CORRESPONDENCE

Reactivation of Human Herpesvirus 6 Infection in an Immunocompetent Host with Chronic Encephalopathy

To the Editor—In a recent article, Razonable et al. [1] reported a selective reactivation of human herpesvirus 6 (HHV-6) variant A in critically ill immunocompetent patients. This reactivation, which was defined on the basis of the detection of HHV-6 DNA in peripheral blood lymphocytes, was observed in patients who had been admitted to an intensive care unit for medical or surgical indications or trauma, but it was not found in healthy volunteers who represented the control group.

These findings led us to review the case of a 13-year-old girl with chronic encephalopathy and whose recrudescence of symptoms was associated with the reactivation of HHV-6 infection both at the systemic and central nervous system (CNS) levels (i.e., detection of HHV-6 DNA in the blood and CNS). Since 3 years of age, the subject had suffered from frequent epileptic seizures that were resistant to treatment. At 8 years of age she began to present cognitive deterioration.

At the time of our evaluation, the girl had ~2 seizures per month, and she was disoriented, amimic, and also showed intermittent episodes of behavioral disorder. Her karyotype, blood and urine screening for metabolic diseases, optic fundi, motor and sensitive conduction velocity studies, immunoglobulins, and T lymphocyte subsets (CD3, CD4, CD8, CD16, and CD19) were normal.

Since both electroencephalogram and magnetic resonance imaging findings were suggestive of a chronic encephalopathy and since we could not exclude a possible CNS infection, we performed a lumbar puncture, which yielded a clear cerebrospinal fluid (CSF) with normal values of glucose, protein, and chloride and normal cell counts. A search for DNA sequences of cytomegalovirus, HHV-6, herpes simplex virus 1 and 2, Epstein-Barr virus, and varicella zoster virus was done, using a nested polymerase chain reaction with homemade specific inner and outer primers. CSF was only positive for HHV-6 sequences, which were also detected in peripheral blood mononuclear cells. Serology for HHV-6, performed using an indirect immunofluorescence assay, showed the presence of IgG antibodies at a titer of 1:40 but no IgM antibodies. CSF was negative for both IgG and IgM antibodies. Serology for other common infectious agents (e.g., measles or rubeola) was not suggestive of acute disease. Human immunodeficiency virus serology was negative.

HHV-6 is a neurotropic virus; however, symptoms of neurologic involvement, such as demyelination and seizures or status epilepticus, have been observed in primary disease (i.e., exanthema subitum) or in immunocompromised children [2, 3]. Our report suggests that HHV-6 reactivation at the CNS level may occur in immunocompetent hosts with severe neurologic disease. It remains to be defined whether, in our patient, viral reactivation was the consequence of illness-related stress, as suggested by Razonable et al. [1], or a factor contributing to the recrudescence of CNS disease.

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Reply

To the Editor—We appreciate the interest of Arpino et al. [1] in our recent study describing the selective reactivation of human herpesvirus 6 (HHV-6) variant A in critically ill nonimmunocompromised hosts [2]. Our study documented a 54% HHV-6 reactivation in a cohort of patients admitted to the intensive care unit for various indications, including 14 patients with neurologic illness or injury. This novel observation prompted Arpino et al. to review one of their patients who had a 10-year history of undefined neurologic disease. In their report [1], Arpino et al. describe the detection of HHV-6 in the peripheral blood and cerebrospinal fluid (CSF) of a 13-year-old patient with chronic encephalopathy. Using a "homebrew" nested polymerase chain reaction (PCR) assay, Arpino et al. support our observation that HHV-6 can be detected during critical illness even in immunocompetent hosts.

Arpino et al. further suggested that HHV-6 reactivation also occurs in the central nervous system (CNS), as indicated by the detection of HHV-6 DNA in CSF. Whether the detection of HHV-6 in their patient is a reflection of illness-induced stress or a direct cause of relapsing CNS disease is unclear. The neurotropism of HHV-6 [3] has led to the evaluation of this virus

as a direct or indirect cause of CNS disease. The role of primary HHV-6 infection in benign febrile seizures in children [4] and its influence in the pathogenesis of multiple sclerosis [5] has been the subject of many studies. Whether it also causes chronic encephalopathy, as suggested by Arpino et al., is an interesting association that needs to be further investigated. In the cohort of patients we investigated, 7 (50%) of the 14 patients with neurologic illness or injury (e.g., seizures, cerebrovascular accident, or neurosurgical procedures for intracerebral bleed and tumor excision) had HHV-6 reactivation. However, none had clinical illness similar to the case described by Arpino et al. Nevertheless, the reactivation of HHV-6 in immunocompetent patients with critical illness, whether systemically or within the confines of the CNS, raises its potential significance in human clinical syndromes.

We have demonstrated elsewhere that HHV-6 reactivation influences the pathogenesis of cytomegalovirus disease [6] and causes distinct clinical illness in immunocompromised transplant recipients [7]. In contrast, the clinical relevance of HHV-6 reactivation in the immunocompetent host is yet to be defined. In our study [2], HHV-6 reactivation was not associated with increased morbidity or mortality. The observation by Arpino et al. of HHV-6 reactivation (in the peripheral blood and in the CSF) in a patient with chronic encephalopathy suggests that this virus may play some role, whether directly or indirectly, in the clinical illness described.

The detection of latent virus is a concern with the use of sensitive qualitative PCR assays. While we do not underscore the important observation by Arpino et al., the use of standardized assays that could quantify virus load may be more useful, as has been demonstrated in the diagnosis and management of cytomegalovirus infection [8]. With real-time detection, one could also provide diagnostic testing with immediate relevance in the clinical setting. The widespread application of this new technology will undoubtedly unravel the still less-defined spectrum of clinical illnesses due to HHV-6 reactivation. With its use, we will be able to correlate the significance of the level of viral reactivation with clinical illness progression or to monitor improvement with antiviral therapy.

In summary, current data suggest that HHV-6 reactivation occurs even in immunocompetent patients. Whether its reactivation in immunocompetent patients is related to specific clinical syndromes and/or is just a reflection of the state of critical illness is yet to be defined. As more evidence-based data is gathered, with the increasing implementation of real-time quantitative HHV-6 PCR assays, the spectrum of clinical illness resulting from HHV-6 reactivation in both the immunocompromised and immunocompetent hosts will be further elucidated.

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Impact of Protease Polymorphisms and Viral Fitness on Human Immunodeficiency Virus (HIV) Type 1 Viremia in Untreated HIV-1 Infection

To the Editor—Perno et al. [1] found a high prevalence (52.8%) of secondary protease mutations in 248 antiretroviral-naive patients. The strongest predictor of virologic failure was the presence of protease mutations at codons 10 and 36 (odds ratio, 2.2), and these mutations were observed in 39.3% and 40.0% of patients, respectively. These results indicate that secondary protease mutations occur frequently, are clinically important, and may even justify the routine assessment of drug resistance in treatment-naive individuals.

In a small pilot study, we found a large number of protease polymorphisms in therapy-naive human immunodeficiency virus (HIV) type 1–infected individuals and studied the hypothesis that protease polymorphisms may affect viral fitness and decrease steady-state plasma HIV-1 viremia in antiretroviral-naive patients. This hypothesis is based on observations that low levels of plasma HIV-1 RNA in untreated HIV-1 infection strongly predict a superior prognosis of HIV-1 infection [2]. In addition, low plasma HIV-1 RNA levels have been associated with a more favorable response to antiretroviral therapy [3].

Table 1. Protease mutations in 15 untreated human immunodeficiency virus (HIV) type 1–infected patients, by level of virus load.

Level of HIV-1 load, patient no.	Protease mutations
Low	
1	I15V, L19I, L63P
2	K14R, I15V, E35D
3	T12K, R41K
4	K43R, I62V, L63T, A71V, V77L, I93L
5	T12S, L63S, V77I, I93L
6	K20Q, E35D, R41T, M46S, Q61H, L63P, E65Q
7	T12S, L63P
8	N37H, R41K, R57K, I93L
9	R41K, I93L
10	None
High	
11	N37D, D60E, Q61E
12	K14R, L63P
13	I3F, T12D, I62V, L63P, I93L
14	I13V, L63P, V771
15	I15V, M36I, R41K, Y59H

NOTE. Patients with low viremia had $< 10^4$ HIV-1 RNA copies/mL; patients with high viremia had $>$100,000 HIV-1 RNA copies/mL.

For this purpose, we selected 10 patients who had low, steady-state HIV-1 loads ($< 10^4$ copies/mL [median, 3.3 $\log_{10}$ copies/mL], hereafter referred to as "low viremia"). These patients were compared with 5 patients with high virus loads ($>$100,000 copies/mL, hereafter referred to as "high viremia"). All study participants were antiretroviral naive and were in a chronic stage of HIV-1 infection, without evidence of a primary illness. The patients with low viremia had a mean age of 36 years, and 80% (8/10) of them were male. They had a mean duration of known HIV-1 seropositivity of 5.3 years and a median CD4 T cell count of 323 cells/μL. The patients with high viremia had a mean age of 37 years, and 80% (4/5) of them were male. They had a mean duration of known HIV-1 seropositivity of 1.6 years and a median CD4 T cell count of 223 cells/μL.

We sequenced the protease genes and performed 2 viral fitness assays, using infectious viral recombinants that consisted of the patient's protease gene and the backbone of the laboratory strain pNL4-3. Recombinant virus was cultivated, using the lymphocytic cell line CEM-SS, and virus production was quantified every 2–3 days in the culture supernatant by a quantitative polymerase chain reaction method [4].

A total of 50 aa codons differed from those of wild-type virus (table 1). All but 1 of the 15 patients showed at least 2 polymorphisms. The most frequent changes included mutations L63P/T/S (8/15), R41K/T (5/15), I93L (5/15), T12K/S/D (4/15), I15V (3/15), V77I/L (3/15), K14R (2/15), E35D (2/15), N37D/H (2/15), Q61E/H (2/15), and I62V (2/15). Only 1 individual showed a primary protease mutation at codon 46 [5]. Surprisingly, the median number of protease mutations was 3 in both the high and low viremia groups ($P = .77$).

In the viral fitness assay, peak virus production was reached after a median time of 11 days (range, 4–14 days), irrespective of the high and low viremia classification. Median peak virus production was 6.0 and 6.3 $\log_{10}$ copies/2.5 μL in the low and high viremia groups, respectively ($P = .44$). Using a second method, which quantifies the *tat*-dependent long terminal repeat activation by a colorimetric assay [4], we could confirm that the peak virus expression was reached after a similar time period.

Conversely, a comparison of HIV-1 strains with good and poor (cutoff, peak virus production of 3×10^6 copies/2.5 μL) viral fitness demonstrated that mutation L63P/T/S was more prevalent in strains with reduced viral fitness ($P = .04$). In contrast, other protease mutations, such as R41K/T or I93L, did not show a relationship with the results of the viral fitness assay. Similarly, the number of polymorphisms was not associated with viral fitness.

In conclusion, our results revealed that the number of protease mutations, as well as individual protease mutations, cannot predict the steady-state viremia in untreated HIV-1–infected individuals, nor could we find a difference in viral fitness between patients with low and high viremia. Instead, our results suggest that the HIV-1–specific immune response, including different patterns of chemokine receptors, may play the dominant role and determine the magnitude of HIV-1 RNA levels in untreated patients. In addition, mutations outside the protease region, which have not been tested for, may affect viral replication. It has been reported that mutations of the p6 Gag protein can influence Vpr incorporation and reduce viral fitness [6]. Nevertheless, the number of polymorphisms found in 10 patients with very low virus loads was surprisingly high. Of importance, mutations at codon 63 were found significantly more frequently in individuals with lower peak virus production, and it is tempting to speculate that this particular mutation affects viral fitness and the subsequent responsiveness to antiretroviral therapy.

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Identification of the *Cryptosporidium* Pig Genotype in a Human Patient

To the Editor—The recent correspondence by Chalmers et al. [1] supports our recent observations that unusual *Cryptosporidium* parasites *(C. meleagridis, C. felis,* and *C. canis)* that are normally associated with animals infect both immunocompromised and immunocompetent humans [2]. In addition to the identification of *C. meleagridis* in 19 immunocompetent patients in England and Wales, Chalmers et al. also found 2 isolates from 2 patients that did not seem to match any *Cryptosporidium* parasites that have been found in humans, which suggests that other unusual *Cryptosporidium* parasites may also infect humans. Herein, we describe the infection of a human immunodeficiency virus (HIV)–positive, but not severely immunosuppressed, individual with a *Cryptosporidium* parasite that previously has been found in pigs: the *Cryptosporidium* pig genotype [3, 4].

The patient, a 24-year-old homosexual man who lived in Lima, Peru, was enrolled on 27 April 2001 in an epidemiologic study of enteric parasites in HIV-positive persons. HIV infection had been diagnosed 8 months before study enrollment, and the patient had no history of opportunistic infections and reported no diarrheal illness at the time of enrollment or over the previous year. He reported no nausea, abdominal pain, vomiting, or weight loss. The patient was receiving isoniazide prophylaxis but not antiretroviral therapy. He reported having been sexually active in the month prior to the interview, had had ≥ 2 sex partners in the previous year, and admitted both active and passive anal intercourse, using a barrier only some of the time. He had a dog but reported no contact with other animals or animal excreta, including pigs or pig feces. His $CD4^+$ T cell count was 533 cells/μL on 3 May 2001.

Daily stool specimens were obtained from the patient on 28–30 April and 12–14 May 2001, and, although he had no gastrointestinal symptoms, the specimen from 30 April was positive for *Cryptosporidium* parasites, as determined by microscopic examination of acid fast–stained slides. The intensity of infection was scored as 1+ according to a system based on the number of oocysts counted in a 20-μL volume of concentrated stool specimen: 1+, 1–50 oocysts; 2+, 51–150 oocysts; and 3+, >150 oocysts per 20-μL volume. The rest of the stool specimens were negative, as determined by microscopic examination in Peru. The oocysts in the specimen appeared very similar in shape and size to those of the *C. parvum* human and bovine genotypes (shown in figure 1*A*). The oocysts were 5.05×4.41 μm in size (95% confidence limits [CLs], 0.07 and 0.08; $n = 56$), with a shape index (length-to-width ratio) of 1.15 (95% CL, 0.02). In contrast, *C. parvum* bovine genotype oocysts ($n = 44$) were 4.85×4.39 μL in size (95% CLs, 0.05 and 0.04), with a shape index of 1.11 (95% CL, 0.02), and *C. parvum* human genotype oocysts ($n = 44$) were 4.91×4.28 μL in size (95% CLs, 0.07 and 0.06), with a shape index of 1.15 (95% CL, 0.03). The oocysts were reactive to 2 monoclonal antibodies (OW3 and OW50) against *C. parvum* bovine genotype [5], and they stained bright green by fluorescein isothiocyanate–labeled antibodies under an epifluorescence microscope.

Polymerase chain reaction (PCR) analysis of the small subunit (SSU) rRNA gene [2] on the DNA extracted from the 30 April 2001 specimen (which was preserved in 2.5% potassium dichromate) resulted in positive amplification in all 6 PCR runs. Restriction fragment–length polymorphism (RFLP) analysis of all PCR products showed an RFLP banding pattern identical to that of the *Cryptosporidium* pig genotype (figure 1*B*) [4]. DNA sequence analysis of the PCR products produced an SSU rRNA sequence identical to that of the *Cryptosporidium* pig genotype (GenBank accession numbers AF108861 and AF115377), confirming the identification. The identification of the *Cryptosporidium* pig genotype was further corroborated by PCR-RFLP analysis of a frozen aliquot of the 30 April sample.

All 5 stool samples that were negative by microscopy were made available for molecular analysis after the detection of the *Cryptosporidium* pig genotype in the 30 April sample. The sample obtained on 29 April 2001 tested positive in all 3 PCR runs; however, the others did not produce any PCR product. RFLP analysis of the PCR products from the 29 April sample also showed the banding pattern of the *Cryptosporidium* pig genotype. Subsequent analysis of the sample by immunofluorescence at the Centers for Disease Control and Prevention (Atlanta) revealed the presence of *Cryptosporidium* oocysts.

The implication of finding the *Cryptosporidium* pig genotype in this patient is not entirely clear. Although the patient in this study was HIV positive, he was not severely immunosuppressed, as determined on the basis of his $CD4^+$ T cell count (533 cells/

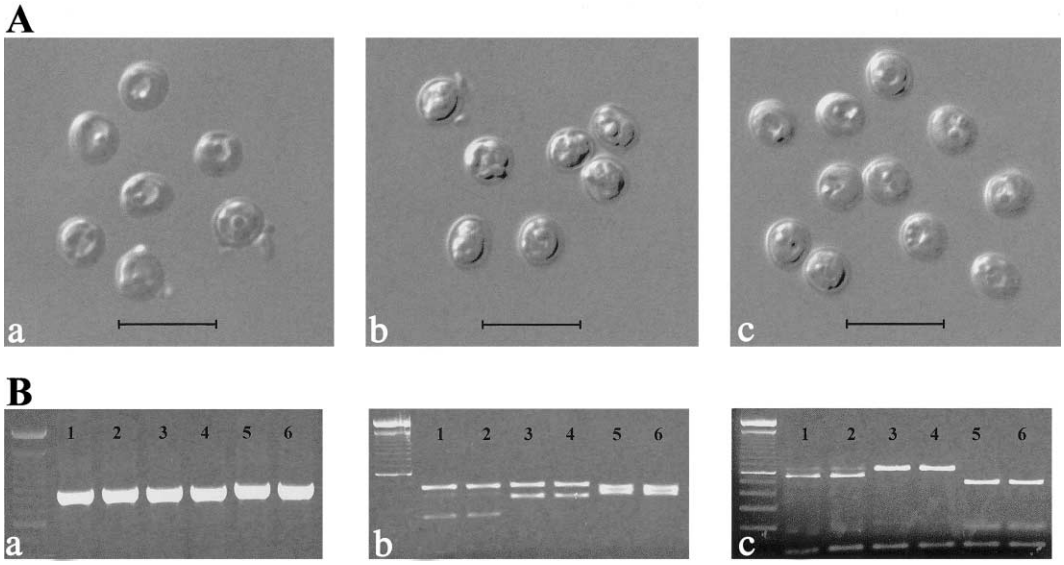

Figure 1. *A,* Oocysts (*bar,* 10 μm) of the *Cryptosporidium* pig genotype in a Peruvian patient *(a),* compared with those of human *(b)* and bovine *(c) C. parvum* genotypes. *B,* Identification of the *Cryptosporidium* pig genotype in a Peruvian human immunodeficiency virus–positive patient, as determined by small subunit rRNA–based polymerase chain reaction (PCR)–restriction fragment–length polymorphism analysis. *a,* PCR products; *b, Ssp*I digestion of PCR products; *c, Vsp*I digestion of PCR products. *Lanes: 1* and *2,* Concurrent infection by the *C. parvum* human genotype and *C. canis* (patient MCDM568); *3* and *4, Cryptosporidium* pig genotype (sample 4193 from patient MCAL321); *5* and *6, C. felis* (patient MCAL379). All samples were from patients involved in the same study in Lima, Peru.

μL), his medical history, and the absence of any symptoms of illness. Other non–*C. parvum Cryptosporidium* parasites, such as *C. meleagridis, C. canis,* and *C. felis,* initially were found in HIV-positive persons and subsequently were found in immunocompetent persons as well, many of whom did not have diarrhea [2, 6–9]. Thus, immunosuppression may not be a prerequisite for *Cryptosporidium* pig genotype infection in humans.

A parasite previously identified as *C. muris* was reported in an HIV-positive patient [10], but the sequence of the SSU rRNA gene from the parasite was more similar to that of *C. andersoni* (a 2-bp difference in a 242-bp region) than to that of *C. muris* (an 8-bp difference). Another 2 cases of *C. muris*–like cryptosporidiosis were reported in 2 healthy Indonesian girls, but little evidence was presented to substantiate the identity of *C. muris* [11]. Finding the *Cryptosporidium* pig genotype in humans supports the conclusion that other *Cryptosporidium* parasites are likely to be found in humans as well as in certain epidemiologic settings.

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