myeloid leukemia (AML; FAB; M1)
with multiple thrombophlebitis. Cytogenetic analysis of bone
marrow cells showed a normal karyotype. Results of coagula-
tion and fibrinolytic tests were as follows: thrombin/antithrombin
III complex (TAT) >60 ng/ml, plasmin/antiplasmin complex
(PAP) 10.7 µg/ml, and D-dimer (D-D) 60.1 ng/dl. A marked
decrease of PC antigen at 45% and activity at 29% were
observed. Thrombomodulin levels did not change significantly,
but plasminogen activator inhibitor-1 (PAI-1) and the tissue
type plasminogen activator (t-PA)-PAI-1 complex increased
slightly. The Von Willebrand factor antigen (VWF), vascular
endothelial cell marker was increased (Table 1). Laboratory
findings confirmed the clinical diagnosis of disseminated intra-
vascular coagulation (DIC). Induction therapy was started on
the first day of hospitalization with a combination of cytarabine
and idarubicin hydrochloride. Intravenous gabexate mesilate
(FOY) was administered for the duration of DIC. After four
days, WBC decreased to 0.6×10^9/l and DIC improved, but
thrombophlebitis was aggravated. After additional treatment
with urokinase, thrombophlebitis markedly improved. Labora-
tory results showed a gradual return to normal levels. The
patient achieved complete remission (CR), with normalized
PC, PS, and plasminogen levels (Fig. 2).

**Discussion**

Hemostatic disturbances observed in patients with acute
leukemia are related to changes in vascular function, damage to
the megakaryocyte system, liver dysfunction, increased fibrin-
olysis, and DIC. The most common hemostatic disorder is
bleeding related to thrombocytopenia. Thrombosis is a much
rarer complication and is usually attributed to DIC. DIC-
duced thrombosis usually occurs in microvasculature such as
arterioles, capillaries, or venules and induces organ failure and
a poor prognosis. Deep venous thrombosis (DVT) is rare in
AML with DIC. Occasionally, patients with acute leukemia
develop thrombosis despite thrombocytopenia and in the ab-
sence of laboratory evidence of DIC. Under such conditions,
other factors are related to thrombosis. Some investigators have
reported PC level abnormalities in acute leukemia (1-3).

PC is a vitamin K-dependent proenzyme of serine protease
which is activated by thrombin and the endothelial cell cofactor
thrombomodulin. It is a major inhibitor of blood coagulation.
Anticoagulant properties of PC are derived from its selective
inactivation of factors Va and VIIIa. PC also generates potent

| Table 1. Coagulation and Fibrinolysis Parameters on Admission. Protein C Activity and Antigen Levels in This Case were Significantly Lower Than Those of AML with DIC |
|-----------------------------------|-------------------------------|-----------------------------------|
| PT (%)                            | 71% (70-130)                  | coagulation factor                |
| PT (ratio)                        | 1.18 (0.95-1.07)              | II                                |
| APTT                              | 30.2 sec (28-43)              | V                                 |
| Fbg                               | 152 mg/dl (150-330)           | VII                               |
| FDP                               | 171 mg/ml (0-4)               | VIII                              |
| D-dimer                           | 60.1 mg/dl (0-1)              | IX                                |
| AT-III                            | 104.1% (80-120)               | X                                 |
| Plg                               | 75.6% (80-120)                | XI                                |
| α2PI                              | 48.7% (80-120)                | XII                               |
| TAT                               | >60 mg/ml (<3)                | XIII                              |
| PAP                               | 10.7 µg/ml (<0.8)             | TF activity                       |
| SFMC                              | (2+) (-)                      | 1.6 U/10^6 cells (<0.8)           |
| Prot. C (%)                       | 29% (55-140)                  |                                   |
| Prot. C (Ag)                      | 45% (70-150)                  |                                   |
| Prot. S (Ag)                      | 10.9 mg/ml (6.6-11.5)         |                                   |

**Endothelial cell markers**

| TM                                | 4.1 FU/ml (<4.5)              | t-PA                              |
| vWF (Ag)                          | 234% (50-155)                 | ACE                               |
| PAI-1                             | 57 ng/ml (<50)                | 13.3 IU//37°C (8.3-21.4)           |
| t-PA-PAI-1                        | 23.1 ng/ml (<10)              |                                   |

ACE: angiotensin converting enzyme, α2PI, α2-plasmin inhibitor, AT-III: antithrombin III, Fbg: fibrinogen,
PAI-1: plasminogen activator inhibitor-1, PAP: plasmin-antiplasmin complex, Plg: plasminogen, Prot. C: protein
activity: tissue factor activity, TM: thrombomodulin, t-PA: tissue plasminogen activator, vWF (Ag): von
Willebrand factor antigen, PT: prothrombin time, APTT: activated partial thromboplastin time, FDP: fibrin
degradation products.
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Figure 2. Clinical course of this case. Ara C: cytarabine, DIC: disseminated intravascular coagulation, FOY: gabexate mesilate, IDA: idarubicin hydrochloride, LMWH: low molecular weight heparin, PC Ag (%): protein C antigen, UK: urokinase. DIC score is based on a modified version of the criteria established by the Japanese Ministry of Health and Welfare. In leukemia, DIC was diagnosed when DIC score was more than 4 points.

fibrinolytic activity in plasma. Reports of hereditary PC deficiency and acquired PC deficiency observed in liver disease, DIC, and warfarin therapy suggest that PC plays an important role in both physiologic hemostasis and many clinical disorders characterized by thrombosis. A PC level of 60% or less of normal can develop thromboembolic complications in patients with hereditary PC deficiencies (4).

It has been reported that PC antigen and activity levels are significantly lower in active AML patients than in patients in remission or in normal controls. In normal subjects, mean PC antigen levels are 123.6% and activity levels are 95.5%. In active AML, these levels are 77.9% and 58.5% (5). Rodighiero et al reported that PC antigen levels in acute leukemia are not lower in patients with DIC than in those without DIC. He suggested that patients with circulating blast cells exceeding $50 \times 10^9/\ell$ had significantly lower concentrations of PC antigen (2). The cause of these low PC levels in AML patients is still a matter of controversy. Törnebohm et al suggest that the release of proteases from leukemic blast cells may be responsible for the destruction of fibrinogen and other coagulation factors (3).

The present case was admitted to our hospital with multiple thrombophlebitis, clinical DIC symptoms, and elevated endotoxin levels, but no signs of sepsis or liver dysfunction. PC antigen levels were 45% and activity levels 29%, which are lower than those of AML with DIC. PC levels were normalized after complete remission. The patient had no hereditary hemostatic abnormalities. Thrombosis was similar to deep venous thrombosis in hereditary PC deficiency. Hyperleukocytosis was not the cause of low PC levels, because her thrombophlebitis was observed with a normal leukocyte count. No liver damage was observed at admission. Although coagulation factor activities were somewhat reduced, the pattern was different from that of vitamin K deficiency. We assume that low PC levels may result from PC consumption by thrombosis formation or DIC, but also from unknown factors released from leukemic cells. Because coagulation and fibrinolysis studies were not performed before admission, it is difficult to define the relationships between leukemia and DVT in this case. We assumed, however, that a low PC level may be one cause of DVT sideration. AML with DIC complicated by multiple thrombophlebitis and deep venous thrombosis is, in any case, extremely rare.

References