PML-IRIS in patients with HIV infection

Clinical manifestations and treatment with steroids

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ABSTRACT

Background: Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection that develops in immunosuppressed patients with HIV infection. Paradoxically, some of these patients may develop PML during combined antiretroviral therapy in the setting of immune reconstitution. We describe the types of PML in relation to immune reconstitution inflammatory syndrome (IRIS) and the effects of steroid use in these patients.

Methods: We performed a retrospective review of the literature (1998 to 2007) and of all HIV-infected patients diagnosed with PML-IRIS at Johns Hopkins Hospital (2004 to 2007). We recorded information on clinical features, microbiologic and virological analysis, neuroimaging, pathology, treatment, and outcome.

Results: Of 54 patients with PML-IRIS, 36 developed PML and IRIS simultaneously (PML-s-IRIS) and 18 had worsening of preexisting PML (PML-d-IRIS) after the initiation of combined antiretroviral therapy. PML-IRIS developed between 1 week and 26 months after initiation of antiretroviral therapy. PML-d-IRIS patients developed IRIS earlier, had higher lesion loads on MRI of the brain, had shorter durations of survival, and had higher mortality rate compared to PML-s-IRIS patients. Twelve patients received treatment with steroids, of which five died and seven showed good neurologic recovery. Patients who survived had received steroids early after IRIS diagnosis for longer durations and had contrast enhancement on IRIS neuroimaging.

Conclusions: Immune reconstitution following initiation of combined antiretroviral therapy may lead to activation of an inflammatory response to detectable or latent JC virus infection. Early and prolonged treatment with steroids may be useful in these patients but requires further investigation.
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GLOSSARY

FLAIR = fluid-attenuated inversion recovery; **HAART** = highly active antiretroviral therapy; **IRIS** = immune reconstitution inflammatory syndrome; **JCV** = JC virus; **JHH** = Johns Hopkins Hospital; **PML** = progressive multifocal leukoencephalopathy; **PML-d-IRIS** = worsening of preexisting PML; **PML-s-IRIS** = PML and IRIS simultaneously.

Despite a dramatic decrease in the incidence of most opportunistic infections in the era of combined antiretroviral therapy, progressive multifocal leukoencephalopathy (PML) continues to occur at a similar frequency in patients with HIV infection. Up to 5% of patients with AIDS develop PML.[1]

This poses a unique challenge for the neurologist, because PML carries a high morbidity and mortality rate and for which there is no effective treatment. PML is caused by reactivation of JC virus (JCV), a polyomavirus, which infects oligodendrocytes and astrocytes in the CNS, inducing a non-inflammatory lytic reaction leading to demyelination, necrosis, and cell death.

The use of combined antiretroviral therapy markedly improves immune function and prognosis in HIV-infected patients[2]; however, PML may develop or worsen with antiretroviral therapy, despite a recovery of the immune system.[3-25] This manifestation is believed to be a result of immune reconstitution inflammatory syndrome (IRIS).[26] PML-IRIS may account for up to 18% of HIV-

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infected patients with PML.[27] The lesions are often characterized by contrast enhancement on neuroimaging.[4,6,8,11-13,15,18-22] Histopathologic examination demonstrates severe inflammatory and demyelinating lesions with marked infiltration by macrophages and CD8+ T lymphocytes.[19]

There are no evidence-based guidelines for the prevention or management of PML-IRIS. Some cases of IRIS are mild and resolve with continuation of combined antiretroviral therapy. Others result in significant morbidity and sometimes death. Anti-inflammatory agents such as steroids have been used and may be effective in the treatment of IRIS following other AIDS-related CNS infections.[28] In this study, we examine the effects of steroid use in HIV-infected patients with PML-IRIS. We also contrast the features of patients who present with PML and IRIS simultaneously vs those whose neurologic deficits from PML worsened following the development of IRIS.

METHODS We performed a retrospective analysis of HIV-infected patients diagnosed with PML-IRIS evaluated at Johns Hopkins Hospital (JHH) between April 2004 and October 2007. We also reviewed the published literature (1998 to 2007) for similar cases of patients with HIV who developed PML-IRIS at the onset or had worsening of neurologic symptoms following initiation of combined antiretroviral therapy as described by the authors. These patients either 1) were asymptomatic but developed new neurologic deficits due to PML and IRIS following combined antiretroviral therapy (PML-simultaneous-IRIS or PML-s-IRIS) or 2) already had existing PML with neurologic deficits, which worsened with the development of IRIS following initiation of combined antiretroviral therapy (PML-delayed-IRIS or PML-d-IRIS). We recorded information on clinical features, microbiologic and virologic analysis, neuroimaging, pathology, treatment, and outcome. Where data were lacking, the authors were contacted to obtain additional information.

PML-IRIS was defined by the following clinical criteria: 1) patient with HIV infection; 2) the diagnosis of PML was established by detection of JCV DNA in the CSF or brain tissue, characteristic histopathologic features in brain tissue, or by the presence of characteristic clinical and neuroradiologic features with exclusion of other opportunistic infections (tuberculosis, toxoplasmosis, cryptococcus, other viral infections) and CNS lymphoma; 3) treatment with combined antiretroviral therapy resulting in a decrease in plasma HIV viral load; 4) symptoms consistent with an infectious or inflammatory condition that appeared while the patient was on combined antiretroviral therapy; and 5) symptoms could not be explained by a newly acquired infection, the expected course of a newly diagnosed opportunistic infection, or drug toxicity.[28]

The extent of disease was determined by lesion load on MRI scan of the brain. A grading system was developed where one point was given for each affected brain region (frontal, temporal, parietal, occipital, deep gray nuclei, brainstem, and cerebellum) on each side. A good outcome was defined as survival with or without neurologic deficits and a poor outcome was defined as death from the condition at the time of report.

Statistical analysis. Differences between groups were assessed using nonparametric Mann-Whitney test for continuous variables and Fisher exact test for differences in proportions. All statistical analyses were done with STATA version 10.2.

RESULTS **Case report.** A 66-year-old man with HIV infection diagnosed in 1991 and hepatitis C infection was restarted on antiretroviral therapy with darunavir, ritonavir, and Atripla (efavirenz, tenofovir, and emtricitabine) in August 2007. He had a CD4 cell count of 166 cells/mm^3 and HIV plasma viral load of 193,379 copies/mL.

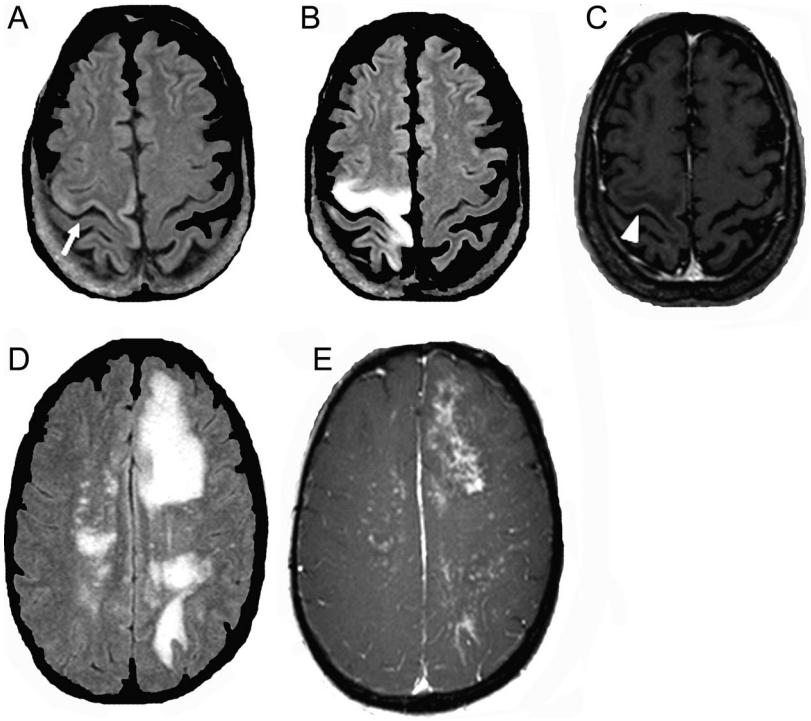
In October 2007, he presented to the hospital with progressive left hand weakness, hypophonia, and mild cognitive slowing. There was no fever, confusion, or other signs of systemic illness. He had a mild left hand weakness and clumsiness, left-sided hyperreflexia, and a left Babinski reflex.

Over the next few days, the patient developed a left hemiplegia. CSF analysis showed glucose of 61 mg/dL, protein of 57 mg/dL, 2 leukocytes, and 37 erythrocytes. CSF bacterial and fungal cultures and cryptococcal antigen were negative. Epstein Barr virus, herpes simplex virus 1 and 2, cytomegalovirus, and varicella zoster virus could not be detected by PCR. CSF JCV PCR was positive (50 copies/mL). At this stage, CD4 cell count was 376 cells/mm^3 and HIV plasma viral load was 1,135 copies/mL. Brain MRI showed a hyperintense FLAIR lesion in the right motor strip, with mild gadolinium enhancement (figure 1A). MRI was of the spinal cord was unremarkable.

The patient was diagnosed with PML in the setting of an immune reconstitution inflammatory syndrome (PML-s-IRIS) and treated with 5 days of IV methylprednisolone (1 g/day) followed by a 6-week oral prednisone taper. His antiretroviral treatment regimen was maintained and he was also commenced on mefloquine (250 mg once weekly), which has been shown to have an inhibitory effect on JCV replication in vitro,[29] which he has continued indefinitely. By day 4 of steroid treatment, the patient began to regain strength in his left arm and was discharged to a rehabilitation facility.

Six weeks later, the patient had residual left hemiparesis (upper extremity motor power grade 3/5 and lower extremity 4/5). His HIV plasma viral load had further decreased to 262 copies/mL and CD4 cell count was 335 cells/mm^3. MRI showed enlargement of the right precentral gyrus lesion and new right frontal and temporal lesions, all of which enhanced with contrast (figure 1, B and C). To demonstrate the wide spectrum of contrast enhancement that may

Figure 1 Axial FLAIR and contrast-enhanced brain MRIs in two patients



Axial fluid-attenuated inversion recovery (FLAIR) (A, B) and contrast-enhanced (C) brain MRI showing abnormal hyperintensity in the right motor strip (arrow in A). Seven weeks later, after completion of steroid treatment, there is enlargement of the contrast-enhanced lesion (B; arrowhead in C) despite clinical improvement. (D) Another patient with HIV infection and progressive multifocal leukoencephalopathy who had extensive patchy white matter involvement on an axial FLAIR image and (E) prominent contrast enhancement.

be seen with PML-IRIS, we have included the MRI of another patient with HIV infection and PML (JCV positive in CSF) who showed dramatic contrast enhancement (figure 1, D and E).

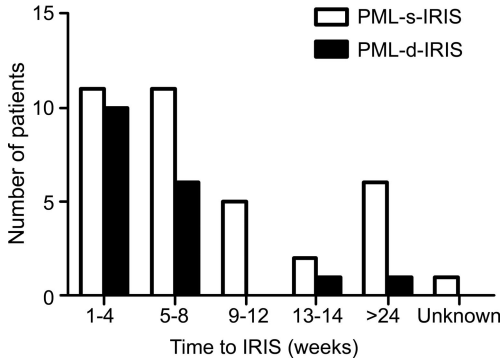
Characteristics of patients. A total of 64 patients who fulfilled the clinical criteria for PML-IRIS were identified (4 from JHH; 60 from the literature).[3-25] There were a total of 13 PML cases out of 2,816 HIV-infected patients treated with combined antiretroviral therapy in JHH over the same period (Richard Moore, personal communication). Nine of the patients described by De Luca et al.[7] were excluded from the analysis because specific information was not reported and we were unable to obtain it from the authors. In one case series the diagnosis of PML was established by PCR for JCV in brain tissue only[10]; hence it is possible that the total number of PML cases may have been overestimated although the detection of JCV in normal brain tissue remains highly controversial. In one patient who was described twice in a case report and a subsequent case series,[11,14] information from the case report was used in the analysis. Of the 54 patients included in the final analysis, 36 patients developed PML-s-IRIS and 18 patients had PML-d-IRIS after the initiation of antiretroviral therapy.

Relationship to initiation of antiretroviral therapy. Antiretroviral therapy had been started at CD4 cell counts ranging between 0 and 450 cells/mm^3 (median = 52.5; n = 46) and plasma HIV viral loads ranging between 3,372 and 1.3×10^6 copies/mL (median = 108,840; n = 38). IRIS was identified between 1 week and 26 months after treatment was initiated, with a median time of 7 weeks. The majority of patients (43/54; 80%) developed PML-IRIS within 12 weeks of initiation of combined antiretroviral therapy, but in 7 patients, PML-IRIS developed after 6 months of initiation of combined antiretroviral therapy (figure 2). Following initiation of combined antiretroviral therapy, CD4 cell counts increased at a median rate of 14.1 cells/mm^3 per week (−6.8–528; n = 44), while HIV viral load decreased at a median rate of 19,838 copies/mL per week (141–258,840; n = 38) (table e-1 on the *Neurology*® Web site at www.neurology.org).

There was no significant difference in the age, sex, CD4 cell counts, and HIV plasma viral loads prior to combined antiretroviral therapy and at onset of IRIS between PML-s-IRIS and PML-d-IRIS patients or their rates of change (table e-1). However, there was a trend for PML-d-IRIS patients to develop IRIS sooner after combined antiretroviral therapy initiation compared to PML-s-IRIS patients (4 weeks vs 8 weeks). PML-d-IRIS patients had a higher lesion load on MRI compared to PML-s-IRIS patients (mean [SD] = 3.27 [1.03] vs 2.0 [0.86], $p = 0.001$). PML-d-IRIS patients also had poorer outcomes compared to PML-s-IRIS patients. PML-d-IRIS patients had shorter overall durations of survival (2.5 weeks vs 8.5 weeks, $p = 0.007$) and died earlier (1 week vs 4.25 weeks, $p = 0.003$) compared to PML-s-IRIS patients. A greater proportion of PML-d-IRIS patients died from the condition compared to PML-s-IRIS patients (52.9% vs 31.3%) (table e-1).

Effect of treatment with steroids. Twelve patients received treatment with steroids. There were no significant differences between patients treated with steroids and those not given steroids in their baseline characteristics of age, sex, CD4 cell counts and HIV plasma viral loads prior to combined antiretroviral therapy and at IRIS onset, the rate of change of CD4 cell counts and HIV plasma viral load, and time to PML-IRIS after initiation of antiretroviral therapy. With steroid treatment, there was no apparent difference in the duration of survival for all patients when only survivors were analyzed, or time to death for the patients who died (table 1).

Figure 2 Time to onset of PML-s-IRIS and PML-d-IRIS after initiation of combined antiretroviral therapy



IRIS = immune reconstitution inflammatory syndrome; PML = progressive multifocal leukoencephalopathy; PML-d-IRIS = worsening of preexisting PML; PML-s-IRIS = PML and IRIS simultaneously.

When steroids were given, it was most often to treat catastrophic deterioration or when there was evidence of an inflammatory component of IRIS on neuroimaging. Although five patients died, seven patients showed good neurologic recovery with steroids use (table e-2). The characteristics of the seven patients who had good outcomes with steroids were compared to the five patients who had poor outcomes (table 2). While not significant, the following trends were noted: patients who survived had received steroids earlier after the recognition of IRIS (mean [SD] = 3 [1.4] vs 12.3 [17] weeks). They also received longer courses of steroids (mean [SD] = 13.3 [7.5] vs 3 [1.7] weeks) (6 months in case 4) and were tapered off steroids more slowly (cases 4 and 7). Patients who died despite steroid therapy were already severely ill when steroids were started (cases 9 and 12) or received steroids late in the course of IRIS (case 11) (table e-2).

The MRI lesion load was similar between the patients treated with or without steroids (table 2). Six of the seven patients (85.7%) with good outcome had contrast enhancement on CT or MRI of the brain. Conversely, four of the five patients (80%) with poor outcome had no contrast enhancement on neuroimaging (table 2, table e-3).

DISCUSSION IRIS is defined as paradoxical worsening of a patient's clinical condition that is attributed to the recovery of the immune system after initiation of combined antiretroviral therapy.[28] CNS

Table 1 Comparison of patients treated with steroids vs no steroids

	Steroids (n = 12)	No steroids (n = 42)	*p* Value
Age, y, mean (range)	36.4 (12-66), n = 12	39.8 (26-57), n = 42	0.12
M/F	11/1 (n = 12)	31/8 (n = 39)	0.67
CD4 cell count, cells/mm^3, median (range)			
Pre-HAART	35 (4-287), n = 10	56 (0-450), n = 36	0.57
Onset of IRIS	200 (21-663), n = 12	152 (23-812), n = 40	0.82
HIV viral load, copies/mL, median (range)			
Pre-HAART	193,379 (49,508-500,000), n = 7	93,617 (3,372-1,300,000), n = 31	0.21
Onset of IRIS	0 (0-6,325), n = 10	100 (0-750,000), n = 39	0.71
Time to IRIS, wk, median (range)	7.5 (4-112), n = 12	5 (1-52), n = 41	0.48
Rate of change/wk, median (range)			
Increase in CD4 cell count	16.9 (0.3-45.8), n = 10	13.1 (−6.8-528), n = 34	0.92
Decrease in HIV viral load	24,031 (1,113-124,709), n = 7	17,200 (141-258,840), n = 31	0.61
Lesion load on PML-IRIS MRI, no. of regions, mean (SD)	2.75 (1.42), n = 12	2.43 (0.99), n = 23	0.55
Contrast enhanced lesions (%)			
Pre-HAART	0/7 (0)	2/13 (15.4)	0.52
Onset of IRIS	7/12 (58.3)	14/25 (56.0)	1.00
Overall duration of survival, mo, median (range)	>7 (1-30), n = 12	>6 (0.07-65), n = 37	0.68
Survivors, duration of survival, mo, median (range)	>12 (3-30), n = 7	>12 (2-65), n = 23	0.70
Time to death, mo, median, (range)	1 (1-13), n = 5	2.5 (0.07-13), n = 14	0.69
Mortality (%)	5/12 (41.7)	14/42 (33.3)	0.73

HAART = highly active antiretroviral therapy; IRIS = immune reconstitution inflammatory syndrome; PML = progressive multifocal leukoencephalopathy.

Table 2 Prognostic factors of patients with PML-IRIS treated with steroids

	Good outcome (n = 7)	Poor outcome (n = 5)	*p* Value
Steroid dose	Prednisone 1–2 mg/kg/day (n = 3); dexamethasone 32 mg/day (n = 1)	Prednisone 1–2 mg/kg/day (n = 2); methylprednisolone 500 mg/day (n = 1); dexamethasone 10 mg/day (n = 1)	
Time to steroid treatment, wk, mean (SD)	3 (1.4), n = 2	12.3 (17), n = 3	0.80
Duration of steroid treatment, wk, mean (SD)	13.3 (7.5), n = 4	3 (1.7), n = 3	0.06
Lesion load on PML-IRIS MRI, no. of regions, mean (SD)	2.71 (1.89), n = 7	2.80 (0.45), n = 5	0.76
No. (%) of patients with contrast enhanced PML-IRIS MRI	6/7 (85.7)	1/5 (20)	0.07

PML = progressive multifocal leukoencephalopathy; IRIS = immune reconstitution inflammatory syndrome.

manifestations of HIV-associated IRIS caused by mycobacteria, cryptococci, herpesvirus, cytomegalovirus, and JCV are increasingly being recognized.[28,30] IRIS presenting during the early phase of combined antiretroviral therapy appears to reflect an immune response against an active or sometimes subclinical infection by opportunistic pathogens, whereas late IRIS may result from an immune response against the antigens of nonviable pathogens.[28] In this article, we used a broad definition of PML-IRIS and included all patients who either developed PML after the initiation of HAART and a drop in HIV viral load or who experienced a progression of PML despite successful treatment with HAART. Using these criteria, it is assumed that the immune restoration may have contributed to the disease progression. However, it is also possible that the JCV infection may progress despite the immune restoration. Interestingly, cytokines under certain circumstances may activate JCV replication.

Factors predictive of development of IRIS include antiretroviral drug naivety, active or subclinical opportunistic infection at initiation of combined antiretroviral therapy, low CD4 count (<50 cells/mm^3), and rapid immune recovery indicated by a prompt decrease in HIV plasma viral load.[31] Higher baseline CD8 cell count, history of multiple opportunistic infections, and initiation of combined antiretroviral therapy in close proximity to the time of diagnosis of opportunistic infection may also be clinical predictors of IRIS.[32] Genetic factors, such as polymorphisms in cytokine genes, have been implicated in IRIS initiated by herpesvirus and mycobacterial infections. These polymorphisms may impact the development of IRIS if they influence the clearance of the opportunistic pathogen before or after combined antiretroviral therapy, or if they exacerbate an immunopathologic response to the pathogen.[33]

The mechanisms leading to reactivation of JCV and the development of PML have not been entirely elucidated. After primary infection, JCV remains dormant in the kidneys, bone marrow, and lymphoid tissues.[34] Reactivation of JCV in most cases occurs in the setting of profound cellular immunosuppression, leading to JC viremia. It is commonly thought that spread of JCV to the CNS occurs via the hematogenous route by white blood cells.[25] On the other hand, although highly controversial, JCV DNA has also been found in the brain tissues of patients with AIDS without clinically evident PML[35] as well as in normal individuals.[36] Potential mechanisms of PML-IRIS development include an unraveling of a latent subclinical infection triggered by immune recovery or JCV-induced reactivation mediated by cytokines.[26]

Among this cohort of patients with PML-IRIS, there was no difference in the age, sex, or immunovirologic factors between PML-s-IRIS and PML-d-IRIS patients. Patients with PML-d-IRIS, however, progressed to IRIS over a shorter period compared to PML-s-IRIS patients. This may represent a priming of the immune system of PML-d-IRIS patients by exposure to preexisting JCV antigens, and thus requires a shorter duration to progress to the inflammatory stage of immune reconstitution. The poorer outcomes of PML-d-IRIS patients may be the result of a greater lesion load as seen on MRI of the brain from delayed recognition of IRIS as the initial neurologic deterioration may have been attributed to worsening of underlying PML.

The concept that treatment of an infectious agent can lead to an augmented immune response with paradoxical deterioration is well recognized in mycobacterium tuberculosis infections. Adjuvant steroid therapy in the treatment of tuberculous meningitis in HIV-negative patients improves survival.[37] Steroids have been used and may be effective in IRIS following AIDS-related CNS infections caused by mycobacteria, cryptococci, and cytomegalovirus.[28,30]

Steroid treatment in PML-IRIS is anecdotal[8,10,12,15,16,18,19,21] and treatment trials are lacking.

The majority of PML-IRIS cases are characterized by mild symptoms and limited CNS inflammation. Some authors advocate use of steroids in IRIS when there is major neurologic worsening, clinical or radiologic evidence of swelling, mass effect, or brain herniation.[26] The optimum time to institute steroid therapy, dose, and duration are not well established.[28] Steroid therapy has been used safely in immunocompromised patients with HIV infection at low dosages for durations of up to 8 weeks.[38] All the same, steroids should be used cautiously since experimental data suggest that it may increase the reservoir of HIV-infected cells.[39]

A major limitation of data collection from published literature is the availability of clinical information and the variation in data reporting. We obtained additional clinical data on the patients directly from the authors where necessary. We also ensured that all the cases fulfilled the clinical criteria for IRIS before inclusion for analysis. However, a drawback of this definition is that clinical deterioration could potentially occur from progression of the opportunistic infection despite immune reconstitution. In the absence of a surrogate marker for IRIS, this is still an acceptable operational definition.

Contrast enhancement is usually absent in classic PML lesions on MRI, and its presence is suggestive of development of an inflammatory response with breakdown of the blood–brain barrier. While contrast enhancement may potentially serve as a surrogate marker for IRIS, the contrast enhancement in patients with PML-IRIS was observed only in 56.7% (21 of 37). This could be because contrast enhancement in PML-IRIS may be subtle and can be missed by visual inspection of the scans, resulting in high interobserver variability. Hence, while contrast enhancement on neuroimaging would be helpful in the diagnosis of IRIS, its absence does not preclude it. For the purpose of this study we used the clinical definition of IRIS and included patients without contrast enhancement who clinically deteriorated after initiation of combined antiretroviral therapy but had an improvement in plasma HIV viral load and CD4 cell counts. Nonetheless, contrast enhancement in PML has been associated with a better prognosis.[40] Consistent with this observation we found that 9 of the 20 patients with contrast enhancing lesions not treated with steroids had a good outcome. Interestingly, however, six of the seven patients who had contrast enhancing lesions and received steroids had a good outcome, suggesting that steroids may have further contributed to the improvement in clinical status.

Based on our series of patients with PML-IRIS, it is possible that some may benefit from treatment with steroids. However, the use of long-term steroids can only be resolved by formal studies on treatment in PML-IRIS. While necessary, these studies are difficult for several reasons: it is a sporadic phenomenon; there is no clear case definition; and some cases may resolve without any additional treatment other than combined antiretroviral therapy.

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