The characteristics of megaloblastic anemia associated with thalassemia

Combined megaloblastic anemia with thalassemia is easily masked because of the loss of macrocytosis. We performed a retrospective study to compare the major parameters in 4 groups of subjects in order to show the characteristics of patients with megaloblastic anemia and thalassemia. Group A comprised 9 patients with megaloblastic anemia and thalassemia, group B comprised 10 patients with uncomplicated megaloblastic anemia. Group C comprised 12 uncomplicated thalassemia trait and group D was formed of 11 healthy controls. The mean corpuscolar volume (MCV) in group A patients was not significantly different from that in normal subjects, but was significantly lower and higher than in those with pure megaloblastic anemia and pure thalassemia, respectively. Other parameters were not different between patients with uncomplicated megaloblastic anemia and megaloblastic anemia complicating thalassemia. Most of the manifestations in megaloblastic anemia complicating thalassemia were similar to those of uncomplicated megaloblastic anemia but not to uncomplicated thalassemia. Combined megaloblastic anemia with thalassemia is still an easily diagnosed disease.

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Uncomplicated megaloblastic anemia is easily diagnosed by an experienced hematologist when a high mean corpuscular volume (MCV) is present.[1] However, if this condition is associated with another disease such as thalassemia, the high MCV can be masked.[2-4] In our country, the prevalence of thalassemia is about 4-8%,[5-7] thus, the chance of megaloblastic anemia associated with thalassemia is possible and can be missed. As there are few data on complete blood counts (CBC) in this situation, the present study tried to find out their characteristics.

Four groups entered the study. Nine patients were found to have a diagnosis of *megaloblastic anemia with thalassemia* (group A) in our hospital between 1960 and 2001. The major criteria for the diagnosis of megaloblastic anemia were typical bone marrow changes and low serum vitamin level (either serum vitamin B_{12} or folate). The diagnosis of α or β thalassemia minor was made by hemoglobin H staining and hemoglobin electrophoresis. The patients' mean age was 51.7±20.1 years (range 23-89 years). We also randomly selected age-matched subjects with complete enough data to rule out any complicated conditions to fit the criteria of the other 3 groups. Group B contained 10 patients with uncomplicated megaloblastic anemia. Group C contained 12 patients with uncomplicated thalassemia minor without any previous transfusion. Group D contained 11 healthy controls without any history of anemia and with normal CBC and vitamin levels. Mann-Whitney's U test was used to test the significance of each main parameter.

Table 1 shows the various parameters in the 4 groups of subjects. There was no age difference between groups. The MCV in group A patients with megaloblastic anemia and thalassemia was not significantly different from that in the normal subjects, but was significantly lower and higher than that in patients with megaloblastic anemia and with thalassemia, respectively. This group's white blood cell (WBC) count and red cell distribution width (RDW) were significantly lower and higher than that in the normal subjects and thalassemias, respectively. The platelet count was significantly lower than that in patients with thalassemias. In the patients with megaloblastic anemia and thalassemia, total bilirubin and lactate dehydrogenase (LDH) levels were not significantly different from those in patients with pure megaloblastic anemia, but were significantly higher than those in the normal subjects and patients with thalassemias. There was no significant difference in serum vitamin B_{12} and folic acid between group A patients and those with megaloblastic anemia. Megaloblastic anemia is a treatable disease and can be readily diagnosed. However, in complicated cases of megaloblastic anemia such as those combined with thalassemia, the classical hallmark of macrocytosis will disappear. Thus, due to the marked elevation of LDH and pancytopenia, the unexperienced physician will usually search for a malignant tumor, performing many unnecessary, cumbersome and even invasive examinations. Thus, awareness of the possibility of complicated megaloblastic anemia with thalassemia is necessary.

In this retrospective study, only 9 patients were documented to have had megaloblastic anemia complicated with thalassemia in the past 41 years. This number was rather low despite folic acid deficiency being very rare in our country,[8-10] and vitamin B12 deficiency not so frequent as in Western countries. Thus, there might be some undiagnosed cases due to unawareness of this so called *masked megaloblastic anemia*.[2,3] If this were true, this disease might be a challenge for internists and even hematologists. MCV is known to be the most important parameter in

Table 1. Hematologic parameters in subjects with MA+thal (group A), MA (group B), thal (group C) and controls (group D).

	Group A	Group B	Group C	Group D	p‡		
					A vs B	A vs C	A vs D
Age (year)	51.7±20.1* (9)†	52.2±13.8 (10)	64.2±23.5 (12)	54.5±8.7 (11)	0.604	0.148	0.131
Hemoglobin (g/L)	50.8±16.6	81.5±21.8	91.7±26.4	139.0±24.4	0.008	<0.0005	<0.0005
MCV (fL)	86.0±11.1	114.5±21.1	64.9±6.2	91.4±2.8	0.008	<0.0005	0.295
RDW-SD (fL)	61.2±11.1	71.5±5.7	39.9±13.8	43.1±3.4	0.381	0.190	0.005
WBC ($\times 10^9$/L)	4.9±5.7	6.3±3.4	10.3±7.0	5.3±1.3	0.113	0.002	0.016
Platelet ($\times 10^9$/L)	156±123	161±113	340±170	191±54	0.863	0.002	0.067
Total bilirubin (mg/dL)	2.0±1.5	3.4±4.3	1.0±0.5	0.53±0.2	0.666	0.035	<0.0005
Direct bilirubin (mg/dL)	0.4±0.4	2.2±3.7	0.2±0.2	0.08±0.06	0.128	0.210	0.014
LDH (U/L)	1762±1251	1108±970	208±87	152±22	0.243	<0.0005	<0.0005
B12 (ng/L)	174±204	233±299	ND	ND	0.897	–	–
Folate (mg/L)	9.1±8.0	7.9±5.3	ND	ND	0.965	–	–

*MA = megaloblastic anemia; thal = thalassemia. *Mean±SD, †sample number; ‡Mann-Whitney U test; #ND= not done.*

CBC data for diagnosing classical megaloblastic anemia. Other features such as pancytopenia, elevated RDW, serum LDH and indirect bilirubin, as well as LDH_1>LDH_2 are also helpful. If a patient has a normal or low MCV, megaloblastic anemia is not usually the first consideration, which might lead to a missed diagnosis or delay in giving treatment. The present study shows that the combined disease is not difficult to diagnose when all features of megaloblastic anemia except a normal MCV are present. Other features including the RDW, WBC and platelet count, total and direct bilirubin, elevated LDH with LDH_1>LDH_2, decreased vitamin levels were similar to those in the patients with uncomplicated megaloblastic anemia. When we compared the parameters between groups, we found that group A was more similar to group B than to group C. Thus, a patient with combined megaloblastic anemia and thalassemia may tend to manifest megaloblastic anemia rather than thalassemia. As only MCV was different between the uncomplicated and the complicated megaloblastic anemia, megaloblastic anemia combined with thalassemia is still an easily diagnosed disease provided the clinician is alert to the possibility of this kind of disease.

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Novel erythropoiesis stimulating protein exerts an effect on platelet function in uremia equivalent to that exerted by recombinant human erythropoietin

Recombinant human erythropoietin (rHuEPO) improves platelet function and signaling through tyrosine phosphorylation in uremic platelets in response to thrombin. Novel erythropoiesis-stimulating protein (NESP) has been recently introduced for the treatment of anemia in uremic patients with the advantage of requiring less frequent dosing. We analyzed the effects of NESP on intraplatelet signaling to thrombin, and compared these with the effects of rHuEPO. Results indicate that NESP is equivalent to rHuEPO with respect to its effects on platelet function.

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Since its introduction into clinical practice rHuEPO has been widely used for the treatment of renal anemia.[1] Although it has improved the quality of life of uremic patients, most patients require 2-3 doses per week.[2] Novel erythropoiesis stimulating protein (NESP), a hyperglycosylated form of rHuEPO, is a new recombinant erythropoietic protein with the same mechanism of action as the native hormone, but developed to reduce the frequency of dosing.[3]

Uremic platelets have functional and biochemical alterations, with a defective association of the contractile proteins that constitute the cytoskeleton in response to activation.[4,5] We demonstrated that treatment with rHuEPO enhances the response of uremic platelets to thrombin, by improving the assembly of contractile proteins and the signaling through phosphotyrosine proteins.[6] In this study we compared the effects of NESP with those of rHuEPO on uremic platelets, using the same experimental design previously applied.[6]

We included 8 patients with end-stage renal disease (ESRD) on hemodialysis. There were 4 men and 4 women, their mean age was 65±3.85 years, and the mean time they had been on hemodialysis was 45.1±13.1 months. The cause of ESRD was: nephrosclerosis (2), polycystic kidney disease (2), unknown (1), analgesic nephropathy (1), diabetic nephropathy (1) and bilateral nephrectomy (1). Studies were performed while patients were under rHuEPO treatment (7500±1225 IU/week, iv, three times a week) and after a month of shifting treatment to NESP (36.7±6.2 μg/week, iv, once a week). These patients were included in an multicenter, open label, prospective protocol to assess the efficay and safety of NESP in hemodialyzed patients already treated with rHuEPO.

The clinical parameters evaluated and platelet aggregation responses to thrombin did not differ between treatments (Table 1). Activation of control platelets with 0.1 U/mL of thrombin