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Acquired α_2 Plasmin Inhibitor Deficiency with Manifestation of Hemarthrosis in a Patient with Spur Cell Anemia

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ABSTRACT. We saw a male patient of alcoholic hepatic cirrhosis with spur cell anemia manifesting accelerated hemolysis and spontaneous hemarthrosis. His plasma antihemophilic factor level was within the normal limits. He was 45 years old, had a history of 20 years of alcoholism and transferred to our hospital because of progressive anemia and bleeding tendency. About 30 per cent of the red cells of his peripheral blood smear were spur cells. The diagnosis of spur cell anemia was made on the basis of elevated free cholesterol contents and high value of free cholesterol/phospholipid (FC/PL) ratio of the red cell membrane lipid. One day during the course of his illness, spontaneous hemarthrosis appeared suddenly in his right knee joint, but his plasma antihemophilic factor level was normal. On the contrary, the level of the α_2-PI was as low as 0.98 mg/dl at that time. It was evident that α_2-PI deficiency was the most important factor for causing hemarthrosis in this patient with hepatic cirrhosis.

Key words : α_2 Plasmin inhibitor — Spur cell anemia — Hemarthrosis

Hemarthrosis is well known to us as one of the clinical manifestations of hemophilia A. There are two possible mechanisms for the causation of hemarthrosis. One is the deficiency of antihemophilic factor (factor VIII), the other is due to lack of α_2 plasmin inhibitor (α_2-PI). Significant decrease in α_2-PI is encountered in liver disease, and its level as low as 40 per cent of the normal is often seen in liver cirrhosis on account of recession of the production of this antiplasmin by the deteriorated liver cells.[1)]

Furthermore, α_2-PI level can drop in intravascular coagulation and in the course of thrombolytic treatment. Therefore, in recent years, measurement of α_2-PI has been attracting our attention as an important test among the bleeding patients.

MATERIALS AND METHODS

Assay methods: Concentrations of α_2-PI were determined by single immunodiffusion method using agarose plate containing antihuman α_2-PI antiserum in concentration of 1%. Ten μl of sample of the patient's plasma was applied to the agarose plate. After 72 hours' incubation at room temperature, the size of precipitation area was measured to determine the concentration of α_2-PI.

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Lipid analysis: Lipid analysis of erythrocyte membrane was performed by Iatroscan method.[2] Plasma lipid was measured enzymatically.

RESULTS

Case history: The patient is a 45-year-old male with a history of alcoholism for 20 years. He was wounded on the right thigh with a pair of scissors. Prolonged bleeding followed the trauma for several days and he was transfused 3.8 liters of packed red cells in total during 10 days. In spite of transfusion therapy, progressive anemia and enlarging hematoma were persistent, and he was transferred to our clinic. Physical examination revealed that he was anemic and jaundiced. Vascular spider and palmar erythema were noted. There was

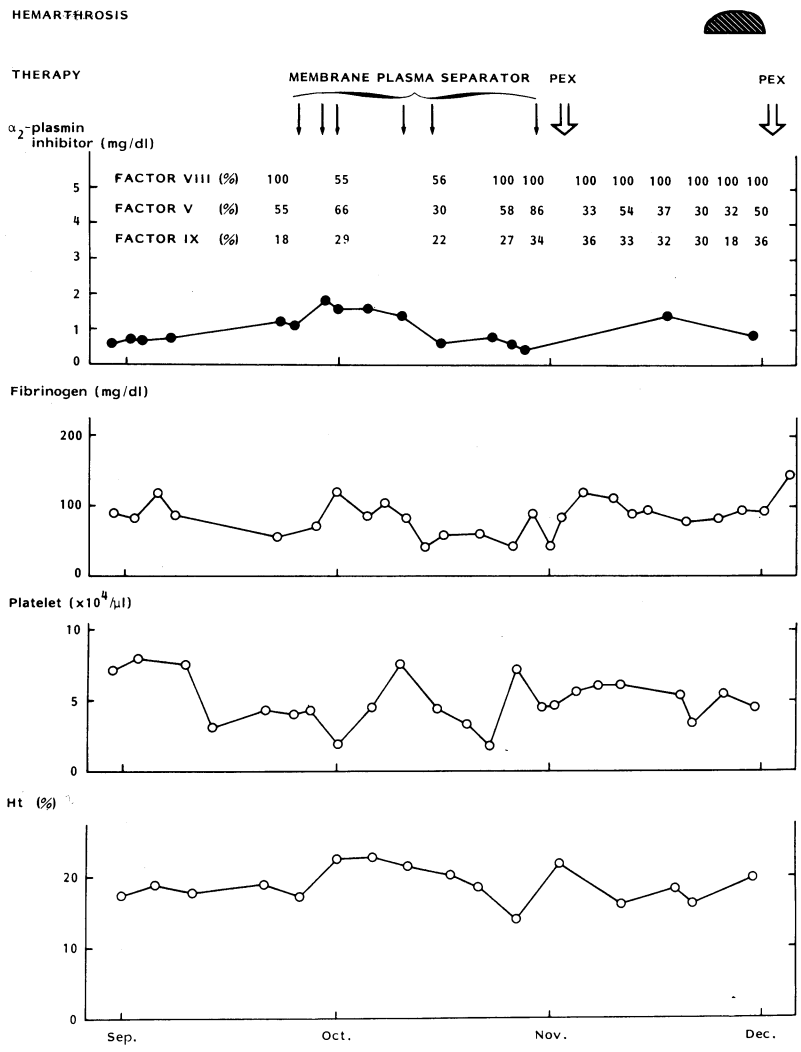

Fig. 1. Clinical course of spur cell anemia. (82-5024)

hepatosplenomegaly in the abdomen. There was no history of easy bruising, cardiac or renal disease. Plasmapheresis was performed to inhibit the progressive anemia. Twenty-four days after the seventh plasmapheresis (November 28th) he suffered from pain and swelling on his right knee joint spontaneously. Bloody fluid which does not coagulate was obtained by knee joint puncture. Platelet count was $3.2\times10^4/\mu l$, fibrinogen 96 mg/dl, Ht 23.1%, coagulation factor VIII, V and IX were 100%, 32% and 18% respectively at that time (Fig. 1).

Laboratory data: Peripheral blood smear of this patient is shown in Figure 2. About 30 per cent of the total red cells are spur-shaped erythrocytes. Laboratory data on admission (August 17th) were as shown in Table 1. Anemia with slight reticulocytosis and thrombocytopenia are noted. Diagnosis of

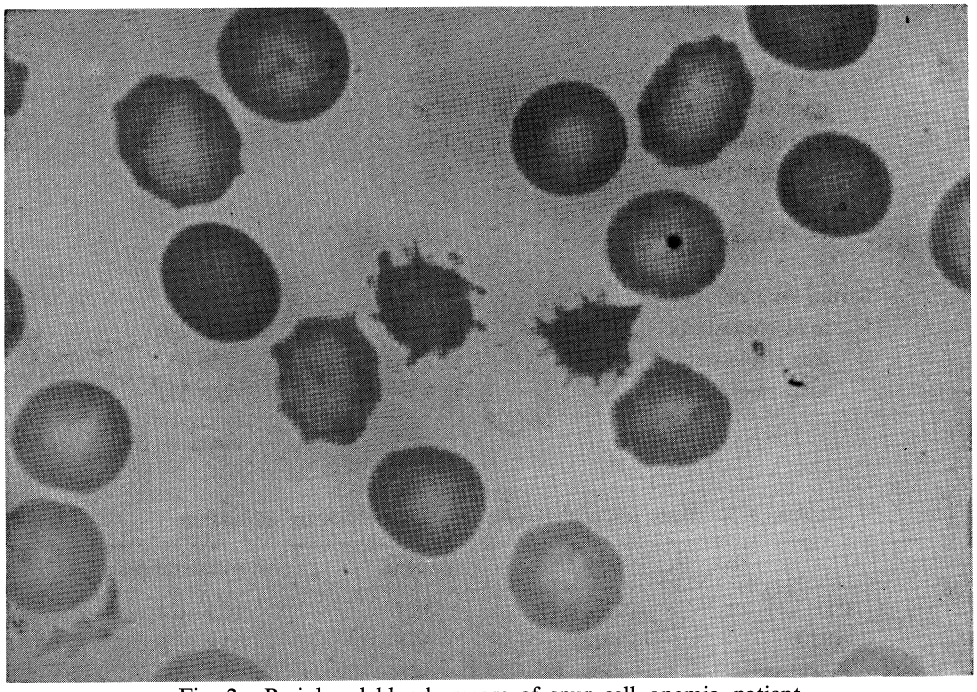

Fig. 2. Peripheral blood smears of spur cell anemia patient. Spur shaped red cells are seen.

TABLE 1. Tests for hematological parameters.

CBC			Serum haptoglobin	<10 mg/dl
WBC	(/μl)	14300	Red cell life span (^{51}Cr-T1/2)	16 days
RBC	(/μl)	303×10^4	Coombs' test	negative
Hb	(g/dl)	10.4	Chemistry	
Ht	(%)	29.8	Serum protein (g/dl)	7.4
MCV	(fl)	97	A/G	0.51
MCH	(pg)	34.4	Total bilirubin (mg/dl)	13.8
MCHC	(%)	34.8	Indirect bilirubin (%)	56
Reticulocyte	(%)	2.1	LDH (IU/l)	352
Platelet	(/μl)	8.3×10^4	GOT (IU/l)	111

hemolytic anemia was entertained from the decreased serum haptoglobin and shortened red cell life span. Hyperbilirubinemia and elevated activities of serum LDH and GOT were thought to afford evidence for increased hemolysis and hepatic damage. There was marked decrease in plasma coagulation factors as well as in plasma fibrinolytic system to the level as low as 20 to 50 per cent of the normal range (Table 3). Lipid analysis of erythrocyte membrane and plasma of the patient were in Table 2. Elevated ratio of free cholesterol/phospholipid (FC/PL) was characteristic feature in spur cell anemia.

TABLE 2. Results of lipid analysis of erythrocyte membrane and plasma.

	patient	Normal ranges
Red cell (mg/10^{10}RBC)		
free cholesterol	2.08	1.41±0.17
phosphatidyl ethanolamine	0.58	0.88±0.12
phosphatidyl serine	0.53	0.54±0.10
phosphatidyl choline	1.12	0.85±0.12
sphingomyelin	0.6	0.76±0.10
		(±SD)
FC/PL (mole/mole)	1.43	0.9
Serum (mg/dl)		
total cholesterol	99	150–220
free cholesterol	57.7	36–45
total phospholipid	111.9	148–182
		mean ± SD

TABLE 3. Tests for coagulation and fibrinolysis on admission.

test		patient	normal ranges
PT	(sec)	15.7	10.2–10.4
APTT	(sec)	36.5	23.8–28.8
Fibrinogen	(mg/dl)	167	200–400
FDP	(μg/ml)	10	< 5
Euglobulin lysis time	(min)	40	> 120
α_2-plasmin inhibitor	(mg/dl)	1.12	5.66±0.86*
Antithrombin III	(mg/dl)	10.4	29.1±3.5*
Hepaplastin time	(%)	32	100
Factor VIII	(%)	100	100
Factor V	(%)	28	100
Factor XI	(%)	50	100

* The means ± SD were obtained from 31 normal adults for α_2-plasmin inhibitor and from 15 for Antithrombin-III.

DISCUSSION

The results of laboratory tests presented in Table 1 indicate that the patient had moderate jaundice, probably because of alcoholic liver dysfunction and accelerated hemolysis. Fibrinolytic tests of the patient's plasma (Table 3) showed a remarkably lowered α_2-PI level (1.12 mg/dl) and euglobulin lysis time was shortened. Antithrombin-III was also decreased (10.4 mg/dl). Coagulation factor V and IX were reduced, being 28% and 50% respectively, but antihemophilic factor (AHF) was entirely normal (100%). It is apparent from these laboratory data on admission, that there was a significant disorder of coagulation and fibrinolysis.

Hemarthrosis is a characteristic clinical manifestation of hemophilia A. However, deficiency of α_2-PI was also found by Aoki[1] in a patient with hemarthrosis and excessive bleeding after trauma.[3] Our patient described above had spontaneous hemarthrosis in his knee joint when his α_2-PI level was very low, being 0.98 mg/dl without being associated with decrease in AHF. According to Aoki α_2-PI decreases in hepatic disorders.[3] The reduction of 40% of normal level was seen decompensated liver cirrhosis. In our case, mean plasma α_2-PI level was as low as 10 to 20 per cent of normal value during his clinical course as illustrated in Fig. 1. It is, therefore, germane to consider that his hemarthrosis was caused by diminution of α_2-PI.

Acknowledgments

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