Letter to the Editor

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 cytarabine 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 theraputic 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 was stopped in early 2011 after an analysis of the first 24 participants randomised identified no virologic benefit, the primary endpoint.[8] This study is yet to be published, and clearly caution must be adopted with continued off-label use of mefloquine. However it is possible subgroups may benefit. We report 2 cases of PML-IRIS in HIV-infected individuals with dramatic responses after mefloquine treatment was started, and postulate an alternative mechanism of action.

Case Report 1

A 57-year-old Eurasian male was diagnosed with HIV/AIDS after presenting with recurrent falls, functional decline, progressive weakness, and weight loss for 3 months. Initial CD4+ counts were less than 20/mm^3 (<1%) and viral load (VL) 352,000 copies/mL (5.5 log). Contrast-enhanced magnetic resonance imaging (MRI) of the brain revealed old lacunae infarcts. No inter-current opportunistic infections or co-infections were identified and 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/mm^3 (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/uL, nucleated cells 10 cells/uL, 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

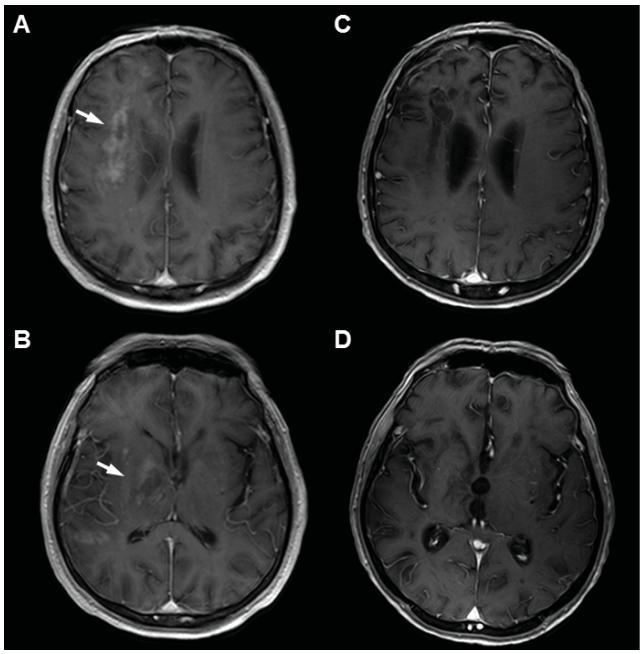

Fig. 1. Axial contrast-enhanced brain MRI showing areas of enhancement (arrows in A and B) in the right basal ganglia, thalamus and subcortical frontal white matter lesions with resolution after mefloquine therapy (C and D).

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 re-gained. 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%). Zidovuidine, lamivudine and efavirenz were started, but despite counseling he achieved less than 70% adherence

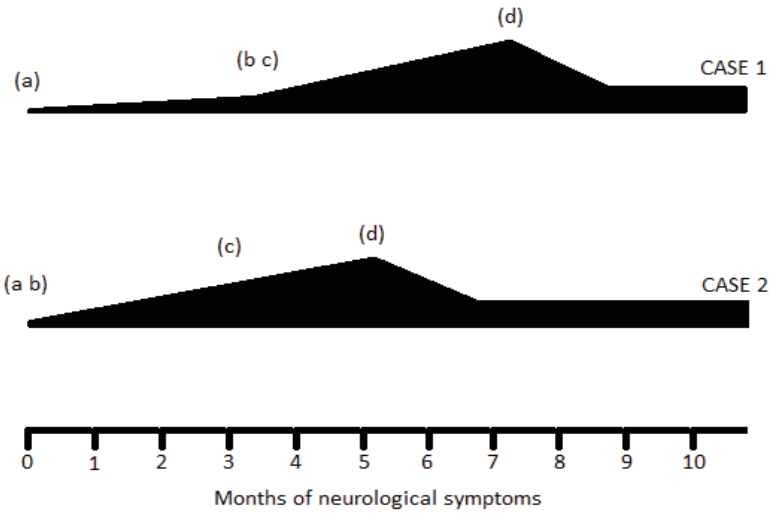

Fig. 2. Timeline approximating neurological symptomology for the2 cases reported. (a) Initiation of antiretroviral therapy (ART); (b) Diagnosis of progressive multifocal leukoencephalopathy (PML); (c) Diagnosis of PML Immune reconstitution inflammatory syndrome (PML-IRIS); Initiation of mefloquine therapy.

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 (Moenster et al[21], Naito et al[22]), steroid taper (Gofton et al[27]) and completion of steroid containing chemotherapy (Kishida et al[25]).

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 hydroxyxhloroquine.[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 meningtis.[16]

AJCV-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 immunopathogeneisis of IRIS.[19] Modulation of this inflammatory axis, rather than direct anti-JCV activity, could be a mechanism for melfoquine action, and warrants further investigation.

Table 1. Summary of Case Reports of PML Treatment with Mefloquine

Case Details	Other Treatment(s)	Histology	Outcomes Reported			References
			Clinical	Radiological	Virological	
67-year-old male with SLE	Corticosteroid, cidofovir	Macrophage infiltrate	Partial recovery, died	Stabilisation of lesions	CSF JCV PCR neg, brain biopsy JCV PCR pos to neg)	Beppu et al[20]
49-year-old male with HIV/AIDS	Corticosteroid, mirtazapine, ART	No biopsy	Partial recovery, died on day 16 after refusing further treatment	Not repeated	Initial CSF JCV PCR pos, no repeat	Moenster et al[21]
55-year-old male with HIV/AIDS	ART	No biopsy	Partial recovery, status after 8/52 of mefloquine not known	Progression of lesions	CSF JCV PCR pos to neg after 8 weeks	Naito et al[22]
60-year-old male with no known immunodeficiency	Corticosteroid	Marked inflammation with B and T lymphocytes	Partial recovery, significant residual impairment	Lesions reduced in size	Brain biopsy positive for JCV by IHC. Not repeated. CSF JCV PCR neg	Hirayama et al[23]
74-year-old female with isolated CD8+ deficiency	Corticosteroid, mirtazapine	Extensive inflammatory infiltrate of B and T lymphocytes, plasma cells and macrophages	Partial recovery, significant residual impairment	Stabilisation, reduced enhancement	CFS JCV PCR pos to neg after 13 days	McGuire et al[24]
37-year-old male with cord blood stem cell transplant	Nil	No biopsy	Partial recovery, significant residual impairment	Stable lesions	CSF JCV PCR pos to neg after 3 months	Kishida et al[25]
41-year-old female with multiple sclerosis with natalizumab	Corticosteroid, mirtazapine	No biopsy	Recovery to pre-morbid	Residual lesions, reduction in contrast enhancement and mass effect	CSF JCV PCR pos to neg after 3 months	Schroder et al[26]
54-year-old female with pulmonary sarcoidosis	Corticosteroid, risperidone, mirtazapine, cidofovir	Demyelination (biopsy performed early in disease process)	Disease progression halted	Stabilisation	CSF JCV PCR pos to neg after 5 months	Gofton et al[27]

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

1. Kedar S, Berger JR. The changing landscape of progressive multifocal leukoencephalopathy. Curr Infect Dis Rep 2011;13:380-6.
2. Khanna N, Elzi L, Mueller NJ, Garzoni C, Cavassini M, Fux CA, et al. Incidence and outcome of progressive multifocal leukoencephalopathy over 20 years of the Swiss HIV Cohort Study. Clin Infect Dis 2009;48:1459-66.
3. Marzocchetti A, Tompkins T, Clifford DB, Gandhi RT, Kesari S, Berger JR, et al. Determinants of survival in progressive multifocal leukoencephalopathy. Neurology 2009;73:1551-8.
4. Harrison DM, Newsome SD, Skolasky RL, McArthur JC, Nath A. Immune reconstitution is not a prognostic factor in progressive multifocal leukoencephalopathy. J Neuroimmunol 2011;238:81-6.
5. De Luca A, Ammassari A, Pezzotti P, Cinque P, Gasnault J, Berenguer J, et al. Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated progressive multifocal leukoencephalopathy: a multicohort analysis. AIDS. 2008;22:1759-67.
6. Hall CD, Dafni U, Simpson D, Clifford D, Wetherill PE, Cohen B, et al. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. AIDS Clinical Trials Group 243 Team. N Engl J Med 1998;338:1345-51.
7. Brickelmaier M, Lugovskoy A, Kartikeyan R, Reviriego-Mendoza MM, Allaire N, Simon K, et al. Identification and characterization of mefloquine efficacy against JC virus in vitro. Antimicrob Agents Chemother 2009;53:1840-9.
8. David Clifford AN, Paola Cinque, Bruce J. Brew, Andy Workman, Leonid Gorelik, Jim Zhao, Petra Duda. Mefloquine Treatment in Patients with Progressive Multifocal Leukoencephalopathy (PML). 63rd American Academy of Neurology Annual Meeting; Honolulu, Hawaii 2011.
9. Cinque P, Koralnik IJ, Clifford DB. The evolving face of human immunodeficiency virus-related progressive multifocal leukoencephalopathy: defining a consensus terminology. J Neurovirol 2003;9:88-92.
10. Martinson JA, Montoya CJ, Usuga X, Ronquillo R, Landay AL, Desai SN. Chloroquine modulates HIV-1-induced plasmacytoid dendritic cell alpha interferon: implication for T-cell activation. Antimicrob Agents Chemother 2010;54:871-81.
11. Lombard-Platlet S, Bertolino P, 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.

12. Labro MT, Babin-Chevaye C. Effects of amodiaquine, chloroquine, and mefloquine on human polymorphonuclear neutrophil function in vitro. Antimicrob Agents Chemother 1988;32:1124-30.
13. Bygbjerg IC, Svenson M, Theander TG, Bendtzen K. Effect of antimalarial drugs on stimulation and interleukin 2 production of human lymphocytes. Int J Immunopharmacol 1987;9:513-9.
14. Pedersen BK, Bygbjerg IC, Theander TG, Andersen BJ. Effects of chloroquine, mefloquine and quinine on natural killer cell activity in vitro. An analysis of the inhibitory mechanism. Allergy. 1986;41:537-42.
15. Piconi S, Parisotto S, Rizzardini G, Passerini S, Terzi R, Argenteri B, et al. Hydroxychloroquine drastically reduces immune activation in HIV-infected, antiretroviral therapy-treated immunologic nonresponders. Blood 2011;118:3263-72.
16. Narayanan S, Banerjee C, Holt PA. Cryptococcal immune reconstitution syndrome during steroid withdrawal treated with hydroxychloroquine. Int J Infect Dis 2011;15:e70-3.
17. Khanna N, Wolbers M, Mueller NJ, Garzoni C, Du Pasquier RA, Fux CA, et al. JC virus-specific immune responses in human immunodeficiency virus type 1 patients with progressive multifocal leukoencephalopathy. J Virol 2009;83:4404-11.
18. Metz I, Radue EW, Oterino A, Kumpfel T, Wiendl H, Schippling S, et al. Pathology of immune reconstitution inflammatory syndrome in multiple sclerosis with natalizumab-associated progressive multifocal leukoencephalopathy. Acta Neuropathol 2012;123:235-45.
19. Mahnke YD, Greenwald JH, DerSimonian R, Roby G, Antonelli LR, Sher A, et al. Selective expansion of polyfunctional pathogen-specific CD4(+) T cells in HIV-1-infected patients with immune reconstitution inflammatory syndrome. Blood 2012;119:3105-12.
20. Beppu M, Kawamoto M, Nukuzuma S, Kohara N. Mefloquine improved progressive multifocal leukoencephalopathy in a patient with systemic lupus erythematosus. Intern Med 2012;51:1245-7.
21. Moenster RP, Jett RA. Mirtazapine and mefloquine therapy for progressive multifocal leukoencephalopathy in a patient infected with human immunodeficiency virus. Am J Health Syst Pharm 2012;69:496-8.
22. Naito K, Ueno H, Sekine M, Kanemitsu M, Ohshita T, Nakamura T, et al. Akinetic mutism caused by HIV-associated progressive multifocal leukoencephalopathy was successfully treated with mefloquine: a serial multimodal MRI Study. Intern Med 2012;51:205-9.
23. Hirayama M, Nosaki Y, Matsui K, Terao S, Kuwayama M, Tateyama H, et al. Efficacy of mefloquine to progressive multifocal leukoencephalopathy initially presented with parkinsonism. Clin Neurol Neurosurg 2012;114:728-31.
24. McGuire JL, Fridman V, Wuthrich C, Koralnik IJ, Jacobs D. Progressive multifocal leukoencephalopathy associated with isolated CD8+ T-lymphocyte deficiency mimicking tumefactive MS. J Neurovirol 2011;17:500-3.
25. Kishida S, Tanaka K. Mefloquine treatment in a patient suffering from progressive multifocal leukoencephalopathy after umbilical cord blood transplant. Intern Med 2010;49:2509-13.
26. Schroder A, Lee DH, Hellwig K, Lukas C, Linker RA, Gold R. Successful management of natalizumab-associated progressive multifocal leukoencephalopathy and immune reconstitution syndrome in a patient with multiple sclerosis. Arch Neurol 2010;67:1391-4.
27. Gofton TE, Al-Khotani A, O'Farrell B, Ang LC, McLachlan RS. Mefloquine in the treatment of progressive multifocal leukoencephalopathy. J Neurol Neurosurg Psychiatry 2011;82:452-5.

Barnaby E Young, [1]*MB BChir, MRCP (UK)*, Tian Rong Yeo, [1]*MBBS, MRCP (UK)*, Hui Ting Lim, [2], Kiat Yee Vong, [2], Kevin Tan, [3] *BM BS, MRCP (UK)*, David C Lye, [1,4]*MBBS, FRACP, FAMS*, Cheng Chuan Lee, [1]*MBBS, FRCP (Edin)*

[1]Department of Infectious Disease, Tan Tock Seng Hospital, Singapore
[2]Yong Loo Lin School of Medicine, National University of Singapore
[3]Department of Neurology, National Neuroscience Institute, Singapore
[4]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore

Address for Correspondence: Dr Barnaby Young, Infectious Diseases, Communicable Disease Centre, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: barnaby_young@ttsh.com.sg