Severe acute hepatitis and cold agglutinin-related hemolytic anemia secondary to prime infection with Epstein-Barr virus

Guillermo Ontanilla-Clavijo¹, Julia Praena-Segovia², Álvaro Giráldez-Gallego¹, Elisa Cordero-Matía² and José Manuel Sousa-Martín¹

Clinical Management Units of ¹Digestive Diseases and ²Infectious Diseases, Microbiology and Preventive Medicine. Hospital Universitario Virgen del Rocío. Sevilla, Spain

ABSTRACT

Epstein-Barr virus, a member of the *Herpesviridae* family, is responsible for the infectious mononucleosis clinical syndrome, which mainly includes the pharyngitis, fever, and lymphadenopathy triad after incubation for 30-50 days. The liver is involved in 80-90% of patients in a self-limiting transient manner, with jaundice being much more uncommon (5%). From a hematological standpoint it may manifest aplastic anemia, neutropenia, and thrombocytopenia. We report a case of infectious mononucleosis that included severe acute hepatitis and was associated with severe hemolytic anemia secondary to cold agglutinins. After exclusion of other etiologies, and given the clinical suspicion of the above association, which was later confirmed by lab tests, empiric therapy was initiated with antiviral agents (aciclovir + valganciclovir) and corticoids, which resulted in a progressive clinical improvement until complete remission. Therefore, we believe that this case report will reinforce the clinical evidence in support of the above combined therapy for serious infectious mononucleosis as a step prior to liver transplantation.

Key words: Epstein-Barr virus. Acute hepatitis. Hemolytic anemia.

INTRODUCTION

Epstein-Barr virus, a member of the *Herpesviridae* family, is responsible for the infectious mononucleosis clinical syndrome, which mainly consists of the pharyngitis, fever, and lymphadenopathy triad after incubation for 30-50 days (1). It is transmitted through saliva, and infects approximately 90-95% of the adult population. During childhood, the infection is usually asymptomatic or mild, but adults present with the aforementioned picture in over 50% of cases (1). Liver involvement usually occurs in 80-90% of patients with self-limiting transient disease, which manifests as mild transaminase increases < 2-3 x ULN (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), whereas jaundice is much more uncommon (5%) (2). On occasions this involvement may be severe and even require liver transplantation for acute liver failure (3). From a hematological perspective, the condition may present with hemolytic anemia, aplastic anemia, neutropenia, and thrombocytopenia. During the course of disease cold agglutinins may develop in up to 60% of patients (1) rarely resulting in hemolytic anemia, 0.5-3% (4,5). We report here a case of infectious mononucleosis that developed severe acute hepatitis and was associated with severe hemolytic anemia secondary to cold agglutinins, which represent two uncommon findings.

CASE REPORT

A 15-year-old female with an unremarkable medical history and no risk factors for liver disease presented initially with a headache, odynophagia, cervical adenopaties, eyelid edema, and a fever of 39 °C. She was admitted on the fourth day. Blood tests were normal, blood culture was negative, and viral serology revealed negative heterophile (Paul-Bunnell) antibodies and negative IgM antibodies against both Epstein-Barr virus (EBV) and cytomegalovirus (CMV). Liver chemistry abnormalities developed after 72 hours with AST at 270 U/l (10-37), ALT at 233 U/l (10-40), gamma-glutamyl transpeptidase (GGT) at 157 U/l (10-50), alkaline phosphatase (AP) at 382 U/l (40-130), total bilirubin (TB) at 2.3 mg/dl (0.1-1.2), international normalized ratio (INR) at 1.2 (0.8-1.3), and a notable decrease in hemoglobin (Hb) from 13.1 to 11.0 g/dl (11.8-15.7). The patient progressed unfavorably with a marked bilirubin increase to 14.8 mg/dl (direct bilirubin 13.8 mg/dl [0-0.35]) and further Hb decrease to 8.9 g/dl, as well as clearly altered coagulation with INR at 2.1, whereupon she was transferred to our institution for potential liver transplantation.

Abdominal ultrasound showed low-volume ascites and pronounced splenomegaly. Negative results were obtained from the etiological study, which included serology for hepatotropic viruses (HAV, HBV, HCV [viral load], her-
pes simplex virus, herpes 6 virus, EBV, CMV), human immunodeficiency virus (HIV), and bacteria (Rickettsia sp., Leishmania sp., Leptospira sp., Coxiella burnetii), as well as autoimmune processes and potential blood neoplasms. Peripheral blood smears revealed normocytic anemia with activated lymphocytes and hemolysis, with positive direct Coombs for cold agglutinins; a bone marrow biopsy ruled out macrophage activation. Concurrently, blood EBV levels were determined using PCR (polymerase chain reaction), which revealed a viral load of 62,445 copies/ml, with subsequent conversion to anti-EBV IgM and IgG (ELISA), which confirmed the diagnosis of acute EBV infection with severe acute hepatitis in association with cold agglutinin-related hemolytic anemia. Treatment was initiated with aciclovir (10 mg/kg/8 hrs, IV) and prednisone (60 mg/24 hrs, PO) on day 13 after symptom onset. Progressively since empiric therapy onset, liver function parameters and anemia improved. After ten days on antiviral therapy (five days on aciclovir and five days on valaciclovir [1,000 mg/8 hrs, PO]) and prednisone in a descending regimen, the lab parameters improved, as shown in table I. The patient remains asymptomatic after 12 months of follow-up.

**DISCUSSION**

This is a rare case of severe acute hepatitis secondary to EBV infection and associated with cold agglutinin-related hemolytic anemia. Although many clinical case reports describe severe EBV-associated hepatitis, an association with this type of anemia has been seldom described previously (6,7). Between 80% and 90% of patients with EBV-related mononucleosis syndrome have mild transaminase elevations, but only 5% manifest jaundice and fewer exhibit severe liver involvement (2,8,9). Similarly, the incidence of hemolytic anemia from cold agglutinins, anti-I, and anti-triphosphate isomerase antibodies (4,5) is 0.5%-3.0%, and occurs within two weeks of disease onset (10). Importantly, anti-VCA detection has a sensitivity of 88-92%, thus due to initial clinical suspicions and possible false negative results, an EBV PCR was performed, which confirmed the diagnosis.

Furthermore, the use of antivirals and corticosteroids proved effective in this case. Few cases reported in the literature have severe disease requiring antiviral agents, and we only found two cases where valganciclovir was used (11,12). Regarding the controversial use of corticosteroids for severe forms, a review of 45 severe EBV infection cases reported between 1982 and 2009 showed that the mortality was higher in the group of subjects receiving antivirals only, whereas those who received associated immunosuppressants had better clinical outcomes (13). In our patients, corticosteroids were used based on the autoimmune component of anemia, as described elsewhere (19), but the extent to which they may have contributed to relieve liver involvement remains unknown. Therefore, we believe that this report will add to the body of clinical evidence supporting this combination therapy for severe infection with EBV as a previous step to liver transplantation.

### Table I

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 7</th>
<th>Day 9</th>
<th>Day 13 Aciclovir Prednisone</th>
<th>Day 16</th>
<th>Day 24 Valaciclovir Prednisone</th>
<th>Day 45</th>
</tr>
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<tbody>
<tr>
<td>Lymphocytes (x 10⁹/l)</td>
<td>1,780</td>
<td>3,000</td>
<td>2,984</td>
<td>3,795</td>
<td>3,730</td>
<td>3,130</td>
<td>5,600</td>
<td>4,190</td>
<td>2,350</td>
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<tr>
<td>Hb (g/dl)</td>
<td>14</td>
<td>11.7</td>
<td>10.3</td>
<td>8.9</td>
<td>8.3</td>
<td>7.2</td>
<td>8</td>
<td>11.6</td>
<td>12</td>
</tr>
<tr>
<td>GPT (IU/l)</td>
<td>19</td>
<td>233</td>
<td>463</td>
<td>295</td>
<td>168</td>
<td>95</td>
<td>101</td>
<td>87</td>
<td>29</td>
</tr>
<tr>
<td>GOT (IU/l)</td>
<td>38</td>
<td>270</td>
<td>463</td>
<td>261</td>
<td>143</td>
<td>100</td>
<td>73</td>
<td>40</td>
<td>22</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>0.9</td>
<td>2.3</td>
<td>8.8</td>
<td>13.8</td>
<td>12.3</td>
<td>3.2</td>
<td>2.4</td>
<td>2.2</td>
<td>0.84</td>
</tr>
<tr>
<td>Direct bilirubin (mg/dl)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>13.2</td>
<td>10.7</td>
<td>2.2</td>
<td>2.3</td>
<td>1.8</td>
<td>NA</td>
</tr>
<tr>
<td>INR</td>
<td>1.06</td>
<td>1.2</td>
<td>NA</td>
<td>NA</td>
<td>2.1</td>
<td>NA</td>
<td>0.95</td>
<td>0.95</td>
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</table>

NA: Not available.

**REFERENCES**