A Case of Marked Hyperlipoprotein(a)emia Associated with Nephrotic Syndrome and Advanced Atherosclerosis

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In 1989, we encountered a 68-year-old male patient with marked hyperlipoprotein(a)emia (hyperLp(a)emia), who was being treated for hypertension and arteriosclerotic obliterans (ASO) at an outpatient clinic of our hospital. He began to develop leg edema in 2002 and was referred to the Department of Internal Medicine. It was determined that he had severe hyperlipidemia (total cholesterol, 362 mg/dl), proteinuria, and hypoalbuminemia, suggesting the presence of nephrotic syndrome. On lipoprotein analysis, he was found to have very high levels of Lp(a) in the plasma (329 mg/dl). Severe atherosclerosis was also found: that is, abdominal aortic aneurysm (AAA) and coronary artery disease (CAD) were detected, in addition to ASO. After remission of the nephrotic syndrome, the plasma Lp(a) level decreased to 204 mg/dl and the total cholesterol concentration decreased to 179 mg/dl, while very high levels of Lp(a) persisted. We estimate that the markedly elevated Lp(a) plasma levels in this patient may have played some role in the progression of atherosclerosis. *J Atheroscler Thromb*, 2004; 11: 293–298.

Key words: Nephrotic syndrome, Atherosclerosis, Lp(a), Arteriosclerotic obliterans

Introduction

Lipoprotein (a) [Lp(a)] is a unique macromolecule formed by a lipoprotein particle with apo(a), apo B and lipids comprising low density lipoprotein (LDL). Apo(a) has a high degree of structural homology with plasminogen, a key enzyme of the coagulation cascade (1). Numerous clinical studies have provided evidence that an elevated level of Lp(a) in plasma is an important risk factor for atherosclerosis (2, 3). However, there have been few reports describing the clinical picture in patients with extremely high levels of Lp(a).

In the present study, we describe a case showing marked hyperlipoprotein(a)emia [hyperLp(a)emia] during the course of nephrotic syndrome. The levels of plasma

lipoproteins were followed in this patient to elucidate the underlying relationship between severe atherosclerosis and elevated plasma Lp(a) levels.

Materials and Methods

Blood was drawn from the subject after an overnight fast. Lipoprotein fractions were serially isolated by ultracentrifugation. Serum total cholesterol (TC), triglyceride (TG), and high density lipoprotein-cholesterol (HDL-C) were determined by enzymatic methods. Lp(a) was determined by a latex immunoassay method (4). Lp(a) phenotyping was performed by SDS-PAGE with immunoblotting using the method described by Abe *et al.* (5), which is similar to the procedure by Utermann *et al.* (6).

Case Presentation

An 83-year-old male patient had a 22-year history of hypertension. In December 1989, at 68 years of age, the

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patient developed intermittent claudication, and a diagnosis of arteriosclerosis obliterans (ASO) was made by angiography, which showed stenosis of the bilateral external iliac artery. Therefore, he was followed by the Department of Surgery of this hospital. Two coronary risk factors were noted: smoking 10 cigarettes per day for about 40 years, and mild hypertension. His serum TC, TG, and HDL-C levels were 200, 60 and 64 mg/dl, respectively. The LDL-cholesterol level calculated by the Friedewald formula was 124 mg/dl. During the 10-year follow-up, the plasma cholesterol concentration ranged between 200 and 220 mg/dl. Plasma TG and HDL-C concentrations were within normal limits. Blood glucose levels were also within normal limits. The patient stopped smoking after ASO was diagnosed. One year before the admission in September 2001, abdominal aortic aneurysm (AAA) was found by computed tomography (CT). At the age of 81 years, in 2002, he was referred to the Department of Internal Medicine because of leg edema. On examination, he demonstrated hypercholesterolemia (362 mg/dl), proteinuria (3.5 g/day), and hypoalbuminemia (2.6 g/dl), suggesting the presence of nephrotic syndrome. The level of Lp(a) was 329 mg/dl and the patient was admitted to hospital. His elder brother, who died of coronary artery disease (CAD), had also been diagnosed with ASO.

This patient's body weight was 50.5 kg and height was 158 cm. Body temperature was 36.5°C and blood pressure was 156/84 mmHg. Edema of the lower left leg was noted and the pedal pulses were weak. There were no

skin lesions. Typical fundoscopic findings of pseudoxanthoma elasticum, termed angioid streaks, were not found. Respiratory and heart sounds were normal. Abdominal examination demonstrated increased pulsation around the umbilical area. On neurological examination, there were no abnormalities.

The urine was positive (++++) for protein; the sediment contained no red blood cells, white blood cells or casts. Hematological, blood chemical, and enzyme values and the results of serological testing on admission are given in Fig. 1. The serum protein level was decreased (5.0 g/dl) and the plasma albumin concentration was 2.6 g/dl. Hematological indices remained within normal ranges. The treponema pallidum hemagglutination test and serological test for syphilis were negative. Hypercholesterolemia was noted. The blood glucose level was 94 mg/dl and Hb_{A1c} was 5.4%. The plasma IgA level was normal (226 mg/dl). Plasma C3, C4 levels were within normal limits (84 and 29 mg/dl, respectively). Lipoprotein disc electrophoresis showed the presence of midband. On lipoprotein fractionation, very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), LDL, HDL2 and HDL3 cholesterol concentrations were 17, 10, 211, 66 and 19 mg/dl, respectively. The IDL cholesterol concentration was not increased, suggesting that the midband was due to high levels of Lp(a) and not to remnant accumulation. The Lp(a) phenotype was F, S3. Chest X-ray demonstrated calcification in the aortic arch.

Ultrasonographic examination of the carotid artery showed diffuse thickening of the intimal-media complex,

Fig. 1. Laboratory data and lipoprotein disc electrophoresis.

U-TP: urinary total protein, U-alb: urinary albumin

and plaques of the vessel walls in the bilateral carotid arteries (Figs. 2a, 2b). Magnetic resonance angiography (MRA) of the lower limb demonstrated stenosis in the right external iliac artery and occlusion in the left external iliac artery (Fig. 3). Abdominal CT demonstrated AAA with a diameter of about 4 cm (Fig. 4). Chest CT showed remarkable calcification of the right and left coronary arteries (Figs. 5a, 5b). Radionuclide imaging with ^{123}I -labeled beta methyl-iodophenyl penta-decanoic acid (BMIPP), and thallium(Tl)-201 single-photon emission computed tomography (SPECT) showed less uptake of BMIPP than of Tl-201 in the inferior area, indicating myocardial ischemia. Since the patient did not present any symptoms of angina pectoris and he declined more detailed examination, coronary arteriography was not performed.

Figure 6 shows the clinical course. Dipyridamole (300 mg/day) and imidapril (5 mg/day) were prescribed, and a protein-restricted diet (less than 20 g/day of protein) was

provided. The proteinuria gradually decreased and the levels of Lp(a) decreased. The leg edema improved and he was discharged in May 2002. After two months, plasma albumin levels decreased again and the leg edema became prominent. Therefore, he was readmitted in August 2002. On this second admission, the highest level of Lp(a) was 356 mg/dl. Again, the albumin levels were decreased and cholesterol levels were increased. Almost the same regimen as that in the first administration was prescribed, and the proteinuria improved, while TC and Lp(a) levels decreased.

Ten months after discharge, the nephrotic syndrome was almost in complete remission: albumin levels were normalized and cholesterol levels had decreased to almost normal (179 mg/dl). The Lp(a) levels decreased with the increase in plasma albumin levels. However, the Lp(a) levels remained markedly elevated (204 mg/dl).

Fig. 2. Ultrasonographic examination of the carotid artery showed diffuse thickening of the intimal-media complex, and plaques in the right common carotid artery (a) and right internal carotid artery (b). There were also plaques and thickening of intimal-media complex in the left carotid artery (data not shown).

Fig. 3. MRA of the lower limb demonstrated stenosis in the right external iliac artery and occlusion in the left external iliac artery.

Fig. 4. Abdominal CT showing AAA with a diameter of about 4 cm.

Fig. 5. Chest CT showed severe calcification of the right (a) and left (b) coronary arteries.

Fig. 6. Clinical course.

U-TP: urinary total protein/day, alb: plasma albumin, T-Cho: total cholesterol, TG: triglyceride

Results and Discussion

We encountered a patient with hyperLp(a)emia complicated by advanced atherosclerosis, detected when nephrotic syndrome developed during the clinical course. We found that changes in Lp(a) levels closely paralleled the severity of nephrotic syndrome. However, after remission of the nephrotic syndrome, Lp(a) levels remained high. Therefore, we estimated that marked hyperLp(a)emia may have played a role in the progression of severe atherosclerosis in this case.

Plasma concentrations of TC and TG are frequently elevated in patients with nephrotic syndrome. This type of hyperlipoproteinemia is mainly caused by an increase in

atherogenic lipoproteins, consisting of apolipoprotein B-100 as a major apoprotein. (7). Concerning changes in Lp(a) levels, there have been some reports showing the elevation of plasma Lp(a) levels in nephrotic syndrome (8–11). Lp(a) levels are much less affected by age, gender, weight and diet than other classes of lipoproteins. Lp(a) plasma levels are under tight genetic control, independent of low-density lipoprotein plasma concentrations, and refractory to dietary or drug treatment. Utermann *et al.* (6) showed an inverse correlation between the size of apo(a) isoforms, that is, the number of repeated kringle 4 domains, and the plasma Lp(a) concentration. In the present study, the patient had a phenotype of F, S3, including the small type of Lp(a). Although the size of the polymorphism does not explain all of the interindividual variations in Lp(a) levels (12), the small apo(a) particles may have been a factor in the elevation of Lp(a) levels in the present case.

Concerning the mechanism involved in increasing Lp(a) in nephrotic syndrome, De Sain-Van Der Velden *et al.* (13) used a stable isotope, ^{13}C valine, to demonstrate that the absolute synthetic rate of Lp(a) was correlated with plasma Lp(a) concentration, suggesting that increased synthesis causes elevated plasma Lp(a) concentrations in nephrotic syndrome. In the present study, we found that Lp(a) levels were relatively closely correlated with the levels of plasma TC and albumin. It has been proposed that hypoalbuminemia and reduced oncotic pressure stimulate hepatic synthesis of albumin and other liver-derived proteins, such as apoproteins (14). However, the precise mechanism driving the increased synthesis of Lp(a) has not yet been clarified.

Elevated plasma concentrations of Lp(a) are recognized as a risk factor for the development of atherosclerotic diseases such as CAD, peripheral vascular disease and

stroke (15). However, clinical profiles of patients with very high levels of Lp(a) have not been fully clarified, although there have been a few reports associated with juvenile CAD (16, 17). Thiery *et al.* reported a case of nephrotic syndrome with hyperLP(a)emia, which also demonstrated severe CAD (8). Although the present case had some risk factors such as smoking and hypertension, high levels of Lp(a) may have played a role in the progression of atherosclerosis, since the combination of high Lp(a) plasma concentrations with other cardiovascular risk factors strongly increases the risk for atherosclerotic disease (18–21).

Whether high Lp(a) itself plays a direct role in the development of nephrotic syndrome is not clear. LDL is reported to have a worsening effect on nephrotic syndrome (22). Hyperlipoproteinemia is occasionally associated with severe glomerular injury, caused by abnormal accumulation of lipids in glomeruli, which occurs in conditions such as lipoprotein glomerulopathy (23). Since renal biopsy was not performed in the present case, the pathological relationship between the high levels of Lp(a) and the development of nephrotic syndrome is not clear.

Finally, extremely high plasma Lp(a) levels may play an important role in the progression of atherosclerosis. Further studies of cases showing marked hyperlipoprotein(a)emia will provide more information, further clarifying the pathological role of Lp(a) in atherogenesis.

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