CD8 Encephalitis in HIV-Infected Patients Receiving cART: A Treatable Entity

François-Xavier Lescure,1,9 Antoine Moulignier,1,2 Julien Savatovsky,3 Corinne Amiel,4 Guislaine Carcelain,5 Jean-Michel Molina,6 Sébastien Gallien,6 Jérôme Pacanovski,7 Gilles Pialoux,1 Homa Adle-Biassette,8,a and Françoise Gray8,a

1Service des Maladies Infectieuses et Tropicales, AP-HP, Hôpital Tenon; 2Service de Neurologie, and 3Service d’Imagerie Médicale, Fondation Adolphe de Rothschild; 4Service de Virologie, AP-HP, Hôpital Tenon; 5Service d’Immunologie, AP-HP, Groupe Hospitalier Pitié-Salpêtrière; 6Service des Maladies Infectieuses et Tropicales, AP-HP, Hôpital Saint Louis; 7Service des Maladies Infectieuses et Tropicales, AP-HP, Hôpital Saint Antoine; 8Service Central d’Anatomie et de Cytologie Pathologiques, APHP, Hôpital Lariboisière–Université Paris 7; and 9CDR Saint-Antoine, Inserm U938, Université Paris 6-UPMC, Paris, France

(See the Editorial Commentary by Langford and Letendre on pages 109–11.)

Background. Despite its overall efficacy, combined antiretroviral therapy (cART) has failed to control human immunodeficiency virus (HIV) infection of the central nervous system (CNS). New acute and chronic neurological complications continue to be reported.

Methods. We conducted a retrospective study of 14 HIV-infected patients with documented encephalitis, which was initially attributed to an undetermined origin. Brain magnetic resonance imaging (MRI) uniformly revealed unusual, multiple linear gadolinium-enhanced perivascular lesions.

Results. All patients had manifested acute or subacute neurological symptoms; the brain MRIs indicating diffuse brain damage. The mean duration of HIV infection was approximately 10 years, and 8 patients were immunovirologically stable. Cerebrospinal fluid abnormalities with mildly elevated protein and pleocytosis with >90% lymphocytes, predominantly CD8, were found in all but 1 patient. The mean cerebral spinal fluid HIV load was 5949 copies/mL. Six patients reported a minor infection a few days prior to neurological symptoms, 2 patients presented criteria for the immune reconstitution inflammatory syndrome of the CNS, 2 were in virological escape, and 1 developed encephalitis after interruption of cART. Brain biopsies revealed inflammatory encephalitis associated with astrocytic and microglial activation as well as massive perivascular infiltration by polyclonal CD8⁺ lymphocytes. All patients had been treated with glucocorticosteroids. The long-term therapeutic response varied from excellent, with no sequalae (n = 5), to moderate, with cognitive disorders (n = 4). The mean survival time was 8 years; however, 5 patients died within 13 months of initiation of treatment.

Conclusions. CD8 encephalitis in HIV-infected patients receiving cART is a clinical entity that should be added to the list of HIV complications.

Keywords. HIV; central nervous system; encephalitis; CD8 lymphocytes; glucocorticosteroids.

Combined antiretroviral therapy (cART) has led to considerable improvement in both the clinical outcome of those with human immunodeficiency virus (HIV) infection and the spectrum of disorders that affect the central nervous system (CNS) [1]. Despite these advances, the CNS remains a major target of HIV infection [2]. Highly active antiretroviral therapy (HAART) cannot fully contain high levels of microglial and macrophagic activation, raising the probability of inadequate long-term control of brain infection [3]. Unexpectedly acute or subacute complications of HIV have been documented, including highly destructive forms of HIV-associated leukoencephalopathy [4], extensive
perivascular CD8 lymphocytic infiltration [5, 6], “burnt out” forms of HIV encephalitis [7], immune reconstitution inflammatory syndrome (IRIS) [8], and discordant HIV diseases [9]. A recent review points out that the causes underlying a growing number of severe, acute inflammatory leukoencephalopathies remain to be identified [10]. HAART has also impacted the patterns of HIV-related neuropathology [11], whether in relation to immune reconstitution [5, 12] or not [11].

We describe the clinical, radiological, and pathological features of and outcome of 14 cases of a new, severe, but treatable, form of HIV-related encephalitis. This form showed extensive infiltration of CD8 cells, affecting patients with satisfactory indices of HIV control.

RESULTS

The clinical and laboratory findings for the 14 HIV-infected patients with inflammatory encephalitis are summarized in Table 1. Seven patients originated from sub-Saharan Africa and 2 originated from North Africa; 5 patients were white. Eight patients were male and 6 were female, with an average age at onset of 42 years (range, 25–59 years). Five men reported homosexual contacts, 8 mentioned exclusively heterosexual contacts, and 1 patient had been infected through blood transfusion; no patients were drug users. The mean duration of HIV infection was 10 years (range, 0.2–19 years). Eight patients had a history of AIDS-defined illnesses, but none of these involved the CNS. In the 8 cases in which the CD4 nadir count was available, it was <200 μL, except for 1 patient (patient 8). From the neurological onset of inflammatory encephalitis, 12 of the 14 patients had received CART for a mean duration of 4.2 years (range, 2 months–14 years), with a mean revised CNS penetration effectiveness (CPE) [14] score of 7.7 (range, 6–10). One patient (patient 8) had received no antiretroviral treatment because the CD4 count was >500/μL and the plasma viral load (pVL) was 1468 copies/mL; the other patient (patient 2) had voluntarily stopped treatment a month before the encephalitis occurred. The mean CD4 cell count during the 6-month period before onset (n = 12) was 369/μL (range, 10–900/μL), dropping to 263/μL at onset (range, 84–742/μL). The plasmatic CD8 count was normal before and at the onset of symptoms in all patients except patient 7, in whom it varied over 2 years from 853/μL to 7020/μL, with a mean value of 5000/μL. This patient was free of the diffuse infiltrative lymphocytosis syndrome (DILS), and the glandular biopsy was negative.

Eight patients (patients 1, 2, 4, 7, 9, 11, 13, and 14) who had received HAART for at least 2 years were immunovirologically stable, with undetectable pVL, CD4 cell counts >350/μL, or CD4/CD8 >0.7. The mean pVL in the 6 months prior to onset of encephalitis was 330 copies/mL (n = 13), rising at onset to 12 400 copies/mL (n = 11).

In an attempt to identify the mode of onset, we noted that 6 patients reported a minor infection of the upper respiratory tract a few days before the first appearance of neurological symptoms (patients 1, 4, 7, 8, 11, and 13), 2 patients presented with criteria corresponding to the immune reconstitution inflammatory syndrome (IRIS) of the CNS (patients 3 and 5), 2 others were clearly in virological escape at the time (patients 9 and 10), and, in one case (patient 2), encephalitis developed at the same time as viral rebound due to the interruption of HAART.

All patients suffered an unexpectedly acute or subacute decline in brain function with dizziness, headache, memory disorders, and confusion with seizures and status epilepticus.
<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>Sex</td>
</tr>
<tr>
<td>1</td>
<td>46 M</td>
</tr>
<tr>
<td>2</td>
<td>41 M</td>
</tr>
<tr>
<td>3</td>
<td>36 M</td>
</tr>
<tr>
<td>4</td>
<td>47 F</td>
</tr>
<tr>
<td>5</td>
<td>39 F</td>
</tr>
<tr>
<td>6</td>
<td>33 F</td>
</tr>
<tr>
<td>7</td>
<td>37 F</td>
</tr>
<tr>
<td>8</td>
<td>54 F</td>
</tr>
<tr>
<td>9</td>
<td>33 M</td>
</tr>
<tr>
<td>10</td>
<td>43 M</td>
</tr>
<tr>
<td>11</td>
<td>35 M</td>
</tr>
<tr>
<td>12</td>
<td>59 F</td>
</tr>
<tr>
<td>13</td>
<td>49 M</td>
</tr>
<tr>
<td>14</td>
<td>39 M</td>
</tr>
</tbody>
</table>

Abbreviations: ABC, abacavir; ARV, antiretroviral; ATV, atazanavir; ATVr, atazanavir boosted with ritonavir; AZT, zidovudine; BB, brain biopsy; cART, combined antiretroviral therapy; CSF, cerebrospinal fluid; DDI, didanosine; IRIS, immune reconstitution inflammatory syndrome; F, female; fAPVr, fosamprenavir boosted with ritonavir; FTC, emtricitabine; IDV, indinavir; IDVr, indinavir boosted with ritonavir; Immu, immunological; LPV, lopinavir; LPVr, lopinavir boosted with ritonavir; M, male; MRI, magnetic resonance imaging; NA, not available; ND, not determined; pVL, plasma viral load; TDF, tenofovir; T20, enfuvirtide; 3TC, lamivudine.
severe enough to necessitate intensive care for 5 of them (patients 1, 5, 7, 9, and 12); none had significant systemic symptoms such as fever or weight loss.

Brain MRIs were similar for all patients and revealed bilateral, diffuse T2 and FLAIR high signal intensities (Figure 1A), localized in both white and gray matter. Postgadolinium T1 showed multiple punctate or linear gadolinium-enhanced lesions (Figure 1B), better seen with spin-echo T1 with magnetization transfer (Figure 1C). Diffusion-weighted imaging, done in 4 patients, showed high signal intensity lesions at the same perivascular locations (Figure 1D).

CSF abnormalities were found in all but 1 patient (patient 9) who had mildly elevated protein (42–157 mg/dL) and pleocytosis (9–220 white blood cells/µL), of which >90% were lymphocytes, predominantly CD8. When specifically tested for in 3 cases, they proved to be activated CD8⁺CD38⁺ lymphocytes. T-cell receptor analysis confirmed the polyclonal pattern, and the CSF cytology was negative for abnormal cells. The mean CSF HIV load was 5949 copies/mL (range, 0–36242 copies/mL). Cell cultures and viral PCRs were negative. Lumbar punctures were performed for 12 patients, and the CSF was normalized over an average period of 3.2 months (range, 2–6 months) after the start of management; the CSF HIV load was undetectable and all viral PCRs were negative.

Brain biopsies constantly showed the association of encephalitic signs, including microglial activation and reactive astrocytosis, with inconstant and weak expression of HIV protein in the absence of multinucleated giant cells. Biopsies also showed infiltrations by T-lymphocytes, mostly CD8⁺ lymphocytes (Figure 2), with a variable number of CD4⁺ lymphocytes. No

Figure 1. Bilateral and diffuse T2 and FLAIR high-signal intensities on brain magnetic resonance imaging. A, Bilateral and diffuse FLAIR high-signal intensities (arrow). B and C, Postgadolinium T1-weighted spin-echo imaging combined with magnetization transfer reveals multiple punctate or linear gadolinium-enhanced lesions (arrowheads). D, Restricted diffusion lesion at the same perivascular locations (arrowhead).
evidence of viral, bacterial, fungal, or parasitic infection was found. Inflammatory demyelinating lesions were observed in only 2 cases (patients 4 and 8).

Before the onset of encephalitis, 8 patients had a CSF CPE score \( \geq 8 \), and only 1 patient had a CPE score \( \leq 6 \). A good score was not a decisive prognostic factor, although the ART combination was modified according to the viral phenotype in order to obtain a better CPE score for 10 patients. The CPE score for these patients increased from 8 to 10. In 1 case (patient 11), a relapse occurred despite a CPE score of 17; in contrast, total and rapid recovery was observed with a CPE of 5 (patient 2) and 6 (patient 8). In 2 cases, maraviroc was added to the ART because of its influence on immune activation and inflammation. One patient (patient 14) recovered fully within a few weeks, whereas the other case (patient 10) improved but remained cognitively affected. Because the plasmatic HIV replication was low in 10 patients, the therapeutic aim was to attain an undetectable pVL.

Because of a severe and rapidly progressive neurological presentation without any identified infectious agent and because of the presence of inflammatory lesions associated with numerous CD8 lymphocytes in the brain biopsies, patients were treated with glucocorticosteroids (intravenous methylprednisolone 1 g daily for 5 days) with a tapering administration of prednisone by mouth (1 mg/kg for 2 months followed by a reduction of 5 mg every 2 weeks) for a median period of 6 months (range, 1–30 months), as proposed in acute disseminated encephalomyelitis (ADEM). The median delay between the onset of encephalitis and the initiation of glucocorticosteroid treatment was 33 days (range, 15–87 days) for the first 10 patients and much shorter (mean delay 14 days) for the other 4 patients when their conditions were better defined, without awaiting pathological confirmation. Corticosteroid therapy, complicated with septicemia due to a Candida infection in 1 case (patient 12), was well tolerated by all the other patients.

The long-term therapeutic response varied, ranging from excellent, free from any sequelae (patients 2, 3, 8, 11, and 14), to moderate (patients 9, 10, and 13) or severe (patient 5) with cognitive disorders. The mean survival time was 8 years (range, 3–13 years). Five patients died within a mean period of 9 months (range, 1–13 months), 4 from no other proven cause than CD8 encephalitis, despite an initial but transient neurological improvement in all cases. Despite undetectable plasmatic and CSF VL and a CD4 count \( >1000/\mu L \), 1 patient’s condition (patient 4) rapidly worsened to a vegetative status, with death occurring 13 months after onset of encephalopathy. The postmortem results for this patient, compared to the initial brain biopsy, are described elsewhere [13].

The follow-up brain MRIs of the patients who survived showed the complete resolution of perivascular enhancements and the improvement of FLAIR high signal intensity lesions that persisted long after the interruption of corticosteroid therapy. Brain MRIs, which were performed in 3 patients who died, also showed the absence of perivascular enhancements and the persistence of FLAIR high signal intensity lesions.

**DISCUSSION**

We describe 14 patients with severe HIV-associated encephalitis despite satisfactory HIV control indices. This complication is characterized by a massively diffuse but predominantly perivascular infiltration of polyclonal CD8\(^+\) lymphocytes [5, 6, 12].

In the setting of acute encephalitis, where bilateral FLAIR high signal intensity lesions might be unspecific, multiple perivascular contrast enhancements in postgadolinium T1 sequences are strongly suggestive of CD8 encephalitis. Differential diagnoses such as endovascular lymphoma, sarcoidosis, and vasculitis were excluded in our cases. Neither these specific enhancements nor the pathological features of the disorder have been described in the context of HIV encephalitis since the first cases reported by Miller et al [5]. Thus, in cases of encephalitis without any obvious etiology, brain MRIs should systematically include a postcontrast T1 spin-echo sequence with magnetization transfer, which is the only means of highlighting the key diagnostic perivascular enhancements. In the absence of this specific MRI feature, here detailed for the first time in this condition, several authors have reported only the specific T2 diffuse white matter signal abnormalities and brain swelling in cases of HIV-infected CD8 encephalitis [5, 6, 8]. CSF abnormalities were mild in these patients, but the pleocytosis was mainly due to CD8 lymphocytes expressing the CCR5...
phenotypes in a proportion greater than that of the plasma, with the majority of CD8 lymphocytes being activated. Only 1 patient had peripheral CD8 hyperlymphocytosis. The blood CD8 count was not a discriminating factor in the cases of HIV-associated encephalitis reported [6].

In our 13-year survey we observed no increase in HIV-associated CD8 encephalitis over time. The overall prognosis was poor, and only 30% of patients achieved total recovery without any sequelae, notably with an absence of cognitive impairment. To date, all documented patients died within a few weeks of disease onset [5, 6]. With a mean follow-up of almost 8 years for the survivors, our study indicates that the set of clinical and radiological findings in association with CSF CD8 lymphocytosis clearly indicates that corticosteroid therapy should be promptly initiated without recourse to a brain biopsy in cases of HIV-associated CD8 encephalitis. Prognostic factors remain undetermined [6], but the sooner corticosteroid therapy was initiated, the better was the prognosis in our series.

In contrast to some reports [4], studies have shown that the absence of florid-productive HIV infection and multinucleated giant cells clearly differentiates CD8 encephalitis from HIV-associated encephalitis [5, 6]. Although the CSF VL was high at the neurological onset of HIV-associated encephalitis, HIV-1 p24 antigen staining was inconsistent and always weak in brain biopsies. The severe inflammatory lesions observed are also very different from those found in various viral encephalitis and inflammatory leukoencephalopathies [12], and other infections were ruled out by microbiological and histopathological techniques. ADEM is characterized by myelin destruction with sleeves of demyelination surrounding small vessels [15]. True demyelination in our series was observed only in patient 8. The clinical and radiological features were also very different from those of multiple sclerosis or acute disseminated encephalomyelitis, even though in a few cases demyelinating lesions were noted in brain biopsies and notably in the autopsied cases [13, 16]. In ADEM, MRI typically shows large, multiple supratentorial lesions with at least 1 lesion >1–2 cm in diameter [17]. In CD8 encephalitis, T2 FLAIR hyperintensities are more diffuse and poorly delineated than in ADEM, but the principal difference is the gadolinium-enhanced lesions. In CD8 encephalitis, lesions are thinner than 2 mm and could be missed if a postcontrast T1 spin echo–echo sequence with magnetization transfer is not performed. These faint gadolinium enhancements follow perivascular spaces with a linear or punctate shape in the middle of the FLAIR hyperintensities, whereas in ADEM the enhancement is peripheral with a ring or incomplete ring-shaped form [18].

We identified 4 potential triggers: minor infection in well-controlled patients (patients 1, 4, 7, 8, 11, and 13), CNS IRIS (patients 3 and 5), virological escape (patients 9 and 10), and HAART interruption (patient 2). The earliest documented cases of CD8 encephalitis were identified within the context of a CNS IRIS [5, 12] with which the disorder was thought to be associated [5, 8, 19]. It is therefore noteworthy that in our series, CNS IRIS affected only 2 patients. In the majority of cases, CD8 encephalitis appeared unexpectedly in clinically and immunologically stable patients [6]. Our hypothesis is that CD8 encephalitis involves a novel HIV presentation, favored by the interruption of cART, virological escape, or a concomitant minor infection. The very specific neurological and radiological features, not previously described in other postinfectious encephalitis, support an HIV-driven mechanism elicited by a precipitating minor infection [20, 21].

Whatever the mechanisms of CD8 encephalitis, the common basis is probably a transient disequilibrium between HIV and brain immunity. The presence of numerous CD8 lymphocytes in association with reactive astrocytosis and microglial activation, which are found in all cases of the disorder, suggests that the immune activation of the brain is triggered by HIV alone, without the intervention of other microorganisms. The inconsistent and weak HIV-1 p24 antigen immunostaining observed on brain biopsies in our cases, as in those reported by others [6], confirmed that microglial activation was not due to an underlying viral replication. Virological investigations failed to individualize any particularly neurovirulent strain, any phenotypic difference between plasmatic and CSF strains, or any compartmentalization [22]. The immediate efficacy of corticosteroid therapy also supports the idea of an inflammatory pathogenesis. It has been suggested that when HIV enters the brain it may initiate several potentially inflammatory cascades that are aimed at controlling the infection [23, 24]. In certain cases, the inflammation may overshoot its objective, with deleterious consequences for the CNS [25, 26]; it could then become self-sustaining and operate as an autonomous mechanism, even in the absence of any productive infection, as in ADEM. The aim of corticosteroid therapy is to block this phenomenon before it becomes a chronic process [24]. The sharp increase in brain CD8 inflammatory infiltration with ADEM-like lesions, which were observed between the biopsy and autopsy samples in 1 of our patients, despite optimal immunovirological control over a whole year, raises the possibility of a potentially autonomous CD8 response in certain patients.

Host genetic factors may also play a role in the development of HIV-associated CD8 encephalitis, as the majority of patients reported [5, 6], and almost half of ours, were African, compared with the overall multicenter cohort that included about a quarter of African patients. HLA was not determined in our series. The severe angiocentric CD8+ lymphocyte infiltration may be similar to that observed in neuropathies associated with DILS [27]. However, we preferred not to label HIV-associated CD8 encephalitis “cerebral DILS” as HIV products were found
CONCLUSIONS

We report 14 cases of CD8 encephalitis in HIV-infected patients. This is a clinical condition that should be added to the list of complications of HIV infection and should be considered when managing such patients. It is important to recognize the clinical implications of the condition so as to deal with it appropriately. Patients who underwent a brain biopsy experienced no adverse effects of the neurosurgical procedure. Although alternative diagnoses could be excluded by complete evaluation of the patients, the clinical, CSF, and radiological features may suffice for the diagnosis of CD8 encephalitis in HIV-infected patients and allow rapid glucocorticoid treatment without further pathological examination. Prospective studies are currently under way to enable a better understanding of the pathophysiology of the disorder and to design the best therapeutic strategy.

Notes

Acknowledgments. We are particularly grateful to Dr Marc Polivka and Pr Françoise Chapon for the histopathology of patient 13, Pr Jacqueline Mikol for discussion of the earliest cases in our series, Dr Jean-Baptiste Thiebaut for stereotactic brain biopsies, Dr François Héran for interpretation of the first brain MRIs, and Ms Anne-Claire Viret for cognitive evaluations.

Financial support. None.

Potential conflicts of interest. F. X. L. has received funding for board membership from BMS, Gilead Sciences, and Viiv Healthcare; for lectures from Abbott, Boehringer Ingelheim, Gilead Sciences, MSD France, Tibotec, and Viiv Healthcare; and for meeting travel from Abbott, Gilead Sciences, MSD France, Tibotec, and Viiv Healthcare. A. M. has received funding for board membership from Biogen Idec; for lectures from Biogen Idec, MSD France, Abbott, and Gilead Sciences; and for meeting travel from Bioden Idec, Teva Pharma and Novartis. J. S. has received funding for lectures from Bayer, Philips, and Gilead Sciences; and for meeting travel from Bayer. G. C. has received funding for lectures from MSD France. J. P. has received funding for board membership from Abbott and Gilead Sciences. J. M. M. has received funding for board membership from BMS, Gilead Sciences, MSD, and Viiv Healthcare; for consultancy from Gilead Sciences and MSD; for lectures from Gilead Sciences, MSD France, and Tibotec; and for meeting travel from Abbott. G. P. has received funding for board membership from Abbott, BMS, Gilead Sciences, Tibotec-Janssen, and Viiv Healthcare; for lectures from Abbott, Boehringer Ingelheim, BMS, GSK, Gilead Sciences, MSD France, Pfizer, Roche, Nephrocare, Tibotec-Janssen and Viiv Healthcare,; and for meeting travel from Abbott, BMS, Gilead sciences and Viiv Healthcare. C. A. has received funding for lectures from BMS, Gilead Sciences, and MSD France and for meeting travel from BMS and Tibotec-Janssen. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

22. Schnell G, Spudich S, Harrington P, Price RW, Swanstrom R. Compart-
mentalized human immunodeficiency virus type 1 originates from
long-lived cells in some subjects with HIV-1-associated dementia.
molecule and chemokine receptor expression on CD8+ T cells traffick-
ing to cerebrospinal fluid in HIV-1 infection. J Infect Dis 2004;
189:2202–12.
24. Wang T, Rumbaugh JA, Nath A. Viruses and the brain: from inflamma-
25. Medana I, Martinic MA, Wekerle H, Neumann H. Transection of
major histocompatibility complex class I-induced neurites by cytotoxic
nervous system pathology caused by autoreactive CD8+ T-cell clones
27. Moulignier A, Authier FJ, Baudrimont M, et al. Peripheral neuro-
pathy in human immunodeficiency virus-infected patients with the
diffuse infiltrative lymphocytosis syndrome. Ann Neurol 1997; 41:
438–45.