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Review

Progressive multifocal leukoencephalopathy in autoimmune diseases

Elisabeth Palazzo*, Salim Ahmed Yahia

Service de rhumatologie, hôpital Bichat, 46, rue Henri-Huchard, 75018 Paris, France

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ABSTRACT

Progressive multifocal leukoencephalopathy (PML) is a subacute central nervous system infection due to reactivation of the JC virus. Most reported cases occurred in HIV-infected patients (80% of cases), patients with lymphoid malignancies (13%) and transplant recipients taking immunosuppressants (5%). Less often, PML has been described in patients with chronic inflammatory joint diseases associated with autoimmune disorders (lupus, rheumatoid arthritis [RA] and vasculitis) (2%). Magnetic resonance imaging of the brain shows suggestive changes and confirmation of the diagnosis is obtained by performing PCR tests to identify the JC virus in the cerebrospinal fluid or, when necessary, a brain biopsy. No treatments have been proven effective. Most patients experience progressive disease that is fatal within a few months or induces incapacitating neurological impairments. The risk of PML is 0.4/100 000 in patients with RA. In the few case-reports of PML in RA patients, the treatments used included methotrexate (five cases) combined with a biological agent such as infliximab (one case), rituximab (four cases), or leflunomide (two cases including one with concomitant rituximab). PML is an extremely rare but devastating complication. Rituximab therapy is associated with an increased prevalence of PML in RA patients (4/100 000), who should be informed of this risk. In patients with lupus, the risk of PML is higher than in RA (4/100 000) and 40% of cases of PML occur during low-dose glucocorticoid therapy without immunosuppressive therapy.

1. Introduction

Progressive multifocal leukoencephalopathy (PML) is a subacute infection of the central nervous system (CNS) due to reactivation of the JC virus (JCV). In most cases, immunosuppression is required for PML to develop. PML has been reported chiefly in patients with HIV infection (80% of cases) or lymphoid malignancies (13%) and in transplant recipients taking immunosuppressant agents (5%). However, PML has also been described in association with chronic inflammatory joint diseases and autoimmune diseases (systemic lupus erythematosus [SLE], rheumatoid arthritis [RA], or vasculitis) (2%) [1].

2. Progressive multifocal leukoencephalopathy

PML was first described by Alstrom in 1958. The causative agent was named the JCV for John Cunningham, the first patient in whom the virus was identified, by Padgett et al. in 1971 [2].

2.1. The JC virus

The JCV belongs to the Polyomavirus family, which also includes the BK virus. The JCV genome is a circular DNA strand of 5000 base pairs including a coding region and a non-coding control region (NCCR). The JCV is ubiquitous in the general population and is acquired by an increasing proportion of individuals during childhood. The prevalence of JCV infection ranges from 60 to 80% in adults and reaches 90% in the elderly [3].

Contamination occurs chiefly via oral ingestion. Primary JCV infection is usually asymptomatic. The virus establishes latency in a variety of sites, chiefly the tonsils, bloodstream and bone-marrow lymphocytes (CD 34+), gastrointestinal tract, kidneys, and urinary tract. The JCV is then released intermittently into the bloodstream and may reach the brain without inducing pathogenic effects. It exists as two variants, the archetype variant and the prototype variant, which differ regarding their NCCR region and cannot be distinguished by serological tests [3,4].

The neurotropic JCV is the prototype variant. PML may result either from rearrangement of the NCCR region of the archetype variant or from co-infection with the prototype variant. In immunocompetent individuals, the periventricular T lymphocytes and the B lymphocytes are capable of controlling the infection of brain cells, most notably of oligodendrocytes and astrocytes [3,4].

2.2. Diagnosis

PML affects the white matter of the CNS in a random distribution. As a result, the clinical manifestations are extremely variable and lack specificity. Therefore, the diagnosis should be considered in

* Corresponding author.
E-mail address: elisabeth.palazzo@bch.aphp.fr (E. Palazzo).

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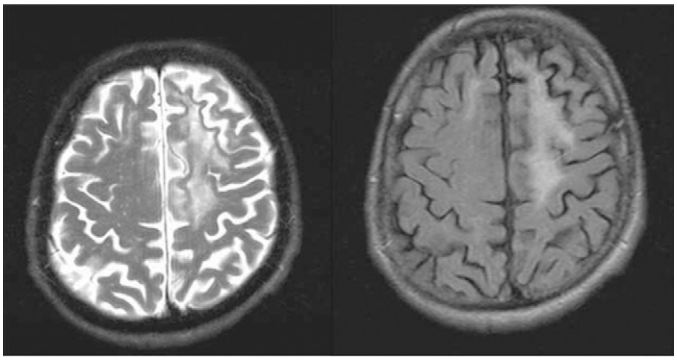

Fig. 1. Bilateral foci of high signal in an asymmetric distribution in the frontal and parietal lobes.

patients with unusual neurological manifestations, particularly of gradual onset.

The most common symptoms are confusion (54%), motor impairment (33%), impaired coordination (25%), speech disorders (21%), and visual disturbances (18%). Seizures are uncommon. The symptoms may vary over time, leading to diagnostic delays [4,5]. Magnetic resonance imaging (MRI) is the best investigation for suspecting the diagnosis. T1- and T2-weighted sequences with gadolinium injection and fluid-attenuated inversion recovery (FLAIR) should be obtained (Fig. 1). Demyelinated areas are visible as high T2 signal and low T1 signal, usually without gadolinium enhancement. These signal abnormalities vary in size and are asymmetrically distributed throughout the subcortical region. They are not distributed in a specific vascular territory and induce neither a mass effect nor brain tissue atrophy. They predominate in the parietal and occipital regions. The optic nerve is usually spared and there is no evidence of transverse myelitis [6].

Confirmation of the diagnosis requires identification of the JCV in a cerebrospinal fluid (CSF) specimen or brain biopsy. CSF obtained by lumbar tap is usually normal but may show a small increase in the protein level or cell count. Identification of the JCV is achieved using PCR technology. The PCR test is 74% sensitive and 96% specific [5].

A stereotactic brain biopsy must be obtained if the PCR test is negative on the CSF specimen. Focal demyelination and neuroglial inflammation with a macrophage-cell infiltrate in a perivascular distribution are the main findings. The astrocytes and oligodendrocytes show particularly marked morphological changes and have enlarged or hyperchromatic nuclei (Fig. 2). The nuclei of the oligodendrocytes contain viral inclusions. Identification of the JCV by PCR and immunolabeling confirms the diagnosis.

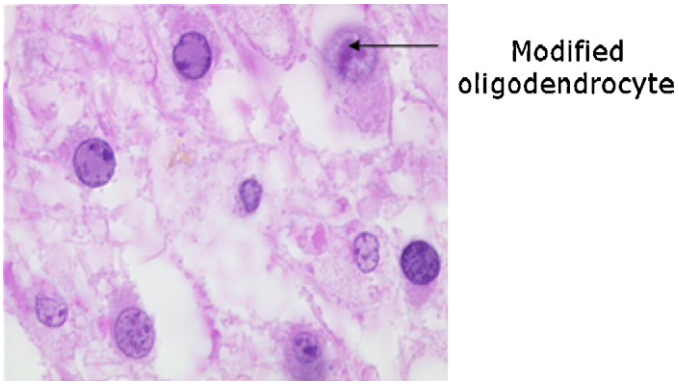

Fig. 2. Autopsy specimen. Hematein-eosin stain, × 400. Modified oligodendrocyte.

PML is fatal in 60 to 90% of patients, and 20 to 50% of patients die within 3 months. Thus, in some cases the diagnosis is established only by autopsy. The least severe cases cause incapacitating neurological impairments [5,7].

2.3. Treatment

To date, the only proven treatment is correction of the immune deficiency, which may paradoxically cause exacerbation of the symptoms within the first few months as part of the immune reconstitution inflammatory syndrome (IRIS). IRIS is associated with the development of gadolinium enhancement of the MRI lesions [4,8]. The recommended treatment of IRIS includes the administration of glucocorticoids, usually as intravenous bolus injections [9].

A number of agents capable of decreasing in vitro replication of the JCV have been suggested. Among them, the antimetabolic agent cytosine arabinoside failed to produce clinical benefits in the only available studies, which were conducted in patients with HIV-associated PML [4]. Mefloquine is a synthetic antimalarial agent that diminishes JCV replication within infected cells [4,10]. However, its clinical usefulness is limited. A study of mefloquine was stopped prematurely because of inadequate efficacy [10]. Antiviral agents (interferon alpha and cidofovir) induced no beneficial effects in patients with JCV infection unrelated to the HIV. A treatment regimen including cytosine arabinoside was used successfully in a patient with PML associated with the SLE [11].

Another approach involves preventing the JCV from attaching to the serotonin receptor on the cell membrane by administering mirtazapine [12]. This strategy has also been suggested to prevent PML in high-risk situations such as natalizumab therapy [4].

2.4. Epidemiology

The mode of expression of the JCV explains the low prevalence of PML in the general population of only about 0.2/100 000 (Table 1). The risk of PML is increased in patients with chronic inflammatory diseases or autoimmune diseases, even in the absence of immune modulating treatments or of the above-mentioned conventional risk factors [5,13].

3. Progressive multifocal leukoencephalopathy in patients with inflammatory diseases

3.1. Multiple sclerosis (MS)

The prevalence of PML is not increased in patients with MS. Reported cases were related to the use of natalizumab [4,14]. As of April 2010, 42 cases had been reported worldwide [4,15–17]. Most of the patients had a history of treatment with immunosuppressants (mitoxanthrone, azathioprine, or methotrexate). Of the first three cases, two occurred in patients with MS treated with interferon-beta and 1 in a patient with Crohn's disease and a history of infliximab and azathioprine therapy [16]. Following these reports, natalizumab was removed from the market in 2005 then licensed for use as single-drug therapy in 2006. However, even when used alone, natalizumab was found to increase the risk of PML, which was estimated at 1/1000 after 18 months of exposure. These data prompted the French Drug Safety Agency (AFSSAPS) to require that each patient and prescribing neurologist sign an informed consent document prior to natalizumab treatment initiation. It is believed that PML may be related to the mechanism of action of natalizumab, which is a monoclonal antibody to α4-integrin. Natalizumab depletes the CD4+, CD8+, and CD19+ lymphocyte populations in the CSF, decreases the CD4+/CD8+ ratio, and