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Unmasking of PML by HAART: Unusual Clinical Features and the Role of IRIS

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Abstract

For patients with HIV/AIDS, highly active antiretroviral therapy (HAART) is currently the only effective therapy for progressive multifocal leukoencephalopathy (PML), a viral-induced demyelinating disease caused by polyomavirus JC. Immune reconstitution inflammatory syndrome (IRIS) following initiation of HAART can cause paradoxical clinical deterioration in patients with established PML. Because the onset of PML follows soon after initiation of HAART in some cases (unmasking), we investigated the role IRIS plays in unmasked PML. We reviewed records of 20 PML cases seen from 1997–2006 at the UCSD HIV primary care clinic. Eight cases presented with PML symptoms within 6 months of initiating HAART (referred to hereafter as unmasked PML), six patients were diagnosed with PML before initiating HAART, and six were diagnosed more than 6 months after starting HAART. Patients with unmasked PML constituted forty percent of our series, had relatively long survival, and commonly (50%) had lesions exclusively in the posterior fossa, a localization not previously reported with such a high prevalence. Only 3 of the 8 patients with unmasked PML had IRIS reactions as evidenced by contrast enhancement around lesions on MRI, suggesting that IRIS is not necessary for the pathogenesis of this syndrome.

Keywords

HIV; PML; HAART; IRIS; immune reconstitution

Introduction

The incidence of progressive multifocal leukoencephalopathy (PML), a viral-induced demyelinating disease caused by reactivation of the polyomavirus JC (JCV), has increased markedly in the last three decades. The primary cause of the immune suppression that enables JCV to replicates is HIV (Holman et al., 1991, Tyler, 2003), but iatrogenic immunosuppression (primarily for organ transplantation) has also played a minor role (Krupp et al., 1985, Shitrit et al., 2005). Molecular evidence suggests the HIV virus also may promote the development of PML via HIV-1 Tat protein induction of JCV late gene expression (Chowdhury et al., 1990). Both mechanisms may contribute to the increased rates of PML in the HIV epidemic compared to the pre-HIV era and in those patients who fail HAART.

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Before the era of HAART, PML usually portended death within months due to a lack of available therapy for either HIV or PML. Currently, restoration of immune function by HAART is the only effective therapy for PML in patients with HIV/AIDS. For many patients, HAART arrests the progressive neurologic dysfunction caused by PML and prolongs survival, but does not fully restore lost function (Antinori et al., 2003, Cinque et al., 1998, Cinque et al., 2001, De Luca et al., 1998, Miralles et al., 1998, Miralles et al., 2001). Also, while the incidence of other CNS opportunistic infections has significantly decreased in the HAART era, the incidence of PML has decreased to a lesser extent (Engsig et al., 2008, Ammassari et al., 2000, Sacktor et al., 2001). It is unclear why the incidence of PML has decreased only slight during the HAART era, but the numerous cases of PML that develop after the initiation of HAART (as discussed below) may contribute to the current incidence rate of PML.

PML occurs in both HAART-naïve and HAART-treated patients, and the clinical characteristics of PML may differ among these patient groups. For instance, patients developing PML soon after successfully initiating HAART have significantly lower plasma levels of HIV than PML patients who are either off or failing HAART (Cinque et al., 2003). Some of these cases of PML appear to represent immune reconstitution inflammatory syndrome (IRIS), an increased inflammatory response to an opportunistic infection that occurs soon after initiating successful HAART. Defined by Shelburne et al. in 2002, immune reconstitution inflammatory syndrome (IRIS) has four criteria: 1) the patient has a diagnosis of AIDS; 2) treatment with HAART leads to an increased CD4 cell count and decreased HIV-1 viral load; 3) symptoms consistent with an infectious or inflammatory condition occur during HAART treatment; and 4) the symptoms cannot be explained by a newly acquired infection, the expected clinical course of a previous known infection or by side effects of therapy (Shelburne et al., 2002). PML IRIS manifests as a paradoxical clinical deterioration with evidence of JCV infection of the CNS, and PML lesions on neuroimaging often present with contrast enhancement representing perilesional inflammation. PML onset can occur soon after initiation of HAART, supporting a possible role of IRIS in unmasking subclinical PML. Clear examples of this syndrome have been documented in the literature (Cinque et al., 2003, Gray et al., 2005, Manzardo et al., 2005, Tan et al., 2009, Vendrely et al., 2005), supporting a possible role of IRIS in unmasking subclinical PML. Alternatively, PML onset can occur soon after initiation of HAART without evidence of concurrent inflammation (Cinque et al., 2003, Gray et al., 2005). PML that occurs substantially after initiating HAART (>6 months) usually represents failure of HAART and resembles PML that occurs in HAART-naïve patients (Gray et al., 2005).

To estimate the relative frequency of various PML presentations at one institution in the HAART era and the role of IRIS in unmasked PML, we reviewed our experience at a large academic primary care HIV clinic in San Diego, California.

Methods

Between 1997 and 2006, 20 cases of HIV-related PML were diagnosed at the UCSD Owen Clinic. Diagnosis was based on typical clinical and radiographic findings confirmed by finding JCV in CSF by PCR amplification. Medical records of these 20 patients were reviewed retrospectively and information was abstracted on demographic characteristics, risk factors, clinical features and course, including survival, pharmaceutical regimens (including HAART and cidofovir treatment), radiology, serology, and other laboratory data. Data on therapy and responses to HAART (defined as at least three antiretrovirals, including at least one NRTI or NNRTI and one PI) included the timing of the exposure to a HAART regimen, CD4 and CD8 cell counts at HAART initiation and at PML diagnosis, HIV viral loads at HAART initiation and PML diagnosis, neuroimaging assessment, and JCV detection in CSF at PML diagnosis.

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Cases were classified in three groups based on the temporal relationship of HAART initiation to PML diagnosis: 1) BH for PML before initiating HAART treatment, 2) EAH or unmasked PML for early after (<6 months) HAART initiation, 3) LAH for PML later after (>6 months) HAART initiation. For comparison to our EAH group, we extracted data from a 2003 review by Cinque et al., reporting thirteen cases of PML diagnosed within six months of initiating HAART.

The University of California, San Diego Human Research Protections Program approved this study.

Results

Of 20 patients presenting with PML in the HAART era, the 6 in the BH group had been untreated, 8 were diagnosed within six months of starting HAART (EAH group or unmasked PML) and 6 were diagnosed more than six months after HAART (LAH group). No patients had clinical evidence of PML before initiation of HAART. Characteristics of patients in these groups are summarized in Table 1.

PML before HAART (BH)

The 6 patients who presented with PML before HAART (group BH) resemble the pattern of PML in the pre-HAART era. Patients presented with weakness/asthenia (N = 2), cognitive impairment (N = 2), visual abnormalities (N = 1), confusion (N = 1) and memory loss (N = 1). Of the four patients with neuroimaging, three had multiple lesions in the cerebral white matter and one patient had lesions confined to the right cerebellar hemisphere and cerebellar peduncle. All patients were started on HAART within a week of PML onset. Half of the patients were lost to follow up; complete records were available for only three individuals. Two of those three patients showed an immunological response to HAART as evidenced by an increased CD4 count (from <100 cells/μl to 285 cells/μl) and marked reduction in viral load, but the neurological course of these patients' PML was not well documented. The third patient did not respond to HAART, with only insignificant changes noted in CD4 and plasma viral load counts and no clinical improvement noted in the month following HAART. Survival rates for this group cannot be determined due to insufficient data.

PML early after HAART (unmasked PML)

Details of 8 EAH patients who were diagnosed with PML within six months of starting HAART are summarized and compared to thirteen published cases in Table 2. The presentation of these patients differed from the other two groups in both clinical symptoms and findings on neuroimaging. Their clinical presentations with ataxia (N = 4) and cranial nerve palsies involving cranial nerves V–VII (N = 4) suggest primarily cerebellar and brain stem damage. Consistent with this pattern, four of the eight had lesions confined to the cerebellum with some also having lesions in the cerebellar peduncles. As only 3 of eight patients had evidence of inflammation (contrast enhancement on MRI), it appears that IRIS is not critical to generation of these lesions.

All eight EAH patients responded to HAART with increased CD4 counts and decreased plasma viral loads. Six of eight patients were also treated with cidofovir. All eight improved clinically, and five patients survived >400 days. The other three patients were lost to follow-up at 10, 16, and 69 days. Given that most were treated with cidofovir, benefits of this drug were difficult to determine. Thus, EAH PML appears to have a relatively good prognosis.

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PML late after HAART (LAH)

In the 6 LAH patients, clinical presentations were headache (N = 2), visual abnormalities (N = 2), impaired coordination (N = 2), dizziness (N = 2), weakness/asthenia (N = 2) and confusion (N = 1). Neuroimaging was available for five patients and revealed non-enhancing multifocal lesions in the cerebral white matter in all and coexistent lesions in the cerebellum in two patients. All of these patients were being treated with HAART at PML onset, and two were also treated with cidofovir. Only one of the five patients responded to HAART as evidenced by an increase in the CD4 count (from 6 cells/μl to 399 cells/μl). The other four cases had either minimal improvement (maximum increase of 6 cells/μl in three) or a decline in one (236 cells/μl to 48 cells/μl). Survival in this group is unknown due to losses to follow- up. Thus, PML late after HAART initiation appears to represent HIV treatment failure, as evidenced by uncontrolled HIV replication.

Discussion

We classified 20 patients with PML in the HAART era into three groups based on the time interval between PML and initiation of HAART and compared their clinical and neuroimaging patterns. The BH PML group (occurring before HAART) and LAH group (occurring more than 6 months after HAART initiation) were similar in clinical findings and neuroimaging, and both groups were characterized by high HIV viral loads and poor survival as compared to the unmasked or EAH PML group. PML cases clinically similar to the BH and LAH groups are noted in numerous published PML case series in the literature (Berenguer et al., 2003, Collazos, 2003, Gray et al., 2003 Von Einsiedel et al., 1993).

Unmasked or EAH PML accounted for 40% (eight of twenty) of our cases of PML in the HAART era, presented a mean of six weeks after initiating HAART and differed from other groups of UCSD PML patients by having both a relatively long survival and frequent localization of lesions exclusively to the posterior fossa (i.e., 50% in our series compared to 7% in a past series [Kuchelmeister et al., 1991]). The majority of these patients had no evidence of the CNS inflammation that is characteristic of IRIS, suggesting that HAART can unmask subclinical PML without generating sufficient inflammation to be visible on neuroimaging. Similar to other published cases of immune reconstitution PML, our unmasked PML group was characterized by adequate immunological response to HAART, long survival and low case fatality (Cinque et al., 2003, Cinque et al., 2009, Tan et al., 2009). The mechanism of immune reconstitution PML is unknown, but the temporal link between starting HAART and onset of PML suggests that HAART either initiates JCV replication or uncovers pre-existing subclinical PML through immune reconstitution, leading to clinically evident PML.

An unexpected finding in our unmasked PML cases was the frequent involvement of the cerebellum. PML occurs most often in the cerebral hemispheres, but lesions the cerebellum, brainstem, and cervical spinal cord have been described (Gagne et al., 1977). In the pre-AIDS era, studies showed approximately 11% of PML cases had a predilection for the cerebellum and/or infratentorial region (D'Amico et al., 2007). In the pre-HAART AIDS era, 58–60% of PML cases had concomitant subtentorial lesions, but only 6–7% of cases had lesions exclusively involving the cerebellum and/or brainstem (Kuchelmeister et al., 1991, Post et al., 1999). Similarly, in a series reporting patients treated with HAART, 58–82% of patients had infratentorial lesions in addition to cerebral lesions (Berenguer et al., 2003, Cinque et al., 1998, Cinque et al., 2003).

The unusual constellation of signs and cerebellar localization of PML lesions in our EAH group has previously been associated with unmasking by HAART-induced immune reconstitution. In 1999, Tantisiriwat et al. reported 3 patients with development of PML on HAART, one of whom had a single cerebellar lesion with compatible symptoms and signs (Tantisiriwat et al.,

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1999), and in 2007, D'Amico et al. reported 2 PML patients receiving HAART with inflammatory lesions confined to the cerebellum and brainstem (D'Amico et al., 2007). Frequent cerebellar localization of PML was documented in an autopsy series of 20 Polish HIV-infected patients dying between 1987 and 1999, with 4 of 20 patients having demyelination of the cerebellar hemispheres and brainstem without significant involvement of the cerebral cortex, leading to the proposal that a cerebellar form of PML may be a separate clinical entity from the cerebral form of PML (Mossakowski and Zelman, 2000).

The mechanism of unmasked PML and other cases with tropism of JCV to the posterior fossa is unknown. Failure of immune control in the cerebellum could result from less effective or more delayed immune reconstitution there compared to other brain regions. Alternatively, JCV's capacity for exclusive infection of the internal granule neuronal layer, rather than oligodendrocytes, of the cerebellum has been recently recognized. This atypical pattern of JCV infection is associated with cerebellar atrophy in HIV patients (Du Pasquier et al., 2000). JCV binds to α-2,6-linked sialic acid residues on cell surfaces and enters via endocytosis (Tyler, 2003). Granule cells neurons may have unique cell surface composition that allows JCV to interact with granule cells to promote their infection (Tyler, 2003).

Regional variants of JCV may provide greater tropism for the cerebellum via interaction with cell factors unique to cerebellar cells. While studies of the regulatory region of the JCV genome have found no regional differences in JCV strains (Du Pasquier et al., 2000), various deletions and amplifications in the JCV control region sequences have been demonstrated in various parts of the same brain (Yasuda et al., 2003). Strains with a predilection for specific brain regions, including the cerebellum, may have independent origins or be mutations from a single archetypal strain (Yasuda et al., 2003).

This retrospective study of a case series of 20 patients at one institution over nine years has important limitations. We were unable to examine possible roles of their many different HAART regimens on the pattern of PML due to the variability of the regimens; the differing CNS penetration of these regimens may have affected the course of PML differently. Additionally, loss to follow-up limited our understanding of functionality and survival after PML. However, our experience is that loss to follow-up among PML patients is usually related to lack of clinical improvement, withdrawal from care and death within a few weeks to months.

PML continues to be an often fatal complication of HIV infection. Improved recognition of an atypical form of PML occurring soon after initiating HAART may be clinically important. Clinical presentations of progressive symptoms of cerebellar or brainstem disease (e.g., ataxia or cranial nerve palsies) in the setting of HIV treatment should suggest PML. Individual cases of arrested progression of PML after starting HAART suggest that immune reconstitution is beneficial to controlling JCV, but other cases of PML have progressed in spite of HAART. Cidofovir does not improve the prognosis of PML (Kraemer et al., 2008, Wyen et al., 2004). Thus, HAART is the only current treatment for PML in patients with AIDS and since not all PML patients will benefit from HAART, other therapies should be pursued (e.g., 5-HT_{2A} inhibitors [Aksamit, 2008, Focosi et al., 2008]). Understanding the role of IRIS that occurs in some cases could lead to use of corticosteroids or other means of suppressing the inflammation, which sometimes causes further neurological deterioration. Further study is needed to understand JCV tropism for the cerebellum and if and how HAART may promote cerebellar infection with JCV and unmasked PML.

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TABLE 1

Demographic and Clinical Characteristics of Patients with Three Patterns of PML in Relationship to HAART*

	PML before starting HAART (group BH) (n = 6)	PML <6 months after HAART (group UPML) (n = 8)	PML >6 months after HAART (group LAH) (n = 6)
Age at HAART initiation (median years, range)	44 (37 – −51)	35 (27 – −52)	40 (34 – 49)
Days from HAART initiation to PML onset	n.a.	79 (30 – −140)	618 (258 – 2402)
CD4 at HAART initiation (cells/μl)	n.a.	18 (2 – 98)	46 (6 – 236)
CD4 at PML onset (cells/μl)	176 (16 – 375)	48 (26 – 274)	48 (8 – 399)
CD4:CD8 ratio at HAART initiation	n.a.	0.11 (0.10 – 0.11)	0.15 (0.02 – 0.4)
CD4:CD8 ratio at PML onset	0.22 (0.11 – 0.33)	0.11 (0.05 – 0.51)	0.17 (0.02 – 0.69)
Plasma HIV-1 RNA at HAART onset (copies/ml)	n.a.	144,100 (1,000 – >750,000)	170,000 (1,000 – >750,000)
Plasma HIV-1 RNA at PML onset (copies/ml)	322,000 (64,800 – >750,000)	0 (0 – 1,800)	30,311 (0 – 100,000)
Lesions confined to cerebellum/cerebral peduncles	1 (17%)	4 (50%)	0 (2 with concomitant lesions)
MRI enhancement at PML onset	0	3 (38%)	0
Treatment with cidofovir	0‡	6 (75%)	2 (33%)
Survival† (days)	34 (13 – 56)	>400 (10 – >400)	27 (6 – 46)

*median values.

†or to date of last contact.

‡treatment for this group was HAART, which was initiated at the time of PML onset in all cases.

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TABLE 2

Evidence of “IRIS” in Patients with PML early after initiating HAART (group UPML)

Case no.	sex, age, ethnicity	HAART initiation to PML onset (days)	HAART regimen	means of diagnosis	clinical features	localization	MRI evidence of inflammatory reactions	CD4 count (cells/μl) at PML onset	HIV viral load (copies/ml) at PML onset	treatment w/ cidofovir	outcome (days of survival)
1	F, 41, Latino	140	3TC, TDF, lopinavir/ritonavir	CSF JCV ⊕, clinical, radiological	headache, photophobia, memory loss	R middle cerebellar peduncle lesion	no enhancement	57	undetectable	+	unknown
2	M, 36, Caucasian	111	3TC, d4T, efavirenz, nelfinavir	CSF JCV ⊕, clinical, radiological	headache, photophobia, CN VI & VII palsies	bilateral cerebellar hemispheric lesions	contrast enhancement	45	undetectable	+	survived (>400 days) with clinical improvement
3	F, 27, Latino	77	3TC, TDF, lopinavir/ritonavir	CSF JCV ⊕, clinical, radiological	speech disturbances, CN VII palsy	L cerebellum & cerebellar peduncle lesions	no enhancement	47	undetectable	+	survived (>400 days) with clinical improvement
4	F, 52, African-American	77	3TC, AZT, d4T, nelfinavir, indinavir	CSF JCV ⊕, clinical	ataxia	n.a.	n.a.	274	undetectable	+	survived (>400 days) with clinical improvement
5	F, 32, African-American	47	FTC, TDF, atazanavir	CSF JCV ⊕, clinical, radiological	ataxia, CN VII palsy	R middle cerebellar peduncle lesion	no enhancement	20	929	−	survived (>400 days) with clinical improvement
6	M, 35, Caucasian	47	3TC, d4T, nelfinavir	CSF JCV ⊕, clinical, radiological	vision abnormalities, speech disturbances, CN V, VI &VII palsies	multiple patchy enhancing lesions	mild contrast enhancement	50	undetectable	+	survived (>400 days) with clinical improvement
7	M, 51, Latino	110	3TC, AZT, saquinavir	CSF JCV ⊕, clinical, radiological	visual abnormalities, ataxia, dizziness	L frontal, temporal; R frontal, brainstem (including VI nucleus)	mild contrast enhancement	26	1800	−	unknown
8	M, 30, African-American	82	abacavir, d4T, amprenavir	CSF JCV ⊕, clinical, radiological	gait abnormalities, ataxia, confusion	diffuse asymmetric lesions in white matter	no enhancement	83	n.a.	+	unknown
Summary of eight UCSD cases	M:F 4:4 median age = 35.5	median = 80 days	2 NRTI + 1 PI regimen	CSF JCV ⊕ clinical + radiological	ataxia (N = 4) CN palsies (N = 4) photophobia (N =2) speech disturbances (N =	4 of 8: lesions confined to the cerebellum +/− cerebellar peduncles	3 of 7: contrast enhancement	median = 48 range = 20 − 274	6 of 8: undetectable viral load	6 of 8: cidofovir treatment	5 survived; 4 unknown

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Case no.	sex, age, ethnicity	HAART initiation to PML onset (days)	HAART regimen	means of diagnosis	clinical features	localization	MRI evidence of inflammatory reactions	CD4 count (cells/μl) at PML onset	HIV viral load (copies/ml) at PML onset	treatment w/ cidofovir	outcome (days of survival)
					2) visual abnormalities (N = 2)						
Summary of thirteen published cases*	M:F 10:3 median age = 37	median = 35 days	2 NRTI + 1 PI regimen	9 of 13: CSF JCV ⊕ 3 of 13: clinical or radiological 1 of 13: biopsy	–	–	4 of 13: contrast enhancement	median = 241 range = 23 – 419	5 of 12: undetectable viral load	–	9 survived; 8 died

*Cinque et al., 2003