performed during the following days were normal. Several blood cultures yielded penicillin-resistant Streptococcus pneumoniae. Sensitivity testing to PT was not undertaken. Nevertheless, because the patient’s condition had improved markedly (she was afebrile and a repeated hemolologic evaluation was normal, including a platelet count of 353,000/mm³), we decided to continue therapy with PT, administering the same dose every 6 hours, rather than every 8 hours as before. She continued to do well until day 11 when she developed a generalized petechial rash. Her platelet count was 15,000/mm³ and coagulation test results were normal. The antibiotic treatment was discontinued. The next day her platelet count increased to 31,000/mm³, and 3 days later it was 208,000/mm³. Antibodies to normal donor platelets were detected with use of a solid phase system (Capture-P; Immucor, Norcross, GA), but only when piperacillin was present (table 1). No antibodies to RBCs or lymphocytes were detected with use of conventional techniques. Three months later the platelet count continued to be normal and antibodies to platelets were no longer detected.

Thrombocytopenia is a rare complication of piperacillin therapy. In a previously reported patient with thrombocytopenia an immune mechanism was hypothesized, but this mechanism was not proven [2]. In the patient we described, severe thrombocytopenia was associated with the presence of antibodies that attached to platelet surfaces in the presence of piperacillin. The agent was required for adherence of the antibodies to platelets, and 3 months later the antibodies were no longer detected. It is of interest that the antibodies were detected with use of a solid-phase assay, an assay that is easier to perform than other techniques. Although we do not have extensive experience with the use of this assay in this context, it might prove to be a convenient method for the investigation of cases suspicious for drug-induced thrombocytopenia.

Although it is well known that the basic requisite for drug-induced thrombocytopenia is an immune response to the drug, the mechanisms involved have not been fully elucidated. The innocent bystander hypothesis held that the drug combined with drug-specific antibody in plasma and secondarily attached to platelets. However, current prevailing theory [3, 4] suggests that the drug induces a reversible conformational change in platelet membranes, thereby generating a neoantigen that induces the synthesis of antibodies (to a membrane element or to parts of the drug-membrane complex). Once the antibody has attached to the membrane in the presence of the drug, the drug-membrane interaction is stabilized, complement is activated, and cell destruction ensues.

Hepatitis A in Human Immunodeficiency Virus—Infected Patients

Hepatitis A is a common HIV coinfection [1, 2], but few published data are available concerning the clinical manifestations of hepatitis A in the setting of existing HIV infection [3]. In addition, it is not known whether acute hepatitis A infection accelerates the progression of HIV disease.

We reviewed seven cases of hepatitis A that occurred during the 1-year period from April 1996 to 1997 among the 600 HIV-infected patients followed at our medical center (San Diego, CA). Diagnoses for all cases were determined by use of hepatitis A IgM EIA (Abbott Laboratories, Chicago). Patients in our clinic undergo CD4 lymphocyte determinations and, since June 1996, quantitative HIV loading by use of Amplicor assay (Roche Diagnostic Systems, Branchburg, NJ) every 2–4 months.

All seven patients were male, aged 27 to 42 years, and had been HIV seropositive for 1–10 years (mean, 5 years). All seven patients were hepatitis C seronegative, five were hepatitis B core antibody seropositive, and none were hepatitis B surface antigen seropositive. The annual incidence of hepatitis A in our facility was 1.1%. Given that 21% of our patients are hepatitis A IgG seropositive at the time

<table>
<thead>
<tr>
<th>Conditions</th>
<th>At time of diagnosis</th>
<th>3 months after diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal donor platelets and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient’s serum</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Patient’s serum and Tazocel</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Patient’s serum and piperacillin</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Patient’s serum and tazobactam</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Positive control serum</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Negative control serum</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

NOTE: + = positive; – = negative.

References

The Chief, Navy Bureau of Medicine and Surgery, Washington, D.C., Clinical Investigation Program, sponsored this report (#58-93-058) as required by NSHSBETHINST 6000.41A.

The views expressed in this article are those of the authors and do not reflect the official policy or position of the U.S. Department of the Navy, U.S. Department of Defense, or the U.S. Government.

Reprints or correspondence: Dr. Mark R. Wallace, c/o Clinical Research Department, Naval Medical Center San Diego, 34800 Bob Wilson Drive, San Diego, California 92134-5000.

Clinical Infectious Diseases 1998;27:651–3
This article is in the public domain.
The effects of hepatitis A on the course of HIV disease.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Pre-hepatitis A phase (1–3 mo before)</th>
<th>During hepatitis A</th>
<th>Post-hepatitis A phase (3–4 mo after)</th>
<th>Antiretroviral therapy during hepatitis A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>613/400</td>
<td>496/399,000</td>
<td>502/5,700 (429/14,000 6 mo later)</td>
<td>AZT, ddC, and indinavir discontinued for 3 w</td>
</tr>
<tr>
<td>2</td>
<td>134/400</td>
<td>120/350,000</td>
<td>149/5,400</td>
<td>ddT, 3TC, and indinavir discontinued for 3 w</td>
</tr>
<tr>
<td>3</td>
<td>578/260,000</td>
<td>762/245,000</td>
<td>829/84,000</td>
<td>AZT, ddC, and indinavir continued through illness; indinavir dose reduced by half during period of jaundice</td>
</tr>
<tr>
<td>4</td>
<td>810/260</td>
<td>1,073/400</td>
<td>N/A</td>
<td>ddT and ddC continued at full dose</td>
</tr>
<tr>
<td>5</td>
<td>125/63,000</td>
<td>150/51,000</td>
<td>182/144,000</td>
<td>AZT, 3TC, and indinavir continued through illness</td>
</tr>
<tr>
<td>6</td>
<td>545/867</td>
<td>324/500</td>
<td>849/11,260</td>
<td>AZT and 3TC discontinued for 3 w</td>
</tr>
<tr>
<td>7</td>
<td>424/400</td>
<td>NA</td>
<td>328/200,000</td>
<td>Refused medications both pre- and post-hepatitis A</td>
</tr>
</tbody>
</table>

NOTE. AZT = zidovudine; ddC = zalcitabine; ddI = didanosine; ddT = stavudine; NA = not available; 3TC = lamivudine.

* Cells/mm

† Copies/mL.

of initial HIV diagnosis [4], the annual incidence among hepatitis A seronegative patients was 1.5%. There was no known common exposure among these seven subjects.

The clinical features of acute hepatitis A in our patients did not differ from those of HIV-negative patients with acute hepatitis A. One of seven patients received immunoglobulin postexposure prophylaxis 5 weeks before the onset of clinical symptoms and then experienced a mild, 1-week illness with minimal transaminase elevations (peak aspartate transaminase (AST) level, 79 U/L; peak alanine aminotransferase (ALT) level, 110 U/L); he did not miss any work. The other six patients had typical hepatitis A, with 3–4 weeks of illness resulting in 1–2 week absences from work. The mean peak laboratory values for these six patients during the acute hepatitis A phase were as follows: AST, 1,836 U/L (range, 353–5,710 U/L); ALT, 2,692 U/L (range, 1,017–6,305 U/L); and bilirubin, 4.5 mg/dL (range, 1.6–9.5 mg/dL). All six had normal coagulation studies (INR [international normalized ratio] range, 1.0–1.2). None had any hematologic, renal, or neurologic complications.

The effects of hepatitis A on the course of HIV disease correlated strongly with the continuation of antiretroviral therapy through the symptomatic phase of hepatitis A. As noted in table 1, three patients discontinued their antiretroviral therapy for 3 weeks during the symptomatic phase of their illness, two because of nausea and the other as per his physician’s recommendation. All three of these patients had statistically significant increases in their viral loads (P = .03, paired t test). Although viral loads decreased when the symptomatic phase resolved and antiretroviral therapy was resumed, they remained elevated when compared to pre-hepatitis levels (P = .047). There were no increases in HIV loads for the three patients who continued their antiretroviral therapy through the episode of acute hepatitis. The effects of hepatitis A on CD4 cell counts were not statistically significant, but one of the patients who interrupted his therapy sustained a decrease in CD4 lymphocyte count which did not recover with resumption of his antiretroviral therapy.

These cases demonstrate that intercurrent viral illnesses can dramatically increase HIV loads, a situation previously documented for HIV-infected patients with herpes simplex infections [5]. In addition, our data suggest that, whenever possible, antiretroviral treatment should be continued through the acute phase of hepatitis A to avoid increases in viral loads that may not return to pre-hepatitis levels after the reinitiation of antiretroviral therapy.

Given the potential morbidity and sequelae of hepatitis A that occurs in HIV-infected persons, it would seem prudent to prevent infection in these patients. Preliminary studies indicate that hepatitis A vaccine appears to be safe and immunogenic in the setting of HIV infection [6, 7]. Larger, ongoing trials of hepatitis A vaccination in HIV-infected individuals, including measurement of HIV load pre- and post-immunization, should help to better establish the risks and benefits of hepatitis A immunization among high-risk HIV patients.

Mark R. Wallace, Hal E. Hill, Sybil A. Tasker, and Larry K. Miller
Infectious Disease Division, Department of Internal Medicine, and Department of Clinical Research, Naval Medical Center
San Diego, San Diego, California

References
Successful Treatment of Human Herpesvirus 6 Encephalitis in a Bone Marrow Transplant Recipient

Human herpesvirus 6 (HHV-6) remains latent after primary infection, but can be reactivated in immunocompromised patients and cause fever, rash, bone marrow suppression, pneumonitis, sinusitis, and coinfection with other viruses [1–4]. In 1994, a case of fatal encephalitis after bone marrow transplantation (BMT) was shown to be caused by HHV-6 [5]. We describe a patient who underwent successful treatment of HHV-6 encephalitis after BMT.

An 18-year-old female underwent an unmodified BMT, with marrow from her HLA-identical brother, for high-risk T cell acute lymphoblastic leukemia. Fifteen months after BMT she presented with a 4-day history of cough and fever (temperature, 40°C). She was admitted to the hospital for treatment with broad-spectrum antibiotics (gentamicin, ticarcillin/clavulanate, and azithromycin) for radiographically confirmed bilateral pneumonia. Respiratory syncytial virus was detected in a respiratory specimen, as well as in fluid obtained via bronchoalveolar lavage which had been performed on hospital day 4 because of persistent fevers. Ribavirin therapy was not initiated at this time, given that the patient’s condition was improving, as indicated by diminishing respiratory symptoms and oxygen requirements. Cultures were negative for other pathogens. We did not test these samples for HHV-6.

On hospital day 3, a diffuse erythematous macular rash developed and the patient’s hemoglobin level, platelet count, and neutrophil count decreased significantly relative to laboratory values on admission. On hospital day 5, the patient developed lethargy, ataxia, and confusion. Neurological examination was nonfocal, except for an altered mental status. A head CT scan showed only pansinusitis. Analysis of CSF obtained via lumbar puncture revealed clear CSF with a normal glucose level, but the protein level was elevated (101 mg/dL; normal, 23–38 mg/dL); additional values included 2 RBCs/mm³ and 53 WBCs/mm³ (80% lymphocytes). Given the clinical picture of fever, rash, respiratory symptoms, and altered mental status in an immunocompromised host, we considered the possibility of infection with HH-6. A CSF specimen was submitted for viral culture and for PCR assay for detection of HHV-6. Therapy with iv foscarnet (60 mg/kg q8h) and iv Ig (400 mg/kg every other day) was initiated.

On hospital day 6, the patient became increasingly lethargic and she had two generalized seizures. While postictal she was significantly hypoxic, and she was thus intubated and transferred to the intensive care unit. An MRI of the brain showed no focal intracerebral lesions and no leptomeningeal enhancement. Her mental status gradually improved. She was extubated and returned to the pediatric ward where she experienced only occasional episodes of disorientation, inappropriate affect, and difficulty with concentration.

A PCR assay of the CSF specimen was negative for HHV-6. However, on hospital day 7, HHV-6 was detected by use of a shell vial assay of the same CSF specimen. Cultures were negative for other pathogens. A second lumbar puncture was performed on hospital day 13, and a PCR assay of the CSF specimen was strongly positive for HHV-6, variant B, although the shell vial assay was negative.

Foscarnet was continued at the induction dosage for a total of 2 weeks, followed by 4 weeks of maintenance therapy (90 mg/ [kg · d]) and weekly iv Ig for 4 weeks. The patient is now well, 11 months after completing her antiviral therapy.

During the course of her illness, the patient developed many of the clinical manifestations that have been attributed to HHV-6 after BMT including fever, rash, marrow suppression, sinusitis, pneumonitis, coinfection with respiratory syncytial virus, and encephalitis. HHV-6 was detected twice in her CSF, once by use of a shell vial assay on the first sample, and once by use of a PCR assay on the second sample. Although the PCR assay can detect either active or latent infections, the shell vial assay has been reported to have a specificity of 100% for active infections among bone marrow or liver transplant recipients [6]. It is possible that the second viral culture was negative because of the week of antiviral treatment; however, it is unclear why the PCR assay of the first CSF specimen was negative.

The optimal treatment for HHV-6 infection after bone marrow transplantation has not been well established in the literature. In vitro, replication of HHV-6 is inhibited by foscarnet or ganciclovir, but HHV-6 is relatively resistant to acyclovir [1]. Reynolds et al. [7] showed that foscarnet was more effective in the inhibition of HHV-6 replication, with a safer selectivity index than either acyclovir or ganciclovir. There are no reports of randomized studies that compare the activity of antiviral agents to HHV-6 in vivo.

Our patient differs from the majority of previously described patients with HHV-6 after BMT in her late presentation, >15 months after BMT. In addition, unlike the one other patient described with HHV-6 encephalitis after BMT, our patient recovered fully. We conclude that successful treatment of HHV-6 encephalitis after BMT can be achieved with prompt initiation of appropriate antiviral therapy, even before laboratory documentation of HHV-6 infection.