Progressive Multifocal Leukoencephalopathy with Immune Reconstitution Inflammatory Syndrome (PML-IRIS): Two Case Reports of Successful Treatment with Mefloquine and a Review of the Literature

Dear Editor,

Failure of cell-mediated immunity allows reactivation of the ‘JC’ polyomavirus (JCV) in oligodendrocytes, and the development of progressive multifocal leukoencephalopathy (PML). This is most commonly associated with advanced human immunodeficiency virus (HIV) infection, but is also described after biological therapies such as natalizumab, and rarely other conditions.1

In the early years of HIV treatment, PML frequently resulted in death irrespective of medical interventions. The development of antiretroviral therapy (ART) has greatly improved this prognosis. In the Swiss Cohort Study, incidence fell 4-fold and attributable 1-year mortality fell from 60% to 20%.2 Despite these advances, PML still has one of the highest mortality rates among acquired immune deficiency syndrome (AIDS) defining illnesses. A rapid early mortality is observed, and less than half of survivors are expected to recover neurologically.3 While re-establishment of the immune system is important for successful outcomes, it can trigger an acute inflammatory response to JCV or host antigens. This immune reconstitution inflammatory syndrome (IRIS) exacerbates symptoms, though may not adversely affect mortality.4

Neither broad spectrum antiviral therapy with interferon alpha nor putative anti-JCV agents such as cidofovir and cidofovir have proved successful PML treatments.5,6 A cell-based screen of several thousand compounds for inhibition of JCV infection rates identified the anti-malarial mefloquine as a new therapeutic candidate.7 Mefloquine appeared to block JCV replication without significant toxicity, and at concentrations achievable in the central nervous system (CNS). A number of case reports have since been published, reporting successful PML treatment with mefloquine in HIV and non-HIV infected patients. A randomised, rater-blinded study sponsored by Biogen Idec (Clinicaltrials.gov identifier NCT00746941) to assess mefloquine efficacy in patients with PML and imaging response to ART was initiated with stavudine, lamivudine and ritonavir-boosted atazanavir. Immunologic and virologic parameters responded rapidly to ART. Over the next 2 months, CD4+ counts rose to 250/mm³ (13%) and VL fell by almost 3 log to 425 copies/mL (2.6 log). Clinical condition deteriorated however. A progressive cerebellar ataxia resulted in further falls, and repeat cerebral MRI revealed a contrast enhancing abnormality in the right basal ganglia and thalamus extending into the subcortical white matter of the frontal lobe (Figs. 1A and B). A lumbar puncture was performed: cerebrospinal fluid (CSF) analysis showed red blood cells 1285 cells/μL, nucleated cells 10 cells/μL, lymphocytes 83% and neutrophils 8%, protein 0.97 g/L and glucose 3.6 mmol/L. CSF JCV real-time polymerase chain reaction (RT-PCR) was positive. All additional microbiological analyses were negative, including PCRs for cytomegalovirus (CMV), herpes simplex virus (HSV), Epstien-Barr virus (EBV), varicella zoster virus (VZV), Toxoplasma gondii, plus cryptococcal antigen, pyogenic, fungal and mycobacterial stains and cultures. Computed tomography of the thorax, abdomen and pelvis did not identify any evidence of lymphadenopathy, infection or malignancy. A presumptive diagnosis of PML was made (Fig. 2).

In the following weeks, neurological status continued to deteriorate with increasing disorientation, left sided hemiparesis and severe oro-pharyngeal dysphagia. Repeat cerebral MRI demonstrated lesion progression and increasing mass effect over the left lateral and third ventricles. An open brain biopsy was performed, and histology confirmed features of polyomavirus infection plus...
an inflammatory infiltrate, consistent with PML-IRIS. ARTs were continued and a tapering regimen of high dose oral dexamethasone for 6 weeks administered. This produced no clinical improvement and only mixed changes by MRI, with less extensive disease in the brainstem but progression in the right frontal and parietal lobes.

A trial of mefloquine was initiated: 250 mg orally daily for 3 days, followed by 250 mg once weekly. A remarkable neurological improvement rapidly ensued, such that within one month, cerebellar dysfunction and left sided hemiparesis regressed to allow ambulation with assistance. Orientation and ability to perform basic activities of daily living were regained. Follow up cerebral MRI confirmed significant reduction in the areas of T2 prolongation and associated mass effect (Figs. 1C and 1D). No apparent adverse reactions were noted, despite close monitoring for gastrointestinal, CNS and electrocardiographic disturbances. Repeat CSF sampling for JCV PCR was not performed. Two years after the initial diagnosis of HIV, the patient remains well, with only residual cerebellar dysfunction of the left side. He is able to perform activities of daily living (ADLs) with minimal assistance, and ambulate with a frame.

**Case Report 2**

A 39-year-old Malay male was diagnosed with HIV infection as part of routine health screening. He was asymptomatic with no clinically detectable opportunistic infections and CD4+ counts 332 cells/mm³ (16%). Soon after he was lost to follow-up, until re-presenting 3 years later with pharyngitis and CD4+ count of 27 cells/mm³ (2%). Zidovudine, lamivudine and efavirenz were started, but despite counseling he achieved less than 70% adherence....
to medications and attendance at follow-up appointments was infrequent.

A further 3 years later, left-sided hemiparesis developed with slurred speech and dysphagia. CD4+ counts remained low, at 33 cells/mm³ (4%), and VL unsuppressed at 59,061 copies/mL (4.77 log). MRI revealed a T2/FLAIR hyperintense and T1 hypointense focus involving the subcortical white matter of the right frontoparietal lobe, extending into the deep white matter. Small foci were also detected in the left frontal lobe. There was no enhancement with gadolinium contrast. CSF contained only occasional lymphocytes and an elevated protein of 0.52g/L. JCV PCR was positive, while PCRs for EBV, CMV, HSV, VZV and T.gondii were negative. Pyogenic and fungal stains and culture were negative, as were cryptococcal antigen, and cytology for malignant cells. The patient was diagnosed with PML, and HIV treatment was switched to abacavir, lamivudine and ritonavir-boosted lopinavir.

Over the next 3 months, weakness of the left upper and lower limb continued to progress, while CD4+ counts improved to 76 cells/mm³ (3%), and VL became undetectable. MRI showed interval progression of bilateral white matter signal change, more prominent on the right, consistent with PML-IRIS. Prednisolone 60 mg daily with a slow taper was started. However, neurological condition deteriorated further such that he became bed-bound, requiring full ADL assistance and nasogastric feeding. Mefloquine with the same dose schedule as Case 1 was started. Neurological symptoms improved dramatically. Over the next 2 months, he was able to perform the majority of ADLs including to feed self orally, and ambulate with assistance. Again, repeat CSF examination was not available (Fig. 2).

Literature Review

All publications reporting in detail the treatment of PML with mefloquine were sought up to June 2012. A search of the Medline database via the PubMed interface was performed using the search terms ‘Mefloquine’AND ‘PML’ OR ‘Progressive Multifocal leukoencephalopathy’. Article titles and abstracts were screened for relevant content, and full papers accessed.

Eight articles were identified, reporting 8 cases of PML treatment with mefloquine. No articles were excluded. Patient characteristics, treatment and outcomes are summarised in Table 1.

Discussion

The 2 new cases reported here meet diagnostic criteria for ‘histology-confirmed’ and ‘laboratory-confirmed’ PML, respectively.9 Additional AIDS associated conditions such as primary CNS lymphoma, CMV meningoencephalitis and cerebral toxoplasmosis have been reasonably excluded. Both developed IRIS after receiving virologically suppressive ART with immune recovery from low CD4+ counts. Clinical improvement after adding mefloquine and despite many months of alternative therapy suggests this may have been due to mefloquine, rather than a chance effect. We believe mefloquine modifies the inflammatory response to JCV or host antigens during immune recovery.

Strikingly, all but one of the cases identified in the literature review also report features suggestive of a vigorous immune recovery and reaction to opportunistic infection. IRIS was explicitly diagnosed in 2 of the 8 cases, while in 5, other features indicating significant inflammation were evident by histopathology or radiology. Furthermore, in 6 cases, mefloquine was only started after a reduction in immunosuppression resulted in a clinical deterioration. This included initiating ART (Moernter et al21, Naito et al22), steroid taper (Goffton et al23) and completion of steroid containing chemotherapy (Kishida et al24).

Quinoline compounds such as hydroxychloroquine have anti-inflammatory activities and are used for the treatment of systemic lupus erythematosus and rheumatoid arthritis. These weak bases are thought to accumulate in the acidic lysosomal compartment of antigen presenting cells, interfering with the processing of phagocytosed material onto class II major histocompatibility complexes (MHC), and suppressing activation of pathogen-recognition receptors (PRR) such as Toll-like receptor 9 (TLR9).10,11 Mefloquine has been demonstrated to suppress the oxidative burst and reduce neutrophil chemotaxis, phagocytosis, and viability in a manner similar to hydroxychloroquine.12 It also inhibits lymphocyte proliferation and production of the inflammatory cytokine Interleukin-2 (IL-2), which contributes to suppressed Natural killer (NK) cell activity.13,14 Hydroxychloroquine significantly reduces lymphocyte markers of immune activation in HIV-infected individuals receiving virologically suppressive ART.15 It has also been reported to successfully mitigate the effects of IRIS in cryptococcal meningitis.16

A JCV-specific cell-mediated immune response correlates with PML disease containment and survival.17 Yet an extensive CD8+ infiltrate with exuberant recruitment of inflammatory cells is observed in histopathological specimens of PML-IRIS.18 The recovery of pathogen specific CD4+ cells—the effector counterpart to MHC Class II antigen complexes, is important in the immunopathogenesis of IRIS.19 Modulation of this inflammatory axis, rather than direct anti-JCV activity, could be a mechanism for mefloquine action, and warrants further investigation.
Table 1. Summary of Case Reports of PML Treatment with Mefloquine

<table>
<thead>
<tr>
<th>Case Details</th>
<th>Other Treatment(s)</th>
<th>Histology</th>
<th>Outcomes Reported</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>67-year-old male with SLE</td>
<td>Corticosteroid, cidofovir</td>
<td>Macrophage infiltrate</td>
<td>Partial recovery, died</td>
<td>Beppu et al 2003</td>
</tr>
<tr>
<td>49-year-old male with HIV/AIDS</td>
<td>Corticosteroid, mirtazapine, ART</td>
<td>No biopsy</td>
<td>Partial recovery, died on day 16 after refusing further treatment</td>
<td>Moenster et al 2012</td>
</tr>
<tr>
<td>55-year-old male with HIV/AIDS</td>
<td>ART</td>
<td>No biopsy</td>
<td>Partial recovery, status after 8/52 of mefloquine not known</td>
<td>Naito et al 2013</td>
</tr>
<tr>
<td>60-year-old male with no known immunodeficiency</td>
<td>Corticosteroid</td>
<td>Marked inflammation with B and T lymphocytes</td>
<td>Partial recovery, significant residual impairment</td>
<td>Hirayama et al 2012</td>
</tr>
<tr>
<td>74-year-old female with isolated CD8+ deficiency</td>
<td>Corticosteroid, mirtazapine</td>
<td>Extensive inflammatory infiltrate of B and T lymphocytes, plasma cells and macrophages</td>
<td>Partial recovery, significant residual impairment</td>
<td>McGuire et al 2012</td>
</tr>
<tr>
<td>37-year-old male with cord blood stem cell transplant</td>
<td>Nil</td>
<td>No biopsy</td>
<td>Partial recovery, significant residual impairment</td>
<td>Kishida et al 2012</td>
</tr>
<tr>
<td>41-year-old female with multiple sclerosis with natalizumab</td>
<td>Corticosteroid, mirtazapine</td>
<td>No biopsy</td>
<td>Recovery to pre-morbid</td>
<td>Schroder et al 2012</td>
</tr>
<tr>
<td>54-year-old female with pulmonary sarcoidosis</td>
<td>Corticosteroid, risperidone, mirtazapine, cidofovir</td>
<td>Demyelination (biopsy performed early in disease process)</td>
<td>Disease progression halted</td>
<td>Goffon et al 2012</td>
</tr>
</tbody>
</table>

PML: Progressive multifocal leukoencephalopathy; SLE: Systemic lupus erythematosus; HIV: Human immunodeficiency virus; AIDS: Acquired immunodeficiency syndrome; CSF: cerebrospinal fluid; JCV: JC Virus; PCR: Polymerase chain reaction; pos: positive; neg: negative; IHC: Immunohistochemistry; ART: antiretroviral therapy

REFERENCES
11. Lombard-Platlet S, Bertolino S, Deng H, Gerlier D, Rabourdin-Combe C. Inhibition by chloroquine of the class II major histocompatibility complex restricted presentation of endogenous antigens varies according to the cellular origin of the antigen-presenting cells, the nature of the T-cell epitope, and the responding T cell. Immunology. 1993;80:566-73.


