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Case Report

Multiple potency of ezetimibe in a patient with macroproteinuric chronic kidney disease and statin-intolerant dyslipidemia

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ABSTRACT

Dyslipidemia is often complicated by chronic kidney disease (CKD). Lipid-lowering medications may be effective, in part, for inhibiting development and progression of CKD. Ezetimibe, a cholesterol absorption inhibitor, has pleiotropic actions, including anti-inflammatory and anti-oxidant effects, contributing to a decreased risk of cardiovascular diseases. A 40-year-old woman was admitted with dyslipidemia and macroproteinuria, whose samples of renal biopsy showed exudative lesions, but without glomerular basement membrane thickening or nodular lesions, in some glomeruli. Blood glycemic parameters were normal. After initiation of atorvastatin, she developed muscle pain and an increase in serum creatine kinase. Twelve months after switching to ezetimibe, serum levels of low-density lipoprotein cholesterol and triglyceride reduced from 170 mg/dL to 116 mg/dL and from 320 mg/dL to 160 mg/dL, respectively. Although serum creatinine levels remained unchanged after 12 months, urinary protein excretion and urinary liver-type fatty acid binding protein were reduced. Flow-mediated dilatation also increased from 4.9% to 5.5% after 12 months, associated with a slight decrease in mean intima-media thickness in the common carotid artery from 0.722 mm to 0.718 mm. These results suggest that ezetimibe protects against renal and vascular damage in patients with CKD and statin-intolerant dyslipidemia.
<**Learning objective:** Little is known whether ezetimibe monotherapy is safe and effective for renal/vascular function in patients with chronic kidney disease (CKD). We report that ezetimibe monotherapy for 12 months improved lipid profiles in a patient with CKD and statin-intolerant dyslipidemia. Ezetimibe also reduced proteinuria and urinary liver-type fatty acid binding protein levels, improved endothelial function, and decreased carotid atherosclerosis. These findings suggest that ezetimibe monotherapy may have beneficial multipotent effects on renal/vascular function.>

Introduction

Chronic kidney disease (CKD) is associated with a higher risk of cardiovascular disease (CVD), an association that is likely to be multifactorial. Dyslipidemia is a major contributor to the pathogenesis of atherogenic cardiovascular events and tends to progress with deterioration of kidney function [1]. It is therefore suggested that lipid-lowering medications may play a critical role in preventing the development of CVD and even progression of renal dysfunction in patients with dyslipidemia and CKD.

Ezetimibe is a lipid-lowering agent that acts in the intestine as a cholesterol absorption inhibitor. There is increasing evidence that adding ezetimibe to statin therapy reduces atherosclerotic events in patients with CKD [2]. In addition, Morita et al. [3] reported that ezetimibe had a protective effect on renal function and arterial stiffness in patients with CKD and dyslipidemia. Ezetimibe can therefore be administered safely to dyslipidemia patients with CKD. However, little is known whether ezetimibe is safe and can improve renal and vascular function in patients with macroproteinuric CKD and statin-intolerant dyslipidemia.

This paper reports a case with macroproteinuric CKD and statin-intolerant dyslipidemia, who was treated by ezetimibe monotherapy for 12 months. Switching from statin to ezetimibe treatment successfully improved lipid profiles and also reduced the levels of proteinuria and urinary liver-type fatty acid binding

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protein (L-FABP). Ezetimibe treatment also increased flow-mediated dilation (FMD) and decreased mean common-carotid artery intima-media thickness (CCA-IMT).

Case report

A 40-year-old woman was referred to our hospital with proteinuria and dyslipidemia. Proteinuria and dyslipidemia had been identified at another clinic when she was aged 38 years, although no drugs were administered at that time. She was a non-smoker and had no history of other diseases including hypertension and diabetes. In addition, none of her family members had a history of CKD, dyslipidemia, or diabetes. At admission, a clinical examination showed body height was 165 cm, weight 74 kg, body mass index (BMI) 27.2 kg/m^2, blood pressure 138/76 mmHg, and heart rate 70 beats/min. Laboratory data were as follows: serum creatinine 0.88 mg/dL, estimated glomerular filtration rate 52.0 mL/min/1.73 m^2, blood urea nitrogen 22 mg/dL, low-density lipoprotein cholesterol (LDL-C) 170 mg/dL, triglyceride (TG) 320 mg/dL, high-density lipoprotein cholesterol (HDL-C) 62 mg/dL, uric acid 5.8 mg/dL, urinary protein excretion 6.6 g/day (24-h urine), and urinary L-FABP 34.8 μg/g Cr. No impairment of glycemic parameters was observed with a fasting plasma glucose of 88 mg/dL, plasma glucose at 2-h after a 75 g oral glucose tolerance test 110 mg/dL, and HbA1c 5.5%. Plasma serology was negative for antinuclear antibody, anti-glomerular basement membrane antibody, myeloperoxidase anti-neutrophil cytoplasmic antibody (ANCA), proteinase 3-ANCA, hepatitis C antibody, and hepatitis B antigen. Serum complement factors and immunoglobulins were within normal limits. Chest and abdominal X-rays, electrocardiography, ultrasound echocardiography, and renal echography showed no abnormalities. FMD and mean carotid IMT were 4.9% and 0.722 mm, respectively. On the 3rd day of admission, a renal biopsy was performed. The kidney specimen contained 30 glomeruli. Light microscopy of renal histopathology showed 4 with global glomerular sclerosis, tubular atrophy, interstitial fibrosis, and interstitial cell infiltrations (Fig. 1A), and 3 glomeruli showed fibrin cap-like lesions (Fig. 1B), but no nodular glomerular lesions were observed. Glomerulomegaly was not recognized, and the mean glomerular size without 4 global glomerulosclerosis was 148 ± 26 μm (normal range: 130–170 μm). On immunohistochemistry, immunoglobulin (Ig) G, IgM, IgA, C3, C1q, kappa, and lambda were negative. Electron microscopy showed the glomerular basement membrane (GBM) had a normal width (mean GBM width: 288 nm) and fusion of the foot process (Fig. 2). Atorvastatin (10 mg/day) was initiated on day 7, although the patient complained of muscle pain with her serum creatine kinase increasing to 1500 IU/l. Ezetimibe (10 mg/day) was therefore started on day 14 instead of atorvastatin. The changes in some clinical and laboratory data after 12 months of ezetimibe are shown in Table 1. During this period, appropriate exercise and dietary therapy [(2100 Kcal, low-protein diet (1.0 g/kg plus equivalents of urinary protein excretion), sodium reduction (5.0 g)] were also performed. Systolic and diastolic blood pressure were unchanged during 12 months of treatment. Body weight decreased from 72.2 kg to 68.8 kg after 12 months, whereas serum albumin increased from 3.4 g/dL to 4.0 g/dL. LDL-C and TG levels were reduced to 116 mg/dl and 160 mg/dl, respectively, while HDL-C levels showed no change. Although serum creatinine showed little change throughout this period, urinary protein excretion and urinary L-FABP levels were markedly reduced to 0.6 g/day and 20.8 μg/g Cr, respectively. After 12 months of ezetimibe treatment, blood pressure remained in the normal range, FMD increased to 5.5%, and mean CCA-IMT decreased slightly to 0.718 mm. No side effects associated with ezetimibe were observed.

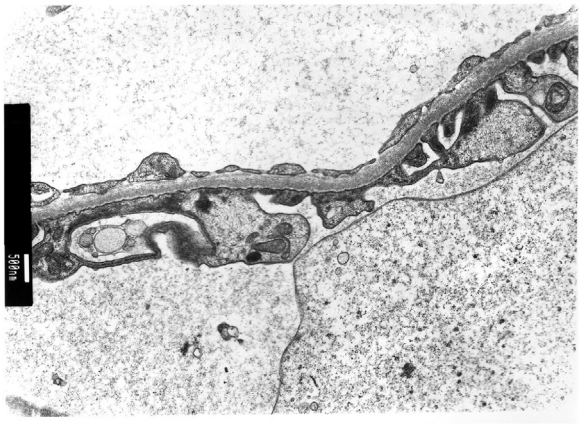

Fig. 2. Electron microscopic findings of kidney specimens. The width of the glomerular basement membrane is normal, although foot process fusions are apparent.

Discussion

Dyslipidemia has a substantial additive risk of causing coronary artery disease in patients with CKD [2]. Statins are recommended as first-line therapy for dyslipidemia because of their pleiotropic effects, including renal protection. Some investigators have proposed a need to prescribe high-potency statins in patients with CKD prior to progression of renal dysfunction, and recommended a combination of statin and ezetimibe to decrease

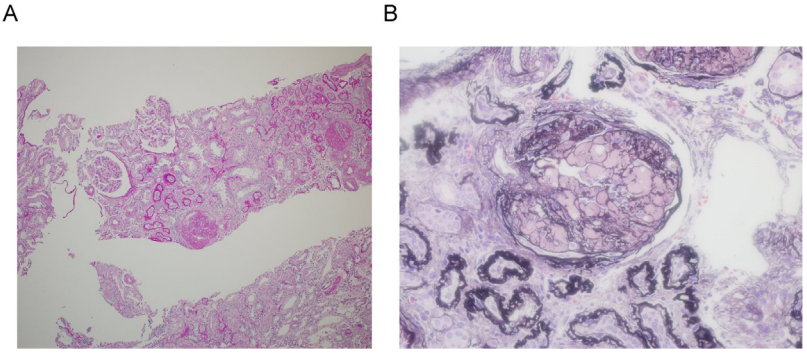

Fig. 1. Light microscopic findings of the kidney biopsy specimens. (A) Periodic acid–Schiff staining (×100). (B) Periodic acid methenamine silver staining (×400). Fibrin cap-like lesion can be seen in the glomeruli.

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