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

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.

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*10^3) 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 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.

Table 1. Changes of biomarkers for muscular tissue damage

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

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-thymi-
dine 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-
emía, 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-thymi-
dine induced myopathy was characterized by muscle pain, weakness and moderately elevated CK levels during treat-
ment [1, 7, 9] and decreased CK levels [9] after discon-
tinuation treatment as shown by our case. Others reported a case of 2'-Deoxy-L-thymidine induced CK-increase in a pati-
ent with previous muscle damage [7] and others a patient without history of muscle damage [1]. Our case had no histo-
ry of muscle damage. Therefore, the diagnosis of 2'-Deoxy-L-
thymidine induced muscle damage was established after discontinuation of the drug because muscle soreness impro-
ved and the level of the specific biomarkers fell.

Muscular damage may lead to renal failure and to diag-
osis of rhabdomyolysis [4]. A relationship between CPK ele-
vation 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 18F-FDG muscle uptake should be considered. Physiological uptake of 18F-FDG in mus-
cles 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 18F-FDG in muscle, which uptake also tends to be more uniform. In addition, medications that have preferential uptake of F-FDG in muscle, which uptake was performed under standardized conditions to con-
trast with the known causes of diffuse 18F-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 mus-
cular disease. Intense, diffuse muscle 18F-FDG uptakes in sta-
tin-induced rhabdomyolysis [10], in muscular infection [11] and in graft-versus-host disease (GVHD)-associated polymy-
ositis [12] have also been reported. In our case increased 18F-
FDG uptake in all muscles indicated muscle damage. The muscular 18F-FDG uptake in our case was more intense than in muscle infection but less intense than in polymyositis and statin-induced rhabdomyolysis. In conclusion, 2'-Deoxy-L-
thymidine treatment induced muscular damage in a 67 ye-
ars old man with chronic hepatitis B. The characteristic of 2'-
Deoxy-L-thymidine induced rhabdomyolysis on 18F-FDG PET/ CT was a diffuse, symmetric, homogeneous increased 18F-
FDG uptake in all muscles with decreased brain 18F-FDG upta-
ke. 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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