Muscular damage in a patient with hepatitis B induced by beta-l-2'-deoxythymidine and detected by ^{18}F-FDG PET/CT

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Abstract
A 58 years old man under 2'-Deoxy-L-thymidine treatment for his hepatitis B was admitted to our hospital complaining for the last 2 months of recurrent upper abdomen discomfort, fatigue and weight loss of 10 kilograms and general muscular soreness, for 2 weeks. He had elevated creatine kinase (CK), myoglobin, CK-MB and other related or common laboratory findings. Fluorine-18- fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) showed a diffuse, homogenous, moderately elevated glucose uptake in all muscle groups. Muscular damage induced by 2'-Deoxy-L-thymidine was suspected and the drug was discontinued. Muscle soreness and the biomarkers for muscular tissue damage improved. Fluorine-18-FDG PET/CT is useful to rule out malignancy and identify muscular tissue damage.

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Introduction

Muscle tissue damage is related to both metabolic and mechanical factors that allow to classify this condition into traumatic and non-traumatic [1-5]. Certain drugs including statins, theophylline, antiH1, benzodiazepines, amphotericine B and antidepressants have been associated with increased blood levels of creatin kinase (CK) and myoglobin that are biochemical markers of musculoskeletal damage [1]. 2'-Deoxy-L-thymidine is an orally administered nucleoside analog drug approved for the treatment of patients with chronic hepatitis B since 2006 [6]. 2'-Deoxy-L-thymidine is generally well tolerated, but cases of myopathy have been reported [6-9]. Fluorine-18-FDG PET/CT is sensitive in identifying muscular disease. Fluorine-18-FDG higher uptakes in statin-induced rhabdomyolysis [10], muscular infection [11] and graft-versus-host disease (GVHD)-associated polymyositis [12] have been reported. In this paper we report ^{18}F-FDG PET/CT detected 2'-Deoxy-L-thymidine-induced muscular damage in a hepatitis B patient. We were unable to find a similar case in medical literature.

Case Report

We present a case of a 58 years old man who was admitted to our hospital complaining for the last two months, of recurrent upper abdomen discomfort, fatigue, weight loss of 10 kilograms and of general muscular soreness for 2 weeks. The muscular soreness was more at the proximal limb muscles. In fact, three months after initiation of the drug he developed slight and neglectable myalgia and tiredness. His initial laboratory values revealed an elevated uric acid (802umol/L, 210-430), urea nitrogen (8.33 mmol/L, 2.5-7.1 mol/L),CK (573U/L, 39-308), myoglobin (151.80ng/mL, <70), CK-MB (27U/L, 0-25), lactate dehydrogenase (LDH,333U/L, 106-211), alpha hydroxybutyrate dehydrogenase (310U/L,72-182) , troponin (0.03 ng/mL, <0.03), aspartate aminotransferase (AST) (77U/L, 8-38). Serum creatinine (65 umol/L, 62-133), alanine aminotransferase (ALT) (37U/L, 9-72) level and tumor markers were normal. He had positive HBsAg, HBeAg and anti-HCV antibodies. The basal HBV DNA level was unknown. Serum HBV-DNA by the fluorescence quantitative method was negative (<1*10\S\3) in our hospital. Other values including potassium, calcium, phosphorus, thyroid function and myoglobin were normal. Metabo-

lic myopathy was excluded. Gastroscopy showed reflux esophagitis, superficial erosive gastritis and duodenal ulcer. Colonoscopy revealed slight inflammation at the rectosigmoid colon. Electrocardiogram was normal. The patient had not before similar episodes with fever, night sweats, weight loss, dizziness, altered vision, weakness or numbness. His past medical history revealed hepatitis B for 1 year, and he began antiviral therapy with 2'-Deoxy-L-thymidine (600mg/day orally) with a satisfactory virologic suppression for 9 months. He had appendicitis and was operated 6 years ago. He also had cholecystectomy for gall stones, 1 year ago. He had no diabetes. His family history was negative for neuromuscular disorder. On a physical examination, there was muscle tenderness, no lymphadenopathy or abdominal organomegaly. A neurological examination was normal. Antinuclear antibodies (ANA) and rheumatoid factor were negative. To rule out the weight-loss related malignancy, We performed ^{18}F-FDG-PET/CT. Fluorine-18-FDG PET/CT coronal (Figure 1A) and maximum intensity projection (MIP, Figure 1B) images showed a diffuse and homogenous moderately elevated glucose uptake, in all muscle groups, in particular in the pelvic muscles, while the liver was not visualized. A possible relationship between 2'-Deoxy-L-thymidine and muscle damage was suspected, and 2'-Deoxy-L-thymidine was discontinued and replaced with entecavir (2-amino-1,9-dihydro-9-[(1s,3r,4s)-4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6h-purin-6-one monohydrate). During hospitalization, benzobromarone was used to decrease uric acid, and celecoxib (C17H14F3N3O2S) was used to kill pain. The 2'-Deoxy-L-thymidine induced muscle damage was confirmed by the improved muscle soreness and the biomarkers for muscular tissue damage. Other special management was not applied. The changes of biomarkers for muscular tissue damage were listed in Table 1.

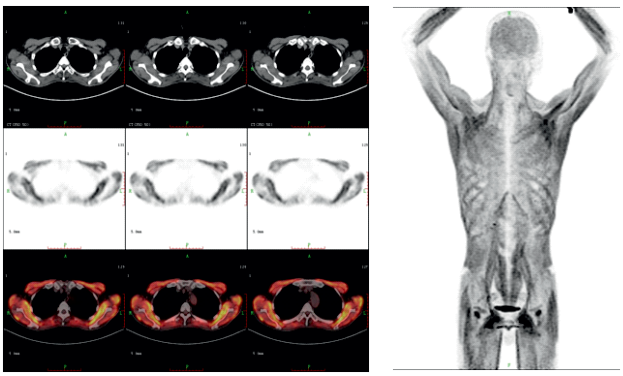

Figure 1. ^{18}F-FDG PET coronal (A) and MIP (B) images showed a diffuse and symmetric, homogeneous increased ^{18}F-FDG uptake in all muscles. The liver was not well visualized with decreased brain FDG uptake.

Discussion

Muscle damage is able to release in blood myoglobin and other important biochemical markers such as CK, LDH, aldolase, myoglobin, troponin, AST, and carbonic anhydrase CAII [13]. Our case had elevated CK, LDH, myoglobin, troponin, AST which indicated muscle tissue injury. In particular, CK is the most used indicator of musculoskeletal damage [14]. Different human tissues exhibit varying levels of cytoplasmic and mitochondrial isoenzymes of CK [15]. Total CK activity included three isoforms, skeletal, cardiac and brain. These enzymes are normally strictly intracellular, and their increased activity in plasma reflects their escape via membrane structures. Myopathy was characterized by mitochondrial dysfunction accompanied by neurogenic damage due to axonal neuropathy. Ultrastructure changes of mitochondria included vacuolisation, simplification of the crista and homogenised matrix [16]. Therefore, although the direct demonstration of muscle damage is histological, in practice the diagnosis is largely based on the measurement of plasma enzymes concentrations [17]. A CK activity >500 IU/L is considered a sign of skeletal muscles damage [18] as shown by our case who had increased total CK>500. Total serum CK is used as a valid index for detection and monitoring of skeletal muscle diseases [1].

Table 1. *Changes of biomarkers for muscular tissue damage*

Month/day	5/10	5/18	5/26	6/6	6/15
Creatine kinase (39-308U/L)	573	692	577	137	150
CK-MB (27,0-25U/L)	16.2	27	33	27	35
Lactate dehydrogenase (106-211U/L)		330	333	302	345
alpha hydroxybutyrate dehydrogenase (72-182 U/L)	310	315	294	268	295
Troponin(<0.03 ng/mL)	0.01		0.03		0.01
Urea nitrogen (2.5-7.1mol/L)	8.33		7.72	6.49	8.18
Aspartate amino transferase (38-126U/L)	77	44	52	47	27

Muscle tissue damage might be related to metabolic and mechanical factors [1]. The differential diagnosis for muscular tissue damage is important. Antinuclear antibodies and rheumatoid factor were negative and so rheumatic disorders i.e polymyositis and dermatomyositis were excluded in our case. Other values including potassium, calcium, phosphorus and thyroid hormones were normal, therefore, metabolic myopathy was also excluded. Certain drugs have been reported to cause musculoskeletal damage. In particu-

lar, statins as well as fluoroquinolones have been associated with muscle pain and weakness [19-21]. 2'-Deoxy-L-thymidine is a L-nucleoside analogue able to inhibit polymerase gamma responsible for mtDNA replication. Myopathy or neuropathy has been associated with 2'-Deoxy-L-thymidine therapy in hepatitis B patients. A systematic review found that 2'-Deoxy-L-thymidine treatment induced in 12%-14% of the cases fatigue, malaise, in 9% asymptomatic hyper-CK-emia, and in 0.5% definite myopathy of the patients [22]. 2'-Deoxy-L-thymidine induced muscle disease may develop weeks or months after starting therapy. Our case had slight muscle pain three months after the initiation of medication that worsened during the last two weeks. 2'-Deoxy-L-thymidine induced myopathy was characterized by muscle pain, weakness and moderately elevated CK levels during treatment [1, 7, 9] and decreased CK levels [9] after discontinuation treatment as shown by our case. Others reported a case of 2'-Deoxy-L-thymidine induced CK-increase in a patient with previous muscle damage [7] and others a patient without history of muscle damage [1]. Our case had no history of muscle damage. Therefore, the diagnosis of 2'-Deoxy-L-thymidine induced muscle damage was established after discontinuation of the drug because muscle soreness improved and the level of the specific biomarkers fell.

Muscular damage may lead to renal failure and to diagnosis of rhabdomyolysis [4]. A relationship between CPK elevation and the severity of the disease has been established (>6000 IU/L predicts renal failure), however patients can have significant morbidity with only moderately elevated CK levels [23, 24]. Although in our case the CK level was not as high as mentioned above the patient had renal insufficiency. Thus, early detection and of CK increase and renal function tests are necessary in similar cases.

Possible causes of abnormal ^{18}F-FDG muscle uptake should be considered. Physiological uptake of ^{18}F-FDG in muscles may occur if there is activity before, during, or after the injection of the tracer; however, this typically involves the entire muscle more or less uniformly, without distribution of the tracer [10]. Patients in hyper-insulinaemic states may have preferential uptake of ^{18}F-FDG in muscle, which uptake also tends to be more uniform. In addition, medications that alter glucose metabolism such as corticosteroids and tacrolimus may also alter ^{18}F-FDG muscles' uptake [25] . The present patient had normal glucose (5.2mmol/L) at the time of tracer injection and was not taking any medications that might have affected his glucose metabolism. Other diagnostic possibilities included viral myositis or inflammatory myopathy such as polymyositis or dermatomyositis but the clinical course of the patient was not consistent with these possibilities. Our patient was not taking these medications. The scan was performed under standardized conditions to control for the known causes of diffuse ^{18}F-FDG uptake, for example, no strenuous exercise or activities for 24 hours, fasting for 6 hours and no insulin injection. In addition to the above mentioned, lymphoma may also involve skeletal muscles but the rapid recovery of our patient without active treatment precluded this possibility [10].

Fluorine-18-FDG PET/CT is sensitive in identifying muscular disease. Intense, diffuse muscle ^{18}F-FDG uptakes in statin-induced rhabdomyolysis [10], in muscular infection [11] and in graft-versus-host disease (GVHD)-associated polymyositis [12] have also been reported. In our case increased ^{18}F-FDG uptake in all muscles indicated muscle damage. The muscular ^{18}F-FDG uptake in our case was more intense than in muscular infection but less intense than in polymyositis and statin-induced rhabdomyolysis. In conclusion, 2'-Deoxy-L-thymidine treatment induced muscular damage in a 67 years old man with chronic hepatitis B. The characteristic of 2'-Deoxy-L-thymidine induced rhabdomyolysis on ^{18}F-FDG PET/CT was a diffuse, symmetric, homogeneous increased ^{18}F-FDG uptake in all muscles with decreased brain ^{18}F-FDG uptake. The liver was not well visualized Fluorine-18-FDG PET/CT is useful to rule out malignancy and identify muscular tissue damage.

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