Parvovirus B19 Encephalitis Presenting as Immune Restoration Disease after Highly Active Antiretroviral Therapy for Human Immunodeficiency Virus Infection

Richard C. Nolan,1 Glenys Chidlow,2 and Martyn A. French1

1Department of Clinical Immunology and Biochemical Genetics, Royal Perth Hospital, Perth, and 2Department of Microbiology, Pathcentre, Hospital Avenue, Nedlands, Australia

Illness occurring during the initial months of highly active antiretroviral therapy (HAART) for human immunodeficiency virus infection may be a consequence of the restoration of an immune response against opportunistic pathogens (i.e., immune restoration disease [IRD]). We describe a young man who had AIDS complicated by parvovirus B19 infection and RBC aplasia and who developed a painless, progressive dyspraxia of the left arm and an expressive dysphasia 4 weeks after commencing effective HAART. Neuroimaging demonstrated multiple right fronto-parietal lesions, and, following extensive investigations, including a brain biopsy, it was concluded that the brain lesions represented IRD associated with parvovirus B19 infection.

The introduction of HAART has revolutionized the management of patients with HIV infection. Consequently, few patients now reach a stage of severe immune deficiency. For those patients that do, suppression of HIV replication by HAART often results in at least partial restoration of the immune system. However, immune restoration is sometimes associated with inflammatory disease [1]. We have argued that these conditions are a consequence of an immunopathological response to the antigens of preexistent (often quiescent) opportunistic pathogens, and we have referred to these conditions as immune restoration disease (IRD) [2–4]. The number of opportunistic pathogens reported to be associated with IRD is increasing.

Here, we describe a patient who developed progressive, painless focal encephalitis 4 weeks after commencing HAART. Parvovirus B19 was implicated as the organism to which the immune response was directed.

Parvovirus B19 is best known as the etiologic agent of erythema infectiosum. It has also been associated with other illnesses, including arthropathy, transient aplastic crisis, and hydrops fetalis [5]. Prior to discovery of the virus, there were reports of a link between erythema infectiosum and CNS infection [6]. Since its isolation, several reports have detailed associations between parvovirus B19 and meningoencephalitis in both immunocompromised and immunocompetent patients [7–15]. However, to our knowledge, parvovirus B19 encephalitis has not been associated with AIDS and certainly not with IRD.

Patient and methods. A 33-year-old, part-Aboriginal man had received a diagnosis of HIV infection in 1989. His risk behaviors included sex with men and injection drug use. Previous opportunistic infections were esophageal candidiasis and chronic parvovirus B19 infection, which had resulted in RBC aplasia. Other medical conditions included chronic hepatitis C virus infection, recurrent perianal herpes simplex virus (HSV) type 2 infection, and chronic Escherichia coli prostatitis. Anemia resulting from parvovirus B19-induced RBC aplasia had been diagnosed 12 months earlier at another hospital on the basis of a bone marrow biopsy that indicated the absence of erythropoiesis, the detection of parvovirus by PCR of a biopsy specimen, and the presence of parvovirus IgM and equivocal IgG antibodies in serum. Treatment for the anemia had included intravenous immunoglobulin (IVIG) therapy (400 mg/kg) and intermittent blood transfusions.

The patient’s previous adherence to treatment regimens had been poor, and he was profoundly immunodeficient, with a CD4+ T cell count of 20 cells/μL and a plasma HIV RNA level of >100,000 copies/mL, despite treatment with nevirapine, lamivudine, and stavudine. His medication regimen was, therefore, changed to lopinavir/ritonavir (Kaletra; Abbott Laboratories) and abacavir in an effort to control HIV replication, restore an immune response to parvovirus B19, and reduce the number of blood transfusions that he was requiring.

After 4 weeks of therapy, the patient had achieved an excellent viral and immunologic response to HAART, with a plasma HIV RNA level of <50 copies/mL and an increase in the CD4+ T cell count to 110 cells/μL. At this time, however, there was a subacute onset of clumsiness of the left hand and a speech disturbance. Physical examination revealed no objec-
tive neurological abnormalities. A cranial CT scan revealed 2 small focal areas of cortical enhancement in the right postcentral and middle frontal gyrus, and MRI revealed multiple foci of increased signal intensity involving the cortex and deep white matter of the right frontal lobe, with little mass effect and no evidence of surrounding edema. A lumbar puncture was performed, and examination of the CSF sample demonstrated a ratio of IgG to albumin of 0.48 (reference range, 0.04–0.24), but erythrocyte count, leukocyte count, and glucose and protein levels were normal. Results of CSF cultures for viruses, bacteria, fungi, and mycobacteria were unremarkable. During this time, it was also noted that the hemoglobin level had dropped quickly, and the patient required an additional transfusion of 4 units of packed cells.

Antiretroviral therapy was continued, and the patient’s symptoms deteriorated. He developed marked apraxia affecting his left hand, a moderately severe expressive dysphasia, and new right retro-orbital pain, without associated ophtalmic abnormalities. Formal neurological examination revealed signs indicating damage to the right frontal and parietal lobes. There was mild left hemiparesis, left-hand apraxia, reduced 2-point discrimination, mild left-right disorientation, and expressive dysphasia. Additional investigation included a second MRI and lumbar puncture and, ultimately, a brain biopsy. The MRI (figure 1A) demonstrated more-extensive changes that affected both cortical and subcortical areas and were predominantly localized to the right temporal, parietal, and posterior frontal lobes. Results of CSF cultures for viruses, bacteria, fungi, and mycobacteria were again unremarkable. The CSF protein level had increased to 0.62 g/L (reference range, 0.15–0.45 g/L), but the erythrocyte count, leukocyte count, and glucose level were normal.

The results of PCR analysis of both CSF samples are shown in table 1. The only consistent abnormal finding was the presence of parvovirus B19 DNA (detected by a nested PCR method modified from that of McOmish et al. [16]) on 2 separate occasions. At this time, parvovirus B19 DNA was also detected by PCR of serum samples. Cytomegalovirus antibodies were detected in the CSF at a level of 1% of the serum concentration, which indicated negligible blood contamination. Parvovirus B19 antibodies were not detected in the CSF by ELISA (Biotrin International).

A biopsy of a lesion in the right parietal lobe was performed with use of an interactive-image guidance system (Stealth; Sofamor-Danek). Histopathologic analysis of the biopsy specimen revealed widespread coagulative necrosis with acute inflammation and occasional macrophages. There was no evidence of the perivascular lymphocytic infiltration usually associated with HSV encephalitis, and note was made of the involvement of both white and grey matter, which would be very atypical for JC virus infection. Staining for fungi and Nocardia and Toxoplasma species was negative, and cultures showed no growth.

Findings of electron microscopy were also unhelpful. However, PCR tests demonstrated the presence of parvovirus B19 DNA (table 1).

It was concluded that the patient had focal encephalitis due to an immune restoration response to parvovirus B19 infection in the brain. This diagnosis was based on the persistent detection of parvovirus B19 DNA in CSF and brain tissue and histopathologic findings that were atypical for common pathogens, namely HSV and JC virus. High-dose IVIG (2 g/kg) was ad-
Table 1. Results of PCR analysis of CSF samples and of a brain biopsy sample obtained from a patient with parvovirus B19 encephalitis.

<table>
<thead>
<tr>
<th>PCR target</th>
<th>PCR result, by specimen type</th>
<th>time obtained, in weeks*a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CSF (6)</td>
<td>CSF (10)</td>
</tr>
<tr>
<td>CMV DNA</td>
<td>Not detected</td>
<td>—</td>
</tr>
<tr>
<td>Enterovirus RNA</td>
<td>Not detected</td>
<td>—</td>
</tr>
<tr>
<td>HSV Type 1 DNA</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
<tr>
<td>HSV Type 2 DNA</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
<tr>
<td>VZV DNA</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
<tr>
<td>JC virus DNA</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
<tr>
<td>B. henselae DNA</td>
<td>Not detected</td>
<td>—</td>
</tr>
<tr>
<td>Parvovirus B19 DNA</td>
<td>Detected</td>
<td>Detected</td>
</tr>
<tr>
<td>EBV DNA</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

NOTE. B. henselae, Bartonella henselae; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; VZV, varicella-zoster virus.  
*a Time from initiation of HAART to recovery of specimen.

ministered to treat the parvovirus B19 infection. Antiretroviral therapy was continued. The patient had a hematologic recovery, with a rise in the reticulocyte count from $2 \times 10^9$ to $175 \times 10^9$ cells/L and a subsequent normalization of the hemoglobin level. However, the dysphasia and dyspraxia persisted, and an MRI performed 3 months after the biopsy showed progression of the brain lesions (figure 1B). This progression necessitated the cessation of HAART, and treatment with high-dose IVIG alone was continued.

Discussion. This case highlights the adverse effects that may occur when an immune response is directed toward an existing pathogen during HAART-associated immune restoration. The patient had no neurological symptoms before the change in antiretroviral therapy, but, after 4 weeks of HAART, he developed progressive symptoms and signs of focal encephalitis, which was confirmed by MRI and CT findings. This was associated with an excellent response to HAART, with a substantial increase in the CD4+ T cell count. The slowly progressive nature of the neurological disease argued against a new infection or a vascular event, whereas the correlation with increased CD4+ T cell counts strongly suggested that this was IRD.

The case also demonstrates the difficulties sometimes found in attempts to identify an etiologic agent in IRD. Examination of CSF samples demonstrated no evidence of infection by common pathogens (HSV, CMV, enterovirus, varicella-zoster virus, or JC virus). A positive result of PCR for parvovirus B19 DNA was seen as unusual and possibly due to contamination. However, subsequent investigations, including a brain biopsy, confirmed the initial findings and did not provide evidence of an alternative pathogen. It was, therefore, concluded that parvovirus B19 was the most likely etiologic agent. The lack of response to IVIG therapy in the brain may have been due to poor penetration of IVIG into the CNS [17] or ongoing inflammation directed against residual viral antigens. The poor CNS penetration of IVIG has previously been described in patients with X-linked hypogammaglobulinemia complicated by echovirus encephalitis for whom intraventricular immunoglobulin therapy was required to effect a cure [18].

Although parvovirus B19 encephalitis has not previously been reported in patients with HIV infection, a plausible explanation for the cerebral lesions in this patient can be offered, on the basis of what is known about parvovirus B19 infection in immunocompetent individuals and about IRD in HIV-infected patients. Thus, it is clear that parvovirus B19 can infect cells in the brain [7-14], and there is evidence that immune responses to parvovirus B19 can be restored by HAART [19-22]. Furthermore, IRD is characterized by immunopathological responses to pathogens [3, 4], and it was notable that histopathologic examination of specimens of the brain lesions in this patient demonstrated changes in acute inflammation. Therefore, restoration of an immune response to parvovirus B19 infection in the brain is the most likely explanation for our patient’s lesions.

In HIV-infected patients commencing HAART, illness that occurs during the restoration of their immune system is emerging as a major problem. This case is a good example of how IRD often presents as an atypical “opportunistic infection” after the commencement of HAART. Furthermore, management of these patients is difficult without established guidelines. However, this case illustrates the importance of suppressing opportunistic infections before HAART is started, if possible. It is most important to recognize that parvovirus B19 is being increasingly identified as a CNS pathogen [13], and parvovirus B19 infection should be considered as a diagnosis for patients...
who develop cerebral IRD after the commencement or revision of HAART.

Acknowledgments

We would like to thank Dr. Gerald Harnett, Dr. David Smith, and the staff of the Molecular Diagnostic Section of the Western Australian Centre for Pathology and Medical Research for performing the PCR and serological testing of CSF and brain samples.

References