Elevated Serum Lipoprotein (a) Levels Associated with Ulcerative Colitis in a Young Japanese Patient

Shigeharu KAWABATA, Shuichi KATAGIRI, Hiroshi NEGORO, Akira NOGAMI,
Iwao YABUUCHI, Masahiro GOMI, Ryoichi ARIMA* and Seiichiro TARUI

Thromboembolism has been shown to play a role in the pathogenesis of inflammatory bowel disease (IBD). A possibility exists that lipoprotein (a) [Lp(a)], a newly-discovered prothrombotic factor, also participates in the development of at least some cases of IBD. Marked elevation of serum Lp(a) levels was observed in a young patient with ulcerative colitis. A biopsy specimen of the rectal mucosa showed findings compatible with ulcerative colitis, as well as small vessel thrombus occurring within the muscularis mucosa in the rectum. Serum Lp(a) levels were markedly elevated on admission (71 mg/dl), with a gradual decrease to 46 mg/dl on discharge. Moreover, serum Lp(a) levels decreased in parallel with clinical improvement. In the quiescent clinical stage, no small vessel thrombus was observed in the mucosa on follow-up colonoscopy. The association between IBD and hyper-Lp(a)-emia would be presumable but it has been, to our knowledge, previously unreported. The case reported here would be the first young patient, suggesting the presence of hyper-Lp(a)-emia and small vessel thrombus formation occurring in association with the development of ulcerative colitis.

(Internal Medicine 36: 389–391, 1997)

Key words: inflammatory bowel disease (IBD), lipoprotein (a) [Lp(a)], hyper-Lp(a)-emia, small vessel thrombus, small vessel thrombosis, hypercoagulation, prothrombotic state

Introduction

The apparent association between thromboembolism and inflammatory bowel disease (IBD) has been described more than half a century ago (1–3). Recently small vessel thrombosis has been implicated as rather an etiological factor in Crohn's disease (4). It has been postulated that lipoprotein (a) [Lp(a)] has both prothrombotic and proatherosclerotic actions, through its plasminogen-like properties and low density lipoprotein (LDL)-like characteristics of apo(a) (5). We report a young patient with ulcerative colitis, who had marked serum Lp(a) levels with small vessel thrombus in the rectal mucosa.

Case Report

A 20-year-old male patient with a history of ulcerative colitis since 1988 was admitted in September 1994 to our hospital because of frequent diarrhea containing blood. He had been treated intermittently with salazosulfapyridine and/or corticosteroids. On admission, laboratory tests revealed a C-reactive protein (CRP) of 0.6 mg/dl, fibrinogen of 266 mg/dl, prothrombin time of 93%, and hepaplastin test of 90%. Platelet

count was 236,000/mm³ and erythrocyte sedimentation rate was 8 mm/h. Colonoscopy showed moderately active ulcerative colitis from the rectum to the left transverse colon (Fig. 1). A mucosal biopsy specimen in the active stage showed moderately inflamed, erosive and edematous colorectal mucosa with mild glandular and goblet cell depletion (Fig. 2). Small vessel thrombus occurring within the muscularis mucosa was also revealed in the specimen (Fig. 2). The administration of corticosteroids (prednisolone 20 mg) and salazosulfapyridine 4.0 g per day resulted in general improvement with reduction of the stool frequency and bleeding episodes, which was in parallel with the gradual decrease in serum Lp(a) levels (71, 59, 54, 46 mg/dl) (normal value; less than 40 mg/dl, with the average of 18 mg/dl) (Fig. 3). On the other hand, the clinical course of serum CRP levels (normal value; less than 0.3 mg/dl) showed a transient rise in the initial period of admission and thereafter maintained normal levels during admission (Fig. 3). In the quiescent clinical stage after discharge, no small vessel thrombus was observed in the rectal mucosa on follow-up colonoscopy. At the same time, serum Lp(a) levels were low (41 mg/dl) compared with those of the active stage. However, serum Lp(a) levels were still higher than the normal value. Furthermore, the

From the Department of Internal Medicine and *the Department of Pathology, Otemae Hospital, Osaka

Received for publication September 17, 1996; Accepted for publication March 13, 1997

Reprint requests should be addressed to Dr. Shigeharu Kawabata, Internal Medicine, Otemae Hospital, 1-5-34 Otemae, Chuo-ku, Osaka 540

Figure 1. Moderate active proctitis in ulcerative colitis.

Figure 2. Histological analysis showing small vessel thrombus occurring within the muscularis mucosa in the rectum (HE stain, A: $\times 33$, B: $\times 66$).

examination of serum Lp(a) phenotype analysis by sodium dodecyl sulfate-gel electrophoresis (SDS-PAGE) using anti-apo(a) and anti-apo B-100 antibodies revealed small size Lp(a) patterns, suggesting that hyper-Lp(a)-emia in this patient is genetically determined (Fig. 4). Neither arteriosclerotic change of vessel nor vasculitis was observed.

Figure 3. Clinical course during admission. SASP: salazosulfapyridine.

Figure 4. Serum Lp(a) phenotype analysis by SDS-PAGE. Patient (P) was detected by anti-apo(a) antibody. Control (C) was detected by anti-apo B-100 antibody. According to their relative mobilities compared with apo B-100, Lp(a) phenotype patterns were categorized into phenotypes F (faster than apo B-100), B (similar to apo B-100), S1, S2, S3, S4, S5, S6, S7, S8 and S9 (slower than apo B-100 by different degrees) and into the respective double-band phenotypes. This patient showed a small size Lp(a) phenotype (S1/S6).

Discussion

Ulcerative colitis is a chronic inflammatory process of unknown etiology. The importance of thromboembolic phenomena in IBD has been focused upon since Bargen and Barker described extensive arterial and venous thrombosis in very ill

young patients with ulcerative colitis (1). Previous studies have also suggested that hypercoagulation is associated with both Crohn's disease and ulcerative colitis (6, 7). Thromboembolic complications have been reported to occur in patients with IBD at rates ranging from 1.2 to 39%, and to be associated with a high mortality (1, 8, 9). Furthermore, a recent study has shown that as many as 77% of peripheral venous thrombosis cases occurred spontaneously, although peripheral arterial and portal vein thrombosis were predominantly postsurgical complications in IBD patients (9). These findings strongly suggest that hypercoagulation plays an important role in the pathogenesis of IBD.

Lp(a), a unique lipoprotein first discovered by Berg (10), has been strongly linked with atherosclerosis and is considered an independent risk factor for myocardial infarction (11–13). More recently, the sequence of apo(a), the characteristic apolipoprotein of Lp(a), was reported to have a striking homology with human plasminogen (14). Considering the structure clarified, the actions of Lp(a) could be not only proatherosclerotic but also prothrombotic. In fact, several studies have now shown that Lp(a) can compete in vitro with the binding of plasminogen to fibrinogen or to fibrin monomer (15, 16). It has also been shown that Lp(a) competes for the binding of plasminogen to the plasminogen receptor on endothelial cells and macrophages, at a concentration equal to physiological levels (17, 18). These findings suggest that Lp(a) can induce a prothrombotic state.

In the present case, the coexistence of elevated serum Lp(a) levels and small vessel thrombus in the rectal mucosa may have reflected a local prothrombotic state induced by Lp(a) in IBD. After the medical treatment with moderate doses of prednisolone, stool frequency and occult blood in stool gradually improved, which was in parallel with the gradual decrease in serum Lp(a) levels. Furthermore, no small vessel thrombus was observed on follow-up colonoscopy during the quiescent stage. These observations show that small vessel thrombus related to elevated serum Lp(a) levels took place in active IBD lesions, suggesting that elevated serum Lp(a) levels and small vessel thrombus were associated with the development of ulcerative colitis in the present patient. Therefore, even in young patients without arteriosclerosis or vasculitis, hyper-Lp(a)-emia can contribute to thrombotic events, resulting in chronic mucosal inflammation possibly as a result of microvascular injury.

Serum Lp(a) concentrations are thought to be determined mainly genetically and little influenced by environmental factors. In the present case, the examination of serum Lp(a) phenotype analysis by SDS-PAGE revealed small size Lp(a) patterns. Moreover, during the quiescent clinical stage, serum Lp(a) levels were still higher than the normal value, indicating the presence of genetically determined hyper-Lp(a)-emia in this patient. On the other hand, serum Lp(a) levels were gradually decreased by the administration of prednisolone. The effect of corticosteroids on serum Lp(a) levels has not yet been reported, but this observation strongly suggests that the administration of prednisolone decreases serum Lp(a) levels in parallel with the strength of its anti-inflammatory effects. Taken together, these findings also imply that serum Lp(a) levels are

in some IBD patients determined not only by genetic factors, but also by acquired factors. Lp(a) may participate in the development of at least some cases of IBD via its prothrombotic effects, although direct proof of this is still lacking. The existence of a link between the inhibitory effects of Lp(a) on fibrinolysis and systemic hypercoagulation remains to be demonstrated.

In summary, this appears to be the first young case, suggesting the presence of hyper-Lp(a)-emia and small vessel thrombus formation occurring in association with the development of ulcerative colitis. Measurements of serum Lp(a) levels in patients with active IBD may be useful for the prediction of thrombotic events, sometimes leading to grave complication.

Acknowledgements: The authors thank Yoshihiko Otsuka for the data research of Lp(a) phenotype analysis.

References

- 1) Bargen JA, Barker NW. Extensive arterial and venous thrombosis complicating chronic ulcerative colitis. *Arch Intern Med* **58**: 17, 1936.
- 2) Ricketts WE, Palmer WL. Complications of chronic nonspecific ulcerative colitis. *Gastroenterology* **7**: 55, 1946.
- 3) Edwards FC, Truelove SC. The course and prognosis of ulcerative colitis. *Gut* **5**: 1, 1964.
- 4) Wakefield AJ, Sawyerr AM, Dhillon AP, et al. Pathogenesis of Crohn's disease: multifocal gastrointestinal infarction. *Lancet* **2**: 1057, 1989.
- 5) Scanu AM, Fless GM. Lipoprotein (a). Heterogeneity and biological relevance. *J Clin Invest* **85**: 1709, 1990.
- 6) Edwards RL, Levine JB, Green R, et al. Activation of blood coagulation in Crohn's disease. Increased plasma fibrinogen levels and enhanced generation of monocyte tissue factor activity. *Gastroenterology* **92**: 329, 1987.
- 7) Webberley MJ, Hart MT, Melikian V. Thromboembolism in inflammatory bowel disease: role of platelets. *Gut* **34**: 247, 1993.
- 8) Graef V, Baggenstoss AH, Sauer WG, Spittell JA, Minn R. Venous thrombosis occurring in nonspecific ulcerative colitis. *Arch Intern Med* **117**: 377, 1966.
- 9) Talbot RW, Heppell J, Dozois RR, Beart RW Jr. Vascular complications of inflammatory bowel disease. *Mayo Clin Proc* **61**: 140, 1986.
- 10) Berg K. A new serum type system in man – the Lp system. *Acta Pathol Microbiol Scand* **59**: 369, 1963.
- 11) Kostner GM, Avogaro P, Cazzolato G, Marth E, Bittolo-Bon G, Quinici GB. Lipoprotein Lp(a) and the risk for myocardial infarction. *Atherosclerosis* **38**: 51, 1981.
- 12) Armstrong VW, Cremer P, Eberle E, et al. The association between serum Lp(a) concentrations and angiographically assessed coronary atherosclerosis. Dependence on serum LDL levels. *Atherosclerosis* **62**: 249, 1986.
- 13) Dahlen GH, Guyton JR, Attar M, Farmer JA, Kautz JA, Gotto AM Jr. Association of levels of lipoprotein (a) Lp(a), plasma lipids, and other lipoproteins with coronary artery disease documented by angiography. *Circulation* **74**: 758, 1986.
- 14) Mclean JW, Tomlinson JE, Kuang WJ, et al. cDNA sequence of human apolipoprotein (a) is homologous to plasminogen. *Nature* **330**: 132, 1987.
- 15) Harpel PC, Gordon BR, Parker TS. Plasmin catalyzes binding of lipoprotein (a) to immobilized fibrinogen and fibrin. *Proc Natl Acad Sci USA* **86**: 3847, 1989.
- 16) Loscalzo J, Weinfeld M, Fless GM, Scanu AM. Lipoprotein (a), fibrin binding, and plasminogen activation. *Arteriosclerosis* **10**: 240, 1990.
- 17) Miles LA, Fless GM, Levin EG, Scanu AM, Plow EF. A potential basis for the thrombotic risks associated with lipoprotein (a). *Nature* **339**: 301, 1989.
- 18) Hajjar KA, Gavish D, Breslow JL, Nachman RL. Lipoprotein (a) modulation of endothelial cell surface fibrinolysis and its potential role in atherosclerosis. *Nature* **339**: 303, 1989.