Haemophagocytic lymphohistiocytosis associated with fulminant hepatitis and multiorgan failure following primary Epstein–Barr virus and herpes simplex virus type 1 infection

Claudia Honsig, Sandra Beinhardt, Josef Tomasits, Hans Peter Dienes

SUMMARY
We present a case of severe fatal hepatitis in a young patient presumably triggered by two ubiquitous viral diseases which occurred in close succession. This case is unusual because of the exceptional chronological sequence of primary Epstein–Barr virus and herpes simplex virus type 1 infection causing systemic immune dysregulation associated with rapidly developing liver failure and consecutive multiorgan failure. Clinical, laboratory and histopathological findings indicated the development of secondary haemophagocytic lymphohistiocytosis triggered by these closely succeeding viral primary infections.

BACKGROUND
Haemophagocytic lymphohistiocytosis (HLH) is a potentially fatal syndrome characterised by an uncontrolled hyperinflammatory response with heterogeneous aetiology.1 2 HLH is categorised as primary HLH (or familial HLH) in patients with underlying genetic causes and as secondary HLH (SHLH) when family history or known genetic causes are absent. SHLH is associated with a wide spectrum of underlying conditions: viral infections have been reported as the most common triggers (29%), followed by other infections, malignancies, autoimmune disorders and immune suppression.3 Among viral infections, Epstein–Barr virus (EBV) has been described as the most frequent virus that associates with SHLH, herpes simplex virus type 1 as the next most common virus.4 5 In healthy, immunocompetent persons at any age, EBV and herpes simplex virus (HSV) infection are usually self-limiting, rarely lead to complications and are both uncommon causes of acute liver failure (ALF).6 7 8 As expected, postmortem analysis of small tissue samples. Particularly high concentrations of HSV1 DNA were detected in liver and spleen tissues by PCR revealed HSV1 and EBV DNA in all of the samples. Particularly high concentrations of HSV1 DNA were detected in liver and spleen tissues (8.40E+06 and 7.20E+06 copies/mg, respectively). EBV DNA concentration in these tissues was 1.76E+03 copies/mg (liver) and 7.60E+04 copies/mg (spleen).

As expected, postmortem analysis of small tissue samples of liver, spleen, kidney and gallbladder by PCR revealed HSV1 and EBV DNA in all of the samples. Particularly high concentrations of HSV1 DNA were detected in liver and spleen tissues (8.40E+06 and 7.20E+06 copies/mg, respectively). EBV DNA concentration in these tissues was 1.76E+03 copies/mg (liver) and 7.60E+04 copies/mg (spleen).
Table 1  Course of laboratory and virological findings during hospital stay

<table>
<thead>
<tr>
<th>Day of hospitalisation</th>
<th>1</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tbody>
<tr>
<td>ALT (U/L)</td>
<td>375</td>
<td>822</td>
<td>1213</td>
<td>1831</td>
<td>2650</td>
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<tr>
<td>AST (U/L)</td>
<td>475</td>
<td>1929</td>
<td>3387</td>
<td>6319</td>
<td>11 150</td>
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<tr>
<td>γGT (U/L)</td>
<td>198</td>
<td>230</td>
<td>248</td>
<td>336</td>
<td>326</td>
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<tr>
<td>ALP (U/L)</td>
<td>263</td>
<td>352</td>
<td>352</td>
<td>570</td>
<td>648</td>
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<tr>
<td>Total bilirubin (mg/dL)</td>
<td>1.9</td>
<td>1.9</td>
<td>3.1</td>
<td>4.32</td>
<td>4.32</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>1844</td>
<td>7058</td>
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<tr>
<td>Creatinine (mg/dL)</td>
<td>0.8</td>
<td>0.9</td>
<td>4.29</td>
<td>4.01</td>
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</tr>
<tr>
<td>WCC (G/L)</td>
<td>11.2</td>
<td>6.32</td>
<td>11.5</td>
<td>10.5</td>
<td>6.5</td>
</tr>
<tr>
<td>HgB (g/dL)</td>
<td>12</td>
<td>11.5</td>
<td>10.5</td>
<td>6.5</td>
<td>6.5</td>
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<tr>
<td>Platelet (G/L)</td>
<td>130</td>
<td>122</td>
<td>113</td>
<td>23</td>
<td>23</td>
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<tr>
<td>sCD25 (U/mL)</td>
<td></td>
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<td>338.6</td>
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<tr>
<td>HSV-1 (cp/mL serum)</td>
<td>1.48E+07</td>
<td>1.88E+08</td>
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<tr>
<td>Anti-HSV IgM</td>
<td>Negative</td>
<td>Negative</td>
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</tr>
<tr>
<td>Anti-HSV IgG</td>
<td>Negative</td>
<td>Borderline/positive</td>
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<tr>
<td>EBV (cp/mL serum)</td>
<td>1.77E+04</td>
<td>2.14E+04</td>
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<tr>
<td>Anti-EBV VCA IgM</td>
<td>Positive</td>
<td>Positive</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Anti-EBV VCA IgG</td>
<td>Positive</td>
<td>Positive</td>
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<tr>
<td>Anti-EBV VCA IgG avidity</td>
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<tr>
<td>Anti-EBV EBNA1</td>
<td>Negative</td>
<td>Borderline/negative</td>
<td></td>
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</table>

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; EBNA, Epstein–Barr virus nuclear antigen 1; EBV, Epstein–Barr virus; HgB, haemoglobin; HSV, Herpes Simplex virus type 1; IgG, immunoglobulin G; IgM, immunoglobulin M; VCA, viral capsid antigen; WCC, white cell count; γGT, γ-glutamyltransferase.

Figure 1  (A) Large confluent areas of necrosis without zonal binding (H&E staining, ×60). (B) In the margin of the necrosis, hepatocytes display nuclei with typical viral inclusions (arrow). The necroinflammatory infiltrate consists of lymphocytes and a lot of polymorph nuclear leucocytes (H&E staining, ×400). (C) HSV1-infected hepatocytes detected with immunoperoxidase staining (×240). (D) In some areas of the liver, typical features of EBV hepatitis with abundant lymphocytic infiltrates in the sinusoids were still present (H&E staining, ×240). (E) EBV LMP1 detected by immunostaining with alkaline phosphatase, ×240 (arrow). (F) After extraction of EBV DNA and subsequent PCR, viral DNA could be demonstrated. (a and f) DNA ladder; (b) empty; (c) patient; (d) negative control; (e) positive control.
Histopathology of the postmortem liver samples displayed the typical necrosis pattern of HSV hepatitis with confluent necroses in a geographical pattern without zonal binding (figure 1A) and a mixed reactive inflammatory infiltrate including a substantial number of polymorph nuclear leucocytes (figure 1B). Hepatocytes showed typical nuclear inclusions with the virus (figure 1B). Immunoperoxidase staining confirmed the diagnosis of HSV1 hepatitis (figure 1C). In some areas, the characteristic features of EBV-hepatitis could still be found (figure 1D). The diagnosis was confirmed by the detection of EBV LMP1 by alkaline phosphatase staining (figure 1E) and the detection of EBV by PCR after extraction of EBV DNA from the liver tissue (figure 1F). In portal macrophages, a trapping of erythrocytes was found and in the sinusoids the activated Kupffer cells showed a conspicuous erythropagocytosis, consistent with SHLH (figure 2).

These characteristic histopathological changes in liver tissue along with the laboratory and clinical findings indicated the initiation of SHLH by these two closely succeeding viral primary infections. Unfortunately, histopathological investigation of bone marrow and spleen, as suggested in the diagnostic guidelines in liver tissue suggest the diagnosis of SHLH based on the HLH-2004 criteria. In our patient serological findings indicated that primary EBV infection preceded primary HSV infection. The impairment of the immune response caused by primary EBV infection, especially the suppression of the T-cell function, may have enabled the vicious course of primary HSV1 infection in a previously healthy young adult, and both the viruses may have been subsequent triggers for the hyperinflammatory syndrome.

Viral infections have been reported as common triggers of SHLH, and the possible synergistic effects of two viral infections in the initiation of SHLH have been described in a previous report of SHLH after the close occurrence of EBV and Hepatitis A infection. SHLH after EBV or HSV1 infection has been described previously, and also induction of SHLH by coinfection with EBV and HSV1 has been observed before in two patients. In these cases of SHLH following EBV and HSV1 coinfection, however, EBV viraemia was due to reactivation of latent infection. Therefore, initiation of SHLH by primary infections with EBV and HSV1 seems to represent a unique feature of our case.

Diagnosing HLH or SHLH as defined by the Histiocyte Society is challenging because of its rare occurrence, variable presentation and non-specific findings and should be suspected routinely in patients with unexplained multiorgan failure. Early diagnosis and appropriate treatment including supportive intensive care, elimination of the triggers and suppression of the inflammatory response are essential to improve the outcome of this syndrome. Our case highlights that in a patient with unexplained fever and elevated liver function tests, HSV in addition to EBV and cytomegalovirus (CMV) should be taken into consideration as causative agent. As reported before, the absence of mucocutaneous lesions—which initially was the case in our patient—does not exclude HSV hepatitis.

Owing to the rapid and malignant course of the disease in our patient, the diagnosis of SHLH could only be established retrospectively. Although the severe immune dysregulation may have been untreatable already on initial admission, we would like to emphasise that a delay in diagnosis and initiation of specific antiviral therapy and immunosuppressive treatment in addition to supportive intensive care may have contributed to the poor outcome.

**OUTCOME AND FOLLOW-UP**

In summary, laboratory, virological and pathological findings together with the clinical presentation suggest multiorgan failure due to SHLH initiated by EBV and closely succeeding HSV1 primary infection in a previously healthy young person.

**DISCUSSION**

Systemic immune dysregulation triggered by an external agent has been described as a cause of a disease continuum including HLH, sepsis, multiple organ dysfunction syndrome and systemic hyperinflammatory syndrome. Here we report a case of foudroyant immune dysregulation following closely succeeding viral primary infections with EBV and HSV1. Clinical findings (fever, splenomegaly), laboratory parameters (cytopenia in two blood cell lines, elevated ferritin and sCD25) and haemophagocytosis in liver tissue suggest the diagnosis of SHLH based on the HLH-2004 criteria. In our patient serological findings indicated that primary EBV infection preceded primary HSV infection. The impairment of the immune response caused by primary EBV infection, especially the suppression of the T-cell function, may have enabled the vicious course of primary HSV1 infection in a previously healthy young adult, and both the viruses may have been subsequent triggers for the hyperinflammatory syndrome.

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**Learning points**

- Primary infection with two different herpes viruses may occur simultaneously or in close succession, adversely affecting the course of the disease.
- Herpes simplex virus (HSV) and Epstein–Barr virus (EBV) should be considered in the differential diagnosis of fulminant hepatitis.
- Early virological diagnosis and immediate initiation of specific antiviral therapy is of high importance.
- EBV and HSV may cause severe disease in immunocompetent persons and secondary haemophagocytic lymphohistiocytosis should be suspected routinely when severe systemic illness develops.
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Contributors CH is responsible for acquisition of patient data, study of literature, virological diagnosis, analysis and interpretation of findings and creating the manuscript. SB is responsible for access to medical history, critical discussion and revision. JT is responsible for access to medical history, critical discussion and revision. HPD is responsible for pathological examination of the liver, photographic documentation (Figure 1A–D), discussion of the case and critical review of the manuscript.

Competing interests None declared.

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