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Systemic Lupus Erythematosus, Progressive Multifocal Leukoencephalopathy, and T-CD4+ Lymphopenia

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Abstract Progressive multifocal leukoencephalopathy (PML) is a rare opportunistic infection caused by the reactivation of JC virus and occurs in patients with severe primary or secondary immunosuppression. Recently, PML is becoming relevant in autoimmune disorders, particularly in patients treated with biologic agents. However, systemic lupus erythematosus (SLE) appears to be associated with susceptibility to PML that cannot be entirely explained by the immunosuppressive therapy. The authors present two patients with the diagnosis of SLE and PML: One had a heavy immunosuppressive therapy history, and the other had never experienced biologic or cytotoxic therapeutics. Both patients had a profound T-CD4+ lymphopenia during their clinical history. These two cases emphasize the importance of CD4+ lymphopenia in SLE patients with and without immunosuppressors regarding opportunistic infections.

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the central nervous system (CNS) that frequently develops from the reactivation of a latent JC virus infection. Most of PML cases are related to severe primary or secondary immunosuppression, such as HIV infection, lymphoma or solid organ malignancies, and organ transplant recipients. Recently, unexpected patients have been also diagnosed with PML, such as patients with autoimmune diseases treated or not with biologic agents. In fact, immunosuppression appears to be the triggering factor in these patients. The clinical course of PML is progressive and most always fatal, with 20 to 50 % of patients dying within 3 months, and even the least severe cases develop incapacitating neurological impairments [1, 2].

There is not enough epidemiological data to establish the frequency of patients with systemic lupus erythematosus (SLE) and PML in the world (Table 1). In a database representing 20 % sample of all US hospital discharges [3], a relative frequency of four PML per 100,000 SLE patients (0.44 % of all PML cases) was found, which is a number substantially higher when compared with other rheumatic diseases (namely the most prevalent rheumatoid arthritis). A retrospective observational study, also from US, used data obtained from a large health insurer and estimated an incidence rate of PML in SLE patients of 2.4 and in vasculitis patients of 10.8 per 100,000 person-years (one case in 42,278 and one case in 9,226 person-years, respectively) [4]. Molloy et al. made an extraordinary effort

Table 1 Summary of published articles concerning patients with PML and autoimmune rheumatic diseases

References	Methods	Study years	Results	Conclusions
Calabrese et al. [5]	Data obtained from search of the world literature in English to identify cases of PML associated with rheumatic diseases	Until 2007	A total of 36 cases of PML associated with rheumatic diseases (23 associated with SLE)	Factors other than iatrogenic immunosuppression contribute to the development of PML in patients with rheumatic diseases, particularly in those with SLE
Molloy and Calabrese [3]	Data obtained from the Nationwide Inpatient Sample database (20 % sample of all hospital discharges) in US	From 1998 to 2005	43 cases of PML associated with SLE (0.44 % of all PML cases)	PML occurs more commonly in SLE than in other rheumatic diseases
Molloy and Calabrese [6]	Data obtained from search of the world literature in English to identify cases of PML associated with rheumatic diseases	Until 2008	A total of 46 cases of PML associated with rheumatic diseases (30 associated with SLE)	SLE patients may be predisposed to development of PML; potential mechanisms are unclear
Amend et al. [4]	Data obtained from US health insurer database	From January 2000 to June 2008	The PML incidence rate was 2.4 per 100,000 person-years in SLE	The incidence rate of medical record-confirmed PML was rare in non-HIV patient cohorts
Molloy [7]	Data obtained from search of the world literature in English to identify cases of PML associated with rheumatic diseases	Until April 2009	A total of 50 cases of PML associated with rheumatic diseases (32 associated with SLE)	There is a predisposition of PML in patients with SLE
Molloy and Calabrese [11]	Autoimmune rheumatic diseases selected from FDA Adverse Event reporting System	From November 1997 to March 2010	A total of 34 cases of PML associated with rheumatic diseases (17 associated with SLE)	PML occurs in autoimmune rheumatic diseases treated with various immunosuppressive therapies

collecting all described clinical cases of PML in patients with rheumatic diseases, based on English language medical literature [5–7]. The most recent published data [7] identified 32 patients with SLE associated PML and 18 cases with other rheumatic diseases after excluding HIV infection, cancer, or organ transplantation history. To our knowledge, since the publication of Molloy's data, only three cases of SLE and PML were described: one related with the use of etanercept [8], other with mycofenolate mofetil [9], and the last one with mycofenolate mofetil in a patient with SLE and T-CD4+ lymphopenia [10]. Another recent work evaluated the association of PML with immunosuppressive therapy for autoimmune rheumatic diseases [11]. The most relevant conclusions of literature are a surplus representation of SLE in the population of PML and rheumatic diseases and a variety of immunosuppressive treatment in the 6 months before the onset of neurological symptoms.

Until 2011, 608 SLE patients were followed in our clinical immunology outpatient clinic. Two patients with SLE and PML were identified: One had a heavy history of immunosuppression, including rituximab in the previous 6 months, the other never had biologic or cytotoxic therapeutics. Curiously, both patients were hospitalized in April 2010. None of them had a history of HIV [1, 2] and HTLV [1, 2] infection, cancer, or organ transplantation. Both patients are alive after 23 months of follow-up.

Case Reports

Patient Number 1 A 26-year-old woman was diagnosed with SLE in 2003, presenting with chorea, psychosis, malar, and discoid rash as main clinical features. Positive antinuclear, anti-Sm, anti-dsDNA, IgM anti-cardiolipin, and IgM anti-beta-2 glycoprotein antibodies (without criteria for antiphospholipid syndrome) and severe lymphopenia ($<500/mm^3$) were detected. The disease was characterized, from the beginning, by skin and neuropsychiatric flares, but she also developed multiple severe infectious complications (viral or intracellular organisms), such as cytomegalovirus with possible related hemophagocytic syndrome, sepsis by listeria monocytogenes, and herpes zooster. To control the disease flares (mainly severe cutaneous), she received treatment with steroids, hydroxychloroquine, cyclophosphamide, azathioprine, methotrexate, off-label intravenous immunoglobulins (IvIg, 1 mg/kg, 2 days), thalidomid, and, finally, rituximab (July and August 2009). The infectious complications were not correlated to the disease activity (SLEDAI <4 in all evaluations). T-CD4+ lymphopenia was detected at the first frequency analysis of T lymphocytes done in 2005, and it persisted since through several evaluations, either during infectious episodes, lupus flares, or during remission phases. An inverted CD4/CD8 ratio was also frequently present during her clinical evolution.

In December 2009, she developed hallucinations and marked psychomotor agitation, with normal brain MRI.

She was treated with a pulse of intravenous steroids, but a month later, she developed a progressive left-sided and tightening headache with a constant character throughout the day and no aggravation induced by Valsalva maneuver. She also presented vertigo, not elicited by head movements, and minor gait imbalance. A month later, she had jerky pursuit, torsional gaze evoked nystagmus, left limbs dysmetria, and gait ataxia. The brain MRI presented at this time disclosed white matter T2 hyperintensities in left cerebellar hemisphere and peduncle, the last one with contrast enhancement. Cerebrospinal fluid (CSF) was positive for JC virus PCR. She started cidofovir and off-label IvIg (0.4 g/kg/month—the same dosage used as a substitution therapy in primary antibody deficiencies). Since then, a major clinical improvement was observed, although she remained with a mild left limb's dysmetria and gait ataxia. The T-CD4+ numbers increased after the beginning of the treatment (T-CD4+=344/mm^3) but not in a consistent way.

We analyzed the surface expression of the activation markers CD69, CD25, and CD71 on stimulated T-CD4+ and T-CD8+ lymphocytes with PMA + ionomycin (PMA + I) and phytohemagglutinin (PHA) by flow cytometry (FC500, Beckman-Coulter). In this patient, it was detected a poor response, related to the expression of CD25 and CD71 on T-CD4+ and T-CD8+ lymphocytes after activation with PHA, but normal for CD69, CD25, and CD71 after activation with PMA + I. The observed reduced expression of CD25 and CD71 in activated T lymphocytes with PHA may be related with the immunosuppressive effects of therapy (because this was long and aggressive) or it could be an intrinsic defect, implicated in the physiopathology of the disease and responsible for the viral and intracellular organism infections.

Patient Number 2 A 57-year-old woman was diagnosed, in 2005, with SLE and secondary antiphospholipid syndrome based on discoid rash, lymphopenia, positive antinuclear antibodies, IgM anticardiolipin and IgM anti-beta 2 glycoprotein antibodies, and deep venous thrombosis. She was treated only with a low dose of steroids (≤15 mg/day), hydroxychloroquine, and oral anticoagulation.

In June 2009, she developed difficulties in accomplishing her regular daily tasks. There was a progressive deterioration, with writing difficulties, left-sided spatial and body neglect, inappropriate social conduct, and a childish behavior. On April 2010, the first time she had contact to our clinic, at neurological examination, she presented a paucity of spontaneous speech, with marked hesitation, moderately impaired naming, and comprehension. There was marked verbal perseveration, inappropriate laugh, and left-sided neglect. Her brain MRI disclosed a corticosubcortical left temporal and multiple periventricular and subcortical white matter T2 hyperintensities. CSF was negative for JC virus, but brain biopsy disclosed nuclear inclusions in oligodendrocytes with immunostaining for the SV40 antigen. Her T-CD4+ cells counts at that time were 123/mm^3, and an inverted CD4/CD8 ratio was also present. She was treated with cidofovir (suspended after a cutaneous reaction) and monthly pulsed of IvIg (0.4 g/kg/month) with moderate memory and behavior improvement and a major T-CD4+ cells count response (between 300 and 450/mm^3). The surface activation of the activation markers was normal for all markers, with PHA and with PMA + I activation.

Discussion

The JC virus is ubiquitous in the general population, and asymptomatic infection is thought to occur during childhood [2, 12]. After primary infection, the virus remains latent in several sites of the body, as kidneys, bloodstream and bone marrow lymphocytes, lymphoid organs, tonsils, gastrointestinal, and urinary tracts [13–17]. It is debated if the CNS is a site of latency [12]. During immunosuppression, JC virus is intermittently released into the bloodstream and may reach the brain causing destruction of the cells, demyelination, and finally PML.

The host factors that determine susceptibility to PML and the mechanisms by which JC virus is controlled in normal individuals during the latency period are unknown. Humoral immune response by itself is not sufficient to prevent reactivation of JC virus. The number of virus-specific T-CD8+ cytotoxic lymphocytes is related to prognosis in HIV patients with PML, as they are the main inflammatory cell type in PML lesions and cause destruction of infected cells in the brain. The generation of T-CD8+ cytotoxic lymphocytes is dependent on the interaction of the virus-specific T-CD4+ lymphocytes, as demonstrated in AIDS patients with low T-CD4+ cells counts and susceptibility to develop PML [5, 6, 12, 15, 18, 19]. Therefore, it is believed that JC virus does not cause illness in healthy adults because the immune system is capable to maintain the virus in a quiescent state. The experience with HIV patients clearly pointed that clinical improvement in PML correlates with the T-CD4+ cells counts increase after antiretroviral therapy.

The diagnosis of PML should be suspected in patients with uncommon neurological manifestations of gradual onset, particularly if they are immunosuppressed. The clinical manifestations correlate with the specific involved areas of the brain and can vary overtime. Common symptoms are disorientation, behavioral changes, mental slowness, hemiparesis, cerebellar gait and limb ataxia, lack of coordination, and visual deficits. Optic nerves and spinal cord are usually spared [1, 2, 5]. On MRI, demyelinated areas are revealed in single or asymmetric multifocal white matter lesions, commonly in parietal and occipital lobes and are hypertense on

T2-weighted and hypotense on T1-weighted imaging compared to normal white matter, without gadolinium enhancement, edema, or mass effect [20]. Contrast enhancement has been described in patients with recovery of immunological competence [21].

For diagnostic confirmation, it is imperative to identify the JC virus in a CSF specimen or in a brain biopsy. CSF studies are usually normal but may show a small increase in the protein level or cell count. Despite a specificity of 96 %, CSF PCR for JC virus has a sensitivity of only 74 %; as a consequence, a negative CSF PCR for JC virus does not exclude the diagnosis [22]. Specimens obtained by stereotactic brain biopsy reveals focal demyelination and neuroglial inflammation with macrophage cell infiltrate in a perivascular distribution; the astrocytes and oligodendrocytes show marked morphological changes and have enlarged or hyperchromatic nuclei. The JC virus can be detected by in situ hybridization and/or immunohistochemistry in the biopsy specimen [12].

The diagnosis of PML can be delayed or even underdiagnosed, as the neurological manifestations may resemble those of neuropsychiatric lupus, for which treatment is considerably different. We should always rule out opportunistic infections in SLE patients, when major disease flares arise.

PML is found in SLE patients receiving modest immunosuppressive therapy (≤15 mg/day prednisone or antimalarial agents) and/or treated with methotrexate, mycofenolate mofetil, calcineurin inhibitors, cyclophosphamide, chlorambucil, anti-TNF therapy, azathioprine, leflunomide, efalizumab, natalizumab, or rituximab; however, PML was also detected in patients not being treated at all [7, 8, 11, 23, 24]. Almost all drugs mentioned above induce both a partial humoral and cellular immune deficiency that may enhance the probability for JC viral reactivation. Despite the alarming reports associating PML with different immunosuppressors, no study was able to prove a peremptory connection between the two [23]. Among rheumatic diseases, PML predominates in SLE patients but has also been described in patients with rheumatoid arthritis, Wegener's granulomatosis, idiopathic inflammatory myositis, Sjögren's syndrome, and scleroderma [1, 2, 6, 12].

We may hypothesize that SLE itself confers a higher risk for PML development. This risk is dependent on immunological dysfunction, by an underlying mechanism that remains unknown. Furthermore, it may represent an additional phenotype in the heterogeneous portrait of lupus disease. In SLE patients, there are a multiplicity of deregulations in the immune system, including dysfunction of B lymphocytes and quantitative and functional alterations of T lymphocytes and its subtypes. Some studies show that lymphopenia, particularly T-CD4+ lymphopenia, can occur in lupus patients, being related to severe and opportunistic infections and correlating also with severity of the disease [24, 25].

PML was also described in primary immunodeficiencies. A case of PML in a patient with common variable immunodeficiency and abnormal T-CD8+ lymphocyte distribution highlighted the importance of naïve and memory T-CD4+ and CD8+ cell subset quantification in these patients [26]. PML was also reported in hyperimmunoglobulin E recurrent infection syndrome [27]. It is well-known that autoimmune manifestations are very prevalent in several patients with primary immunodeficiencies, which might even be their second commonest clinical manifestation [28]. Idiopathic CD4+ lymphopenia (ICL) is an extremely rare syndrome defined as a T-CD4+ cell count less than 300 cells/mm^3 (or less than 20 % of the total T cell count) on two occasions (at least 6 weeks apart), after exclusion of HIV1, HIV2, HTLV1, and HTLV2 infection, and absence of any other defined immunodeficiency or therapy capable of lowering T-CD4+ cell levels [29]. ICL has been reported to occur along with numerous opportunistic infections including PML [30, 31] and can also be linked to autoimmune diseases [32].

Therefore, patients with cellular immunity dysfunctions are at risk for a JC virus reactivation and development of PML. Lymphopenia, particularly T-CD4+ lymphopenia, is a major risk factor for PML development. Our patients had T-CD4+ lymphopenia, although not evaluated at baseline diagnosis of SLE. However, they had repeated T-CD4+ determinations during the disease evolution and presented always with T-CD4+ lymphopenia less than 500/mm^3, or even less than 200/mm^3 (in patient number 1). This had no relationship with immunosuppressive therapy in patient number 2, but could have played a role in patient number 1. However, we could prove that lymphopenia persisted in the later, even during several periods without immunosuppressive treatment. Meanwhile, patient number 1 had a poor response after activation with PHA, which may represent an intrinsic defect, perhaps implicated in the physiopathology of the disease and maybe an explanation for infections, apart from iatrogenic immunosuppression.

In our clinical experience, we have patients that suffer from multiple infections and others that never do, a fact that is not always related to immunosuppressive therapy. Hence, we could hypothesize that SLE patients may have two types of lymphopenia: The first and most common type of lymphopenia is associated with lupus activity, which may improve with immunossupressive treatment, and the other type is a more sustained lymphopenia, always present during the clinical history of the patient, not correlated with disease activity, and associated with a higher risk for infections, behaving as an immunodeficiency.

Isolated T-CD4+ lymphopenia may represent an immunodeficiency associated to SLE and should be thought in patients

with multiple infections. So, we propose that T-CD4+ and T-CD8+ lymphocytes should be evaluated at baseline diagnosis and monitored in patients with lymphopenia.

There is no proven treatment for PML; however, it is paramount to attempt the reversal of the immunosuppressive state, whenever possible, as it can change the survival. Highly active antiretroviral therapy is the indicated treatment for HIV/AIDS patients because it promotes the immune system reconstitution. For patients without HIV/AIDS, the first thing to do is to suspend the immunosuppressive therapy. Some antiviral agents have been suggested without consistent results though, such as cytosine arabinoside, mefloquine, interferon alpha, cidofovir, topotecan, and camptothecin. Preventing JC virus attaching to the serotonin receptor on the cell membrane by administering mirtazapine is a strategy that has also been suggested to prevent PML in high-risk situations (for example, with the use of biologic agents) [33–40]. Patel et al. [31] emphasize the importance of mechanisms to increase CD4+ cell counts in non-HIV patients, particularly in ICL, using with success a combination of therapies, including interleukin-2.

There are no hard data to justify the use of IvIg, at immunodeficiency replacement dosages, in PML treatment. We used it as an off-label indication and decided to maintain it with the improvement and stabilization operated in patients. The mechanism of action of IvIg is largely unknown, but indeed it has an impact on immunological repertoire and, most certainly, in immunological dysfunctions also.

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