Case Report

Successful treatment of pediatric acute liver failure with steroids

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Abstract: Acute liver failure is a devastating disease in children and has been treated supportively with or without liver transplantation for decades. Indeterminate hepatitis causes nearly half the cases of pediatric acute liver failure, which may be a different cause than in adults. Immune dysregulation may play a role in the pathogenesis, and steroids are considered a possible treatment choice for indeterminate hepatitis. Nevertheless, considering side effects such as sepsis, it remains a difficult decision to initiate treatment. Here, we present a young girl with indeterminate pediatric acute liver failure whose clinical course seemed irreversible and for whom liver transplantation seemed inevitable. However, with the identification of CD8+ T-cell predominance on immunohistochemical staining, the patient finally responded well to intravenous immunoglobulin and methylprednisolone therapy. This case offers helpful information regarding when to administer steroids in pediatric acute liver failure.

Keywords: Indeterminate pediatric acute liver failure, steroids, immune dysregulation

Introduction

Acute liver failure is a major cause of pediatric liver transplantation. The underlying etiology of acute liver failure is diversified, and the outcome varies depending on diagnostic group. The causes include the following: paracetamol intoxication, drug-induced hepatitis, viral hepatitis, autoimmune hepatitis, metabolic disease, and mitochondrial disease. However, nearly half of cases are attributed to indeterminate hepatitis, which has no definite treatment and an unfavorable prognosis [1, 2]. Patients usually receive supportive care and are closely monitored to see if liver function spontaneously recovers. If the disease progresses to the point where hepatocytes fail to regenerate, timely liver transplantation is recommended. Steroid treatment for acute liver failure was introduced in the 1950s [3]. Researchers hypothesized that steroids could benefit patients with autoimmune hepatitis or autoimmune-like hepatitis, such as drug-induced hepatitis and indeterminate hepatitis. Although studies in adults have failed to reveal consistent benefits from such treatment in adults [4, 5], indeterminate hepatitis with acute liver failure in children may be different from that in adults. Immune dysregulation has been considered the underlying pathogenesis of indeterminate pediatric acute liver failure (iPALF), and the efficacy of steroids in children with features of immune dysregulation has been under investigation. Here, we report a case of iPALF successfully treated with intravenous immunoglobulin (IVIG) and intravenous methylprednisolone therapy.

Case report

A 20-month-old healthy girl started excreting tea-colored urine and intermittent clay-colored stool 1 week before admission to our hospital. Three days before her admission, she developed jaundice and was brought to a local hospital for help. Physical examination confirmed jaundice and mild fever, and laboratory data revealed elevated levels of liver enzymes and serum bilirubin. Further, she was transferred to
our emergency department for diagnosis and treatment. At the emergency department, she had a body temperature of 38.4°C, tachycardia (140 bpm), and low blood pressure (87/51 mmHg). She was alert and her capillary refilling time was less than 2 s. Palpation revealed hepatomegaly without splenomegaly, and she had icteric sclera and yellowish discoloration of the skin. No spider angiomata or caput medusa was noted. The laboratory data revealed elevated levels of transaminases (alanine aminotransferase [ALT], 1748 IU/L and aspartate aminotransferase, 1709 IU/L), total bilirubin (6.8 mg/dL), direct bilirubin (3.9 mg/dL), prothrombin time (PT, 16.7 s), international normalized ratio (INR, 1.72), and ammonia (85 µg/dL). No drowsiness, altered sleep habits, or tremors were observed. We admitted her for further evaluation and treatment of suspected acute fulminant hepatitis. She was administered supportive treatment with vitamin K and ursodeoxycholic acid. Abdominal sonography revealed moderate hepatomegaly with increased echogenicity and minimal ascites; however, no splenomegaly or vascular anomaly was found. A virologic survey for hepatitis A, B, and C viruses, herpes simplex virus, Epstein-Barr virus, and cytomegalovirus revealed negative results. The inborn errors of metabolism, Wilson disease and autoimmune hepatitis were ruled out. We performed diagnostic liver biopsy on the fifth day of hospitalization and found portal and pericellular hepatitis with focal confluent necrosis confirming our diagnosis of acute fulminant hepatitis (Figure 1A). Further, diffused lymphocytic infiltration was noted and immunohistochemical staining demonstrated a predominance of CD8+ T cells (Figure 1B). Unfortunately, the patient experienced post-procedure bleeding with decreased blood pressure and tachycardia. Whole blood, packed RBCs, and fresh frozen plasma were transfused to the patient and the vital signs were stabilized. However, the symptoms became worse on the eighth day of hospitalization due to the deterioration of the liver function with total bilirubin 11.1 mg/dL, direct bilirubin 5.9 mg/dL, and PT 20.3 s (INR 2.11). The patient’s pediatric end-stage liver disease score was 18 points. Diagnosis of acute liver failure was established and iPALF was considered due to the negative results of the etiological survey. We started preparations for living-related liver transplantation with a surgeon. Before the liver transplantation, we attempted to treat the patient with intravenous immunoglobulin (IVIG) and steroids after discussing the risk and benefits of the treatment with her parents. She was administered one dose of IVIG (1 g/kg/dose) on the ninth day of hospitalization and intravenous methylprednisolone pulse therapy (20 mg/kg/day) for 3 days with gradual tapering to 5 mg/kg/day and then oral prednisolone (2 mg/kg/day) before discharge. The patient tolerated the treatment well with no signs of infection. After treatment for 2 days, laboratory data indicated improvement in the liver function (Figure 2). The patient was discharged 9 days after the steroid treatment. After discharge, she received a course of steroids for 43 days, tapering with oral steroids (half the dose every week). The PT, total bilirubin, and ALT levels were found to be normal on days 9, 43, and 71 after the initiation of the steroid treatment (Reference ranges: PT, 9.5-11.7 s; alanine aminotransferase, 10-50 U/L; and total bilirubin, 0.2-1.2 mg/dL). Monthly follow-ups were conducted during the first year and pancytopenia was detected after 6 months of the treatment. Fortunately, pancytopenia was resolved spontaneously during follow-ups without requirement of any intervention. Further, we followed her condition every 6 months for 2 years. No episodes of cytopenia were noted and the PT, total bilirubin, and ALT levels have remained normal to date.

Discussion

Based on increasing knowledge regarding indeterminate hepatitis, hepatitis in children seems
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Liver transplantation is the last choice for treating acute liver failure because mortality and posttransplantation complications, including long-term use of immunosuppressants, must be considered. Given the poor prognosis of iPALF, studies have focused on rescue treatment before liver transplantation. Immune dysregulation may play a role in the pathogenesis of iPALF, as demonstrated by studies on hemophagocytic lymphohistiocytosis [10, 11]. Overt systemic inflammation from uncontrolled CD8+ T-cell activation may be the cause and may interfere with hepatocyte regeneration by affecting pathways such as those that activate sinusoidal endothelial cell progenitor cells [10]. One study revealed that patients exhibiting a CD8+ T-cell predominant stain in liver histopathological tests may benefit from steroid treatment [12]. Other immunophenotypes, such as elevated sIL2Rα, decreased natural killer cell function, and decreased CD4/CD8 ratio, may help differentiate patients with immune dysregulation and identify appropriate immunosuppressive therapies [10, 12, 13].

An observational study that included 380 patients with iPALF from the Pediatric Acute Liver Failure Study Group (PALFSG) [2], which is a multicenter collaborative study formed in 1999, revealed a native liver survival rate of approximately 52% (Table 1). However, the intervention for iPALF in the study was variable, and steroids were not the standardized treatment. A recent study that investigated steroid treatment for 28 patients with iPALF during 2009-2018 showed patient improvement after steroid therapy, although the native liver survival rate was not different from those found in other studies [14]. A limitation of the study was that at the time of treatment decisions, no standardized diagnostic criteria were available for the immune dysregulation phenotype. Furthermore, patients received different corticosteroid dosing regimens, which may have influenced treatment responses. The study was
### Table 1. Steroid treatment for indeterminate pediatric acute liver failure

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Year</th>
<th>case</th>
<th>Immune dysregulation</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>McKenzie [12]</td>
<td>United states</td>
<td>2012–2013</td>
<td>7</td>
<td>Serum immune markers, liver biopsy</td>
<td>Intravenous immunoglobulin plus methylprednisolone</td>
<td>Native liver survival (3/7, 42%)</td>
</tr>
<tr>
<td>Li [2]</td>
<td>United states</td>
<td>1999–2010</td>
<td>380</td>
<td>NA</td>
<td>NA</td>
<td>Native liver survival (195/380, 52%)</td>
</tr>
<tr>
<td>Chapin [14]</td>
<td>United states</td>
<td>2009–2018</td>
<td>28</td>
<td>NA</td>
<td>methylprednisolone</td>
<td>Native liver survival (13/28, 46%)</td>
</tr>
</tbody>
</table>

Native liver survival means patient survival without liver transplantation. Information of immune dysregulation phenotype is not applicable due to incomplete data or lack of data. Information of treatment for 380 patients is not mentioned although steroids comprise part of the treatment.
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also conducted in centers that were part of the PALFSG, and it disclosed a trend for patients with iPALF to undergo a survey for immune dysregulation phenotypes and empirical steroid treatment. However, randomized controlled clinical trials are required to confirm the risks and benefits of steroids for iPALF.

We successfully treated our patient with IVIG and intravenous pulse methylprednisolone therapy followed by oral prednisolone tapering. We provided the patient with a higher methylprednisolone dose (20 mg/kg/day) than most studies, which have used 0.5-10 mg/kg/day and have yielded differing results [14]. Immunohistochemical staining of our patient demonstrated diffused portal and periportal inflammation with a predominance of CD8+ T-cells (Figure 1A, 1B). This means that a cytotoxic T-cell predominant inflammation occurred in our patient and it might be resulted from a previous infection. This finding was consistent with related research and indicated that some benefit would possibly accrue from steroid treatment [12]. The changes of ALT levels, total bilirubin, and prothrombin time after therapy were so evident that we believed the strong effects of steroids in our patient (Figure 2). The INR, total bilirubin and ALT levels were found to be normal on days 9, 43, 71 after treatment. To our disappointment, even though we used a higher dose of methylprednisolone than related research (2 mg/kg/day), the time to INR normalization was not shorter than related research (average time: 6.5 days) [12]. Therefore, the dose of methylprednisolone should be adjusted cautiously according to effects and unwanted side effects. Studies have presented only one case of severe infection after steroid treatment [14]. Our patient also tolerated the treatment well and without any infection. Some patients with iPALF may present with features of pancytopenia or aplastic anemia unrelated to liver transplantation. For those patients, special care is required to prevent infections due to neutropenic status.

In summary, steroid treatment reversed the liver failure of our patient. Through treatment of our patient, we also confirmed that patients exhibiting a predominance of CD8+ T-cells on liver histology benefit from immunosuppressive therapies. With updated knowledge and a better understanding of it, the evaluation and treatment of iPALF can become more precise and efficacious in the future.

Disclosure of conflict of interest

None.

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