Cytokine Profile in Fatal Human Immunodeficiency Virus-Tuberculosis-Epstein-Barr Virus-Associated Hemophagocytic Syndrome

Hemophagocytic syndrome (HPS), characterized by fever, lymphadenopathy, hepatosplenomegaly, and pancytopenia, results from the abnormal function and proliferation of macrophages and their uncontrolled phagocytosis of various reticuloendothelial cell lines. Secondary (or “reactive”) HPS is associated with infection, malignancy, or autoimmune diseases, whereas primary HPS has no identifiable cause and may be genetic. Reactive HPS has been described in association with infectious agents, but Epstein-Barr virus (EBV) is the most commonly associated infection, and EBV-associated HPS is almost universally fatal. At present, there is no diagnostic or treatment consensus, so HPS is generally dealt with on a case-by-case basis, depending on the associated infection(s) identified.

Report of a Case. A 46-year-old Chinese man diagnosed as having human immunodeficiency virus (HIV) infection 8 months earlier presented with fever, lower back pain, bilateral lower limb numbness, and foot drop. He had been receiving highly active antiretroviral treatment in the 4 months before admission, during which his CD4 cell count had increased (37/μL to 204/μL) and his HIV load decreased (130 000 to 820 copies/mL). A magnetic resonance image of his lower spine revealed an epidural mass over the L5 lamina, compressing the thecal sac, and findings from a computed tomography–guided biopsy showed caseating granulomatous inflammation, although mycobacterial cultures were negative. Antimycobacterial therapy was started.

Progressive pancytopenia with high fever (38.8°C) developed over the next 4 weeks. A bone marrow examination confirmed a histological diagnosis of HPS. Again, results from mycobacterial staining and cultures were negative. A real-time quantitative EBV assay showed assistance with the diagnosis and treatment of patients with this disease.

Otha Myles, MD
Glenn W. Wortmann, MD
James F. Cummings, MD
R. Vincent Barthel, MD, MPH
Sugat Patel, MD
Nancy F. Crum-Cianflone, MD, MPH
Nathan S. Negin, MD
Peter J. Weina, MD, PhD
Christian F. Ockenhouse, MD, PhD
Daniel J. Joyce, DO
Alan J. Magill, MD
Naomi E. Aronson, MD
Robert A. Gasser Jr, MD

Correspondence: Dr Myles, Division of Retrovirology, Walter Reed Army Institute of Research, 1 Taft Ct, Ste 250, Rockville, MD 20850 (omyles@hivresearch.org).

Author Contributions: Study concept and design: Myles, Wortmann, Cummings, and Gasser. Acquisition of data: Myles, Wortmann, Cummings, Barthel, Patel, Crum-Cianflone, Negin, Weina, Ockenhouse, Joyce, Magill, Aronson, and Gasser. Analysis and interpretation of data: Myles, Wortmann, Cummings, Barthel, Crum-Cianflone, Negin, Weina, Ockenhouse, Joyce, Magill, Aronson, and Gasser. Drafting of the manuscript: Myles, Wortmann, Patel, Magill, and Gasser. Critical revision of the manuscript for important intellectual content: Myles, Wortmann, Cummings, Barthel, Crum-Cianflone, Negin, Weina, Ockenhouse, Joyce, Magill, Aronson, and Gasser. Administrative, technical, and material support: Myles, Cummings, Pattel, Negin, Weina, Ockenhouse, and Aronson. Study supervision: Myles, Wortmann, Crum-Cianflone, Magill, and Gasser.

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a plasma EBV DNA rise from 2062 to 26 480 copies/mL over 3 weeks. No other viruses were detected in the plasma. A course of intravenous immunoglobulin, foscarnet sodium (3 g/d), and etoposide (150 mg/d for 5 days) was given. The EBV DNA became undetectable after 1 week. To reduce adverse effects, highly active antiretroviral treatment was discontinued 5 weeks after starting foscarnet therapy. The HIV load at this time was undetectable (<400 copies/mL).

The patient’s condition, however, deteriorated with fulminant sepsis and multiorgan failure, requiring intensive care. Three sets of blood cultures from different sites grew Staphylococcus epidermidis. Although the patient responded well to empirical broad spectrum antibiotics and was extubated 4 days later, he remained neutropenic, thrombocytopenic, and in renal failure and died a week later.

Because this patient’s infections (HIV, tuberculosis, and EBV) were effectively suppressed, a possible role for cytokines was investigated. Plasma Th1 cytokine interferon gamma (IFN-γ), Th1-related chemokine MIG/CXCL9, and interferon-induced protein 10 (IP-10)/CXCL10 levels were found to be markedly elevated to 103, 17, and 9 times their upper normal limits, respectively, before foscarnet treatment. After 8 days of foscarnet treatment and EBV suppression, these levels normalized. Plasma interleukin (IL)-8/CXCL8 and IL-6 levels were also elevated, approximately 7-fold, before foscarnet treatment. CXCL8, IL-6, and monocyte chemotractant protein 1 (MCP-1)/CCL2 levels continued to increase while the patient was receiving foscarnet (Table). More details of the methods and results for this case report can be found online at http://ihome.cuhk.edu.hk/~b576778/Online%20Appendix.pdf.

Comment. Patients with advanced HIV infection may have increased plasma levels of IFN-γ and IL-2, as well as macrophage chemokines MIP-1α/CCL3 and MIP-1β/CCL4. Epstein-Barr virus infection can induce CXCL10 expression, and CXCL9 and CXCL10 may be secreted by IFN-γ-stimulated macrophages that are overproduced in HIV infection, and CXCL-9 and CXCL10 may be secreted by IFN-γ-stimulated macrophages that are overproduced in HIV infection. A plasma EBV DNA rise from 2062 to 26 480 copies/mL 1 day before the first dose of foscarnet sodium.

Table. Plasma EBV Viral Load and Cytokine Profile of an HIV-Infected Patient With HPS in Relation to Foscarnet Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Plasma EBV, Copies/mL</th>
<th>IFN-γ, ng/L</th>
<th>IL-1β, ng/L</th>
<th>IL-6, ng/L</th>
<th>IL-10, ng/L</th>
<th>IL-12p70, ng/L</th>
<th>TNF-α, ng/L</th>
<th>CXCL8, ng/L</th>
<th>CXCL10, ng/L</th>
<th>CCL2, ng/L</th>
<th>CCL9, ng/L</th>
<th>CCL5, ng/L</th>
<th>CCL3, ng/L</th>
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<tbody>
<tr>
<td>Reference range</td>
<td>0</td>
<td>&lt; 15.6</td>
<td>&lt; 7.2</td>
<td>&lt; 3.1</td>
<td>&lt; 7.8</td>
<td>&lt; 7.8</td>
<td>&lt; 10.0</td>
<td>&lt; 5</td>
<td>202-1480</td>
<td>&lt; 10-57</td>
<td>48-482</td>
<td>4362-18 783</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>Before foscarnet treatment</td>
<td>6571-26 480ab</td>
<td>1616.9</td>
<td>&lt; 7.2</td>
<td>20.5</td>
<td>15.9</td>
<td>3.0</td>
<td>1.2</td>
<td>39.4</td>
<td>12 749.7</td>
<td>50.4</td>
<td>8357.2</td>
<td>1580.1</td>
<td>2.0</td>
</tr>
<tr>
<td>After foscarnet, second week</td>
<td>&lt; 5</td>
<td>3.9</td>
<td>&lt; 7.2</td>
<td>37.0</td>
<td>8.3</td>
<td>&lt; 1.9</td>
<td>1.2</td>
<td>157.2</td>
<td>162.2</td>
<td>224.1</td>
<td>97.1</td>
<td>1127.1</td>
<td>3.1</td>
</tr>
<tr>
<td>After foscarnet treatment, third week</td>
<td>ND</td>
<td>&lt; 7.1</td>
<td>250.3</td>
<td>9.7</td>
<td>&lt; 1.9</td>
<td>&lt; 3.7</td>
<td>461.0</td>
<td>255.0</td>
<td>640.5</td>
<td>423.5</td>
<td>783.7</td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HPS, hemophagocytic syndrome; IFN, interferon; IL, interleukin; ND, not done; TNF-α, tumor necrosis factor α.

a Increased to 26 480 copies/mL 1 day before the first dose of foscarnet sodium.

TB-EBV–induced hyper-Th1 immune response. Although foscarnet, an anti-EBV agent, would have significantly curtailed the Th1 immune response, the subsequent elevation of IL-6, CXCL8, and CCL2 may have been due to the immune restoration associated with the rising CD4 cell count. Together with any residual hyperactive Th1 cell-mediated immunity, this continued increase of IL-6, CXCL8, and CCL2 levels may have resulted in an exaggerated host immune response and fatal outcome.

This case suggests that immunosuppressive agents (ie, steroids and anticytokine antibodies) may be beneficial in such severe HPS cases and demonstrates that cytokine profiling enhances the understanding and management of immune-mediated diseases.

Chun K. Wong, PhD
Bonnie C. K. Wong, MRCP
K. C. Allen Chan, MRCP, FRCPA
Gavin M. Joynt, FCCP, FHKAM
Florence Y. H. Y. Yap, MRCP, FHKAM
Christopher W. K. Lam, PhD, FRCPath(Hon)
Nelson Lee, MRCP, FHKAM
Shui S. Lee, FRCP, FHKAM
Clive S. Cockram, MD, FRCP
Joseph J. Y. Sung, MD, PhD, FRCP
Paul K. S. Chan, MSc, MD, FRCPath
Y. M. Dennis Lo, FRCP, FRCPath
Julian W. Tang, PhD, MRCP, MRCPath

Correspondence: Dr Tang, Department of Microbiology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong SAR (julian.tang@cuhk.edu.hk).

Author Contributions: All authors had full access to all of the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Tang. Acquisition of data: C. K. Wong, B. C. K. Wong, K. C. A. Chan, Joynt, Yap, Lam, N. Lee, S. S. Lee, and Tang. Analysis and interpretation of data: C. K. Wong, B. C. K. Wong, K. C. A. Chan, Lam, N. Lee, Cockram, Sung, P. K. S. Chan, Lo, and Tang. Drafting of the manuscript: C. K. Wong, Yap, N. Lee, Cockram, and Tang. Critical revision of the manuscript for important intellectual content: B. C. K. Wong, K. C. A. Chan, and Tang.
Noroviruses are a major cause of foodborne disease outbreaks. Our primary understanding of norovirus disease manifestations stems from volunteer studies, but a norovirus outbreak at a small college provided the opportunity to delineate findings in naturally occurring illness.

Methods. On April 19, 2005, students at Worcester Polytechnic Institute (WPI), Worcester, Massachusetts, began developing gastroenteritis symptoms. During the next 48 hours, more students became ill, with most reporting symptoms the evening of April 20, 2005, after the student health clinic had closed. Ultimately, 39 students were referred to 3 local hospital emergency departments (Figure).

A systematic review of available medical records was undertaken with the Worcester Division of Public Health and approved by the institutional review boards of WPI, St Vincent Hospital, and University of Massachusetts Medical School. Inclusion criteria for the study included the following: (1) symptom onset between 6 AM April 20 and midnight April 21, 2005; (2) on-campus residence; (3) symptoms of nausea, vomiting, diarrhea, or abdominal pain; and (4) the absence of another likely cause of their symptoms. Available stool specimens from students and food handlers were tested for norovirus by reverse transcription–polymerase chain reaction (RT-PCR) at the Massachusetts Department of Public Health, Boston.

Results. No common food source was identified, but norovirus genogroup II was detected by RT-PCR in 4 of 9 students’ stool specimens and in 1 food handler specimen. Ninety students reported possible gastroenteritis, but 6 cases occurred outside of the time criteria. Two students had other, more probable, causes of illness. A total of 82 students met inclusion criteria, and 55 clinical profiles were available from questionnaires and medical charts. Sixty individuals (73%) were male, with a mean age of 19.1 years (range, 18-23 years). Predominant symptoms were vomiting (n=75; 91%), diarrhea (n=67; 82%); 34 (41%) of students seen in emergency departments had a fever (temperature ≥ 38°C). No bloody, nonbilious vomiting varied in frequency (1 to 8 episodes) and lasted up to 12 hours. Within 17 hours of symptom onset, all treated individuals were able to tolerate oral fluid intake. A few students reported illness persistence for 72 hours.

Clinical laboratory results were most notable for leukocytosis with a neutrophil predominance; the mean absolute neutrophil count was 11,414 cells/µL (Table). For 10 of 11 students, results from a manual differential cell count demonstrated increased immature band forms. Other test results were essentially normal except for mild

Clinical and Laboratory Findings in Individuals With Acute Norovirus Disease

<table>
<thead>
<tr>
<th>Date</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 19</td>
<td>10</td>
</tr>
<tr>
<td>April 20</td>
<td>15</td>
</tr>
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</tr>
<tr>
<td>April 28</td>
<td>30</td>
</tr>
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<td>May 1</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure. Epidemiologic curve of symptom onset for gastroenteritis-like symptoms from April 19, 2005, to May 1, 2005. Those individuals whose symptoms began before April 20, 2005, or after midnight on April 21, 2005, were excluded from this study.

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