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Review Article

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JC Virus Encephalopathy: A Bibliographic Review

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1. Introduction

JC virus encephalopathy (JCE) includes progressive multifocal leukoencephalopathy (PML), a demyelinating disease, and granular cell neuronopathy (GCN), a less frequent disease that affects the neurons of the cerebellar granular cells [1].

Progressive multifocal leukoencephalopathy, PML, or JCV is a disease caused by the John Cunningham (JC) virus, an opportunistic brain infection characterized by fatal demyelination of the central nervous system (CNS) due to infection of oligodendrocytes, which are myelin-producing cells of the central nervous system, and specifically targets of the JC virus [2]. The function of these glial cells is to myelinate the axons that project from the neuronal cell bodies of the cortex. Astrocytes are also infected [3].

Pathological cases were described in 1930 by a German pathologist, Hallervorden, but the disease was first described in 1958 in Boston in the United States of America, by Astral, Mancall and Richardson in three cases of cancer, two cases of chronic lymphocytic leukemia and one case of Hodgkin's lymphoma [3-6].

Through optical microscopy, years later, viral particles were identified in the nuclei of oligodendrocytes. In 1971 the virus was isolated from glial cells [6].

2. Objective

This literature review aims to conduct a mini-review on LEMP and JC virus.

3. Methodology

This is a mini-review with a qualitative approach.

Databases used: Cochrane, PubMed/MEDLINE, and SciELO.
Languages considered: Portuguese and English.

Inclusion criteria: articles published between 1956 and 2026 that directly addressed the proposed topic.

Forty-eight articles on the topic were reviewed, excluding those that did not have a direct relationship with the proposed topic.

The data were evaluated qualitatively, organizing the findings into thematic categories relevant to the study's objective.

4. Viral Etiology

JC Virus is a human polyomavirus (formerly known as papovavirus) belonging to the Polyomaviridae family, which also includes BK virus (human polyomavirus 1), simian vacuolating virus 40 (SV40), and the more recent Merkel cell polyomavirus (MCPyV) [4].

It is likely that there are at least 14 JC virus subtypes linked to different human populations; types 3 and 6 are found in Africans, type 7A in Southeast Asians, and types 1 and 4 in Europeans, which are believed to be responsible for the initial appearance of the virus [4].

5. Epidemiology of JC Virus

JC virus infection is evident globally, and its prevalence varies across age groups, with older people showing higher incidence rates. Although JC virus neuropathology affects the central nervous system, research shows that most people worldwide are latently or transiently infected with the virus, with population heterogeneity and evidence that seropositivity increases with age [4,7].

Epidemiological data indicate that 61–80% of the world's population is infected with the virus [3,8] and approximately half of this infection occurs during childhood [9,10]. Currently, PML affects one in every 200,000 people [11].

Prior to the AIDS epidemic (Human Immunodeficiency Syndrome - AIDS), PML was considered a rare complication, affecting middle-aged and elderly patients with lymphoproliferative diseases, and the incidence in the pre-AIDS era was considerably low (0.07%) [3].

Before 1981, pre-AIDS epidemic, there were only 238 documented cases of PML in the literature. These cases included organ transplant recipients, patients with hematological malignancies, lymphoproliferative diseases, and cases of chronic inflammatory disorders after immunosuppressive therapy. The major risk groups are patients infected with the Human Immunodeficiency Virus (HIV) (about 80% of cases), patients with malignant hematological pathology (about 10%), and patients treated with natalizumab (less than 5%). [11,12].

Currently, AIDS is the most common underlying medical condition in patients with PML [4]. It is unclear why PML is more frequent in patients with AIDS versus other contexts of immunosuppression. Possible causes include the duration of immunosuppression, interactions between HIV and JCV (JC virus), and brain damage from HIV infection [11].

Research conducted by Berger et al. between 1982 and 1987 found results based on histopathological and imaging findings, suggesting a prevalence of approximately 4% of PML in individuals with AIDS [9].

A study conducted at the Emílio Ribas Institute of Infectology identified a prevalence of classic PML of 6% among HIV-infected patients with opportunistic diseases of the central nervous system, similar to that reported in developed countries in the pre-HAART era, confirming that this disease is relevant in our environment and constitutes the fourth leading cause of opportunistic disease after cerebral toxoplasmosis, cryptococcal meningoencephalitis, and neurotuberculosis [13].

JC virus infection can vary widely [4]. Portugal, Austria, and the Netherlands showed the highest seroprevalence of JC virus compared to Australia and the United Kingdom [4].

A study conducted in a Portuguese population revealed a significant difference in JC virus isolation from urine and serum between HIV-infected patients (51%) and healthy individuals (33%) [14].

6. JC virus Pathophysiology

Although there is little evidence of JC virus detection in saliva, it is believed that the first infection occurs in tonsillar tissue due to the frequency with which viruses are transferred via the ororespiratory route [3,15]. and/or fecal-oral route and transmitted within and outside families [6].

The tonsils are believed to be the first site of transmission leading to further hematogenous dissemination, even though the virus is frequently found in urine samples from healthy and immunocompromised individuals, indicating urine as the main source of transmission [16].

The virus is frequently found in urine samples from people [3]. Healthy and immunocompromised, indicating urine as a source of transmission [4].

High levels of JCV in sewage systems also suggest fecal-oral transmission as a possible mechanism [17]. Although little evidence of JC virus detection in saliva has been demonstrated, it is believed that the first infection occurs in tonsillar tissue.

The virus remains latent in the gastrointestinal tract and in the tubular epithelial cells of the kidney in B cells, and can be reactivated in cases of immunosuppression [2,3,17]. It is estimated that it latently infects rinses in more than 50% of healthy adults [12].

The disease is symptomatic in patients with severe immunosuppression, usually with CD4 levels below 200, but can manifest with this T lymphocyte count above 200 [18]. It is believed that high rates of PML cases in people living with HIV result from a number of factors, such as the presence of HIV in the CNS, which may contribute directly or indirectly to the neuropathogenesis of PML, loss of CD4+ T cells with impairment of CNS immune surveillance and activation of CD8+ cytotoxic T lymphocyte (CTL) responses with destruction of infected oligodendrocytes [4].

The disease affects subcortical white matter and exhibits signs and symptoms indicative of involvement in multiple brain regions [3]. Astrocytes, as well as oligodendrocytes, support the multiplication of the JC virus. Therefore, JC virus infection of neuroglial cells may be impaired other neuroglial functions besides the production and maintenance of myelin [10].

A national study conducted at the Emílio Ribas Institute of Infectology found motor deficit as the most common clinical manifestation, followed by language impairment [19]. The role of the host response is extremely important in eliminating this virus, marked by the large perivascular infiltration of immune system cells, HIV antigens, and viral proteins, resulting in a state of demyelination. This defense is largely mediated by the cellular immune response, notably by cytotoxic T lymphocytes, whose presence has proven crucial in this protection mechanism [19].

Studies have revealed increased levels of these lymphocytes in cerebrospinal fluid (CSF) samples from patients capable of suppressing viral activity, leading to disease inactivation [20]. There are several reports in the literature indicating that B lymphocytes infected with the JC virus can cross the blood-brain barrier and initiate new infections throughout the course of the disease [20,21]. The disease progresses slowly, causing death in 4 to 6 months; however, clinical signs and symptoms may occasionally remain stable for a much longer period of time [3].

7. Predisposing Factors

According to studies, 80% of patients with JCV have AIDS, 13% have lymphoproliferative diseases, 5% are transplant recipients, and 2% is attributed to chronic inflammatory, rheumatological, and granulomatous diseases [3,22].

In transplant cases, kidney recipients may present with nephropathy and graft rejection if JC virus reactivation occurs [23].

About 5% of HIV patients develop PML, which is defined as a disease associated with AIDS [3].

The virus can also cause disease in individuals on antiretroviral therapy due to the incitement of immune reconstitution. This specific case is called PML-IRIS [18].

This condition can manifest between 1 week and up to 26 months after the start of HAART (Highly Active Antiretroviral Therapy) [24].

This unexpected occurrence of the disease among this patient population reaffirms the existence of a strong link between underlying immunosuppressive conditions and the development of PML [3].

Studies indicate that highly active antiretroviral therapies (HAART) against HIV infections have considerably reduced the virulent behavior of the HIV virus, however, the same does not apply to JC virus infections [3].

8. Histological Findings

Histologically, PML is characterized by the lysis of oligodendrocytes and astrocytes with multiple areas of demyelination [25,26].

9. Diagnosis: Imaging, Clinical and Laboratory

The diagnosis of PML is considered definitive if the clinical features and imaging features are compatible, along with a positive CSF PCR test for possible PML if the clinical features and imaging findings are compatible but the PCR is not performed/equivocal result, or the opposite, i.e., a positive PCR test but no compatibility in the others and negative for PML/not PML if only the clinical features or imaging findings are compatible but a PCR test is negative [3,12].

10. Clinical

The clinical presentation depends on the extent of demyelination and the brain structures involved. Although demyelination is multifocal, in an initial phase it can be unifocal and occur in any region of the white matter, with distribution of small lesions in the thalamus, brainstem and/or cerebellum [3].

The disease does not appear to affect the peripheral nervous system, and spinal cord involvement is believed to be rare [9,27,28].

Although JCV primarily infects the white matter of the brain, gray matter infection can occur.

It may present with: [3,9].

- Cognitive and behavioral dysfunction such as personality changes, emotional lability, rapidly progressive subcortical dementia, and memory loss. Memory difficulties and dementia are observed in approximately one-third of cases [3,9].
- Visual deficits (homonymous hemianopia, diplopia, or cortical blindness).
- Visual deficit is the most common symptom of PML, developing in 35 to 45% of cases; [3,9].
- Motor deficits (paresis, plegia, and muscle weakness). Motor weakness is observed in 25 to 33% of cases; [3,9].
- Sensory deficits; [3,9].
- Language alterations (aphasia and dysarthria); [3,9].
- Incoordination and/or gait difficulties (ataxia and dysmetria): [3,9].

Hemispheric lesions are the most common, however the brainstem and cerebellum are affected in 18% of patients [3].

Symptoms may include complaints of vertigo, headaches, seizures and parkinsonian signs [3].

Usually, the symptoms are organized in a classic triad of motor deficits (25 to 33% of patients), visual deficits (35 to 45%) and cognitive behavioral dysfunction (about 33%) with a subacute, fatal evolution in weeks, without the existence of treatment [18,22].

10. Diagnosis of PML

When PML is suspected, clinical evaluation should be performed, followed by imaging studies, cerebrospinal fluid analysis and, if necessary, brain biopsy [21].

11. Imaging Diagnosis

MRI-CE is considered the imaging method of choice for PML [29]. However, since these patients present with a nonspecific clinical picture, CT-CE ends up being the first examination performed [29].

The affected brain lesions are usually detected in the white matter and do not correspond to specific vascular territories. These lesions appear as hypodense or irregular on CT, while MRI shows areas of hypersignal on T2-weighted and FLAIR (fluid attenuation inversion recovery) images and hyposignal on T1-weighted images [6].

In an initial phase, the lesions may be circular and unifocal [29]. The most affected lobes are the parietal and occipital, followed by the frontal. Classic PML does not present cerebral edema, mass effect, and does not enhance with contrast [30].

Lesions can be identified in gray matter structures, such as the corpus callosum, thalamus, and basal ganglia, since they are made up of myelinated elements [6].

12. Histopathological Diagnosis

The gold standard for diagnosing JCV is brain biopsy. Biopsy

findings include: JC virus-infected oligodendrocytes with enlarged amphophilic nuclei at the periphery of the lesions; reactive gliosis with increased bizarre astrocytes; macrophages containing myelin and cellular debris [31,32].

13. Laboratory Diagnosis

Isolation of viral DNA in cerebrospinal fluid (CSF) with PCR confirms the diagnosis [18]. In the case of PML-IRIS, the DNA may not be detected due to an improved immune system acting against viral replication, making it undetectable in a viral assay [18]. This condition can manifest between 1 week and up to 26 months after the start of HAART (Highly Active Antiretroviral Therapy) [24].

14. Differential Diagnosis

- Toxoplasmosis [18]
- Primary CNS lymphoma [18]
- HIV encephalopathy [18]
- CMV encephalitis [18]

15. Treatment

Current treatment focuses on strengthening the adaptive immune response, varying according to the clinical context [3]. For HIV patients, the recommendation is to immediately start HAART (Highly Active Antiretroviral Therapy) [3]. Some studies have explored the benefits of strengthening the adaptive immune response through dendritic cell vaccines. Activation of dendritic cells with JC antigens can induce a significant CD8 response, associated with prolonged survival in patients with PML. However, these studies were conducted in a limited group of three patients, justifying the need for more research with a larger sample size to validate the use of these agents [3]. Different treatment regimens, such as cytarabine, interferons, and heparin sulfate, have been used to treat PML [3].

16. Cidofovir

Studies with Cidofovir have not shown an impact on morbidity and mortality [31,33].

17. Cytarabine

It has not shown clinical efficacy in HIV-positive patients with classic PML, although in vitro there is a decrease in JC virus replication. However, in a study involving 19 patients with classic PML who are HIV-negative, neurological stabilization was achieved in 36% of patients within four and a half years of follow-up. The dose administered was 2 mg/kg/day for 5 days and the most common adverse effect was myelotoxicity. For HIV-negative patients who developed classic PML due to immunosuppressive therapy, discontinuation of the same is recommended [34,35].

18. Glucocorticoids

The pathophysiology is fundamentally inflammatory, justifying the beneficial effect. The prognosis is usually favorable with short cycles of corticosteroids associated with temporary interruption of HAART. Dexamethasone 32 mg intravenously per day divided into 4 doses for a total of 2 weeks, followed by progressive weaning. Great care must be taken, as corticosteroids at this dosage are a significant immunosuppressant; therefore, the diagnosis of PML associated with IRIS must be well substantiated [36,37].

19. Interferon alpha

Studies with it have not shown an impact on morbidity and mortality [33,38].

20. Lenflunomide

An immunomodulatory drug, lenflunomide, is commonly used to treat rheumatoid arthritis and has also been used to treat patients with PML with limited success, and further studies are needed [3].

21. Mefloquine

This antimalarial drug has shown in-vitro activity against the JC virus [35,39].

22. Mirtazapine

Mirtazapine, a medication that inhibits serotonin reuptake, is being used, although with very preliminary results. In vitro studies have shown that the JC virus can infect cells through serotonin 5HT2a receptors [40].

23. Pembrolizumab

A study with pembrolizumab induced downregulation of PD-1 expression in lymphocytes in peripheral blood and cerebrospinal fluid in all patients, a total of eight [9].

Five of eight patients showed clinical improvement or stabilization of PML, accompanied by a reduction in JC viral load in the CSF and an increase in CD4+ and CD8+ antiviral activity in vitro against JC virus. In the other three patients, no significant change in viral load or magnitude of the antiviral cellular immune response was observed, and there was no clinical improvement [12].

In the months prior to the first infusion, seven of the eight patients presented with progressive neurological deterioration, and magnetic resonance imaging showed an increase in PML lesions [12].

After treatment with pembrolizumab, five of the eight patients showed clinical improvement or stabilization, and magnetic resonance imaging showed corresponding stabilization or reduction in lesion burden; none of the patients had complete disappearance of PML lesions [12].

24. Heparin sulfate

Regarding heparin sulfate therapy, it has been shown that heparin sulfate inhibits activated lymphocytes from crossing into the brain by removing cell surface receptors, including glycoproteins on cerebrovascular endothelial cells in a mouse model system [3].

25. Topotecan

Topoisomerase inhibitor. It is a candidate under study due to the knowledge that topoisomerases are necessary to unwind the DNA strand and allow viral replication. In a pilot study, 3 of 11

patients with HIV and classic PML showed consistent clinical and radiological improvement. However, adverse effects make its use unfeasible: severe anemia, leukopenia and thrombocytopenia [41].

26. Monoclonal antibodies and JC virus

New cases of PML are associated with the use of new immunomodulatory therapies in patients affected by hematological autoimmune disorders, rheumatoid arthritis, systemic lupus, non-Hodgkin lymphoma, Crohn's disease and multiple sclerosis [13,14].

Structurally, mAbs – monoclonal antibodies or monoclonal antibodies – can be classified into four types: murine, chimeric, humanized and human. The latter three resulted from some alterations in the forms of development, in order to increase the similarity of mAbs to human antibodies and thus reduce the occurrence of adverse events [31]. mAbs can lead to cytotoxicity in the cancer cell by activating the complement cascade so that cytolysis occurs or by the action of cells effector cells of the immune system, such as natural killer cells, causing lysis of the cell marked by mAb [31].

In the literature, PML was considered a rare disease, and, before the HIV pandemic and the availability of immunomodulatory drugs, it was associated only with neoplasms that affect the immune system, such as chronic lymphocytic leukemia or Hodgkin's lymphoma. In the last two decades, the incidence of PML has begun to increase exponentially [31].

New cases of PML are associated with the use of new immunomodulatory therapies in patients affected by various diseases, such as multiple sclerosis (MS), Crohn's disease, non-Hodgkin's lymphoma, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and hematological autoimmune disorders [31]. The incidence of PML in patients undergoing immunomodulatory therapy depends on the drug used and the disease treated [31].

27. Drugs that predispose to PML

27.1. PML and Daratumumab

Researchers from São Paulo, Brazil reported a case of a patient with multiple myeloma who was found to have PML during treatment with daratumumab. Because it is an isolated case, further studies are needed [27].

27.2. PML and Efalizumab

An even higher incidence (1/500) was observed in patients with psoriasis treated with efalizumab, a humanized mAb against a T lymphocyte adhesion molecule, and as a consequence efalizumab was voluntarily withdrawn from the market [36]. Researchers reported 2 cases of patients with severe psoriasis treated for 3 years or more with efalizumab, a neutralizing antibody of LFA-1 [38]. Both patients developed progressive cognitive and motor deficits, and the JC virus was identified in the CSF. Both died of PML 2 and 6 months after the onset of the disease [38].

27.3. PML and natalizumab

Despite advances in therapy, the monoclonal antibody is associated with reactivation of the JC virus in the body [36]. Natalizumab is a humanized mAb, which interferes with the interaction between the Very Late Antigen 4 (VLA-4), expressed on leukocytes, and the vascular adhesion molecule 1 (VCAM-1) expressed on endothelial cells, thus preventing leukocyte extravasation at sites of inflammation [36].

Natalizumab is generally well tolerated, but due to its observation with PML, it was approved with a restricted distribution format in 2006 [36]. The risk of developing PML during treatment is very high, and was assessed at 3.85/1000 [36]. Natalizumab is used in several autoimmune diseases, but in particular for the treatment of Multiple Sclerosis (MS) [36].

In a study conducted by Brazilian researchers in Brasília – DF in 2014, 23 patients with an average natalizumab use time of 17 months underwent the evaluated radiological examinations and no lesions suggestive of PML were found [30].

27.4. PML and Ocrelizumab

A study conducted in 2021 evaluated the use of Ocrelizumab after Natalizumab in patients with relapsing-remitting multiple sclerosis positive for the JC virus [42]. The protocol involved a direct switch from Natalizumab to Ocrelizumab. The status of absence of evidence of multiple sclerosis activity (NEDA) is defined as the absence of relapses, absence of evidence of radiological disease activity, and absence of progression [42].

Interestingly, JCV indices decreased during treatment with ocrelizumab [42]. The authors concluded that future data are needed, as a low JCV index in MS patients treated with ocrelizumab should not necessarily be interpreted as JCV seronegativity or a low-risk category for PML [42].

27.5. PML and rituximab

The risk of PML during the administration of rituximab, a humanized monoclonal antibody, has been estimated at approximately 1/4,000 when used in patients with systemic lupus erythematosus and 1/25,000 when used in rheumatoid arthritis [36].

27.6. Prognosis

PML is a progressive and fatal disease. Currently, the main goal of treatment is to increase survival [18]. Factors that improve survival rates include low JC virus viral load in cerebrospinal fluid PCR samples, high CD4 count [18].

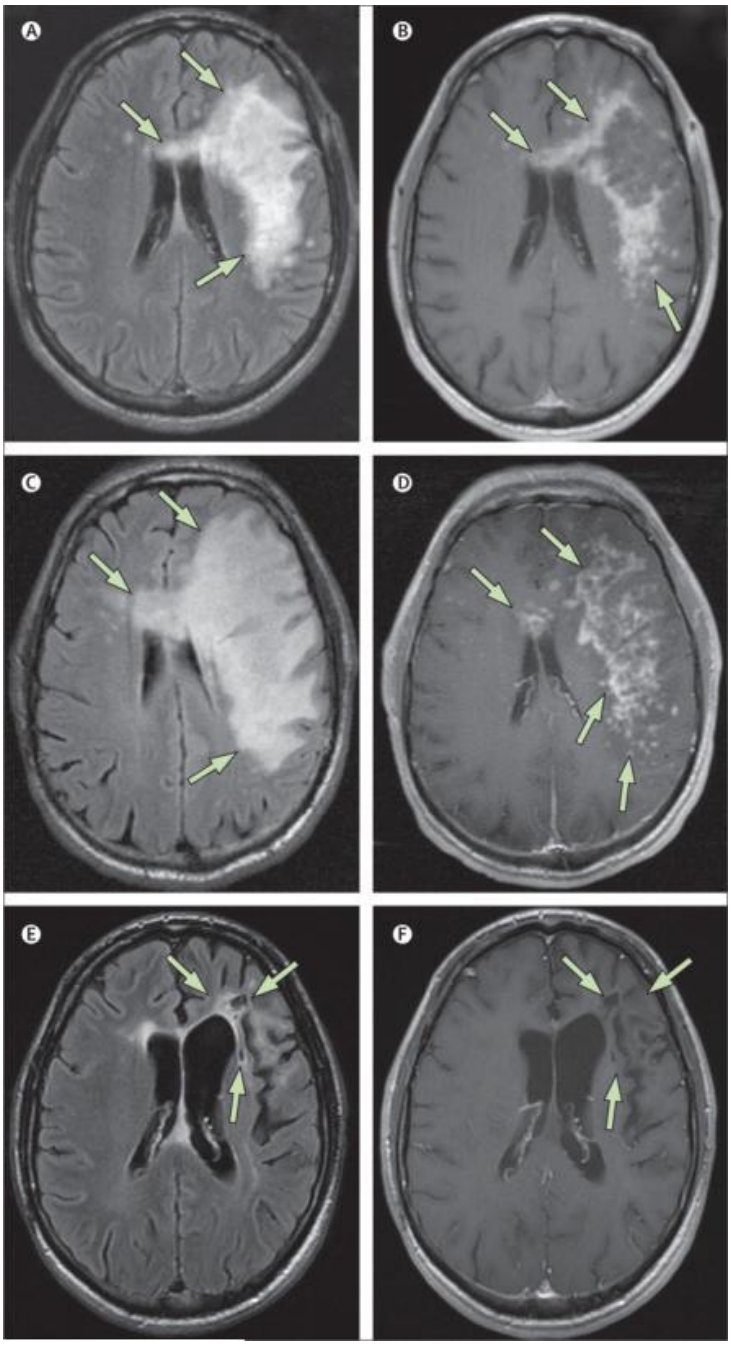
In AIDS patients, it is known that the initiation of antiretroviral therapy improved survival rates. A robust adaptive cellular immune response is a good indicator of prolonged survival, as evidenced by the presence of PML-specific CTL lymphocytes (cytotoxic T lymphocytes) in the serum of patients [3]. Before therapeutic HAART, the median survival in HIV/AIDS patients was six months and less than 10% of patients were still alive after one year [43].

27.7. Lethality in PML

The natural course of the disease is fatal within a period of months [6,44]. According to a study conducted in São Paulo, Brazil, the in-hospital and one-year mortality rates after PML diagnosis were 24.7% and 52.7%, respectively [19]. The introduction of highly effective antiretroviral therapy (HAART) leads to a decrease in the incidence and mortality of PML, since the restoration of the immune response by antiretroviral therapy (ART) is the best predictor of PML survival [43]. One-year survival increases from 10% in the 1980s to 50% after ART [45].

28. Conclusions

This mini-review allowed us to conclude that although it was described in 1930, today, almost a century later, further studies are still needed, mainly related to the development of vaccines to prevent JC virus infection, targeting immunocompromised individuals, as well as drugs acting on the central nervous system, allowing for the cure of PML or at least an increase in quality and life expectancy [46-48].



Fonte: [6].

Figure 1: Macroscopic Examination of JCV-Induced Lesions Occurring in The Subcortical White Matter

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