Key words : prekallikrein deficiency, complication, acute liver failure, gastric ulcer

Acute liver failure and intractable gastric ulcer in plasma prekallikrein deficiency

Kouji JOKO* and Takaaki HATO**

Abstract

Although severe prolongation of activated partial thromboplastin time is observed in patients with plasma prekallikrein (PKK) deficiency, clinical bleeding is not seen. Instead, the possibility that impaired fibrinolysis contributes to thrombosis, myocardial infarction and cerebral thrombosis has been postulated. We report a case of cross-reacting material-negative plasma PKK deficiency associated with thrombophlebitis of the lower extremities. This patient developed progressively deteriorating drug-induced liver injury and showed a state of acute liver failure. The patient also had intractable gastric ulcer with a history of repeated recurrence. Microcirculatory disorder associated with a reduction in fibrinolytic activity appeared to be involved in the deterioration of liver injury and also in the process of the gastric ulcer becoming intractable.

Introduction

In 1965, Hathaway et al[1]. discovered a family with an autosomal-recessive hereditary disease characterized by prolonged activated partial thromboplastin time (APTT) without bleeding tendency, and called this pathology "Fletcher factor deficiency". Wuepper later reported that the Fletcher factor was plasma prekallikrein (PKK)[2]. PKK deficiency is a very rare disease, with only a few cases reported to date[3)~13)]. Myocardial infarction[5)] and cerebral thrombosis[10)] have been reported as complications, and several reports[14)~16)] have described plasma PKK as required for the expression of a plasminogen activator. In this paper, we report a case of cross-reacting material-negative (CRM-) plasma PKK deficiency associated with acute liver failure, intractable gastric ulcer and thrombophlebitis of the lower extremities.

Case report

Patient

The patient was a 44-year-old Japanese woman without any family history of consanguinity. The first hospital admission in January 1980 was for gastric ulcer. After discharge, she experienced repeated exacerbations of gastric ulcer (**Fig. 1**). No evidence of abnormal liver function was seen. Beginning around November 1982, the patient noted the onset of appetite loss, nausea

*Center for Liver-Biliary-Pancreatic Diseases, Matsuyama Red Cross Hospital
**Japanese Red Cross Ehime Blood Center

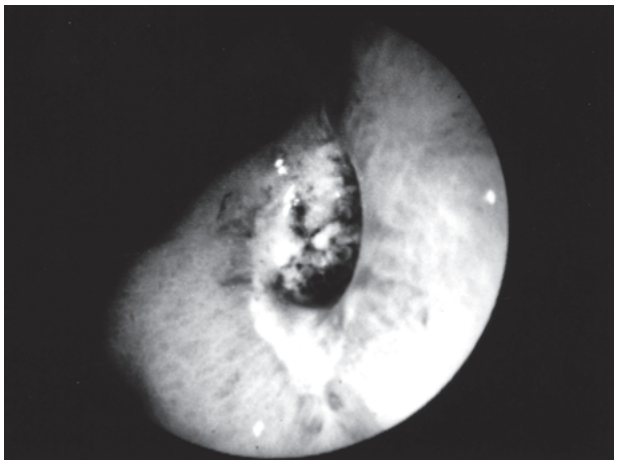

Fig. 1 Endoscopic findings of gastric ulcer situated on the posterior wall of the body of the stomach. The ulcer was intractable and repeated recurrence had been seen throughout 10 years in almost the same place.

and vomiting. After undergoing treatment with 400 mg/day of cimetidine, the patient developed jaundice followed by hepatic encephalopathy, and was admitted to our hospital for a second time in December 1982. The results of laboratory tests performed at the time of admission were: total bilirubin, 19.0 mg/dl (normal, 0.1−1.1 mg/dl); direct bilirubin, 17.0 mg/dl (normal, 0.1−0.6 mg/dl); prothrombin time (PT), 40% (normal, 80−125%); APTT, 45.3 sec (normal, 21.5−43.1 sec). Taking these liver function test results into account, the prolonged PT and APTT appeared to attributable to liver injury, with no apparent clotting factor deficiencies or clotting factor inhibitors. All virus markers were negative, including immunoglobulin (Ig) M-Hepatitis B core antibody, IgM-Hepatitis A antibody, and Hepatitis C Virus antibody. The cimetidine lymphoblast transformation reaction was negative, but a subsequent challenge test yielded positive results, indicating the presence of cimetidine-induced liver injury. After admission, hepatic encephalopathy improved in response to conservative systemic management including intravenous hyper-alimentation, administration of fresh frozen plasma, etc. A gradual improvement in liver function was also observed. While serum bilirubin decreased and PT gradually normalized, APTT contrarily became longer. At the time PT became normal, APTT was between 70 and 80 sec (**Fig. 2**). Liver biopsy performed during the third month of hospitalization revealed bridging necrosis, with massive lobular necrosis in one portion (**Fig. 3**). The patient was subsequently followed-up as an outpatient, but the prolonged APTT persisted. Onset of epigastralgia was noted around September 1990, and because of exacerbation of the gastric ulcer and accompanying thrombophlebitis of the lower extremities (**Fig. 4**), the patient was admitted for a third time in February 1991. The following laboratory examinations were performed during this admission.

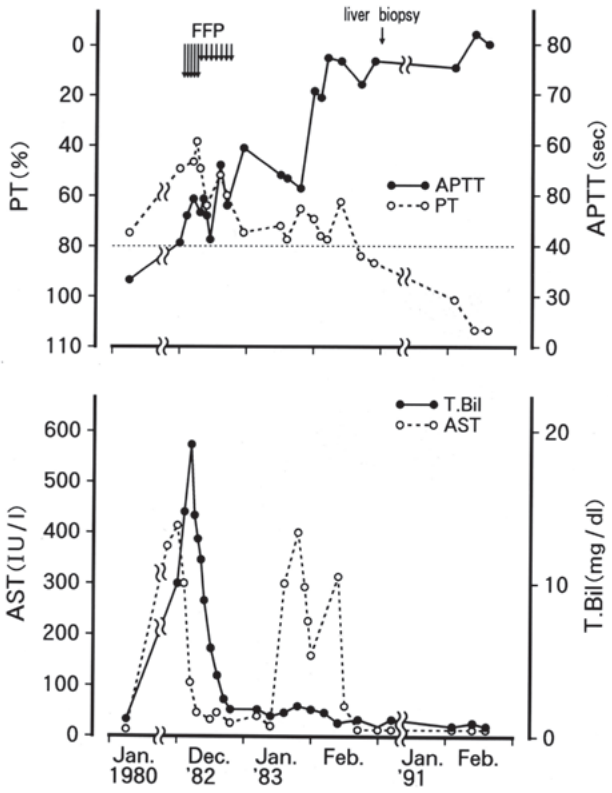

Fig. 2 Clinical course. The patient developed acute liver failure in November 1982. Serum AST concentration showed a biphasic elevation. While serum bilirubin decreased and PT gradually normalized, APTT contrarily became longer.

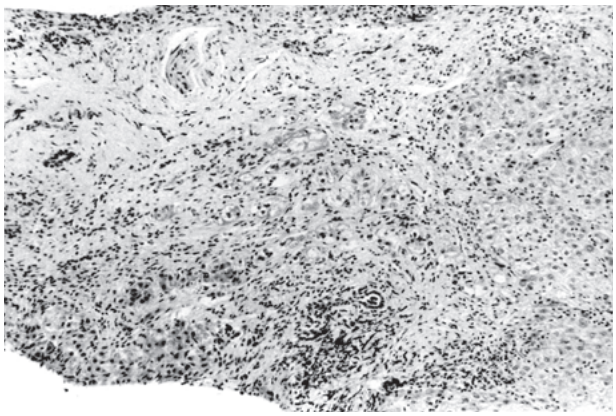

Fig. 3 Photomicrogram of the liver specimen. Bridging fibrosis and an enlarged portal tract with inflammatory reaction are noted. Massive lobular necrosis is also noted in one portion.

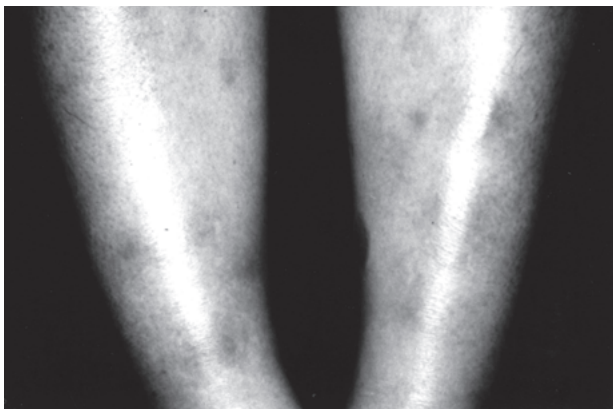

Fig. 4 Thrombophlebitis in the lower extremities.

Materials and methods

Venous blood was collected from a cubital vein and immediately mixed with 0.109 mol/l trisodium citrate (9:1, v/v). Platelet-poor plasma was obtained by centrifuging the blood at 4℃ for 20 min at 3,000 *g*. Coagulation tests were performed using fresh plasma. Plasma for immunological studies was stored frozen at −80℃. Normal plasma was obtained from 20 healthy doctors by the same method. PKK-deficient plasma and high-molecular weight (HMW) kininogen-deficient plasma were purchased from George King Bio-Medical (Overland park, KS). Anti-PKK goat serum was purchased from Nordic Immunological Laboratories (Susteren, the Netherlands). Chromozyme PK (BZ-Pro-Phe-Arg-pNA) was purchased from Boehringer (Mannheim, Germany). The activity of Factors II, V, VII, VIII, IX, X, XI and XII was measured with commercially available one-stage assays using plasma that was deficient in each factor. PKK activity was measured by one-stage assay using PKK-deficient plasma and by chromogenic peptide substrate assay[17]. We measured PKK antigen concentration by Laurel rocket immunoelectrophoresis[18]. The activity of HMW kininogen was measured by a one-stage assay using HMW kininogen-deficient plasma[19].

Clinical course and results of laboratory examination

At the time of the third admission, PT was within normal limits, but APTT was found to be prolonged. No particular abnormalities were detected in levels of any clotting factors. Results of quantitative determination of HMW kininogen and PKK activity by one-stage assay using plasma deficient in each of them showed HMW kininogen to be within normal limits, but PKK level was markedly reduced, and a PK deficiency was therefore diagnosed (**Table 1**). During the second admission, while serum bilirubin decreased and

Table 1 Results from coagulation tests of the patient

Bleeding time (2–6 min)	1.5 min
Prothrombin time (80–125%)	102%
Activated partial thromboplastin time (21.5–43.1 sec)	76.9 sec
Fibrinogen (180–400 mg/dl)	345 mg/dl
FDP (0.4-1.4 μg/ml)	1.1 μg/ml
Antithrombin III (25.7–33.7 mg/dl)	30.1 mg/dl
Plasminogen (91.2–121.8%)	91.5%
Factor Ⅱ (80–120%)	72%
Factor V (80–120%)	92%
Factor VII (80–120%)	72%
Factor VIII (80–120%)	180%
Factor IX (80–120%)	140%
Factor X (80–120%)	80%
Factor XI (80–120%)	82%
Factor XII (80–120%)	100%
HMW kininogen (63–146%)	78%
Prekallikrein (58–155%)	0.3%

Values in parentheses represent institutional normal ranges

PT gradually normalized, APTT contrarily became longer (**Fig. 2**). This phenomenon suggested that while clotting factor production had recovered as a result of liver cell regeneration, and PT had become normal, the regenerated liver cells might have lost their ability to produce PKK. Accordingly, we thought that we should evaluate any changes in serum PKK activity before the patient developed acute liver failure. Fortunately, we had stored samples of serum from the patient at −80℃ when she was hospitalized the first time in January 1980, and we were thus able to determine PKK antigen levels as of that time (**Fig. 5**). The serum antigen level in January 1980 was 51%; this was low, but still far higher than the 1% in plasma as of February 1991.

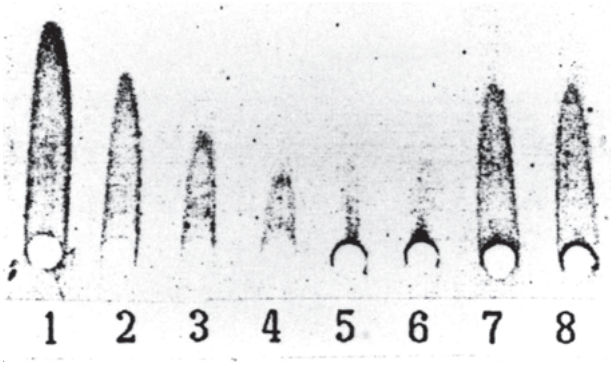

Fig. 5 Rocket immunoelectrophoresis studies of PKK in plasma from the patient. 1) Normal plasma; 2) diluted normal plasma(1/2); 3) diluted normal plasma(1/4); 4) diluted normal plasma(1/8); 5, 6) plasma from the patient (February 1991); 7, 8) serum from the patient (January 1980).

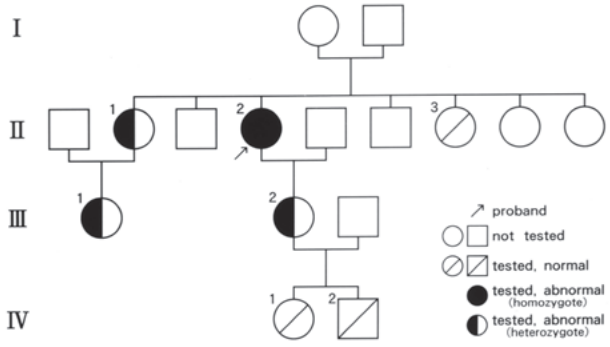

Fig. 6 Family tree.

Table 2 PKK values of family members

Family member	Prekallikrein activity (%)		Prekallikrein antigen concentration (%)
	One-stage assay	Chromogenic peptide substrate assay	
II-1	14.0	72	65
II-2	0.3	7	1
II-3	125.0	106	90
III-1	32.0	60	60
III-2	44.0	50	43
IV-1	98.0	90	90
IV-2	120.0	101	100
Normal range	58–155	80–120	70–130

Worsening of PKK deficiency in this patient seemed very likely to be triggered by the development of acute liver failure. To determine whether a genetic element was involved in the etiology, we determined PKK activity and antigen levels in blood relatives of the present patient (**Fig. 6**; **Table 2**). Her daughter, grandchild and niece all showed slightly reduced levels of PKK, suggesting these individuals were heterozygotes.

Discussion

Plasma PKK values decrease in patients with liver disease, and the etiology is believed to involve diminished PKK synthesis in the liver[20] and endotoxemia[21]. The patient presented in this paper showed completely normal results from liver function tests when admitted to hospital for a third time (when the decrease in plasma PKK was detected). No liver injury was suggested from other clotting factors or results of blood coagulation tests. The decrease in plasma PKK thus did not seem attributable to the direct effects of decreased liver function.

There are two very interesting observations regarding the association between PKK deficiency and other associated diseases in this patient. The first point is that the worsening seemed very likely if PKK deficiency in this patient was triggered by the development of acute liver failure. Hepatic PKK production decreased as

liver regenerated; in other words, the decrease in PKK production was due to changes in the nature of the regenerated hepatocytes. PKK antigen levels were very low, meaning that generation of an inhibitor against PKK unlikely. Because the patient had relatives who were heterozygotes, this patient could have been a hetero- or homozygote with a defective PKK gene. As a result, whether this represents aggravation by acute liver failure in a heterozygote or a homozygote manifesting the disease as a result of triggering by acute liver failure remains obscure.

The second point is that the PKK deficiency may have contributed to the increasing severity of the liver injury and to the intractable nature of the gastric ulcer. Plasma PKK (along with HMW kininogen, Factor XI and Factor XII) is referred to as a contact factor, and not only participates in intrinsic systemic clotting, but is known to be intimately involved in processes such as extrinsic systemic clotting, the fibrinolytic system, kinin production, and complement activation[22]. Plasma PKK is activated to kallikrein by activated Factor XII, and this kallikrein then activates HMW kininogen to kinin and converts Factor XI to activated Factor XI, thereby activating the clotting system. Kallikrein also activates the fibrinolytic system by converting plasminogen into plasmin[23]. Clinically, while no bleeding tendency has been observed in PKK deficiency, thrombosis has been reported instead[5),10),14)~16)]. On the other hand, impaired circulation in the gastric mucosa has been cited as one of the pathogenetic mechanisms underlying gastric ulcer[24], and impaired microcirculation in the liver is regarded as a factor adversely affecting liver function in acute liver failure[25),26)]. The decrease in fibrinolytic activity appears highly likely to further impair the microcirculation through the liver sinusoids and gastric mucosal blood flow in this case, and the liver damage and condition of the gastric ulcer would thus have become more severe.

PKK deficiency is not thought to have contributed to the initiation of liver damage or gastric ulcer, but it seems reasonable to assume that this deficiency was involved in both becoming more severe and intractable. When we consider the mechanisms underlying the development of acute liver failure and by which the gastric ulcer became more severe, the existence of patient-specific background factors such as abnormalities of the coagulation/fibrinolytic system and thrombogenesis-promoting factors, along with ensuing microcirculatory impairment, must always kept in mind.

Acknowledgments

Although the authors were working at Ehime University School of Medicine when this article was written in the 1990s, it was a time when I (as corresponding author) was just moving to an overseas research facility, and very busy, so that I forgot to submit this paper to any journal. This paper was therefore left unpublished for nearly 30 years. I found this paper by chance while organizing my bookshelf, but I had to give up submitting it because of many problems in publishing in light of the current medical level. However, I wanted to publish it because this was a very academically interesting case. This time, through the kindness of Matsuyama Red Cross Hospital, we were able to publish the case report in the Matsuyama Red Cross Hospital Medical Journal. I would like to thank my supervisors in the 1990s, Dr. Kouichi Akamatsu and the late Professor Yasuyuki Ohta of the Third Department of Internal Medicine, Ehime University School of Medicine. I would also like to thank Dr. Shiro Bando for measuring concentrations of prekallikrein and other coagulation factors.

References

1) Hathaway WE. *et al*.: Evidence for a new plasma thromboplastin factor. I. Case report, coagulation studies and physicochemical properties. Blood **26**: 521-532, 1965.
2) Wuepper KD.: Prekallikrein deficiency in man. J Exp Med **138**: 1345-1355, 1973.
3) Abildgaard DF., Harrison J.: Fletcher factor deficiency: family study and detection. Blood **43**: 641-644, 1974.
4) Aznar JA. *et al*.: Fletcher factor deficiency: report of a new family. Scand J Hematol **21**: 94-98, 1978.
5) Currimbhoy Z. *et al*.: Fletcher factor deficiency and myocardial infarction. Am J Clin Pathol **65**: 970-974, 1975.
6) Essien EM., Ebhota MI.: Fletcher factor deficiency-detection of a severe case in a population survey. Acta Haematol **58**: 353-358, 1977.
7) Hattersley PG., Hayse D.: Fletcher factor deficiency: a report of three unrelated cases. Br J Haematol **18**: 411-416, 1970.
8) Poon M. *et al*.: Severe Fletcher factor (plasma prekallikrein) deficiency with partial deficiency of Hageman factor (factor XII): report of a case with observation on in vivo and in vitro leukocyte chemotaxis. Am J Clin Path **12**: 261-270, 1982.
9) Kyrle PA. *et al*.: CRM+ severe Fletcher factor deficiency associated with Graves' disease. Haemostasis **14**: 302-306, 1984.
10) Harris MG. *et al*.: Multiple cerebral thrombosis in Fletcher factor (prekallikrein) deficiency: A case report. Am J Hematol **19**: 387-393, 1985.
11) Bouma BN. *et al*.: Characterization of a variant prekallikrein, prekallikrein Long Beach, from a family with mixed cross-reacting material-positive and cross-reacting material-negative prekallikrein deficiency. J Clin Invest **78**: 170-176, 1986.
12) Saito H. *et al*.: Heterogeneity of human prekallikrein deficiency (Fletcher trait): evidence that five of 18 cases are positive for cross-reacting material. New Eng J Med **305**: 910-914, 1981.
13) Stefano VD. *et al*.: Association of Graves' disease and prekallikrein congenital deficiency in a patient belonging to the first CRM+ prekallikrein-deficient Italian family. Thrombosis Research **60**: 397-404, 1990.
14) Vennerød AM., Laake K.: Prekallikrein and plasminogen proactivator: Absence of plasminogen proactivator in Fletcher factor deficient plasma. Thrombosis Research **8**: 519-522, 1976.
15) Espana F. *et al*.: Factor XII-induced fibrinolysis. Diminished proactivator activity and drastic reduction of activator activity in Fletcher factor-deficient plasma gamma globulin. J Lab Clin Med **100**: 756-770, 1982.
16) Estelles A. *et al*.: The absence of release of the plasminogen activator after venous occlusion in a Fletcher trait patient. Thromb Haemostas **49**: 66, 1983.
17) Gallimore MJ., Friberger P.: Simple chromogenic peptide substrate assay for determining prekallikrein, kallikrein inhibition and kallikrein- "LIKE" activity in human plasma. Thrombosis Research **25**: 293-298, 1982.
18) Laurell CB.: Electroimmuno assay. Scand J Clin Lab Invest 29, Suppl **124**: 21-37, 1972.
19) Saito H. *et al*.: Fitzgerald factor (high molecular weight kininogen) clotting activity in human plasma in health and disease, and in various animal plasmas. Blood **48**: 941-947, 1976.
20) Colman RW., Wong PY.: Participation of Hageman factor dependent pathways in human disease states. Thrombos Haemostas **38**: 751-775, 1977.
21) van Vliet ACM. *et al*.: Plasma prekallikrein and endotoxemia in liver cirrhosis. Thromb Haemost **45**: 65-67, 1981.
22) Sollo DG., Saleem A.: Prekallikrein (Fletcher factor) deficiency. Annals Clin Labo Science **15**: 279-285, 1985.
23) Murano G.: The "Hageman" connection: interrelationships of blood coagulation, fibrino (geno) lysis, kinin generation, and complement activation. Am J Hematol **4**: 409-417, 1978.
24) Boyd EJS., Wormsley KG.: Etiology and pathogenesis of peptic ulcer. In: Berk JE, ed. Bockus Gastroenterology. Volume 2. 4th ed. Philadelphia: Saunders: 1013-1059, 1985.
25) Vogel GE.: Early treatment with AT III in acute liver failure. Behring Inst Mitt **73**: 79-93, 1983.
26) Tada K. *et al*.: Importance of measuring plasma thrombin-antithrombin III complex levels when using antithrombin III concentrate therapy in fulminant hepatic failure. Scand J Gastroenterol **26**: 1188-1192, 1991.

急性肝不全と難治性胃潰瘍を合併したプレカリクレイン欠乏症の一例

上甲　康二*，羽藤　高明**

*松山赤十字病院　肝胆膵センター
**愛媛県赤十字血液センター

プレカリクレイン（PKK）欠乏症においては活性化部分トロンボプラスチン時間が延長するにもかかわらず出血傾向は見られないが，繊維素溶解が障害されることにより血栓症，心筋梗塞や脳梗塞を発症する可能性が指摘されている．著者らは下肢血栓性静脈炎を伴う先PKK欠乏症の一例を経験した．この症例は以前より再発を繰り返す難治性胃潰瘍があり，また経過観察中に薬物性肝障害が重症化し急性肝不全を呈した．繊維素溶解障害が微小循環障害を引き起こすことにより，胃潰瘍の難治性化や肝障害の重症化に関与した可能性があり，疾病重症化の機序を考える上で興味ある症例と思われたので報告した．

Matsuyama R. C. Hosp. J. Med.　44(1)；　21～27，2019