

Acute Myeloid Leukemia Associated with Acute Myocardial Infarction and Dural Sinus Thrombosis: The Possible Role of Leukemia-related Hyperhomocysteinemia

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The association of acute myeloid leukemia (AML) and acute myocardial infarction (AMI) is rare. We encountered a 40-year-old female with inferior wall myocardial infarction that occurred simultaneously with the diagnosis of AML. She developed subsequent dural sinus thrombosis during chemotherapy for AML. The screen for thrombophilia revealed that she had hyperhomocysteinemia. In the English literature, only 4 cases have been reported previously. Remission induction was not affected by the occurrence of AMI, although anthracyclines were avoided in all cases. In the absence of conventional risk factors for coronary artery disease, AMI can be related to leukemia *per se* and the role of homocysteine is worth further investigation. [*J Chin Med Assoc* 2008;71(8):416–420]

Key Words: acute myeloid leukemia, acute myocardial infarction, dural sinus thrombosis, homocysteine, thrombophilia

Introduction

Myocardial infarction commonly results from atherosclerosis of the coronary arteries. For relatively young patients, myocardial infarction is associated with unconventional risk factors such as hyperhomocysteinemia.^{1,2} Acute myeloid leukemia (AML) may predispose patients to hypercoagulable states such as disseminated intravascular coagulation or hyperleukocytosis.^{3,4} The association of acute myocardial infarction (AMI) and AML is rare and the pathogenic relationship between these entities undefined. We herein report the case of a patient with concurrence of AML and AMI. We propose that leukemia-related hyperhomocysteinemia may have a pathogenic role in the development of thrombosis.

Case Report

In June 2006, a 40-year-old female had epigastric pain with radiation to the chest and left axillary areas. It was

accompanied by vomiting and cold sweating. She did not smoke and had neither family history of coronary artery disease nor past history of diabetes mellitus, hypertension or hyperlipidemia. She visited a local hospital. The initial electrocardiography (ECG) and echocardiography showed normal results, but the hemogram revealed leukocytosis with blasts.

She was referred to our hospital. ECG revealed pathological Q-wave and ST elevation in leads II, III and AVF (Figure 1). The physical examination was unremarkable. The initial biochemical study revealed creatine kinase-MB of 51.9 ng/mL (normal, <10.4 ng/mL) and troponin-I of 30.64 ng/mL (normal, <0.16 ng/mL). The patient was admitted to the coronary care unit. Hemogram showed hemoglobin of 11.6 g/dL, platelet count of 122,000/mm³ and white blood cell count of 11,000/mm³ with 83% blasts, 2% promyelocytes, 1% metamyelocytes, 6% neutrophils, 7% lymphocytes and 1% eosinophils. Serum creatinine was 0.7 mg/dL and cholesterol was 199 mg/dL. Her homocysteine level was 13.7 μmol/L. Protein C, protein S and antithrombin III activities



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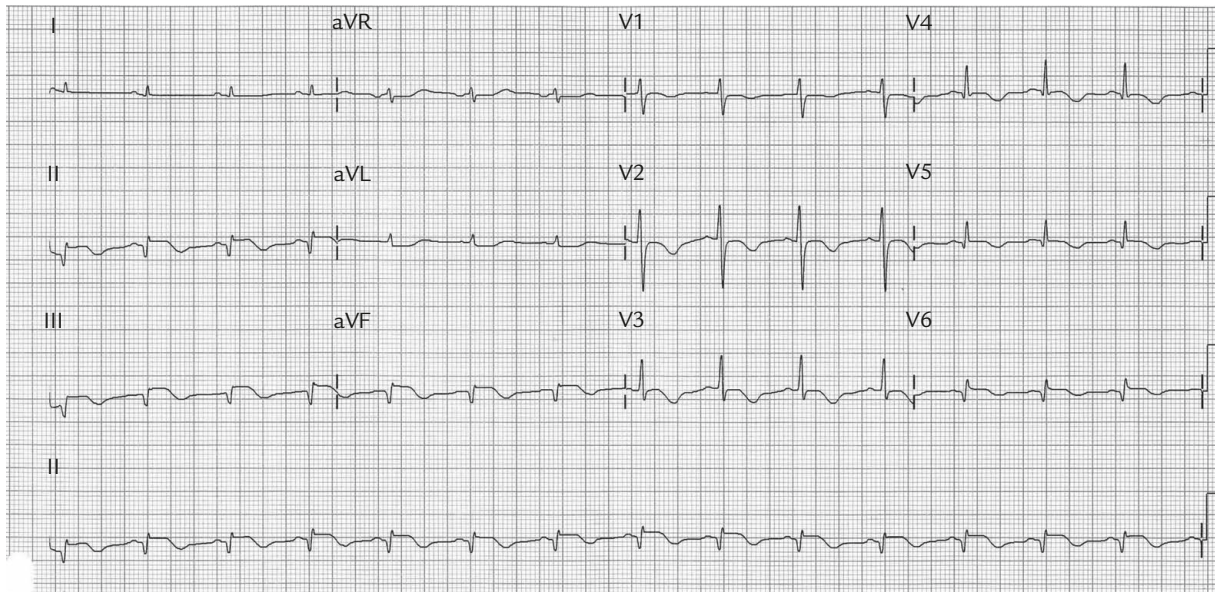


Figure 1. Electrocardiography shows pathological Q-wave and ST elevation in leads II, III and AVF.

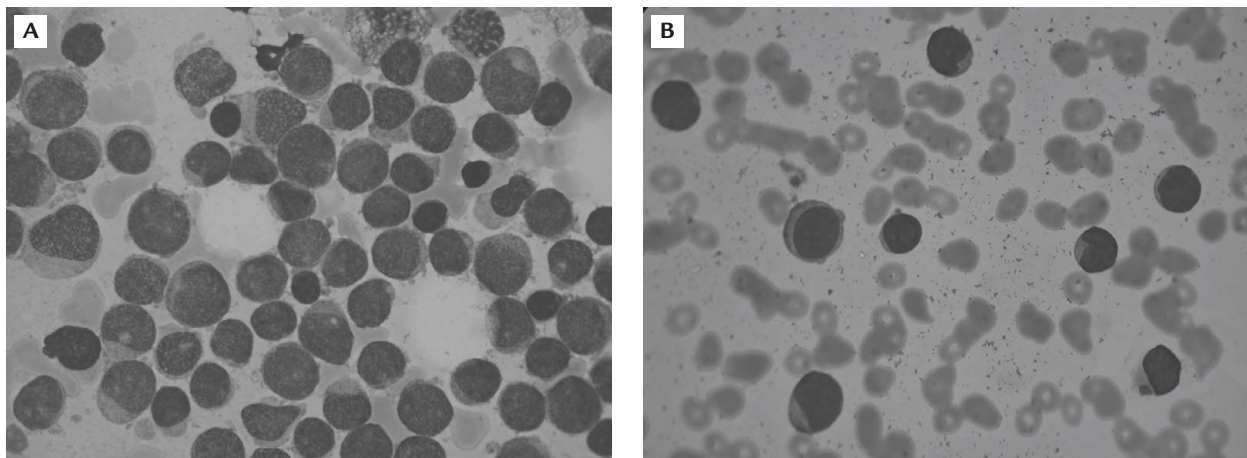


Figure 2. (A) Bone marrow and (B) peripheral blood smears show many blast cells.

were 100.7%, 102% and 110%, respectively. Coagulation profile showed prothrombin time of 13.4 seconds (control, 10.8 seconds; international normalized ratio [INR], 1.22), activated partial thromboplastin time of 33.1 seconds (control, 28.4 seconds), fibrinogen of 411 mg/dL, and D-dimer of 7,002.79 ng/mL. Lupus anticoagulant was negative. The patient received medical treatment with aspirin, clopidogrel, nitrate, propranolol and enoxaparin 60 mg subcutaneous injection per day. The diagnosis of AML, M1, was established by a bone marrow aspiration smear (Figure 2). The karyotype was 46,XY. Flow cytometry showed that the leukemic cells were positive for CD33, CD13 and CD117, and negative for CD7 and CD19.

On the 12th day after the onset of chest pain, the patient received chemotherapy with cytarabine 100 mg/m² continuous intravenous infusion for 7 days and etoposide 100 mg/m² intravenous drip 3 hours for 3 days. She had sudden blurred vision on the 14th day after the initiation of chemotherapy and the 26th day after the onset of chest pain. The ophthalmologist was consulted. Bilateral retinal hemorrhage was observed. Sinus thrombosis was suspected and cerebral magnetic resonance imaging confirmed the diagnosis of right lateral dural sinus thrombosis (Figure 3). Hemogram at that time showed hemoglobin 8.4 g/dL, platelets 35,000/mm³ and white blood cells 900/mm³. We gave enoxaparin 60 mg/day subcutaneous injection,

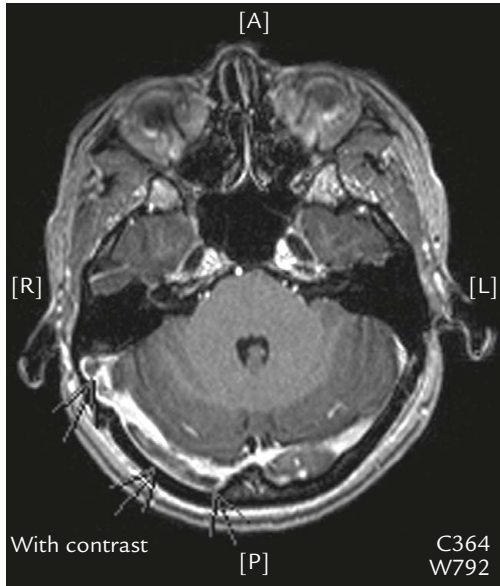


Figure 3. Brain magnetic resonance imaging shows thrombosis of the right lateral dural sinus (arrows).

followed by warfarin 5 mg/day, adjusted to keep the INR of prothrombin time within 2–3 times the normal range. The patient’s visual acuity gradually improved. Subsequent bone marrow aspiration smear confirmed that she had complete remission.

During the period of remission, her homocysteine level fell to 10.9 $\mu\text{mol/L}$ after folic acid supplementation for 2 months, after which she stopped taking folic acid. Another 6 weeks later, her homocysteine level fell to 9.8 $\mu\text{mol/L}$. She completed post-remission treatment with 6 cycles of high-dose cytarabine. No further chest pain or visual disturbance was noted.

Discussion

The association of AML and AMI is rare, and the relationship between these 2 entities is undefined.⁵ For acute promyelocytic leukemia (AML, M3), AMI may result from a hypercoagulable state caused by disseminated intravascular coagulation.³ Patients with AML, other than M3, who present with a hypercoagulable state are few in number, and its association with AMI is rare. We reviewed the English-language literature and found no more than 4 cases.^{4–7} The clinical features of these cases and our own are summarized in Table 1. Compared with the average age of AMI patients, these cases are relatively young. One of them had smoking history⁵ and another had a positive family history of coronary artery disease.⁶ The risk factors for myocardial infarction appeared less prominent than generally considered. The hypercoagulable states have never been

Table 1. Clinical features of all reported cases of acute myocardial infarction (AMI) associated with acute myeloid leukemia (AML)

Case	Age (yr)	Sex	AML subtype	WBC (/mm ³)	Infarct wall	Occluded vessel	AMI risk factor	Thrombophilia state	Remission	Anthracycline	Reference
1	33	M	ND	16,000	Inferior lateral	ND	None	ND	No	Not used	7
2	42	M	M2	4,500	Anterior	LAD	FH	None	Yes	Not used	6
3	56	F	M1	316,000	Inferior	RCA	ND	Hyperleukocytosis	Yes	Not used	4
4	54	M	M4	9,400	Inferior lateral	RCA	Smoking	ND	ND	ND	5
5	40	F	M1	11,000	Inferior	ND	None	Homocysteine	Yes	Not used	This study

WBC = white blood cell count; ND = not described; LAD = left anterior descending artery; FH = family history; RCA = right coronary artery.

described in detail. One of them had hyperleukocytosis, which was considered to be the major contributor to infarction.⁴ The homocysteine level was normal in 1 case,⁶ elevated in our case, and not mentioned in the remaining cases. As for the treatment of AML, complete remission was successfully induced in 3 cases, while blasts could still be found in the peripheral blood of the earliest case.⁷ The treatment result was not available in 1 case.⁵ Anthracycline was avoided due to concern regarding its potential cardiotoxicity in all 4 cases whose treatment regimens were described.^{4,6,7} In our case, we replaced anthracycline with etoposide. The induction therapy was also successful. Although there is only limited experience, avoiding anthracycline appears to be safe and equally effective in remission induction.

Several mechanisms are proposed for myocardial infarction in patients with AML, including leukemic infiltration into the myocardium,⁵ effects of the antileukemic chemotherapy, especially anthracycline,⁵ occlusion of coronary arteries by leukemic thrombus,^{5,6} hemorrhage in the myocardium or intima of a coronary artery,⁵ leukostasis syndrome,^{4,5} disseminated intravascular coagulation,⁵ and deficiency of coagulation factors.^{5,8} Jachmann-Jahn et al suggested leukemic thrombus as the etiology.⁶ Cohen et al considered AMI as part of leukostasis syndrome as their patient had extreme leukocytosis.⁴ Deficiency of protein C, protein S and antithrombin III has been demonstrated,⁸ but whether such deficiencies lead to AMI is still not clear.

In our case, the white blood cell count at presentation was 11,000/mm³, which made leukostasis less likely. The unique feature of our case is the subsequent dural sinus thrombosis, which developed during treatment of AML. The white blood cell count was 900/mm³, indicating further that leukostasis was unlikely to have been the cause of thrombosis. In the presence of indwelling catheter, catheter-related thrombosis is another consideration. However, the majority of catheter-related thromboses developed in the upper extremities,⁹ and the myocardial infarction in our case actually occurred before catheter implantation. On the other hand, our patient had hyperhomocysteinemia, which is a risk factor for both arterial and venous thromboembolism.¹⁰⁻¹² The risk of AMI is increased 2-fold when homocysteine level is > 10.2 μmol/L and 9-fold when it is > 20 μmol/L.¹¹ Homocysteine was found to be frequently elevated in rapidly proliferative tumors even though they were not treated with antifolate drugs.¹³ It was also proposed that homocysteine could serve as a potential tumor marker.¹³ The levels of homocysteine in leukemic patients have not been

studied extensively. In our case, homocysteine level was increased on diagnosis but declined after chemotherapy and folic acid supplement. Although direct evidence of hyperhomocysteinemia resulting from leukemia is weak, our patient's homocysteine level was normal after cessation of folic acid during the remission phase of her leukemia. This suggests that her hyperhomocysteinemia was related to leukemia rather than to genetic defects in homocysteine metabolism.

Our report is limited in several aspects. Homocysteine level may vary with the menstrual cycle in young females,¹⁴ and the levels measured in our spot samples may be affected. The causal relationship between hyperhomocysteinemia and AMI or dural sinus thrombosis cannot be established with such limited evidence. Considering that she did not have any risk factor for coronary artery disease and that the other screening tests for thrombophilia, including protein C, protein S, antithrombin III and lupus anticoagulant, were normal, we suggest that the patient's AMI and sinus thrombosis stemmed from leukemia *per se* or the resultant hyperhomocysteinemia.

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