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# New and Old Concepts and Strategies for Progressive Multifocal Leukoencephalopathy

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## Abstract

There has been recent progress in the area of John-Cunningham virus (JCV) infection and progressive multifocal leukoencephalopathy (PML). New drugs and better reporting identify new risk cohorts and importantly development of new risk assessment strategies. The clinical presentation has not changed, but presentation of rarer forms of JCV infection are now apparent. Brain magnetic resonance imaging (MRI) continues to be a pillar of PML diagnosis. The imaging correlation with pathology and the new understanding of the biology and improved methods to detect JCV significantly help with recent diagnostic criteria. Unfortunately a small number of trials for specific treatment of PML have not proven beneficial, and the possibility remains to improve the JCV- specific immune response. Sometimes this response creates an exacerbation of neurological features – immune reconstitution inflammatory syndrome – that helps resolve the infection but can cause damage in itself. Overall, the prognosis of PML has improved with much lower mortality but still severe neurological deficits.

This review aims to bring together old and new knowledge of PML and help reconsider practical clinical strategies.

**Keywords:** Progressive multifocal leukoencephalopathy; Immune reconstitution inflammatory syndrome; John Cunningham virus;

## Introduction

Our objective is to review the latest data on progressive multifocal leukoencephalopathy (PML) ranging from clinical characteristics to treatments and also relate the biological aspects of John-Cunningham virus (JCV) to the understanding of the disease. In particular, we propose to compare the features of PML in the context of human immunodeficiency virus (HIV) positive individuals – HIV-PML- and PML in the context of natalizumab treated multiple sclerosis (MS) patients – Nat-PML to evolve learning points across areas of medicine (Table 1).

It is striking that PML has become a misnomer: a) the progressive nature of disease may be halted; b) unifocal rather than multifocal lesions would not avert the diagnosis; c) the possibility of clinical and imagiological features in grey matter only reflects the presence of oligodendrocytes that has been highlighted, making it more than a leukoencephalopathy.

## Individuals at risk of PML

The individuals affected by PML are typically immunocompromised people who have a deficient specific immune response to JCV, either isolated or in a broader immunocompromised context.

PML in people with very low CD4 count in the context of HIV infection constituted the majority of presentations before the combined anti-retroviral treatment (cART) era and it still is the cohort where we derive a significant part our knowledge about JCV and PML. In pre-cART days, PML occurred in 3%-7% of AIDS patients [1,2] and was mostly terminal. Current treatments with cART from an earlier stage of infection, with CD4 counts over 200 and reasonable viral load suppression, have made PML significantly less frequent [3,4]. But late presenters and people who do not adhere to medication have increased risk of PML, often without having presented with the opportunistic infections that characterise earlier stages of immunosuppression.

PML in the context of immunosuppression with chemotherapeutic regimens or oncologic disorders is recognised but not frequently encountered. Possibly the recurrent nature of the regimens, rather than long standing hits at the immune system, allows a better integrity of the JCV immunity.

| | HIV-PML | Nat-PML |
|---|---|---|
| Supratentorial clinical presentation | 93.8% | 87.5% |
| Infratentorial clinical presentation | 58.3% | 33.3% |
| Gadolinium-enhancing lesions | 15% | 40% |
| Treatment | cART; steroids could be added | Natalizumab removal (plasma exchange and/or immunoadsorption); steroids could be added |
| PML-IRIS risk | cART naïve; cART initiation close to opportunistic infections treatment; higher HIV viral load; | Virtually all patients |

| | | |
|---|---|---|
| | rapid immune reconstitution | |
| Survival | Without cART: 5% or lower<br>With cART: 46-58% | 71-100% |
| Good prognostic factor | Higher CD4+ count; low HIV RNA load; presence of JCV specific cytotoxic T response; low JCV viral load in the CSF; inflammatory CSF profile; PML as the heralding manifestation of AIDS; older age | Less pre-PML neurological disability; short time from symptom onset to diagnosis; more localized lesions on the MRI; younger age |

**Table 1:** Summary of comparison between HIV-PML and Nat- PML. HIV-PML -Progressive multifocal leucoencephalopathy in the context of human immunodeficiency syndrome virus positive individuals; Nat-PML-PML in the context of natalizumab treated multiple sclerosis patients; IRIS-immune reconstitution inflammatory syndrome; cART-combined anti-retroviral treatment; CSF-cerebrospinal fluid; AIDS-acquired immune-deficiency syndrome; JCV-John Cunningham virus.

Since the introduction of natalizumab treatment – monthly infusions of humanized monoclonal IgG antibodies against the cellular adhesion molecule α4-integrine preventing lymphocytes to cross the blood-brain barrier (BBB) and reducing inflammation within CNS - for MS and Crohn's disease, the occurrence of PML in this population has highlighted a specific immunodeficiency to JCV infection. The risk of PML in people who are treated with natalizumab increases with the titre of JCV IgG, with the number of infusions and with previous treatment with immunosuppressors, often mitoxantrone [5-7]. Risk stratification algorithms model the probability that an individual has to develop PML, but have not been shown to reduce its incidence [8]. There are exceptional cases where PML was detected in JCV sero-negative individuals [9].

Patients with transplants, rheumatologic and other inflammatory disorders (e.g. allogeneic hematopoietic cell transplantation, systemic lupus erythematosus, inflammatory bowel disease, primary biliary cirrhosis) are currently treated with diverse regimens that include steroids, steroids sparing immunosuppressive drugs, specific immunosuppressive treatments and biologicals antibodies [10] that can cause immunosuppression but also compound the immunodeficiency of diseases [11-15].

Specific immunodeficiencies such as low CD4 or CD8 counts are found in individual cases who present with PML without known risk factors. But conditions such as diabetes or pregnancy or old age can induce immunosuppressive states [16]. A few individuals may present with PML without any evidence for immunosuppression, the so called healthy cases [17].

## Clinical Presentation

Clinical presentations of PML are quite diverse and nonspecific. The symptoms are dependent on the location and size of the lesions and virtually any area of the brain can be involved [18,42]. It is usually multisymptomatic, but can also present with only one prominent objective neurologic abnormality at onset and remain monofocal clinically and radiologically [42]. In fact, any clinical presentation is possible for an individual affected with PML. Common clinical findings include behavioural and cognitive abnormalities (seen in 25-30% of all patients), pyramidal signs, visual field defects (if the occipital lobe or optic radiation are involved), aphasia (if there is involvement of the dominant parietal lobe), cerebellar dysmetria or ataxia and gait abnormalities. About 20% of patients with PML present seizure activity associated with lesions immediately adjacent to the hemispheric cortex [19]. Sensory loss, headache and diplopia are reported less frequently [20,21]. It is usually a subacute process (progressing over days to weeks) with an insidious, frequently misdiagnosed, onset but with a fast accumulation of deficits [22].

It was commonly accepted that PML lesions spared the optic nerves (and other cranial nerves), the spinal cord and the peripheral nervous system. But a postmortem examination of an acquired immunodeficiency syndrome (AIDS) patient revealed PML lesions in the spinal cord and demonstrated that JCV can infect and affect any part of the CNS [23].

Comparing the clinic presentation of HIV related PML (HIV-PML) with natalizumab related PML (Nat-PML) it seems that infratentorial manifestations are more frequent in HIV-PML. A study of 48 HIV-PML patients showed that supratentorial manifestation of PML occur in 93,8% and infratentorial manifestations in 58,3% of the patients. The most affected infratentorial areas were the brainstem, mainly the pons, followed by middle cerebellar peduncle and finally the cerebellar white matter [24]. In a series of 15 patients with Nat-PML, at the onset of the PML 12 patients had only supratentorial lesions, mostly in frontal and parietal lobe, followed by occipital lobe and more rarely temporal lobe. Only one patient presented with an infratentorial (cerebellar) lesion and two patients had both supratentorial and infratentorial lesions [25]. When this series was extended to include a second hospital, 8/24 (33,3%) of patients had infratentorial manifestations and of those, 3 were exclusively infratentorial and 5 were infratentorial and supratentorial [26]. The pons and cerebellum were the most commonly affected infratentorial regions.

HIV-PML can present before cART even as the initial manifestation of AIDS, early after initiation of cART (also known as unmasked PML) and even later after cART (occurring more than 6 months after cART initiation). There are no clinical or imaging differences between the three situations [27]. In rare occasions, PML late after cART is described in patients with high CD4+ T cell count and undetectable HIV viremia, probably due to lack of specific JCV immunity [28]. When PML presents early after initiation of cART it possibly reflects an immune reconstitution inflammatory syndrome (IRIS) with unmasking of the lesion or, less likely, cART would initiate JCV replication. But it is uncommon to detect brain magnetic resonance imaging (MRI) characteristics of IRIS in patients with unmasked PML, which suggests the presence of inflammation is below the imaging threshold. Patients with unmasked PML tend to develop an adequate immunological response to cART and have better prognosis [27].

In addition to this classic PML, some specific variants have been described: JCV granular cell neuronopathy, JCV meningitis and JCV encephalopathy [29,30].

Patients who have JCV granular cell neuronopathy present an isolated progressive cerebellar syndrome and histopathologically only cerebellar granule cell neurons are affected, with preservation of the oligodendrocytes and astrocytes [31,32]. Wüthrich et al. [34] found over two thirds of 43 PML patients (40 were HIV-positive) who had hemispheric, but not cerebellar white matter lesions to have JCV infection of the cerebellar granule cell layer (including glial cells and cerebellar granule cell neurons). Granule cell neurons infection and destruction may cause cerebellar dysfunction and atrophy, irrespective of the presence of PML lesions in cerebellar white matter.

JCV meningitis is described patients, both immune -deficient and -competent individuals, who presented with meningitis in whom the only etiological agent identified was JC virus [29].

JCV encephalopathy is considered with isolated progressive cognitive deterioration and brain MRI lesions consistent with PML. Neurological signs progress independently of initiation of cART with viral suppression and CD4+ >200 and an increased number of larger and enhancing lesions. Some cases have been shown to have a preferential infection of the cortical pyramidal neurons and astrocytes located in the cortical grey matter and grey-white junction and it was found an extensive infection of the pyramidal cell neurons with confirmation of JCV proteins in the nuclei, axons, and dendrites of pyramidal cell. In white matter there was only a discreet infection of the oligodendrocytes without the "typical" demyelination of PML [35].

### Progression of the disease

PML remission is uncommon and might take several weeks, so no strict criteria define clinical response. Currently, an assessment of PML progression combines neurological features, brain MRI, and JCV DNA measurement in cerebrospinal fluid [36]. This approach is useful for showing disease stabilization or progression over a period of weeks to months, but methods that help clinical decisions are yet to be developed or validated. Because of the frequently rapid evolution of the disease, clinical assessment every 2–4 weeks and MRI and cerebrospinal fluid examination every 4–8 weeks seem reasonable options. Additional MRI investigation can be recommended in case of rapid clinical deterioration, particularly when inflammatory changes associated with IRIS are suspected and to help exclude other diagnosis. PML is considered inactive when there are no new or enlarging MRI lesions, and the pattern of Gad enhancement is reduced. The inflammatory PML appears in the setting of IRIS and will be considered in that chapter [35].

## Brain imaging and pathology

PML lesions may occur anywhere in the brain. Typically they are single or multiple asymmetric white matter lesions that become confluent and enlarge as disease progresses, without mass effect, in the cortico-subcortical regions [37]. Brain MRI is significantly more sensitive than CT [38] to identify PML lesions and it should be the preferred imaging method. It is also the most sensitive tool to screen suspected patients for PML, as it can detect early stage lesions, even before they are clinically detectable [22]. In extremely rare cases the patients can have clinically detectable neurologic deficits but no MRI abnormalities due to the subcortical nature of the demyelination that occur in PML, which may affect the cortex and not be easily visualized on the currentl MRI scan sequences [38].

In MRI, PML shows lesions that are hyperintense on T2-weighted and fluid-attenuated insertion recovery (FLAIR) images and hypointense on T1-weighted images [39]. Nat-PML lesions are more likely to have Gadolinium (Gad) enhancement then HIV-PML. At the time of diagnosis, Gad enhancement may be present in as many as 15% of patients with HIV-PML [20]. and in 40% of Nat-PML [40]. Gad enhancement is usually sparse, with thin or reticulated appearance adjacent on the edge of the lesions. These characteristics may change with IRIS after cART.

Although it is considered a white matter disease, PML lesions are mostly located in the the arcuate fibers (U fibers) between cortex and white matter [22]. A revision of 40 Nat-PML patients detected cortical involvement in 50% of early and in 71% of PML-IRIS patients. In this series all lesions had a subcortical location, which was attributed to the presence high blood flow [37,41]. The lesions are principally located in supratentorial regions. The frontal lobes and parieto-occipital regions are the regions that appear to be most commonly affected, presumably as a consequence of their volume. However involvement of the basal ganglia, external capsule and posterior fossa structures (cerebellum and brainstem) are also seen [42]. The periventricular white matter is usually spared [22]. Spinal cord lesions are possible but unusual and raise the possibility of other alternative diagnosis. PML can also be located primarily in the deep grey matter and display localizing signs [43].

Advanced PML shows increased size and confluence of lesions, further areas involved, varying degrees of cortical atrophy and ventricular dilatation [22,44]. Metabolic characterisation by 1H-MR spectroscopy shows that PML lesions have decreased N-acetylaspartate (marker of neurons viability), increased lactate (correlated with inflammation) and increased myoinositol. Increase in choline (a constituent of cell membranes and indicative of cell membrane breakdown) or increase in lipids (related to cell membrane breakdown, or to infiltrating macrophages around inflammatory lesions) were occasionally seen [45,46].

Many diseases can be mistaken for PML and need to be excluded, particularly in patients with HIV, such as HIV encephalopathy, cytomegalovirus infection, varicella-zoster leukoencephalitis, MS-like illness, acute disseminated encephalomyelitis, CNS vasculitis, reversible leukoencephalopathy associated with nucleoside analogue antiretrovirals or white matter oedema associated with primary or metastatic brain tumours [42] or even CD8 encephalitis [48]. Although cART alters the clinical course of the disease, it does not seen to significantly influence the MRI PML patterns [44].

It is particularly difficult to distinguish PML and MS lesions in Nat-PML. This is of extreme importance due to the risk of MS patients on natalizumab to develop PML. While MS lesions tend to be periventricular and small, Nat-PML lesions tend to be larger, confluent and subcortical. The border of PML lesions tends to be sharp toward the gray matter and ill-defined toward the white matter, and punctate T2 hyperintensities may be seen in approximately 70% of the cases in the vicinity of PML lesions [37,48].

Classic PML presents with focal neurologic deficits that gradually worsen and histopathologically is characterized by multifocal areas of demyelination, JCV-infected oligodendrocytes with intranuclear inclusions (enlarged amphophilic nuclei) at the periphery of the lesions, absent or mild inflammation, reactive gliosis with enlarged, bizarre astrocytes, some of them sustaining JCV infection, and lipid-laden macrophages [22,49] and the presence of JCV is confirmed by immunohistochemistry, in situ nucleic acid hybridization, or electron microscopy [50].

### Infection with John-Cunningham virus (JCV), a human polyomavirus

The prevalence of infection with various human polyomaviruses (HPyVs), in particular JCV, is probably over 80%, but varies in different populations and with detection method [44]. Typically the primary infection is asymptomatic and occurs during childhood but

can also happen at any stage in life. JCV infection evolves into a chronic asymptomatic carrier state and the virus DNA can be detected in urine (30%) and tonsils (40%) of healthy adults. In immunocompromised people, JCV reactivates, becomes neurotropic infects oligodendrocytes and causes PML [51]. Other HPyVs cause trichodysplasiaspinulosa or Merkel cell carcinoma or polyomavirus associated nephropathy. The specific factors that induce reactivation and lytic infection seems associated with a defective host cellular immune responses [52].

Recently, JCV has been shown to latently infect CD34+ bone marrow cells that enter circulation and differentiate to CD19+ cells in the peripheral blood and allow the growth of JCV [53].

The JC virus has two important genomic regions: the NCCR and the VP1. The expressed VP1 binds the host cell surface receptors and changes in its coding sequence are important in the pathogenesis of PML [18]. The NCCR is a regulatory element that controls viral transcription and replication. There are two forms of the virus that differ in the NCCR region: the archetypal form that is typified by the CY stain of the virus and is the form always found in kidney and urine; and the prototypical form of the virus, also known as PML-type, that is typified by the Mad-1 stain, the form always found in brain and the one associated with PML. [54]. Whether the PML-type JCV originates from a transmitted virus or arises from genetic rearrangements is unknown. PML-type JCV is a more active viral variant because of the deletion of negative control elements and/or the duplication of positive control elements, and has the potential to cause lysis of glial cell and PML [54]. Nevertheless, PML-type JCV is also found in the peripheral blood cells in individuals without PML, indicating that more factors are necessary for the pathogenicity of this virus [55].

Rarely, in the cerebellar syndrome that heralds the JCV granular cell neuronopathy, unlike what is observed in the JCV infection in PML, the majority of granule cell neurons expressed JCV T Ag (a protein expressed early in the viral cycle) more frequently than JCV VP1 (that is expressed late in the viral cycle,) which in conjunction with the fact that one HIV-positive control patient, with no PML, had granule cell neurons infection, led them suggest that granule cell neurons may be the initial site of JC virus infection in the CNS.

The ability to detect the JCV depends on the sensitivity of the quantitative polymerase chain reaction (PCR) techniques and on cART. In the pre-cART era the detection of JCV in CSF by PCR had a sensitivity of 90% with a specificity of 92-100%, but after the introduction of cART the sensitivity dropped to 58%. In fact, IRIS with CD4 above 100 cells/uL was an independent factor predict of the failure to detect JCV in CSF of PML patients [56]. Nowadays, with ultrasensitive PCR techniques, the sensitivity to detect JCV in CSF is >95% [42]. Most diagnostic laboratories are able to detect >200 copies of JC virus DNA/mL of CSF [42]. But despite the high sensitivity of the PCR assays, a negative result does not exclude PML. In HIV-infected patients, the viral load is usually high, but in HIV patients under cART, in MS patients and other autoimmune diseases, the viral loads are often lower and more likely to induce false negative results [42]. In contrast, JCV can be detected in MS patients without PML [57]. CSF analysis may be repeated if JCV PCR is negative but suspicion remains high, and alternative diagnoses (e.g., focal VZV or primary CNS lymphoma) were reasonably excluded by negative VZV PCR and IgG and EBV PCR analysis respectively. Brain biopsy may be needed when all else fails. In Nat-PML, as many as 70% have a JCV DNA level in CSF under 100 copies/mL at the time of diagnosis [25,57].

A very sensitive two-step anti-JCV antibody assay (STRATIFY JCV™; Focus Diagnostics, Cypress, CA, USA) [58] determines previous JCV infection and helps stratify PML risk, if only in people who have not taken immunosuppressors. JCV-specific cellular immune response is highly prevalent in all JCV-seropositive MS patients, regardless of treatment [59] but are more difficult to set up.

CSF JCV IgG index, rather than CSF JCV IgG to exclude pure diffusion and disturbance of blood–CSF barrier, has been proposed to help PML diagnosis. The argument is that in cases where the adaptive immune response to JCV is maintained, the viral load is low but the local production of JCV IgG is raised, but there are sensitivity problems [57].

The diagnosis of PML remains rooted in a combination of unspecific clinical presentation, reasonably distinct brain MR imaging, plasma JCV IgG positivity and CSF JCV DNA in the appropriate risk factor context.

## Diagnostic criteria

In 2013 the AAN Neuroinfectious Disease Section, proposed new diagnostic criteria for PML [42]. PML can be definitive or probable or possible based on a combination of factors with or without histopathological confirmation. In the cases when a brain biopsy or post-mortem is available, definitive PML is based on histopathologic features and requires the classic histopathologic triad of demyelination, bizarre astrocytes and enlarged oligodendroglial nuclei, associated with the presence of JC virus by electron microscopy, immunohistochemistry or tissue PCR to have a definitive diagnosis. Probable PML is defined if the classic histopathologic triad is present but is not possible to demonstrate the presence of the JCV and is possible if the virus is identified by electron microscopy or immunohistochemistry but the classic histopathologic triad is not present. Alternatively, the clinical features consistent with the diagnosis associated with classic MRI findings and a positive CSF JCV DNA is sufficient for a definitive diagnosis of PML. Probable PML is determined if the clinical or the imaging features are not present but CSF JCV DNA is present; and it is possible if both clinical or the imaging features are present but CSF JCV DNA are not identified or if both are absent but CSF JCV DNA is present. When clinical, MRI and classic histopathologic features are present, and other diagnosis are excluded, definitive diagnosis can be made even in the absence of JCV identification by electron microscopy, immunohistochemistry or CSF or tissue PCR.

In the reasonable clinical context, patients with probable PML should be managed as definitive PML, while the management of patients with possible PML remains a clinical decision.

## Treatment

There are no specific anti-JCV infection treatments. The best therapeutic option is to restore the immune system.

For people with HIV infection ART improves the prognosis of the disease. The incidence of PML decreased after the introduction of cART and it continued to decline over time probably associated with its increase effectiveness [4]. The recommendations of the CDC, the National Institutes of Health (NIH), and the HIV Medicine Association of the Infectious Diseases Society of America (IDSA) [50] depend on the patient's antiretroviral treatment status and its efficacy. In patients who have PML and who are not on therapy, ART should be

started immediately (AII). For patients with PML who remain HIV-viremic because of antiretroviral resistance, their ART regimen should be optimized for virologic suppression (AIII). Patients who have PML despite successful virologic suppression while taking cART are more problematic: ART-intensification strategy with four classes of ART is a possibility, but its effectiveness requires further studies (CIII). Approximately half of patients with PML in the setting of HIV infection experience a remission after initiating effective ART.

When ART-induced immune reconstitution is associated with either unmasking or paradoxical worsening of PML, corticosteroids have also been used. However, no evidence supports the routine use of corticosteroids in HIV-PML without an inflammatory response on neuroimaging (DIII). In patients with inflammatory PML, corticosteroid treatment might have a more rational basis [50]. Some authors recommend corticosteroids in all cases of PML, even when there is little evidence for inflammatory syndrome.

Especially when treatment fails to suppress HIV viral load, but also when CD4+ count fails to recover, ART modification is needed. Augmenting ART even when plasma HIV RNA is below detection is controversial and under study. When PML progresses despite HIV suppression, the informed use of unproven strategies is reasonable, [50].

In HIV-negative patients potential sources of immunosuppression should be removed or decreased as clinically possible [60] in order sustain a JCV immune response.

In patients with Nat-PML treatment of PML depends on the immune reconstitution after the removal of natalizumab. Plasma exchange (PLEX) and immunoadsorption are used to hasten the removal of natalizumab from circulation and allow JCV-specific lymphocytes to cross the BBB. In a study of 15 patients with Nat-PML, all patients received PLEX and / or immunoadsorption to re-establish an immune response (5 only received PLEX, 1 only received immunoadsorption and 9 patients received both treatments) associated with a supportive therapy with mefloquine and mirtazapine [25]. All patients showed initial improvement or stabilisation in the weeks after PLEX and/or immunoadsorption, but 14 of the 15 patients developed IRIS. There were no fatal cases recorded, with a median follow-up time was 21.5 months from PML diagnosis. However, the first 42 cases of Nat-PML cases since the reintroduction of natalizumab showed that early IRIS in Nat-PML had worse survival and neurologic outcome and that PLEX and/or immunoadsorption may accelerate IRIS but the authors would not make a conclusion about the strategy [40]. The use of corticosteroids is also advocated when there is evidence of IRIS, which is more frequent in Nat-PML than HIV-PML.

There are fewer options for HIV negative patients without iatrogenic causes. The interaction between JCV and the serotonin 2A receptor (5-HT2AR) is necessary for viral to entry the cell [61] so, trials with drugs with 5HT2AR antagonism effect have been attempted, such as risperidone [62] or mirtazapine [63]. Chlorpromazine [64] was also tried, due to its inhibition of clathrin-dependent endocytosis required for virus infection. Drugs that inhibit viral replication, such as cytarabine [65], cidofovir [66] or topotecan [67], drugs that have immunomodulatory effect such as IL-2 [68-70], IL-7 and interferons alfa e beta [71,72] and drugs, such as mefloquine, which action mechanism is unknown [73] were also tried. However none have proven any clinical benefit.

The research for specific anti-JCV infection causing PML continues and is necessary to improve the outcomes of all individuals who succumb to PML.

## PML-IRIS

IRIS is clinically defined as the paradoxical worsening of disease when the immune system is restored and the subsequent response to antigens exacerbates the pathology. Systemically, it can affect many organs systems, including central nervous system. In HIV-infected patients, the initiation of ART decreases HIV-1 RNA level and increases CD4+ cells from baseline; symptoms and signs must be consistent with an inflammatory process to a recognised opportunistic infection or tumour diagnosis and other diagnosis or drug toxicity are excluded [74]. When treatment for the opportunistic infection is initiated prior to cART, there will be a decreased microbial antigen burdens and less risk of IRIS [74] In general, patients at highest risk for IRIS are the ones who were ART naïve, or initiate CART closer to the treatment of the opportunistic infections [74]. The higher initial HIV viral load and the desired speed of immune reconstitution also increase the risk of IRIS [74]. In the cases of PML, cART induces restoration of a pathogen-specific immune response that leads to the recognition of JCV antigens [29].

As previously mentioned, virtually all patients with Nat-PML develop IRIS. This is probably because natalizumab does not alter the JCV specific immune response, only prevents lymphocyte to cross the BBB. So, when natalizumab is removed, the lymphocytes readily enter the brain and develop an inflammatory reaction that both helps eradicated the JCV infections and causes damage in itself [75]. IRIS associated with PML can occur in two ways: “paradoxical” IRIS that presents after the initiation of cART as an exacerbation of already established PML; and “unmasking” IRIS when it reveals PML pathology [76].

The pathophysiology of IRIS is not completely understood. In a functioning immune system, T cells more than the humoral immune response seem to control JCV reactivation and dissemination. Compared to patients with PML, the ones that have PML-IRIS (either HIV-PML or Nat-PML) have an inflammatory response that is dominated by CD8+ T-cells directed against JCV and not to other (self-) antigens [77]. This CD8+ T-cell response allows the control of JCV dissemination, but also causes oligodendrocyte cell death and demyelination. The influence of CD4+ T cell is less clear, but must be important as HLA class II restricted immune responses are pivotal for JCV infection control [78]. In HIV infected patients with PML-IRIS CD4+ T-cells responses are not characteristic [77]. In Nat-PML, the ratio of CD8+ T cell within the total of CD3+ T cell ranges from 24 to 70% [79].

There is no biomarker of IRIS. IRIS imaging shows limited CNS inflammation and unlike typically PML where contrast enhancement is usually absent, the PML-IRIS lesions are more likely to have Gad enhancement suggestive of development of an inflammatory response with breakdown of the BBB. However this only occurs in 56% of the patients [79]. It had been shown that even when intense CD8+ T cell infiltration is present Gad-enhancing lesions at the disease onset are not consistently present [77]. So, a non-enhancing PML lesion with clinical deterioration does not exclude the diagnosis of IRIS. By proton magnetic resonance spectroscopy (1H-MRS), an increase in lipid/creatine, coline/creatine and myo-inositol/creatine and a decrease in NAA/creatine ratios in PML-IRIS lesions comparatively with patients

with PML without IRIS is proposed [81]. Lipid / creatine ratios were elevated in PML-IRIS lesions independently of contrast enhancement. This way, 1H-MRS could become a tool to help in the diagnosis of IRIS, but it has not been easy to use in clinical practice.

There is no consensus for PML-IRIS treatment. CDC, NIH, and the HIV Medicine Association of IDSA recommend that corticosteroid treatment should be as short as possible and not overused. Mild swelling, oedema, or Gad enhancement might be noted in some patients who respond favourably to ART, but most often these complications require no additional treatment if the patient is clinically stable and has no sign of impending brain herniation. However, in those with progressing clinical deficits and neuroimaging features suggesting inflammatory response (oedema, swelling, and contrast enhancement), corticosteroid treatment is justified (BIII). Although some have suggested stopping ART in the face of PML-IRIS, this is likely counterproductive and is not recommended (DIII) [49]. In clinical practise, corticosteroids are used in high doses in PML-IRIS patients who are progressing and have signs of inflammatory response, associated with rapid weaning once there is clinical stabilization. When the MRI signs of inflammation are vague, even if we know that more than a third of patients will have inflammation, there is no agreement and it usually depends on the severity of the clinical picture.

### Prognosis

In HIV patients the main risk factor for the development of PML is low CD4+ cell count, the risk of PML being low when the CD4+ cell count is over 200 cells/uL [4]. During the pre-cART area, the median survival time of PML patients was only a few months after the diagnosis [82]. Since the introduction of cART, survival has improved significantly, with a 1-year survival of about 46-58%, compared with 5% or lower in patients not receiving cART [83-85]. A study with 28 patients that tried a regimen of 5 ARV drugs after PML reached a 1-year survival of 75% without increasing the risk of PML-associated IRIS [86]. The factors that appear to be associated with better survival include a higher CD4+ count, low HIV RNA load, presence of JCV specific cytotoxic T lymphocytes, low JCV viral load in the CSF, inflammatory CSF profile, PML as the heralding manifestation of AIDS and older age [85].

In Nat-PML patients, in one study 71% of 35 PML patients were alive at the time of the analysis and in another study 100% of 15 patients had survived [25,88]. Better prognostic factors were younger age, lower pre-PML Expanded Disability Status Scale scores, a short time from symptom onset to diagnosis and more localized lesions on the MRI [88]. Despite the low numbers, Nat-PML has a better survival compared with HIV-PML. However, PML patients who survive frequently have irreversible severe neurological sequelae.

It was suggested that the CD4+ and CD8+ T cells against JC virus have an important role in the clinical outcome of PML and PML-IRIS. A study that tested the IFN-gamma production and the intracellular cytokine staining to determine the activity of CD4+ and CD8+ T-cells demonstrated that the cellular immune response against JCV is associated with a better clinical outcome. PML survivors had an early CD8+ T cell response more frequently than PML progressors (100% versus 27,3%). For CD4+ T cells the difference between the two groups was smaller (80% versus 45,5%). This suggests that these laboratorial tests could be useful prognostic markers of PML evolution and may help in the clinical management of these patients. Although IRIS was more frequent in the PML survivor group, there was no difference in IFNgamma production between IRIS and non-IRIS patients [89].

Patients who experience remission of PML after starting cART seem to rarely suffer a subsequent recrudescence of PML, although no formal study of this has been undertaken. The main preventive measure is a good immunologic status [50].

## Conclusion

PML has evolved from a deadly fate into a disease that is possible to contain or even reverse, from multifocal to occasionally unifocal and from white matter to whole brain disease sometimes with only gray matter being affected. We reviewed some of the new findings in context with old knowledge and put them into the context of new cohorts of people at risk. The new cohorts have also informed us on some aspects of JCV biology that may prove important to develop the much-needed specific treatments for PML. In fact, even if the death rate has improved consistently, the neurological outcomes of the survivors need to be improved.

Current research in PML has been hindered by the small numbers of cases that present in centres with active programmes and resources, but more collaborative projects and better awareness of clinical trials may develop knowledge and improve outcomes.

This review helps to highlight new and old information that is important to address clinical practice and better diagnostic and therapeutic strategies.

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