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Myopathy due to Chronic Clevudine Therapy
- A Case Report -

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A 40-year-old man with chronic hepatitis B complained of progressive weakness of the proximal muscles and edema of both legs. He had been receiving long-term clevudine (nucleoside analogue reverse transcriptase inhibitor, NRTI) therapy for his hepatitis. The serum creatine kinase level was increased on the laboratory tests. His electromyography showed a generalized myopathic process. The muscle biopsy showed numerous ragged-red fibers, degenerating myofibers with variable sized cytoplasmic bodies, the prominence of type 1 fibers with type 2 fiber atrophy and an endomysial mononuclear cell infiltration. The electron microscopic examination revealed necrotic myofibers, including extremely dysmorphic mitochondria with extensive loss, blunting and focal clumping of the cristae and concentric cristae. Although clevudine is known to be a less cytotoxic agent among the various NRTIs, careful clinical attention should be paid to the patients who are receiving long-term clevudine therapy for the occurrence of myopathy.

Key Words : Clevudine; Mitochondrial Myopathies

Hepatitis B virus (HBV) is a DNA virus and its replication relies on reverse transcription, which is similar to that of human immunodeficiency virus (HIV).[1] Nucleoside analogue reverse transcriptase inhibitors (NRTIs), including zidovudine (3′-azido-2′,3′-deoxythymidine, azidothymidine, AZT), fialuridine, lamivudine and other nucleoside analogues, suppress viral replication by inhibiting viral RNA-dependent DNA polymerase (reverse transcriptase) and these NRTIs have been used for treating many viral infections, including hepatitis B and HIV infection, as well as cancer.[2-11] The toxicity of pyrimidine NRTIs (AZT, fialuridine and others) includes cardiac dysfunction, hepatic failure, skeletal myopathy, lactic acidosis with defective mitochondrial DNA (mtDNA) replication, mtDNA depletion and an altered mitochondrial ultrastructure in selected tissues.[3-11] In addition, experimental studies have documented the mitochondrial changes in selected tissues from rats, mice, other rodent species and primates with a variety of NRTI dosing schedules.[9] Compared with that, some NRTIs like the "L-drugs", lamivudine (3TC) and the newer related compounds have not demonstrated significant mitochondrial toxicity.

Clevudine (1-[2-deoxy-2-fluoro-β-L-arabinofuranosyl] thymine, L-FMAU, Revovir) is a nucleoside analog with an unnatural β-L configuration that has potent activity against HBV.[12-14] It is licensed in Korea for anti-HBV therapy (Bukwang Pharmaceuticals, Seoul, Korea). The clinical trials have demonstrated no specific adverse events and the several authors have explained that the reason for the lack of cytotoxicity was the inability of human cellular DNA polymerase α, β, γ, and δ to utilize the 5′-triphosphate of clevudine as a substrate.[13,15,16] Recently and for the first time, four consecutive cases of severe myopathy associated with long term clevudine therapy in HBV infected patients were reported as an abstract.[17] We report here on an additional case of long term clevudine treatment-associated myopathy that arose in a 40-year-old man, and the man is a HBV carrier.

CASE REPORT

A 40-year-old male patient was referred with the clinical impression of motor neuron disease. He had chief complaints of edema and heaviness of both legs, myalgia after exercise and generalized weakness for last 5 months. The past history revealed

that he had been diagnosed as a HBV carrier since high school. He has been treated for hypertension for three years and his herniated lumber disc had been surgically treated 31 months ago. After the operation, lamivudine treatment (Zeffix, GlaxoSmithKline, London, England, 100 mg/day) was started and this was switched to clevudine after one year and then continued for 18 months (Revovir 30 mg/day).

The blood tests showed AST 93 IU/L, ALT 46 IU/L, CK 960 IU/L, LD 811 IU/L, positive hepatitis B surface antigen, negative hepatitis B virus e antigen and negative hepatitis B surface antibody. The vital signs were normal and the physical examination revealed icteric sclera, edema of both legs, atrophy of the bilateral shoulder muscles and congestion of the right jugular vein. Any skin lesions were not noted. Abnormality of the extraocular movement, ptosis, facial muscle weakness, dysarthria, dysphagia, tongue atrophy, fasciculation or myotonia was not observed on the cranial nerve function tests. The ophthalmoscopic examination showed no evidence of optic nerve atrophy or retinal pigmentation. The muscle strength test revealed proximal muscle weakness (MRC grade IV) of both the upper and lower extremities. The muscle tone was normal and the cerebellar function test and sensory examinations were insignificant. The deep tendon reflexes of all the extremities were symmetric and normoactive with no pathologic reflexes. The sensory nerve conduction study (NCS) showed slow conduction velocities with normal amplitudes of the sensory nerve action potentials between the finger and wrist in both the median and ulnar nerves. The motor NCS showed slightly low amplitudes of the compound motor action potentials in the right ulnar and left median nerves. The electromyography (EMG) documented increased insertion-

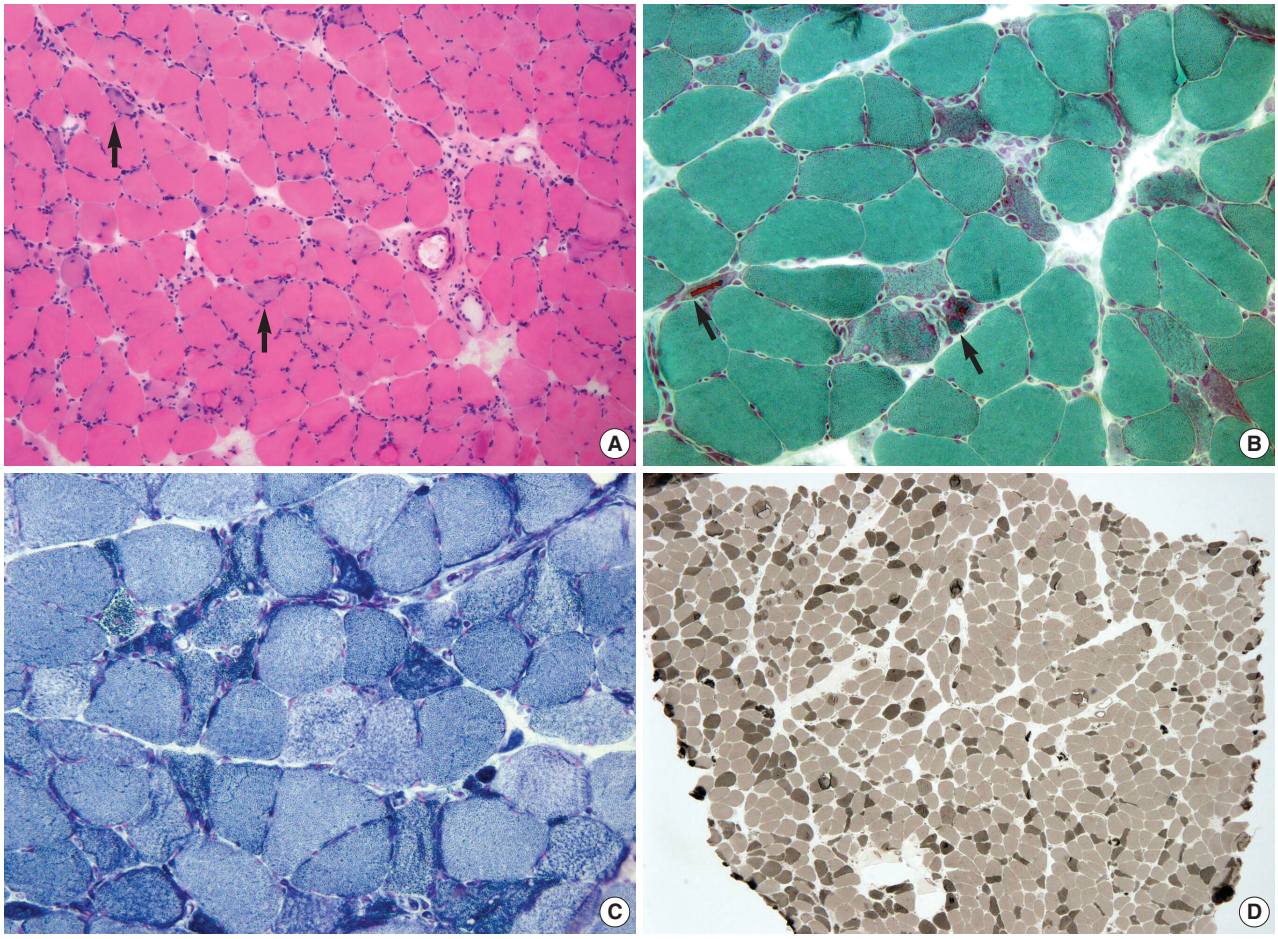

Fig. 1. The light microscopic examination shows marked variation of the fibers' size and shape, many scattered necrotic fibers (arrows) and infiltration of mononuclear cells (A). The modified trichrome stain (B) shows ragged-red like features of the myofibers with many cracks, granular degeneration, cytoplasmic bodies (arrows) and mononuclear cell infiltration in the necrotic fibers. NADH-TR shows increased numbers of mitochondria in the degenerating fibers (C). ATPase with pH 9.4 preincubation shows the predominance of type 1 fibers with type 2 fiber atrophy (D).

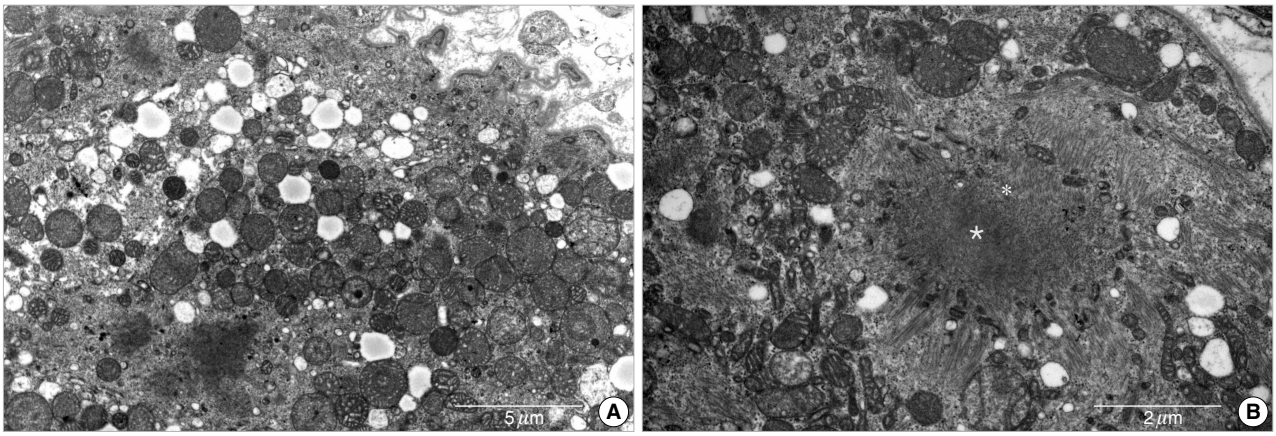

Fig. 2. The electron microscopic examination shows degenerating myofibers filled with abnormal enlarged mitochondria and lipid vacuoles (A). The mitochondria show a markedly dysmorphic appearance with extensive loss, blunting and focal clumping of cristae and concentric cristae (B). A cytoplasmic body with an amorphous center and surrounding radiating fibrils is also noted (asterisk). (A: ×12,000, B: × 20,000).

al activities with abnormal spontaneous activities, a small amplitude and a short duration of the motor unit action potentials in the left first dorsal interosseous, extensor digitorum communis, deltoid, triceps, tibialis anterior, peroneus longus, rectus femoris, adductor longus and mid-thoracic paraspinal muscles. These electrophysiological findings were suggestive of generalized myopathy and mild sensory-dominant peripheral neuropathy.

A muscle biopsy was performed on the vastus lateralis muscle to rule out the possibility of inflammatory myopathy or metabolic myopathy. The light microscopic examination showed marked variations of the fibers' size and shape, many degenerating or necrotic myofibers and an endomysial mononuclear cell infiltration (Fig. 1A). The degenerating or necrotic myofibers showed an intensive positive NADH-TR reaction and ragged-red like myofibers with variable sized cytoplasmic bodies were frequently noted on Gomori's trichrome stain (Fig. 1B, C). The ATPase with different pH preincubation and immunostaining with Myosin Heavy Chain (fast) (NCL-MHCf, monoclonal, 1:20, Vision Biosystems, Newcastle, UK) and Myosin Heavy Chain (slow) (NCL-MHCs, monoclonal, 1:40, Vision Biosystems) showed a predominance of type 1 fibers with type 2 fiber atrophy (Fig. 1D). On the electron microscopic examination, some myofibers showed well preserved sarcomeres with diffusely scattered small vacuoles. Admixed were myofibers with slight to moderately disorganized sarcomeres, a dilated T system, swollen sarcoplasmic reticulum, lipid vacuoles and abnormal swollen mitochondria with concentric cristae. In addition, there were myofibers showing variable stages of degenerative changes with many abnormal enlarged mitochondria, lipofuscin granules and cytoplasmic bodies. Totally necrotic myofibers were also noted, and these were filled with granular, amorphous material and extremely dysmorphic mitochondria with extensive loss, blunting and focal clumping of the cristae and concentric laminated cristae (Fig. 2).

Since the muscle biopsy findings were consistent with NRTI induced myopathy, his clevudine medication was discontinued. On the follow up examination after one month, he was able to go up and down stairs without any help and hop on one leg. The motor strength of the proximal muscles was remarkably improved (MRC grade V). The muscle volume of his shoulder was somewhat increased.

DISCUSSION

Ever since the highly active antiretroviral therapy regimes consisting of NRTIs such as AZT and other nucleoside analogues have revolutionized the treatment of AIDS in recent years, NRTI-related mitochondrial toxicity has manifested with such serious side effects as hepatic failure and lactic acidosis.[3-11] In addition, the clinical effectiveness of AZT is constrained due to its association with increased adverse effects such as hematological effects (anemia and neutropenia), hepatotoxicity, cardiomyopathy and myopathy. The mechanisms to explain the AZT-induced toxicity include mtDNA depletion due to inhibition of DNA polymerase γ, AZT-induced oxidative stress, direct inhibition of the mitochondrial bioenergetic machinery and mitochondrial depletion of L-carnitine and/or other mechanisms such as apoptosis.[7-9]

The patients with NRTI-induced myopathy usually complain of progressive generalized muscle pain, weakness, fatigue and muscle atrophy and their increased serum concentration of cre-

atine kinase indicates muscle necrosis.[7] AZT-associated myopathy is characterized by atrophic ragged-red fibers with marked myofibrillary alterations (AZT fibers), marked myonecrosis with cytoplasmic bodies, accumulation of abnormal mitochondria and lipid droplets, type 2 fiber atrophy and inflammatory changes.[4-7] In addition to the compatible clinical symptoms in this patient, the muscle biopsy also shows findings that are similar to the previously described findings of AIDS patients treated with the NRTI regimes.[4-7] Four hepatitis B carrier patients with 8 to 12 months clevudine treatment also showed similar clinical manifestations and muscle biopsy findings.[17] The diagnostic NRTI treatment-specific findings of mitochondrial myopathy noted on the muscle biopsy of this case, as well as the prompt recovery of muscle strength at one month after discontinuation of clevudine treatment, strongly suggest the relation between the clinical symptoms and clevudine treatment in this patient.

Previous clinical trials have evaluated the safety and efficacy of clevudine 30 mg daily for 24 weeks in chronic hepatitis B patients, which did not show any adverse effects on muscle.[13,15,16] Compared with those studies, the previously reported four cases with myopathy[17] and the present case were treated for a much longer period (8-12 months and 18 months, respectively), which suggests that the duration or possibly the dosage of clevudine might be related with the occurrence of myopathy. Since March 2006, about 60-70 patients have been treated with clevudine for HBV infection at Ewha University Medical Center and two additional patients have complained muscle weakness after 12 months and 3-4 months of treatment, respectively. Unfortunately, the cause of muscle weakness in those patients remains unknown, but the possibility of mitochondrial myopathy can not be excluded without further studies, including muscle biopsy. In addition, the possible augmentation effects of other NRTIs (lamivudine in this case) on the occurrence of mitochondrial myopathy should be considered and further studies that will focus on the proper dosage and duration of treatment will be mandatory for properly treating the patients.

In conclusion, recognizing mitochondrial myopathy associated with chronic clevudine therapy is very important for making the correct diagnosis and providing proper treatment.

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