Drug-induced Liver Injury with HHV-6 Reactivation

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Abstract

Liver dysfunction was identified in a 16-year-old boy hospitalized with high fever and abdominal pain and fullness. He had received pharmacotherapy for a headache 2 months previously and other drugs for a high fever 4 days prior to being admitted to our hospital. The patient’s liver dysfunction was consistent with and fulfilled the criteria for drug induced liver injury, but the laboratory findings showed elevated procalcitonin levels, hyponatremia and leukocytosis. Moreover, we confirmed the presence of human herpesvirus 6 (HHV-6) DNA. The patient exhibited symptoms of high fever and abdominal pain and fullness but no exanthema. The clinical and laboratory findings did not satisfy the criteria for drug-induced hypersensitivity syndrome, and we speculate that the diversity of clinical and laboratory findings may have resulted from HHV-6 reactivation. To the best of our knowledge, this is the first case report on drug-induced liver injury with various findings due to HHV-6 reactivation. HHV-6 reactivation should be considered in patients with drug induced liver injury even in the absence of exanthema.

Key words: drug induced liver injury, pleural effusion, ascites, HHV-6 reactivation

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Introduction

Human herpesvirus 6 (HHV-6) is a lymphotropic virus in the beta herpesvirus family. Primary infection occurs in most individuals within the first 2 years of childhood and results in exanthema subitum (1). Primary HHV-6 infection is a lifelong infection and HHV-6 can be found in the peripheral blood, kidneys, salivary glands and central nervous system (2).

HHV-6 reactivation does not typically result in significant morbidity in healthy individuals but has been associated with chronic fatigue syndrome (3), myocarditis (4) and drug-induced hypersensitivity syndrome (DIHS) (5, 6). Liver dysfunction associated with HHV-6 reactivation is almost always eventually diagnosed as DIHS, for which exanthema is a major symptom (7). We herein describe a case of drug-induced liver injury with HHV-6 reactivation without exanthema.

Case Report

A 16-year-old boy had occasionally taken analgesics (acetaminophen, isopropylantipyrine and/or allylisopropyl-acetylurea) for headache relief 2 months prior and was subsequently treated with acetaminophen, maobushiaishinto, lysozyme hydrochloride, and cefcapene pivoxil hydrochloride for high fever and abdominal pain and fullness 4 days prior to being admitted to our hospital. Three days after, he was treated with clarithromycin, tranexamic acid, carbocysteine and ibuprofen for the same symptoms. The next day, the patient was referred to our hospital for symptoms of high fever and abdominal pain and fullness (Fig. 1). He did not regularly consume alcohol and his family medical history was uneventful. On admission, the patient was alert and his body temperature was 39.2°C. The conjunctivae were not jaundiced, and heart and respiratory sounds were normal. No abnormalities were identified in the chest or on the skin. Furthermore, there was no lymph node enlargement or joint swelling throughout the whole body. The patient’s abdomen was slightly hard and showed tenderness in the epigastic re-

<table>
<thead>
<tr>
<th>Hematologic test</th>
<th>ALT</th>
<th>Hepatitis B core antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Blood Cells 21,400/μL</td>
<td>1,979 IU/L</td>
<td>(-)</td>
</tr>
<tr>
<td>Neutrophil 80.0%</td>
<td>158 IU/L</td>
<td>Hepatitis C virus antibodies</td>
</tr>
<tr>
<td>Lymphocyte 12%</td>
<td>2.4 mg/dL</td>
<td>IgM-hepatitis A virus antibody</td>
</tr>
<tr>
<td>Monocyte 6%</td>
<td>0.2 mg/dL</td>
<td>EB virus</td>
</tr>
<tr>
<td>Eosinophil 2%</td>
<td>949 IU/L</td>
<td>Anti VCA IgG</td>
</tr>
<tr>
<td>Basophil 0%</td>
<td>19 mg/dL</td>
<td>Anti VCA IgM</td>
</tr>
<tr>
<td>Red Blood Cells 583×10⁶/μL</td>
<td>Creatinine 0.89 mg/dL</td>
<td>Anti EBNA antibodies</td>
</tr>
<tr>
<td>Hemoglobin 17.6 g/dL</td>
<td>Sodium 124 mmol/L</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Platelet count 15.2×10⁴/μL</td>
<td>Potassium 4.9 mmol/L</td>
<td>IgG</td>
</tr>
<tr>
<td></td>
<td>Chloride 97 mmol/L</td>
<td>IgM</td>
</tr>
<tr>
<td>Coagulation</td>
<td>CRP 3.98 mg/dL</td>
<td>HHV-6 DNA 360 copies/mL</td>
</tr>
<tr>
<td>PT 39.2%</td>
<td>Ferritin 357 ng/mL</td>
<td>(-)</td>
</tr>
<tr>
<td>APTT 34.2 sec</td>
<td>Procalcitonin 9.43 ng/mL</td>
<td>(-)</td>
</tr>
<tr>
<td></td>
<td>IgG 703 mg/dL</td>
<td>Blood</td>
</tr>
<tr>
<td>Chemistry</td>
<td>IgA 87 mg/dL</td>
<td>Urine</td>
</tr>
<tr>
<td>Total protein 5.9 g/dL</td>
<td>IgM 64 mg/dL</td>
<td>Sputum</td>
</tr>
<tr>
<td>Albumin 3.3 g/dL</td>
<td>Anti-nuclear antibody &lt;160</td>
<td>Stool</td>
</tr>
<tr>
<td>AST 1104 IU/L</td>
<td>Hepatitis B surface antigen (-)</td>
<td></td>
</tr>
</tbody>
</table>


The lymphocyte stimulation testing for acetaminophen was positive, and according to the criteria for drug-induced liver injury (DILI) (8), the score for our patient was 10, in-
well-known as a cause of DILI, inducing liver damage. Other drugs could be the causal agent. Acetaminophen is recognized on the criteria for DILI (8), although it is possible that such as repeated doses and receiving the highest score possible on the criteria for DILI, indicating a high probability of DILI. Almost all the clinical findings suggested a diagnosis of DILI due to acetaminophen, but the symptoms of pleural effusion, elevated procalcitonin levels and hyponatremia were atypical for drug-related liver failure.

We discontinued all drugs the patient was taking prior to admission at our hospital. After receiving treatment with neo-minophagen C, cefmetazole and thrombomodulin, the pleural and pericardial effusions rapidly diminished, and the patient’s liver enzyme levels normalized.

Discussion

DILI is a major cause of acute liver injury and may induce serious liver injury. The causal drugs in DILI vary, and reports of DILI associated with dietary supplements and Chinese herbal drugs have recently increased (9). Although our patient had received treatment with numerous drugs before admission to our hospital, acetaminophen was suspected as the most likely causal agent based on the clinical course, such as repeated doses and receiving the highest score possible on the criteria for DILI (8), although it is possible that other drugs could be the causal agent. Acetaminophen is well-known as a cause of DILI, inducing liver damage through its metabolite N-acetyl-p-benzoquinone imine (10).

The clinical presentation of DILI varies, ranging from an asymptomatic elevation of the hepatic enzyme levels to fulminant hepatic failure. General malaise is the most frequent symptom, followed by jaundice, anorexia, fever, nausea, pruritus and subsequent skin rash (9). Conversely, symptoms such as marked ascites, pleural effusion and hyponatremia were difficult to explain by DILI alone in the present case although the liver damage was severe. Moreover, the patient had an elevated level of procalcitonin despite negative findings for all laboratory cultures.

These findings required us to consider other potential causes affecting the clinical presentation in the present case. We therefore checked for and confirmed HHV-6 reactivation. HHV-6 reactivation is an integral part of DIHS (6, 7) and a severe drug-induced adverse reaction. The diagnosis of typical DIHS can be confirmed if the following 7 criteria are fulfilled: 1) maculopapular rash developing after administration of the specific causative drug; 2) prolonged clinical symptoms; 3) fever >38°C; 4) liver dysfunction; 5) leukocytosis, atypical lymphocytosis and eosinophilia; 6) lymphadenopathy; and 7) HHV-6 reactivation. The presence of 5/7 criteria is indicative of atypical DIHS (10).

Drugs commonly associated with DIHS include antiepileptic drugs, diaphenylsulfone, allopurinol, minocycline and mexiletine (10). One case of suspected DIHS associated with acetaminophen has been previously reported (11). The present case did not satisfy the criteria for DIHS due to the absence of rash. Thus, the present case is worthy of reporting because DILI with diverse findings due to HHV-6 reactivation is rarely seen. DIHS may be accompanied by numerous systemic complications, including encephalitis, pneumonia, pancreatitis, eosinophilic colitis or esophagitis and myocarditis (7, 12, 13). HHV-6 reactivation is one criterion for DIHS, and severe liver dysfunction in DIHS is more frequent with HHV-6 reactivation than without (14). Moreover, a relapse of high fever and liver dysfunction is also more frequent with HHV-6 reactivation than without. HHV-6 reactivation may have also induced diverse symptoms in our patient. In fact, some reports have described HHV-6 reactivation after drug administration inducing marked pleural effusion, ascites and hyponatremia (15-17).


