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Case Report

Clevudine myopathy in patients with chronic hepatitis B☆

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Clevudine (L-FMAU) is a thymidine L-nucleoside analogue that was recently introduced for the treatment of chronic hepatitis B virus infection. Previous studies showed that clevudine has potent and sustained antiviral activity without causing viral resistance. No severe adverse event occurred during clinical trials. We describe two cases of drug-induced myopathy during long-term treatment of chronic hepatitis B with clevudine.

***Keywords*: Clevudine; Hepatitis B; Adverse effects; Myopathy**

1. Introduction

Clevudine [L-FMAU, (1-(2-fluoro-5-methyl-β,L-arabinofuranosyl) uracil)] is a pyrimidine L-nucleoside analogue with potent and sustained antiviral activity against hepatitis B virus (HBV) [1–3]. It is an enantiomer of [D-FMAU, (1-(2-fluoro-5-methyl-β,D-arabinofuranosyl) uracil)] and is structurally related to fialuridine [D-FIAU, (1-(2-deoxy-2-fluoro-β, D-arabinofuranosyl) iodouracil)], lamivudine and telbivudine [4]. Although previous studies have demonstrated the antiviral efficacy and safety of clevudine during and after short-term treatment, corresponding data on long-term treatment with clevudine is limited.

Antiviral nucleoside/nucleotide analogue-induced myopathies were reported for fialuridine treatment for chronic hepatitis B and zidovudine treatment for HIV [5,6]. The mechanism by which myopathy is induced by these drugs involves inhibition of mitochondrial DNA polymerase γ, which results in mitochondrial DNA dysfunction *in vitro* [7]. Recently, cases of telbivudine-induced myopathy have been reported. However, there were no severe adverse effects, including myotoxicity, in clinical clevudine trials [8–12].

We describe clinical features and pathologic findings for two patients with myopathy who received clevudine therapy for chronic hepatitis B. To our knowledge, this is the first report of clevudine-related myopathy that is not associated with mitochondrial damage.

2. Case report

Case 1. A 42-year-old female who received clevudine therapy for chronic hepatitis B presented with progressive weakness of both lower legs and had experienced difficulty in chewing over the previous four months. She had chronic hepatitis B for more than 10 years

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Abbreviations: L-FMAU, (1-(2-fluoro-5-methyl-β, L-arabinofuranosyl) uracil); HBV, hepatitis B virus; D-FMAU, (1-(2-fluoro-5-methyl-β, D-arabinofuranosyl) uracil); D-FIAU, (1-(2-deoxy-2-fluoro-β, D-arabinofuranosyl) iodouracil); ALT, alanine aminotransferase; EMG, electromyography; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

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and had been taking 30 mg of clevudine once daily for 16 months. She had not taken any other medication during the clevudine therapy. After clevudine therapy, her HBV DNA level decreased to an undetectable level and her serum ALT level normalized. The patient suffered from progressive and generalized weakness, especially of the legs, and experienced difficulty in climbing stairs. However, she did not have dysphagia, cramps or sensory symptoms. She exhibited motor weakness (grade 4) of the hip flexor making her difficult to stand up from the sitting position, but there was no sign of abnormal deep tendon reflex, muscle atrophy or hypertrophy on physical examination. Laboratory analyses showed an elevated creatine kinase level (220 U/L), whereas lactic acid concentration was within the normal range (Table 1, Case 1). Tests for serum autoimmune markers (anti-nuclear antibody, anti-double-strand-DNA antibody, acetylcholine receptor antibody, and anti-Jo1 antibody) were all negative. Tests for serum tumor markers (alphafetoprotein, carcinoembryonic antigen, CA19-9, and CA-125) were all within the normal range. Stool occult blood test was negative. Abdominal sonography and gastroduodenoscopy showed no malignant lesion. Electromyography (EMG) showed a few positive sharp waves or fibrillation potentials with early recruitment of myopathic motor unit action potentials (MUAPs) in the right deltoid, vastus medialis, gastrocnemius, lumbar paraspinal and orbicularis oris muscles, which is consistent with the active stage of generalized myopathy (Fig. 1A and B). A biopsy specimen was taken from the left vastus lateralis muscle. On light microscopic examination of the specimen, there was significant size variation of myofibers revealing many degenerating and necrotic myofibers (Fig. 2A). The necrotic myofibers showed inflammatory cellular infiltrate that was mainly composed of macrophages (Fig. 2A). There were little infiltrate of inflammatory cells in perivascular spaces and no endomysial fibrosis. The specific findings of other primary myopathies such as inclusion myopathy or mitochondrial myopathy were not observed during the electron microscopic examination. The patient took 50 mg prednisolone once daily

Table 1
Laboratory results in the two cases with clevudine myopathy.

	Patient 1			Patient 2			Normal reference range
	Before clevudine therapy (April 26, 2007)	Diagnosis of myopathy (July 29, 2008)	Last follow-up (January 12, 2009)	Before Clevudine therapy (May 29, 2007)	Diagnosis of myopathy (October 10, 2008)	Last follow-up (February 24, 2009)	
WBCs (10^9/L)	5760	4.53	4.83	4.64	2.03	2.92	4 ~ 10
Hemoglobin (g/dL)	13.1	12.6	14.0	13.0	12.7	12.5	11.5 ~ 14.5
Platelets (10^9/L)	170	162	187	105	99	86	140 ~ 400
Prothrombin time (INR)	–	1.11	1.08	1.08	1.10	1.11	0.8 ~ 1.2
Total bilirubin (g/dL)	0.6	0.4	0.7	0.5	0.7	0.6	0.2 ~ 1.2
AST (IU/L)	110	40	26	59	111	59	7 ~ 38
ALT (IU/L)	172	32	24	39	59	35	4 ~ 43
Albumin (μg/dL)	4.5	3.9	4.3	4.0	3.8	4.0	3.3 ~ 5.3
LDH (IU/L)	154	650	432	433	1403	430	263 ~ 450
Creatinine (mg/dL)	0.6	0.7	0.8	0.9	0.6	0.7	0.6 ~ 1.3
Creatine kinase (U/L)	43	220	96	69	526	68	29 ~ 145
Myoglobin (ng/mL)	–	120.6	–	–	–	–	~116.3
Aldolase (U/L)	–	8.3	–	–	33.3	–	~7.6
Calcium (mg/dL)	9.5	8.9	9.0	9.1	9.7	9.6	8.0 ~ 10.8
Phosphate (mg/dL)	4.3	3.6	4.6	4.2	4.5	4.2	2.5 ~ 5.5
Lactic acid (mmol/L)	–	–	1.7	–	–	–	0.5 ~ 2.2
HbsAg	Positive	Positive	Positive	Positive	–	–	–
Anti-HBs	Negative	Negative	–	Negative	–	–	–
HbeAg	Negative	Negative	Negative	Positive	Negative	Positive	–
Anti-HBe	Positive	Positive	Positive	Positive	Positive	Positive	–
HBV DNA (copies/mL)	3.22×10^7	<300	<300	6.23×10^5	<300	<300	300 copies/mL (detect limit)
HCV antibody	Negative	Negative	–	Negative	–	–	–
HIV antibody	–	Negative	–	Negative	–	–	–
Alphafetoprotein (ng/mL)	3.0	2.99	2.20	2.83	43.12	1.79	~7.0

Abbreviations used: AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; HBsAg, hepatitis B surface antigen; Anti-HBs, anti-hepatitis B surface antibody; HbeAg, hepatitis B e antigens; Anti-Hbe, anti-hepatitis B e antibody; HBV DNA, hepatitis B virus DNA; –, not available.